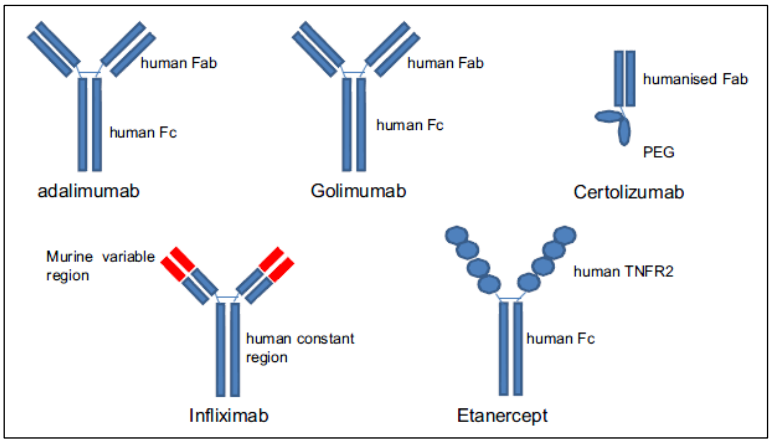
UNIVERSITY OF CRETE

Faculty of Medicine

Thesis for doctoral degree

LONG TERM RESPONSE AND SAFETY OF BIOLOGIC THERAPIES IN GREEK PATIENTS WITH RHEUMATIC DISEASES

Μακροχρόνια αποτελεσματικότητα και ασφάλεια βιολογικών θεραπειών σε Έλληνες ασθενείς με ρευματικά νοσήματα



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To my family

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ABSTRACT

Background

Inflammatory arthritides [rheumatoid arthritis (RA) and spondyloarthritis (SpA)] are chronic diseases with long-term consequences which affect 2-3% of the population resulting in a significant individual and societal burden. The advent of biologic agents, such as tumor necrosis factor inhibitors (TNFis), has dramatically transformed the management of these diseases. TNFis were proven effective in randomized controlled studies (RCTs) of both RA and SpA patients. However, questions that influence clinical decision making are insufficiently addressed by RCTs. Longitudinal observation studies and registry data can provide valuable information to optimize clinical use of these novel and expensive drugs. Greek nationwide data regarding effectiveness and safety of TNF inhibitors in RA and SpA patients are lacking. This is important in view of the variations in disease severity of inflammatory arthritides across different ethnic backgrounds and local variations of clinical practice.

Objectives

In the present study we sought to assess the effectiveness and the safety of the TNFi therapy in a nationwide cohort of Greek patients with inflammatory arthritides focusing in patients with RA and SpA. In the study of patients with RA we aimed to compare the effectiveness, the drug survival and the safety between the three TNFis infliximab, adalimumab, and etanercept, and to identify potential predictors of response, drug survival and serious adverse events. In the study of SpA patients, our objective was to evaluate the 10-year drug survival of the first TNFi in patients overall and comparatively between SpA sub-diagnoses and between different TNFis. Predictors of drug retention were also sought among baseline parameters and early major response variables.

Methods

We organized the “Hellenic Registry of Biologic Therapies (HeRBT)”, a prospective observational cohort of patients who receive biologic therapies for inflammatory arthritides in 8 hospitals of Greece. All consecutive patients in the participating centers are included in HeRBT when they start their first biologic agent. According to the protocol, baseline data, response data and events are collected every 6 months for the first 2 years and every year thereafter. For the first study, 1208 adult RA patients starting infliximab, adalimumab or etanercept between January 2004 and December 2009 were identified. The observational period was until May 2011. Clinical responses were assessed by several outcome measures (DAS28, CDAI, EULAR response criteria). Drug survival and serious adverse events during entire follow-up (median 2.9 years) were also monitored. For the second study, 1077 adult spondyloarthritis patients starting their first TNFi between 2004 and the end of 2014 were analyzed. Monitoring period was until May 2015. 10-year drug survival rates and 6- and 12- month rates of response to therapy were calculated applying standard outcome measures (BASDAI50, ASDAS). We used standard descriptive statistics, Kaplan-Meier curves and logistic and Cox

regression models. In the second study we used multiple imputation for our main Cox regression analyses, but complete-case analyses were also performed.

Results

Concerning RA patients, EULAR response (good and moderate combined) was achieved by 79% of the patients at 12 months in the three TNFi groups while remission rates were low: 13-16% and 15-23% of patients (DAS28-remission at 6 and 12 months respectively) and was comparable between the three TNFis. In multivariate analysis adalimumb was associated with greater odds for remission [adjusted odds ratio (OR) for EULAR/ACR remission at 12 months (reference: infliximab): 4.1 for adalimumab and 2.7 for etanercept]. Other baseline factors independently predicting remission were male gender (OR 2.2), use of glucocorticoids (OR 2.2) and swollen joint count >7 (OR 0.26). Five-year drug survival was 31%, 43%, and 49% for infliximab, adalimumab and etanercept, respectively (log-rank p=0.010). Although efficacy-related survival was comparable, infliximab was associated with significantly more withdrawals due to adverse events (p<0.001). Lower baseline disease activity, higher baseline CRP and the use of glucocorticoids predicted longer efficacy-related drug survival. Younger age, no use of methotrexate, use of adalimumab and etanercept and less prior DMARDs failures predicted longer safety-related survival. Interestingly, adjusted 5-year drug survival was highest for patients with sustained (both at 6 and 12 months) DAS28 remission compared to patients with poorer clinical responses during the 1st year (p<0.001). The incidence rate of serious adverse events (SAEs) was 8.5, 5.3 and 3.5 per 100 patient-years in the infliximab, adalimumab and etanercept groups respectively (p<0.001). The risk a first serious infection was lower with adalimumab (OR 0.62) or etanercept (OR 0.39) than with infliximab. Other independent predictors of a serious infection at baseline were higher age (OR 1.65 per 10-years), tender joint count >10 (OR 1.86), and glucocorticoids >35 mg/week (OR 1.83).

Concerning SpA patients, we analysed 561 with AS, 375 with PsA, 108 with uSpA and 33 with IBD-related SpA. Five- and 10-year drug survival was 60% and 49% respectively. In the unadjusted analyses, TNFi survival was associated to isolated axial disease (p=0.001). Regarding SpA subdiagnosis, AS patients had longer drug survival compared to uSpA and PsA patients [(significant beyond the first 2.5 (p=0.003) and 7 years respectively (p<0.001)]. In the multivariable analysis, men had a significantly longer TNFi adherence [hazard rate (HR) 0.68], both for efficacy (HR 0.6) and safety-related (HR 0.57) reasons of discontinuation. Use of a monoclonal antibody was associated with a longer overall drug survival (HR 0.64), but etanercept had less safety-related stops compared to infliximab (HR 0.52). Finally, the use of methotrexate was protective, mainly through preventing safety-related stops (HR 0.6). Among patients having axial SpA, 59% and 42% achieved BASDAI50 or had ASDAS-ID respectively within the first year of therapy. Achievement of major responses during the first year of therapy in either axial or peripheral arthritis was the strongest predictor of longer therapy retention (HR 0.33 for ASDAS-ID and HR 0.35 for DAS28 remission respectively).

Conclusions

These data based on the largest Greek cohort of patients with systemic arthritides reassured about safety of TNFis in clinical practice. Greek RA patients starting TNF inhibitors have comparable response rates across the 3 different TNFis, while remission rates are low in clinical practice. Overall, 5-year drug survival was below 50%, with infliximab demonstrating increased safety-related discontinuations. The long-term retention of the first TNFi in SpA patients is high, especially for males with axial disease. The strongest predictor of long-term TNFi survival is a major response within the first year of treatment. Strategies to increase effectiveness and long-term survival of TNF inhibitors in RA and SpA are needed.

ΠΕΡΙΛΗΨΗ

Εισαγωγή

Η ρευματοειδής αρθρίτιδα (ΡΑ) και οι σπονδυλοαρθρίτιδες (ΣπΑ) είναι χρόνιες φλεγμονώδεις νόσοι με μακροχρόνιες συνέπειες που επηρεάζουν 2-3% του πληθυσμού. Η έλευση των βιολογικών παραγόντων, όπως οι αναστολείς του παράγοντα νέκρωσης όγκων (tumor necrosis factor –TNF), έχει αλλάξει δραματικά τη θεραπεία αυτών των ασθενειών. Η αποτελεσματικότητα των αναστολέων του TNF σε σχέση με εικονικό φάρμακο και η βραχυπρόθεσμη ασφάλειά τους έχουν αποδειχτεί σε πολλές τυχαιοποιημένες κλινικές μελέτες. Ωστόσο, πολλά από τα ερωτήματα που τίθενται στη θεραπεία ασθενών της καθημερινής κλινικής πράξης δεν απαντώνται επαρκώς από τις τυχαιοποιημένες κλινικές μελέτες. Οι μακροχρόνιες μελέτες παρατήρησης και τα δεδομένα από αρχεία παρακολούθησης ασθενών έχουν συμπληρωματικό ρόλο στο να παρέχουν πολύτιμες πληροφορίες για τη βελτιστοποίηση της κλινικής χρήσης αυτών των νέων και σημαντικού κόστους φαρμάκων. Ελληνικά εθνικά δεδομένα σχετικά με την αποτελεσματικότητα και την ασφάλεια των αναστολέων του TNF σε ασθενείς με ΡΑ και ΣπΑ δεν υπάρχουν. Τα δεδομένα αυτά θα ήταν σημαντικά λόγω της διαφοροποίησης στη σοβαρότητα και τις πρακτικές αντιμετώπισή τους στα εθνικά συστήματα υγείας διαφορετικών χωρών.

Στόχοι

Στην παρούσα μελέτη επιδιώξαμε να αξιολογήσουμε την αποτελεσματικότητα και την ασφάλεια της θεραπείας με αναστολείς του TNF σε Έλληνες ασθενείς με ΡΑ και ΣπΑ. Στοχεύσαμε να εκτιμήσουμε την αποτελεσματικότητα, την παραμονή στη θεραπεία («επιβίωση του φαρμάκου») και την ασφάλεια συγκριτικά για τους τρεις TNF αναστολείς infliximab, adalimumab και etanercept. Επίσης, επιδιώξαμε να προσδιορίσουμε παράγοντες που θα μπορούσαν να προβλέψουν καλύτερη ανταπόκριση, μεγαλύτερη παραμονή στη θεραπεία και τις σοβαρές ανεπιθύμητες ενέργειες κατά τη χρήση τους.

Μέθοδοι

Οργανώθηκε το «Ελληνικό Αρχείο Βιολογικών Θεραπειών (ΕΑΒΘ)», μια κοόρτη που περιελάμβανε όλους τους ασθενείς που ξεκινούσαν βιολογική θεραπεία για φλεγμονώδεις αρθρίτιδες σε 8 νοσοκομεία της Ελλάδας. Οι ασθενείς παρακολουθούνταν προοπτικά και, σύμφωνα με το πρωτόκολλο, συλλέγονταν δημογραφικά δεδομένα, στοιχεία νόσου και φαρμακευτική θεραπεία στην έναρξη του βιολογικού παράγοντα. Δεδομένα ενεργότητας νόσου, λειτουργικότητας και ποιότητας ζωής συλλέγονταν στην έναρξη και κάθε 6 μήνες για τα 2 πρώτα χρόνια και ετησίως στη συνέχεια, ενώ όλα τα ανεπιθύμητα συμβάματα καταγράφονταν κατά τη χρονική στιγμή που εμφανίζονταν. Για την πρώτη μελέτη, αναλύθηκαν 1208 ενήλικες ασθενείς με ΡΑ που ξεκίνησαν infliximab, adalimumab ή etanercept μεταξύ 1/2004 και 12/2009 (παρακολούθηση μέχρι 5/2011). Η απάντηση στη θεραπεία αξιολογήθηκε με διάφορους δείκτες ανταπόκρισης (DAS28, CDAI, απάντηση κατά EULAR). Στη δεύτερη μελέτη αναλύσαμε 1077 ενήλικες ασθενείς με σπονδυλοαρθρίτιδα που ξεκίνησαν την πρώτη θεραπεία με αναστολέα του TNF μεταξύ του 2004 και του τέλους του 2014 (παρακολούθηση μέχρι

5/2015). Η απάντηση στη θεραπεία υπολογίστηκε με τη χρήση τυποποιημένων δεικτών ανταπόκρισης (BASDAI50, ASDAS) στους 6 και 12 μήνες αγωγής. Χρησιμοποιήθηκαν τυπικές περιγραφικές στατιστικές, καμπύλες Kaplan-Meier και μοντέλα παλινδρόμησης (λογιστική παλινδρόμηση, παλινδρόμηση του Cox). Στη δεύτερη μελέτη χρησιμοποιήθηκε η μέθοδος του πολλαπλού καταλογισμού (multiple imputation) για την αντικατάσταση των ελλιπών τιμών στην έναρξη για τις κύριες αναλύσεις παλινδρόμησης Cox, αλλά πραγματοποιήσαμε και αναλύσεις ξεχωριστά μόνο με τους ασθενείς με πλήρη δεδομένα (complete-case analysis).

Αποτελέσματα

Στους ασθενείς με PA, η ανταπόκριση κατά EULAR (καλή και μέτρια) επιτεύχθηκε σε 79% των ασθενών στους 12 μήνες θεραπείας, όμως τα ποσοστά ύφεσης (βάσει DAS28) ήταν χαμηλά: 13-16% και 15-23% των ασθενών στους 6 και 12 μήνες αντίστοιχα και ήταν συγκρίσιμα μεταξύ των τριών αντι-TNF φαρμάκων. Στις πολυπαραγοντικές αναλύσεις, το adalimumab συσχετίστηκε με μεγαλύτερες πιθανότητες για ύφεση [προσαρμοσμένος λόγος πιθανοτήτων (adjusted odds ratio; OR) για ύφεση σύμφωνα με τα EULAR/ACR κριτήρια στους 12 μήνες (αναφορικά με το infliximab): 4,1 για adalimumab και 2,7 για etanercept]. Άλλοι ανεξάρτητοι προγνωστικοί παράγοντες ύφεσης ήταν το ανδρικό φύλο (OR 2.2), η χρήση κορτικοειδών (OR 2.2) και οι οιδηματώδεις αρθρώσεις (>7, OR 0.26) στην έναρξη της θεραπείας. Η 5-ετής επιβίωση των TNF αναστολέων ήταν 31%, 43% και 49% για το infliximab, το adalimumab και το etanercept αντίστοιχα (log-rank p = 0.010). Η χαμηλότερη ενεργότητα νόσου, η υψηλότερη CRP και η χρήση των κορτικοειδών στην έναρξη της θεραπείας προέβλεπαν μεγαλύτερη επιβίωση φαρμάκου σχετιζόμενη με την αποτελεσματικότητα. Η μικρότερη ηλικία, η χρήση μεθοτρεξάτης, η χρήση του adalimumab και του etanercept και ο μικρότερος αριθμός προηγούμενων DMARDs προέβλεπαν μεγαλύτερη επιβίωση σχετιζόμενη με την ασφάλεια. Είναι ενδιαφέρον ότι η προσαρμοσμένη 5ετής επιβίωση των TNF αναστολέων ήταν υψηλότερη στους ασθενείς με σταθερή (στους 6 και 12 μήνες) ύφεση με βάση το δείκτη DAS28 σε σύγκριση με ασθενείς με φτωχότερες κλινικές αποκρίσεις κατά τη διάρκεια του 1ου έτους (p <0,001). Η συχνότητα εμφάνισης σοβαρών ανεπιθύμητων ενεργειών ήταν 8,5, 5,3 και 3,5/100 ασθενείς/έτος στις ομάδες infliximab, adalimumab και etanercept αντίστοιχα (p <0,001). Ο κίνδυνος μιας πρώτης σοβαρής λοίμωξης ήταν χαμηλότερος με το adalimumab (OR 0.62) ή το etanercept (OR 0.39) σε σχέση με το infliximab. Άλλοι ανεξάρτητοι παράγοντες (κατά την έναρξη της θεραπείας) πρόβλεψης σοβαρής λοίμωξης ήταν η μεγαλύτερη ηλικία (OR 1,65 για κάθε 10 χρόνια), ο αριθμός ευαίσθητων αρθρώσεων (>10, OR 1,86) και η χρήση κορτικοειδών σε δόση > 35 mg/εβδομάδα (OR 1,83).

Όσον αφορά στους ασθενείς με ΣπΑ, αναλύσαμε 561 με ΑΣ, 375 με ΨΑ, 108 με αδΣπΑ και 33 με εντεροπαθητική ΣπΑ. Η 5-ετής και 10-ετής επιβίωση των αναστολέων του TNF ήταν 60% και 49% αντιστοίχως. Στις μη προσαρμοσμένες αναλύσεις, η επιβίωση συσχετίστηκε με μεμονωμένη αξονική νόσο (p = 0,001) ενώ, αναφορικά με τους διαφορετικούς τύπους ΣπΑ, οι ασθενείς με ΑΣ είχαν μεγαλύτερη επιβίωση φαρμάκου σε σύγκριση με τους ασθενείς με αδΣπΑ και ΨΑ (στατιστικά σημαντική διαφορά μετά τα πρώτα 2,5 (p = 0,003) και 7 έτη (p <0,001) αντίστοιχα]. Στις πολυπαραγοντικές αναλύσεις, οι άνδρες είχαν σημαντικά μεγαλύτερη επιβίωση φαρμάκου συνολικά [σχετικός κίνδυνος - hazard rate (HR) 0.68]. Η χρήση μονοκλωνικού αντισώματος (infliximab ή adalimumab) συσχετίστηκε με μεγαλύτερη επιβίωση φαρμάκου (HR 0,64), αλλά το etanercept είχε

σημαντικά μικρότερο σχετικό κίνδυνο διακοπής λόγω ανεπιθύμητων συμβαμάτων σε σχέση με το infliximab (HR 0,52). Μεταξύ των ασθενών με αξονική ΣπΑ, το 59% και 42% πέτυχαν BASDAI50 ή είχαν ύφεση νόσου σύμφωνα με το δείκτη ASDAS μέσα στον πρώτο χρόνο θεραπείας. Η επίτευξη σημαντικής ανταπόκρισης στη θεραπεία κατά τη διάρκεια του πρώτου έτους, είτε όσον αφορά στην αξονική νόσο, ή στην περιφερική αρθρίτιδα, ήταν ο ισχυρότερος προγνωστικός παράγοντας για μεγαλύτερη επιβίωση των φαρμάκων (HR 0,33 για την επίτευξη ύφεσης κατά ASDAS και HR 0,35 για την ύφεση κατά DAS28 αντίστοιχα).

Συμπεράσματα

Η παρούσα είναι η μοναδική κοόρτη Ελλήνων ασθενών με επιθετική φλεγμονώδη αρθρίτιδα υπό βιολογική θεραπεία με μακροχρόνια προοπτική παρακολούθηση. Επιβεβαιώθηκαν τα δεδομένα σχετικά με την ασφάλεια των αναστολέων του TNF στην κλινική πράξη. Οι Έλληνες ασθενείς με ΡΑ που ξεκινούν αντι-TNF παράγοντες έχουν συγκρίσιμα ποσοστά ανταπόκρισης στο infliximab, το adalimumab και το etanercept, ενώ τα ποσοστά ύφεσης είναι χαμηλά στην κλινική πρακτική. Συνολικά, η 5-ετής επιβίωση ήταν λιγότερο από 50%, με το infliximab να έχει μικρότερη επιβίωση λόγω ανεπιθύμητων ενεργειών. Η μακροχρόνια παραμονή στη θεραπεία με τον πρώτο TNF αναστολέα σε ασθενείς με ΣπΑ είναι υψηλή, ειδικά για τους άνδρες με αξονική νόσο. Ο ισχυρότερος προγνωστικός δείκτης μακροχρόνιας επιβίωσης των αναστολέων του TNF ήταν η μείζονα ανταπόκριση κατά το πρώτο έτος της θεραπείας. Απαιτούνται περαιτέρω στρατηγικές για την βελτίωση της αποτελεσματικότητας και της μακροχρόνιας επιβίωσης των αναστολέων του TNF σε ΡΑ και ΣπΑ.

GENERAL PART

CHAPTER I. BIOLOGIC AGENTS IN RHEUMATOLOGY: STRUCTURE AND INDICATIONS

1. What are biologic agents

Biologic agents are products that, in contrast to more commonly used chemical synthetic drugs, are produced from living organisms or contain components of living organisms and are derived by using biotechnology. Vaccines, blood components and genes can be types of biologic drugs.

In the field of rheumatology, a variety of biologic treatment approaches to autoimmune inflammatory arthritides, especially rheumatoid arthritis (RA) and the spondyloarthritides (SpA), have emerged since the late 1990s through significant advances in molecular biology, immunology and drug development. These biologic therapies, also called biologic response modifiers, are genetically engineered proteins, most commonly monoclonal antibodies, used to target specific molecules involved in the mechanisms of the immune system which propagate inflammation.

Specificity is the most important feature of biologic agents in rheumatic diseases, as potentially they can have a distinct effect on certain cytokines and immune cells, instead of provoking widespread non-specific immunosuppression. However the immune system is intricate and functions in a micro-environment of cell-cell interactions, with multiple negative and positive regulatory influences and networks not entirely understood. This is why *in vivo* mechanisms of action of biologic therapies can differ from those predicted *in vitro* or *ex vivo*. Indeed, though several different agents and different targets successful *ex vivo* have been tried in pilot studies for inflammatory arthritides over the past 20 years or more, most of them were proven ineffective *in vivo* and/or not safe [1].

A number of biologic drugs, however, most notably the class of tumor necrosis factor inhibitors (TNFis), were a major success of translational research as their efficacy in animals was confirmed in randomized controlled studies (RCTs) of humans and their potential benefit outweighed their potential risks [2] and their high cost [3]. These agents have gained a widespread use and have revolutionized the management of inflammatory arthritides in a way it would have been difficult to predict even 20 years ago [4, 5].

Nevertheless, everyday clinical use of these agents has shown that their efficacy, immunogenicity, as well as their adverse events can differ in “real world” patients from that predicted in preclinical studies or even RCTs [6-9]. Variable clinical response is observed between patients with the same formal diagnosis: in some patients they induce disease remission and in others there is no response [10]. Even more, different agents, even of the same class have differential efficacy in the same patient, an effect exemplified by the fact that failure of one TNFi therapy does not preclude efficacy of a second TNFi [11-13]. Similarly, adverse events can occur with one TNFi but not another [14] and some may be time-dependent [15].

As a result, while acknowledging the fact that biologic therapies were a significant and potent addition to our therapeutic armamentarium for rheumatic diseases, many authorities and rheumatology societies recognize the need for long-term studies of patients in everyday clinical practice, independent from the pharmaceutical industry, with the use of rigorous clinical outcomes and head-to-head comparisons of therapeutic agents [9] and the establishment of national registries of biologic agents as an appropriate way to capture effectiveness and adverse events in "real" patients [1, 16-18].

2. Types of approved biologic agents and mechanisms of action

To date, thirteen biologic agents have been approved for the treatment of rheumatic diseases (**Table 1.1**), exerting their effect by cytokine inhibition, T-cell co-stimulation blockade, or B-cell depletion and inhibition (**Figure 1.1**). More molecules are currently being tested in laboratories and clinical trials.

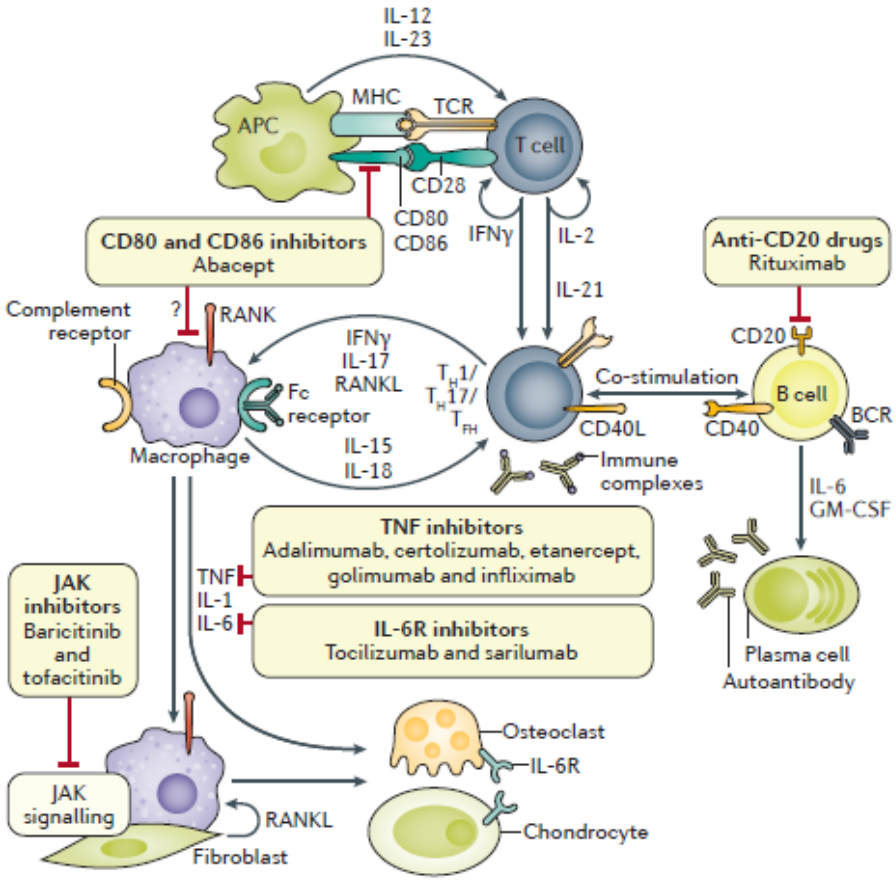

Figure1.1. Mechanism of action of biologic agents in rheumatoid arthritis. TNF inhibitors and IL-6 receptor inhibitor block the action of pro-inflammatory cytokines, while T-cell blockade by abatacept and B cell depletion by rituximab target upstream events leading to downregulation of these inflammatory cytokines.

APC: antigen-presenting cell; BCR: B cell receptor; CD: cluster of differentiation; CD40L: CD40 ligand; GM-CSF: granulocyte-macrophage colony-stimulating factor; MHC: major histocompatibility complex; RANKL: receptor activator of nuclear factor-κB ligand; TCR: T cell receptor; T_{FH}: T follicular helper cell; T_H: T helper cell. Smolen, J.S., et al., *Rheumatoid arthritis.* Nat Rev Dis Primers, 2018. **4**: p. 18001.

a. Cytokine inhibition

Cytokines are the first and most commonly used targets of bDMARDs for immune system regulation in inflammatory arthritides: pro-inflammatory cytokines, including, among others, tumor necrosis factor (TNF) and interleukins such as interleukin (IL)-1β, IL-6, IL-12, IL-23 and IL-17, play a pivotal role in the final common pathway of joint destruction and their blockade by TNFis and the inhibitors of specific interleukins has been found efficacious in reducing signs and symptoms of these diseases.

TNF inhibitors

TNF is a pro-inflammatory cytokine considered to be high in the hierarchy of the cascade of cytokines induced in inflammatory arthritides [19]. It is synthesized as a membrane-bound protein and released after proteolytic cleavage by TNF convertase. As a result, it exists in two forms: soluble (sTNF) and membrane-associated TNF (mTNF), both of which are biologically active. In RA it is mainly produced by synovial macrophages and binds to specific receptors (TNFR1 and TNFR2) which are expressed, among others, in immune, inflammatory and endothelial cells, where they signal through nuclear factor kappa B (NFκB) and MAP kinases to initiate pro-inflammatory gene transcription. TNF can induce macrophages and other cells to secrete other proinflammatory cytokines, (eg. IL-1, IL-6 and IL-8), it can lead to T-cell activation and can induce endothelial cells to express both adhesion molecules that increase T-cell infiltration and vascular growth factors that promote angiogenesis. TNF also stimulates the release of metalloproteases by fibroblasts, decrease the synthesis of proteoglycans by chondrocytes and promote the differentiation of monocytes to osteoclasts promoting cartilage and bone destruction [20]. In axial spondyloarthritis (axSpA), in which the arthritic bone disorder is predominantly proliferative instead of destructive, the role of TNF is less clear, but it has been implicated in synovitis, bone destruction and gut inflammation [19].

Five biologic therapies designed to inhibit TNF are licensed (**Table 1.1** and **Figure 1.2**), four of which are monoclonal antibodies (mAbs): *infliximab*, a chimeric human/murine mAb, *adalimumab*, and *golimumab*, two fully human mAbs produced using recombinant DNA technology and *certolizumab pegol*, which consists of the F(ab') fragment of humanized mAb against TNF, bound to a polyethylene glycol (PEG) moiety. The attachment of PEG moiety increases the half-life of certolizumab to that of an intact mAb. The absence of an Fc fragment prevents effector function such as complement-dependent lysis and antibody-dependent cell-mediated cytotoxicity (ADCC) [20, 21]. The fifth TNFi, etanercept, is a fusion protein of two TNFR2 receptor extracellular domains and the Fc fragment of human immunoglobulin G 1 (IgG1).

Even though all five TNF inhibitors act on the same target, there are subtle differences in their mechanism of action, their epitope specificities, pharmacokinetics and non-cross-reactive neutralizing anti-globulins [19]. Therefore, their immunomodulatory effects can differ in important ways from agent to agent. This can be clinically observed for example, in the lack of efficacy of etanercept in inflammatory bowel disease, in contrast to monoclonal antibody TNFis, or the fact that most patients who fail to respond, have lost response, or are intolerant to one TNFi, respond well when switched to another. Their immunogenicity also differs, with the chimeric agent infliximab inducing anti-drug antibodies most frequently and etanercept being the least immunogenic of the five TNFis, although less data exist regarding golimumab and certolizumab [20, 22].

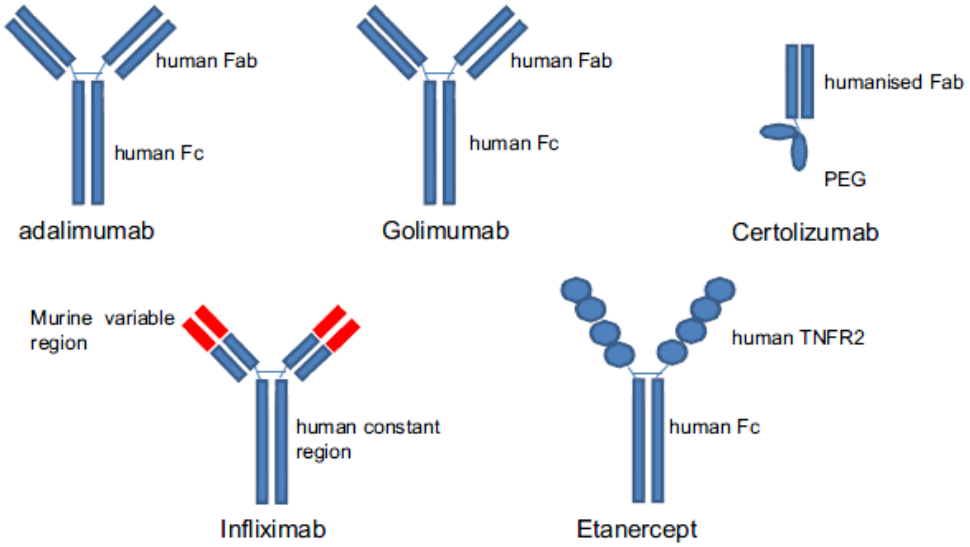

Figure 1.2. Schematic diagram of the structures of the 5 TNFis. Adapted from Thalayasingam, N. and J.D. Isaacs, *Anti-TNF therapy*. Best Pract Res Clin Rheumatol, 2011. **25**(4): p. 549-67.

Inhibitors of interleukins

Interleukin-6 (IL-6) is another pleiotropic cytokine that plays a central role in the pathogenesis of inflammatory arthritides, especially in RA. It contributes to B- and T-cell activation, synoviocyte stimulation, osteoclast maturation, angiogenesis, and the production of acute phase proteins (**Figure 1.1**) [23]. *Tocilizumab* is a humanized anti-IL-6 receptor monoclonal antibody, designed to target both membrane-bound and soluble IL-6 receptors [24]. More biologic agents targeting IL-6 (e.g. sarilumab, sirukumab) have also proven effective and will soon be available [25].

Interleukin-1 is also implicated in autoimmune inflammatory disorders and *anakinra*, an IL-1 receptor antagonist, was approved in the early 2000s for the treatment of RA. However, it is rarely used today for this indication, due to its only modest clinical and radiological benefits compared with csDMARDs or TNFis [26]. Nevertheless, anakinra is very effective in patients with Muckle-Wells syndrome and in Still's disease, suggesting that possibly IL-1 has a less "central" role in RA pathogenesis than in other autoimmune inflammatory diseases [1].

The interleukin-23/interleukin-17 axis has also been extensively studied in the past decade. Especially for SpA, there has been a striking convergence of evidence from genetic studies, animal models, translational studies and, finally, therapeutic trials firmly implicating a key role of IL-23/IL-17 axis in its pathogenesis. IL-23 is found to stimulate Th17 cells to produce IL-17, but cells from the innate immune system also respond to IL-23 stimulation. IL-12, a key cytokine driving Th1 development, shares a common subunit with IL-23. IL-17, in turn, has a range of biological effects, including induction of IL-6, IL-8, TNF, chemokines and matrix metalloproteinases in a variety of target cells, serving a protective role in mucosal immunity to bacteria and fungi, but also promoting

inflammation and bone and cartilage destruction when expressed chronically and in inappropriate locations [27]. Two biologic agents designed to target interleukins in this pathway were recently approved: *secukinumab*, which is mAb directed against IL-17 and *ustekinumab*, a human mAb targeting the common p40 subunit of IL-12 and IL-23.

b. T cell co-stimulation blockade

T cells play a major role in the pathogenesis of RA as they provide stimulation to B cells and macrophages both by means of soluble mediators and by cell-cell contact. Monoclonal antibodies targeting T-cell-surface antigens were the first to be systematically tested in RA but they were not proven effective. It is now recognized that binding of CD28 on T cells with protein CD80/86 on the surface of antigen-presenting cells is the so-called "second signal" necessary for T-cell activation and resultant release of inflammatory cytokines (**Figure 1.1**). Cytotoxic T lymphocyte-associated (CTLA)-4 is a protein with a high affinity to CD80/86, which inhibits T-cell activation by blocking the CD28 binding.

Abatacept is a CTLA-4 IgG1 fusion protein that has been developed to act as a T-cell co-stimulator inhibitor, but it might also interfere with macrophage migration, a pivotal event in RA pathogenesis [28].

c. B cell depletion

B-cells also play a key role in inflammatory arthritides, as they secrete antibodies, but also cytokines and chemokines and are effective antigen-presenting cells that can maintain T-cell activation in the synovium. *Rituximab* is a chimeric anti-CD20 monoclonal antibody targeting and depleting the B-cells. CD20 is a membrane-associated phosphoprotein restricted to B cells, which regulates the early steps in B-cell activation. CD-20 positive B-cell precursors, transitional B cells and naïve B cells are most susceptible to depletion by rituximab, while B1, marginal zone and germinal center B cells are more resistant [25].

3. Overview of biologic agents indications and doses in rheumatology

Infliximab and etanercept were the first biologic agents for rheumatology to be approved in Greece in the year 2000, initially for the indication of RA. Adalimumab was also licensed for RA in 2004 and the most recent TNFis, certolizumab pegol and golimumab were approved for the same indication in 2009. To date all TNFi are approved for the treatment of RA and all sub-types of SpA (including PsA) except for infliximab which is not indicated in non-radiographic axSpA and etanercept which is not effective in the treatment of inflammatory bowel disease (IBD) and therefore it is not indicated when SpA is associated with IBD. Infliximab is administered intravenously while all the others are applied subcutaneously. In RA, infliximab and golimumab are approved only in combination with a csDMARD, preferably methotrexate (MTX), while etanercept, adalimumab and certolizumab can also

be prescribed as monotherapy. Nevertheless, all TNFis are most effective when used in combination with methotrexate, providing a better clinical response and reduced radiographic progression [29, 30].

Tocilizumab is approved for the treatment of active RA, but not SpA, as monotherapy or in combination with a csDMARD. Tocilizumab can be administered via the intravenous or subcutaneous routes. Ustekinumab and secukinumab are subcutaneously administered agents shown to be effective in radiographic axSpA (only secukinumab) and in psoriatic arthritis (PsA) (both secukinumab and ustekinumab).

Abatacept is used in the treatment of RA as a monotherapy or in combination with csDMARDs and it can be administered via the intravenous or subcutaneous routes. Finally, rituximab is administered only intravenously. Treatment causes rapid depletion of certain B cells within the first treatment infusions and the effect can last for 6-9 months, therefore infusions are given in cycles of approximately 6 months.

A summary of the indications and dosages of biologic agents used in rheumatology is given in **Table 1.1.**

4. Safety of biologic agents: contraindications and side effects

Overall, all biologic agents are usually well tolerated [31]. Their primary risk is serious infections, with a rate of ~4-5 events/100 patient years [32, 33]. Registries demonstrate that the increased risk of serious infections is probably time-dependent, being highest in the first 6-12 months of therapy and decreasing with longer treatment duration [34, 35]. Specific properties of the individual bDMARD classes include a risk of tuberculosis with TNFi –especially with mAbs and less with etanercept [14]. However, the risk can be reduced by >80% using proper screening and pre-emptive treatment of latent tuberculosis [36].

Other, albeit rare, bDMARD-specific side effects include the risk of gastrointestinal perforations (2-3 events per 1,000 patient-years) with tocilizumab and a risk of progressive multifocal leukoencephalopathy with rituximab therapy [28]. bDMARDs do not confer a higher risk of malignant diseases, with the possible exception of melanoma [37].

Infusion reactions to intravenous bDMARDs can be frequent and include acute and delayed-type hypersensitivity reactions, but serious symptoms develop in <1% of patients. Infusion reactions have been linked to the development of anti-drug antibodies in many cases and the co-administration of methotrexate can reduce their incidence in RA [38].

The contraindications to bDMARD therapy and the most common clinically important side effects of biologics are described in **Table 1.2**.

Table 1.1. Biologic agents used in rheumatology. Adapted from the *Hellenic registry of Biologic Therapies: Manual of biologic agents use -2016 update*

Class	Agent	Molecule type	Route and dosage	Indications	Type of indication
TNF inhibitors	**Infliximab**	Chimeric monoclonal Ab against TNF	iv infusion 3-5mg/kg iv every 4-8 weeks after loading at 0, 2, 6, 8 wks	**-RA** :all agents **-PsA** : all agents **-Radiographic axSpA**: all agents **-Non-radiographic axSpA:** ETA, ADA, GOL, CERT **-Peripheral SpA**: all agents **-JIA:** ADA, ETA	-1st-line bDMARD -As monotherapy or in combination with csDMARDs (usually MTX, LEF, SSZ) [Infliximab & Certolizumab: always in combination with csDMARD]
	Etanercept	Fusion protein of soluble TNF receptor with Fc IgG fragment	50 mg/ week sc.		
	Adalimumab	Human recombinant monoclonal Ab against TNF	40mg/15 days sc.		
	Certolizumab pegol	F(ab') fragment of humanized monoclonal Ab against TNF, bound to polyethylene glycol	Initially sc 400 mg at weeks 0, 2, 4 and then 200mg /15 days sc.		
	Golimumab	Human monoclonal antibody against TNF	Patients < 100 kg 50 mg/ month sc. Patients > 100 kg, 100 mg/ month sc.		
Interleukin 1 receptor inhibitors	**Anakinra**	Recombinant human IL-1 receptor antagonist	sc 100mg/day	**-RA -JIA** **-Adult onset Still's disease -CAPS**	-1st-line bDMARD -Monotherapy/ with csDMARDs
	Canakinumab	Human monoclonal antibody against IL-1B	4mg/kg/4 wks, up to maximum dose 300 mg	**-CAPS** **- Systemic JIA**	Therapy of choice
Interleukin 6 receptor inhibitor	**Tocilizumab**	Humanized monoclonal Ab against IL-6 receptor	iv 8mg/kg /4 weeks or s.c. 162 mg/week	**-RA** **-SOJIA**	-As 1st/ 2nd-line bDMARD -Monotherapy or with MTX

TNF: Tumor necrosis factor; INF: Infliximab; ETA: Etanercept; ADA: Adalimumab; CERT: Certolizumab pegol; Ab: Antibody; RA: Rheumatoid arthritis; PsA: Psoriatic arthritis; SpA: spondyloarthritis; axSpA: axial SpA; JIA: Juvenile Idiopathic arthritis; CAPS: Cryopyrine-associated periodic syndrome; bDMARD: biologic disease modifying anti-rheumatic drug; csDMARD: conventional synthetic DMARDS; MTX: Methotrexate; LEF: Leflunomide; SSZ: Sulphasalazine

Table 1.1 (continued). Biologic agents used in rheumatology.

