BIOLOGIC TREATMENTS (OTHER THAN ANTI-TNF THERAPY) LICENSED FOR USE IN RHEUMATOID ARTHRITIS

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ABSTRACT

Despite the huge progress made by the use of tumour necrosis factor (TNF) inhibitors in the treatment of rheumatoid arthritis (RA), there was still an unmet need for discovering and implementing new biologic therapies for RA patients who lost response or had side-effects to TNF inhibitors. The advances in molecular biology and understanding of the complex pathogenesis of RA enabled the identification of other pivotal molecules, whose blockage was associated with clinical benefits in RA. This chapter reviews the clinical efficacy, safety profile and cost-effectiveness of

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several biologic agents licensed for use in RA patients, which target different interleukins (IL), such as IL1 (anakinra) and IL6 (tocilizumab), or are associated with B cell depletion (rituximab), T cell co-stimulatory blockage (abatacept) and small molecule inhibition (tofacitinib). In addition, we discuss the national and international guidelines for use of these biologic agents in relation to the use of TNF inhibitors in patients with moderate-severe RA, providing examples of switching between various biologic therapies.

Keywords: rheumatoid arthritis, licensed biologic therapies, anakinra, tocilizumab, rituximab, abatacept, tofacitinib, efficacy, safety, cost-effectiveness

INTRODUCTION

After the introduction of TNF inhibitors, new biologic agents have been developed and used in large randomised controlled trials (RCTs), which led to their licensing for treatment in RA patients. These new biologic treatments can be used in patients with or without previous exposure to anti-TNF therapy, based on the available evidence regarding their efficacy. There are differences between the licensing of these biologic therapies in European countries and the USA, mainly due to the evidence of their cost-effectiveness for RA treatment. In addition to data about their safety and efficacy, here we also discuss the costs of different biologic agents in the UK, as per the British National Formulary, version 70 (BNF70).

IL6 INHIBITION

Tocilizumab (RoActemra™, Roche)

Mechanism of Action

IL6 is a pleiotropic cytokine with important biologic effects on liver cells, lymphocytes, monocytes and platelets. IL6 can activate these cells via both membrane-bound (IL6R) and soluble receptors (sIL6R).

IL6 stimulates B cells to differentiate into plasma cells and produce immunoglobulins. It also influences T cell development by stimulating the proliferation and differentiation of T lymphocytes into Th17 cells which

produce IL17 [1-3]. IL6 has a direct role in the development of synovitis and articular symptoms. It is one of most abundantly expressed cytokines [4]. IL6 increases the levels of the angiogenic mediator, vascular endothelial growth factor (VEGF), which promotes migration of endothelial cells and induces vascular permeability [5-6]. IL6 also influences osteoclastogenesis, increasing osteoclast recruitment, a key cell involved in mediating erosions [7]. It also increases proteinases (e.g., matrix metalloproteinases) which correlate with articular cartilage destruction.

IL6 is also involved in the development of systemic symptoms. It is a principal stimulator of acute-phase protein synthesis through hepatocyte stimulation, and serum IL6 levels correlate with C-reactive protein (CRP) levels. IL6 also induces the expression of hepcidin by hepatocytes. This peptide regulates iron metabolism and can decrease serum iron levels, contributing to the anaemia of chronic inflammation. IL6 can affect lipid metabolism by stimulating hepatic fatty-acid synthesis and adipose-tissue lipolysis, increasing cholesterol synthesis and decreasing cholesterol secretion. Combined with endothelial dysfunction, this contributes to atherosclerosis and increased risk of cardiovascular disease [4], [8].

Early studies in knockout mice demonstrated IL6 as essential in the development of RA [9]. Wild-type animals developed joint inflammation after intra-articular injection of antigen, whilst IL6 knockout mice were resistant with no inflammatory response or synovial inflammation induced.

Structure, Dosing and Pricing

Tocilizumab is a humanised monoclonal antibody (mAb) that binds the IL6 receptor, thereby inhibiting its affinity for IL6. It is given as a dose of 8 mg/kg, once every 4 weeks as an intravenous (IV) infusion over 1 hour. Doses exceeding 800 mg per infusion are not recommended. A 400mg vial costs £512 in the UK (excluding VAT, BNF70) [10]. The drug cost per year for a patient weighing approximately 70kg is £9295 (BNF70) via a pre-agreed patient access scheme in the UK. Subcutaneous (SC) tocilizumab is given at a dose of 162 mg per week. The annual cost is also £9295 (BNF70). This does not include administration related costs.

