Chapter 9

TUMOUR NECROSIS FACTOR INHIBITORS USED IN THE TREATMENT OF RHEUMATOID ARTHRITIS: EVIDENCE OF SAFETY, EFFICACY AND HEALTH IMPLICATION

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ABSTRACT

Rheumatoid arthritis (RA) is a systemic autoimmune condition characterised by inflammation and destruction of synovial joints. The pathogenesis of inflammation is underpinned by interaction and activation of immune cells, which release inflammatory cytokines such as tumour necrosis factor (TNF) and interleukins. These mechanisms of disease pathogenesis were targeted by specific drugs in the form of monoclonal antibodies (mAb) or soluble receptors. The advent of biological disease

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modifying therapies (bDMARDs) has revolutionised the management of RA. These agents dramatically reduce synovial inflammation, halt the progression of radiographic joint damage, and improve functional ability and health related quality of life outcomes. This has a positive impact on the socioeconomic burden of RA. This chapter reviews the pathogenesis of RA and evidence behind the use of TNF inhibitors licensed for RA treatment. We focus on clinical efficacy, safety profile and cost-effectiveness of infliximab, etanercept, adalimumab, certolizumab, golimumab. Additionally, we discuss national and international recommendations for the clinical use of TNF inhibitors, with further consideration of the financial implications. Examples of clinical randomised controlled trials (RCTs), which have proven the efficacy of different TNF inhibitors in RA are also included in this chapter. The use of TNF inhibitor biosimilars will be discussed in chapter 11.

Keywords: rheumatoid arthritis, TNF inhibitors, efficacy, cost-effectiveness, safety

INTRODUCTION

RA is a common and debilitating autoimmune inflammatory disease. It affects approximately 0.5-1% of European and North-American adults with considerable regional variation. Women are three times more frequently affected than men, with a peak age incidence of 50-60 years [1].

AETIOLOGY

The initiation of RA results from a combination of predetermined (genetic) and stochastic (immune, random and environmental) events. The human leukocyte antigen (HLA) major histocompatibility (MHC) genes are the most important, but many other genes are involved and contribute to RA susceptibility and severity. Less is understood regarding the mechanisms for the environmental component. The most likely mechanism is repeated activation of the innate immune system. This process can take many years, with gradually increasing autoimmunity, until an unknown process tips the balance toward clinically apparent disease. One key element is citrullination. This is conversion of the amino acid arginine to citrulline, which occurs with any environmental stress, including in alveolar macrophages in cigarette smokers [2], [3]. In RA,

clearance of citrullinated cells is inadequate, which increases the propensity for immune reactivity to neoepitopes [4]. Specific HLA-DRB1 genotypes, termed shared epitopes, no longer recognise proteins as "self", leading to the production of anti-citrullinated protein antibodies (ACPAs). Later consequences are immune complex deposition and continued loss of tolerance to self [5],[6].

PATHOGENESIS

All elements of the immune system have fundamental roles in initiating, propagating, and maintaining the autoimmune process of RA. The exact orchestration of cellular and cytokine events is complex, involving T and B cells, antigen-presenting cells, and both pro-inflammatory, anti-inflammatory cytokines, and cytokine pathways.

Immune cells invade the normally relatively pauci-cellular synovium. These cells and their cytokine messengers propagate the inflammatory response. The stimulation of angiogenesis and the development of organised lymphoid structures sustain the inflammatory response within the synovium [7], [8]. In time, mesenchymal transformation and osteoclastogenesis lead to the destructive lesions characteristic of established RA (local cartilage destruction and bone erosions) [9] (Figure 1).

Historically, RA followed a pattern of relentless progression to irreversible joint damage. In the last two decades, there has been a vast transformation in the landscape of this disease. It is now recognised that the longer the interval from diagnosis to starting treatment, the poorer the outcome. This is due to the apparent ability of the disease to activate aggressive phenotypes, and to the accrual of irreversible joint damage. Early intensive treatment strategies within this 'window of opportunity' have resulted in improved outcomes and long-term prognosis with subsequent increased probability of drug free remission [10].

In the last two decades, the research in RA has been dominated by clinical trials of biologic therapies. Development of these agents has provided further insight into the pathogenesis of RA, revealing disease mechanisms. These biologic therapies are mAbs or soluble receptors that target specific aspects of disease pathogenesis. They have the potential to rapidly and completely arrest inflammation and joint damage.
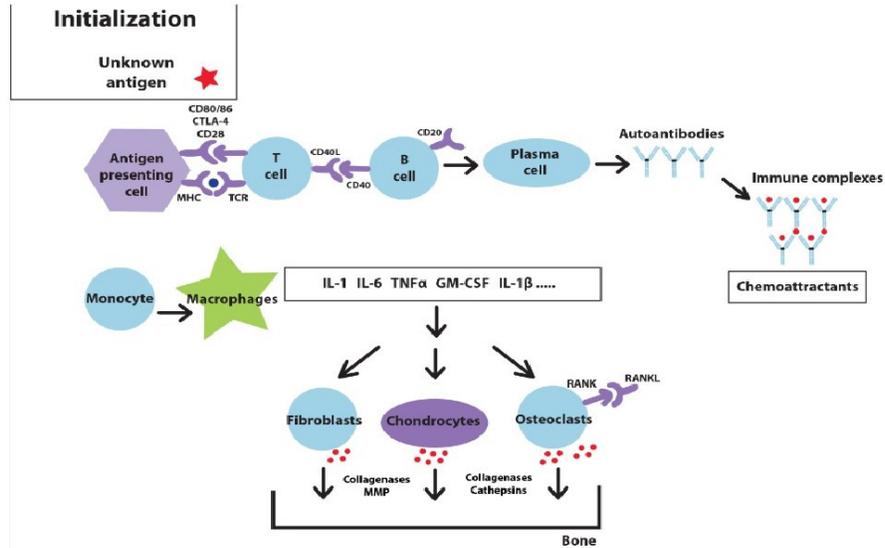
Figure 1. Overview of RA pathogenesis.

Antigen presenting cells present antigens to T cells, causing them to differentiate into Th1 or Th17 cells. These cells then stimulate macrophages to secrete pro-inflammatory cytokines, which in turn promote production of autoantibodies by B cells. These autoantibodies bind to antigens to form immune complexes. These immune complexes then engage receptors on complement and macrophages; thereby further increasing secretion of cytokines such as TNFα and IL6. These cytokines exert cartilage and bone damage through chondrocyte and osteoclast activation via the receptor activator of nuclear factor kappa-B ligand (RANKL)/RANK system. Biologic drugs target different cytokines known to contribute to synovial inflammation.