Class	Agent	Molecule type	Route and dosage	Indications	Type of indication
Interleukin 12/23 inhibitor	**Ustekinumab**	Monoclonal Ab against the p-40 subunit of IL-12 and IL-23	s.c. ≤100 kg: 45 mg > 100 kg : 90 mg at 0 and 4 weeks and then every 12 weeks	**-PsA** **-Peripheral SpA**	-2nd-line after TNFi -As monotherapy or in combination with csDMARDs
Interleukin 17 inhibitor	**Secukinumab**	Human monoclonal antibody against IL-17A	150-300 mg/week s.c. for the first 5 doses and then 150-300 mg/month	**-PsA** **-Radiographic axSpA** **-Peripheral SpA**	-2nd-line after TNFi -As monotherapy or in combination with csDMARDs
T cell co-stimulation blockers	**Abatacept**	Fusion protein of extracellular domain of CTLA4 receptor with Fc region of IgG1	iv 750-1000mg /4 weeks after loading at 0, 2, 4 wks or 125 mg/week sc.	**-RA** **-JIA**	- As initial or 2nd-line bDMARD in moderate-severe RA -As monotherapy or in combination with MTX
Antibodies against B cells	**Rituximab**	Chimeric monoclonal Ab against CD20 surface protein of B cells (depletes B clls)	2000 mg iv. (in 2 infusions given 15 days apart) every 6 months	**-RA** **-GPA (Wegener's)** **-MPA** -SLE (off-label) -Polymyositis-dermatomyositis (off-label)	-Moderate-severe PA –Not as initial bDMARD except if other bDMARDs contraindicated (e.g. cancer) -As monotherapy or in combination with MTX
	Belimumab	Human mAb against BlyS (inhibits B cells)	10mg/kg/4 weeks	SLE	

TNFi: Tumor necrosis factor inhibitor; IL: interleukin; Ab: Antibody; CTLA4: Cytotoxic T lymphocyte-associated protein 4; RA: Rheumatoid arthritis; PsA: Psoriatic
SpA: spondyloarthritis; axSpA: axial SpA; JIA: Juvenile Idiopathic arthritis; SOJIA: systemic JIA; bDMARD: biologic disease modifying anti-rheumatic drug; csDM
conventional synthetic DMARDS; MTX: Methotrexate; GPA: Granulomatosis with polyangiitis, MPA: Microscopic polyangitis; SLE: Systemic lupus erythematosus

Table 1.2. Biologic agents used in inflammatory arthritides: contraindications and clinically important side effects. Adapted from the *Hellenic registry of Biologic Therapies: Manual of biologic agents use -2016 update*

Class/Agent	Contraindications	Clinically important side effects
TNF inhibitors	❖ **Active infection** - Serious bacterial infection (septic arthritis, infection of prosthetic joint, osteomyelitis, abscess, sepsis) -Opportunistic infection - Systemic fungal infection - Infection with intracellular microorganism (herpesvirus, listeria) - Tuberculosis ❖ **Severe hepatic disease** (cirrhosis, advanced fibrosis) due to HBV, HCV, alcoholism ❖ **Lymphoproliferative disease** in past 5 years ❖ **Solid organ neoplasm** <5 yrs, except basal cell ca. ❖ **Severe heart failure** (NYHA III or IV) ❖ Multiple sclerosis or other **demyelinating disease** ❖ **Severe respiratory failure**	❖ Common (>10%) ◦ **Infusion/injection site reactions**, hypersensitivity reactions ◦ Induction of **autoantibodies such as ANA** and rarely (<1%) lupus-like syndrome ◦ Anemia, Neutropenia, thrombocytopenia ◦ **Immunogenicity**: antibodies especially against infliximab&adalimumab, related to reduced response and infusion/injection site reactions ❖ Uncommon (<3%) ◦ Hepatic disorders: hepatitis, jaundice, cholestasis, acute hepatic failure ◦ Hepatitis B reactivation (in chronic, or latent HBV infection) ◦ Increased risk of **serious bacterial and opportunistic infections** (legionella, listeria, Aspergillus, blastomyces, candida, coccidiomyces, histoplasma, pneumocystis jiroveci**), reactivation of latent tuberculosis** ◦ Optic neuritis & other demyelinating diseases (multiple sclerosis, G. Barré) ◦ **Psoriatic-like rashes**
IL-1 inhibitor (anakinra)	❖ **Serious bacterial infection /active or latent tuberculosis** ❖ Hypersensitivity to anakinra or E.coli-originating proteins ❖ **Neutropenia** ❖ **Severe kidney dysfunction** (Creat. Cl. <30 ml/min) ❖ **Severe hepatic disease** ❖ **History of solid tumor or hematologic malignancy**	❖ Common (>10%) ◦ **Injection site reactions** ❖ Uncommon (<3%) ◦ **Bactrerial infections** (upper&lower respiratory tract, bon, soft tissue infections) ◦ **Tuberculosis**

Table 1.2 (continued). Biologic agents used in inflammatory arthritides: contraindications and clinically important side effects		
Class/Agent	**Contraindications**	**Clinically important side effects**
IL-6 inhibitor (Tocilizumab)	❖ **Active hepatic disease** ❖ **Neutropenia** (<2000/ mm^3) ❖ **Thrombocytopenia**(<100,000/ mm^3) ❖ **Serious bacterial or opportunistic infection** ❖ **Familial dyslipidemia**	❖ Common (>10%) ◦ **Increase of liver function tests** ◦ **Neutropenia** ❖ Uncommon (<3%) ◦ Thrombocytopenia ◦ **Cholesterol elevation** ◦ Skin rashes/Infusion site reactions ◦ Anaphylaxis/Hypersensitivity reactions ◦ **Increased risk of serious infections** (bacterial, viral, opportunistic and tuberculosis)
B-cell depleting agents (Rituximab)	❖ **Serious active bacterial/opportunistic infection** ❖ **Severe hepatic disease** ❖ **Severe heart failure** ❖ **Severe respiratory failure**	❖ Common (>5%) ◦ **Infusion reaction** ◦ Neutropenia ◦ **Increased risk of infections** ◦ Reactivation of chronic HBV infection ❖ Uncommon (<1%) ◦ Progressive multifocal leukoencephalopathy (especially in SLE patients)
T-cell costimulation inhibitors (Abatacept)	❖ **Serious active bacterial/opportunistic infection** ❖ Drug hypersensitivity ❖ **Chronic respiratory disease** ❖ **Co-administration with TNF inhibitors**	❖ Uncommon (<5%) ◦ **Increased risk of infections** ◦ **Infusion reaction** ◦ Hypertension ◦ Rash

CHAPTER II. OVERVIEW OF MAIN INFLAMMATORY ARTHRITIDES

1. Rheumatoid arthritis

a. Epidemiology, clinical manifestations and diagnosis

Rheumatoid arthritis (RA) is one of the most prevalent chronic inflammatory diseases and the prototype of the inflammatory polyarthritides. It primarily affects the joints, but it is actually a syndrome that includes extra-articular manifestations such as rheumatoid nodules and interstitial lung disease, as well as systemic comorbidities [39-42]. The disease is chronic and can be devastating for both the individual and the society [43]. The individual burden results from the decline in physical function and quality of life and the increased associated morbidity and mortality [44, 45]. Significant societal burden results from the high direct medical costs and the substantial indirect costs from work disability which leads to reduced productivity and early retirement as well as the decreased societal participation of patients [46, 47].

RA affects approximately 0.5-1% European and North American adults [48]. There is a considerable geographic and ethnic variation in prevalence, with an apparent reduction from north to south and from urban to rural areas [49]. A cross-sectional study in Greece among 8740 people indicated the prevalence being similar to that of other Southern European countries (0.68%) [50]. Annual incidence rates are estimated to be 20-50 cases per 100,000 population in North America and Northern Europe and 9-24 cases in Southern Europe [49]. The onset of disease can occur at any age, but peak incidence occurs within the fifth and sixth decades of life. RA is more common in women than in men, the female-to-male ratio being 2-3:1. The relative risk of developing RA for an offspring of an affected parent is three times that of the normal population, while that of an individual with an affected sibling is almost 5 times higher [51].

Rheumatoid arthritis typically is a symmetrical polyarthritis, usually with insidious onset, occurring over weeks to months. In early disease, the wrists, metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints of the fingers, intephalangeal joints of the thumbs and metatarsophalangeal (MTP) joints are most commonly affected. As the disease progresses, larger joints such as the ankles, knees, elbows and shoulders frequently become involved. Morning stiffness of the joints lasting more than an hour is a hallmark symptom of RA [52].

In addition to articular symptoms, patients with early RA frequently have constitutional symptoms (fever, fatigue, etc) due to systemic inflammation, while localized extra-articular manifestations can be seen in up to 40-50% of RA patients at some time during the course of the disease. These usually occur in long-standing disease, although severe extra-articular manifestations can also be seen in recently diagnosed RA [53]. Extra-articular manifestations of RA include firm subcutaneous nontender nodules (rheumatoid nodules) mostly on the elbows, Achilles tendons and fingers; pleuropulmonary involvement; secondary Sjögren syndrome (keratoconjuctivitis sicca and xerostomia); hematologic, cardiac, ophthalmologic, neurologic, vascular and other more rare manifestations (**Table 2.1**) [54].

Table 2.1. Most common extraarticular manifestations of RA according to organ system involved. Percentage range of RA patients reported to have some frequent manifestations is presented in parentheses.

Skin	Rheumatoid nodules (25-50%)
Hematologic	Normocytic, normochromic anemia (25-30%), thrombocytosis, lymphadenopathy, Felty syndrome
Hepatic	Nonspecific transaminitis
Pulmonary	Pleural thickening/effusions, pulmonary nodules, interstitial lung disease, Cryptogenic organizing pneumonia, Caplan syndrome, cricoarytenoid arthritis, obstructive lung disease
Cardiac	Pericarditis, myocarditis
Ophthalmologic	Keratoconjuctivitis sicca (10-15%), episcleritis, scleritis
Neurologic	Peripheral sensorimotor neuropathy, mononeuritis multiplex
Renal	Glomerulonephritis, nephritic syndrome due to reactive amyloidosis
Vascular	Small vessel vasculitis

Modified from Klippel, J.H., et al., Primer on the Rheumatic Diseases. 13th ed

Some non-articular features have been classified as complications of RA rather than extra-articular manifestations; these include osteoporosis and osteoporotic fractures, carpal tunnel syndrome, cervical myelopathy due to atlantoaxial subluxation and chronic leg ulcers [55].

Moreover, the chronic inflammatory state of RA has been associated with higher incidence of co-morbidities like lymphoma, accelerated atherosclerosis with resultant cardiovascular disease, chronic obstructive pulmonary disease and infections [56]. The comorbidity burden in RA patients, unlike many of the extra-articular features described above, has not become lower in recent years [39, 40, 57].

Mortality rates are higher among RA patients than in the general population [58]. Life expectancy decrease is about 3 to 10 years and it had remained unchanged until the beginning of this century. The main causes of death in RA patients are cardiovascular, infectious, hematological, gastrointestinal and pulmonary complications [59]. Two recent studies have found a decrease in 5-year mortality rate in RA cases incident after the years 2000-2006 compared to incident cases before 2000, which could be due to improved management and early implementation of biologic agents [60-62]. However, even in cohorts from recent years, RA still associates with higher mortality rates than the general population [61, 62].

Rheumatoid arthritis is a heterogeneous disease and no diagnostic criteria exist. The diagnosis is rather based on careful and thorough history and physical examination and depends upon the aggregation of characteristic symptoms, signs, laboratory data and radiological findings. Thus, the typical patient presents with tender and swollen joints of recent onset, morning joint stiffness and high erythrocyte sedimentation rate (ESR) and abnormal concentration of C-reactive protein (CRP). However, this presentation is not specific to RA and differential diagnosis should include infectious arthritis (viral or bacterial), spondyloarthropathies (especially psoriatic arthritis), crystal-induced arthritis, osteoarthritis and connective tissue diseases like systemic lupus erythematosus, systemic sclerosis and Sjögren's syndrome [42].

The presence of specific autoantibodies is also important for the diagnosis of the disease. These are the rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies. RFs are

antibodies (most commonly of IgM class) directed against the Fc portion of IgG and are present in up to 90% of patients with RA; however, Greek RA patients have reportedly lower prevalence of RF antibodies than that seen in other European countries [63]. RF in low levels can be also associated with a number of other chronic inflammatory conditions, while it also occurs in approximately 5% of healthy, especially elderly individuals [54]. Thus, a high level of RF is more likely indicative of RA.

Anti-CCP antibodies (also called ACPAs) are auto-antibodies that recognize citrullinated peptides and have been found to have similar sensitivity (approximately 80%), but higher specificity (up to 95%) for RA than RF [54]. Moreover, they enhance diagnostic yield, as one-third of patients with negative RF at presentation will test positively for anti-CCP antibodies. Both RF and anti-CCP can be detected very early in the disease course and anti-CCP antibodies appear somewhat earlier than RF. Patients with either RF or anti-CCP antibodies ("seropositive" patients) typically have a worse radiologic and functional outcome than "seronegative" patients and are associated with more extra-articular disease, and the higher the level of these auto-antibodies, the higher the correlation [52].

Radiographs of the small joints of the hands and feet can aid in diagnosis and follow-up of the patients with RA. The earliest change found is periarticular osteopenia while the more typical changes of juxta-articular bony erosions at the medial and lateral joint margins and symmetrical joint space narrowing can develop within the first year of disease if effective treatment is not implemented. Late radiographic findings include joint subluxation and formation of osteophytes [54].

Table 2.2 The 1987 revised criteria for the classification of rheumatoid arthritis. A patient shall be said to have rheumatoid arthritis if he/she has satisfied at least four of these seven criteria. Criteria 1 through 4 must have been present for at least 6 weeks.

Criterion	Definition
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.
2. Arthritis of ≥3 joint areas	≥3 joint areas simultaneously have soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.
3. Arthritis of hand joints	≥1 area swollen (not bony overgrowth alone) in a wrist, MCP, or PIP joint.
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in item 2) on both sides of the body
5. Rheumatoid nodules	Subcutaneous nodules over bony prominences/ extensor surfaces / juxta-articular regions observed by a physician
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects
7. Radiographic changes	Radiographic changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in/ adjacent to the involved joints

Adapted from *Arnett, F.C., et al., The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum, 1988. 31(3): p. 315-24*.

Until 2010, classification of RA was typically based on the 1987 American College of Rheumatology (ACR) Classification Criteria (**Table 2.2**) [64]. These criteria were used to standardize patient recruitment into clinical trials and provide the basis for a common approach to disease definition that could be used to compare patients across studies and centers.

However, these criteria were not sensitive enough to identify patients with early RA as they included features of chronicity like rheumatoid nodules and bone erosions [65]. Thus, new classification criteria were presented in 2010 to facilitate the study of patients at earlier stages of the disease, the 2010 European League Against Rheumatism (EULAR)/ACR Classification criteria (**Table 2.3**) [66].

While classification criteria can potentially aid in patient diagnosis, they are by no means diagnostic criteria and the gold standard at the level of the individual patient is the rheumatologist expert's diagnosis; classification merely aims to maximize homogeneous populations for study purposes [42].

Table 2.3. The 2010 ACR/EULAR classification criteria for RA.

Target population: Patients who have at least 1 joint with definite synovitis (swelling), with the synovitis not better explained by another disease	
Score-based algorithm: add score of categories A-D; a score of ≥6/10 is needed for classification of a patient as having definite RA. Patients with erosive disease or long-standing disease (even if inactive at present) typical of RA with a history compatible with prior fulfillment of the 2010 criteria should also be classified as having RA.	
Classification criteria	**Score**
A. *Joint involvement*	
1 large joint (i.e. shoulder, elbow, hip, knee, ankle)	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
> 10 joints (at least 1 small joint)	5
B. *Serology*	
Negative RF *and* negative ACPA	0
Low positive RF *or* low-positive ACPA (≤3 times the upper limit of normal [ULN])	2
High positive RF *or* high positive ACPA (>3 times the ULN)	3
C. *Acute phase reactants*	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. *Duration of symptoms*	
<6 weeks	0
≥ 6 weeks	1

Adapted from *Aletaha, D., et al., 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis, 2010.* ***69****(9): p. 1580-8.*

b. Pathogenesis and pathophysiology

Genetic background is an important contributor in the development of rheumatoid arthritis. Indeed, twin studies have estimated that the heritability (the proportion of phenotypic variance that is due to genetic variance in the population) of RA is ~60% for patients who are positive for ACPAs, whereas estimates in seronegative disease are lower. However, identical twins show a disease concordance of only 12-15%, which indicates that non-coding factors play an important role in susceptibility [28]. The most potent genetic risk for RA is conveyed by the human leukocyte antigen (HLA) system (particularly HLA-DRB1). RA-associated alleles have a common amino acid sequence in the peptide-binding groove (glutamine-leucine-arginine-alanine-alanine), the so-called "shared epitope" (SE) [67]. The presence of the SE is linked with seropositivity for anti-CCP antibodies and RF and is associated with increased susceptibility to and severity of RA. Other genetic loci have been found to contribute smaller effects in the pathogenesis of RA, presumably by causing altered co-stimulatory pathways (e.g. CD28, CD40), cytokine signaling, or lymphocyte receptor activation threshold (e.g. protein tyrosine phosphatase N22, PTPN22) [42]. Additional epigenetic modifications (e.g. altered histone acetylation and DNA methylation) have been found to promote the genetic risk [28].

Apart for the genetic predisposition, exposure to various environmental factors is also associated with the development of the disease. Cigarette smoking is one of the best characterized environmental triggers, enhancing the risk of developing anti-CCP positive RA in patients with the SE [68]. Periodontal disease is also associated with RA, presumably via aberrant citrullination promoted by Porphyromonas gingivalis, a bacterium frequently involved in periodontitis. Other infectious agents (e.g. Epstein-Barr virus, parvovirus B19, Proteus mirabilis, Escherichia coli) and alterations in the microbiome of oral and gastrointestinal sites have been implicated as possible etiologic or progressing factors in RA, but the precise mechanisms underlying these observations remain as yet unclear [42].

The presence of circulating ACPAs, other antibodies, such as RF, and circulating pro-inflammatory cytokines and chemokines can be detected up to 10 years before clinical disease onset, which points to immune activation during the preclinical period. However, the formation of ACPAs alone is not sufficient to cause synovitis; a "second hit" is likely required, such as immune complexes formed by ACPAs with citrulline-containing proteins (e.g. vimentin, fibronectin, fibrinogen, histones, type II collagen) and subsequent binding of RF, which can lead to complement activation, or microvascular insult. This, in turn, leads to increased vascular permeability with leukocyte infiltration of the synovial compartment and resultant synovial membrane inflammation and articular destruction [28, 69].

A healthy synovium lines the non-weight-bearing aspects of the joint and consists of an intimal lining composed of macrophage-like synoviocytes and fibroblast-like synoviocytes (FLS) and a sublining composed of fibroblasts, adipocytes, blood vessels and scattered immune cells. The intimal lining lacks a basement membrane and tight junctions; it is leaky and allows relatively free transfer of cells and proteins into the synovial fluid (**Figure 2.1**).

In RA, the intimal lining greatly expands owing to an expansion and activation of both synoviocyte types. The macrophage-like synoviocytes produce TNF, IL-6, IL-1 and other pro-inflammatory cytokines. FLS express IL-6, matrix metalloproteinases, prostaglandins and leukotrienes, while they assume an invasive phenotype that is responsible for cartilage damage. Additionally, adaptive immune cells, especially CD4+ memory T cells, but also B cells, plasmablasts and plasma cells infiltrate into the synovial sublining (**Figure 2.1**)[28].

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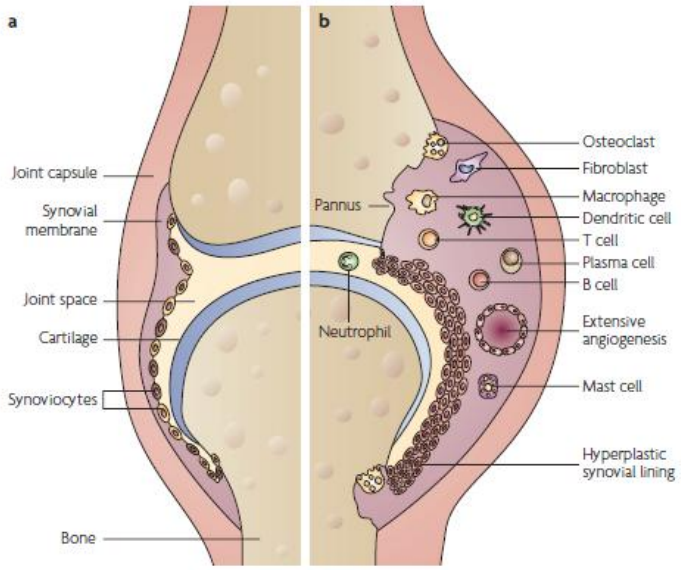

Figure 2.1. Comparison of a normal joint and a rheumatoid arthritis joint. In the healthy joint (a) the thin synovial membrane lines the non-weight-bearing aspects of the joint. In RA (b) the synovial membrane becomes hyperplastic and infiltrated by chronic inflammatory cells. Ultimately it develops into "pannus", which migrate onto and into the articular cartilage and underlying bone. Adapted from Strand, V., R. Kimberly, and J.D. Isaacs, *Biologic therapies in rheumatology: lessons learned, future directions.* Nat Rev Drug Discov, 2007. **6**(1): p. 75-92.

Cytokines and chemokines produced by synovial macrophages and fibroblasts are the regulators of the inflammation by forming a network which induces or aggravates the inflammatory response (**Figure 1.1**). Bone erosions are largely due to activation of osteoclasts by receptor activator of nuclear factor-κB (RANK) produced by T cells, together with TNF, IL-6 and IL-1 produced by synoviocytes. Clinical interventions in the past few years demonstrated that, of the cytokines involved, tumor necrosis factor (TNF), interleukin 6, and probably granulocyte-monocyte colony stimulating (GM-CS) factor are essential to the process, whereas others (e.g. interleukin 1) may be less important [42].

c. Disease activity assessment

Early and aggressive therapy with disease modifying anti-rheumatic drugs (DMARDs) is indicated in rheumatoid arthritis aiming at diminishing joint inflammation and reaching disease remission [70]. Achievement of sustained clinical remission has been proved critical to halt progression of joint erosions and functional limitation, as well as to prevent comorbidities and increased mortality [71]. Consequently, remission (or at least low disease activity) is the target of treatment efforts and regular patient assessments are crucial for evaluating disease activity and guide the therapeutic decisions towards reaching this treatment goal and sustaining it [72]. Validated composite measures of disease activity that include joint counts, physician and patient subjective assessments of pain and disease activity, levels of acute phase reactants and questionnaires concerning functional disability are used both in daily practice and in clinical and epidemiological studies for this purpose [73].

Disease Activity Score using 28 joint counts (DAS28) is the most widely used composite index of disease activity in RA [74]. It is calculated according to a complex weighted equation that includes swollen (SJC) and tender joint counts (TJC) among 28 pre-specified joints (left and right MCP, PIP, wrists, elbows, shoulders and knees), acute phase reactants –either ESR (*DAS28-ESR*) or CRP (*DAS28-CRP*) –and patient's global assessment of disease activity as a score noted on a visual analogue scale (VAS) (VASglobal). The *simplified disease activity index (SDAI)* and *clinical disease activity index (CDAI)* are also popular validated indices and are calculated by simply adding TJC, SJC, VASglobal and physician's global assessments on a VAS (PhGA) (in centimeters) [CDAI] plus CRP (in mg/dl) [SDAI] [75-77]. All these three indices provide continuous numerical scales reflecting disease activity and the higher their score, the worse the arthritis. They can also classify disease activity states as remission, low, moderate, and high disease activity. The cut-points for these disease states can be seen in **Table 2.4**. [78]. There is almost linear relationship between these disease states and physical function impairment or damage progression [42, 79].

Table 2.4. Disease activity measures used for RA

Scoring system	Formula	Disease activity states			
		Remission	Low disease activity	Moderate disease activity	High disease activity
SDAI	SJC28+TJC28+PGA+EGA+CRP	≤3.3	>3.3–11	>11–26	>26
CDAI	SJC28+TJC28+PGA+EGA	≤2.8	>2.8–10	>10–22	>22
DAS	Complex formula including the Ritchie index, SJC44, ESR and GH	≤1.6	>1.6–2.4	>2.4–3.7	>3.7
DAS28	Complex formula including the TJC28, SJC28, ESR (or CRP) and GH	≤2.6	>2.6–3.2	>3.2–5.1	>5.1

SDAI: Simplified disease activity index; CDAI: Clinical disease activity index; DAS: Disease activity score; PGA: patient global assessment; EGA: evaluator global assessment; GH: General health (equals to patient's VAS global assessment); SJC: swollen joint count; TJC: tender JC (the number indicates the number of joints taken into account). Adapted from Smolen, J.S., et al., *Rheumatoid arthritis.* Nat Rev Dis Primers, 2018. **4**: p. 18001.

Regarding the preferred composite disease activity index for attesting disease remission in patients, much research has been done in recent years. It was realized that remission according to DAS28 criteria could be still associated with residual disease activity in many patients (e.g. several swollen joints) and progression of joint damage [80, 81]. Therefore, the European League against Rheumatism (EULAR) recently developed *new remission criteria based on a Boolean approach or on an index approach* [82]. The index approach uses the remission cut-points for SDAI (≤3.3) and CDAI (≤2.8), while in the Boolean-based definition remission is achieved if SJC, TJC, VAS global (in centimeters) and CRP (in mg/dl) are all ≤1. These criteria were primarily developed for the setting of clinical trials, but they can be used in clinical practice as well.

In clinical trials, the *American College of Rheumatology (ACR) improvement criteria* are also commonly used [83]. These classify the change from baseline of seven parameters (TJC, SJC, PhGA VAS global, patient's pain assessment of disease activity in VAS (VAS pain), patient's functional impairment (using the health assessment questionnaire –HAQ) and acute phase reactants -either ESR or CRP) as being at least 20% (*ACR20*, minimal response); 50% (*ACR50*, moderate response); or 70% (*ACR70*, major response). These criteria, though, depend on patient baseline values which differ between different patients and between different time-points and therefore they are not applicable in everyday clinical practice.

Other widely used improvement criteria are the *EULAR response criteria* [84]. These are based on DAS28 index measurements and they classify improvement as "no response", "moderate response", or "good response". They require not only a certain degree of improvement but also attainment of a good (or moderate) disease activity state as defined by DAS28 (**Figure 2.2**) [52].

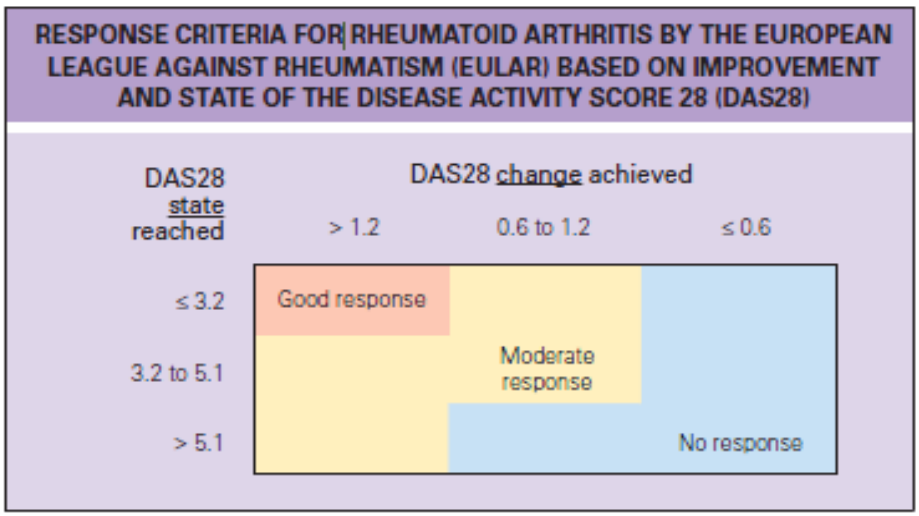

Figure 2.2. EULAR response criteria. Adapted from *Hochberg, M.C. and A.J. Silman, Rheumatology;2011*

Finally, structural progression of the disease is important to be monitored [85]. Hands and feet radiographs are done usually annually while other imaging modalities like ultrasound with power Doppler measurements are increasingly being used to evaluate the extent of synovial inflammation [86].

d. Treatment of rheumatoid arthritis

Treatment of RA has to be instituted early and intensively due to the recognition that disability and joint damage accrue during the first several years of disease [54, 87, 88]. Inflammation is driving the clinical symptoms, the joint damage and the resulting functional disability and the comorbidity, therefore the goal of therapy is its reduction to a minimum, or even its elimination [89]. This has been made possible with the expansion of the therapeutic armamentarium over the past 18 years which now includes not only corticosteroids and conventional synthetic DMARDs (csDMARDs), but also biologic DMARDs (bDMARDs) and, recently, targeted synthetic DMARDs (tsDMARDs). A brief description of biologic DMARDs is given in **Tables 1.1 and 1.2,** while csDMARDs and tsDMARDs used in the treatment of RA can be seen in **Table 2.4**.

Table 2.4. **Conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) and targeted synthetic DMARDs (tsDMARDs) used in the treatment of RA.**

Name	Molecule type	Dosage	Clinically important side effects
Conventional synthetic DMARDs:			
Methotrexate	Small chemical (hippuric acid derivative)	10-25 mg once per week p.o.	Nausea, diarrhea, stomatitis, fatigue, alopecia, elevated liver enzymes, myelosuppression, pneumonitis, increased risk of infection, teratogenic
Leflunomide	Small chemical (anilide)	1-3 g/day p.o.	Nausea diarrhea, rash, alopecia, elevated liver enzymes
Sulphasalazine	Small chemical (aminobenzene-sulphonamide)	20 mg/day p.o.	Nausea, abdominal bloating, rash, granulocytopenia
Hydroxy-chloroquine	Small chemical (4-aminoquinoline)	400 mg/day p.o.	Nausea, skin hyperpigmentation, retinopathy
Cyclosporine	Small chemical (cyclic peptide)	50-250 mg/day p.o.	Hypertrichosis, Hypertension, Gum hyperplasia, headache, renal and liver dysfunction, nausea, increased risk of infection and lymphoma, potassium retention
Targeted synthetic DMARDs:			
Tofacitinib	Small chemical (Janus Kinase inhibitor)	5 mg twice daily per os	Increased risk of infections, hypertension, bone marrow suppression, elevated liver enzymes, possibly increase risk of malignancy, latent tuberculosis reactivation

DMARDs comprise a diverse group of drugs that aim to improve the clinical signs and symptoms of RA and retard the radiographic progression of joint damage. According to the EULAR recommendations, treatment should be initiated with a csDMARD, ideally methotrexate, plus low-

dose glucocorticoids, which serve as a bridge between the initiation of csDMARD therapy and its onset of action, which is often delayed by a few months [70]. Oral glucocorticoids should then be tapered and stopped since csDMARDs should have induced significant improvement.

Methotrexate (MTX) is considered to be the mainstay of DMARD therapy in RA. Its exact mechanism of anti-inflammatory action remains largely unclear but it has been empirically used for many years either orally or by subcutaneous route and it has been shown in randomized controlled trials to reduce the signs and symptoms of RA and slow its radiographic progression [54, 90]. Moreover, MTX has a well-known efficacy and safety profile and can be combined with most other DMARDs, and especially with bDMARDs, with additive effect [91]. Other csDMARDs, like leflunomide or sulphasalazine can also be used alternatively to MTX if the latter is contraindicated or not tolerated. Hydroxychloroquine can be used only in very mild disease or as part of multi-drug combinations, while the use of cyclosporine has declined owing to its several side effects [70].

As already mentioned, the recently adopted treat-to-target strategy requires that disease activity is regularly monitored using a composite index and changes of doses or drugs are in accordance with such activity, aiming at disease remission (or at least low disease activity). Studies reveal that if a state of low disease activity, or approximately 80% improvement in SDAI or CDAI, has been attained within 3 months after therapy start, the likelihood of reaching remission at 6 months is very high. Therefore, the most recent treatment guidelines suggest that if disease activity is still moderate to high at 3 months after a DMARD initiation, therapy should be modified. Similarly, if a state of remission (or at least low disease activity) is not achieved at 6 months, treatment should be re-evaluated. Dosage optimization is tried first before drug switches [70, 92, 93].

When the first csDMARD treatment cycle fails, EULAR recommends stratification for predictors of serious progressive disease as suggested by some *risk factors*. These include high disease activity despite previous therapy, seropositive disease (anti-CCP or RF, especially at high titers) and early erosions on radiography. Patients with these risk factors should receive a biologic DMARD, whereas those without could add another csDMARD to MTX, or alternatively switch to another csDMARD, again in combination with corticosteroids (**Figure 2.3**) [42].

Of the biologic DMARDs currently employed in the treatment of RA, the group of TNFis – i.e. infliximab, etanercept, adalimumab, golimumab and certolizumab pegol (**Table 1.1** and **Table 1.2**) - is the first and most widely used [94]. These agents significantly improve patients' signs and symptoms as well as they retard the radiographic progression of joint damage [95-97], thus they comprise a significant and potent addition to our therapeutic armamentarium for RA. All TNFis exhibit enhanced efficacy when combined with MTX and presumably any other csDMARDs, especially leflunomide [29, 98, 99].

Non-TNFi biologic DMARDs are newer drugs in the treatment of RA and include rituximab [100], abatacept [101] and tocilizumab [24]. They have been shown to exert a significant beneficial effect in patients with RA, probably similar to TNFis [102]. In practice, they may be used as the first bDMARDs in case of csDMARD(s) failure, or as subsequent therapeutic options after TNFis have been tried [70]. Current recommendations suggest that rituximab should be used after other biologics have failed; however it is often used as the first bDMARD in patients with a history of lymphoma or demyelinating disease, when TNFis are contraindicated. Similar to TNFi, non-TNFi should be used

in conjunction with MTX or another csDMARD because of the incremental effect of this combination compared with monotherapy. However, if monotherapy of a bDMARD must be given because of intolerance of all csDMARDs, then tocilizumab could be the bDMARD of choice, as some data support that monotherapy with tocilizumab has better efficacy than monotherapy with other bDMARDs [103].

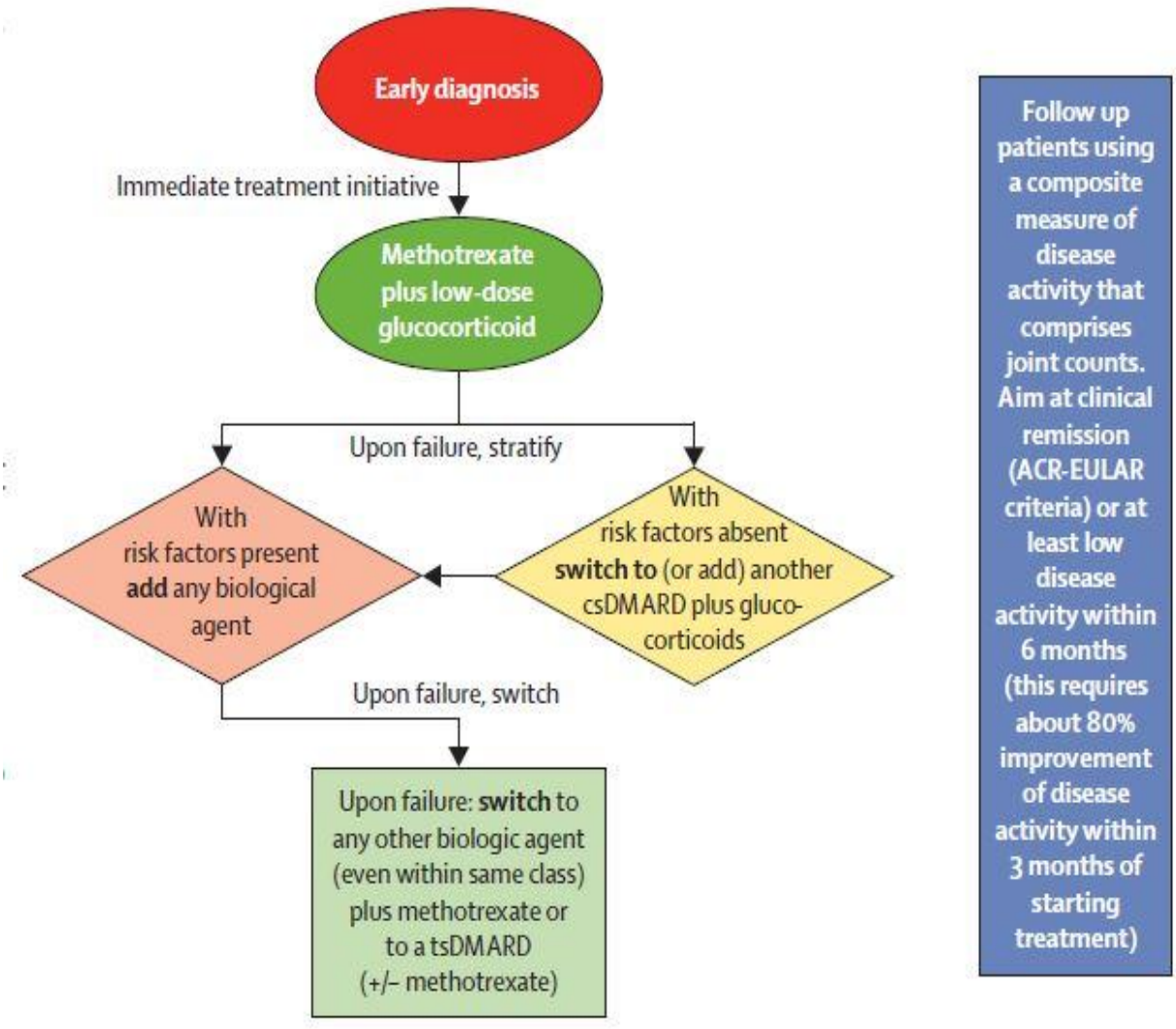

Figure 2.3. Therapeutic approach to rheumatoid arthritis. Adapted from *Smolen, J.S., D. Aletaha, and I.B. McInnes, Rheumatoid arthritis. Lancet, 2016. 388(10055): p. 2023-2038*

Finally, targeted synthetic DMARDs (tsDMARDs) are the most recent tools added in the therapeutic armamentarium of moderate-to-severe RA. Tofacitinib is the only tsDMARD currently

approved. It is a pan-JAK inhibitor which interferes with cell activation elicited by IL-6, GM-CS factor, interferons and other cytokines. It is orally administered and its efficacy appears to be similar to that of biologics. However, a better-understood efficacy and safety profile remains to be established after it has been more widely used in clinical practice [104].

Biologic agents and tsDMARDs can be used sequentially when a patient does not achieve the treatment target, or in cases of intolerable side effects [70]. Cohort studies have shown, though, that response rates and drug retention decrease with increasing number of previous DMARD failures [105]. In real-world practice this results in a group of patients who still have moderate or high disease activity after use of several combinations of csDMARDs and bDMARDs. Therefore, although remission (or low disease activity) is today's therapeutic goal, for a significant subset of patients it is not attainable and this is an unmet need in the therapy of rheumatoid arthritis [42].

Patients who reach sustained remission (or low disease activity) with a biologic therapy for several months should be considered for tapering of therapy [70]. If glucocorticoids are administered, these should be reduced and discontinued first, usually within 6 months. Then biologics should be reduced by halving the dose or increasing the interval between the doses. The risk of a flare of disease activity after gradual reduction of dose is lower than that after abrupt withdrawal of the biologic; and it even decreases with increasingly lower disease activity and longer duration of sustained response [106]. However, if a flare occurs, reintroduction of the same agent usually leads to a similar to the initial good response, although there is a risk in a few patients not to respond as well [107]. Therefore, gradual dose reduction and close follow-up of the patients are recommended.

When feasible, this tapering of the biologic therapy should be tried both because of their high costs and, more importantly, for the adverse events associated with them, some of which may have long-term consequences [108]. Because of their longer use, TNF inhibitors have currently a better understood safety profile than non-TNFis. Serious infections and especially reactivation of latent tuberculosis, demyelinating disease, infusion reactions, psoriatic-like rashes and drug-induced lupus are some of the disorders linked to TNFi use (**Table 1.2**), while the association to others, like lymphoproliferative disorders and heart failure are still under investigation in long-term epidemiological studies [34, 109-111].

2. Spondyloarthritis

a. *Epidemiology, clinical manifestations and diagnosis*

Spondyloarthritis (SpA) defines a group of closely related chronic inflammatory arthritides, comprising ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, enteropathic or inflammatory bowel disease (IBD) - related SpA, a subgroup of juvenile idiopathic arthritis and undifferentiated SpA (uSpA). These different subtypes of the disease share a strong common genetic background, largely common pathophysiologic mechanisms and overlapping clinical features and hence are classified as a unique disorder with diverse phenotypes.

Spondyloarthritis is characterized by inflammation that can affect the axial skeleton (spine and sacroiliac joints), the peripheral joints (especially the large joints of the lower extremities), the entheses (the attachment sites of ligaments, tendons and joint capsules to the bone) and extra-articular sites, such as the eye (uveitis), skin (psoriasis) and gastrointestinal tract (IBD). Nowadays, the different SpA disorders are rather grouped in two main subtypes, namely axial (axSpA) and peripheral SpA (pSpA), based on the predominant clinical picture at patient presentation [112, 113]. Axial SpA is further subdivided as radiographic AxSpA (formerly known as ankylosing spondylitis) when there is evidence of sacroiliitis on plain X-Rays and nonradiographic AxSpA (nr-AxSpA) in the absence of such findings on conventional radiographs.

SpA is not an uncommon disease. The estimated prevalence for the whole group of SpA (including both axial and peripheral disease) in the general white population seems to be similar, or even higher than RA (1.5-2%) [114-116]. The disease is rarer in Japan (0.01% of the population) [117] and more frequent in northern Arctic populations (2.5%)[118]. Its incidence in Southern Europe (Spain) was calculated as high as 62.5 cases per 10^5 person years [119] but, again, the incidence ranges substantially in different parts of the world.

These differences in incidence and prevalence depend on the criteria used for case definition, the population heterogeneity and most importantly, are closely related to the frequency of HLA-B27, the disease's most significant genetic risk factor. Indeed, the prevalence of HLA-B27 is higher in northern countries and is highest in populations around the Arctic (the Haida indigenous people in Canada, 50%; the Chukotka natives in eastern Russia, 40%), resulting in a SpA prevalence as high as 6% in these populations [120]. On the contrary, HLA-B27 prevalence is very low in Japan (1%), whereas it is virtually absent in indigenous people from South America and Australia and in black Africans. The prevalence of HLA-B27 in Greece is intermediate (~6%) [121] and in the lowest range among other European Caucasian populations (6-10%) [122, 123]. Similarly, the prevalence of SpA in Greece was estimated in one study as 0.49% [124], which is similar to RA prevalence in Greece (0.68%).

According to recent data coming mostly from North American population studies, the prevalence of *axial* SpA in specific was estimated at 0.7-1.4% [125, 126]. Non-radiographic and radiographic axial SpAs seem to have an equal contribution, with an estimated prevalence of about 0.4-0.7% of the general population each. These results are consistent with earlier works reporting a prevalence of AS of about 0.5% [115].