Efficacy [Table 1]

There are three randomised double-blind, placebo-controlled trials assessing the clinical effectiveness of tocilizumab in patients who responded inadequately to methotrexate (MTX) (OPTION and LITHE) [11],[12], or conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs)

(TOWARD) [13]. All three studies demonstrate significantly greater American College of Rheumatology (ACR) 20 responses at week 24. The LITHE study also demonstrated protection from structural damage at 52 weeks. The TOWARD study reviewed the efficacy of tocilizumab added to MTX or other csDMARDs, which may be a more clinically representative population. A meta-analysis of these RCTs confirms that tocilizumab is numerically and statistically more effective at a dose of 8mg/kg than at a dose of 4mg/kg [14].

Table 1. IL6 Inhibition

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Smolen et al. 2008	RCT Group 1: Tocilizumab 8mg/kg every 4 weeks + MTX Group 2: Tocilizumab 4mg/kg every 4 weeks + MTX Group 3: Placebo every 4 weeks + MTX N = 623	Week 24, ACR20 Group 1: 59% Group 2: 48% Group 3: 26%
Fleischmann et al. 2013 LITHE	RCT Group 1: Placebo+ MTX Group 2: Tocilizumab 4mg/kg + MTX Group 3: Tocilizumab 8mg/kg + MTX	Week 104, mean change from baseline in GmTSS, adjusted mean AUC of change from baseline in HAQ-DI Group 1: 1.96, -139.4 Group 2: 0.58 (P=0.0025), -287.5 (P<0.0001) Group 3: 0.37, -320.8 (P<0.0001 for both)
Genovese et al. 2008 TOWARD	RCT, multicenter study Group 1: Tocilizumab 8mg/kg + csDMARDs Group 2: Placebo + csDMARDs N = 1220	Week 24, ACR20: Group 1: 61% Group 2: 25% (P<0.0001)

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Gabay et al. 2013 ADACTA	Phase IV double-blind parallel-group, multicentre superiority study in RA > 6months, in those intolerant to MTX Group 1: Tocilizumab 8mg/kg every 4 weeks Group 2: Adalimumab 40mg every 2 weeks. N = 452	Week 24, mean change from baseline in DAS28 Group 1: -3.3 (P<0.0001) Group 2: -1.8

Legend: ACR 20 – American College of Rheumatology 20% response criteria; AUC – area under curve; csDMARDs – conventional synthetic disease modifying antirheumatic drugs; GmTSS – Genant-modified total Sharp score; HAQ-DI – health assessment questionnaire – damage index; MTX – methotrexate; N – number of patients; RA – rheumatoid arthritis; RCT – randomised control trial.

The RADIATE trial assessed efficacy of tocilizumab in RA patients who failed treatment with a TNF inhibitor. This study demonstrated significantly greater ACR20, 50 and 70 responses compared with placebo, with significantly more patients entering remission (disease activity score 28 (DAS28) <2.6) in the higher dose group [15].

The AMBITION study reviewed tocilizumab monotherapy in patients who were MTX and biologics naïve. Tocilizumab monotherapy demonstrated superior efficacy compared to MTX monotherapy [16]. Several Japanese studies in patients with an inadequate response to MTX have demonstrated similar results, with superiority of tocilizumab monotherapy in ACR response criteria at all-time points [17-18]. A Cochrane systematic review [19] concluded that patients on tocilizumab monotherapy are 21 times more likely to achieve an ACR50 compared with placebo, and 2.76 times more likely compared with MTX. The CHARISMA study suggested that tocilizumab monotherapy was inferior to combination therapy with MTX, although it was not powered to look at this aspect [20]. The ACT-RAY study suggested similar findings, with a numerical superiority in DAS28 remission rates in combination therapy compared to tocilizumab monotherapy for most outcomes although no statistically significant difference was found [21].

The ADACTA study was one of the first head-to-head superiority RCTs comparing tocilizumab monotherapy and adalimumab monotherapy in a study population of MTX inadequate responders. It demonstrated tocilizumab

superiority in all main efficacy endpoints; European League against Rheumatism (EULAR) remission, low disease activity, ACR20/50/70 and clinical disease activity index (CDAI) remission [22]. It is recognised that tocilizumab treatment is associated with a profound decrease of the inflammatory markers (CRP and erythrocyte sedimentation rate - ESR). Many disease activity tools require use of inflammatory marker levels; therefore, tocilizumab could falsely lower the disease activity scores on this basis alone. However, tocilizumab was proven effective for treatment of RA patients, even when disease activity was appreciated using the CDAI, which is calculated without using inflammatory markers [23].