This chapter will discuss the different biologic treatments licensed for the treatment of RA and their impact on clinical efficacy and safety whilst highlighting new emerging biologic agents. Current national and international recommendations for the clinical use of biologics are also illustrated below. Efficacy data from relevant RCTs is included in reference tables as appendages, to provide further details to accompany the body of the text.

TUMOUR NECROSIS FACTOR ALPHA (TNF) INHIBITORS

History

Advances in research on the pathogenesis of RA and cytokine biology converged on TNF and interleukin 1 (IL1) as key factors in joint inflammation and matrix destruction [11],[12]. The theory arose that increased concentrations of TNF at the sites of inflammation were driving disease, and the removal of excess became a therapeutic goal [13], [14]. Transgenic mice expressing high concentrations of TNF spontaneously developed arthritis, which was clinically and histopathologically similar to RA [15]. Following the promising results in controlling experimental arthritis by blocking TNF in animal models, the first pilot study was performed in patients with RA using a neutralizing, chimeric, monoclonal anti-TNF antibody, infliximab [16]. This study opened the era of multiple RCTs using biologic agents targeting TNF, which unequivocally demonstrated the efficacy of anti-TNF therapies in reducing disease activity in RA [17].

Mechanism of Action

TNF is produced by numerous cell types, including immune (macrophages, B and T lymphocytes, natural killer cells, basophils, eosinophils, dendritic cells, neutrophils and mast cells), and non-immune cells (astrocytes, fibroblasts, glial cells, granuloma cells and keratinocytes) and many tumour cells. TNF must bind to one of two structurally distinct receptors present in all cell types (except erythrocytes) to exert its biological function [18]:

TNF has the following physiological action. It:

1. Is a potent inducer of the inflammatory response, activating the synthesis of a large range of proinflammatory cytokines and chemokines.
2. Induces the expression of vascular endothelial growth factor (VEGF), which promotes angiogenesis, and secretion of matrix metalloproteinases (MMPs) involved in the degradation of components of the cellular matrix.
3. Stimulates vascular endothelial cells to express adhesion molecules allowing leukocytes to adhere to the endothelial surface.

4. Inhibits the function of T regulatory cells. These cells play a role in the development of immunological tolerance and the prevention of an excessive immune response.
5. Is involved in 'reverse signalling'; TNF exists both as a soluble and transmembrane cytokine. This membrane-integrated ligand form can receive signals, act as a receptor and transmit positive and negative feedback signals into the cell.

Structure, Dosing and Price

All TNF inhibitors except etanercept are mAbs or fragments thereof. Natural mAbs are derived from single B cells that clonally express copies of a unique heavy and light chain, which are covalently linked to form an antibody molecule of unique specificity (Figure 2). Engineered mAbs can be structurally identical to natural mAbs but are created by gene splicing and mutation procedures, mimicking natural gene rearrangement and somatic mutation events [19].

Below we detail the characteristics of every TNF inhibitor and their current costs in the UK, according to the British National Formulary version 70 (BNF70).

Adalimumab (Humira[TM], Abbvie) is a human-sequence immunoglobulin G1 (IgG1) antibody. It binds to soluble and transmembrane forms of TNF and neutralises its biological function by blocking its interaction with cell-surface TNF receptors. It is given as a subcutaneous (SC) injection at a dose of 40 mg every other week. The half-life is 10-20 days. The price of a 40-mg prefilled syringe in the UK is estimated at £352.14 excluding VAT (BNF70) [20]. The annual cost for 26 doses at a dose of 40 mg every other week is £9156.

Etanercept (Enbrel[TM], Amgen) is a recombinant human TNF-receptor fusion protein. It consists of two extracellular domains of human soluble TNF receptor 2, which binds to TNF and a Fc fragment of human IgG that serves as a stabiliser. It interferes with the inflammatory cascade by binding to TNF, thereby blocking its interaction with cell-surface receptors. It is given as a SC injection at a dose of 50 mg once weekly or alternatively 25mg twice weekly. The half-life is 3 days. The price of a 50-mg injection in the UK is £178.75 (excluding VAT; BNF70). The annual cost is £9295.

Infliximab (Remicade[TM], Janssen) is a chimeric mAb, 25% murine and 75% human derived with a constant human region (IgG1) and a variable mouse region that binds to soluble and transmembrane TNF. It is given at a dose of

3 mg/kg as an intravenous (IV) infusion over 2 hours at weeks 0, 2 and 6 and thereafter every 8 weeks. If there is an inadequate response, the dose can be incremented to a maximum of 7.5 mg/kg every 8 weeks or administrated 4 weekly. The half-life is 8-10 days. The price for a 100 mg vial in the UK is £419.62 (excluding VAT; BNF70). Assuming an average weight of 70 kg and a dose of 3 mg/kg, the annual cost (including the loading doses) is between £7553 and £8812. This does not include administration related costs.

Certolizumab pegol (Cimzia™; UCB) is a PEGylated Fab fragment of a humanized mAb. It contains a TNF-specific Fab fragment of a humanised mAb, which binds to both soluble and membrane-bound TNF and a fragment conjugated to 40-kDa polyethylene glycol to enhance its plasma half-life. It does not contain an Fc region and therefore does not engage complement or cause antibody-dependent cell-mediated cytotoxicity. This also means it may be less likely to cross the placenta, with implications for use in pregnancy [21]. It is given at a dose of 400 mg subcutaneously at weeks 0, 2 and 4, followed by a maintenance dose of 200 mg subcutaneously every 2 weeks. The half-life is 14 days. The price for 200 mg in the UK is £715 (excluding VAT, BNF70). The cost for the first year including loading doses is £10,367.50 with an annual cost thereafter of £9295. These costs may vary in different settings with negotiated procurement discounts; currently in the UK, the manufacturer has agreed with the Department of Health that the first 12 weeks therapy (10 pre-loaded syringes of 200 mg each) is free of charge.