The clinical presentation of SpA is characterized by highly heterogeneous phenotypes in different patients. This is a result of inflammation in various tissues -articular (axial or peripheral), entheseal, extra-articular – and of different degrees (from extensive joint destruction to new bone formation and complete ankylosis). The main features of patients presenting with SpA are listed in **Table 2.5**.

Table 2.5. Features of patients with SpA
• Inflammatory back pain • Enthesitis • Peripheral arthritis • Dactylitis ("sausage"-like digits) • History of recent urogenital or gastrointestinal infection • Inflammatory bowel disease • Psoriasis • Acute anterior uveitis • Sacroiliitis detected by imaging (radiography or MRI) • Positive family history of SpA • HLA-B27 positivity • Increased CRP concentration • Good response to NSAIDs

Due to clinical heterogeneity of the disease, similarly to RA, no diagnostic criteria exist for the conditions comprising SpA. Diagnosis usually depends on a combination of the above features, either from history, symptoms, physical examination, imaging or laboratory investigations. The more features are present, the higher the probability of a diagnosis of SpA, although some of them are weighted more heavily than others in making the diagnosis [127]. A diagnostic algorithm was developed by the Assessment of SpondyloArthritis international Society (ASAS) recently for the approach to diagnosis in patients with chronic back pain that began when they were younger than 45 years of age [128, 129]**.**

Inflammatory back pain (IBP) is the hallmark of axial SpA. Its onset occurs usually in the third decade of life and it is often insidious, while the patients can be pain-free for long periods of time. Similarly, other signs and symptoms of early axial SpA are often subtle and can fluctuate over time, resulting in a delayed diagnosis. Peripheral arthritis, usually asymmetric and predominantly of the lower limbs is also common, especially in peripheral SpA. Differential diagnosis of SpA symptoms presents difficulties, as early disease can mimic other rheumatic diseases (rheumatoid arthritis, gout and pseudogout) and chronic back pain due to mechanical causes or non-specific pain syndromes, which are common in the general population.

Radiographs are frequently normal in early disease and can remain normal for many years after disease onset. However, sacroiliitis and inflammation in the spine can be visible on MRI during the early ("non-radiographic stage") and thus MRI has been increasingly used in the last decade to assess patients with clinically suspected axial SpA [129].

Most epidemiological studies –as is the case for most studies of SpA- focus on the two most frequent historically used subtypes of SpA: ankylosing spondylitis and psoriatic arthritis. This classification of the SpA spectrum of disorders was based on the clinical presentation of the disease: the associated extra-articular symptoms (PsA and IBD-related SpA), the outcome (AS), or its etiology (reactive arthritis) and the age of onset (juvenile SpA), plus a residual group called undifferentiated SpA (uSpA). It was widely adopted as it is easy to implement in daily clinical practice where different SpA patients present with highly heterogeneous features and diagnosis usually is made on the basis of the predominant clinical picture.

Classification criteria are available for these phenotypical subtypes of spondyloarthritis; again, similarly to RA, these criteria are intended for research purposes and not for diagnosis at the individual patient level. The 1984 modified New York (mNY) criteria [130] and the Classification for Psoriatic Arthritis (CASPAR) criteria [131] are the most widely used classification criteria for AS and PsA respectively.

According to *mNY criteria*, a patient can be classified as having AS when sacroiliitis is present on plain X-rays of the pelvis (at least grade 2 bilaterally or grade 3 unilaterally) and at least one clinical criterion is met. The clinical criteria include inflammatory back pain (IBP), limited spinal mobility and restricted chest expansion. IBP is defined as low back pain for at least 3 months' duration improved by exercise and not relieved by rest. Spinal mobility and chest expansion are measured during clinical examination by using specific tests (e.g. the Schober's test). Important restrictions of the mNY criteria in the clinical practice are that they focus exclusively on the axial features of the disease and that they are only useful in the assessment of advanced disease, as both the radiographic structural changes and the limited mobility of the spine and chest expansion usually occur late in the disease course and they represent the results of inflammation rather than active inflammation itself. Moreover, other important features of the disease are not considered, such as MRI findings, HLA-B27 status, family history and the response to NSAIDs.

The *CASPAR criteria* were published in 2006 and can provide guidance to clinicians for the diagnosis of psoriatic arthritis, although they were initially developed for the purpose of enrolling patients in clinical trials. According to these criteria, psoriatic arthritis is considered to be present in patients with inflammatory musculoskeletal disease (disease involving the joints, the spine, or the entheses) whose score on the five criteria listed in the **Table 2.6** totals at least 3 points. Based on the CASPAR criteria, up to 30% of patients with psoriasis have psoriatic arthritis, many times undiagnosed by the treating dermatologist [132, 133].

However, this phenotypic classification of SpA subtypes presents a number of major disadvantages. First, it does not reflect the increasing evidence from genetics, immunopathology, pathophysiology and clinical observation that these phenotypes represent different presentations of a single disorder rather than a spectrum of distinct, though related, disorders [134-138]. Clinical evidence supporting this unifying approach comes from the observation that a single patient can display more than one SpA phenotypes at once (e.g. a patient can have AS plus PsA) or can evolve from one phenotype to another over time (e.g. from uSpA to AS). Second, the phenotypic subclassification favors clinical research in the major subtypes, AS and PsA, at the expense of less prevalent subtypes. For example, TNF inhibitors have been well studied and broadly used in AS and PsA, but not in other SpA

Table 2.6. Classification Criteria for Psoriatic Arthritis (CASPAR criteria).

Criterion	Explanation	Points
1. Evidence of psoriasis		
Current psoriasis	Skin or scalp psoriasis as judged by a physician	2
Personal history of psoriasis	According to the patient or as judged by a physician	1
Family history of psoriasis	Psoriasis in a first- or second-degree relative	1
2. Psoriatic nail dystrophy	Onycholysis, pitting or hyperkeratosis during current physical examination	1
3. Negative test for RF	Preference for ELISA method or nephelometry	1
4. Dactylitis		
Current dactylitis	Swelling of an entire digit on physical examination	1
History of dactylitis	According to a rheumatologist	1
5. Radiographic evidence of juxta-articular new bone formation	On plain radiographs of hand or foot (excluding osteophytes formation)	1

Adapted from Taylor, W., et al., *Classification criteria for psoriatic arthritis: development of new criteria from a large international study.* Arthritis Rheum, 2006. **54**(8): p. 2665-73.

subforms. And finally, this phenotypic classification recognizes established, advanced forms of SpA but does not adequately capture less typical and early presentations of the disease [139].

In the early 1990s, two sets of classification criteria for the entire group of SpA phenotypes were proposed: the *Amor criteria* [140] and the *European Spondyloarthropathy Study Group (ESSG) criteria* [141]. Even though these criteria sets were a step forward to define SpA at its whole spectrum, they have some limitations needing to be addressed. First, they did not provide information regarding axial versus peripheral manifestations in individual patients, a feature which is found to be important pathophysiologically as well as clinically, since it influences the results of studies evaluating treatment effects and disease outcomes. In addition, neither criteria set incorporates the findings of sacroiliitis on MRI. ESSG criteria also do not consider the HLA-B27 status, while the Amor criteria define peripheral arthritis only as an oligoarticular form of arthritis, thereby excluding patients presenting with monoarthritis or polyarthritis [142].

The recognition of these drawbacks led recently to the development of novel *classification criteria* for SpA *by the Assessment of SpondyloArthritis international Society (ASAS)* [112] (**Table 2.7**). Key aspects of these criteria are that (i) SpA is subdivided into axial SpA and peripheral SpA, (ii) imaging abnormalities are not only defined by X-Ray, but also by MRI and (iii) HLA-B27 positivity is an important entry criterion, allowing to SpA patients without imaging abnormalities to be identified. As already mentioned, according to the ASAS criteria, the diagnosis of AxSpA encompasses two subsets: non-radiographic AxSpA and classic AS (i.e. radiographic AxSpA). Progression to AS occurs in a minority of patients who have non-radiographic AxSpA [143, 144]. In general, it is unclear whether nr-AxSpA and AS reflect a single entity that varies along a continuum of duration and severity or whether nr-AxSpA includes one or more pathogenetically distinct subsets of disease that either have not been previously recognized or have been given other diagnoses, including undifferentiated SpA.

Table 2.7. ASAS classification criteria. Adapted from Rudwaleit, M., et al., *The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection.* Ann Rheum Dis, 2009. **68**(6): p. 777-83.

	Criteria for Axial SpA	**Criteria for Peripheral SpA**
Inclusion entry criteria	≥3 months back pain, at age <45 yrs and either *sacroiliitis (radiographic* or MRI) plus ≥1 other SpA feature* (**imaging arm**) or *HLA-B27 positive plus ≥2 other SpA features* (**clinical arm**)	Arthritis or Enthesitis or Dactylitis plus ≥1 SpA feature marked with [a] or ≥2 other SpA features marked with [b]
SpA features to be considered		
Inflammatory back pain (IBP)	√ **	√ (past)[b]
Arthritis ‡	√	√ [b]
Dactylitis	√	√ [b]
Enthesitis†	√	√ [b]
Good response to NDAIDs	√	
Psoriasis	√	√ [a]
Inflammatory bowel disease	√	√ [a]
Uveitis	√	√ [a]
Preceding infection		√ [a]
Positive family history for SpA	√	√ [b]
HLA-B27	√	√ [a]
Elevated CRP	√	
Sacroiliitis		√ [a] (radiographic*/ on MRI)

* Radiographic sacroiliitis is considered present when at least grade 2 bilaterally or grade 3-4 unilaterally.

** Current IBP defined according to the ASAS experts definition: at least 4/5 parameters present: (1) age at onset < 40 years; (2) insidious onset; (3) improvement with exercise; (4) no improvement with rest; (5) pain at night (with improvement upon getting up). ‡ Current peripheral arthritis compatible with SpA (usually asymmetric and/or predominant involvement of the lower limb) diagnosed clinically by a doctor. † Past or present spontaneous pain or tenderness at examination of an enthesis. In the criteria for axial SpA only enthesitis of the heel is considered, whereas in the criteria for peripheral SpA any site of enthesitis can be affected.

a. *Pathogenesis and pathophysiology*

Advances in the classification of SpA depict how progress in the understanding of genetics and the pathophysiology of inflammation and structural damage can affect clinical practice in the context of diagnosis and classification. The etiology of SpA is still largely unknown but is thought as an interplay of genetic and environmental factors. Familial aggregation studies indicate that genetic risk factors contribute to 80-90% of the susceptibility to ankylosing spondylitis, while the stronger concordance rates between monozygotic (50-75%) versus dizygotic (15%) twins confirms this dominant genetic influence [145]. The strong genetic predisposition also applies to other SpA subtypes as well, as indicated by a recurrence rate of SpA (any subtype) in 12% of the first-degree relatives of SpA patients.

The major genetic risk factor is HLA-B27, an MHC class I molecule present in 74 to 89% of patients with either nonradiographic axial SpA or ankylosing spondylitis [146]. The absolute risk of spondyloarthritis in persons with HLA-B27 positivity is estimated to be 2-10%, but is higher (~20%) if a first-degree relative is affected [122]. HLA-B27 is associated with a significantly younger age at onset [147] and predispose to axial involvement in SpA, as its frequency is highest in AS, whereas in peripheral arthritis such as reactive arthritis or uSpA the frequency of HLA-B27 ranges between 20-70%. The basis of the association between this molecule and SpA remains largely unexplained. The two major hypotheses are the arthritogenic-peptide theory, which proposes that HLA-B27 presents self-peptides to CD8-restricted T lymphocytes leading to autoimmunity and the autoinflammatory origin theory which argues that B27 has a role in triggering innate immune responses rather than its canonical role of antigen presentation [148].

Despite the dominant effect of the gene encoding HLA-B27, only a small proportion of people in the general population who harbor this molecule develop AS and HLA-B27 explains only 20-40% of the genetic susceptibility to AS, suggesting the contribution of additional genes. Association studies based on single nucleotide polymorphisms (SNPs) have recently revealed more than 30 non-MHC genes or genetic regions that influence susceptibility to AS [135]. Genes that affect the interleukin-23-interleukin-17 pathway, like IL23R and CARD9, are prominently represented in this group. Intense interest has focused also on the functional significance of ERAP1 gene variants associated with AS. ERAP1 encodes for an aminopeptidase that trims peptides within the endoplasmic reticulum to generate ligands that are the appropriate length for binding to MHC class I molecules [149]. The majority of these loci also confer susceptibility to other immune-mediated diseases, particularly inflammatory bowel disease and, to a lesser degree, psoriasis [150].

Environmental factors including microbes, mechanical stress and trauma, obesity and smoking have been hypothesized to contribute to the pathogenesis of SpA. Alterations in the gut microbiome and subclinical gut inflammation are present in the majority of patients with SpA and have been shown to be strongly associated with joint inflammation [151]. Microbes are postulated to trigger altered autoimmunity through molecular mimicry [152]. Cigarette smoking has also been implicated in SpA susceptibility, underscoring its role in multiple inflammatory and autoimmune diseases [153]. Finally, the contribution of mechanical stress in the development of inflammatory enthesitis in different SpA subtypes has recently gained interest [154], while there is evidence that preceding bone or joint trauma in patient with psoriasis is associated with the development of PsA [155].

Although the basic trigger for the inflammation of spondyloarthritis remains unknown, several lines of evidence implicate the cells and molecules in the pathway involving interleukin-23 (IL-23) and interleukin-17 (IL-17) [27, 156]. Aberrant features of HLA-B27 that are related to its tendency to misfold and dimerize may trigger the production of IL-17 through interaction with the killer immunoglobulin-like receptor 3DL2 (KIR3DL2) on CD4+ T cells or through excess production of IL-23 mediated by the response to stress in the endoplasmic reticulum [157]. Autoreactive CD8+ T cells may also recognize the arthritogenic peptides displayed by HLA-B27. In addition, HLA-B27 may generate an immune response that promotes microbial dysbiosis in the gut, contributing to inflammation and further driving the production of IL-23 and other proinflammatory cytokines. These cytokines can act on an array of different immune cells, promoting the production of IL-17, IL-22, TNF, interferon-γ and other cytokines and chemokines [158].

TNF has a key role in the propagation and perpetuation of inflammation in SpA, as shown through the effectiveness of TNF inhibitors in SpA treatment. This role fits with the genetic associations with TNFR1 and the TNFR1 signaling molecule TRADD [159]. Exactly how TNF drives SpA is unclear, but it has been implicated in synovitis and the resulting bone destruction and in gut inflammation. The two other cytokines of interest are IL-23 and IL-17, as recently two agents –ustekinumab and secukinumab- targeting these cytokines showed efficacy in clinical trials and have been approved for the treatment of PsA and axial SpA.

In SpA, skeletal damage is a consequence of bone erosion and, more importantly, aberrant osteoproliferation, which may occur simultaneously. Osteoproliferation results in the characteristic formation and growth of syndesmophytes in the axial skeleton and entheseophytes in peripheral SpA. Syndesmophytes' progression is highly variable, but in severe cases they can lead to the complete fusion of the spinal joints. Interestingly, bone formation in SpA is exclusively confined to the periosteal bone compartment leading to apposition of cortical bone along its outer surface (bony spur). In contrast, trabecular bone does not show any signs of anabolic changes but, in contrast, frequently shows bone loss, leading to osteopenia and osteoporosis associated with increased fracture risk.

Much remains to be learnt about the factors underlying this process of tissue remodeling. Cellular and molecular pathways of cartilage and bone destruction are activated at the sites of pathology by mechanical or other triggers and, as in RA, are largely dependent on TNF [160, 161]. Resolution of inflammation might reduce the inhibition of Wnt signaling and lead to reactive osteoproliferation [162]. Another emerging possibility is that osteoproliferation in SpA is, at least partly, uncoupled from inflammation. It is postulated that the same trigger that initiates synovitis might also directly activate stromal pathways, including the pathways of bone morphogenic protein, leading to new tissue formation independent of inflammation or early erosive changes. Although the two hypotheses are not mutually exclusive, the relative contribution of the two mechanisms and the exact relation between inflammation and stromal-cell activation has important clinical implications for the optimal management of SpA, since it has to be defined whether early anti-inflammatory treatment will prevent structural damage or a separate assessment and therapeutic targeting of stromal pathways is also needed [163].

b. *Disease activity and outcome assessment*

Activity in SpA is a reference to the inflammation caused by the disease, which has many possible clinical presentations: axial, peripheral (including enthesopathy) and extra-articular. The heterogeneity of the disease manifestations hampers the evaluation of SpA as a whole, especially in patients with combined axial and peripheral SpA, since most disease activity and outcome parameters either capture only a single disease manifestation (axial, peripheral or extra-articular) or are only validated in a single phenotypic SpA subtype (AS or PsA). Moreover, since ESR and CRP are often normal in SpA, there is an unmet need for additional blood and/or target tissues' biomarkers to monitor disease activity and outcomes.

Axial SpA

Regarding axial SpA, several tools are used in clinical trials and everyday practice to assess disease activity, most notably the *Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)* [164] and *Ankylosing Spondylitis Disease Activity Score (ASDAS)* [165]. BASDAI is a self-administered patient questionnaire assessing fatigue, axial symptoms, peripheral symptoms, enthesopathy, and duration and intensity of morning stiffness using visual analogue scales (VAS 0-10). ASDAS has been developed to improve the objectivity of this index and includes the questions of BASDAI concerning the level of axial and peripheral symptoms and the duration of morning stiffness, but also the level of acute phase reactants – either ESR or CRP - and an overall global assessment in VAS (0-10). Both indices provide continuous numerical scales reflecting disease activity and the higher the score the more active the disease. ASDAS can also classify disease activity states as "inactive disease", "moderate disease activity", "high disease activity" and "very high disease activity". The three cut-offs selected to separate these states were: 1.3 separating inactive and moderate disease activity, 2.1 separating moderate and high disease activity and 3.5 separating high and very high disease activity [166]. This year, in an update of the nomenclature of disease activity states, "moderate disease activity" state was replaced by "low disease activity" state, a wording found to better reflect the opinion of patients and physicians about what ASDAS values ≥1.3 and <2.1 represent (**Figure 2.4**) [166].

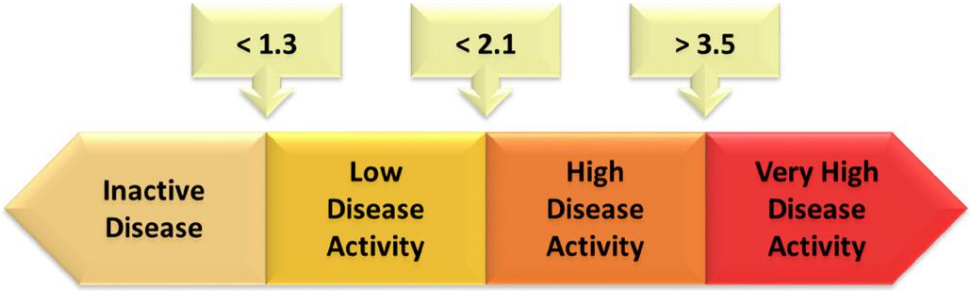

Figure 2.4. 2018 update of the nomenclature for Ankylosing Spondylitis Disease Activity Score (ASDAS) disease activity states. Adapted from Machado, P.M., R. Landewe, and D.V. Heijde, *Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states.* Ann Rheum Dis, 2018.

Both BASDAI and ASDAS can assess improvement of disease activity upon treatment; *BASDAI50* denotes 50% improvement in the BASDAI score between any two assessments, while in ASDAS, a change of ≥1.1 units indicate a *"clinically important improvement*" and a change of ≥ 2.0 a *"major improvement*" [167]. The ASDAS has been found to perform well in patients with radiographic as well as non-radiographic axial SpA [168] and to be more discriminative than BASDAI when assessing response to TNF inhibitors [169]. Global measurements, such as patient's and physician's global assessments of disease activity (in VAS scales) are also used [170].

The *severity* of axial SpA is determined both by irreversible structural damage, often due to tissue remodeling, and by reversible spinal inflammation. Impairment of spinal mobility is influenced primarily by inflammation in early disease and by structural damage in later disease [171]. For clinical studies, several outcomes have been proposed to show severity of axial SpA: job loss, functional impairment, range of motion and hip involvement. For the measurement of function, the *Bath Ankylosing Spondylitis Function Index (BASFI)*, a questionnaire filled-in by the patient is the most frequently applied instrument [172]. Spinal mobility is often assessed by the modified Schober's test, the chest expansion test and the occiput-wall distance test [173]. Bath Ankylosing Spondylitis Metrology Index (BASMI) is a validated combined tool to assess spinal mobility and hip function. Involvement of one or often both hips, in the coxofemoral joint, occurs in 24-36% of patients with radiographic AxSpA and is associated with greater functional impairment than when there is no hip involvement [174]. Radiographic damage should also be monitored in axial SpA using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), which focuses on development of erosions and syndesmophytes in the lumbar and cervical spine [175]. In contrast to radiographic imaging, which may take several years to detect the consequences of inflammation, magnetic resonance imaging (MRI) can detect acute inflammation of the enthesis, bone and synovium and is used for monitoring of axial SpA. A scoring system for the quantification of acute lesions of the spine and the sacroiliac joints has been proposed [176].

To assess improvement of patients with axSpA in randomized clinical studies the Assessment of SpondyloArthritis international Society (ASAS) 20 and ASAS 40 improvement criteria have been frequently utilized [177, 178]. The *ASAS 20* is a combined measure of response and is defined as improvement ≥ 20% and absolute improvement of ≥ 1 unit (on a scale of 0-10) in at least three of the four following domains: patient global assessment, pain, function (BASFI) and inflammation (defined as the mean of morning stiffness-related BASDAI VAS scores for questions 5 and 6) and no worsening of ≥ 20% and ≥ 1 unit in the remaining domain. Accordingly, *ASAS 40* is defined by improvement of ≥ 40% and absolute improvement of ≥ 2 units (on a scale of 0-10) in at least three of the aforementioned four domains, but no worsening at all in the fourth domain. *ASAS partial remission* is achieved when none of the aforementioned four domains has a value above two units on a 0-10 scale.

However, it was recently noted that composite measures of response which combine a measure of inflammation with a measure of structural damage or physical function have a diminished ability to detect improvement in patients with long-lasting disease who nevertheless experience clear-cut absence of inflammation [179]. Therefore, in the recent treat-to target recommendations for SpA it was stated that ASAS improvement criteria and partial remission criteria are less discriminative and appropriate than the respective ASDAS categories [180].

Peripheral SpA and specific outcome measures for PsA

In SpA patients with peripheral arthritis, measures of disease activity and response to therapy are most commonly derived from clinical studies in RA and include swollen and tender joint counts and composite indices such as *DAS28* and the associated *EULAR response* and *ACR response criteria (20/50/70%)*. These have shown reliable discriminant and response characteristics in randomized controlled trials (RCTs) of PsA [181]. Because of the involvement of distal interphalangeal joints (DIP) and the tendency of peripheral arthritis in SpA to be more asymmetric and oligoarticular than RA, an expanded joint count of 44 joints in AxSpA and 68 tender and 66 swollen joints in PsA is recommended, especially for RCTs [176].

Several enthesitis scoring measures have been developed based on the patient's response to palpation over a different number entheseal sites. *Leeds Enthesitis Index (LEI)* requires examination of only 6 entheses and has been found to have the highest validity and reliability and the least floor effect, i.e. has the ability to identify the majority of patients with enthesitis [182, 183]. Dactylitis is most commonly found in PsA, but it can also occur in patients with other types of SpA [184]. It may present acutely, as inflamed painful digits or in its quiescent, asymptomatic (non-tender) form. This is why, although in everyday practice assessment of dactylitis is usually performed by simple counting of tender dactylitic digits, the most objective measure is the *Leeds Dactylitis Index (LDI)*, which assesses the ratio of the circumference of the affected digit to the contralateral, non-affected digit as near to the base as possible using tape or a pre-calibrated loop and multiplies it by a tenderness score [185]. Information regarding episodes of uveitis and diagnosis of an inflammatory bowel disease should also be collected systematically in all SpA patients of any subtype [18].

Concerning skin assessment in SpA patients with psoriasis, a wide variety of scoring systems have been proposed. Among these, the *Psoriasis Activity and Severity Index (PASI) score* is the most extensively studied and the most thoroughly validated in PsA [186]. It reflects both the surface area of skin involvement and the severity of psoriatic lesions by evaluating four body areas (head, trunk, upper and lower extremities) for erythema, induration and desquamation. Nail psoriasis should also be evaluated as it is associated with a higher prevalence of joint involvement and a more progressive form of PsA [187].

Several *composite indices* of disease activity have been developed specifically for PsA to include joint counts, acute phase reactants, skin involvement, enthesitis and dactylitis, such as the Disease Activity in Psoriatic Arthritis (DAPSA) score, the Composite Psoriatic Disease Activity Index (CPDAI), the Psoriatic Arthritis Response Criteria (PsARC) and the Psoriatic Arthritis Disease Activity Score (PASDAS) [188, 189]. Further data are needed to inform the preferred composite measure for use as the primary outcome in PsA RCTs and cohort studies [190].

Many RCTs have utilized DAS28-defined criteria developed for RA to also define remission in PsA, although it has been shown that a greater percentage of PsA patients were able to achieve this degree of response because a "joint-centered" definition of remission is probably a less comprehensive approach to evaluation of PsA [191, 192]. Therefore, a composite measure for defining "*minimal disease activity" (MDA)* in PsA has been developed and validated and includes assessments of joints, skin, entheses and physical function. A patient is classified as achieving MDA when meeting 5 of the 7 following criteria: TJC ≤1.; SJC ≤1; PASI ≤1 or body surface area (BSA)

≤3; patient VAS pain ≤15; patient VAS global ≤20; HAQ ≤0.5; tender entheseal points ≤1. Importantly, MDA score lacks a laboratory component of an acute phase reactant [193].

c. *Treatment of spondyloarthritides*

The aim of treatment in SpA is to optimize health-related quality of life and social participation through control of musculoskeletal and extra-articular signs and symptoms, prevention of structural damage and preservation or normalization of function [194, 195]. Avoiding drug toxicities and decreasing the complications associated with the disease are also important treatment goals [180]. Similarly to RA, it has been recognized that higher disease activity, both in axSpA and PsA results in more structural damage and disability in affected patients [196-198]. Furthermore, treatment-to-target by measuring disease activity and adjusting therapy accordingly has been found to improve outcomes [180, 199]. Therefore, treat-to target recommendations for SpA, including axial and peripheral SpA (with an emphasis on PsA) were formulated in 2012 and updated in 2017 by an international task force [180]. These recommendations aim at remission/inactive disease of musculoskeletal (arthritis, dactylitis, enthesitis, axial disease) and extraarticular manifestations as the main treatment target, with low/minimal disease activity considered as a secondary target.

In the case of axial SpA –both radiographic AxSpA and non-radiographic AxSpA – remission was defined by a low (<1.3) ASDAS score as the preferred measure, while in PsA, DAPSA or MDA composite scores should be considered to define the target. The treatment target should be individualized based on the current clinical manifestations of the disease and the choice of the target (remission or low disease activity) should always take comorbidities, patient factors and drug-related risks into account. Once the target is achieved, it should ideally be maintained throughout the course of the disease by adapting therapy if the desirable disease state is lost [180].

Management recommendations regarding specific treatment options and treatment escalation steps to achieve such targets have been formulated by different committees separately for axial SpA and PsA [194, 195] and are discussed briefly below. An overview of all therapy choices that are currently recommended are summarized in an algorithm for therapeutic management of patients with SpA [200] in **Figure 2.5.**

Axial SpA

The ASAS and EULAR have collaborated to issue management recommendations for axial SpA in 2016, which provide guidance on state-of-the-art management of these patients [194]. A multidisciplinary approach -coordinated by the rheumatologist- is essential as approximately 40% of the patients experience at least one extra-articular manifestation during the course of the disease [201]. Furthermore, the optimal management of patients with axSpA requires a combination of non-pharmacological and pharmacological treatment modalities. Non-pharmacologic interventions that were proven efficacious include patient education, encouragement of regular exercise and physical therapy if indicated [202-204]. Smoking cessation is also considered important due to the association

between smoking and disease activity, inflammation on MRI and syndesmophyte formation [205]. As previously noted, treatment should be guided according to a predefined treatment target, based on a shared decision between the patient and the rheumatologist.

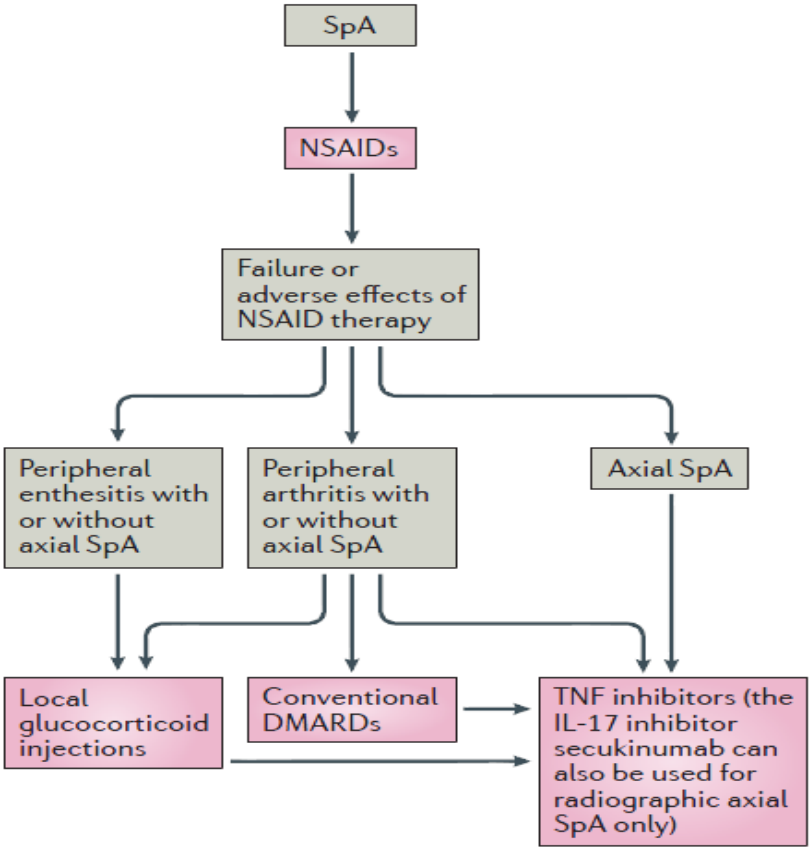

Figure 2.5. Algorithm for therapeutic management of active (symptomatic) SpA. Adapted from Sieper, J. and D. Poddubnyy, *New evidence on the management of spondyloarthritis.* Nat Rev Rheumatol, 2016. **12**(5): p. 282-95.

The first-line drug treatment for patients suffering from pain and stiffness is a non-steroidal anti-inflammatory drug (NSAID), such as diclofenac, ibuprofen, naproxen, celecoxib and etoricoxib, up to the maximum tolerated dose. However, due to the potential adverse events of chronically administered NSAID therapy, these should be only prescribed if patients are symptomatic [194]. NSAIDs remain a first-line therapy for axial SpA as data from a randomized controlled trial suggest that they can induce ASAS partial remission in up to 35% of patients with active *early* axSpA within 6 months (compared to 62% of patients treated with a combination of infliximab and NSAID) [206]. However, this effect is higher than that found by a previous study in patients with *long-standing* disease (12% reach ASAS partial remission after 12 weeks of NSAID treatment) [207]. Some studies have also found that NSAIDs can retard radiographic progression in axSpA [208, 209], but others did not confirm this effect [210]. Concerning long-term safety, and especially the well-known risks of

adverse cardiovascular and gastrointestinal events [211], no robust or adequately powered studies specifically in patients with axial SpA have been performed so far, and whether the results observed in patients treated with NSAIDs for other diseases can be extrapolated to axSpA is not clear [200]. Cohort studies and population-based retrospective studies of administrative health data indicate that patients with AS have increased mortality and increased cardiovascular risk relatively to the general population, but also that long-term NSAID use had a protective effect and was associated with reduced cardiovascular morbidity and mortality [212, 213].Conventional synthetic DMARDs are generally not effective in the treatment of axial manifestations of SpA and should only be considered when peripheral arthritis coexists with axial disease. In this case, sulfasalazine is the csDMARD of choice. Systemic corticosteroids are also not indicated in axSpA [194].

TNF inhibitors are the second-line therapy, recommended if non-pharmacologic therapy and at least two NSAID courses, over 4 weeks in total, fail to control disease activity, induce side effects, or are contraindicated [194]. **Figure 2.6** summarizes the requirements for axial SpA to be treated with TNF inhibitors. Correct diagnosis by a rheumatologist, based on a full evaluation of all available clinical, laboratory and imaging information and excluding other potentially more likely diagnoses is very important. Only formally fulfilling classification criteria (such as the ASAS axSpA criteria) does not suffice [194]. Patients with symptomatic disease - based preferentially on ASDAS score (≥2.1) - plus elevated CRP and/or inflammation on MRI and/or radiographic sacroiliitis (according to the New York grading) and a positive opinion of their rheumatologist can be considered for initiation of a biologic DMARD (i.e. initially a TNF inhibitor).

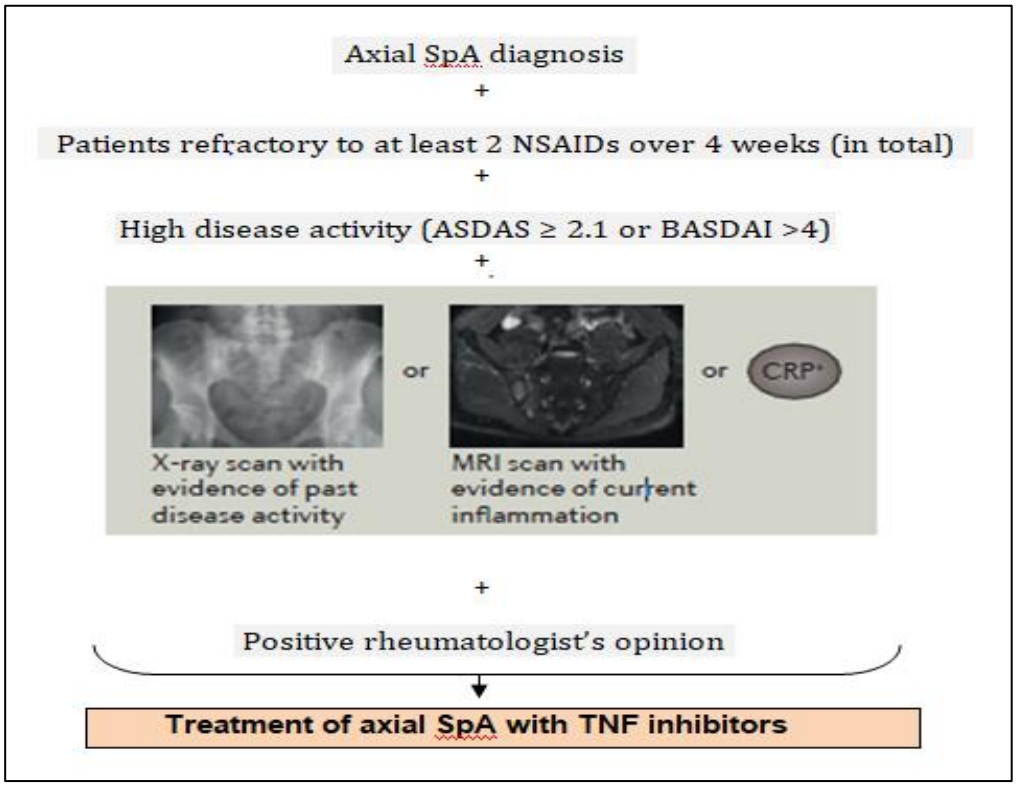

Figure 2.6. Requirements for treatment of axial SpA with TNF inhibitors. Positive X-ray scan is *mandatory* for initiation of *infliximab*. Modified from Sieper, J. and D. Poddubnyy, *New evidence on the management of spondyloarthritis.* Nat Rev Rheumatol, 2016. **12**(5): p. 282-95.

All five different TNFis have indications for axSpA; infliximab is indicated only for radiographic axSpA due to lack of trial data concerning non-radiographic axSpA; adalimumab, etanercept, golimumab and certolizumab pegol are indicated both for radiographic and non-radiographic axSpA. However, in non-radiographic axSpA, the presence of elevated CRP and/or inflammation on MRI (i.e. objective sign(s) of inflammation) is mandatory for TNFi initiation. The efficacy of all five TNFis with regard to musculoskeletal disease seems very comparable in RCTs, although no head-to-head comparisons are available. However, there seems to be a difference in efficacy with regard to extra-articular manifestations: monoclonal antibodies are efficacious in the treatment of IBD and in preventing the recurrence of uveitis, whereas etanercept has shown contradictory results for uveitis and no efficacy in IBD [194, 214]. Moreover, etanercept seems to be less efficacious in psoriatic skin involvement than other TNFis, although no head-to-head comparisons are available [195].

Very recently, secukinumab, (an anti-IL-17 mAb), has shown efficacy [215] and was approved for the treatment of axial SpA. To date, only trial data on IL-17 inhibition in radiographic axSpA are available and thus secukinumab is not approved for the treatment of patients with nr-axSpA [194]. Patients with AS who received secukinumab had a similar response rate to that of earlier studies with TNFi in the same patient groups [216]. Secukinumab has also been proven efficacious in psoriasis, but not in Crohn's disease [217, 218]. Since the body of experience with TNF inhibitors concerning efficacy as well as safety and variety of indications greatly outweighs that of secukinumab, only the former are recommended as initial biologic DMARDs in axSpA treatment [194].

Response to biologic DMARD therapy should be monitored by the same outcome measure used to initiate therapy. After 12 weeks of treatment, a clinically important improvement of ASDAS score ≥1.1 is required (≥2.0 for BASDAI), along with the rheumatologist's positive opinion for bDMARD continuation [194]. If initial TNFi therapy fails, switching to another TNFi or an IL-17 therapy should be considered. Toxicity to a TNFi may also be a reason to switch to secukinumab.

If a patient is in sustained remission/inactive disease, preferably for more than 6 months, tapering of a bDMARD can be considered, either by dose reduction or by increasing the dose interval. Complete discontinuation of biologics seems to lead to disease relapse in most of the cases and it is only recommended after very slow tapering, assuring a sufficient period of time remaining in remission after the previous step of tapering [194].

Peripheral SpA and specifically PsA

Interventional, as well as non-interventional trials of treatment options for patients with peripheral SpA as a group are sparse, with the exception of trials involving specifically patients with PsA. However, in PsA, nearly all of the treatment trials were focused on patients with polyarthritis in whom the hands were predominantly affected; this pattern of joint involvement is not typical of peripheral SpA as a group [200]. Therefore, an unmet need exists for more studies examining treatment options in patients with active peripheral SpA.

Subgroup analyses of patients with peripheral manifestations in AS and PsA trials led to the conclusion that, similarly to axSpA, patients with peripheral SpA should be treated with NSAIDs first. If these fail, a conventional DMARD should be initiated, preferably sulfasalazine [194]. Conventional DMARDs do not seem to be effective for enthesitis or dactylitis and local

corticosteroid injections can be considered in these patients [194, 195]. TNF inhibitors are considered next, if the previous steps fail. Both etanercept and adalimumab have shown promising results in SpA patients with peripheral manifestations [219-221], but more data are needed in these patients as a group.

EULAR recommendations have been published regarding the pharmacological management of patients with PsA [195]. While taking extra-articular manifestations of PsA into account, these recommendations focus mainly on musculoskeletal involvement and stress again the importance of tight disease activity control with regular patient monitoring. The goal of therapy should be disease remission as defined by validated scores, such as DAPSA [222]. However, minimal/low disease activity based on DAPSA or MDA scores may also be a treatment target, especially in patients with long-standing disease or comorbidities that preclude escalation of therapy.

NSAIDs are, again, first-line therapy to relieve musculoskeletal signs and symptoms of PsA. However, in patients with poor prognostic factors such as peripheral polyarthritis (≥5 swollen joints), structural damage in the presence of inflammation, high ESR or CRP and/or extra-articular manifestations, csDMARDs should be considered at an early stage [195]. Methotrexate is preferred in those with significant skin involvement given its demonstrated efficacy on psoriatic skin disease [223]. Other csDMARDs, such as leflunomide, sulfasalazine or ciclosporine, can be considered if MTX is not an option and csDMARDs combinations can be used, although there is little evidence on their efficacy [195, 224].

In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a bDMARD, usually a TNF inhibitor should be commenced. All available TNFis have demonstrated efficacy in PsA, for skin and joint involvement, as well as in preventing radiographic damage [195, 225, 226]. However, for psoriatic skin involvement, it seems that etanercept is less efficacious, or at least has a slower onset of action than the TNF monoclonal antibodies. Co-administration of a csDMARD along with TNFi therapy seems to be of benefit in PsA, in most studies, regarding response as well as TNFi survival, but some studies did not find this effect [170, 227-229] and more data are warranted.

In case TNFis are not appropriate or fail to control disease activity, the newest biological agents ustekinumab (targeting IL-12/23 pathway) and secukinumab (targeting IL-17 pathway) may be considered. However, both agents are less efficacious when used after a TNFi compared to use as a 1st bDMARD, an effect observed also with sequential TNFi use [195]. Phosphodiesterase-4 (PDE-4) inhibitor apremilast is an oral agent which has shown moderate efficacy on joint, skin and entheseal disease in PsA and can be used as a 4th-line agent in patients with peripheral arthritis and an inadequate response to at least one csDMARD, in whom biologic DMARDs are not appropriate. A summary of the treatment algorithm in patients with predominantly peripheral PsA is described in **Figure 2.7** [230].

In patients with active enthesitis and/or dactylitis and insufficient response to NSAIDs and local corticosteroids, initiation of a TNFi should be considered, as csDMARDs are not effective in these cases [195].