There are no other head-to-head studies reviewing the clinical effectiveness of tocilizumab compared to other biologic agents. Systematic reviews have however attempted to compare these agents. A meta-analysis from 2010 in MTX inadequate responders found anti-TNF to have a similar probability of achieving an ACR50 response in comparison to 'non-anti-TNF' biological agents (after exclusion of certolizumab trials) [odds ratio (OR) 1.30, 95% confidence interval (CI) 0.91 to 1.86]. However, when comparing agents individually, the meta-analysis concluded that anti-TNF drugs demonstrated a higher probability of reaching an ACR50 response than abatacept (OR 1.52; 95% CI 1.0 to 2.28), but not in comparison to rituximab and tocilizumab. After an inadequate response to anti-TNF, no differences were found between tocilizumab, abatacept, rituximab or golimumab [24]. A separate meta-analysis of mixed treatment comparisons suggested that tocilizumab was associated with significantly greater rates of ACR70 when compared to TNF inhibitors and abatacept; however, there was no significant difference in ACR20 or 50 responses [25].

SC tocilizumab demonstrated comparable efficacy and safety to IV tocilizumab in head-to-head studies. Serum trough concentrations were similar between the two forms of administration [26]. In general, the data for SC tocilizumab is similar to IV tocilizumab, albeit with a higher frequency of injection site reactions. Given that most patients prefer SC administration, this is likely to become a mainstay treatment option [27].

Safety

IL6 is essential for CRP production in the liver [28]; therefore, CRP levels are reduced and signs of clinical infection potentially diminished in patients treated with tocilizumab. A Cochrane review of safety in RA patients on tocilizumab however did not show any statistically significant differences in serious adverse effects, or withdrawals due to adverse events [19]. French

registry data have shown serious infection rates with tocilizumab to be in the higher range compared to other biologics after 1.3 years of follow up [29]; however, 5 year UK safety data showed tocilizumab treatment to have a similar risk to that of anti-TNF drugs [30]. A German study of RA patients in an outpatient setting showed a higher level of infection (23.2%, 58/100 patient-years) [31] compared to other RCTs [11], [13] or Cochrane safety data [19]. The patients in this study had a longer duration of disease, and higher number of previous csDMARD use compared to other RCTs, possibly accounting for this increased risk [32]. The main adverse events (AEs) reported are nasopharyngitis, respiratory tract disorders and, skin and soft tissue pathologies [33].

Tocilizumab may be associated with a transient alteration in lipid profile. However, this is not linked to an increase in cardiovascular events or episodes of pancreatitis [13], [33]. Trials have reported significantly reduced neutrophil counts compared with controls, but importantly, there were no reported associations between neutrophil levels and infection rates or infection severity. Neutropenia detected was usually transient but may require dose adjustments [11], [13], [15].

Cases of gastro-intestinal (GI) perforation have been reported with tocilizumab. In a pooled meta-analysis of 5 RCTs and 2 long-term extension studies, GI perforation occurred at a rate of 2.0 per 1000 patient-years in the control population, and 2.8 per 1000 patient-years in the tocilizumab population [34]. Sixteen of the 18 cases of lower GI perforation occurred in patients with diverticulitis, with the majority having concomitant treatment with corticosteroids and non-steroidal anti-inflammatories (NSAIDs) [35]. A different systematic review found the risk of diverticular perforation with tocilizumab slightly higher than with anti-TNF drugs and lower than with corticosteroids and NSAIDs [36].

Following immune system suppression, concern exists regarding possible reactivation of latent infections, most notably tuberculosis (TB). A large meta-analysis of 6 trials [33] did not encounter patients with TB reactivation, and they included patients who were not screened for TB. However, cases of TB have been reported [18], and it is therefore advisable to continue to screen patients for TB prior to initiating treatment with tocilizumab. In the same meta-analysis, no studies found a significant increase in the rate of malignancy in those treated with tocilizumab.

Cost-effectiveness

Tocilizumab may improve cost-effectiveness in patients with moderate to severe RA, when used first or second line, by enhancing quality-adjusted life years (QALYs) expectancy [37]. A Swedish study has shown tocilizumab combined with MTX to be more cost-effective as a first line biologic than adalimumab and etanercept combination therapy [38]. There were 5.87 QALYs gained with IV tocilizumab compared with 4.76 QALYs gained with csDMARDs. The incremental cost-effectiveness ratio (ICER) was estimated to be £35,949 per QALY gained for tocilizumab compared with csDMARDs [39].