Golimumab (Simponi™, Janssen) is a fully human anti-TNF IgG mAb with affinity for both soluble and transmembrane forms of TNF. It prevents the binding of TNF to its receptors thereby neutralising its activity. It is given subcutaneously at a dose of 50 mg per month. If there is an inadequate clinical response after 3-4 injections and the patient's weight is greater than 100 kg, the dose can be increased to 100 mg monthly. The half-life is 7-20 days. The price for a 50 mg injection in the UK is £762.97, with an annual drug cost is £9156. The UK Department of Health has agreed that a 100 mg dose is available to the National Health Service (NHS) at the same cost as a 50 mg dose.
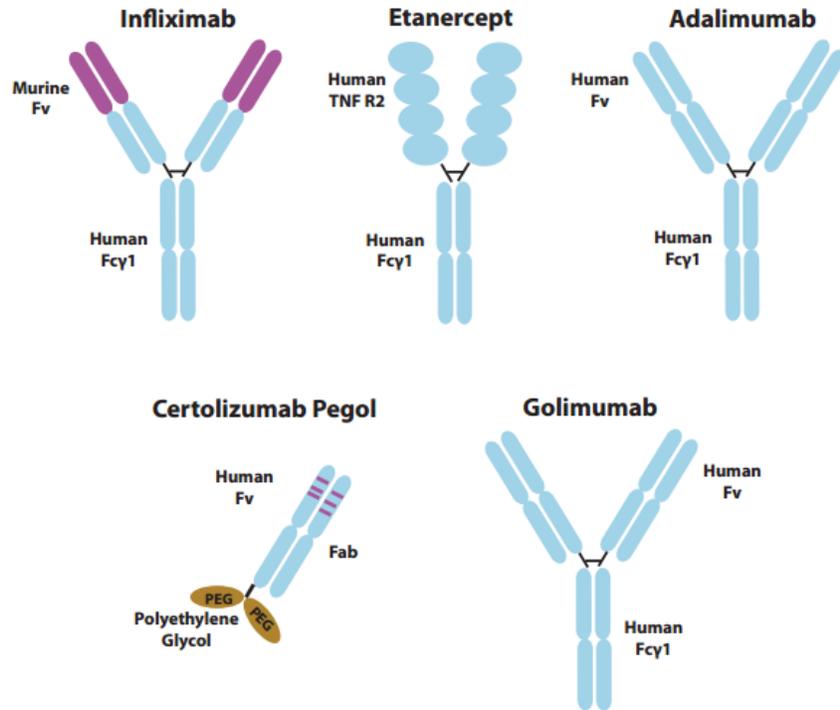
Figure 2. Anti-TNF Structure.

National/International Guidelines

British (British Society of Rheumatology (BSR) [22] and National Institute of Clinical Excellence (NICE) [23] and European (European League Against Rheumatism, EULAR) [24] guidelines recommend anti-TNF therapy in patients with high disease activity who have failed a trial of two csDMARDs, including methotrexate (MTX), unless contraindicated, over a 6 month period. Anti-TNF therapy should be continued only if there is an adequate response at 6 months.

American guidelines (American College of Rheumatology, ACR) [25] recommend the use of agents, plus or minus MTX, in patients with early or established RA (disease duration <6 months) who have failed csDMARD monotherapy. However, double csDMARD therapy is stipulated as an alternative.

Switching Anti-TNF Therapy

Data from trials, open-label studies and registries confirm that switching TNF inhibitors is effective. Furthermore, intolerance may be idiosyncratic rather than a TNF inhibitor class effect. Therefore, despite non-response to one TNF agent, patients may respond to another drug in this class. There is some evidence that switching may be less beneficial than treatment with the first TNF inhibitor, especially in seropositive patients [26]–[30]. In the UK, seropositive patients who fail first anti-TNF are switched to a different bDMARD; rituximab is the most preferred option. Patients intolerant to MTX who have failed the first TNF inhibitor can be switched to a second TNF agent, as recommended by NICE in the UK; however data from the Swiss RA registry suggested that it is more beneficial to switch to rituximab as a second biologic agent after TNF treatment failures, irrespective of additional csDMARD therapy [31]. Analysis of the Finnish registry of biologics found that a second TNF blocker can restore the response in cases of secondary loss of efficacy to a first TNF blocker, and maintain it after switching due to an adverse event (AE), irrespective of the concomitant MTX therapy [32].

Monotherapy

British and European guidelines [23], [24] clearly prefer maintenance of combination therapy and all anti-TNF agents are recommended to be used in combination with csDMARD therapy (such as MTX). However, UK guidance does recommend adalimumab or etanercept monotherapy in patients who have had an inadequate response to at least one TNF inhibitor, as rituximab therapy is preferred in patients able to take MTX.

American guidelines recommend anti-TNF treatment with or without MTX after failure of csDMARD therapy [25].

EFFICACY

Infliximab [Table 1]

In established RA, the pivotal phase III study, ATTRACT, reviewed patients with an inadequate response to MTX therapy. The study compared MTX + placebo with MTX + infliximab, at four dose regimens. Infliximab groups exhibited significantly greater improvement after 1 year with higher ACR20, ACR50 and ACR70 responses and reduced progression of total Sharp score (TSS) [33]. Several studies have replicated and extended this data [34]–[36]. The Sharp score is a scoring system for assessing erosions and joint space narrowing in hand radiographs. The modified version (Sharp/van der Heijde score - SHS), which also includes foot joints, gives each joint a separate score for erosion and joint space narrowing, whereas the total score combines the results to give one score per joint [37].

The ACR established a core data set that was more likely to show efficacy in trials and represent the breadth of RA manifestations. ACR20 response represents a 20% improvement in tender and swollen joint count, patient's assessment of pain, global assessment of disease activity and physical function, physician's assessment of physical function, and acute phase reactant value [38]. ACR50 and 70 responses represent a 50% and 70% improvement respectively.

A meta-analysis concluded the benefit of infliximab is significantly larger in patients with longer disease duration and MTX failure [39]. Recent studies have demonstrated improved efficacy when infliximab is used in early disease. The ASPIRE study indicated higher response rates at each ACR category compared to rates in established disease [40]. Other studies have produced similar findings [41]. The Behandel Strategieen (BeSt) study concluded that the introduction of infliximab to MTX at an early disease stage led to significant improvements in clinical disease activity and prevention of erosive progression. Additionally, this strategy induced a remission state that was maintained upon cessation of infliximab [42], [43]. The results of BeST study suggest additional benefit of early treatment with a biologic agent, supporting the hypothesis of a "window of opportunity" in improving the long-term outcome of patients with RA. It is also recognised that infliximab can induce the generation of regulatory T cell subsets that may promote reinstitution of immune tolerance [44].