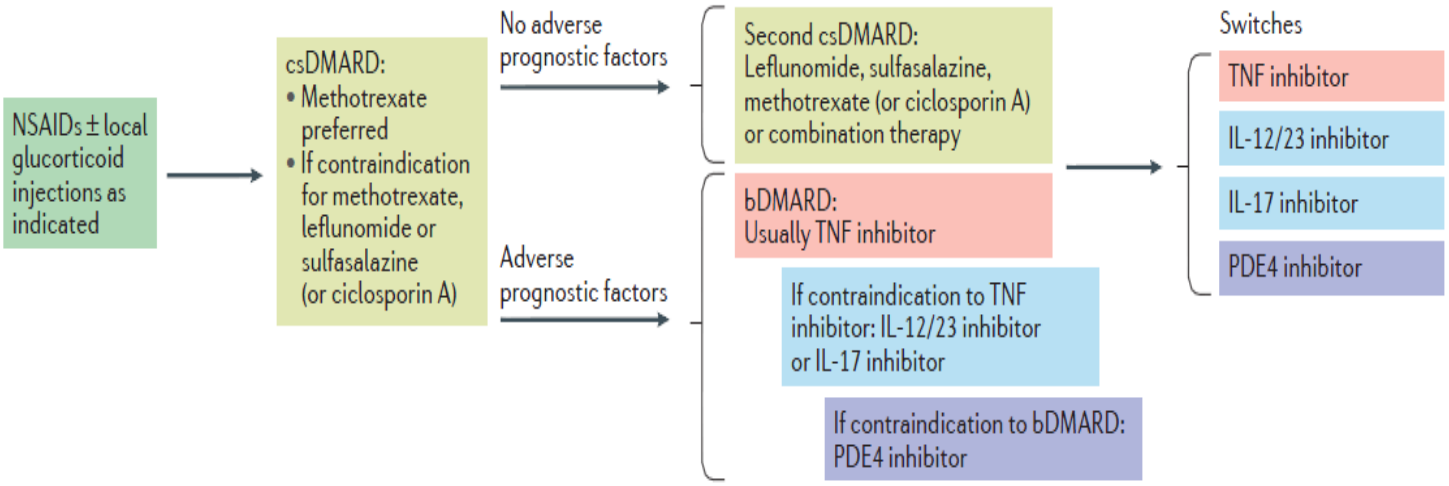

Figure 2.7. Simplified EULAR treatment algorithm for predominantly peripheral PsA. Modified from Gossec, L., et al., *Management of psoriatic arthritis in 2016: a comparison of EULAR and GRAPPA recommendations.* Nat Rev Rheumatol, 2016. **12**(12): p. 743-750.

CHAPTER III. TUMOR NECROSIS FACTORS INHIBITORS IN INFLAMMATORY ARTHRITIDES: FROM RANDOMIZED CONTROLLED TRIALS TO OBSERVATIONAL STUDIES

1. Randomized controlled studies of TNFis in RA and SpA

As already discussed, TNFis are the most commonly used class of biologic agents for the treatment of active inflammatory arthritides. Indeed, they are the initial bDMARD for all types of SpA and the preferred by physicians in clinical reality 1st-line bDMARDs in RA for their better-known efficacy and safety profile [231]. Among different TNFi drugs, adalimumab, etanercept, and infliximab, are the three most widely used. Although these agents differ in their mode of action, pharmacokinetics, and immunogenicity, it is not clear whether clinical outcomes of effectiveness and safety also differ.

a. Rheumatoid arthritis

After the first formal randomized phase II double-blind trial with a TNFi (infliximab) in patients having RA in 1994 [232], numerous RCTs of TNFis in RA followed. At first, RCTs referred to a population with a long-standing severe joint disease while years later, early diagnosis of RA, the more effective use of treatments and the treat-to-target strategy allowed trials to be carried out in early stages of the disease when patients had less functional disability [233]. Evidence suggests that treating RA early is much better than treating it late. This can be observed directly, in RCTs where a TNFi is given at different time-points in the course of the disease and a significantly greater response in the treatment arm of the study with the early introduction of a TNFi is found [234]; and indirectly, by comparing results of trials in patients with very short disease duration showing a much greater response to TNFi than in previous trials that used long-standing disease populations [235].

In all performed RCTs, TNF inhibitors showed enhanced efficacy when combined with MTX in particular and, among other csDMARDs, with leflunomide [236]. Trials based on a population of patients with early RA (<3 years), which in practice most of the times correspond to newly diagnosed patients naïve to DMARDs, demonstrated the superiority of TNFi + MTX combination therapy over monotherapy with either TNFi or MTX [29, 237-239]. The favorable outcomes included disease activity, function, and radiographic changes. However, it should be noted that a substantial proportion of patients in these trials responded well to MTX monotherapy as well [240].

Similar results were obtained in the, more clinically relevant, population of patients who have failed to respond adequately to ≥1 csDMARDs, usually including MTX. The clinical responses after 6 months of therapy with all five available TNFis + MTX vs. placebo + MTX in this population are summarized in **Figure 3.1** [25, 241-245].

However, many patients do not tolerate csDMARDs. Biologic monotherapy in patients who have failed csDMARDs was still proved superior to placebo for etanercept and adalimumab [246, 247],

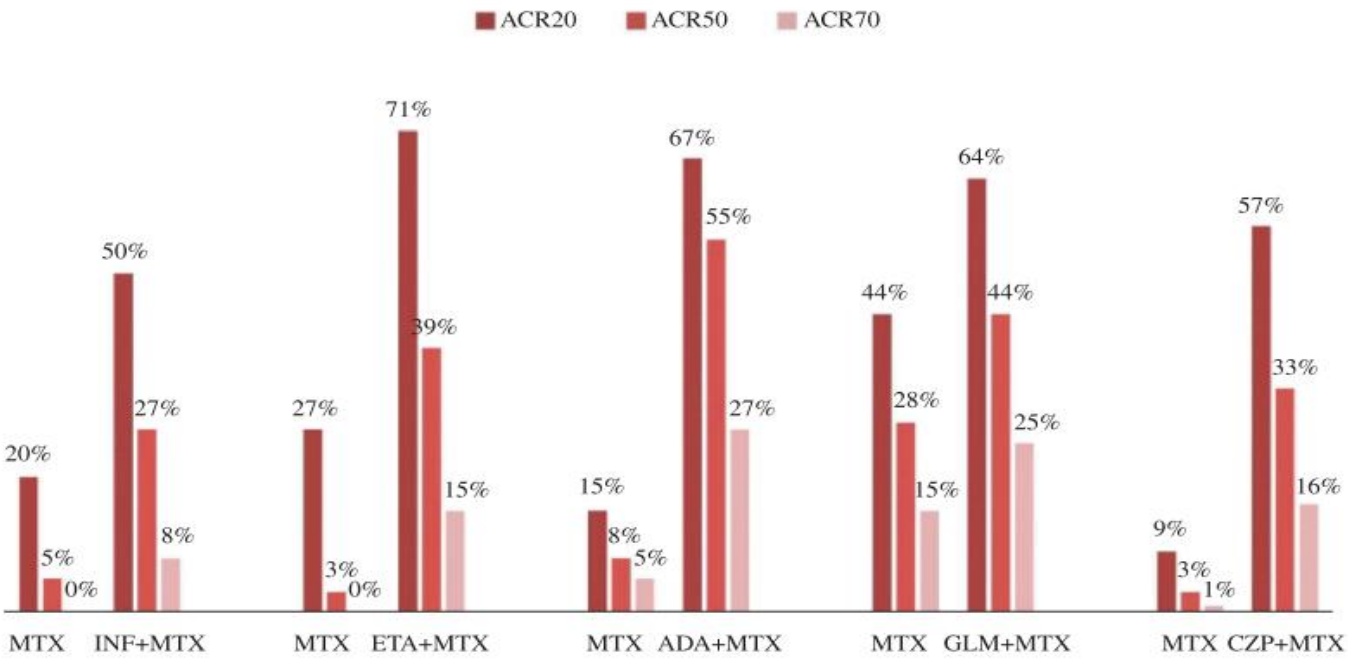

Figure 3.1. Efficacy of the five TNF inhibitors approved for RA after 6 months of therapy, as demonstrated in five large RCTs in RA patients who had previously failed methotrexate (MTX). INF: infliximab; ETA: etanercept; ADA: adalimumab; GLM: golimumab; CZP: certolizumab pegol. Adapted from Chatzidionysiou, K., *Optimizing biological treatments for rheumatoid arthritis.* Scand J Rheumatol, 2016. **45**(sup128): p. 64-75.

but with infliximab, this effect was short-lived and it was shown that low-dose MTX (7.5-15 mg/week) acts synergistically with infliximab, possibly by reducing the development of human anti-chimeric antibodies (HACAs) [248].

A significant number of patients from all different patient groups discontinue TNFi treatment for various reasons, mainly due to inefficacy or intolerance. For those patients who have failed a TNF inhibitor, switching to a second TNFi is justified based on the results of several RCTs which have demonstrated significant efficacy of the second TNFi versus placebo [249-251]. Another approach to the treatment of these patients would be a change to a bDMARD with a different mechanism of action, an approach also proven effective by many RCTs [252-254].

The appearance of anti-drug antibodies against TNFis is another important issue when efficacy of TNFi therapy and treatment persistence is investigated. Currently no evidence has been provided to support routine testing for antidrug antibodies, but MTX has been shown to reduce the incidence of immunogenicity and higher doses in combination with adalimumab have been shown to improve clinical outcomes [255].

b. Spondyloarthritis

Several randomized controlled trials in patients with ankylosing spondylitis have been published after 2000, indicating a good to very good efficacy of TNF inhibitors concerning both clinical symptoms and MRI-detectable inflammation in patients in whom all other therapies had failed. Improvements were observed in RCTs of infliximab [256, 257], etanercept [258-260], adalimumab [261, 262], golimumab [263] and certolizumab pegol [264]. The ASAS40 responses in some of the main trials of TNFi in AS are summarized in **Table 3.1**. These trials (except for the certolizumab pegol study) were performed before the newer ASAS classification criteria of SpA had been developed and therefore included only patients with AS classified according to the modified New York criteria. Only the certolizumab pegol study included a broader population of patients with axial SpA [264].

Table 3.1. ASAS 40 response to TNFi in patients with axial SpA in phase III clinical trials [256, 259, 261, 263-267]

	AS			Non-radiographic axSpA*		
	Measurement time point (week)	Responders in TNFi group % (n/N)	Responders in placebo group % (n/N)	Measurement time point (week)	Responders in TNFi group % (n/N)	Responders in placebo group % (n/N)
ADA	12	40 (83/208)	13 (14/107)	12	41 (28/69)	14 (10/73)
CERT	12	40 (26/65)	19 (11/57)	12	48 (22/46)	16 (8/50)
ETA	12	45 (58/128)	16 (21/129)	12	35 (33/94)	17 (16/93)
GLM	14	45 (62/138)	15 (12/78)	16	60 (47/78)	23 (18/80)
INF	24	47 (93/201)	12 (9/78)	-	-	-

*The target population of these trials were non-radiographic axSpA patients fulfilling the criteria required for treating these patients with TNFi in EU; i.e. elevated CRP and/or active sacroiliitis seen by MRI. AS: ankylosing spondylitis; ASAS: Assesssment of Spondyloarthritis International Society; ASAS40:ASAS 40% response criteria; ADA: Adalimumab, CERT: Certolizumab pegol; ETA: Etanercept; GLM: Golimumab; INF: Infliximab

Adapted from Sieper, J. and D. Poddubnyy, *New evidence on the management of spondyloarthritis.* Nat Rev Rheumatol, 2016. **12**(5): p. 282-95.

More recent studies focus on the efficacy of TNF inhibitors in patients with non-radiographic axSpA [264-267] (**Table 3.1**). Patients in these trials could fulfill either the imaging (but radiographically negative), or the clinical arm of the ASAS criteria to be classified as nr-AxSpA for inclusion. In the adalimumab trial [267], patients only had to have a BASDAI ≥4 for inclusion; additional parameters such as CRP positivity or evidence of inflammation on MRI were not necessary. After 12 weeks, 36.3% of patients in the adalimumab arm, but only 14.9% in the placebo arm, reached the primary outcome, an ASAS40 response. Subgroup analyses revealed that CRP-positive patients responded better to adalimumab therapy than CRP-negative patients. In the subgroup of patients who had objective markers of inflammation (CRP positivity or bone marrow edema detectable by MRI) at inclusion, 41% of patients treated with adalimumab reached an ASAS40 response, compared with 14% in the placebo group. No difference in the primary outcome was observed between the adalimumab and placebo arms in patients who did not have objective signs of inflammation at baseline (23% and 20% respectively).

Similar results were obtained in the golimumab trial [263], while in the study of certolizumab pegol all patients were either CRP-positive or with MRI-detectable inflammation at inclusion, so no CRP-negative or MRI-negative subgroup is available for comparison [264]. Of note, a similar proportion of patients with AS and nr-axSpA in the latter study (40% and 48% respectively) reached an ASAS40 response. In the etanercept trial, an ASAS40 response was reached in 33.3% of the actively treated patients and 14.8% of the patients who received placebo [265]. No statistically significant differences in outcomes were observed between the subgroup of patients who were CRP- or MRI-positive and those who were both CRP- and MRI-negative. However, higher CRP level was a predictor of reaching an ASAS response in multivariable analyses.

These results led to the approval in the EU of these four TNF inhibitors for the treatment of patients with nr-axSpA, but only in those who have abnormal CRP and/or evidence of inflammation seen by MRI. The response rates in these patients are at least as good as those in patients with AS, with the exception of the responses in etanercept, which are better in the AS trials (**Table 3.1**), a result probably attributed to different trial designs [200]. The indications for treatment in patients with AS (which almost identify with radiographic axial SpA) do not require CRP positivity or evidence of inflammation on MRI. However, an elevated CRP and a positive spine MRI test result have been found to predict a good clinical response to TNF inhibitors in AS as well [268, 269].

Long-term data on the treatment of radiographic and nr-axSpA with TNFis were published after 2010, indicating that improvements in disease activity were maintained after more than two years of follow-up [270, 271]. Additionally, good results have been found for improvements in physical function as measured by BASFI and in health-related quality of life outcomes and for reduction in MRI-detected spine inflammation [270, 272, 273].

Regarding radiographic progression in the sacroiliac joints and spine of patients with axSpA, any effects of drug therapy on the prevention of structural changes are difficult to prove as the disease progresses very slowly and it can only be assessed in long-term follow-up studies [274]. Indeed, while earlier RCTs of AS patients treated with TNFis for up to 4 years did not show retardation of new bone formation when compared to a historical control group not treated with TNFis [275-277], a recent study suggested that these therapies might decelerate or even halt structural progression after long-term (>4 years) use [278].

Unfortunately, trials of TNFis for peripheral SpA as a group are scarce, with the exception of RCTs involving specifically patients with PsA. However, even in PsA nearly all trials have been focused on patients with polyarthritis primarily affecting the hands, a pattern of joint involvement not typical of peripheral SpA. Therefore, an unmet need exists for interventional and non-interventional studies involving patients with different forms of peripheral SpA grouped together [200]. Two RCTs of adalimumab in patients with non-psoriatic peripheral SpA (one in 40 and the other in 165 patients) have been performed [220, 279]; these indicate that treatment with adalimumab leads to statistically significant improvement in patients' and physicians' global assessment of disease activity and/or in SJC, TJC, dactylitis and enthesitis count compared with baseline values and compared with placebo.

The efficacy of TNFis in PsA has been evaluated in several clinical trials enrolling patients with active PsA despite the use of previous csDMARDs and/or NSAIDs [280-284]. Significant

improvements were observed in musculoskeletal symptoms (ACR 20, ACR50, ACR70, **Table 3.2** [285]), but also in other major endpoints including reduction of psoriasis PASI score by 75% (PASI75, **Table 3.2**), HAQ, enthesitis and dactylitis indices and health-related quality of life. TNFis were also shown to retard radiographic joint damage in PsA patients [286, 287]. Of note, all RCTs found no or minor numerical differences in efficacy for peripheral arthritis between patients treated with or without methotrexate. However, these studies were not sufficiently powered to answer this question and no statistical tests were conducted [229]. A recent randomized trial designed to compare etanercept monotherapy vs. combination with concomitant MTX indicated similar benefits of the two strategies in various PsA outcomes [288], but more data are warranted, especially concerning differences in immunogenicity of TNFis and drug survival of the two treatment strategies.

Table 3.2. Percentage of responders to TNFi therapy at 24 weeks* in patients with PsA in phase III clinical trials [280-284]

	PASI75		**ACR20**		**ACR50**		**ACR70**	
	TNFi	Placebo	TNFi	Placebo	TNFi	Placebo	TNFi	Placebo
Infliximab	60	1	54	16	41	4	27	2
Etanercept*	23	3	59	15	-	-	-	-
Adalimumab	59	1	57	15	39	6	23	1
Golimumab	56	1	52	12	-	-	-	-
Certolizumab pegol	62	15	64	24	44	13	28	4

*Except for etanercept, in which results given were at 12 weeks of therapy. Adapted from D'Angelo, S., et al., *Review of the treatment of psoriatic arthritis with biological agents: choice of drug for initial therapy and switch therapy for non-responders.* Open Access Rheumatol, 2017. **9**: p. 21-28.

c. Comparative effectiveness and safety of TNFis

Information about the comparative effectiveness and safety of TNFis, and generally bDMARDs, can guide treatment decisions in clinical practice. However, well-designed head-to head randomized controlled trials of the different bDMARD therapies are scarce in RA [289-292] and absent in SpA. Indeed, although numerous RCTs have been conducted for all five different TNFis after their approval, these are placebo-controlled RCTs which focus on searching for new indications or for better use in the approved indications, while the demand for more comparative trials which could be of greater clinical relevance, still remains unanswered [293].

The only currently published head-to-head RCT between two TNF inhibitors [290], compared the efficacy and safety of certolizumab pegol to that of adalimumab, both in combination with methotrexate, in 915 patients with RA over 104 weeks; 457 patients were assigned to certolizumab pegol plus MTX and 458 to adalimumab plus MTX. Patients had active disease despite previous use of MTX, and had risk factors for severe disease. The study had two primary endpoints: ACR20 response and DAS28 low disease activity and it was designed to examine superiority of certolizumab over adalimumab. No difference was noted between the two TNFis for both the primary endpoints, while also the secondary endpoints and safety were overall similar. Patients without improvement at 12 weeks were switched from certolizumab to adalimumab or vice versa. The effectiveness of these

switches was also similar between the two treatments. This negative trial provided important information for clinicians and regulatory authorities and more head-to-head RCTs of bDMARDs are needed to deepen our knowledge regarding choice of bDMARD and switching treatments in patients with insufficient improvement.

Until such studies are widely available, data from meta-analyses of RCTs have been used for indirect comparison of TNF inhibitors. However, for a standard meta-analysis comparing two different interventions, the major assumption is that results from different trials are sufficiently homogeneous to allow pooling of the data. This assumption is often not met because of the significant differences encountered in studies' design and conduct [294]. More complex methods such as network meta-analysis are used to conduct adjusted indirect comparisons of multiple interventions [295]. With this method, also biased results can arise if details which can modify treatment efficacy such as patient characteristics, trial settings and trial outcomes are not (or cannot be) taken into account [296]. For example, exclusion criteria frequently differ between clinical trials; assessed endpoints may also differ; or certain comorbidities may be more prevalent in particular regions [297].

Due to these methodological problems many published network meta-analyses for targeted therapies in RA have come to different conclusions regarding their relative efficacy and safety: a systematic review of RCTs and prospective cohort studies demonstrated comparable efficacy of the three TNFis adalimumab, etanercept, and infliximab in rheumatoid arthritis [298]. A network meta-analysis of TNFis for RA patients demonstrated differences in response to TNFis: etanercept appeared superior to infliximab regarding efficacy and function and adalimumab appeared superior to infliximab regarding function [299]. Another network meta-analysis based on RCTs of biologics in RA concluded that there were no significant differences in efficacy measures between TNF inhibitor agents though etanercept was probably safer than adalimumab and infliximab [300]. A more recent similar analysis showed that although the odds for serious infections were comparable between the three TNF inhibitors, withdrawals due to adverse events were more likely with infliximab [301].

Consequently, until these agents are directly compared in well-designed trials, there is probably no reliable way to compare the clinical, radiographic, or functional efficacy of biologic agents from RCT data [302]. The only reasonable conclusion could be that all of them are effective in reducing signs and symptoms and improving patient function in patients with inflammatory arthritides treated in these RCTs compared to placebo.

2. Limitations of RCTs and the role of observational studies

The value and importance of RCTs to determine the efficacy of a therapy is indisputable. RCTs mimic a laboratory "scientific experiment" by testing an intervention or a drug, versus placebo or a control drug, with the use of randomization to adjust for confounding which may affect the results. However, RCTs are most effective in acute diseases, and many limitations are seen when applied in chronic diseases, such as the inflammatory arthritides [303-305].

The most widely recognized limitation of RCTs is their limited generalizability. Strict exclusion criteria are applied in the recruitment of inflammatory arthritis patients for a clinical trial, many of which affect outcomes, such as higher age, lower disease activity and higher severity, comorbidities, previous and concomitant interventions and others. Inclusion and exclusion criteria enhance the comparability of various groups in clinical trials, in the expense of significantly affected generalizability (so-called external validity) of their results. Indeed, the vast majority of "real-world" rheumatology patients, which ultimately use biologic agent treatments, do not satisfy criteria for participation in the respective RCTs that led to the approval of these drugs. For example, in the German biologics register, only 21-33% of the RA patients who were treated with infliximab, adalimumab, or etanercept, would have been eligible for the major clinical trials of these TNFis, and ACR response rates were lower in those patients considered ineligible for the trials [306]. In a more recent study, the eligibility criteria of 30 RCTs for biologic agents to treat RA patients were reviewed and applied to two observational clinical cohorts: the Veterans Affairs Rheumatoid Arthritis (VARA) and the Rheumatology and Arthritis Investigational Network Database (RAIN-DB) [307]. The authors concluded that only 3.7% of patients in VARA and 7.1% in RAIN-DB would have been eligible for participation in biologic agents RTCs. Similar results have been published in several studies contrasting eligibility criteria for RCTs of biologic agents to patients recruited in observational cohorts of clinical practice [308-310].

In fact, clinical trial results do not even reflect those of patients who fulfill the inclusion and exclusion criteria for the particular trial (and would have been willing to participate in the trial), but they can be generalized only to patients who have similar baseline characteristics to those enrolled in the trial. For example, even if men and women were eligible to enter a trial, its results can only be generalized to women if no men were recruited [311]. In a recent review of RCTs and observational studies of bDMARDs in RA, patients enrolled in observational studies were found to be on average 3 years older, have 3.1 years longer disease duration, 1.6 more prior DMARDs, lower DAS28 by 0.6 units, lower CRP and ESR and higher HAQ index than those enrolled in RCTs [305].

The internal validity of RCTs is considered to be high, owing to the randomization and blinding processes. However, it is threatened in many cases where the patients are not properly randomized (e.g. quasi-random methods), or are not analyzed by an intention-to-treat analysis, which ensures that randomization is maintained [312]. The study design of an RCT and the outcomes selected may also greatly influence the results, despite inclusion of a control group (design bias) [303]. The primary and the secondary outcomes of the trial should be defined *a priori*. In 2004, Chan et al. found that more than 60% of trials had at least one primary outcome that was changed, introduced, or omitted between the protocol was approved by a scientific ethics committee and the publication of the results [313]. This situation is now improved with clinical trials registries (e.g. www.clinicaltrials.gov and www.controlled-trials.com), in which protocols of clinical trials, with pre-planned primary outcomes, are made publicly available to enable the identification of outcome-reporting bias. Finally, the conflicts of interest may threaten the validity of the study: the results of an industry-supported study, as most RCTs are, could be less objective than those of an academic-supported study [312].

Outcomes of RCTs have to be clinically relevant, with good reliability and reproducibility. Statistical significant results of RCTs are not necessarily clinically significant. Indeed, clinically meaningless differences can be statistically significant if the sample size is sufficiently large.

Conversely, clinically important differences can be statistically insignificant if the sample size is too small (i.e. if the study lacks power) [312].

Another important limitation of RCTs in chronic diseases such as the inflammatory arthritides is their relative short observation period. The length of follow-up of a drug trial has to be consistent with disease evolution. Thus, follow-up times of 6 or 12 months are not meaningful for a chronic disease such as RA or SpA in respect of both efficacy and safety outcomes. To assess long-term efficacy in inflammatory arthritides, "surrogate" outcomes are frequently used, usually disease activity measures, or laboratory and imaging markers of inflammation. They are easier to measure, require a much smaller sample size and shorter follow-up than a long-term clinical outcome such as damage and they are believed to be indirect measures of the clinically relevant outcome. However, even though surrogate outcomes may broadly correlate with the severe long-term consequences of arthritis, this correlation is often suboptimal and markers of response may be misleading.

Reporting of harms from RCTs has received much less attention than reporting of efficacy, and is often inadequate, despite the fact that safety information is actually more important to clinicians, according to the *primum non nocere* principle. The high costs of RCTs often impose short trial durations and sample sizes too small to study any but the most common short-term adverse events. In addition, clinical trials often have strict inclusion criteria that prevent many patients with comorbidities to be enrolled. The reactivation of latent tuberculosis in patients receiving TNFis, which was not detected in the first RCTs of these drugs, is a well known example of the underestimation of risk of adverse events in RCTs [6].

The role of observational studies

Even though RCTs represent the gold-standard of medical evidence to assess the bDMARDs efficacy (how a drug works in ideal circumstances), they may not reflect real-world effectiveness or safety. Treatment effectiveness (how a drug works in the routine clinical setting) and long term safety can be better judged in large prospective observational studies, which have the potential to complement findings from RCTs [314]. These studies include a large number of patients assessed in routine clinical practice, who receive multi-drug treatments with potential interactions, and may have multiple conditions influencing the outcome [304]. Apart from effectiveness and treatment safety, the observational setting enables the study of additional clinically relevant issues which are not (or cannot be) studied in RCTs, such as the direct comparison of drugs under real-world circumstances and the long-term adherence to treatment in chronic diseases such as the inflammatory arthritides. Moreover, observational studies can provide information on how clinical practice evolves over time and about the patterns and effectiveness of switching between different therapies. Outcomes such as functional disability, work disability and mortality also require long-term observational studies [315]. **Table 3.3** describes the main limitations of RCTs in inflammatory arthritides and the respective advantages of observational studies which can be used to complement results from RCTs.

Variations in disease severity and response to therapies across different ethnic backgrounds and clinical settings can also not be automatically drawn from the results of RCTs. Well-designed observational studies of various populations, and especially national multi-centered prospective

observational registries have played an important role in defining the role of new therapies in the unique genetic, environmental and medical backgrounds of different countries [316].

Table 3.3. Main limitations of randomized controlled studies and the respective advantages of observational studies which can be used to overcome these RCT drawbacks

Limitations of RCTs	Observational studies (including national registries) advantages
Ideal conditions created for drugs to be tested: low generalizability	Better generalizability as they represent real-world patients
Expensive: time and money	Less costly
Short follow-up time	Long follow-up time
Small sample sizes	Large sample sizes
Clinical relevance of outcomes may be low	Can answer many types of research questions relevant to clinicians
Inflexible dosage schedules	Variation of dosage schedules
Volunteer bias	Ideally all cases included
Cannot detect late-onset or rare adverse effects	Best to detect rare/late-onset adverse effects
Evaluate effects of already known risk factors for an outcome	Can explore new associations of risk factors on an outcome (diverse population)

3. Registries of biologics in RA and SpA

Registries are longitudinal prospective observational cohorts, which have a structured protocol and enroll patients with a specific purpose; it could be either drug- or disease-based, or both. With the advent of TNFis for RA and SpA, several biologics registries for rheumatic diseases have been established in numerous countries in Europe (**Figure 3.2**) and worldwide with the primary goal of studying treatment outcomes following the use of bDMARDs in regional cohorts [317-324]. Biologic registries capture detailed data on the exposure of patients to bDMARDs, such as details of underlying diagnoses, initiation and termination of rheumatologic therapies, as well as treatment outcomes. These outcomes usually include disease activity parameters, patient reported outcomes, such as HAQ and quality of life questionnaires or the occurrence of adverse events, and newly diagnosed comorbidities [325].

Each registry is different in design: some were developed *de novo* to recruit a certain number of patients at the point of starting their first bDMARD with a comparator group receiving csDMARDs, like the British Society for Rheumatology Biologics Register (BSRBR)[318] and the German Rheumatoid Arthritis oBservation of Biologic Therapy (RABBIT) [321]. In others, like the Antirheumatic Therapies in Sweden (ARTIS) registry [323], the Danish National Registry for Biologic Therapy (DANBIO)[319] and the Swiss Clinical Quality Management (SCQM) registry [322], captured biologics data is embedded in a larger national patient registry that aims to gather outcome data on all patients regardless of whether they receive bDMARDs or not [325]. Some registries enroll RA patients only, for example RABBIT, but most have gradually included patients

with spondyloarthritis as well after 2006-2007. The largest European registries have a nationwide coverage, and although in most of the cases it is not mandatory for individual rheumatologists to enter patients, they cover a high percentage of eligible patients.

Other registries include only specific centers in the country, like the Norwegian Disease-Modifying Anti-Rheumatic Drug registry (NOR-DMARD) [326], which includes all patients with inflammatory arthritides who receive any DMARD at five centers in Norway, covering approximately one-third of the population [325].

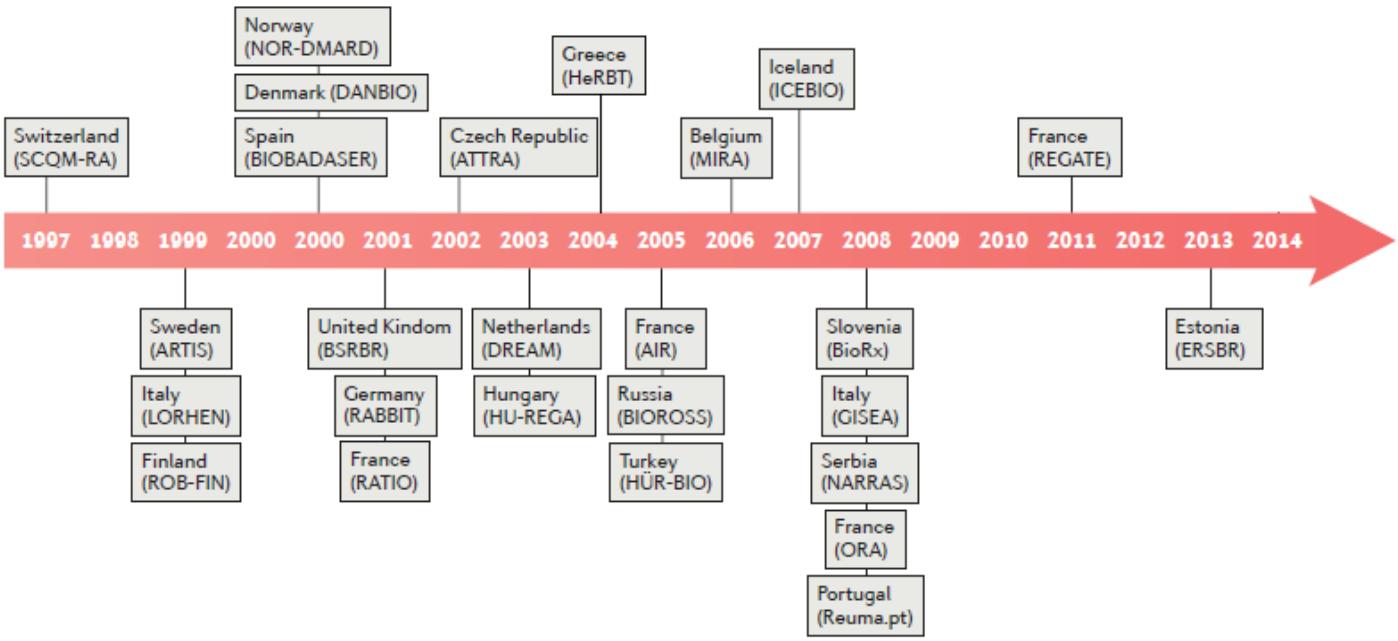

Figure 3.2. Timeline showing the establishment of different biologics registries in Europe. Modified from Nikiphorou, E., M.H. Buch, and K.L. Hyrich, *Biologics registers in RA: methodological aspects, current role and future applications.* Nat Rev Rheumatol, 2017. **13**(8): p. 503-510.

European registries also differ in other aspects, such as their size, and their control groups, which may be either newly established comparator cohorts (RABBIT, BSRBR) or national population registers (ARTIS) and historic control groups (Base de Datos de Productos Biologicos de a Sociedad Espanola de Reumatologia –BIOBADASER registry [327]) as comparisons. Differences are also noted in the frequency, duration and methods of follow-up (paper versus electronic forms) applied [328]. More importantly, a recent survey on the collected data items among 27 European registries and cohort studies revealed large heterogeneity in data items collected as well as the data definition in each registry [329].

Despite of these differences, European registries also share a number of common features. Most notably, all registries were initiated by or in collaboration with the national rheumatology societies, and the initiative was based on the perceived need to study these novel therapies independently from industry. The registries are supported by joint grants from all pharmaceutical companies whose products are under observation. They are not drug-specific, but instead they include all licensed bDMARDs and follow-up patients irrespective of whether they remain on the initial drug, or not. This feature enables them to compare different treatments and identify long-term effects or adverse events [17].

A wealth of important data to guide everyday clinical decisions has been collected to date from biologics registries of RA and SpA patients, the majority of which has focused on TNF inhibitors. In addition to data describing the baseline characteristics of patients who receive TNFis in everyday clinical practice over time [306, 308, 330], registries have also provided data for describing and comparing TNFi treatment responses [331-334], differential treatment adherence [227, 335, 336], switching to a second TNFi [11, 337, 338] and response and adherence to the second TNFi [13, 339, 340]. Comparative analysis of different TNFis in most European registries of RA patients indicates differential drug response rates in favor of etanercept and adalimumab as compared to infliximab [331, 332]. In contrast, the Portuguese and the US CORRONA registries reported comparable effectiveness of adalimumab, etanercept and infliximab [341, 342]. In the latter study, infliximab was associated with higher adherence rates. However, data from SCQM [336], DANBIO [331], the Italian Lombardy Rheumatology Network (LOHREN) registry [343] and ARTIS [335] indicated that infliximab had the lowest and etanercept the highest drug adherence rates.

Moreover, registries have also identified factors associated with a good response to TNFi treatment [344-346], or longer persistence to therapy [343, 347]. In RA, factors identified as being associated with good response to treatment include young age, short disease duration, good functional status at the start of therapy, lower disease activity and use of methotrexate co-therapy.

Regarding SpA, most of the studies from biologics registries have focused on individual clinical subtypes within the spectrum of SpA, mainly ankylosing spondylitis and psoriatic arthritis [346, 348]. Only a limited number of studies, mainly in the early years of TNFi use and with a short-tem follow-up, analyzed SpA patients as a whole group and compared data between sub-diagnoses [349-351]. In view of the recent advances in the classification of SpA, the comparative analysis of TNFis in the whole group of patients with SpA and separately for patients with axial or peripheral disease would be of clinical interest, given the many common clinical manifestations and the similar treatment approaches to these diseases.

The very large sample sizes and long follow-up periods of biologics registries have enabled an analysis of safety of TNFis that goes beyond that available from clinical trials. In RA, most registries have confirmed a small but statistically significant increase in the risk of serious infections occurring early in the course of TNFi therapy, which seems to decrease over time [35, 325, 352]. Further exploration of the data held within the German RABBIT registry suggests that this observation is attributable both to a reduction in the number of patients at high risk of infection in the cohort, and to improvements in disease activity and reductions in steroid use among those patients who respond to therapy, thus reducing the overall infection risk [15]. Treatment with etanercept was associated with lower risk for serious infections compared to adalimumab and infliximab in the DREAM registry

[353], while drug discontinuations due to adverse events were significantly lower for etanercept than for infliximab in the RADIUS registry [354]. A number of registries have also provided data on the observed risk of cancer in patients receiving biologics compared with patients receiving conventional synthetic DMARDs, and have not confirmed an increased risk or solid organ cancer or lymphoma [355-357].

Registries have also enabled the study of the potential benefits of treatment with respect to safety outcomes, for example the association between use of TNFis and a reduced risk of cardiovascular events in patients with RA [358]. Furthermore, biologics registries have reported on safety in patients with a history of cancer [359] and the elderly [34], and have revealed information about the risk of exposure to TNFis and other biologics during pregnancy [360].

Of note, data on the comparative efficacy and safety of different TNF inhibitors in Greece are lacking, while scarce data exist for southern European patients in general [341, 361, 362]. This is important in view of the variations in disease severity across different ethnic backgrounds and clinical settings [363, 364]. It has been shown that registry data have to be always interpreted in light of the eligibility criteria for biologic treatment, the different healthcare systems and the different background endemic diseases (such as tuberculosis) and the comorbid conditions of the population [325].

Collaborations between biologics registries exploring drug effectiveness and safety have been tried to increase power of the studies and provide information on a diverse population of patients [365-369]. Such collaborations were feasible, but significant differences in coverage, prescription patterns, eligibility criteria for registry entry and patient characteristics across countries were found, a heterogeneity which led to difficulties in analyzing and interpreting the data.

4. Limitations of registry-based studies and ways to address them

Observational studies are relatively easy to conduct compared to RCTs. However, analyzing them is trickier, because numerous pitfalls related to epidemiological bias and confounding may appear to jeopardize the interpretation of the study results. To some extent these pitfalls can be accounted for with current analytical techniques, or at least they can made visible so that research is transparent and limitations understandable to the reader. Some of the main limitations of registry-based data for research and some of the possible ways to address them are described in **Table 3.4.**

As patients in registries are not randomized to a treatment group, the outcomes can be strongly affected by confounding by indication, or selection bias, which may exaggerate or reduce the magnitude of a particular association [370]. Confounding by indication in bDMARD registries implies in brief that patients with the most severe disease are preferentially treated with bDMARDs; or, within the registry, e.g. patients with less comorbidities receive treatments associated with more adverse events. Specific statistical methods such as covariate adjustments, covariate matching, and propensity scoring, can be used to minimize the effect of any confounding factors and reduce bias [371]. However, strong confounding cannot be corrected for by statistical techniques [372] and each

of those statistical techniques has its own specific limitations and should be used appropriately. Covariate adjustment can lead to overfitting, matching requires very large registries to achieve groups with sufficient patient numbers and propensity scoring can only be used if the patient could actually receive either treatment being compared, as it assumes that there is an equal probability of the patient receiving each treatment [373]. Furthermore, these methods do not include unobserved covariates, so residual confounding may still take place.

Table 3.4. Main limitations of registry-based studies and possible ways to address them

Limitations	Ways to address these limitations
1. Confounding: selection, channeling, lack of variables, residual	-Statistical methods (propensity scoring, covariate adjustment, etc). -Careful planning of registry: collect all variables necessary
2. Pre-collected data: necessary variables may be unavailable	-Careful planning of registry: collect all variables necessary -Data linkage to external sources
3. Generalizability is not universal	-Transparent and complete reporting of participants and methods -Data harmonization and collaborations
4. Low or unknown data quality: -Variations in data coding between persons and institutions -Weak case definitions at enrollment -Weak case ascertainment and follow up of adverse event	-Centralized data entry -Detailed instructions on data entry, training, audits -Simple protocol with restricted amount of information gathered (core data set) -Robust case definitions, ascertainment of adverse events
5. Data dredging and misleading post-hoc analyses	Logical analysis
6. Large datasets: statistically significant results might not be clinically relevant	Logical interpretation of results
7. Missing values	-Avoid as much as possible: meticulous data collection, web-based system - Multiple imputation, mixed linear models
8. Difficult to maintain: Needs high levels of administrative support, long-term funding, highly motivated physicians	-Mandatory registry (part of patient medical record or legally regulated to monitor quality of treatment) -Less workload when external linkage of data -Web-based to minimize manpower needed -Patient involvement: dedicated touch screens in waiting room -Incentives for physicians: site reimbursement, real-time feedback at patient visit, frequent reports from registry, encourage participation in research, etc
9. Time delays until valid results can be produced	-Avoid missingness -Collaboration of registries to combine data

For unobserved variables to be characterized as residual confounding, they need to meet both of the two criteria of confounding, namely (1) association with the outcome and (2) no association with the observed variables used for statistical adjustment. Ideally, to minimize unobserved confounding by indication, it is important for the treating physician to record why the patient is being given the therapy selected. This information would be a powerful adjustment covariate, but it needs much consideration on how to collect it [315].

Another source of bias in registries, in which data are always pre-collected and researchers have a specific set of variables available, is the confounding due to lack of data of important confounders, or only crude information on confounders [374]. Some of those variables, for example comorbidities, socio-economic factors, genome variants, or laboratory results could be derived from external sources by linking patient data to national databases or bio-repositories, or by having access to laboratory data. This is possible for example in the Nordic countries, where external linkage also enables further validation of events reported in the registry and ensures a more complete dataset. However, in all cases, careful pre-planning should take place at the registry initiation to include all possible data items pertaining to the treatment, treated disease and treatment outcomes for a sufficiently long follow-up time, as these variables cannot be captured independently if they are unavailable [325].

An additional limitation is that generalizability, although better than that of RCTs, is not universal and many of the registries' characteristics may influence the study outcomes. The country, the health care system, recruitment from primary, secondary, or tertiary care; selection of participating centers and clinicians; selection of patients (eligibility criteria, for example using classification criteria); severity or stage in the natural history of the disease; co-morbidities; the racial group and other baseline clinical characteristics; the year of enrollment and the ongoing co-treatments can all modify the effectiveness and safety of the treatments. Specifically in respect to adverse events, the frequency of follow-up, the adequacy of the length of follow-up, the rate of discontinuation of therapy and the rate of loss to follow-up can also greatly influence the completeness of their reporting. Therefore, registry methods and settings should be reported so that clinicians can judge to whom the results can reasonably be applied.

If data are not centrally submitted (e.g. in paper forms) to be entered into the database at a coordinating center, it is often hard to know exactly how data was generated because of the variation in data coding between persons and institutions [374]. Wrong information, missing values and erroneous and invalid results would result if data entered is loosely defined. Data coding should be detailed and explicitly described (e.g. in a registry booklet) and only trained personnel (preferably nurses or doctors) should enter data to ensure high quality and consistency. Frequent meetings of people involved in data entry and supervisors to discuss potential issues and audits are useful to maintain high dataset quality.

A robust case definition has not been used uniformly across biologics registries. Case definitions are important at the time of inclusion in both clinical trials and cohort studies as they can be used to compare outcomes between different studies. Classification criteria issued by EULAR and ACR serve this purpose. Similarly, robust outcome measures, valid and reproducible measures of treatment

response and a robust system of case ascertainment and follow-up in case of adverse events are necessary not only in RCTs, but also in patient registries [311, 375].

The improvements in computer power in the past few decades has enabled observational studies to be conducted with very large databases and huge quantities of health-related data from a large number of individuals in a systemic fashion and at an affordable cost. Advanced statistical methodologies can address multiple hypotheses simultaneously and focus on one specific risk factor by adjusting for confounders. These developments have brought another challenge to the researcher: the need for robust and logical study design since databases and statistical methods cannot determine whether the question being addressed is plausible. Moreover, analyses based on such large datasets present the possibility for increased "false positive" studies, and in many cases weak associations might have statistical significance but lack clinical relevance [311].

Missing data are unavoidable in clinical research, especially in observational studies, and their potential to undermine the validity of research results is an important issue. Researchers usually address missing data by including in the analysis only complete cases – those individuals who have no missing data in any of the variables required for that analysis. However, results produced in these analyses can be biased. Moreover, the cumulative effect of missing data in several variables leads to exclusion of a substantial proportion of the original sample, which in turn causes a substantial loss of precision and power [376].

Addressing the problem of missing data requires an understanding of whether data are missing at random or if data for specific time points or types of individuals are systematically absent. If the data are missing at random –an assumption which must be tested – missing data can be imputed. An example of single imputation is the "last observation carried forward" (LOCF) method, often used in the analysis of clinical trials. In LOCF approach, the missing values are imputed by the last observed value for that specific variable, but this could give significantly biased results as it may underestimate the treatment effects in an effective intervention and exaggerate the effect in interventions aiming to preserve present status. Thus this method has been frequently criticized recently [377]. Other approaches to singly impute missing data include replacing the missing value with the mean of values for that variable in the remainder of the dataset; or using a regression model to estimate the missing value based on the variables available for that individual and the entire dataset.

A general problem with single imputation is that the dataset tends to become more homogeneous and the uncertainty around the missing data is artificially removed, so the resulting analysis is more likely to be statistically significant than if the dataset had included no missing values. This problem can be solved by applying multiple imputation, a method which reintroduces the full uncertainty associated with missing data [376]. When multiple imputations are carried out, the researchers should also conduct sensitivity analyses to establish whether the conclusions are sensitive to assumptions about the pattern of "missingness" [378]. The process of data imputation often involves complex modeling and it is important for the authors who use these methods to explain clearly both the rationale for the choice of a model, the details of the process and the variables used in the models either in the manuscript or in an online supplement so that the reviewers and the readers can understand the steps and the assumptions made [378].

The issues of incomplete or missing data and missing patients (lost to follow-up) pertain also to the problem of delays between entry of a biologic drug into the market and the accumulation of sufficient outcome data for valid analyses. Therefore, encouragement of physicians and data collectors to reduce missing data is crucial. Delays in reporting potentially unrecognized adverse events relate to the power of individual registries, that is, their sample size. However, even the largest national registries might not be sufficiently powered to measure the risk of very rare adverse events and combined registry data are required [325].

Developing and running a biologics registry is difficult; it needs thorough planning, long-term funding, a robust and high quality software for data input, high levels of administrative support, and, especially, highly motivated physicians who will contribute accurate and complete data in the setting of a busy clinical reality. These challenges are often the biggest obstacle in gathering good quality from registries and some ideas on how to address them are in **Table 3.4**.

In response to the many issues that emerge when rheumatologists establish a new registry, or analyze and report from existing registries, EULAR has published a series of points to consider when establishing, analyzing and reporting from a biologics registry [16]. Another set of EULAR recommendations were recently published regarding the core data items that should be collected in observational research [379] to limit heterogeneities and registries' isolation and improve collaborative work. A separate EULAR publication dealt with points to consider when reporting comorbidities in chronic inflammatory rheumatic diseases in clinical practice [380]. Finally, ASAS has also issued recommendations for variables to be collected in clinical trials and epidemiological studies of patients with spondyloarthritis [18]. And, as a rule, to enhance the studies' quality and reliability, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [381] should be always followed by researchers reporting from biologics registries.

SPECIFIC PART

CHAPTER IV. RESEARCH QUESTIONS AND AIMS OF THIS THESIS

Research in inflammatory arthritides has come a long way in the last 20 years, yet several unmet needs still exist. Some of these, specifically in regard to the treatment of these diseases with biologic agents were addressed in the present study:

1. The comparison of the effectiveness and safety between TNFis that can guide clinical decision-making is an important unmet need. Since there is a paucity of data from RCTs, observational data can be used for the comparison of outcomes such as response rates and disease remission on treatment; treatment adherence and reasons of discontinuation; and serious adverse events occurrence.

2. Real-world patient adherence to the bDMARD treatment (so-called drug survival) is regarded as a global measure of treatment efficacy and safety, while also reflecting patient and physician expectations, comorbidities considerations and medication compliance. Unlike RCTs, registry data can give valuable information concerning drug survival in everyday practice to evaluate treatment strategies and guide further research.

3. Since patients receiving TNFis have variable outcomes, it would be very important to define baseline factors predicting a good response to TNFi therapy; longer drug survival; and less adverse events on treatment. Identification of such predictors would be a step towards the much-needed personalized medicine, both for preventing unnecessary harms and for better resource allocation.

4. Active surveillance for adverse events when patients are treated with biologic agents is very important. Registries can provide more information regarding adverse events than RTCs due to their large sample size and long-term follow up.

5. In SpA, interventional and non-interventional studies of patients receiving TNFis have focused on the two major clinical subtypes, AS and PsA. Drug-based registries which include patients with different diseases followed with a common protocol can be utilized to analyze SpA patients as a whole group and compare data between sub-diagnoses.

6. Greek nationwide data regarding effectiveness and safety of TNF inhibitors in RA and SpA patients are lacking. This is important in view of the variations in disease severity of inflammatory arthritides across different ethnic backgrounds, and variations in response and safety of TNFis due to the different healthcare systems, clinical practices and comorbid conditions of the population.

Based on these unmet needs, the **specific aims** of the present thesis were to:

1. Describe the demographics, disease-related and drug-related characteristics of patients initiating TNF inhibitor therapies for inflammatory arthritides in Greece
2. Define and compare the response to therapy between different TNF inhibitors in inflammatory arthritis patients of everyday clinical practice
3. Evaluate the adherence to TNF inhibitor treatment and determine the reasons for therapy discontinuations.
4. Identify factors that can possibly predict response, adherence to therapy and adverse events among baseline demographics, disease characteristics, drug parameters and early response to therapy
5. Explore the long-term safety of these drugs in unselected "real world" patients

To address these research questions in both rheumatoid arthritis and spondyloarthritis patients, **the study consisted of two main "sub-studies" as follows:**

A. The effectiveness, survival and safety profile of three TNF inhibitors, namely infliximab, adalimumab, and etanercept, in a Greek RA population, evaluating also predictors of clinically important outcomes such as major treatment responses, drug withdrawal, and serious infections.

B. A comparative analysis of drug adherence and prognostic factors for therapy persistence for up to 10 years of follow-up among Greek patients with SpA treated with their first TNFi. The effect of different TNFis administered, different clinical SpA sub-diagnoses and of axial versus peripheral involvement of SpA on therapy response and adherence was assessed.

CHAPTER V. THE FOUNDATION: THE HELLENIC REGISTRY OF BIOLOGIC THERAPIES

1. Registry establishment and aim

In 2004, an initiative was taken by several rheumatologists to establish a nationwide prospective multi-centered observational registry of biologic therapies for inflammatory arthritides in Greece. In this registry, detailed longitudinal clinical information about the diseases and relevant clinical outcomes and medical treatments would be collected as part of routine care, aiming to study the real-life experience regarding indications for therapy, efficacy and safety of these new treatments in rheumatologic patients. Seven academic and national health system rheumatology referral centers located in 5 cities of Greece agreed to participate. The initiative was under the auspices of the Hellenic Rheumatology Society, which provided support by funding and administrative assistance.

Participating centers since the beginning of the project included the Rheumatology Departments of the University Hospital of Ioannina, the "Sismanoglio" General Hospital of Athens, the "NMITS" Veterans Administration Hospital of Athens, the "Euroclinic" Hospital of Athens, the General Hospital of Kavala, the University Hospital of Heraklio and the Pediatric Clinic of Aristotelio University Hospital of Thessaloniki. All patients in the aforementioned clinics starting their first biologic agent for an inflammatory arthritis were invited to enroll and be followed prospectively with a fixed protocol in the *Hellenic Registry of Biologic Therapies (HeRBT)* (referred to as "the Registry").The Rheumatology Department of "AHEPA" University Hospital of Thessaloniki also joined the Registry in year 2010. Enrolment in the HeRBT was started in January 2004 and closed in May 2015.

The whole study and the data collection protocol of HeRBT followed that of the *South Swedish Arthritis Treatment Group* (SSATG) registry, founded in 1999 [317, 382]. The database software, based on Microsoft Access, was kindly provided by Prof. Pierre Geborek, the developer of this software used for data entry in the SSATG registry. Prof. Geborek had an important and active involvement in the initial organization of the project and made significant updates in the software throughout the study. The coordinating center, in which the software was installed and run, was the Rheumatology Department of the University Hospital of Heraklio.

2. Registry protocol

As this was an observational study, patients had an unrestricted access to bDMARD agents based on the decision made by their treating physician and in accordance with the Hellenic Society of Rheumatology recommendations (issued in 2004 and updated every four years) [383, 384]. According to the protocol, no predefined level of disease activity was required to enter the Registry, while the choice of bDMARD was left at the discretion of the treating physician. All patients treated

for any inflammatory arthritis diagnosis in the 8 centers were enrolled (if they consented) and the inclusion time in the Registry was the initiation of their first bDMARD.

Treatment decisions after biologic agent initiation were also left entirely at the attending rheumatologists' judgment. Follow-up in the Registry continued in cases of biologic agent switches and was only terminated if patients permanently discontinued all biologic agents, allowing for one year after discontinuation as an observation period. Observation was also terminated if patients withdrew the informed consent and in cases of death and loss of follow-up.

Paper case report forms (CRFs) specifically designed for the Registry with demographic, clinical, laboratory and patient-reported variables were completed during routine patient evaluation at fixed time-points. These time-points were: at inclusion (time 0), when "patient characteristics", "baseline variables" and "follow-up variables" were collected and prospectively at 6 (±2), 12 (±2), 18 (±2) and 24 (±2) months and every 12 (±3) months of therapy thereafter as long the specific bDMARD was administered, collecting the "follow-up variables". Any withdrawal from bDMARD treatment was registered prospectively and the treating physician was reporting the cause of withdrawal. If patients switched biologic agent, CRFs were again completed at the start of the new bDMARD ("baseline variables" again) and every 6 (±2) months in the first 2 years and annually (±3 months) thereafter (with the "follow-up variables"). Additionally, treating physicians were urged to record and describe all events during the whole follow-up. Extra forms with the "event variables" were completed at the time of an event or if drug discontinuation occurred for any reason.

According to the Registry protocol, short-term bDMARD treatment interruptions (e.g. due to adverse events, surgeries, loss of insurance, etc) were allowed providing they were of less than 6 months. If bDMARD therapy was interrupted for 6 months or more, then this was considered as a discontinuation. If a patient was lost to follow-up for more than one year, then he/she was censored at the date of the last available visit.

Completed forms were made anonymous based on an identity code and mailed to the coordinating center, the Department of Rheumatology in the University Hospital of Heraklio, for data entry and analysis. Review of all patients' forms was instituted in our center by the main researcher (I.F.) and a dedicated rheumatology nurse (E.K.) and when missing data, uncertainties or discrepancies were encountered, we communicated with the treating physicians for more information or to verify accuracy of the data.

Ethical approvals were obtained by local institutional review boards (decision number 1476 for Heraklio University Hospital) and all participants signed informed consent forms at inclusion.

3. Variables collected

a. Patient characteristics:

- *Demographics*: gender, date of birth, hospital following the patient

- *Disease characteristics*: primary clinical diagnosis, other rheumatological diagnosis (if any), date of primary and other diagnosis, date of disease (symptom) onset
- *Additional* disease characteristics *for RA patients*: rheumatoid factor (RF) positivity

b. Baseline variables:

- *Disease characteristics in all patients:* date of bDMARD initiation, number and names of previously –to bDMARD initiation- administered csDMARDs, number of ongoing co-administered csDMARDs, previous use of corticosteroids (yes/no) and presence of significant permanent joint destruction (yes/no). The date of bDMARD initiation was defined as the date of the first infusion for intravenous bDMARDs, or the date of the first prescription for the subcutaneous bDMARDs.

- *Additional* disease characteristics *for SpA patients:* present or past history of inflammatory axial disease according to treating rheumatologist (yes/no) and present or past history of peripheral arthritis according to treating rheumatologist (for lower limbs, defined as arthritis distal to the hip) (yes/no).

- In the Rheumatology Clinic of the University Hospital of Heraklio, the protocol was more comprehensive, recording *additional data* concerning anti-CCP positivity and the presence of erosions on hand and/or feet X-Rays in RA patients, the presence of radiological spondylitis (yes/no) and radiological sacroiliitis (yes/no) in axSpA patients, the *smoking status* in all patients (as current smoker/ ex-smoker / non-smoker) and all *co-morbidities* of the patients at baseline. This extra work was done as part of this PhD study, aiming at including as much information about the patients as possible and was not part of the HeRBT protocol due to feasibility constraints.

c. Follow-up variables:

- *Disease activity and function measures in all patients*: physician's global assessment (PhGA) on a 5-grade Likert scale (choice between: disease remission- low disease activity – moderate disease activity – high disease activity and very high disease activity), patient global assessment of disease activity on a visual analogue scale (VAS global), patient assessment of pain on a visual analogue scale (VAS pain), the modified health assessment questionnaire (HAQ) for physical function

- *Additional* disease activity measures *in RA patients and in SpA patients with reported (at baseline) peripheral arthritis:* the 28-tender (TJC) and 28-swollen joint counts (SJC)

- *Additional* disease activity and function measures *in SpA patients with reported (at baseline) axial inflammatory disease:* Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath

Ankylosing Functional Index (BASFI) –the individual components as well as the calculated composite scores

- *Laboratory data:* the erythrocyte sedimentation rate (ESR), the C-reactive protein (CRP) and hemoglobin at the time of the visit.

- *Quality of life data:* the Euroqol questionnaire for assessment of quality of life (EQ-5D)

- *Other data:* Weight and height

- *Rheumatologic drug therapies:* names of all ongoing rheumatologic drugs –bDMARDs, csDMARDs and per os corticosteroids- their dosage and time interval of administration. Drugs were recorded both with their "prescribed dose" (dose and interval prescribed by the treating rheumatologist at the current visit) and the "taken dose" (dose that the patient actually received since last follow-up in the Registry, from which the cumulative dose since the last follow-up could be calculated).

d. Event variables:

- *Withdrawal from treatment*: if the bDMARD was discontinued, the date and the stop cause were reported by the treating physician. Causes were classified as related to adverse event(s) [AE(s)], primary treatment failure (lack of response), secondary treatment failure (loss of initial good response), pregnancy, disease remission, patient decision, financial reasons, lost to follow-up, or "other". If both treatment failure and AE(s) were reported, the cause of withdrawal was assigned to AE(s). The date of bDMARD stop was set at the time of the first missed intravenous infusion/ subcutaneous injection, or one day before the next bDMARD was initiated, whichever came first.

- In *all adverse events*, either causing bDMARD termination or not, the *date* was reported as well as a *description in free text*. They were also *classified according to*: the main -and possibly secondary- organ or system involved, their type (infection, cancer, drug reaction, other), the occurrence of hospitalization (yes/no), their outcome (healthy –still unhealthy – permanent disability – death – unknown) and their seriousness (mild – moderate – serious - life-threatening - lethal) according to the Rheumatology Common Toxicity Criteria, MEDDRA Version 1.5 [385]

- *All rheumatologic drugs* at the time of the event were also reported, along with any modifications in the rheumatic drugs due to the event

- *Surgeries* and *pregnancies* were reported separately. These were only described in free text, especially concerning their outcome.

4. Participants in the Registry

Eligible patients for inclusion in the Registry were those who initiated the first bDMARD for any inflammatory arthritis diagnosed according to the treating doctor. Similarly to SSATG and other registries [170, 334, 386, 387], patient diagnosis was based on the clinical judgment of the attending rheumatologist and not on the classification criteria for each disease.

In Greece, bDMARDs for rheumatic diseases are primarily prescribed by rheumatologists and no formal level of disease activity or specific number of previously tried csDMARDs is required other than the doctor's judgment. However, physicians generally follow the national and international guidelines for biologic agents' initiation. According to the Hellenic Society of Rheumatology recommendations [383, 384], RA patients are considered candidates for biologic treatment if they have active disease despite adequate treatment (≥3 months at recommended doses) with at least one csDMARD, which should be either methotrexate or leflunomide, if not contraindicated. Active disease is defined as DAS28 > 5.1, or DAS28 > 3.2 plus at least two out of the following five adverse prognostic factors: (a) RF positivity, (b) anti-CCP positivity, (c) erosions on the X-Rays of hands and/or feet, (d) HAQ > 1 and (e) large joint(s) involvement. In the same recommendations, axSpA patients are eligible for biologic therapy if they have active disease (BASDAI > 4) for ≥ 4 weeks, failure of at least 2 treatment courses with NSAIDs (maximum recommended/tolerated doses for ≥3 months each, if no toxicity or contraindications) and positive opinion of the treating rheumatologist. In patients with peripheral SpA, biologics can be considered in active disease despite adequate therapeutic trials with NSAIDs as above, plus at least one treatment course with either sulphasalazine (at maximum tolerated dose for ≥4 months) or methotrexate (≥7.5 mg for ≥2 months), if no toxicity or contraindications.

By the end of 2015, 2874 patients had been included in the Registry, bearing various diagnoses: rheumatoid arthritis (RA, 1608 patients), ankylosing spondylitis (AS, 572 patients), psoriatic arthritis (PsA, 398 patients), undifferentiated spondyloarthritis (uSpA, 120 patients), juvenile chronic arthritis (JCA, 73 patients), inflammatory bowel disease-associated spondyloarthritis (IBD-SpA, 42 patients), adult Still's disease (14 patients), Adamantiades-Behcet's disease (13 patients) and other arthritides: undifferentiated polyarthritis, RA/systemic lupus erythematosus (SLE) overlap syndrome, giant cell arteritis, systemic vasculitis (34 patients). The total follow-up time of these patients was 14.445 patient-years and the median time of follow-up per patient was 1.9 years.

The biologic treatment courses registered for these patients were 4352 in total: 1443 courses with infliximab, 934 with etanercept, 933 with adalimumab, 283 with abatacept, 261 with rituximab, 192 with tocilizumab, 160 with golimumab, 88 courses with anakinra, 46 with certolizumab pegol and 12 with ustekinumab.

Patients for the two main sub-studies of this Thesis were selected from the patients of the registry according to the clinical questions addressed.

CHAPTER VI. FIRST STUDY: COMPARATIVE EFFECTIVENESS AND DRUG SURVIVAL OF INFLIXIMAB, ADALIMUMAB AND ETANERCEPT IN GREEK PATIENTS WITH RHEUMATOID ARTHRITIS

1. Aims of the study

In this study, Greek patients with *rheumatoid arthritis* initiating their *1st, 2nd, or 3rd treatment* with *infliximab, adalimumab, or etanercept* were analyzed. The specific aims of this study were to:

- Describe the baseline characteristics of patients
- Define and directly compare response rates of different TNFis
- Identify baseline predictors of response
- Estimate the long-term adherence to therapy with TNFi (referred to as drug survival) stratified according to the cause of withdrawal, specific TNFi used and line of TNFi therapy
- Identify possible baseline predictors of drug survival
- Examine the association between first-year treatment responses and long-term TNFi survival
- Assess dose escalation of TNFis during the first 2 years of follow-up, along with baseline predictors and outcomes of these dose increments
- Explore the long term safety of these drugs in RA patients of routine clinical practice.

2. Methods

Patients

We analyzed Registry patients ≥18 years old with a diagnosis of RA**,** who initiated a TNFi treatment between January 2004 and December 31st, 2009 as the first or subsequent courses of biologic therapy. Since golimumab and certolizumab were not yet widely available, we only included patients who received infliximab, adalimumab, or etanercept. No specific exclusion criteria were applied. The observational period was from 01/2004 until 05/2011 to allow for a follow-up period of approximately two years for every patient.

Outcome measures

Outcome measure regarding response to therapy included:

a) *low disease activity* defined by DAS28
b) *disease remission* defined by DAS28, CDAI and the ACR/EULAR criteria (Boolean definition)
c) *good and moderate responses* based on the EULAR criteria, and
d) *CDAI–defined improvement*

The outcomes concerning response were examined separately *at 6* and *12 months* of TNFi therapy. Both *crude and LUNDEX-corrected* responses ([fraction of starters still in the study after y months] × [fraction responding at y months]) [388] were calculated.

Statistical analysis

Descriptive data are presented as medians with interquartile ranges (IQR) for continuous variables, or frequencies and percentages for categorical variables. Differences between groups were analyzed using the non-parametric Kruskal-Wallis test and the chi-squared test as appropriate. Concerning response to therapy, LUNDEX-corrected figures were calculated as the fraction of patients adhering to therapy (obtained through life table analysis) multiplied by the fraction of patients fulfilling the selected response criterion at a given time.

Using the Kaplan-Meier method, estimates of the probability for drug survival were plotted and drugs were compared using the log-rank statistic. Kaplan-Meier curves for TNFi survival adjusted for baseline demographic and clinical characteristics were also plotted and presented. For the analysis of time to discontinuation of treatment due to AE(s), discontinuations due to ineffectiveness were treated as censored observations. Similarly, discontinuations due to AE(s) were handled as censored observations in the analysis of time to discontinuation due to ineffectiveness.

Hazard ratios (HRs) with 95% confidence intervals (95% CIs) were calculated using the Cox proportional hazards model for response to TNFi treatment and also for drug withdrawal, adjusting for baseline demographic and clinical characteristics. Regarding response to therapy, an event was defined as achievement of treatment response (CDAI remission, ACR/EULAR remission) during the first 18 months since TNFi initiation assessed by 6-month time intervals. In a separate analysis, multivariable logistic regression was used for the identification of factors associated with treatment responses at 12 months of therapy. The results of these analyses are presented as odds ratios (ORs) with 95% CIs. Regarding drug withdrawal, therapy stops during the whole follow-up time or during the first 5 years after TNFi initiation were assessed with Cox regression analyses. Potential predictors tested in regression analyses were chosen based on previous studies and on clinical relevance. SJC, TJC and CRP were used as dichotomous variables according to median baseline levels. The variables with least significance where excluded stepwise (backward selection).

This study had 81% power at a 5% significance level to detect 5–10% difference in response or remission rates at 6 months between the three TNFi agents. Moreover, in Cox regression analyses with an anticipated hazard rate of 10–20%, we had 82% power at a 5% significance level to detect a regression coefficient equal to 0.15 (corresponding to hazard risk 1.40).

All analyses were performed using the Statistical Package for Social Sciences version 20 (SPSS, SPSS Inc) and p-values of 0.05 (two- tailed) were considered statistically significant.

3. Results

Participants

By 31/12/2009, 1028 patients with RA who received 1297 treatments with infliximab (n = 560), adalimumab (n = 435), and etanercept (n = 302) were analyzed (**Table 6.1**). All treatments were consecutive courses of the first (n = 1028), second (n = 233), and third (n = 36) TNFi agent. Patients were followed up until 30/04/2011 or until they discontinued TNFi treatment, whichever came first. The median (interquartile range) follow-up time was 3.0 (1.2-6.2) years for infliximab, 2.9 (1.1-5.9) years for adalimumab, and 2.9 (1.1-5.0) years for etanercept. The cumulative number of patient-years was 2182, 1560 and 973, for infliximab, adalimumab and etanercept, respectively.

The demographic and clinical characteristics of the patients at the time TNFi treatment was initiated are shown in **Table 6.1**. Patients on infliximab received more often concomitant csDMARDs ($p<0.017$), although combination therapy was also highly prevalent in adalimumab and etanercept-treated patients (>87%). Despite variations in patients' global and pain assessments and serum CRP levels, disease activity assessed by DAS28, SDAI, and CDAI, was comparable across the three agents. Patients naïve to TNF inhibitors (first TNFi) had shorter disease duration and lower number of previous non-biological DMARDs compared to 'switchers' (second and third TNFi), although disease activity characteristics were comparable between the groups (**Table 6.2**). Therefore, we performed subsequent analyses assessing all treatments irrespective of whether patients were TNFi naïve or switchers.

Response rates of infliximab, adalimumab, and etanercept

At 6 months of therapy, 21-29% of the patients had low disease activity and 13-16% achieved remission based on DAS28 (**Table 6.3)**. Both crude and LUNDEX-corrected responses were calculated. The number of valid observations varied across different measures of effectiveness since some patients lacked one or more variables at follow-up. LUNDEX-corrected remission rates assessed by CDAI and the EULAR/ACR criteria were lower for infliximab, than for adalimumab or etanercept.

Table 6.1. Baseline characteristics of the RA patients treated with anti-TNF agents (*analysis per treatments*).

	Valid N	Infliximab (n = 560)	Adalimumab (n = 435)	Etanercept (n = 302)	p value [1]
Female gender, %	1297	74 *	81 *	80	**0.009**
Age (years)	1296	58 (17)	59 (18)	57 (19)	0.995
Disease duration (years)	1296	8.5 (12.7)	7.8 (12.8)	7.4 (10.6)	0.354
Destructive arthritis, %	991	43	41	41	0.820
Failure of previous TNFi, %	1297	7.0 *,#	29.7 *	33.4 #	**<0.001**
One TNFi, %	1297	5.0 *,#	28.0 *	27.5 #	**<0.001**
Two TNFi, %	1297	2.0 #	1.6	6.0 #	**0.001**
Follow-up (years)	1297	3.0 (5.0)	2.9 (4.8)	2.9 (3.9)	0.062
Glucocorticoids use, %	1142	59	55	53	0.259
Dose (prednisone mg/week)	1142	31.5 (52.5)	17.5 (35.0)	17.5 (52.5)	0.138
Previous DMARDs (number)	1142	2 (1) *,#	3 (2) *	3 (1) #	**0.002**
Previous DMARDs except TNFi	1142	2 (1)	2 (1)	2 (1)	0.229
Concomitant DMARD(s), %	1157	93 *,#	88 *	87 #	**0.017**
Single DMARD, %	1157	68	80	75	
≥2 DMARDs, %	1157	25 *	8 *	12	**<0.001**
Methotrexate use, %	1157	70	65	66	0.225
Dose of MTX (mg/week)		12.5 (5.0)	15.0 (5.0)	12.5 (5.0)	0.100
Leflunomide use, %	1157	18	20	17	0.490
CRP (mg/dL)	816	1.4 (2.8) *	0.9 (2.0) *,$	1.5 (2.4) $	**0.030**
ESR (mm/hr)	972	41 (37)	37 (25)	37 (30)	0.072
Hemoglobin (g/dL)	251	12.7 (1.7)	12.7 (1.5)	12.7 (1.6)	0.619
Swollen joint count (0-28)	963	6 (9)	8 (10)	8 (8)	0.135
Tender joint count (0-28)	963	10 (10)	10 (11)	10 (11)	0.554
Physician's global assessment (0-10)	821	7.5 (2.5)	7.5 (2.5) $	7.5 (2.5) $	**0.044**
Patient's global assessment (0-100)	968	70 (30) *	60 (34) *,$	70 (30) $	**<0.001**
Patient's pain assessment (0-100)	908	70 (24) *,#	60 (33) *	60 (30) #	**<0.001**
HAQ (0-3)	589	1.0 (0.9)	1.0 (0.9)	1.0 (0.9)	0.634
DAS-28 (0-9.35)	963	5.4 (1.5)	5.6 (1.6)	5.7 (1.6)	0.331
SDAI	696	32 (19)	31 (20)	33 (20)	0.327
CDAI	817	30 (19)	31 (21)	33 (20)	0.546

[1]Chi-squared test or Kruskal-Wallis test as appropriate. All values are medians (interquartile range) unless otherwise indicated.

Table 6.2. Baseline characteristics of the RA patients according line of TNF inhibitor (*analysis per patients*).

	1st TNFi (*n* = 1028)	2nd TNFi (*n* = 233)	3rd TNFi (*n* = 36)	P value [1]
Gender (female), %	78	80	64	0.102
Age (years)	57.8 (17.6)	58.4 (18)	55 (15.6)	0.849
Disease duration (years)	7.2 (11.7)	9.2 (11.9)	11.5 (12.7)	<0.001
Erosive arthritis, %	41	44	50	0.572
Follow-up (years)	3.0 (4.8)	2.2 (3.9)	2.4 (4.4)	<0.001
Glucocorticoids use, %	57	52	69	0.167
Dose (prednisone mg/week)	28.0 (52.5)	17.5 (35.0)	35.0 (52.5)	0.128
Previous DMARDs (number)	2 (1)	4 (2)	5 (3)	<0.001
Previous DMARDs except TNF	2 (1)	3 (2)	3 (3)	<0.001
Concomitant DMARD(s), %	91	85	87	0.056
Single DMARD, %	73	77	71	
≥2 DMARDs, %	18	8.6	16	
Methotrexate, %	70	58	63	0.004
Dose (mg/week)	12.5 (5.0)	15.0 (5.0)	15.0 (2.5)	0.041
Leflunomide, %	18	21	16	0.627
Current anti-TNF agent				
Infliximab, %	50	12	31	
Adalimumab, %	30	52	19	
Etanercept, %	20	36	50	<0.001
CRP (mg/dL)	1.3 (2.5)	0.9 (2.0)	1.9 (2.6)	0.018
ESR (mm/hr)	40 (34)	35 (32)	43 (46)	0.280
Hemoglobin (g/dL)	12.8 (1.7)	12.7 (1.4)	10.9 (2.2)	0.001
SJC-28	7.0 (10.0)	7.0 (10.0)	6.5 (11.0)	0.722
TJC-28	10.0 (11.0)	9.0 (11.0)	7.5 (13.0)	0.553
Physician global assessment (0-10)	7.5 (2.5)	7.5 (2.5)	7.5 (1.25)	0.036
Patients global assessment (0-100)	67 (30)	70 (30)	80 (30)	0.023
Patients pain assessment (0-100	70 (30)	65 (30)	75 (30)	0.254
HAQ (0-3)	1.0 (0.9)	1.0 (0.8)	1.3 (1.6)	0.488
DAS-28	5.9 (1.6)	5.9 (1.6)	6.2 (2.5)	0.548
SDAI	32 (20)	30 (18)	32 (21)	0.255
CDAI	31 (20)	30 (19)	36 (23)	0.598

[1]Chi-squared test or Kruskal-Wallis test as appropriate. All values are medians (interquartile range) unless otherwise indicated.

At 12 months, the percentage of patients with low disease activity based on DAS28 was 27%, 34% and 31% for infliximab, adalimumab, and etanercept, respectively (p = 0.309). A good EULAR response was noted in 20%, 23% and 19% of patients on infliximab, adalimumab, and etanercept, respectively (**Table 6.4**). LUNDEX-corrected remission rates were 6.1-12% for infliximab, 11-17% for adalimumab, and 5.1-15% for etanercept.

In agreement with previous reports [389], fewer patients achieved the CDAI and more patients achieved the DAS28 definition for remission at both 6 and 12 months of treatment. CDAI and ACR/EULAR remission rates were significantly lower for infliximab compared to adalimumab or etanercept (p=0.022 and p<0.001, respectively at 12 months). EULAR and CDAI response rates were comparable between the three agents (EULAR good/moderate response rates 76-79%).

Table 6.3. Treatment response **at 6 months** of therapy with TNF inhibitors in RA patients				
	Infliximab	**Adalimumab**	**Etanercept**	**P value** [1]
DAS28 remission: Number of patients [2]	357	220	171	
Remission (%)	13	16	16	0.587
LUNDEX-corrected: Number of patients	560	435	302	
Remission (%)	12	14	14	0.619
CDAI remission: Number of patients	334	187	143	
Remission (%)	5.7	11	9.8	0.061
LUNDEX-corrected (%)	5.2	9.9	8.5	**0.015**
ACR/EULAR remission				
Boolean-based definition: No. of patients	334	183	144	
Remission (%)	6.9	16	12	**0.005**
LUNDEX-corrected (%)	6.2	14	10	**<0.001**
SDAI-based definition: No. of patients	306	154	125	
Remission (%)	5.6	12	11	**0.024**
LUNDEX-corrected (%)	5.1	11	9.8	**0.003**
DAS28 low disease activity: No. of patients [2]	357	220	171	
Low disease activity (%)	21	29	24	0.073
LUNDEX-corrected (%)	19	25	21	**0.034**
EULAR response: No. of patients	338	203	150	
Good (%)	20	24	19	
Moderate (%)	49	48	59	
No response (%)	31	29	22	0.137
LUNDEX-corrected				
Good (%)	18	21	16	
Moderate (%)	44	42	51	
No response (%)	38	38	33	0.110
CDAI response: No. of patients	300	167	122	
CDAI 25 (%)	73	74	86	**0.012**
CDAI 50 (%)	52	56	60	0.275
CDAI 75 (%)	20	26	17	0.131
LUNDEX-corrected				
CDAI 25 (%)	67	65	75	**0.010**
CDAI 50 (%)	48	50	52	0.451
CDAI 75 (%)	19	23	15	**0.023**

[1]Chi-square test,

[2] The number of valid observations varied across different measures of effectiveness since some patients lacked one or more variables at follow-up

Table 6.4. Treatment response **at 12 months** of therapy with TNF inhibitors in RA patients

	Infliximab	**Adalimumab**	**Etanercept**	**P value**[1]
DAS28 remission: Number of patients [2]	316	179	137	
Remission (%)	15	23	19	0.098
LUNDEX-corrected: Number of patients	560	435	302	
Remission (%)	12	17	15	**0.049**
CDAI remission: Number of patients	296	161	121	
Remission (%)	7.8	15	6.6	**0.022**
LUNDEX-corrected (%)	6.1	11	5.1	**0.001**
ACR/EULAR remission				
Boolean-based definition:No. of patients	305	144	118	
Remission (%)	7.5	21	17	**<0.001**
LUNDEX-corrected (%)	6.0	16	13	**<0.001**
SDAI-based definition: No. of patients	276	121	108	
Remission (%)	7.6	17	8.3	**0.009**
LUNDEX-corrected (%)	6.1	14	6.5	**<0.001**
DAS28 low disease activity: No. of patients [2]	316	179	137	
Low disease activity (%)	27	34	31	0.309
LUNDEX-corrected (%)	22	26	24	0.336
EULAR response: No. of patients	292	151	115	
Good (%)	26	30	24	
Moderate (%)	53	46	52	
No response (%)	22	25	24	0.674
LUNDEX-corrected				
Good (%)	20	23	19	
Moderate (%)	42	35	40	
No response (%)	38	42	41	0.214
CDAI response: No. of patients	258	124	98	
CDAI 25 (%)	83	82	81	0.831
CDAI 50 (%)	64	65	71	0.368
CDAI 75 (%)	25	31	25	0.467
LUNDEX-corrected				
CDAI 25 (%)	67	64	64	0.519
CDAI 50 (%)	52	50	56	0.289
CDAI 75 (%)	20	24	19	0.185

[1]Chi-squared test,

[2] The number of valid observations varied across different measures of effectiveness since some patients lacked one or more variables at follow-up

Predictors of response to TNFi treatment

In Cox regression analysis, independent predictors for CDAI and ACR/EULAR remission during the first 18 months after treatment initiation included male gender (HR 1.72 and 1.64, respectively), baseline SJC >7 (HR 0.43 and 0.36, respectively), higher patient's VAS for pain (HR 0.89 per 10 units), higher number of past non-biological DMARDs (HR 0.82 and 0.81 per 1 agent, respectively) and treatment with adalimumab versus infliximab (HR 2.01 and 2.65, respectively) (**Table 6.5**). Use of glucocorticoids at baseline and treatment with etanercept versus infliximab were additional predictors for ACR/EULAR remission (HR 1.98 and 2.09, respectively).

Baseline variables associated with increased risk for both DAS28 low disease activity and EULAR good response included male gender (HR 1.33 and 1.45, respectively), patient age (HR 0.90 and 0.86 per 10 years, respectively), SJC >7 (HR 0.46 and 0.59, respectively), and use of glucocorticoids (HR 1.30 and 1.40, respectively) (**Table 6.6**). Higher patient's VAS for pain was associated with reduced risk for DAS28 low disease activity (HR 0.89 per 10 units) and TJC > 10 with reduced risk for EULAR good response (HR 0.73). There was no consistent association between treatment with specific TNFi and risk for DAS28 low disease activity or EULAR good response. Similar results were obtained by multivariate logistic regression analysis for the aforementioned efficacy outcomes at 12 months after TNFi treatment initiation (**Supplementary Tables 1 and 2**).

Table 6.5. Cox regression analysis for CDAI and EULAR/ACR remission with TNFi therapy in RA patients

	CDAI remission		ACR/EULAR remission [1]	
Baseline characteristics	**Univariate [2]**	**Multivariate**	**Univariate**	**Multivariate**
Gender (male *vs.* female)	2.02 (1.41-2.89) [c]	1.72 (1.10-2.68) [c]	1.90 (1.37-2.64) [c]	1.64 (1.12-2.42) [a]
Age (per 10-years)	0.87 (0.76-0.99) [a]		0.88 (0.78-0.99) [a]	
RA duration (per 1-year)	0.97 (0.94-0.99) [b]		0.98 (0.96-1.00) [a]	
SJC-28 (> *vs.* ≤ 7)	0.41 (0.26-0.64) [c]	0.43 (0.27-0.69) [c]	0.33 (0.23-0.50) [c]	0.36 (0.24-0.55) [c]
TJC-28 (> *vs.* ≤ 10)	0.47 (0.30-0.73) [b]		0.51 (0.35-0.75) [c]	
CRP (> *vs.* ≤ 1.4 mg/dL)	0.82 (0.53-1.26)		1.11 (0.76-1.60)	
VAS global (per 10-units)	0.87 (0.79-0.95) [b]		0.85 (0.79-0.92) [c]	
VAS pain (per 10-units)	0.85 (0.77-0.93) [b]	0.89 (0.80-0.98) [a]	0.84 (0.77-0.91) [c]	0.89 (0.82-0.97) [b]
Methotrexate use (yes *vs.* no)	0.98 (0.66-1.45)		0.88 (0.62-1.25)	
Leflunomide use (yes *vs.* no)	0.98 (0.59-1.64)		0.90 (0.56-1.45)	
Glucocorticoid use (yes *vs.* no)	1.35 (0.92-1.99)		1.90 (1.30-2.77) [b]	1.98 (1.29-3.04) [b]
Previous DMARDs (per 1 drug)	0.81 (0.71-0.93)	0.82 (0.70-0.96) [c]	0.85 (0.75-0.97) [a]	0.81 (0.71-0.93) [b]
TNFi agent used				
INF (*reference*)	1.00 (*reference*)	1.00 (*reference*)	1.00 (*reference*)	1.00 (*reference*)
ADA	1.79 (1.22-2.63) [b]	2.01 (1.23-3.27) [b]	2.14 (1.48-3.10) [c]	2.65 (1.71-4.11) [c]
ETA	1.14 (0.70-1.86)	1.13 (0.62-2.07)	1.94 (1.28-2.94) [b]	2.09 (1.30-3.37) [b]
Previous TNFis (per 1 agent)	1.13 (0.78-1.63)		1.00 (0.69-1.44)	

[1] Boolean definition

[2] Cox regression analysis (forward conditional model applied for multivariate analysis) using baseline characteristics as independent predictors. In this model, an event was defined as achievement of treatment response (CDAI remission, ACR/EULAR remission) during the first 18 months since TNFi initiation assessed by 6-month time intervals. Results are given as HRs (95% CI);

[a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$

Table 6.6. Cox regression analysis for DAS28 low disease activity and EULAR good response with TNFi therapy in RA patients

	DAS28 low disease activity		EULAR good response	
Baseline characteristics	**Univariate***	**Multivariate***	**Univariate***	**Multivariate***
Gender (male *vs.* female)	1.54 (1.22-1.95) [c]	1.33 (1.02-1.73) [a]	1.60 (1.22-2.08) [b]	1.45 (1.10-1.90) [b]
Age (per 10-years)	0.85 (0.79-0.92) [c]	0.90 (0.83-0.99) [a]	0.83 (0.76-0.91) [c]	0.86 (0.79-0.95) [b]
RA duration (per 1-year)	0.99 (0.98-1.01)		0.98 (0.97-1.00)	
SJC-28 (> *vs.* ≤ 7)	0.40 (0.31-0.51) [c]	0.46 (0.36-0.61) [c]	0.47 (0.36-0.61) [c]	0.59 (0.44-0.79) [c]
TJC-28 (> *vs.* ≤ 10)	0.46 (0.36-0.60) [c]		0.54 (0.42-0.71) [c]	0.73 (0.54-0.98) [a]
CRP (> *vs.* ≤ 1.4 mg/dL)	0.90 (0.70-1.15)		1.07 (0.82-1.39)	
VAS global (per 10-units)	0.86 (0.81-0.91) [c]		0.94 (0.89-1.00)	
VAS pain (per 10-units)	0.87 (0.82-0.92) [c]	0.90 (0.85-0.95) [c]	0.95 (0.89-1.01)	
Methotrexate use (yes *vs.* no)	1.12 (0.88-1.43)		1.32 (0.99-1.75)	
Leflunomide use (yes *vs.* no)	0.91 (0.67-1.24)		0.90 (0.64-1.28)	
Glucocorticoid use (yes *vs.* no)	1.43 (1.13-1.81) [b]	1.30 (1.01-1.68) [a]	1.53 (1.18-2.00) [b]	1.40 (1.07-1.83) [a]
Previous DMARDs (per 1 drug)	0.90 (0.86-1.01)		0.92 (0.84-1.01)	
TNFi agent used				
INF (*reference*)	1.00 (*reference*)		1.00 (*reference*)	
ADA	1.24 (0.97-1.58)		1.11 (0.84-1.47)	
ETA	1.14 (0.86-1.51)		0.98 (0.71-1.35)	
Previous anti-TNF (per 1 agent)	0.96 (0.75-1.22)		0.77 (0.56-1.05)	

* Cox regression analysis (forward conditional model applied for multivariate analysis) using baseline characteristics as independent predictors. In this model, an event was defined as achievement of treatment response (DAS28 low disease activity, EULAR good response) during the first 18 months since TNFi initiation assessed by 6-month time intervals. Results are given as HRs (95% CI);
[a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$

Differential drug survival of infliximab, adalimumab, and etanercept

Overall drug survival rates were 64%, 67%, and 68% at 1 year, and 31%, 43%, and 49% at 5 years for infliximab, adalimumab, and etanercept, respectively (log-rank p = 0.010). Although efficacy-related drug survival rates were comparable among the three agents (**Figure 6.1.A**), infliximab had more safety-related discontinuations compared to adalimumab and etanercept (p < 0.001) (**Figure 6.1.B**). Similar results were observed within patients who received their first TNFα inhibitor (**Figure 6.1.C and 6.1.D**). Patients who were started on second and third TNF-inhibitor had significantly lower efficacy-related survival compared to anti-TNFα naïve patients (p = 0.012), although safety-related survival was comparable (**Figure 6.1.E and 6.1.F**).