Table 1. Infliximab

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Maini et al. 1999 ATTRACT	30 week phase III RCT Group 1: Infliximab 3mg/kg every 4 weeks + MTX Group 2: Infliximab 3mg/kg every 8 weeks + MTX Group 3: Infliximab 10mg/kg every 4 weeks + MTX Group 4: Infliximab 10mg/kg every 8 weeks + MTX Group 5: Placebo + MTX (N = 88) N = 340 for combined infliximab groups	Week 30 ACR20: Group 1: 53% Group 2: 50% Group 3: 58% Group 4: 52% Group 5: 20% (P<0.001)
Smolen et al. 2006 ASPIRE	54 week RCT in MTX naïve patients. Group 1: Escalating doses of MTX to 20 mg/week Group 2: Infliximab at weeks 0, 2, and 6, and every 8 weeks thereafter + escalating doses of MTX to 20 mg/week N= 1004	Week 54 results: CRP, ESR and swollen joint count were associated with greater joint damage and progression in MTX/placebo group, while none of these parameters were associated with progression in the infliximab group. Mean changes in SHS with highest CRP/ESR tertiles in placebo group were 5.62 and 5.89 respectively, compared with 0.73 and 1.12 in infliximab group (P<0.001). Patients with greater joint damage at baseline (SHS ≥ 10.5) showed less progression in infliximab group compared with MTX/placebo (-0.39 vs. 4.11; P<0.001).

Table 1. (Continued)

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Goekoop-Ruiterman et al. 2008 BeST	52 week RCT in early RA Group 1: sequential csDMARDs (N = 126) Group 2: step up combination csDMARDs (N = 121) Group 3: combination csDMARDs with tapered prednisone (N = 133) Group 4: combination csDMARD and infliximab (N = 128)	3 Months, Dutch-HAQ: Group 1: 1.0 Group 2: 1.0 Group 3: 0.6 Group 4: 0.6 (P<0.001) 12 Months, Dutch-HAQ: Group 1: 0.7 Group 2: 0.7 Group 3: 0.5 Group 4: 0.5 (P=0.009) Groups 3 and 4 resulted in earlier functional improvement than groups 1 and 2, with mean scores on Dutch-HAQ at 3 months; 1.0 in groups 1 and 2 and 0.6 in groups 3 and 4 (P<0.001). The median increases in total SHS were 2.0, 2.5, 1.0, and 0.5 in groups 1 to 4, respectively (P<0.001).
Quinn et al. 2005	12 month RCT with attempted remission induction in DMARD naïve patients. Clinical observation to 24 months Group 1: Infliximab + MTX (N = 10) Group 2: Placebo + MTX (N = 10)	54 weeks, ACR20: Group 1: 80% Group 2: 60% 104 weeks, ACR20: Group 1: 70% Group 2: 50% Importantly, at 1 year after stopping induction therapy, response was sustained in 70% in MTX/infliximab group, with median DAS28 of 2.05 (remission range).

Legend: ACR 20 - American College of Rheumatology 20% response criteria; CRP - C reactive protein; DAS 28 - disease activity score 28; csDMARDs - conventional disease modifying anti-rheumatic drugs; ESR - erythrocyte sedimentation rate; HAQ - health assessment questionnaire; MTX - methotrexate; N - number of patients; RA - rheumatoid arthritis; RCT - randomised controlled trial; TSS - total Sharp score; SHS - Sharp/van der Heijde score.

Adalimumab [Table 2]

Several RCTs support the use of adalimumab in RA, and indicate its superiority to placebo in controlling disease activity and retarding progressive radiological damage [45], [46]. The pivotal phase III study in established RA (ARMADA) found adalimumab, in conjunction with MTX, to be superior to placebo in reducing erosive progression and improving ACR responses [47]. These findings were maintained at 4 years of open follow up [48]. In early RA, of less than 3 years duration, the PREMIER study compared adalimumab + MTX treatment with MTX, and adalimumab monotherapy.

Combination therapy was significantly better than either monotherapy agent, as assessed by ACR50 response and radiographic progression outcomes. The only advantage of adalimumab monotherapy over MTX was a reduction in radiographic joint damage [49]. Furthermore while adalimumab is effective for RA irrespective of disease duration, there is a trend towards superior clinical, functional and radiographic outcomes in patients with early disease [50].

A meta-analysis of five studies in patients with an inadequate response to csDMARDs suggested adalimumab was statistically significantly more effective than control (either placebo or existing csDMARDs) across a range of outcomes, including ACR20 and ACR70 response, HAQ score and SHS per year [51]. Subsequent meta-analyses have suggested similar results, with more robust evidence regarding the efficacy of combination therapy [52], and adalimumab appearing to be more effective in comparison to etanercept and infliximab in long-term treatment [53].

The HAQ score is a patient reported outcome measure looking at five different domains: disability, pain, medication effects, costs of care and mortality [54].

Table 2. Adalimumab

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Wienblatt et al. 2003	24 week RCT in MTX inadequate responders. Group 1: Adalimumab SC 20mg every other week (e.o.w..) + MTX (N = 62) Group 2: Adalimumab SC 40mg e.o.w. + MTX (N = 69) Group 3: Adalimumab SC 60mg e.o.w. + MTX (N = 67) Group 4: Placebo + MTX (N = 73)	Week 24 ACR20: Group 1: 47.8% Group 2: 67.2% Group 3: 65.8% Group 4: 14.5% (P<0.001)
Breedveld et al. 2006.	52 week multicenter, double-blind, active comparator-controlled study in MTX naïve. Group 1: Adalimumab SC 40mg e.o.w. + MTX (N = 268) Group 2: Adalimumab monotherapy (N = 274) Group 3: MTX monotherapy (N = 257)	Week 52 ACR50: Group 1: 62% P<0.001 Group 2: 41% Group 3: 46%
Furst et al. 2003. STAR study	24 week RCT in MTX poor responders Group 1: Adalimumab 40mg e.o.w. + csDMARDs (N = 318) Group 2: Placebo (N = 318)	Week 24 ACR20: Group 1: 52.8% P ≤ 0.001 Group 2: 34.9%
Keystone et al. 2004	52 week RCT study in RA patients with inadequate response to MTX Group 1: Adalimumab 20mg SC e.o.w. + MTX (N = 207) Group 2: Adalimumab 40mg SC e.o.w. + MTX (N = 212) Group 3: Placebo (N = 200)	Week 52 ACR20: Group 1: 59% Group 2: 55% Group 3: 24% (P<0.001)
Jamal et al. 2009	52 week RCT to compare response to adalimumab Group 1: Early RA ≤ 3 years) vs. Group 2: Established RA (>3years) N = 407	Group 1: ACR20 61%, HAQ improvement 0.44, mean reduction in TSS 5.32 Group 2: ACR20 56%, HAQ improvement 0.25, mean reduction in TSS 2.06.