Predictors for survival of TNF inhibitors

In multivariate Cox regression, previous TNF inhibitor discontinuation (HR 1.92 per 1 agent), baseline use of leflunomide (HR 1.53), SJC >7 (HR 1.61), TJC >10 (HR 1.52), and higher patient's VAS for pain (HR 1.11 per 10 units) were associated with reduced efficacy-related drug survival (**Table 6.7**). In contrast, use of glucocorticoids (HR 0.58) and CRP >1.4mg/dL (HR 0.64) at baseline were associated with longer time to TNFi discontinuation. In a more detailed analysis regarding specifically discontinuations due to primary and secondary (after the first year) inefficacy, treatment with adalimumab (OR 0.37) and etanercept (OR 0.48) compared with infliximab was associated with lower risk for secondary loss of efficacy (data not shown).

Predictors for reduced safety-related survival included older age (HR 1.15 per 10 years) and higher number of past non-biological DMARDs used (HR 1.12 per 1 agent). Use of MTX (HR 0.55) and treatment with etanercept or adalimumab compared with infliximab (HR 0.38 and 0.40, respectively) were associated with longer time to TNFi discontinuation due to safety reasons.

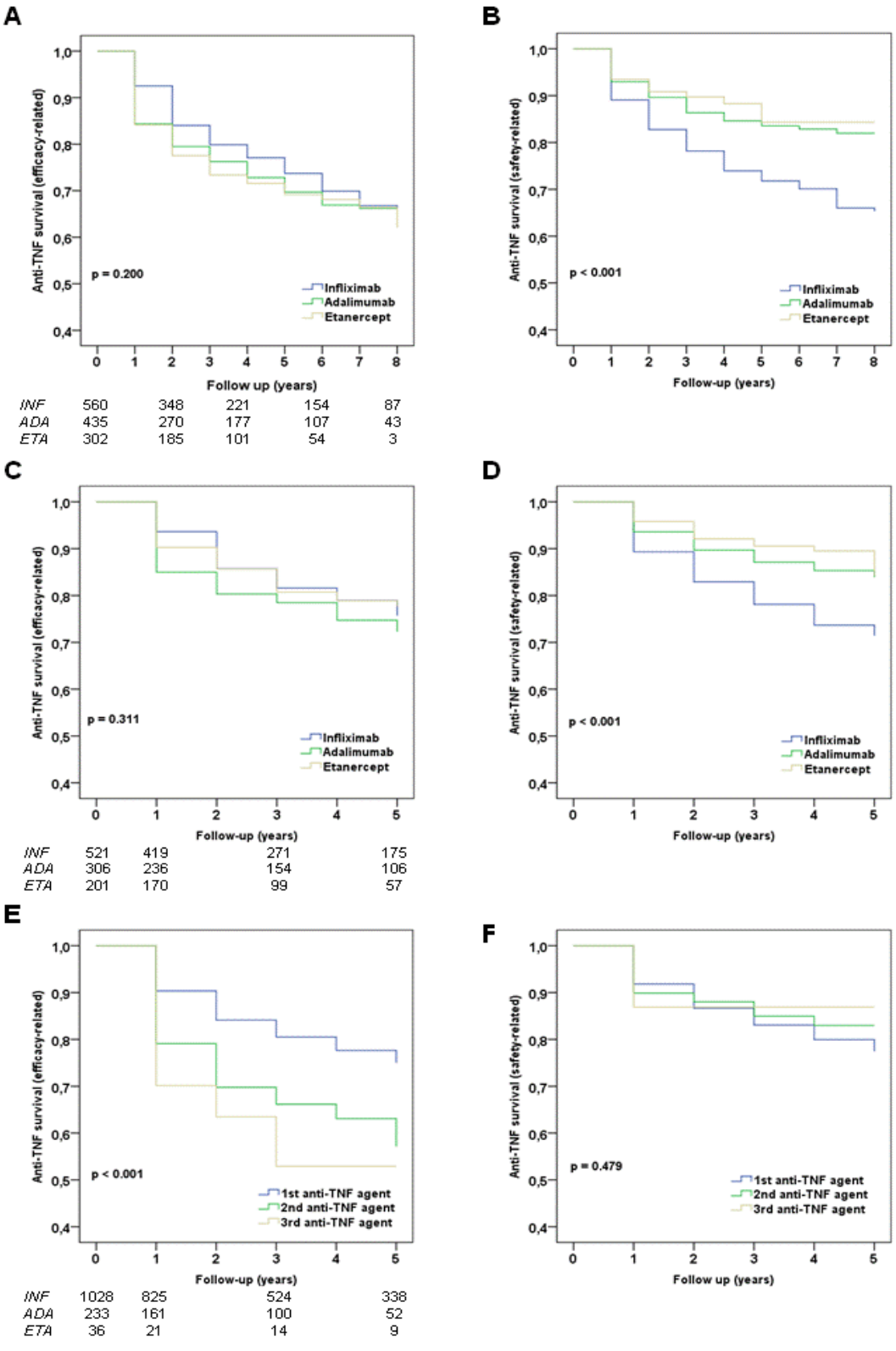

Figure 6.1. Efficacy- and safety-related survival rates of anti-TNF therapy in RA patients**.**

(A) Efficacy- and **(B)** safety- related survival of anti-TNF therapy in the total cohort of RA patients. **(C)** Efficacy- and **(D)** safety- related survival of anti-TNF therapy in anti-TNF naïve RA patients. **(E)** Efficacy- and **(F)** safety- related drug survival according to the number (1^{st}, 2^{nd}, or 3^{rd}) of anti-TNF agent used.

Table 6.7. Baseline determinants of TNF inhibitor treatment discontinuation during follow-up

Baseline characteristics	Cause of anti-TNF discontinuation			
	Lack of efficacy		Adverse events	
	Univariate [1]	Multivariate[1]	Univariate[1]	Multivariate[1]
Gender (male vs. female)	1.00 (0.77-1.30)	–	1.32 (0.98-1.77)	–
Age (per 10-years)	1.02 (0.94-1.10)	–	1.14 (1.03-1.27)[a]	1.13 (1.00-1.28)[a]
RA duration (per 1-year)	1.00 (0.98-1.01)	–	1.01 (1.00-1.02)	–
SJC-28 (> vs. ≤ 7)	2.12 (1.59-2.83)[c]	1.61 (1.10-2.35)[a]	0.84 (0.61-1.15)	–
TJC-28 (> vs. ≤ 10)	2.02 (1.53-2.67)[c]	1.52 (1.04-2.23)[a]	0.86 (0.63-1.18)	–
CRP (> vs. ≤ 1.4 mg/dL)	0.57 (0.41-0.79)[b]	0.64 (0.45-0.92)[a]	0.88 (0.63-1.24)	–
VAS global (per 10-units)	1.14 (1.06-1.22)[c]	–	0.99 (0.92-1.07)	–
VAS pain (per 10-units)	1.10 (1.02-1.18)[a]	1.11 (1.02-1.22)[a]	1.02 (0.94-1.10)	–
Methotrexate use (yes vs. no)	0.81 (0.63-1.04)	–	0.59 (0.45-0.79)[c]	0.55 (0.40-0.75)[c]
Leflunomide use (yes vs. no)	1.79 (1.35-2.37)[c]	1.53 (1.03-2.28)[a]	1.52 (1.08-2.14)[b]	–
Glucocorticoid use (yes vs. no)	0.45 (0.35-0.57)[c]	0.58 (0.41-0.81)[b]	1.09 (0.81-1.47)	–
No. of previous DMARDs (per 1 drug)	1.19 (1.10-1.28)[c]	–	1.12 (1.02-1.22)[c]	1.13 (1.03-1.24)[a]
TNFi used				
INF (reference)	1.00	–	1.00	1.00
ADA	1.19 (0.92-1.53)		0.53 (0.39-0.73)[c]	0.39 (0.27-0.56)[c]
ETA	1.26 (0.96-1.67)		0.46 (0.31-0.67)[c]	0.34 (0.22-0.54)[c]
No. of previous anti-TNF (per 1 agent)	1.72 (1.42-2.07)[c]	1.92 (1.45-2.55)[c]	0.83 (0.60-1.13)	–

[1] Cox regression analysis (backwards elimination model applied for multivariate analysis) using baseline characteristics as independent predictors. Results are provided as HRs (95% CI); [a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$

Association between first-year treatment responses and long-term TNFi survival

After adjusting for baseline parameters, efficacy-related 5-year drug survival was highest for patients with sustained (both at 6 and 12 months) DAS28 remission (10% of our cohort), intermediate for patients with non-sustained remission (only at 6 or at 12 months; 15%) or with sustained EULAR response (46%), lower for patients with non-sustained EULAR response (17%), and lowest for those who did not respond to TNF inhibitor treatment (12%) ($p<0.001$) (**Figure 6.2**). In contrast, safety-related drug survival was not associated with first-year treatment responses (data not shown).

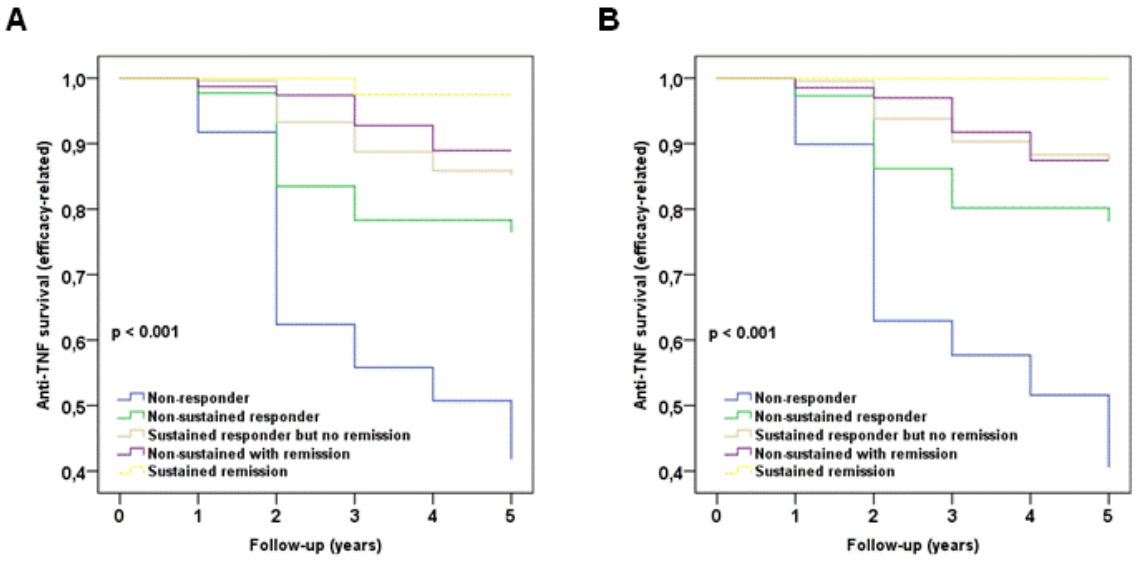

Figure 6.2. Efficacy-related survival of anti-TNF therapy according to first-year clinical response in RA patients based on DAS28 in the total cohort (A) and in anti-TNF naïve (B) RA patients. Clinical responses were categorized as follows: sustained (DAS28) remission, non-sustained remission, sustained (EULAR) response but without fulfilling the remission criteria, non-sustained response, and non-responder.

TNF inhibitor dose adjustments

Dose adjustments in TNF inhibitors were decided by the treating physician based on patient's disease activity. 44%, 48% and 55% of the patients treated with infliximab had their dose increased by the 6th, 12th and 24th month, respectively. Median (IQR) dose increased from 25.0 (12.5) mg/week at baseline, to 35 (25) mg/week on the 6th month, and 37.5 (25) mg/week at 12 and 24 months (Wilcoxon signed ranks test $p<0.001$ for paired-sample comparisons with baseline dose). Conversely, doses of adalimumab and etanercept remained unchanged (at the recommended doses) during the 24-month period.

Use of glucocorticoids and higher SJC at baseline were independent predictors for increase in infliximab dose at 6 months (OR 0.58, $p < 0.001$, and OR 1.04 per 1-joint, $p < 0.05$, respectively). Although increase in infliximab dose is common in clinical practice, its impact on controlling disease activity remains unclear. Since in the majority of cases, infliximab dose escalation was done early (44% during the first 6 months), we sought to examine its association with disease activity. In multivariate analysis controlling for baseline demographic and clinical characteristics, infliximab dose increase at 6 months was associated with lack of EULAR response both at 6 months (OR 0.36, $p<0.001$) and at 12 months (OR 0.48, $p = 0.016$).

Serious AEs (SAEs) and predictors of serious infections

SAEs occurred in 185 cases of treatment with infliximab, 82 cases with adalimumab, and 34 cases with etanercept, resulting in incidence rates of 8.5, 5.3, and 3.5 per 100 person-years, respectively ($p < 0.001$) (**Table 6.8**). Treatment with infliximab was associated with higher incidence of serious infections and malignancies ($p < 0.001$ and $p = 0.018$, respectively). Serious infusion reactions occurred in eleven patients all treated with infliximab.

Incidence rates for first serious infection were 3.5, 2.2 and 1.7 per 100 person-years for infliximab, adalimumab, and etanercept, respectively; the respective numbers for combined first and recurrent serious infections were 4.0, 2.7, and 2.1 per 100 person-years ($p < 0.001$). The median time to first serious infection was 20, 11, and 31 months in patients treated with infliximab, adalimumab, and etanercept, respectively ($p = 0.125$). Most cases were lower respiratory tract ($n = 33$) and urinary tract ($n = 14$) infections, together accounting for 47% (**Table 6.9**).

In multivariate analysis, baseline patient age (OR 1.65 per 10-years), TJC >10 (OR 1.86), and use of glucocorticoids at a dose >35mg/week (OR 1.83) were significant predictors for the first serious infection (**Table 6.10**). Treatment with adalimumab or etanercept was independently associated with reduced risk for first serious infection compared with infliximab (OR 0.62 and 0.39, respectively).

Since 42% of first serious infections occurred within the first year of TNFi treatment, we studied their association with the cumulative exposure to glucocorticoids during this time period. Patients who developed infection received significantly higher median dose of glucocorticoids than those who did not (at baseline: 35 versus 21 mg/week, at 6 months: 35 versus 26 mg/week, at 12 months: 35 versus 18 mg/week; $p < 0.001$ for all comparisons). At the time of infection, 65% of the patients were on glucocorticoids at a median dose of 35 mg/week. We found no significant association with the dose of infliximab (data not shown).

Table 6.8. Serious adverse events in RA patients treated with TNF inhibitors

	Infliximab (n=185)	Adalimumab (n=82)	Etanercept (n=34)	P value [1]
Gender (female), %	67	85	82	**0.003**
Age at the time of event (years), median (IQR)	64 (16)	65 (11)	68 (20)	0.442
Time to SAE (months), median (IQR)	23 (36)	20 (32)	23 (39)	0.248
Type of SAEs				
Infections, per 100 patient-years	4.0	2.7	2.1	**0.0002**
Circulatory events, per 100 patient-years	0.9	0.4	0.5	**0.0510**
Malignancies, per 100 patient-years	0.9	0.5	0.2	**0.0183**
Musculoskeletal, per 100 patient-years	0.5	0.6	0.1	0.1054
Airway, per 100 patient-years	0.4	0.3	0.2	0.4771
Any SAE, per 100 patient-years	8.5	5.3	3.5	**<0.0001**
SAE severity				
Serious/life threatening, %	94.61	98.8	94.1	
Lethal, %	5.4	1.2	5.9	
Change in anti-TNF treatment				
No change, %	50.3	35.4	26.5	
Dose adjustment, %	1.1	0.0	0.0	**0.001**
Temporary stop, %	17.3	32.9	50.0	
Permanent stop, %	31.4	31.7	23.5	
Long-term outcome				
Healthy without sequelae, %	74.1	74.4	79.4	
Healthy with sequelae, %	10.3	12.2	2.9	0.812
Still Unhealthy, %	4.9	4.9	5.9	
Death, %	5.4	1.2	5.9	
Unknown, %	5.4	7.3	5.9	

[1] Chi-squared test or Kruskal-Wallis test as appropriate; IQR: Interquartile range

Table 6.9. Serious infections in RA patients treated with TNF inhibitors

	Pts. with serious infections	Pts. with no serious infections*	p
Cases, *n*	149 (125 patients)	903	
Age (years)	64.1 (16.0)	56.8 (18.0)	<0.001
Disease duration (years)	8.5 (11.9)		
Time to infection (months)	21.5 (33.6)		
Follow-up duration in Registry (months)	44.0 (66.7)	34.7 (56.4)	0.070
Grading of severity			
Serious/Life threatening, %	96.7		
Lethal, %	3.4		
Long-term outcome			
Healthy without sequelae, %	89.3		
Healthy with sequelae, %	2.0		
Still unhealthy, %	3.4		
Death, %	3.4		
Unknown, %	2.0		
Baseline characteristics			
SJC-28	9.0 (14.0)		
TJC-28	12.0 (11.0)	10.0 (10.0)	0.002
CRP (mg/dL)	1.7 (3.0)		
ESR (mm/hr)	48.0 (42.0)	38.0 (32.0)	0.010
HAQ	0.9 (1.0)		
VAS-Global	65 (30)		
VAS-Pain	70 (30)		
Physician's Global	3.0 (1.0)		
DAS28	6.1 (1.6)	5.9 (1.6)	0.024
SDAI	37.7 (23.1)	31.4 (18.7)	<0.001
Hemoglobin (g/dL)	12.8 (1.7)		
DMARDs previous	2.0 (1.0)		
Change in TNFi treatment			
No change, %	34.9		
Temporary discontinuation, %	40.3		
Permanent discontinuation, %	24.8		
Type of infection			
Lower respiratory tract infection, %	33		
Urinary tract infection, %	14		
Skin-Soft tissue infection, %	9		
Tuberculosis, %	9		
Gastrointestinal infection, %	6		
Biliary tract infection, %	4		
Upper respiratory tract infection, %	4		
Osteomyelitis, %	4		
Septic arthritis, %	4		
Zoster infection, %	2		
Unknown fever, %	1		
Abdominal abscess, %	1		
Surgical site infection, %	1		
Sepsis, %	1		
Eye infections, %	1		
Other, %	6		

All values are medians (interquartile range, unless indicated otherwise;*Only statistically significant values shown

Table 6.10. Risk factors for first severe infection in RA patients treated with anti-TNF agents

	Risk for first severe infection	
Baseline characteristics	Univariate [1]	Multivariate
Gender (male *vs.* female)	1.07 (0.70-1.65)	
Age (per 10-years)	1.60 (1.36-1.88) [c]	1.65 (1.37-2.00) [c]
RA duration (per 1-year)	1.01 (0.99-1.03)	
SJC-28 (> *vs.* ≤ 7)	1.42 (0.94-2.13)	
TJC-28 (> *vs.* ≤ 10)	1.85 (1.22-2.79) [b]	1.86 (1.21-2.86) [b]
CRP (> *vs.* ≤ 1.4 mg/dL)	1.16 (0.76-1.78)	
VAS global (per 10-units)	0.96 (0.88-1.06)	
VAS pain (per 10-units)	0.98 (0.90-1.08)	
Methotrexate use (yes *vs.* no)	0.82 (0.56-1.22)	
Leflunomide use (yes *vs.* no)	1.33 (0.85-2.09)	
Glucocorticoid use		
No use	1.00 (*reference*)	1.00 (*reference*)
≤35 mg/week	1.23 (0.77-1.97)	1.26 (0.73-2.19)
>35 mg/week	1.60 (1.03-2.50) [a]	1.83 (1.12-2.99) [a]
Previous DMARDs (per 1 drug)	1.03 (0.91-1.17)	
TNFi agent used		
INF (*reference*)	1.00 (*reference*)	1.00 (*reference*)
ADA	0.56 (0.37-0.85) [b]	0.62 (0.38-1.00) [a]
ETA	0.38 (0.22-0.66) [b]	0.39 (0.21-0.72) [b]
Previous TNFi (per 1 agent)	0.64 (0.41-1.01)	

[1] Logistic regression analysis (backward elimination model applied for multivariate analysis) using baseline characteristics as independent predictors

[a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$

4. Discussion

This first report of the Hellenic Registry of Biologic Therapies was a study of the long-term efficacy and safety of treatment with infliximab, adalimumab, and etanercept in RA patients. Our main finding is that, although treatment responses were comparable between the three agents, disease remission rates were lowest for infliximab, intermediate for etanercept, and highest for adalimumab. Moreover, drug survival was lowest for infliximab due to increased safety-related withdrawals compared to adalimumab and etanercept. Patients who achieved sustained remission during the first year of treatment had better long-term (5 years) drug survival rates. Importantly, infliximab-treated patients experienced significantly more serious infections than adalimumab- or etanercept-treated patients even after adjusting for potential confounding factors.

We found comparable response rates between the three TNF inhibitors. At 6 months, 21-29% of the patients had low disease activity and 13-16% achieved remission based on DAS28, and the respective rates at 12 months were 27-34% and 15-23%. These figures tend to be lower than those reported by the nationwide Danish Biologics (DANBIO) [390], the Dutch Rheumatoid Arthritis

Monitoring (DREAM) [332], and the Consortium of Rheumatology Researchers of North America (CORRONA) [342] registries but are higher than those reported by the British Society for Rheumatology Biologics Register (BSRBR) where only 8-9% of etanercept- and infliximab-treated patients were on remission after 6 months of treatment [344].

By using the more stringent criteria of CDAI and ACR/EULAR remission, we found that adalimumab was associated with significantly higher remission rates at 12 months compared to etanercept and infliximab. After adjusting for differences in baseline characteristics, the ORs for CDAI remission were 4.1 (95% CI 2.0-8.2) for adalimumab and 2.7 (95% CI 1.2-5.9) for etanercept, with infliximab as the reference drug. These results are in agreement with those reported by the DANBIO registry, where DAS28 and CDAI remission rates at 6 and 12 months were highest for adalimumab, intermediate for etanercept, and lowest for infliximab [390]. Similarly, in the DREAM registry, improvement in DAS28 after 12 months of treatment was significantly greater for adalimumab and etanercept than for infliximab [332]. On the contrary, the US-based CORRONA registry [342] and a Portuguese study [341] reported comparable rates of DAS28 and CDAI remission for the three anti-TNF agents.

Differences in the characteristics of the included patients and the dosing schemes of the TNF inhibitors may partly account for the discrepant results in the aforementioned studies. Patients included in the CORRONA registry had low to moderate disease activity at baseline (mean DAS28 4.4 to 4.5), while in the European registries patients had higher disease activity (mean DAS28 5.2 to 5.5) comparable to our patients. Moreover, infliximab dose was higher in patients in the CORRONA registry (mean 5.5 mg/kg) as compared to 3 mg/kg in the DREAM and 3.5 mg/kg in the DANBIO registry. Finally, the timing of clinical assessment could have biased outcome measures, since infliximab-treated patients were evaluated on the day of infusion (at trough infliximab levels), whereas subcutaneously-treated patients were scored independently of the day of injection.

A number of demographic and baseline clinical parameters have been described as predictors of response to anti-TNFα treatment. In our cohort, male gender and use of glucocorticoids were independently associated with higher odds, whereas high number of SJC and longer RA duration were associated with lower odds for achieving CDAI or ACR/EULAR remission at 12 months. Increasing patient age, high number of TJC, and previous use of non-biological DMARDs were negative predictors for DAS28 low disease activity or EULAR good response to TNF inhibition. Importantly, several of these prognostic factors have been identified in cohorts of RA patients with different ethnic backgrounds, including the association of older age, female gender, longer disease duration, higher baseline disease activity and number of previously failed DMARDs with lower treatment responses and remission rates [344, 390] [345].

In line with the previous results, we found that high number of swollen and tender joint counts and higher VAS pain at baseline were associated with shorter survival of TNF inhibitor treatment due to lack of efficacy. Previous failure of TNF inhibitor treatment, although not associated with differential response rates, was also a strong predictor for efficacy-related discontinuation. Conversely, higher CRP and concomitant use of glucocorticoids were protective against such outcome. Similar results have been reported by du Pan *et al.* [336], who identified previous failure of a TNF inhibitor, absence of treatment with glucocorticoids, and high baseline DAS28 as significant predictors for TNFi

withdrawal. High CRP level at treatment initiation has been associated with prolonged drug adherence in Swedish RA patients [391].

In our cohort of long-standing RA, patients who achieved sustained remission during the first year of anti-TNFα treatment had better long-term (5 years) drug survival rates compared to patients with non-sustained remission or patients who did not meet the remission criteria. This is the first time that sustained remission early at treatment with TNF inhibitors is found as a predictor for long-term drug survival. Gulfe *et al.* have reported similar results albeit for a shorter follow-up; treatment response at 6 and 12 weeks predicted continuation of TNF inhibitor treatment for at least 6 months [392]. The ultimate goal of treating RA is to achieve remission and halt the progression of joint damage. A number of studies have shown that achieving remission at a single time-point is not strongly associated to radiological remission [393, 394]. Interestingly, the early RA observational study (ERAS) showed that patients in sustained clinical remission had less structural damage and better functional outcomes [395]. It would be important to determine whether patients in sustained remission have less joint damage accrual compared with those not in sustained remission, but follow-up radiographs were not available.

Drug survival was lower for infliximab than for adalimumab and etanercept, with 5-year retention rates of 42%, 48%, and 53%, respectively. This difference was due to more discontinuations related to AEs that occurred with infliximab, whereas efficacy-related survival was comparable between the three TNF inhibitors (**Figure 6.1**). After adjusting for demographic and clinical characteristics, treatment with adalimumab or etanercept was associated with 61-66% lower risk for premature treatment termination due to AEs compared with infliximab. Although there is paucity of head-to-head comparative studies, a Cochrane meta-analysis of RCTs found that patients on etanercept had significantly fewer withdrawals due to AEs than patients on adalimumab ($p = 0.009$), infliximab ($p = 0.002$) or anakinra ($p = 0.003$) [300]. Our results also agree with those from other observational studies [391]. In the DANBIO, 2-year drug retention rates were 41% for infliximab, 52% for adalimumab, and 56% for etanercept [390]. The difference was most relevant for withdrawals due to AEs (HR 1.8-2.7). In the DREAM, treatment discontinuations at 12 months were significantly higher for infliximab compared to adalimumab or etanercept [332]. Similarly, in the Swiss Clinical Quality Management RA cohort, treatment with infliximab was associated with more discontinuations (HR 1.2) owing to a higher rate of adverse events [336]. In Japanese RA patients, the adjusted risk for treatment withdrawal due to AE(s) was higher in patients using infliximab (HR 1.7) and tocilizumab (HR 2.0) compared with etanercept [396]. In contrast, two US-based studies have reported higher retention rates for infliximab compared to adalimumab or etanercept; however, these results were not stratified according to the cause of discontinuation [342, 397].

Similar to what other registries have reported [391, 396], increasing age and higher number of previous csDMARD failures were significant predictors for shorter TNFi survival due to adverse events. In contrast, concomitant treatment with MTX independently reduced this risk by 45% (**Table 6.6**). Kristensen *et al.* have previously shown higher adherence to TNFi treatment in RA patients receiving concomitant MTX compared to patients on TNFi monotherapy and patients receiving other csDMARDs [391]. Co-treatment with csDMARDs – especially MTX – was also independent predictor for drug survival at 4 years in the Italian GISEA registry [362]. Possible explanations for this association include that MTX may be a more potent anti-rheumatic drug in itself, or that it can

effectively inhibit the formation of anti-drug antibodies, or that patients not tolerating MTX also possess yet-unidentified characteristics or comorbidities predisposing to lower adherence to TNFi therapy [391].

Rates of first serious infection were 3.5, 2.2, and 1.7 per 100 person-years for infliximab, adalimumab, and etanercept, respectively. These figures are comparable to those reported in a Dutch cohort (3.9, 2.6, and 1.7 per 100 person-years, respectively) [353]. Increasing age and high-dose glucocorticoids (>35 mg/week) were major risk factors for serious infections, in line with the results from several other observational studies [361, 398-401].

In accordance with the drug survival data, treatment with adalimumab and etanercept was associated with a lower risk for serious infections compared to infliximab. The same trend has been demonstrated in other RA cohorts [402] [361]. In a recent report from the DREAM registry, the risk of serious infections was significantly lower in patients treated with etanercept compared with infliximab (HR 0.49) and adalimumab (HR 0.55) [353]. Moreover, combined data from four large US databases with a total 10,484 RA patients showed that use of infliximab was associated with more infections requiring hospitalization compared with etanercept (HR 1.26) and adalimumab (HR 1.23) [400]. On the other hand, Sakai *et al.* analyzed 727 RA patients who started treatment with either infliximab or etanercept and found no difference in the relative risk for serious infection between the two agents [401]. Accordingly, data from the BSRBR showed that although crude rates of serious infections were higher with infliximab than adalimumab and etanercept, adjusted rates were comparable between the three TNF inhibitors [34]. These discrepant results might be due to differences in the characteristics of the patients, in the dosages of administered treatments, or other methodological variations.

CHAPTER VII. SECOND STUDY: COMPARATIVE ANALYSIS AND PREDICTORS OF 10-YEAR TUMOR NECROSIS FACTOR INHIBITORS DRUG SURVIVAL IN GREEK PATIENTS WITH SPONDYLOARTHRITIS

1. Aims of this study

In this study patients with *spondyloarthritis* initiating their *first TNF inhibitor* were included. The aims of the study were to:

a) Describe *baseline characteristics* of Greek spondyloarthritis patients at initiation of their first TNFi
b) Estimate the *10-year drug survival* in the whole cohort of patients as well as stratified according to the *cause of withdrawal*, the *two major sub-diagnoses* and to the *presence of axial versus peripheral arthritis*
c) Define *baseline predictors* for drug discontinuation
d) Define the *rates of response* to TNFi therapy within the first year after TNFi initiation using different response measures for axial and peripheral arthritis, and
e) Examine whether *response within the first year* of therapy could *predict drug survival*.

2. Methods

a. Patients

In this sub-study, patients of at least 18 years of age with a primary diagnosis of SpA, initiating the first TNFi course between 1/1/2004 and 31/12/2014 were included for analysis. For diagnosis, former classification criteria were applied since data register begun in 2004 and therefore patients had either AS, PsA, undifferentiated SpA (uSpA) or inflammatory bowel disease (IBD)-related SpA. Only 2 registered patients had a diagnosis of juvenile SpA and 1 patient had reactive arthritis and these were excluded. Furthermore, since only one patient started certolizumab pegol, he was not included in this analysis. Thus we only included patients on infliximab, adalimumab, etanercept and golimumab.

Patients in the study were characterized at baseline as having isolated axial disease, isolated peripheral arthritis or combined axial and peripheral arthritis based on information by the treating clinician at baseline. Drug survival was calculated as the time period between the start date (date of the first infusion for infliximab and the first prescription of the subcutaneously administered TNFi) and the date of the first missed dose of the drug, death, or 30/4/2015. Discontinuations due to remission of disease (n=9) were censored at the date of the first missed dose and patients lost to follow-up were censored at their last recorded visit. Patients were followed until discontinuation of the first TNFi, death, loss of follow-up, or 30 April 2015, whichever came first.

b. Outcome measures regarding treatment response

Rates of response to therapy were assessed at 6 and 12 months after TNFi initiation by:

- R*esponse measures for axial disease*: BASDAI50 and ASDAS-inactive disease (ASDAS-ID) in patients with axial involvement, and
- R*esponse measures for peripheral dis*ease: EULAR-good response (EULAR-good), ACR70 response and DAS28–remission in patients with peripheral arthritis

c. Statistical analysis

Descriptive statistics and Kaplan-Meier plots

Data are presented as medians with interquartile ranges (IQR) for continuous variables, or frequencies and percentages for categorical variables. Differences between groups were analyzed using the non-parametric Kruskal-Wallis test and the chi-squared test as appropriate. Using the Kaplan-Meier method, unadjusted estimates of the probability for drug survival were plotted according to diagnosis, specific TNFi employed and other baseline characteristics and disease activity measures and compared using log-rank tests. However, the log-rank test could not be used in the comparisons of drug survival between sub-diagnoses and between different TNFi because the assumption of the proportionality of hazards was not met. Cox extended models were used in these cases, both un-adjusted and adjusted. For the analysis of time to discontinuation of treatment due to AE(s), discontinuations due to ineffectiveness were treated as censored observations. Similarly, discontinuations due to AE(s) were handled as censored observations in the analysis of time to discontinuation due to ineffectiveness.

Cox regressions

To explore potential predictors for drug discontinuation, we employed the Cox proportional hazards models adjusted for baseline characteristics as well as the occurrence of a major response within the first year of treatment. Separate models were developed for (a) the whole SpA group of patients for all reasons of stop, as well as stratified for reasons of ineffectiveness and adverse events (b) the two major SpA sub-diagnoses and (c) patients with axial and patients with peripheral arthritis.

Gender, age (per 10 years) , symptom duration (<5 years or ≥5 years), TNFi agent used, clinical diagnosis (classified as AS / PsA / other), year of TNFi start (per 2 years), csDMARD use (yes/no), current methotrexate use (yes/no), presence of axial (yes/no) or peripheral arthritis (yes/no), baseline CRP, physician's global assessment (PhGA) and VAS global were included in all models. Additionally, BASDAI and BASFI were included when investigating for predictors in AS patients and in SpA patients with axial disease and SJC, TJC and the 28-disease activity score (DAS-28) were included in the PsA patients group and in patients with peripheral arthritis. CRP, VAS global, BASDAI, BASFI, SJC, TJC and DAS28 were tested both as continuous variables and as

dichotomous variables based on the median baseline levels. A stronger association was found in univariable regressions when they were used as dichotomous variables and thus they are presented as such. “Clinical diagnosis” and “TNFi agent” variables were also dichotomized (“AS versus other” and “monoclonal antibody agents versus etanercept”) when necessary for the proportionality of hazards assumption to be satisfied.

Moreover, validated response measures for axial disease –BASDAI50 and ASDAS-ID - at 6(±2) and/or 12(±2) months after TNFi initiation were included in the multivariable model for predictors of TNFi discontinuation in patients with axial SpA. Accordingly, response measures for peripheral disease (EULAR-good, ACR70 and DAS28–remission at 6 (±2) and/or 12(±2) months after treatment start) were evaluated as predictors of therapy persistence in patients with peripheral arthritis. A patient was a “responder” if he fulfilled the relevant response criteria in at least one of the two time-points. If data was missing for one of the time-points the patient was classified according to the available data on the other time-point.

All these variables were first tested in univariable Cox regression analyses and were only included in the multivariable Cox regression if they were shown to have a p-value <0.20. In the multivariable models adjusting for response indices, we also included the relevant baseline disease activity index (baseline BASDAI/ ASDAS/DAS28). Variables with least significance were then excluded stepwise until only variables with a p value <0.10 remained in the model. All interactions between gender, TNFi used, clinical diagnosis, ongoing MTX use, and presence of axial or peripheral arthritis were tested.

Missing data and multiple imputation

Data about patient gender, age, symptom duration, clinical diagnosis, TNFi agent used, year of therapy start and reason of stop was complete in all of our patients, whereas previous csDMARDs therapy, ongoing MTX use, presence of axial and/or peripheral arthritis, baseline VAS global, CRP, TJC, SJC, physician’s global assessment, BASDAI, BASFI and DAS28 variables, as well as all response variables had missing values (as described in **Table 6.10**). As a result, information for at least one covariate in Cox regression analyses was missing in 2%-44% of the patients, depending on the analysis. To avoid bias and increase power, our main Cox regression analyses were based on multiple imputation of missing covariate data, but complete-case analyses were also done and are presented in the supplementary material. Multiple imputation was performed on the missing at random assumption, separately for: (a) all patients, (b) patients with axial disease (only known cases, not imputed), (c) patients with peripheral disease (only known cases) and (d) patients with PsA. Markov chain Monte Carlo method was used with 30 imputations obtained after 20 iterations. Variables included in the imputation models were all baseline covariates for the different analyses. Covariates of treatment response were not imputed. Variables with missing data were imputed and used as predictors and variables with complete data were used as predictors only. Additionally, we included whether the patient stopped treatment for the three pre-specified causes, the time of follow-up, the hospital which sent the data, whether other concomitant DMARDs were used (yes/no), baseline ESR and VAS pain, all as indicators only. Interactions between gender, clinical diagnosis, MTX use, axial/peripheral phenotype and type of TNFi agent were also included. All linear variables were transformed to become normally distributed or were turned to categorical values. A diagnostic

check of imputation models was performed and there was no difference found in the distribution of the imputed compared to the un-imputed values.

Complete data-set for assessing BASDAI50 and ASDAS-ID in the first year were available for 354 (46%) and 403 (52%) patients with axial involvement respectively, while the EULAR response, ACR response and DAS28 remission state was evaluable in 374 (57%), 390 (60%) and 448 (68%) patients with peripheral involvement respectively. These covariates were not imputed and thus Cox regression analyses adjusting for these response indices were restricted to the above mentioned percent of patients with available data. Baseline demographics and disease characteristics of the excluded patient group were similar to those of patients included in the analysis, except for more patients with peripheral arthritis ($p=0.001$) and with disease duration <5years ($p<0.001$) in patients without response data in axial disease and the use of etanercept being higher in patients without response data in peripheral disease ($p=0.004$). Age, disease duration in peripheral SpA, TNFi used in axial SpA, clinical diagnosis, year of therapy start, previous csDMARDs use, co-therapy with methotrexate and presence of axial disease in peripheral SpA had no statistically significant differences between the included and excluded patients.

All analyses were performed using the Statistical Package for Social Sciences version 22 (SPSS, SPSS Inc) and p-values of 0.05 (two- tailed) were considered statistically significant.

3. Results

Patient characteristics

A total of 1077 registered SpA patients started treatment with the first TNFi drug, either infliximab (61%), etanercept (19%), adalimumab (17%), or golimumab (3.5%). Of them, 561 patients had a diagnosis of AS, 375 PsA, 108 uSpA and 33 IBD-related SpA.

Patients with AS had longer disease duration and less previous and ongoing conventional synthetic DMARDs (csDMARDs) ($p<0.001$), corticosteroids ($p<0.001$) and higher baseline CRP ($p=0.001$) than patients with other diagnosis. Although half of them had peripheral arthritis (past or current), it was milder (lower DAS28 score) compared to PsA or uSpA patients with peripheral arthritis ($p<0.001$). Concerning inflammatory burden at baseline, BASDAI, BASFI and ASDAS-CRP indices were comparable in patients with axial involvement, irrespectively of specific diagnosis. Patients with PsA were older and had received more csDMARDs before TNFi initiation, compared to AS and uSpA. Almost all patients with PsA had peripheral arthritis which was more active compared to other SpA patients ($p<0.001$ for all). Combined axial and peripheral arthritis was reported in 42% of PsA, 57% of uSpA and 48% of IBD-related SpA patients. Demographics and disease characteristics are in **Tables 6.11 and 6.12** and baseline activity of the whole group and for each sub-diagnosis while for patients having peripheral arthritis versus those with isolated axial spondylitis are in **Supplementary Table 3**.

Table 6.11. Baseline demographics, disease characteristics and activity overall and according to clinical subdiagnosis*

	Valid (n)	**All (n=1077)**	**AS (n=561)**	**PsA (n=375)**	**uSpA (n=108)**	**IBD-SpA (n=33)**	**p- value‡**
Gender (male), N (%)	1077	711 (66)	446 (80)[c,d,f]	203 (54)[c]	51 (47)[d]	15 (46)[f]	<0.001
Age, years	1077	44 (35-54)	41 (33-50)[c]	49 (39-59)[c,e,g]	41 (33-52)[e]	43 (33-54)[g]	<0.001
Symptom duration, years	1077	9 (3-17)	13 (6-20)[c,d,f]	6 (2-12)[c]	4 (1-11)[d]	6 (2-11)[f]	<0.001
Symptom duration <5 years, N (%)	1077	352 (33)	115 (21)[c,d,f]	166 (44)[c]	56 (52)[d]	15 (46)[f]	<0.001
TNFi used: Infliximab, N (%)	1077	655 (61)	382 (68)[c,d]	203 (54)[c]	49 (45)[d]	21 (64)	<0.001
Etanercept, N (%)	1077	200 (19)	81 (14)[c,d]	89 (24)[c,g]	27 (25)[d,h]	3 (9)[g,h]	<0.001
Adalimumab, N (%)	1077	184 (17)	87 (16)	64 (17)	24 (22)	9 (27)	0.144
Golimumab, N (%)	1077	38 (3.5)	11 (2)[c,d]	19 (5)[c]	8 (7)[d]	0 (0)	0.005
Follow-up, years	1077	2.8 (1.0-5.9)	2.9 (1.0-7.3)[d]	2.8 (1.0-5.4)	2.1 (0.7-4.5)[d]	2.3 (0.9-3.9)	0.024
Axial inflammatory arthritis N (%)	913	770 (85)	561 (100)[c,d,f]	121 (53)[c,e,g]	70 (73)[d,e]	22 (76)[f,g]	<0.001
Peripheral arthritis N (%)	944	652 (69)	209 (46)[c,d,f]	336 (94)[c,e,g]	88 (87)[d,e]	22 (76)[f,g]	<0.001
Nr of previous csDMARDs	1059	1 (0-2)	0 (0-1)[c, d]	1 (1-2)[c,e]	1 (1-2)[d,e]	1 (1-2)	<0.001
Nr of coadministered	1070	0 (0-1)	0 (0-1)[c,d,f]	1 (1-1)[c]	1 (0-1)[d]	1 (0-1)[f]	<0.001
Co-administered csDMARD,							
Methotrexate	1020	405 (40)	100 (18)[c,d,f]	232 (66)[c,g]	62 (58)[d,h]	11 (36)[f,g,h]	<0.001
Other	1020	124 (12)	29 (5)[c,d,f]	62 (18)[c,g]	18 (17)[d,h]	13 (42)[f,g,h]	<0.001
Monotherapy , N (%)	1070	544 (51)	417 (74)[c,d,f]	86 (23)[c]	32 (30)[d]	12 (36)[f]	<0.001
Ongoing corticosteroids, N(%)	1010	115 (11)	24 (5)[c,d,f]	61 (17)[c]	25 (24)[d]	5 (16)[f]	<0.001

*Except when stated otherwise values are medians (interquartile range). ‡p values are determined by chi-square test or Kruskal-Wallis test as appropriate

[c] $p < 0.05$ for the comparison between AS and PsA patients; [d] $p < 0.05$ for the comparison between AS and uSpA patients; [e] $p < 0.05$ for the comparison between PsA and uSpA patients; [f] $p < 0.05$ for the comparison between AS and IBD-related SpA patients; [g] $p < 0.05$ for the comparison between PsA and IBD-related SpA patients; [h] $p < 0.05$ for the comparison between uSpA and IBD-related SpA patients

Table 6.12. Baseline disease activity overall and according to clinical subdiagnosis*

		Diagnosis					
	Valid (n)	**All (n=1077)**	**AS (n=561)**	**PsA (n=375)**	**uSpA (n=108)**	**IBD-SpA (n=33)**	**p- value‡**
BASDAI (0-10) [a]	507	5.1 (4.0-6.4)	5.1 (3.8-6.4)	5.2 (4.2-6.2)	5.6 (4.3-7.2)	5.2 (4.1-6.9)	0.303
BASFI (0-10)[a]	453	5.1 (3.3-6.9)	5.1 (3.2-7.0)	5.1 (3.4-6.9)	5.0 (3.4-6.6)	3.7 (2.6-6.8)	0.891
ASDAS-CRP [a]	440	3.4 (2.8-4.1)	3.5 (2.8-4.1)	3.5 (2.5-4.1)	3.4 (2.4-4.2)	3.4 (3.0-3.8)	0.743
CRP (mg/dl)	712	1.2 (0.4-2.7)	1.5 (0.6-3.0)[c, d,f]	1.1 (0.3-2.3)[c]	0.9 (0.3-2.6)[d]	0.6 (0.3-1.1)[f]	0.001
ESR (mm/h)	785	30 (16-48)	29 (16-49)	30 (18-48)	25 (13-48)	24 (18-45)	0.545
VAS global (0-100)	796	60 (50-80)	60 (50-80)	65 (50-80)	70 (45-80)	70 (60-80)	0.213
VAS pain (0-100)	760	65 (50-80)	60 (50-80)	70 (50-80)	70 (50-80)	70 (58-80)	0.709
Physician's global assessment (0-4)	692	3 (2-3)	3 (2-3)[d]	3 (2-3)[e]	3 (3-3)[d,e]	3 (2.8-3)	0.001
Tender joint count[b]	519	3 (1-8)	1 (0-3)[c,d]	5 (2-11)[c,e]	2 (0-5)[d,e]	5 (0-11)	<0.001
Swollen joint count[b]	519	2 (0-6)	0 (0-1)[c,d,f]	4 (1-8)[c,e]	2 (1-4)[d,e]	2 (0-6)[f]	<0.001
DAS28-ESR[b]	483	4.5 (3.6-5.4)	3.8 (3.1-4.6)[c,d,f]	5.1 (4.2-	4.4 (3.6-5.3)[d,e]	4.7 (4.0-5.5)[f]	<0.001
HAQ (0-3)[b]	305	0.8 (0.5-1.3)	0.9 (0.5-1.3)	0.9 (0.5-1.3)	0.6 (0.3-1.1)	0.8 (0.3-1.1)	0.241

*Except when stated otherwise values are medians (interquartile range). ‡p values are determined by chi-square test or Kruskal-Wallis test as appropriate.
[a] In patients with axial involvement; [b] In patients with peripheral involvement; [c] $p < 0.05$ for the comparison between AS and PsA patients; [d] $p < 0.05$ for the comparison between AS and uSpA patients; [e] $p < 0.05$ for the comparison between PsA and uSpA patients; [f] $p < 0.05$ for the comparison between AS and IBD-related SpA patients; [g] $p < 0.05$ for the comparison between PsA and IBD-related SpA patients; [h] $p < 0.05$ for the comparison between uSpA and IBD-related SpA patients

Table 6.13. Reasons for discontinuation overall and according to clinical subdiagnosis N (% of stops) [N/100patients/year]

Reasons of discontinuation	**All (n=1077)**	**AS (n=561)**	**PsA (n=375)**	**uSpA (n=108)**	**IBD-SpA (n=33)**
Inefficacy	175 (43)[4.1]	71 (36)[2.9]	70 (47)[5.1]	23 (55)[7.3]	11 (61)[9.8]
Primary inefficacy	83 (21)[1.9]	34 (17)[1.4]	32 (22)[2.3]	15 (36)[4.7]	2 (11)[1.8]
Secondary	92 (23)[2.2]	37 (19)[1.5]	38 (26)[2.8]	8 (19)[2.5]	9 (50)[8.0]
Adverse events	159 (39)[3.7]	90 (46)[3.6]	53 (36)[3.9]	11 (26)[3.5]	5 (28)[4.5]
Other	70 (17) [1.6]	34 (17) [1.4]	26 (18) [1.9]	8 (19) [2.5]	2 (11) [1.8]
Total	404 [9.4]	195 [7.8]	149 [10.9]	42 [13.3]	18 [16.1]

Therapy discontinuations

Overall, 404 (37.5%) patients discontinued TNFi treatment during a total follow-up of 4288 patient-years and 87% of the stops occurred within the first 5 years. Median time for discontinuation was 1.6 (0.6-3.1), 1.4 (0.6-3.1) and 1.1 (0.5-3.3) years for AS, PsA and uSpA respectively.

Treatment inefficacy was the most frequent cause of discontinuation (43% of cases), followed closely by adverse events (39%). However, for patients with AS, therapy withdrawals were more often due to an adverse event than due to treatment failure (**Table 6.13**). Reasons for treatment discontinuation according to the presence of peripheral arthritis are shown in **Supplementary Table 4**. Most prevalent adverse events leading to stop of treatment in the whole group were the infusion/injection reactions (61 cases) and psoriatic-like rashes (18 cases), both more common in infliximab-treated patients ($p<0.001$). Other important adverse events leading to TNFi discontinuation included cancer (11 patients), tuberculosis (9 patients), other serious infections (8 patients) and demyelinating disease (4 patients).

Unadjusted drug survival analyses

The 5- and 10-year retention rates of the first TNFi therapy in SpA were estimated to be 60% and 49% respectively. The estimated 10-year drug retention rates in AS, PsA and uSpA were 55%, 42% and 38% respectively. Accordingly, the 5-year drug retention rates in AS, PsA and uSpA, were estimated to be 63%, 59% and 49% respectively. Patients with IBD-related SpA had the lowest TNFi drug survival (5-year: 35%).

The median (95% CI) TNFi survival time in AS patients was not estimable as less than 50% of patients discontinued treatment during follow-up, while in PsA, uSpA and IBD-related SpA it was 7.8 (6.0-9.5), 4.9 (2.0-7.9) and 3.5 (1.6-5.4) years respectively. Since the survival curves of AS and uSpA crossed at around 2.5 years and those of AS and PsA diverged after approximately 7 years two separate analyses were performed for each comparison; up to 2.5 and 7 years of follow-up no significant differences in drug survival between AS and uSpA and AS and PsA patients respectively were found. However, after those time-points significant differences were observed (**Figure 6.3.A**).

Of note, AS patients had a higher survival due to primary failure compared with uSpA patients (log rank, p=0.004) and due to secondary failure compared with PsA patients (p=0.030).

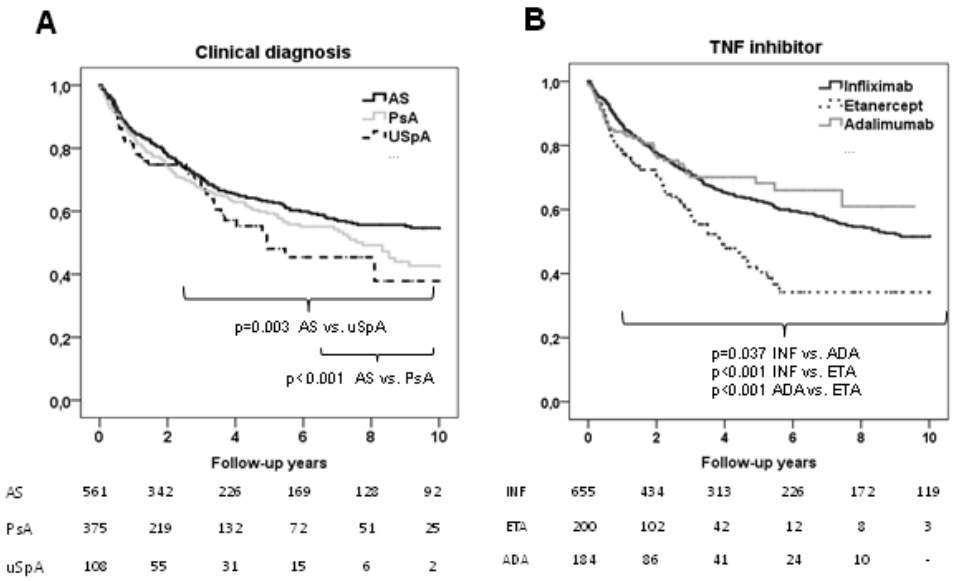

Figure 6.3. Crude drug survival curves stratified according to diagnosis and TNFi agent used. Results from Kaplan-Meier analyses and log-rank test. In both [A] and [B] significant differences were observed between AS and PsA and AS and uSpA during the periods 7-10 years and 2.5-10 years respectively as well as between INF and ETA, ADA and ETA and INF and ADA during the period 6 months-10 years. These results were verified in unadjusted Cox-extended analyses and the interactions with time as described were significant, except for the hazard rate of discontinuation of ETA versus INF which was stable over time. The number of patients still on therapy at different time-points is shown below the graphs.

Similarly, a time-dependent association of drug retention according to the specific TNFi used was found. Up-to the first 6 months, infliximab had the highest retention rate relatively to adalimumab and etanercept, the latter having a comparable survival. However, after the first 6 months, adalimumab was the TNFi best retained, with infliximab being intermediate and etanercept having the lowest survival (**Figure 6.3.B**). Selecting for reasons of discontinuation, infliximab had significantly less stops due to primary inefficacy compared to etanercept (log rank, p<0.001) and adalimumab (p<0.001) and due to secondary inefficacy compared to etanercept (p <0.001). In contrast, safety-related drug survival was better with etanercept (p=0.018) and adalimumab (p=0.002) than with infliximab. Finally, etanercept had significantly more stops for "other reasons" compared to both infliximab (p=0.001) and adalimumab (p=0.008).

Furthermore, overall unadjusted survival rates were higher in men (p<0.001), in patients with baseline CRP >1.2 mg/dl (p=0.005) and in patients without peripheral arthritis (p=0.001). Patients with isolated axial disease had a higher TNFi survival compared to both isolated peripheral (p=0.017) and combined peripheral and axial disease (p=0.003) (**Figure 6.4)**.

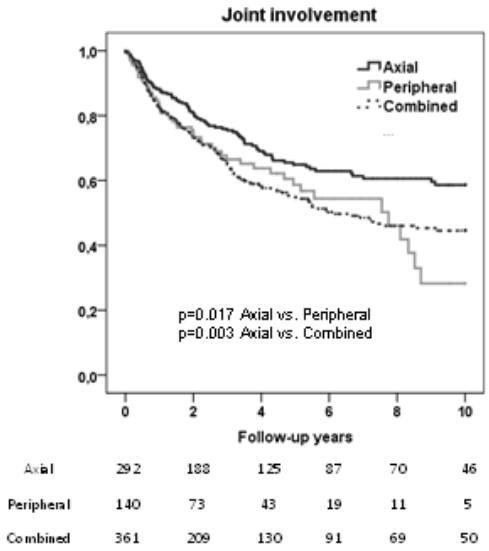

Figure 6.4. Crude drug survival curves stratified according to joint involvement phenotype - Kaplan-Meier analyses and log-rank test. The number of patients still on therapy at different time-points is shown below the graphs.

Adjusted analyses of drug survival in the whole group

In the multivariable Cox regression analysis, male gender [HR(95%CI)= 0.68 (0.55-0.84), p<0.001], use of a monoclonal antibody TNFi versus etanercept [HR=0.64 (0.50-0.82), p<0.001], methotrexate co-therapy [HR=0.69 (0.55-0.87), p=0.001] and absence of peripheral disease [HR=0.68 (0.52-0.88), p=0.004] were shown to independently predict longer drug retention in SpA patients, while high baseline CRP had a borderline significance [HR=0.81 (0.64-1.03), p=0.087] (**Table 6.14**). Significant interactions regarding TNFi survival were found for the effect of methotrexate co-therapy according to patient gender and to the presence of axial disease. Methotrexate co-therapy was only protective against treatment terminations in men (p=0.002) and in patients with isolated peripheral disease (p=0.006). Furthermore, monoclonal TNFi had a better survival than etanercept in AS (p<0.001) and in uSpA (p=0.002) but not in patients with PsA (p=0.576).

Significant predictors for better efficacy-related survival were male gender [HR=0.60 (0.44-0.82), p=0.001], use of infliximab versus etanercept [HR=0.37 (0.26-0.54,) p<0.001], adalimumab [HR=0.58 (0.37-0.89), p=0.013] and golimumab [HR=0.28 (0.14-0.57), p<0.001], no peripheral arthritis involvement [HR=0.53 (0.34-0.80), p=0.003] and baseline VAS global ≤ 60mm {HR=0.68 (0.48-0.97), p=0.032] (**Table 6.14)**. Similarly, better safety-related survival was predicted by male gender [HR=0.57 (0.40-0.81), p=0.002], MTX co-therapy [HR=0.60 (0.39-0.91), p=0.017], use of etanercept [HR=0.52 (0.30-0.89), p=0.018] and adalimumab [HR=0.34 (0.18-0.64) p=0.001] versus infliximab and prior use of at least one conventional synthetic disease modifying antirheumatic drugs (csDMARD) [HR=0.68 (0.47-0.99), p=0.042].

Table 6.14. Cox regression analysis for TNFi discontinuation in the whole group of SpA patients, stratified by reason of stop†

	All reasons		**Discontinuations due to inefficacy**		**Discontinuations due to adverse events**	
	Univariate	Final model after backward selection	Univariate	Final model after backward selection	Univariate	Final model after backward selection
Gender (male versus female)	0.63 (0.52-0.77)[c]	0.68 (0.55-0.84)[c]	0.45 (0.34-0.61)[c]	0.60 (0.44-0.82)[b]	0.79 (0.57-1.11)**	0.57 (0.40-0.81)[b]
Age (per 10 years)	1.01 (0.93-1.09)		1.04 (0.92-1.17)		1.00 (0.73-1.38)	
Symptoms duration (< versus ≥5 years)	1.20 (0.97-1.48)*		1.41 (1.03-1.92)[a]		0.95 (0.67-1.35)	
TNFi agent used (ETA versus other)	1.65 (1.30-2.10)[c]	1.56 (1.22-1.99)[c]				
TNFi agent used: INF (reference)			1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
ETA			3.16 (2.21-4.51)[c]	2.67 (1.86-3.84)[c]	0.52 (0.31-0.90)[a]	0.52 (0.30-0.89)[a]
ADA			1.89 (1.23-2.90)[b]	1.74 (1.13-2.68)[a]	0.38 (0.20-0.73)[b]	0.34 (0.18-0.64)[b]
GOL			4.38 (2.17-8.81)[c]	3.53 (1.74-7.18)[c]	0.25 (0.04-1.78)**	0.24 (0.04-1.69)**
Clinical diagnosis (AS versus other)	0.77 (0.63-0.94)[a]					
Clinical diagnosis: AS (reference)			1.00 (ref)		1.00 (ref)	
PsA			1.55 (1.10-2.16)[a]		0.93 (0.66-1.32)	
other			2.31 (1.53-3.48)[c]		0.85 (0.50-1.45)	
Year of TNFi therapy start (per 2 years)	1.12 (1.04-1.20)[b]		1.30 (1.17-1.44)[c]		0.89 (0.79-1.01)*	
Previous csDMARDs (yes versus no)	0.96 (0.78-1.17)		1.88 (1.33-2.66)[c]		0.61 (0.44-0.85)[b]	0.68 (0.47-0.99)[a]
Methotrexate co-therapy (yes vs no)	0.84 (0.68-1.04)*	0.69 (0.55-0.87)[b]	1.18 (0.86-1.62)		0.55 (0.38-0.79)[b]	0.60 (0.39-0.91)[a]
Axial disease (yes versus no)	0.86 (0.65-1.16)		0.65 (0.44-0.97)[a]		1.15 (0.65-2.04)	
Peripheral disease (yes versus no)	1.44 (1.13-1.83)[b]	1.47 (1.14-1.91)[b]	2.25 (1.49-3.38)[c]	1.91 (1.25-2.90)[b]	0.90 (0.63-1.29)	
CRP (> versus ≤1.2 mg/dl)	0.78 (0.62-0.99)[a]	0.81 (0.64-1.03)*	0.80 (0.57-1.13)		0.81 (0.56-1.18)	
VAS global (> versus ≤60)	1.16 (0.92-1.46)		1.64 (1.15-2.34)[b]	1.47 (1.03-2.10)[a]	0.91 (0.64-1.30)	
PhGA (> versus ≤2)	1.03 (0.81-1.30)		1.13 (0.72-1.77)		0.87 (0.61-1.26)	

† Numbers are Hazard Rates (95% confidence intervals). TNFi: tumor-necrosis factor inhibitor; INF: Infliximab; ETA: Etanercept; ADA: Adalimumab; GOL: Golimumab; AS: Ankylosing Spondylitis; PsA: Psoriatic Arthritis; csDMARDs: conventional synthetic Disease Modifying Anti-Rheumatic Drugs; CRP: C-reactive protein; VAS: Visual Analogue Score; PhGA: Physician's Global Assessment

*: p<0.1
**: p<0.2
a: p<0.05
b: p<0.01
c: p<0.001

Prediction of drug survival in AS and PsA

In AS patients, therapy with etanercept versus a monoclonal antibody [HR=1.79 (1.2-2.65), p=0.01], the presence of peripheral disease [HR=1.46 (1.07-1.98), p=0.05] and, a most recent calendar year of TNFi initiation [HR=1.17 (1.17-1.31), p<0.05] independently predicted therapy discontinuation, while the use of csDMARD(s) prior to TNFi start [HR=0.65 (0.47-0.89), p=0.009], predicted longer drug survival. A trend for male gender predicting higher survival was observed (p=0.082) (**Table 6.15**).

Accordingly, in PsA patients male gender [HR=0.62 (0.45-0.86), p=0.005] and co-therapy with methotrexate [HR=0.61 (0.43-0.87), p=0.006] were the significant predictors of longer overall TNFi survival (**Table 6.15**).

Prediction of drug survival according to the pattern of arthritis: association of first-year responses to TNFi survival

Since we have found that a major response in the first year of therapy may predict long-term TNFi survival in RA patients, we sought to explore if a similar effect can be seen in SpA patients as well. In order to perform this analysis and due to different response indices for different phenotypes, patients were grouped in those with axial or peripheral disease at baseline. We used different response measures for axial and peripheral arthritis: for axial disease we calculated percentage of patients achieving reduction of BASDAI by more than 50% (BASDAI50) and percentage reaching AS disease activity index-inactive disease state (ASDAS-ID). Similarly, in patients having peripheral disease we calculated percentage of patients having good response based on the EULAR criteria (EULAR-good), ≥70% improvement based on the American College of Rheumatology criteria (ACR70) and remission of disease according to DAS28 score (DAS28–remission) at 6 and 12 months.

Univariable and multivariable analyses for baseline predictors of TNFi retention in patients having axial or peripheral arthritis are described in **Tables 6.16 and 6.17**. Complete data-set for assessing BASDAI-50% response (BASDAI50) and AS Disease Activity Score –inactive disease state (ASDAS-ID) in the first year were available for 354 (46%) and 403 (52%) patients respectively with axial disease. Among them, 59% and 42% achieved BASDAI50 or had ASDAS-ID respectively at least once within the first year of therapy. After adjusting for baseline parameters, a state of ASDAS-ID or a BASDAI50 response within the 1st year were the strongest predictors of longer TNFi survival [HR=0.33 (0.26-0.41), p<0.001 and HR=0.49, (0.34-0.71), p<0.001, respectively) (**Table 6.16**).

Accordingly, in patients with peripheral arthritis, DAS28 remission state (evaluable patients: n=448, 68%), the European League Against Rheumatism –good response (EULAR-good) (n=374, 57%) and the American College of Rheumatology 70% response (ACR70) (n=390, 60%) were achieved by 55%, 58% and 20% of the patients respectively at least once within the 1st year of therapy. In the multivariable model adjusting for baseline variables and DAS28-remission in the 1st year this was again the strongest predictor of longer TNFi retention [HR=0.35 (0.24-0.50), p<0.001]. Similar results were obtained when adding EULAR-good or ACR70 response to the model (**Table 6.17**).

Table 6.15. Cox regression analysis for TNFi discontinuation stratified by diagnosis†

	AS		PsA	
	Univariate	**Multivariate $**	**Univariate**	**Multivariate $**
Gender (male versus female)	0.66 (0.48-0.93)[a]	0.73 (0.51-1.04)*	0.64 (0.46-0.88)[b]	0.62 (0.45-0.86)[b]
Age (per 10 years)	0.94 (0.74-1.32)		0.91 (0.64-1.29)	
Symptoms duration (< versus ≥5 years)	1.40 (1.00-1.97)*		0.90 (0.65-1.26)	
TNFi agent used (ETA versus other)	2.17 (1.50-3.15)[c]	1.77 (1.19-2.63)[b]		
TNFi agent used: INF (reference)			1.00 (ref)	
ETA			1.22 (0.81-1.83)	
ADA			1.25 (0.75-2.06)	
GOL			2.35 (1.12-4.91)[a]	
Year of TNFi therapy start (per 2 years)	1.24 (1.11-1.38)[c]	1.17 (1.04-1.31)[a]	1.04 (0.92-1.18)	
Previous csDMARDs (yes versus no)	0.72 (0.53-0.99)[a]	0.65 (0.47-0.90)[b]	1.06 (0.65-1.74)	
Methotrexate co-therapy (yes versus no)	0.89 (0.62-1.30)		0.65 (0.46-0.92)[a]	0.61 (0.43-0.87)[b]
Axial disease (yes versus no)			0.91 (0.60-1.37)	
Peripheral disease (yes versus no)	1.41 (1.02-1.94)[a]	1.53 (1.11-2.10)[b]	1.98 (0.82-4.76)**	2.20 (0.90-5.34)*
CRP (> versus ≤1.2 mg/dl)	0.83 (0.58-1.19)		0.74 (0.49-1.11)**	
VAS global (> versus≤60)	1.15 (0.82-1.63)		1.09 (0.76-1.56)	
PhGA (> versus ≤2)	1.07 (0.73-1.58)		1.06 (0.71-1.58)	
BASDAI (> versus ≤5)	1.07 (0.74-1.53)			
BASFI (> versus ≤5)	1.27 (0.84-1.94)			
SJC-28 (> versus ≤2)			1.05 (0.72-1.52)	
TJC-28 (> versus ≤3)			1.24 (0.84-1.84)	
DAS28-ESR baseline (> versus ≤4.5)			1.06 (0.70-1.62)	

† Numbers are Hazard Rates (95% confidence intervals). $ Final model after backward selection. TNFi: tumor-necrosis factor inhibitor; INF: Infliximab; ETA: Etanercept; ADA: Adalimumab; GOL: Golimumab; AS: Ankylosing Spondylitis; PsA: Psoriatic arthritis; csDMARDs: conventional synthetic Disease Modifying Anti-Rheumatic Drugs; CRP: C-reactive protein; VAS: Visual Analogue Score; PhGA: Physician's Global Assessment; BASDAI: Bath Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Functional Index; SJC-28: Swollen Joint Count in 28 joints; TJC: Tender Joint Count in 28 joints; DAS28-ESR: Disease Activity Score in 28 joints using the Erythrocyte Sedimentation Rate level
*: p<0.1; **: p<0.2; a: p<0.05; b: p<0.01; c: p<0.001

Table 6.16. Cox regression analysis for predictors of TNFi discontinuation in patients with axial inflammatory arthritis†

	Univariable	Final model adjusting for **baseline variables only**	Final model when adjusting for **baseline variables plus 1st year BASDAI50 response**	Final model when adjusting for **baseline variables plus 1st year ASDAS-ID response**
Gender (male versus female)	0.67 (0.52-0.87)[b]	0.74 (0.56-0.98)[a]	0.62 (0.40-0.95)[a]	0.66 (0.43-1.02)*
Age (per 10 years)	0.92 (0.73-1.17)			
Symptoms duration (< versus ≥5 years)	1.40 (1.08-1.82)[a]			
TNFi agent used (ETA versus other)	1.94 (1.44-2.61)[c]	1.68 (1.24-2.28)[b]		1.88 (1.40-2.53)[a]
Clinical diagnosis: AS (ref)	1.00 (ref)			
PsA	1.06 (0.76-1.48)			
other	1.52 (1.09-2.14)[a]			
Year of TNFi therapy start (per 2 years)	1.20 (1.10-1.31)[c]	1.13 (1.03-1.24)[a]		
Previous csDMARDs (yes versus no)	0.84 (0.66-1.07)**	0.68 (0.52-0.88)[b]	0.64 (0.42-0.96)[a]	0.71 (0.48-1.05)*
Methotrexate co-therapy (yes vs no)	0.96 (0.73-1.25)			
Peripheral disease (yes versus no)	1.41 (1.08-1.84)[a]	1.47 (1.12-1.93)[b]		
CRP (> versus ≤1.2 mg/dl)	0.72 (0.54-0.96)[b]			
VAS global (> versus≤60)	1.15 (0.88-1.53)			
PhGA (> versus≤2)	0.87 (0.64-1.19)			
BASDAI (> versus ≤5)	1.09 (0.81-1.48)			
BASFI (> versus ≤5)	1.15 (0.83-1.59)			
BASDAI50 (yes versus no)	0.49 (0.34-0.72)[c]		0.49 (0.34-0.71)[c]	
ASDAS-ID (yes versus no)	0.33 (0.22-0.51)[c]			0.33 (0.26-0.41)[c]

† Numbers are Hazard Rates (95% confidence intervals); TNFi: Tumor-Necrosis Factor Inhibitor; ETA: Etanercept; AS: Ankylosing Spondylitis; PsA: Psoriatic Arthritis; csDMARDs: conventional synthetic Disease Modifying Anti-Rheumatic Drugs; CRP: C-reactive protein; VAS: Visual Analogue Score; PhGA: Physician's Global Assessment; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASDAI50: 50% improvement of Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-ID: Ankylosing Spondylitis Disease Activity Score-Inactive Disease state

*: p<0.1; **: p<0.2; a: p<0.05; b: p<0.01; c: p<0.001

Table 6.17. Cox regression analysis for predictors of TNFi discontinuation in patients with peripheral arthritis†

	Univariable	Multivariable model adjusting for **baseline variables only**	Final model when adjusting for baseline variables plus **1st year DAS28-remission**	Final model when adjusting for baseline variables plus **1st year EULAR good response**	Final model when adjusting for baseline variables plus **1st year ACR70 response**
Gender (male versus female)	0.60 (0.47-0.76)[c]	0.63 (0.49-0.81)[c]			0.74 (0.52-1.06)*
Age (per 10 years)	0.90 (0.70-1.15)				
Symptoms duration (< versus ≥5 years)	1.10 (0.86-1.41)				
TNFi agent used (ETA versus other)	1.53 (1.15-2.03)[b]	1.45 (1.09-1.93)[a]	1.92 (1.21-3.04)[b]	1.62 (1.05-2.50)[a]	1.65 (1.06-2.56)[a]
Clinical diagnosis: AS (ref)	1.00 (ref)				
PsA	1.06 (0.81-1.38)				
other	1.21 (0.84-1.73)				
Year of TNFi therapy start (per 2 years)	1.08 (1.00-1.17)*				
Previous csDMARDs (yes versus no)	0.95 (0.72-1.26)				
Methotrexate co-therapy (yes vs no)	0.72 (0.56-0.92)[b]	0.65 (0.51-0.84)[b]		0.73 (0.50-1.05)*	0.65 (0.46-0.93)[a]
Axial disease (yes versus no)	0.97 (0.72-1.29)				
CRP (> versus ≤1.2 mg/dl)	0.74 (0.55-0.99)[a]	0.76 (0.57-1.02)*			
VAS global (> versus ≤60)	1.28 (0.98-1.67)*				
PhGA (> versus ≤2)	1.00 (0.73-1.37)				
SJC-28 (> versus ≤2)	1.26 (0.96-1.66)**				
TJC-28 (> versus ≤3)	1.32 (1.00-1.74)[a]	1.32 (1.00-1.75)*	1.84 (1.10-3.06)[a]	1.82 (1.26-2.62)[b]	1.81 (1.26-2.59)[b]
DAS28 baseline (> versus ≤4.5)	1.10 (0.84-1.46)		0.61 (0.36-1.03)*		
DAS28-remission (yes versus no)	0.39 (0.29-0.55)[c]		0.35 (0.24-0.50)[c]		
EULAR-good response (yes versus no)	0.42 (0.30-0.60)[c]			0.41 (0.29-0.58)[c]	
ACR70 (yes versus no)	0.33 (0.19-0.60)[c]				0.29 (0.21-0.40)[c]

† Numbers are Hazard Rates (95% confidence intervals); TNFi: tumor-necrosis factor inhibitor; ETA: etanercept; AS: Ankylosing Spondylitis; PsA: Psoriatic arthritis; csDMARDs: conventional syntheticdisease modifying anti-rheumatic drug; CRP: C-reactive protein, VAS: visual analogue score; PhGA: physician's global assessment; SJC: swollen joint count; TJC: tender joint count; DAS28: Disease Activity Score based on 28 joints; EULAR: European League Against Rheumatism; ACR70: American College of Rheumatology criteria 70% improvement

*: p<0.1; **: p<0.2; a: p<0.05; b: p<0.01; c: p<0.001

4. Discussion

Individual diseases of the SpA spectrum share common genetic, pathophysiological and clinical characteristics and this report from the HeRBT was the first to provide combined, long-term, real-life data, registered prospectively with a common protocol for the SpA group of patients. In this study, Greek SpA patients treated with the first TNFi had a rather favorable drug survival of 60% and 49% at 5 and 10 years respectively. Among the different baseline parameters assessed, having a diagnosis of AS and limited axial phenotype predicted longer drug adherence. Most interestingly, the strongest independent predictor for long-term drug survival was achievement of a major response in axial or peripheral disease during the first year.

In observational studies, drug survival is regarded as a global measure of treatment efficacy and safety, while also reflecting patient and physician expectations, comorbidities considerations and medication compliance. To our knowledge, our data are the only available for 10-year TNFi retention in a prospective observational setting in SpA patients. Carmona *et al* analyzed SpA patients as a group, albeit for a shorter follow-up time and reported a 3-year TNFi survival of 74%, while in a recent retrospective study the 8-year survival in axial SpA and PsA patients was 55.1%, both rather comparable to our results (3-year: 69% and 8-year: 52%) [349, 403].

A crude comparative analysis of TNFi survival between individual SpA subtypes showed a time-dependent association, with ultimately higher retention rates in AS versus uSpA and PsA patients. This was verified in unadjusted and adjusted for baseline covariates Cox-extended models (data not shown). Accordingly, Lie *et al* showed a similar to our data higher retention rate in AS compared to uSpA [351]. However, in other studies of significantly shorter follow-up, a comparable TNFi drug survival was found between PsA and AS patients [349, 350, 403]. These discrepancies could be possibly attributed to different study populations as well as to varying physician therapy withdrawal criteria.

An interesting finding of our analysis was that disease phenotype -axial versus peripheral arthritis- predicted drug survival and this is of clinical importance. In the multivariate analyses it was shown that absence of peripheral arthritis was an independent predictor of longer drug survival in the whole SpA group, as well as in AS patients, and this was due to a lower chance of inefficacy withdrawals. We have to note that baseline demographics and disease characteristics of the different SpA sub-types of our cohort are well in accordance with available epidemiologic data and those reported by other registries [334, 347, 404]. Concerning the effect of peripheral involvement on TNFi retention, data are sparse. Kristensen *et al* have reported that peripheral disease was shown to predict a more favorable TNFi retention in AS at 2 years of follow-up [347]. Shorter follow-up and other factors may be implicated in this difference and more studies are necessary, especially nowadays with the growing group of patients classified as peripheral SpA becoming more clinically significant.

Male gender predicted higher treatment retention both for efficacy and for safety reasons, while use of methotrexate was protective against discontinuations due to adverse events. The effect of gender on TNFi treatment response and survival has repeatedly been shown in both AS and PsA patient studies [346, 405]. Concerning the effect of csDMARDs, the only study for patients with SpA (excluding PsA), from the Rheumatic Diseases Portuguese Register, reported no protective effect of

csDMARDs [406]. Sulphasalazine was the most commonly administered csDMARD in that study, as opposed to methotrexate mainly used in our cohort. Since the effect of csDMARDs is both disease and individual TNFi agent dependent, differences in these parameters among different cohorts may explain observed discrepancies. In the adjusted Cox-extended analyses, both MTX and AS were proved to be independent predictors favoring drug retention in the whole SpA group. Therefore, we consider that both the underlying disorder and methotrexate had a predictive role, independently.

We as others [346] found no protective effect of MTX co-medication in AS and this is supported by smaller studies [407, 408]; on the contrary investigators from the ARTIS registry reported a positive effect of MTX [351]. Although not strongly supported by the evidence thus far and not proposed for the treatment of axial disease by ASAS/EULAR recommendations [409], a favorable effect of MTX especially for those with peripheral arthritis cannot be excluded. Concerning PsA, we and others have found a favorable effect of MTX co-administration [170, 227] while a recent report from CORRONA US-based registry found no effect [228]. A recent systematic literature review showed that the use of MTX prolongs TNFi drug survival of monoclonal TNFi [229] and this also accords to our findings.

Early clinical improvements were shown to predict 1 or 5 years clinical responses in SpA patients, albeit in the context of clinical trials of TNFi [410, 411]. Interestingly, major response rates within the first year in the present cohort were high and comparable to those in previous studies [191, 227, 346, 412]. After grouping patients to those with axial or peripheral disease and after adjusting for different baseline factors, a state of ASDAS-CRP inactive disease for patients with axial disease and DAS28-remission for those with peripheral disease were the strongest independent predictors of long-term TNFi retention. We are the first to report that a clinical parameter quantifiable early in the treatment course could predict a 2- up-to 3.5- fold higher chance of 10-year drug survival in every-day clinical practice. We consider this of major clinical importance and justify once more the need for close monitoring of SpA patients initiating TNFi with composite indices of response.

CHAPTER VIII. STUDY LIMITATIONS

A primary limitation of our studies is related to their observational design. The lack of randomization and blinding may have resulted in channeling bias and performance bias. Nevertheless, appropriate statistical methods have been utilized to mitigate the effects of confounding. If observational studies are properly designed and carefully analyzed, even with their inherent limitations, they can provide data that complements findings from RCTs by evaluating treatment effectiveness for longer follow-up periods of "real-life" patients and, most importantly, their results on adverse effects are as valid as those from RCTs [314, 413].

No classification criteria were applied for patients to be eligible for enrollment in HeRBT. This may had an impact on the comparability of our results to other studies as it would be interesting to know the percentage of our patients that fulfill criteria for any particular diagnosis. However, the decision that no specific inclusion and exclusion criteria would be applied was made to enhance generalizability of our results and reflect actual routine clinical practice, as all patients with a diagnosis of an inflammatory arthritis provided by the treating physician who were treated with a bDMARD would be included. Compared to some other registries, HeRBT had generally less restrictions as to which patients are enrolled regarding patient age and previous rheumatologic therapies and for how long they would be followed. For example, in RABBIT, only RA patients ≥16 years old who meet the 1987 ACR criteria and have failed at least one csDMARD can be enrolled and they are followed up for 5 years, which can be extended up to ten years after additional informed consent of the patients [321]. In contrast, the eligibility criteria and design of this registry was similar to DANBIO and ARTIS registries.

The follow-up visits after enrollment, although pre-specified, were not always adhered to and deviations from schedule visits (±2 months for the first 2 years and ±3 months after the first two years) were accepted by the protocol. This could have affected the comparison of effectiveness of the different bDMARDs at very similar time-points; however it is not feasible to schedule exact dates of the follow-up visits in registries such as the HeRBT which follow a large number of patients in busy and unpredictable clinical settings.

The documentation in HeRBT was paper-based. CRFs were completed by rheumatologists and patients and were sent to the Rheumatology Dpt. of the University Hospital of Heraklio via mail. The major drawbacks of this type of documentation are the remote and delayed entering of the data into the database and the heavy workload at the Registry center. Inquiries to rheumatologists for supplementary information were necessary for approximately 20% of the CRFs, which was very time-consuming. Nevertheless, this communication was necessary to ensure data quality. No audits at the Registry centers were performed but detailed verification of every discrepancy in CRFs by e-mails or phone was easily conducted. Centralized data entry ensured uniform interpretation of information on CRFs and paper forms were widely accepted by physicians as they were less time-consuming and no computer was necessary at the doctor's office.

Between 5-12% of all patients enrolled in each center of the Registry dropped out during follow-up. This is an inherent problem of the observational studies, but also of RCTs, which can possibly

result in selection bias when reporting either effectiveness or safety results. Bias occurs because patients lost to follow-up could be those having less treatment response or those with increased rate of adverse events. In HeRBT, investigation of the reasons for drop-out was carried out thoroughly by contacting the respective rheumatologist and/or patient to inquire about the reason that the patient was lost to follow-up. Additionally, in the RA sub-study both the crude and the LUNDEX-corrected responses were calculated. LUNDEX is a valuable tool for evaluating drug effectiveness in observational settings as it has the advantage of integrating clinical response as well as adherence to therapy in a composite value [388].

Missing data is another concern in observational studies. In the second study (SpA patients), we tried to address this by performing multiple imputation of the missing values. Complete-case analyses were also performed and the results were comparable to that of the imputed data (**Supplementary Tables 5-8**).

Another weakness, affecting especially the sub-study of SpA patients, was that we had no data on extra-articular activity (enthesitis, dactylitis, psoriasis or IBD-related relapses), which may have influenced physician's treatment decisions. Nevertheless, generally we may assume that "stop failure" was assigned to possible activity of these manifestations. In the same sub-study, we could not control also for HLA-B27 status, which has been shown to influence TNFi response [414]. This examination was not routinely prescribed in Greece due to cost considerations and thus it was not available in most of the patients of the Registry.

Comorbidities, which may also interfere with drug response and survival, were recorded only in patients in the University Hospital of Heraklio, and therefore these were not included in our multivariable analyses. Multiple imputation of missing data could not be performed in this case as data was not missing at random. Concerning smoking, we analyzed available data in the sub-study of SpA patients (n=234, 55% current, 12% past smokers, 33% never smoked). Both in univariate and multivariable regression analyses, smoking status (treated either as ever/never or as non/past/current smoking) was not a significant predictor for TNFi survival (data not shown). This is an interesting issue with conflicting available data from the literature either supporting a negative effect or no role of smoking in drug survival [406, 415].

Patient body mass index (BMI) has also been reported to have an effect on TNFi response [416], but unfortunately height was missing in many patients of the Registry and thus it was also not included in our main multivariate analyses. Sub-analysis in SpA patients with available data on BMI [n=312, median (IQR) BMI=26.3 (23.9-29.6)] showed that higher BMI was associated with lower chance to achieve BASDAI50 and EULAR-good response within the first year in patients with axial and peripheral involvement respectively. However other response indices (ASDAS-inactive disease state, DAS28-inactive state and ACR70 response index) were not found to be associated with BMI (data not shown). Nevertheless, these results should be considered with caution due to the limited data available.

CHAPTER IX. CONCLUSIONS

Concerning rheumatoid arthritis patients, we evaluated and compared the long-term response and drug adherence of three TNF inhibitor agents in real-life Greek patients. Our data are in line with most European registries showing a comparable response, but a more favorable long-term drug adherence of adalimumab and etanercept compared to infliximab, mostly due to adverse events.