Table 2. (Continued)

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Van de Putte 2004	26 week RCT in RA with inadequate response to csDMARDs. Group 1: Monotherapy adalimumab 20mg e.o.w. (N = 106) Group 2: Monotherapy adalimumab 20mg weekly (N = 112) Group 3: Monotherapy adalimumab 40mg e.o.w. (N=113) Group 4: Monotherapy adalimumab 40mg weekly (N = 103) Group 5: Placebo (N = 110)	26 Week ACR20, mean HAQ improvements: Group 1: 35.8%, – 0.29 Group 2: 39.3%, –0.39 Group 3: 46.0%, – 0.38 Group 4: 53.4%, –0.49 Group 5: 19.1%, –0.07 (P⩽0.01)

Legend: ACR 20 - American College of Rheumatology 20% response criteria; csDMARDs - conventional disease modifying anti-rheumatic drugs; e.o.w. - every other week; HAQ - health assessment questionnaire; MTX - methotrexate; N - number of patients; RA - rheumatoid arthritis; RCT - randomised controlled trial; SC - subcutaneously; TSS - total Sharp score.

Etanercept [Table 3]

Several RCTs provide evidence for the benefit of etanercept in reducing clinical inflammation and radiographic progression, and improving functional and quality of life indices.

In early RA, a pivotal phase III study comparing MTX monotherapy with etanercept monotherapy demonstrated rapid rates of improvement, with etanercept monotherapy superior in reducing disease activity, arresting structural damage, and decreasing disability [55].

A significant trial demonstrating superior benefits with combination etanercept and MTX was the TEMPO study [56]. The combination therapy demonstrated superiority as far as the ACR responses and retardation of radiographic progression were concerned. However, most of the patients were MTX naïve and had a shorter disease duration, which might explain the superiority of the combination treatment. The ADORE study [57], in patients with true MTX resistance showed combination MTX and etanercept therapy

was no better than etanercept alone, suggesting that etanercept monotherapy may be an option for patients unable to take MTX or unresponsive to it. Another study which demonstrated the benefit of combination therapy, assessed the efficacy of etanercept added to MTX in MTX partial or non-responders [58]. Similarly, a further RCT demonstrated the superiority of etanercept alone or in combination with sulphasalazine compared with sulphasalazine alone [59].

The COMET study assessed the efficacy of etanercept as first line therapy in patients with early RA and high disease activity (DAS28 > 5.1). The DAS28 score is a disease activity score (DAS) comprising of the patient's global visual analogue score (GVAS), ESR or CRP, and the number of tender and swollen joints out of 28 joints in the upper limbs and knees [60]. In the etanercept + MTX combination treatment arm, 50% of patients achieved clinical remission (DAS28 < 2.6) compared with 28% on MTX monotherapy. Very early RA patients (defined as having <4 months disease duration) demonstrated higher rates of remission [61], [62].

Table 3. Etanercept

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Bathon et al. 2000. ERA Study	52 week RCT Group 1: Etanercept 10 mg twice weekly (N = 208) Group 2: Etanercept 25 mg twice weekly (N = 207) Group 3: Methotrexate (N = 217)	Mean increase in erosion score during the first 6 months Group 1: Numerical value not available Group 2: 0.30 Group 3: 0.68 (P=0.001) Group 2: more rapid rate of improvement, with significantly more patients achieving ACR20, 50 and 70 during the first six months (P<0.05)
Weinblatt et al. 1999.	24 week RCT Group 1: Etanercept 25 mg + MTX (N = 59) Group 2: Placebo + MTX (N = 30)	24 Week, ACR20: Group 1: 71% Group 2: 27% (P<0.001)

Table 3. (Continued)

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Klareskog et al. 2004. TEMPO	24 week RCT Group 1: Etanercept 25 mg Group 2: MTX Group 3: Etanercept + MTX N = 682	24 weeks, numeric index of the ACR response (area under the curve AUC), mean TSS Group 1: 14.7% (P<0.0001), 0.52 (P=0.0006) Group 2: 12.2%, 2.8 (P<0.0001) Group 3: 18.3%, -0.54 (P<0.0001)
van Riel et al. 2006 ADORE Study	16 week randomised open-label study Group 1: Etanercept + MTX (N = 155) Group 2: Etanercept (N = 160)	16 Week, ACR20: Group 1: 71.0% Group 2: 67.1%, DAS28 improvement of >1.2 units Group 1: 75.2% Group 2: 72.8% (P=0.658). EULAR good or moderate response Group 1: 82.4% Group 2: 80.0%
Emery et al. 2008	52 week RCT in MTX naïve RA patients Group 1: MTX (N = 268) Group 2: Etanercept 50 mg/week + MTX (N = 274)	52 Week, DAS28 clinical remission: Group 1: 28%, (95% CI 23-33%) Group 2: 50% (95% CI 44-56%) (P<0.0001).
Combe et al. 2006	24 week RCT in inadequate responders to sulphasalazine Group 1: Sulphasalazine (N = 50) Group 2: Etanercept (N = 103) Group 3: Etanercept + Sulphasalazine (N = 101)	24 week, % of patients achieving ACR20: Group 1: 28% Group 2: 73.8% Group 3: 74% (P<0.01)

Legend: ACR 20 - American College of Rheumatology 20% response criteria; ACR 50, 70 - American College of Rheumatology 50% and 70% response criteria; AUC - area under the curve; CI - confidence intervals; DAS 28 - disease activity score 28 joints; EULAR - European League Against Rheumatism; MTX - methotrexate; N -

number of patients; RA - rheumatoid arthritis; RCT - randomised controlled trial; TSS – total Sharp score.

Newer TNF Inhibitors

The frequency of primary and secondary non-response (defined as lack of initial response and loss of response, respectively) has contributed to the perceived need for developing new agents, such as: certolizumab pegol and golimumab.

Each drug within the TNF class has its own specific pharmacokinetic properties and thus potential different mechanisms of action. This was hypothesised as useful in overcoming the problem of non-responsiveness [63].