Yet, the most clinically important finding for a chronic disease like RA is that overall 5-year TNF inhibitor survival in real life is less than 50%. Whether newer treatment strategies, like the treat-to-target approach, improve long-term outcome for patients with aggressive RA have to be evaluated.

On the contrary, we report a rather favorable 5- and 10-year TNFi survival in SpA patients as a group: half of our patients were shown to adhere to therapy for at least 10 years. Women and patients with peripheral disease involvement, though, had shorter TNFi treatment adherence.

In both diseases, patients with major treatment responses within the first year of therapy had the longest TNFi drug survival. We consider this of major clinical importance, since a clinical parameter quantifiable early in the treatment course could predict a higher chance of long-term drug survival in every-day clinical practice. We thus support close disease activity monitoring with composite indices of response as a valuable tool to predict long-term outcomes in rheumatologic patients initiating TNF inhibitors.

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SUPPLEMENTARY TABLES

Supplementary Table 1. Predictors for CDAI and EULAR/ACR remission at 12 months of TNF inhibitor therapy in RA patients

	CDAI remission		ACR/EULAR remission [1]	
Baseline characteristics	Univariate [2]	Multivariate	Univariate	Multivariate
Gender (male *vs.* female)	2.72 (1.53-4.81) [b]	2.83 (1.37-5.85) [b]	1.98 (1.18-3.33) [a]	2.22 (1.16-4.22) [a]
Age (per 10-years)	0.98 (0.79-1.21)		0.78 (0.65-0.94) [b]	
RA duration (per 1-year)	0.93 (0.89-0.97) [b]	0.93 (0.88-0.98) [b]	0.97 (0.93-1.00) [a]	0.94 (0.90-0.98) [b]
SJC-28 (> *vs.* ≤ 7)	0.31 (0.15-0.64) [b]	0.21 (0.09-0.49) [c]	0.26 (0.14-0.49) [c]	0.26 (0.13-0.51) [c]
TJC-28 (> *vs.* ≤ 10)	0.53 (0.27-1.05)		0.43 (0.24-0.77) [b]	
CRP (> *vs.* ≤ 1.4 mg/dL)	1.18 (0.58-2.42)		1.17 (0.66-2.07)	
VAS global (per 10-units)	0.89 (0.76-1.04)		0.84 (0.74-0.96) [b]	
VAS pain (per 10-units)	0.87 (0.75-1.01)		0.83 (0.73-0.94) [b]	
Methotrexate use (yes *vs.* no)	0.84 (0.46-1.54)		0.93 (0.54-1.60)	
Leflunomide use (yes *vs.* no)	1.40 (0.68-2.92)		1.13 (0.56-2.25)	
Glucocorticoid use (yes *vs.* no)	1.19 (0.65-2.16)		2.35 (1.29-4.28) [b]	2.18 (1.07-4.41) [a]
Previous DMARDs (per 1 drug)	0.76 (0.60-0.96) [a]		0.85 (0.70-1.03)	
TNFi agent used				
INF (*reference*)	1.00 (*reference*)	1.00 (*reference*)	1.00 (*reference*)	1.00 (*reference*)
ADA	2.08 (1.13-3.82) [a]	2.78 (1.30-5.92) [b]	3.23 (1.80-5.79) [c]	4.05 (2.00-8.21) [c]
ETA	0.84 (0.37-1.93)	0.67 (0.21-2.12)	2.50 (1.32-4.75) [b]	2.69 (1.24-5.87) [a]
Previous TNFi (per 1 agent)	1.04 (0.56-1.94)		1.15 (0.66-2.01)	

[1] Boolean definition

[2] Logistic regression analysis (backward elimination model applied for multivariate analysis) using baseline characteristics as independent predictors. Results are given as ORs (95% CI); [a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$

Supplementary Table 2. Predictors for DAS28 low disease activity (LDA) and EULAR good response at 12 months of TNF inhibitor therapy in RA patients

	DAS28 LDA		EULAR good response	
Baseline characteristics	Univariate[1]	Multivariate	Univariate	Multivariate
Gender (male *vs.* female)	1.58 (1.08-2.32) [a]		1.67 (1.09-2.55) [a]	
Age (per 10-years)	0.76 (0.67-0.87) [c]	0.82 (0.71-0.96) [a]	0.78 (0.67-0.90) [b]	0.85 (0.73-0.99) [a]
RA duration (per 1-year)	0.98 (0.96-1.00)		0.96 (0.94-0.99) [b]	0.96 (0.93-0.99) [b]
SJC-28 (> *vs.* ≤ 7)	0.22 (0.15-0.33) [c]	0.32 (0.20-0.51) [c]	0.27 (0.18-0.41) [c]	0.34 (0.22-0.54) [c]
TJC-28 (> *vs.* ≤ 10)	0.31 (0.21-0.47) [c]	0.61 (0.38-0.97) [a]	0.38 (0.26-0.57) [c]	0.63 (0.40-1.00) [a]
CRP (> *vs.* ≤ 1.4 mg/dL)	0.88 (0.60-1.31)		1.12 (0.74-1.67)	
VAS global (per 10-units)	0.83 (0.75-0.91) [c]		0.94 (0.86-1.03)	
VAS pain (per 10-units)	0.87 (0.79-0.95) [b]		0.96 (0.88-1.06)	
Methotrexate use (yes *vs.* no)	1.18 (0.81-1.73)		1.36 (0.89-2.07)	
Leflunomide use (yes *vs.* no)	0.96 (0.60-1.55)		0.99 (0.59-1.67)	
Glucocorticoid use (yes *vs.* no)	1.70 (1.18-2.45) [b]	1.61 (1.04-2.48) [a]	1.73 (1.16-2.59) [b]	1.59 (1.04-2.45) [a]
Previous DMARDs (per 1 drug)	0.88 (0.77-1.00) [a]	0.86 (0.74-0.99) [a]	0.86 (0.74-0.99) [a]	
Anti-TNF agent used				
INF (*reference*)	1.00 (*reference*)		1.00 (*reference*)	
ADA	1.35 (0.91-2.01)		1.23 (0.79-1.90)	
ETA	1.22 (0.79-1.90)		0.93 (0.56-1.54)	
Previous anti-TNF (per 1 agent)	0.96 (0.66-1.41)		0.73 (0.45-1.17)	

[1] Logistic regression analysis (backward elimination model applied for multivariate analysis) using baseline characteristics as independent predictors. Results are given as ORs (95% CI); [a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$

Supplementary Table 3. Baseline demographics, disease characteristics and activity according to the presence of peripheral arthritis

	Peripheral arthritis			
	Yes (n=655)	**No (n=289)**	**Yes vs. No p-value***	**Unknown (n=133)**
Gender (male), N (%)	379 (58)	233 (81)	<0.001	103 (77)
Age, years	47 (36-56)	41 (34-48)	<0.001	40 (33-48)
Symptom duration, years	7.8 (2.7-15.6)	11.0 (5.6-20.3)	<0.001	9.9 (2.8-17.8)
Symptom duration <5 years, N (%)	246 (38)	66 (23)	<0.001	40 (30)
TNFi used, N (%)				
Infliximab	378 (58)	183 (63)	0.106	94 (71)
Etanercept	139 (21)	41 (14)	0.011	20 (15)
Adalimumab	109 (17)	58 (20)	0.203	17 (13)
Golimumab	29 (4)	7 (2)	0.138	2 (2)
Diagnosis, N (%)				
AS	209 (32)	248 (86)	<0.001	104 (78)
PsA	336 (51)	21 (7)	<0.001	18 (14)
uSpA	88 (13)	13 (5)	<0.001	7 (5)
IBD-related SpA	22 (3)	7 (2)	0.442	4 (3)
Axial inflammatory symptoms ever, N (%)	366 (73)	289 (100)	<0.001	119 (100)
Nr of previous csDMARDs	1 (1-2)	0 (0-1)	<0.001	0 (0-1)
Nr of coadministered csDMARDs	1 (0-1)	0 (0-0)	<0.001	0 (0-1)
Co-administered csDMARD, N(%): Methotrexate	336 (54)	36 (13)	<0.001	33 (27)
Other	99 (16)	14 (5)	<0.001	9 (7)
Monotherapy , N (%)	229 (35)	237 (82)	<0.001	81 (62)
Co-administered corticosteroids, N(%)	104 (17)	6 (2)	<0.001	5 (4)
BASDAI (0-10)[a]	5.4 (4.2-6.8)	4.9 (3.6-5.9)	<0.001	4.8 (3.5-6.1)
BASFI (0-10)[a]	5.5 (3.5-7.1)	4.3 (2.9-6.1)	<0.001	5.2 (2.4-6.3)
ASDAS-CRP [a]	3.4 (2.7-4.1)	3.4 (2.7-4.0)	0.211	3.3 (2.9-3.9)
CRP (mg/dl)	1.1 (0.34-2.5)	1.6 (0.7-3.1)	0.003	1.2 (0.6-2.8)
ESR (mm/h)	30 (16-50)	27 (18-45)	0.353	32 (16-45)
VAS global (0-100)	69 (50-80)	60 (50-80)	0.168	50 (30-76)
VAS pain (0-100)	70 (50-80)	60 (50-80)	0.039	50 (30-78)
Physician's global assessment (0-4)	3 (2-3)	3 (2-3)	0.177	2 (2-3)

Except when stated otherwise values are medians (interquartile range). *p values are determined by chi-square test or Kruskal-Wallis test as appropriate.

Supplementary Table 4. Reasons for therapy discontinuation according to the presence or not of peripheral arthritis

	Peripheral arthritis			
	Yes (n=655)	**No (n=289)**	**Yes vs. No p-value***	**Unknown (n=133)**
Inefficacy	131 (20)	28 (10)	<0.001	12 (9)
Primary inefficacy	67 (10)	9 (3)	<0.001	7 (5)
Secondary inefficacy	64 (10)	19 (7)	0.062	5 (4)
Adverse events	88 (13)	46 (16)	0.313	20 (15)
Other	51 (8)	16 (6)	0.172	2 (2)
Total	270 (41)	90 (31)	0.003	34 (26)

Supplementary Table 5. Cox regression analysis for TNFi discontinuation in the whole group of SpA patients, stratified by reason of stop: complete-case analysis†

	All reasons		Discontinuations due to inefficacy		Discontinuations due to adverse events	
	Univariate	Final model after backward selection	Univariate	Final model after backward selection	Univariate	Final model after backward selection
Gender (male versus female)	0.63 (0.52-0.77)[c]	0.62 (0.47-0.82)[b]	0.45 (0.34-0.61)[c]	0.63 (0.41-0.96)[a]	0.79 (0.57-1.11)**	0.55 (0.38-0.79)[b]
Age (per 10 years)	1.01 (0.93-1.09)		1.04 (0.92-1.17)		1.00 (0.73-1.38)	
Symptoms duration (< versus ≥5 years)	1.20 (0.97-1.48)*		1.41 (1.03-1.92)[a]		0.95 (0.67-1.35)	
TNFi agent used (ETA versus other)	1.65 (1.30-2.10)[c]		2.56 (1.84-3.57)[c]		0.60 (0.35-1.03)*	
TNFi agent used: INF (reference)			1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
ETA			3.16 (2.21-4.51)[c]	2.38 (1.45-3.90)[b]	0.52 (0.31-0.90)[a]	0.44 (0.24-0.80)[b]
ADA			1.89 (1.23-2.90)[b]	1.07(0.55-2.08)	0.38 (0.20-0.73)[b]	0.33 (0.17-0.65)[b]
GOL			4.38 (2.17-8.81)[c]	4.13 (1.89-9.02)[c]	0.25 (0.04-1.78)**	0.26 (0.04-1.87)**
Clinical diagnosis (AS versus other)	0.77 (0.63-0.94)[a]		0.58 (0.42-0.78)[c]		1.10 (0.80-1.51)	
Clinical diagnosis: AS (reference)			1.00 (ref)		1.00 (ref)	
PsA			1.55 (1.10-2.16)[a]		0.93 (0.66-1.32)	
Other			2.31 (1.53-3.48)[c]		0.85 (0.50-1.45)	
Year of TNFi therapy start (per 2 years)	1.12 (1.04-1.20)[b]		1.30 (1.17-1.44)[c]		0.89 (0.79-1.01)*	
Previous csDMARDs (yes versus no)	0.96 (0.79-1.18)		1.92 (1.35-2.72)[c]	1.71 (1.06-2.75)[a]	0.62 (0.45-0.85)[b]	0.68 (0.46-0.99)[a]
Methotrexate co-therapy (yes vs no)	0.82 (0.66-1.02)*	0.67 (0.50-0.89)[b]	1.21 (0.88-1.66)		0.51 (0.35-0.74)[c]	0.57 (0.38-0.87)[b]
Axial disease (yes versus no)	0.81 (0.60-1.09)		0.52 (0.35-0.77)[b]		1.59 (0.86-2.96)**	
Peripheral disease (yes versus no)	1.47 (1.16-1.89)[b]	1.44 (1.06-1.94)[a]	2.29 (1.52-3.45)[c]		0.93 (0.65-1.33)	
CRP (> versus ≤1.2 mg/dl)	0.70 (0.54-0.90)[b]	0.76 (0.59-0.99)[a]	0.73 (0.49-1.09)**		0.71 (0.49-1.04)*	
VAS global (> versus ≤60)	1.16 (0.91-1.47)		1.80 (1.22-2.64)[b]	1.49(0.98-2.27)*	0.92 (0.63-1.32)	
PhGA (> versus ≤2)	1.06 (0.81-1.38)		1.39 (0.91-2.13)		0.94 (0.63-1.41)	

† Numbers are Hazard Rates (95% confidence intervals). *: p<0.1, **: p<0.2, a: p<0.05, b: p<0.01, c: p<0.001

Supplementary Table 6. Cox regression analysis for TNFi discontinuation stratified by diagnosis: complete-case analysis†				
	AS		PsA	
	Univariate	Final model after backward selection	Univariate	Final model after backward selection
Gender (male versus female)	0.66 (0.48-0.93)[a]	0.64 (0.37-1.08)*	0.64 (0.46-0.88)[b]	0.57 (0.36-0.88)[a]
Age (per 10 years)	0.94 (0.74-1.32)		0.91 (0.64-1.29)	
Symptoms duration (< versus ≥5 years)	1.40 (1.00-1.97)*	1.62 (0.94-2.78)*	0.90 (0.65-1.26)	
TNFi agent used (ETA versus other)	2.17 (1.50-3.15)[c]			
TNFi agent used: INF (reference)			1.00 (ref)	
ETA			1.22 (0.81-1.83)	
ADA			1.25 (0.75-2.06)	
GOL			2.35 (1.12-4.91)[a]	
Year of TNFi therapy start (per 2 years)	1.24 (1.11-1.38)[c]	1.33 (1.12-1.58)[b]	1.04 (0.92-1.18)	
Previous csDMARDs (yes versus no)	0.71 (0.52-0.97)[a]	0.47 (0.28-0.79)[b]	1.03 (0.63-1.69)	
Methotrexate co-therapy (yes versus no)	0.88 (0.60-1.28)		0.64 (0.45-0.91)[a]	0.56 (0.36-0.88)[a]
Axial disease (yes versus no)			0.78 (0.50-1.20)	
Peripheral disease (yes versus no)	1.46 (1.07-1.98)[a]	1.59 (1.02-2.50)[a]	1.60 (0.66-3.91)	
CRP (> versus ≤1.2 mg/dl)	0.77 (0.53-1.10)**		0.67 (0.44-1.04)*	0.64 (0.41-1.01)*
VAS global (> versus≤60)	1.13 (0.80-1.59)		1.11 (0.75-1.65)	
PhGA (> versus ≤2)	1.09 (0.74-1.59)		1.13 (0.73-1.75)	
BASDAI (> versus ≤5)	1.05 (0.73-1.52)		1.39 (0.78-2.50)	
BASFI (> versus ≤5)	1.48 (0.99-2.20)*	1.67 (1.05-2.67)[a]	1.37 (0.71-2.65)	
SJC-28 (> versus ≤2)			1.08 (0.73-1.59)	
TJC-28 (> versus ≤3)			1.37 (0.91-2.06)**	1.61 (1.01-2.56)[a]
DAS28 baseline (> versus ≤4.5)			1.06 (0.70-1.62)	

† Numbers are Hazard Rates (95% confidence intervals).
*: p<0.1, **: p<0.2, a: p<0.05, b: p<0.01, c: p<0.001

Supplementary Table 7. Cox regression analysis for predictors of TNFi discontinuation in patients with axial inflammatory arthritis: complete-case analysis†

	Univariable	Multivariable model adjusting for **baseline variables only**	Final model when adjusting for baseline variables **plus 1st year BASDAI50 response**	Final model when adjusting for baseline variables **plus 1st year ASDAS-ID response**
Gender (male versus female)	0.67 (0.52-0.87)[b]	0.71 (0.49-1.03)*	0.68 (0.45-1.03)*	
Age (per 10 years)	0.92 (0.73-1.17)			
Symptoms duration (< versus ≥5 years)	1.40 (1.08-1.82)[a]			
TNFi agent used (ETA versus other)	1.94 (1.44-2.61)[c]			1.78 (0.94-3.39)*
Clinical diagnosis: AS (ref)	1.00 (ref)			
PsA	1.06 (0.76-1.48)			
other	1.52 (1.09-2.14)[a]			
Year of TNFi therapy start (per 2 years)	1.20 (1.10-1.31)[c]	1.15 (1.02-1.29)[a]		
Previous csDMARDs (yes versus no)	0.84 (0.66-1.07)**	0.64 (0.46-0.90)[a]		
Methotrexate co-therapy (yes vs no)	0.94 (0.72-1.23)			
Peripheral disease (yes versus no)	1.44 (1.11-1.86)[b]	1.44 (1.03-1.99)[a]		
CRP (> versus ≤1.2 mg/dl)	0.64 (0.48-0.86)[b]	0.75 (0.54-1.02)*		
VAS global (> versus≤60)	1.16 (0.88-1.53)			
PhGA (> versus≤2)	0.95 (0.69-1.30)			
BASDAI (> versus ≤5)	1.09 (0.80-1.48)			
BASFI (> versus ≤5)	1.22 (0.88-1.69)			
BASDAI50 (yes versus no)	0.49 (0.34-0.72)[c]		0.47 (0.32-0.70)[c]	
ASDAS-ID (yes versus no)	0.33 (0.22-0.51)[c]			0.29 (0.18-0.46)[c]

† Numbers are Hazard Rates (95% confidence intervals). *: p<0.1, **: p<0.2, a: p<0.05, b: p<0.01, c: p<0.001

Supplementary Table 8. Cox regression analysis for predictors of TNFi discontinuation in patients with peripheral arthritis: complete-case analysis†

	Univariable	Multivariable model adjusting **for baseline variables only**	Final model when adjusting for baseline variables **plus 1st year DAS28-remission**	Final model when adjusting for baseline variables **plus 1st year EULAR good response**	Final model when adjusting for baseline variables **plus 1st year ACR70 response**
Gender (male versus female)	0.60 (0.47-0.76)[c]				
Age (per 10 years)	0.90 (0.70-1.15)				
Symptoms duration (< versus ≥5 years)	1.10 (0.86-1.41)				
TNFi agent used (ETA versus other)	1.53 (1.15-2.03)[b]				2.12 (1.08-4.16)[a]
Clinical diagnosis: AS (ref)	1.00 (ref)				
PsA	1.05 (0.81-1.38)				
other	1.21 (0.84-1.73)				
Year of TNFi therapy start (per 2 years)	1.08 (1.00-1.17)*				
Previous csDMARDs (yes versus no)	0.96 (0.73-1.27)				
Methotrexate co-therapy (yes vs no)	0.72 (0.56-0.93)[a]				
Axial disease (yes versus no)	0.95 (0.69-1.30)				
CRP (> versus ≤1.2 mg/dl)	0.65 (0.48-0.89)[b]	0.65 (0.44-0.97)[a]			
VAS global (> versus ≤60)	1.24 (0.93-1.65)**				
PhGA (> versus ≤2)	0.99 (0.73-1.39)				
SJC-28 (> versus ≤2)	1.35 (1.02-1.80)[a]				
TJC-28 (> versus ≤3)	1.43 (1.08-1.91)[a]	1.65 (1.12-2.44)[a]	1.58 (0.98-2.55)*	1.70 (1.05-2.76)[a]	1.80 (1.13-2.87)[a]
DAS28 baseline (> versus ≤4.5)	1.18 (0.88-1.59)				
DAS28-remission (yes versus no)	0.39 (0.29-0.55)[c]		0.40 (0.24-0.67)[b]		
EULAR-good response (yes versus no)	0.42 (0.30-0.60)[c]			0.43 (0.26-0.71)[b]	
ACR70 (yes versus no)	0.33 (0.19-0.60)[c]				0.14 (0.05-0.38)[c]

† Numbers are Hazard Rates (95% confidence intervals).
*: p<0.1, **: p<0.2, a: p<0.05, b: p<0.01, c: p<0.001

PUBLICATIONS

A. JOURNAL PUBLICATIONS RELATED TO THIS THESIS

1. Thomas T, Shaddick G., Charlton R, Cavill C, Holland R, Iannone F, Lapadula S, Lopriore S, Zavada J, Uher M, Pavelka K, Szczokova L, Sidiropoulos P, **Flouri I,** Moller B, Nissen M, Mueller R, Scherer A, McHugh N, Nightingale A. Tumor necrosis factor inhibitor monotherapy versus combination therapy with conventional synthetic disease-modifying anti-rheumatic drugs for the treatment of psoriatic arthritis: a combined analysis of European biologics databases. *Under submission in the Annals of Rheumatic Diseases*

2. **Flouri I**, Markatseli T, Boki K, Papadopoulos I, Skopouli F, Voulgari P, Settas L, Zisopoulos D, Iliopoulos A, Geborek P, Drosos A, Boumpas D, Sidiropoulos P. Comparative analysis and predictors of 10-year tumor necrosis factor inhibitors drug survival in patients with spondyloarthropathies: first year response predicts long-term drug persistence**. J Rheumatol. 2018** Jun;45(6):785-794 Pubmed PMID: 29606666

3. Boubouchairopoulou N*****, **Flouri I***, Drosos AA, Boki K, Settas L, Zisopoulos D, Skopouli FN, Papadopoulos I, Iliopoulos A, Kyriopoulos J, Boumpas DT, Athanasakis K, Sidiropoulos P. Treatment with the first TNF inhibitor in rheumatoid arthritis patients in the Hellenic Registry of Biologic Therapies improves quality of life, especially in young patients with better baseline functional status. **Clin Exp Rheumatol. 2016** Nov-Dec;34(6):999-1005. PubMed PMID: 27749220 (*equal contribution)

4. **Flouri I**, Markatseli TE, Voulgari PV, Boki KA, Papadopoulos I, Settas L, Zisopoulos D, Skopouli FN, Iliopoulos A, Bertsias GK, Geborek P, Drosos AA, Boumpas DT, Sidiropoulos P. Comparative effectiveness and survival of infliximab, adalimumab, and etanercept for rheumatoid arthritis patients in the Hellenic Registry of Biologics: Low rates of remission and 5-year drug survival. **Semin Arthritis Rheum. 2014** Feb;43(4):447-57. PubMed PMID 24012040

B. JOURNAL PUBLICATIONS USING DATA OF OUR CENTER FROM THE HELLENIC REGISTRY OF BIOLOGIC THERAPIES DATABASE

1. Thomas K*, **Flouri I***, Repa A, Fragiadaki K, Sfikakis PP, Koutsianas C, Kaltsonoudis E, Voulgari PV, Drosos AA, Petrikkou E, Sidiropoulos P, Vassilopoulos D. High 3-year golimumab survival in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis: real world data from 328 patients**. Clin Exp Rheumatol. 2017** Nov 9. [Epud ahead of print] PubMed PMID: 29148406 *equal contribution

2. Papalopoulos I, Fanouriakis A, Kougkas N, **Flouri I**, Sourvinos G, Bertsias G, Repa A, Avgoustidis N, Sidiropoulos P. Liver safety of non-tumor necrosis factor inhibitors in rheumatic patients with past hepatitis B virus infection: an observational, controlled, long-term study. **Clin Exp Rheumatol. 2017** Aug 28. [Epud ahead of print] PubMed PMID: 28850029

3. Zervou MI, Myrthianou E, **Flouri I**, Plant D, Chlouverakis G, et al. Lack of Association of Variants Previously Associated with Anti-TNF Medication Response in Rheumatoid Arthritis Patients: Results from a Homogeneous Greek Population**. PLoS ONE 2013** Sep 10;8(9): e74375 PubMed PMID 24040234

C. SELECTED CONFERENCE PROCEEDINGS RELATED TO THIS THESIS

1. Genitsaridi I, **Flouri I**, Repa A, Avgoustidis N, Kougkas N, Papalopoulos I, Polia S, Marias K, Plexousakis D, Bertsias G, Sidiropoulos P. In Clinical Practice a Substantial Group of Rheumatoid Arthritis (RA) Patients on Biologic Therapy (bDMARDs) Has Persistent Moderate Disease Activity Despite Treatment Switches That Correlates with Unfavourable Long-Term Outcome. **2018 American College of Rheumatology (ACR) Annual Scientific Meeting** (Chicago, USA, 19-24 October 2018). *Arthritis Rheumatol. 2018; 70 (suppl 10).*

2. **Ε. Φλουρή**, Θ. Μαρκατσέλη, Α. Δρόσος, Ι. Παπαδόπουλος, Κ. Μποκή, Φ. Σκοπούλη, Δ. Ζησόπουλος, Λ. Σέττας, Δ. Καρράς, Δ. Μπούμπας, Φ. Κανακούδη, P. Geborek, Π. Σιδηρόπουλος. Υψηλή μακροχρόνια παραμονή σε βιολογική θεραπεία ασθενών με σπονδυλαρθρίτιδες: δεδομένα του Ελληνικού Αρχείου Βιολογικών Θεραπειών. **24ο Πανελλήνιο Ρευματολογικό Συνέδριο,** Αθηνα, 11-14 Δεκεμβρίου **2014** *Ελληνική Ρευματολογία 2014 (συμπληρωματικό τεύχος)* (προφορική παρουσίαση)

3. **Ε. Φλουρή**, Θ. Μαρκατσέλη, Ι. Παπαδόπουλος, Κ. Μποκή, Φ. Σκοπούλη, Δ. Ζησόπουλος, Λ. Σέττας, Δ. Καρράς, Δ. Μπούμπας, Α. Δρόσος, Φ. Κανακούδη, P. Geborek, Π. Σιδηρόπουλος. Γηριατρικοί ασθενείς με ρευματοειδή αρθρίτιδα υπό βιολογική θεραπεία: δεδομένα από το Ελληνικό Αρχείο Βιολογικών Θεραπειών. **24ο Πανελλήνιο Ρευματολογικό Συνέδριο,** Αθηνα, 11-14 Δεκεμβρίου **2014** *Ελληνική Ρευματολογία 2014 (συμπληρωματικό τεύχος)* (αναρτημένη ανακοίνωση)

4. **I. Flouri***,* A. Drosos, F. Skopouli, K. Boki, L. Settas, I. Papadopoulos, A. Iliopoulos, T. Markatseli, D. Zisopoulos, P. Geborek, D.T. Boumpas, P. Sidiropoulos. High rate of discontinuation of the first anti-TNFa agent during long term follow-up of RA patients of the Hellenic Biologics Registry. **2011 European League Against Rheumatism (EULAR) Annual Scientific Meeting** (London, United Kingdom 25-28 May 2011). *Ann Rheum Dis 2011;70(Suppl3):257*

5. **Ε. Φλουρή** και Π. Σιδηρόπουλος εκ μέρους των ερευνητών του Αρχείου Βιολογικών Θεραπειών: Σε ασθενείς με ρευματοειδή αρθρίτιδα η διακοπή του 1ου βιολογικού παράγοντα είναι συχνή μετά το 3ο έτος αγωγής. **22ο Πανελλήνιο Ρευματολογικό Συνέδριο,** Αθηνα, 1-4 Δεκεμβρίου **2010** *Ελληνική Ρευματολογία 2010* (προφορική παρουσίαση)

6. **I. Flouri**, A. Drosos, F. Skopouli, K. Boki, I.P. Papadopoulos, I. Kriticos, M. Mavromati, T. Markatseli, D. Zisopoulos, D. Karras, L. Settas, P. Geborek, D. Boumpas, P. Sidiropoulos. Predictors of response and serious infections in a large cohort of rheumatoid arthritis patients treated with anti-TNF agents in clinical practice: results from the Hellenic Registry of Biologicals. **2010 European League Against Rheumatism (EULAR) Annual Scientific Meeting** (Rome, Italy 16-19 June 2010) *Ann Rheum Dis 2010;69(Suppl3):68*

7. **I. Flouri**, A. Drosos, K. Boki, F. Skopouli, D. Karras, I. Papadopoulos, P. Geborek, S. Panagiotakis, D.T. Boumpas, P. Sidiropoulos. Geriatric rheumatoid arthritis patients receive anti-TNFa agents later, have

higher disease activity and experience more often serious adverse events compared to younger adults. **XIIIth Mediterranean Congress of Rheumatology** [Cavtat- Dubrovnik, Croatia 18-21 November 2009] *Clin Exp Rheum 2009;27 (5)*

8. **Flouri I,** Drosos A, Boki K, Skopouli F, Karras D, Papadopoulos I, Kanakoudi F, Geborek P, Boumpas DT and Sidiropoulos P. Geriatric rheumatoid arthritis patients receive anti-TNFa agents later, have higher disease activity at baseline and experience more often serious adverse events compared to younger adults. **2009 American College of Rheumatology (ACR) Annual Scientific Meeting** (Philadelphia, USA, 16-21 October 2009) *Arthritis Rheum 2009;60 Suppl 10 :1024*

9. **I. Flouri**, A. Drosos, F. Skopouli, K. Boki, I. Papadopoulos, F. Kanakoudi, D. Karras, H. Kriticos, P. Geborek, D. Boumpas, P. Sidiropoulos Long term follow-up of RA patients of the Hellenic Biologics Registry: comparison of first versus second therapy on anti-TNFa agents. **2009 European League Against Rheumatism (EULAR) Annual Scientific Meeting**, (Copenhagen, Denmark, 10-13 June 2009). *Ann Rheum Dis 2009;68(Suppl3):430*

10. **Flouri I**, Sidiropoulos P, Drosos A, Boki K, Skopouli F, Karras D, Papadopoulos I, Kanakoudi F, Geborek P, Boumpas DT. Long term efficacy of anti-TNFa agents in ankylosing spondylitis and psoriatic arthritis patients: results from the Hellenic Registry for Biologics. **2008 European League Against Rheumatism (EULAR) Annual Scientific Meeting**, (Paris, France, June 11-14) *Ann Rheum Dis* 2008; 67 (Suppl II): AB0617

11. Sidiropoulos P**, Flouri I**, Drosos A, Boki K, Skopouli F, Karras D, Papadopoulos I, Florentia Kanakoudi, Pierre Geborek, Dimitrios T. Boumpas. Geriatric Patients Receiving anti-TNFa Agents Have Comparable to Younger Adults Response but Increased Incidence of Serious Adverse Events. **2008 European League Against Rheumatism (EULAR) Annual Scientific Meeting**, (Paris, France, June 11-14) *Ann Rheum Dis* 2008; 67 (Suppl II): THU0141

12. **Ε. Φλουρή** και Π. Σιδηρόπουλος εκ μέρους των ερευνητών του Αρχείου Βιολογικών Θεραπειών: Παρατεταμένη κλινική απάντηση σε αντι-TNFα θεραπεία ασθενών με ρευματοειδή αρθρίτιδα και προγνωστικοί δείκτες απάντησης: δεδομένα του Ελληνικού Αρχείου Βιολογικών Θεραπειών. **20ο Πανελλήνιο Συνέδριο Ρευματολογίας**, Δεκέμβριος **2008** *Ελληνική Ρευματολογία 2008 (Συμπληρωματικό τεύχος)* (προφορική παρουσίαση)

13. **Ε. Φλουρή** και Π. Σιδηρόπουλος εκ μέρους των ερευνητών του Αρχείου Βιολογικών Θεραπειών: Παρατεταμένη αποτελεσματικότητα και παραμονή στη θεραπεία με τον πρώτο anti-TNFα παράγοντα ασθενών με σπονδυλαρθρίτιδες: δεδομένα του Αρχείου Βιολογικών Θεραπειών. **20ο Πανελλήνιο Συνέδριο Ρευματολογίας**, Δεκέμβριος **2008** *Ελληνική Ρευματολογία 2008 (Συμπληρωματικό τεύχος)* (προφορική παρουσίαση)

D. SELECTED CONFERENCE PROCEEDINGS USING DATA OF OUR CENTER FROM THE HELLENIC REGISTRY OF BIOLOGIC THERAPIES DATABASE

1. **Irini Flouri**, Argyro Repa, Nestor Avgoustidis, Nikolaos Kougkas, Antonios Fanouriakis, Ioannis Papalopoulos, Christina Adamichou, Paraskevi Kyfonidou, Eleni Kampouraki, Maria Terizaki, Dimitrios T. Boumpas, Georgios Bertsias, Prodromos Sidiropoulos. After discontinuation of the first tumor necrosis factor inhibitor (TNFi), non-TNFi biologic agents have similar responses but higher retention rates compared to a second course of a different TNFi: long-term prospective observational study of patients with rheumatoid arthritis in a tertiary hospital of Greece. **2017 European League Against Rheumatism (EULAR) Annual Scientific Meeting** (Madrid, Spain 14-17 June 2017). *Annals of the Rheumatic Diseases* 2017;76:574.

2. **Irini Flouri**, Argyro Repa, Nestor Avgoustidis, Nikolaos Kougkas, Antonios Fanouriakis, Ioannis Papalopoulos, Christina Adamichou, Paraskevi Kyfonidou, Eleni Kampouraki, Maria Terizaki, Dimitrios T. Boumpas, Georgios Bertsias, Prodromos Sidiropoulos. Abatacept survival in rheumatoid arthritis patients at 2 years is 59%; its use as a 2nd line biologic agent and lower baseline HAQ predict better survival in clinical practice: a prospective, observational single center study. **2017 European League Against Rheumatism (EULAR) Annual Scientific Meeting** (Madrid, Spain 14-17 June 2017). *Annals of the Rheumatic Diseases* 2017;76:850.

3. Nestor Avgoustidis, **Irini Flouri**, Christina Adamichou, Eleni Kampouraki, Anastasios Eskitzis, Paraskevi Kyfonidou, Ioannis Papalopoulos, Antonios Fanouriakis, Argyro Repa, Nikolaos Kougkas, Georgios Bertsias, Prodromos Sidiropoulos. Low dose of Rituximab is effective for maintenance of clinical remission or low disease activity in patients with rheumatoid arthritis. **2017 European League Against Rheumatism (EULAR) Annual Scientific Meeting** (Madrid, Spain 14-17 June 2017). *Annals of the Rheumatic Diseases* 2017;76:577.

4. **Ε. Φλουρή**, Α. Ρέπα, Ν. Αυγουστίδης, Ν. Κούγκας, Α. Φανουριάκης, Χ. Αδαμίχου, Ι. Παπαλόπουλος, Ε. Καμπουράκη, Μ. Τεριζάκη, Δ. Μπούμπας, Γ. Μπερτσιάς, Π. Σιδηρόπουλος. Μετά την διακοπή του 1ου αναστολέα TNFα (TNFi) οι βιολογικοί παράγοντες με διαφορετικό τρόπο δράσης (non-TNFi) έχουν συγκρίσιμη αποτελεσματικότητα αλλά καλύτερη επιβίωση από έναν δεύτερο TNFi: μακροχρόνια παρακολούθηση ασθενών με Ρευματοειδή Αρθρίτιδα της Πανεπιστημιακής Κλινικής Ηρακλείου. **25^{ο} Πανελλήνιο Ρευματολογικό Συνέδριο,** Αθηνα, 8-11 Δεκεμβρίου **2016** *Meditterannean Journal of Rheumatology Vol. 27, Issue 4 (supplemental)* (αναρτημένη ανακοίνωση επιλεγμένη για παρουσίαση)

5. Ν. Αυγουστίδης, **Ε. Φλουρή**, Χ. Αδαμίχου, Ε. Καμπουράκη, Α. Εσκιτζής, Π. Κυφωνίδου, Ι. Παπαλόπουλος, Α. Φανουριάκης, Α. Ρέπα, Ν. Κούγκας, Γ. Μπερτσιάς, Π. Σιδηρόπουλος. Η χορήγηση της χαμηλής δόσης rituximab φαίνεται αποτελεσματική για τη διατήρηση κλινικής ύφεσης και χαμηλής ενεργότητας νόσου σε ασθενείς με ρευματοειδή αρθρίτιδα. **25^{ο} Πανελλήνιο Ρευματολογικό Συνέδριο,** Αθηνα, 8-11 Δεκεμβρίου **2016** *Meditterannean Journal of Rheumatology Vol. 27, Issue 4 (supplemental)* (αναρτημένη ανακοίνωση)

6. **I. D. Flouri**, P.P. Sfikakis, A.A. Drosos, A. Boubougianni, P. Retsa, V. Tzouma, T.E. Markatseli, K. Fragiadaki, C. Koutsianas, K. Thomas, P. Voulgari, A. Repa, D. Vassilopoulos, P. Sidiropoulos. High Longterm Survival of Golimumab in Rheumatoid Arthritis and Spondylarthropathies in a Real World Study of 328 patients in Greece. **10th International Congress on Autoimmunity**, Leipzig, 6–10 Apr **2016**

7. **Ε. Φλουρή**, Α. Ρέπα, Ν. Αυγουστίδης, Α. Φανουριάκης, Ν. Κούγκας, Χ. Αδαμίχου, Ι. Παπαλόπουλος, Ε. Καμπουράκη, Μ. Τεριζάκη, Δ. Μπούμπας, Γ. Μπερτσιάς, Π. Σιδηρόπουλος. Στην κλινική πράξη 58% των ασθενών με ρευματοειδή αρθρίτιδα (ΡΑ) υπό Tocilizumab παραμένει στην αγωγή στα 2 έτη και αυτό είναι ανεξάρτητο από τη χορήγηση μεθοτρεξάτης: δεδομένα ασθενών της Πανεπιστημιακής Κλινικής Ρευματολογίας Ηρακλείου. **25ο Πανελλήνιο Ρευματολογικό Συνέδριο,** Αθηνα, 8-11 Δεκεμβρίου **2016** *Meditterannean Journal of Rheumatology Vol. 27, Issue 4 (supplemental)* (αναρτημένη ανακοίνωση)

8. **Irini D. Flouri**, Argyro Repa, Nestor Avgoustidis, Antonios Fanouriakis, Eleni Kambouraki, Maria Terizaki, Panayiota Rapsomaniki, Nikolaos Kougkas, Alexandra Pompieri, Dimitrios T. Boumpas, Georgios Bertsias, Prodromos Sidiropoulos. Rheumatoid Arthritis patients treated with Abatacept i.v. have better responses and drug survival rate when Abatacept is first or second line biologic agent. **American College of Rheumatology (ACR) Annual Scientific Meeting (October 2015).** *Arthritis Rheumatol.* 2015; 67 (suppl 10).

9. **Ε. Φλουρή**, Α. Ρέπα, Ν. Αυγουστίδης, Α. Φανουριάκης, Ε. Καμπουράκη, Μ. Τεριζάκη, Π. Ραψομανίκη, Ν. Κούγκας, Α. Πομπιέρη, Δ. Τ. Μπούμπας, Γ. Μπερτσιάς, Π. Σιδηρόπουλος. Σε ασθενείς με ρευματοειδή αρθρίτιδα (ΡΑ) οι μη-TNFi (ΜΤΑ) βιολογικοί παράγοντες (ΒΠ) έχουν παρόμοια αποτελεσματικότητα και παραμονή στην αγωγή ως 1ος ΒΠ αλλά μεγαλύτερη παραμονή ως 2ος ΒΠ. **24ο Πανελλήνιο Ρευματολογικό Συνέδριο,** Αθηνα, 11-14 Δεκεμβρίου **2014** *Ελληνική Ρευματολογία 2014 (συμπληρωματικό τεύχος)* (προφορική παρουσίαση)

10. **Ε. Φλουρή**, Α. Ρέπα, Ν. Αυγουστίδης, Α. Φανουριάκης, Ε. Καμπουράκη, Μ. Τεριζάκη, Π. Ραψομανίκη, Ν. Κούγκας, Α. Πομπιέρη, Δ. Τ. Μπούμπας, Γ. Μπερτσιάς, Π. Σιδηρόπουλος. Η παραμονή στην αγωγή και η κλινική απάντηση ασθενών με ρευματοειδή αρθρίτιδα στο Abatacept είναι υψηλότερα σε ασθενείς που το λαμβάνουν ως 1η η 2η βιολογική θεραπεία. **24ο Πανελλήνιο Ρευματολογικό Συνέδριο,** Αθηνα, 11-14 Δεκεμβρίου **2014** *Ελληνική Ρευματολογία 2014 (συμπληρωματικό τεύχος)* (αναρτημένη ανακοίνωση)

11. M.I. Zervou, P. Sidiropoulos, E. Myrthianou, **I. Flouri**, D. Plant, P. Rapsomaniki, A. Barton, D.T. Boumpas, G. N. Goulielmos. Lack of association of variants previously associated with anti-TNF medication response in rheumatoid arthritis patients : results from a homogeneous Greek population. **2013 European League Against Rheumatism (EULAR) Annual Scientific Meeting** (Madrid, Spain 12-15 June 2013).*Annals of the Rheumatic Diseases* 72(Suppl 1):A53.1-A53

12. M. Nakou, E.D. Papadimitraki, C. Choulaki, N. Goulidaki, M. Moutafi, E. Koutala, **I.D. Flouri**, G. Bertsias, D.T. Boumpas. [OP-0171] Synergistic action of Interleukin 21 (IL-21) and TLR-9 to promote B-cell differentiation in active SLE. **2008 European League Against Rheumatism (EULAR) Annual Scientific Meeting**, (Paris, France, 11-14 June 2008). *Ann Rheum Dis 2008;67(Suppl II):102*