Certolizumab [Table 4]

Three pivotal phase III clinical trials provide evidence for the efficacy and safety of certolizumab in patients for whom MTX or other csDMARDs have been ineffective.

Certolizumab was superior to placebo in MTX non-responder patients, with significantly more patients achieving ACR20 response in the certolizumab treatment arm (RAPID I, and RAPID II trials). There was no difference in efficacy between 200mg or 400mg doses. Further post-hoc analysis of RAPID I data has confirmed that response within the first 12 weeks of treatment determines the likelihood of achieving a good long-term response. Both trials demonstrated prevention of progression of structural damage. Patients who did not achieve ACR20 response were withdrawn at week 16. Interestingly this group still demonstrated improved radiographic scores implying that inhibition of joint damage occurs even in poor clinical responders. This has also been demonstrated with other TNF inhibitors [64], [65].

The REALISTIC trial stratified patients according to concomitant use of MTX, prior anti-TNF treatment and disease duration and showed a significant difference in ACR20 response in the certolizumab treatment group vs. placebo, regardless of disease duration, concomitant DMARDs or prior anti-TNF therapy [66].

Induction of remission in patients with low or moderate disease activity was evaluated in the CERTAIN trial. A significant difference in remission rates (defined by the clinical disease activity score – CDAI) was achieved (19% of

certolizumab group vs. 7% of controls). A loading regimen was shown to improve the speed of treatment's onset of action [67].

Evidence for certolizumab effectiveness as monotherapy, administered as a 4-weekly 400mg dose, was provided by the FAST4WARD trial, which established that this dose regimen was clinically effective, and led to lower rates of ACR20, 50 and 70 responses compared with combination therapy [68]. The differences in the study design might be responsible for the disparity of the reported efficacy of different TNF inhibitors. In two of the trials of certolizumab, the patients considered as treatment failures were withdrawn at week 16 (likely to represent a large proportion of the patients on placebo). As less patients receiving placebo remained in the study at week 24, the placebo response rate was low. It is possible that some patients would have responded to csDMARDs from 16–24 weeks.

Table 4. Certolizumab

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Keystone et al. 2008 RAPID 1	52 week RCT Group 1: Certolizumab 200mg e.o.w. (N = 393) Group 2: Certolizumab 400mg e.o.w. + MTX (N = 390) Group 3: Placebo + MTX (N = 199)	Week 52, ACR20 Group 1: 60.8% Group 2: 58.8% Group 3: 13.6% (P<0.001)
Smolen et al. 2009	24 week RCT Group 1: Certolizumab 200mg e.o.w. + MTX (N = 246) Group 2: Certolizumab 400mg e.o.w. + MTX (N = 246) Group 3: Placebo e.o.w. + MTX (N = 127)	Week 24 ACR20, mean HAQ-DI Group 1: 5.7.3%, -0.50 Group 2: 57.6%, -0.50 Group 3: 8.7%, -0.14 (P≤0.001). Week 24, radiographic progression mean changes from baseline mTSS Group 1: 0.2 Group 2: -0.4 Group 3: 1.2 (P≤0.01).

Table 4. (Continued)

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Fleishmann et al. 2009.	24 week RCT Group 1: Certolizumab 400mg every 4 weeks (N = 111) Group 2: placebo every 4 weeks (N = 109)	Week 24, ACR20 Group 1: 45.5% Group 2: 9.3% (P<0.001)
Weinblatt et al. 2010 REALISTIC	12 week RCT Group 1: Certolizumab 400 mg at weeks 0, 2, 4 with subsequent 200mg (N = 851) Group 2: Certolizumab 400 mg at weeks 0, 2, 4 with subsequent placebo added to current treatment. (N = 212)	Week 12, ACR20 Group 1: 51.1% Group 2: 25.9% (P<0.001)
Smolen et al. 2015	52 week RCT Group 1: Certolizumab (400mg at weeks 0, 2, 4, then 200 mg e.o.w.) + current csDMARDs Group 2: Placebo + current csDMARDs (N= 194)	52 week DAS28 low disease activity Group 1: 63% (P<0.001) Group 2: 29.7% 52 week CDAI remission Group 1: 18.8% Group 2: 6.1% (P≤0.05) 52 week HAQ-DI change from baseline Group 1: -0.25 Group 2: -0.03 (P≤0.01)

Legend: ACR 20 - American College of Rheumatology 20% response criteria; CDAI - clinical disease activity index; csDMARDs - conventional disease modifying anti-rheumatic drugs; e.o.w. - every other week; HAQ - health assessment questionnaire; HAQ-DI - health assessment questionnaire damage index; MTX - methotrexate; mTSS - modified total Sharp score; N - number of patients; RCT - randomised controlled trial.

As a consequence, the benefits of treatment may appear greater with certolizumab than with other TNF inhibitors mainly because of the use of a

loading dose and the study design incorporating a short duration of csDMARDs in the comparator arm [69].

Golimumab [Table 5]

A pivotal RCT demonstrated the efficacy and safety of golimumab in MTX-naïve patients (GO-BEFORE), MTX inadequate responders (GO-FORWARD) and those after anti-TNF failure (GO-AFTER).

The GO-BEFORE study enrolled patients with early RA (less than 3 years). A reduction in joint progression was demonstrated [70], but there was no significant ACR50 difference between golimumab + MTX and MTX monotherapy. However, lower response rates, as assessed by ACR20 criteria, were not considered, and it was hypothesized that this was the cause of failing to meet the primary endpoint. ACR20 response improved significantly with the same dose regimen in another similar study [71]. The GO-FORWARD study demonstrated significantly higher ACR20 responses detected as early as 4 weeks, and sustained unto 52 weeks [72], [73]. The GO-AFTER study demonstrated that golimumab in combination with csDMARDs led to a significantly greater proportion of patients achieving ACR20 compared with placebo [74]. In all the aforementioned trials there was no difference in efficacy of golimumab doses 50mg and 100mg, but the 100mg dose was associated with higher rates of serious adverse events.

A Cochrane systemic review found that when used with MTX, golimumab was associated with greater efficacy than placebo for achieving ACR20/50/70 responses and lower DAS28 scores. The ACR50 rates were similar to those reported in systematic reviews of other TNF-blockers, suggesting that all the TNF inhibitors are equivalent [75].

Meta-Analyses

Unfortunately, there are few head-to-head studies comparing the efficacy of one anti-TNF agent to another. In the absence of superiority studies, indirect comparisons prove the best evidence for demonstrating differences between these agents [76].

The Cochrane review of biologic agents demonstrated no significant difference in the proportion of patients achieving ACR50 between the first generation TNF inhibitors (adalimumab, infliximab, etanercept) [77]. Other meta-analyses have demonstrated similar results [76],[78]. One systemic review suggested infliximab may require an increased dose to reach comparable

effectiveness to the standard doses of etanercept and adalimumab [76]. A meta-analysis from 2010 demonstrated that the highest proportion of ACR20 and 50 responses was achieved with etanercept, and the highest risk ratio for achieving ACR70 was with adalimumab. Over a longer treatment course (1-3 years) adalimumab demonstrated the highest relative risk (RR) for achieving all these response parameters [53].

Meta-analyses comparing newer anti-TNF agents (certolizumab and golimumab) have not revealed improved efficacy over already existing first generation agents [79],[80]. An indirect treatment comparison found no significant difference in efficacy between different agents [81]. A mixed treatment comparison demonstrated improved outcomes with etanercept and certolizumab, which may relate to reduced immunogenicity compared with the antibody therapies. Due to the lack of anti-TNF head-to-head trials, mixed treatment comparisons combine evidence from placebo-controlled trials of different treatments and thereby derive an estimate of effect of one treatment against another. The rank order of efficacy for HAQ improvement as an outcome measure was etanercept, certolizumab, adalimumab, golimumab and then infliximab [82].

Table 5. Golimumab

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Emery et al. 2009. GO-BEFORE.	52 week RCT in early RA, MTX-naïve patients. Group 1: MTX + placebo every 4 weeks (N = 160) Group 2: Golimumab 100mg + placebo every 4 weeks (N = 155) Group 3: Golimumab 50mg + MTX every 4 weeks (N = 158) Group 4: Golimumab 100mg + MTX every 4 weeks (N = 159)	52 week, mean change in SHS from baseline Group 1: 1.4 ± 4.6 Group 2: 1.3 ± 6.2 (P=0.266) Group 3: 0.7 ± 5.2 (P=0.015) Group 4: 0.1 ± 1.8 (P=0.025)
Kay et al. 2008	48 week RCT dose-ranging study in inadequate responders MTX. Group 1: Placebo + MTX Group 2: Golimumab 50 mg every 2 weeks + MTX Group 3: Golimumab 100 mg 4 weeks + MTX	Week 16, ACR20 61% golimumab groups compared with 37% in placebo (P=0.010).

Table 5. (Continued)

Author/Date published	Duration, Type of study, treatment, number of patients (N)	Main results
Keystone et al. 2009. GO-FORWARD	RCT in active RA despite MTX. Group 1: Placebo + MTX Group 2: Placebo + Golimumab 100mg Group 3: Golimumab 50mg + MTX Group 4: Golimumab 100mg + MTX N = 444	Week 14, ACR20 Group 1: 33.1% Group 2: 44.4% (P=0.059) Group 3: 55.1% (P=0.001) Group 4: 56.2% (P<0.001)
Keystone et al. 2010.	52 weeks RCT. Extension of GO-FORWARD study. Group 1: Placebo + MTX (From week 24 Golimumab 50mg + MTX i.e., group 3) Group 2: Golimumab 100mg + Placebo Group 3: Golimumab 50mg + MTX Group 4: Golimumab 100mg + MTX N = 444	Week 52, ACR20 Group 1: 44% Group 2: 45% Group 3: 64% Group 4: 58%
Smolen et al. 2009. GO-AFTER.	Multicentre RCT Group 1: Placebo Group 2. Golimumab 50mg every 4 weeks + csDMARDs. Group 3: Golimumab 100mg every 4 weeks + csDMARDs At week 16 patients with <ACR20 were given rescue therapy and changed from placebo to golimumab 50mg or from golimumab 50mg to 100mg. N = 461	Week 14, ACR20 Group 1: 18% Group 2: 35% (P=0.0006) Group 3: 38% (P=0.0001)

Legend: ACR 20 - American College of Rheumatology 20% response criteria; csDMARDs - conventional disease modifying anti-rheumatic drugs; e.o.w. - every other week; HAQ - health assessment questionnaire; HAQ-DI - health assessment questionnaire damage index; MTX - methotrexate; N - number of patients; RA - rheumatoid arthritis; RCT - randomised controlled trial; TSS - total Sharp score; SC - subcutaneously; SHS - Sharp/van der Heijde score.

Cost-effectiveness

Economic evaluations have generally shown anti-TNF to be cost effective across multiple healthcare settings for patients in whom csDMARD therapy has failed, in comparison to continuing management with csDMARD therapies [83]–[85]. There were 5.87-6.16 quality-adjusted life years (QALYs) gained with anti-TNF compared with 4.76 QALYs gained with cDMARDs. The incremental cost-effectiveness ratio (ICER) was estimated to be £23,577-£30,112 per QALY gained for anti-TNF compared with cDMARDs [86]. The use of two sequential anti-TNF therapies only increases the cost per QALY by 2% [83]. Anti-TNF therapy is not thought to be cost effective in a csDMARD naïve population [87].

Safety

Because of the immunological alterations it provokes, anti-TNF therapy is associated with an increased risk of infection and/or reactivation of viral, bacterial or fungal organisms. Safety data from clinical trials and post marketing registries has provided mixed results [88]. Serious infection events are rare and as such, their absolute risk of occurrence remains small. Several registries have shown the risk of infection in patients treated with anti-TNF compared to those with csDMARDs is highest during the first 6 months of treatment [89]. Analysis of data from the US CORRONA registry revealed an increase in all non-opportunistic infections with an adjusted rate per 100 person-years of 30.9 for MTX monotherapy and 40.1 for anti-TNF monotherapy [90].

TNF is essential for the control of tuberculosis (TB) and is implicated in the disease immunopathogenesis [91]. The alveolar macrophages and dendritic cells ingest TB bacilli. These cells fuse to form giant cells and isolate TB bacilli within a granuloma. TNF enables the formation and maintenance of a granuloma via activation of focal adhesion kinases. TNF signalling via TNF receptor-1 is particularly required for this function. TNF works in synergy with IFN-γ stimulating the production of reactive nitrogen intermediates thereby mediating the tuberculostatic function of macrophages [92].

Several studies have showed that TNF inhibitors increase the risk of both TB and other granulomatous infections. The first clinical observation came from a FDA report which found an increase in TB shortly after initiation of infliximab therapy suggesting reactivation of latent disease [93]. An increased risk of TB was seen in the Spanish BIOBADASER database of patients receiving infliximab before TB screening was introduced routinely. A review of the French database concluded the risk of TB was 12 fold for patients taking TNF

inhibitors [94]. The BSR Biologics Register (BSRBR) identified that infliximab and adalimumab were associated with a three to four fold higher rate of TB compared to etanercept [89]. The observed difference rates with etanercept may be due to its mechanism of action (via TNF receptor Fc fusion protein) or pharmacokinetics, although no consensus has been reached [88].

Prior to commencing anti-TNF, all patients should be screened for mycobacterial infections, and consideration of prophylactic anti TB therapy should be given to patients with evidence of latent disease. Screening standards vary from country to country, depending on endemic rates of TB, and may include TB skin testing, serum interferon y release assays (IGRA) and/or chest radiograph. The role of IGRA screening has not been fully validated in RA populations and is not widely available; however the test is sensitive when used in immunosuppressed hosts or patients who have received BCG immunisation [95].

Screening for latent TB prior to initiation of biologic therapy decreased the risk of reactivation of this organism in susceptible patients; however, no screening test can assess the risk of infection with atypical mycobacteria. Non tuberculosis mycobacterial infections have been found to be twice as frequent as TB in US patients treated with anti-TNF agents [96].

Data from two national registries reveal a significantly higher risk of varicella zoster virus (VZV) reactivation in patients treated with TNF inhibitors than those receiving csDMARD. Spanish registry (BIODABASER) data estimates an incidence rate (IR) of hospitalisation due to chickenpox of 26 cases per 100,000 patient-years with an expected IR in the general population of 1.9. German registry (RABBIT) data shows a significantly increased risk occurring with the use of mAbs but not with etanercept [97], [98].

TNF inhibitors have also been associated with reactivation of hepatitis B. Hepatic failure is more likely to occur in patients with active infection rather than chronic carriers [99]. There are several case reports and an open label case series describing the use of anti-TNF therapy in human immunodeficiency virus (HIV) positive patients. The consensus is that biologic treatment is reasonably safe if HIV treatment is started and effective in keeping the HIV infection under control. There were no significant clinical adverse effects (disease progression related to CD4 counts and HIV viral loads, and no opportunistic infections) [100].

A meta-analysis of clinical registries and prospective observational studies between 1999 and 2010 identified no increase in malignancies, other than skin cancers, including lymphoma, associated with the use of TNF inhibitors [101]. A large study, reviewing databases of health care utilization, found no

significant increase in malignancy rates with TNF inhibitors compared to MTX alone, whilst post approval data suggesting that the rate of Hodgkin's and Non Hodgkin lymphoma were not significantly raised [102]. Data from an American national data bank of incident cancers found an increased rate of skin cancers (OR 2.3 for melanoma and OR 1.5 for non-melanoma skin cancer) in patients receiving anti-TNF therapy [103]. Another study comparing RA to osteoarthritis, found a significantly increased risk of developing non melanoma skin cancer, with history of anti-TNF and prednisolone use also being implicated [104].

Psoriasis has been reported in patients treated with anti-TNF therapy. Interestingly the rash might resolve with topical treatment alone, temporary discontinuation and re-challenge with anti-TNF, a switch to an alternative anti-TNF agent or introduction of MTX [105], [106].

Current recommendations are to avoid use of anti-TNF agents in patients with clinically significant heart failure (New York Heart Association, NYHA, class III/IV). Concerns about possible adverse effects stem from a RCT of TNF inhibitors when trialled as a potential therapy for patients with stable heart failure (NYHA class III/IV). The combined risk of death from any cause or hospitalization for heart failure through 28 weeks was increased in patients randomised to 10 mg/kg infliximab vs. placebo (hazard ratio 2.84, 95% CI 1.01-7.97; nominal P=0.043 [107], [108]. Registry data has generally been reassuring [109], [110].

Patients with interstitial lung disease (ILD) should be monitored and the anti-TNF agent stopped if lung function deteriorates or new features of ILD develop. Data suggests that anti-TNF therapy may worsen ILD specific mortality but further studies are required before firm conclusions can be drawn [111].

An increased risk of demyelinating conditions was reported in BSRBR and the general recommendation is that patients with a history of demyelinating diseases should not receive TNF blocking agents. There are case reports in the literature of demyelinating disease complicating the use of all three 1st generation anti-TNF agents. In terms of central nervous system involvement, the highest rate of demyelinating events is reported with etanercept. In peripheral nerve disease, symptoms develop over a wide range of time intervals (from 8 hours to 2 years), and withdrawal of biologic medication most often resulted in slow resolution of symptoms [95], [112].

Injection site reactions are frequently reported with all the TNF inhibitors, but in different proportions. Localised skin reactions are usually managed with topical treatment. Severe infusion reactions have been described in the case of

infliximab administration, but they are rare. The general recommendation is that appropriate resuscitation facilities should be available for patients treated with infliximab [95].

A prolonged activated partial thromboplastic time was reported in 5% of patients in the RAPID II trial with certolizumab. This is due to an interference of polyethylene glycol with phospholipids used in the commercial assay and it is considered that it does not translate into any effect on coagulation *in vivo* [65].

CONCLUSION

The age of biologic treatment, in the past 20 years, has transformed the treatment of RA with subsequent reduced morbidity and socio-economic burden [113]. Well established biologics, such as anti-TNF blockers, have extensive data on safety and efficacy. The long-term experience of the use of these biologic agents in real-life clinical settings has increased the confidence of patients and clinicians in their benefits. The lack of direct comparison between the effectiveness of different TNF inhibitors or their safety profile makes the decision of choosing a certain anti-TNF agent instead of another quite difficult to justify. Differences in their mechanism of action and safety profile in the context of increased risk of TB, along with patients' choice based on frequency and route of administration are the main reasons for the selection of a certain TNF inhibitor in clinical practice. Observational data provided by national biologic registries will continue to inform practitioners and patients about the long-term efficacy of TNF therapy.

As highlighted in this chapter, the introduction of first biologic therapeutic agents changed the landscape of RA treatment leading to a real progress in achieving better disease control in RA patients who had exhausted conventional treatment options. This led to significant improvement in the quality of life of RA patients.

ACKNOWLEDGMENTS

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