National/International Guidelines on Use

The 2012 National Institute of Clinical Excellence (NICE) guidance stated that tocilizumab can be used as a first line biologic agent in csDMARD failure. It is also recommended for use in patients whom have an inadequate response to anti-TNF agent at 6 months (improvement in DAS28 <1.2) and have a contraindication or inadequate response to rituximab, or are intolerant to MTX [40]. The 2013 European guidelines recommend treatment with tocilizumab as an initial biological DMARD. This differs from the 2010 previous recommendations, which stated current practice would be to start a TNF blocker. This change is related to increasing clinical experience and registry data on tocilizumab [41]. The ACR guidelines on the use of tocilizumab recommend its use for treatment of patients who failed csDMARD monotherapy. They also recommend alternative treatment strategies with combination csDMARD therapy or another biologic agent [42].

CO-STIMULATORY SIGNAL INHIBITION

Abatacept (Orencia™, Bristol-Myers Squibb)

Mechanism of Action

Abatacept inhibits the co-stimulation of T cells by binding to cluster of differentiation (CD) 80/86 epitopes on antigen presenting cells and modulating its interaction with CD28 on the T cell receptor. This leads to reduced T cell proliferation and reduced production of inflammatory cytokines [43], [44].

Abatacept, if administered at time of immunisation, prevents the development of collagen induced arthritis in mouse models and improves symptoms if given after disease onset [45].

Structure, Dosing and Pricing

Abatacept is a fully humanized protein construct, consisting of the extracellular domain of human cytotoxic T lymphocyte associated antigen 4 (CTL4) and a genetically engineered fragment of the Fc region of human immunoglobulin G1 (IgG1).

IV abatacept is administered as a 30-minute infusion. After an initial baseline infusion, subsequent infusions are at week 2, week 4, and then every 4 weeks.

IV abatacept is available in 250 mg vials at a cost of £302.40 per vial in the UK (excluding VAT; BNF70) [10]. The dose of abatacept is weight dependent. People weighing less than 60kg, 60-100kg, and over 100kg are administered 500mg, 750mg and 1000mg respectively. The annual cost for a person weighing 60-100kg is £12,700.80 in the first year and then £11,793.60 in subsequent years. This does not include administration related costs. SC abatacept is administered as a 125 mg pre-filled syringe per week with an annual cost of £15,724.8. Procurement agreements within the UK have meant that healthcare services pay the same price for SC abatacept as they do for the IV formulation.

Efficacy [Table 2]

IV abatacept has been shown to be effective in MTX naïve patients and patients who have not responded to DMARDs, including MTX, and anti-TNF.

IV abatacept is more efficacious than placebo in patients with early RA who are MTX naïve [46-47], with a significantly different ACR50 response of 64.7% vs. placebo response of 50.2% at 1 year (P<0.001). DAS28 remission was similarly impressive with a 46.1% occurrence in the abatacept group vs. 26.1% in the placebo group. Results were maintained up to a further year at follow up [47].

IV abatacept has also been shown to delay the progression of inflammatory joint symptoms in patients who have undifferentiated inflammatory arthritis/very early rheumatoid arthritis not fulfilling the ACR criteria for RA [48].

A phase II trial investigating abatacept in patients with an inadequate response to MTX showed superiority of 10mg/kg dosing over lower doses. ACR20/50/70 responses were consistently greater for the higher dose [49]. Various 6 month [50] and 12 month [49], [51] study results showed similar statistically significant ACR responses, and confirmed 10mg/kg to be the most effective, yet safe, dose.

Table 2. Abatacept

Author	Duration, type of study, treatment, number of patients (N)	Main results
Kremer et al. 2005	12-month results for a phase IIb RCT of CTLA4-Ig in those with an inadequate response to MTX. Group 1: Placebo (N = 119) Group 2: CTLA-4Ig 2mg/kg (N = 105) Group 3: CTLA-4Ig 10mg/kg (N = 115)	12 month ACR20 Group 1: 36.1% Group 2: Numerical results unavailable Group 3: 62.6%
Kremer et al. 2006 AIM	12 month RCT of abatacept vs. placebo Group 1: Abatacept + MTX (N = 433) Group 2: Placebo + MTX (N = 219)	12 month ACR20 Group 1: 73.1% Group 2: 39.7%
Schiff et al. 2008 ATTEST	12 month randomised, double-blind, double-dummy, placebo- and active-controlled trial Group 1: Abatacept +MTX (N = 156) Group 2: Infliximab + MTX (N = 165) Group 3: Placebo + MTX (N = 110)	12 month ACR20 Group 1: 72.4% Group 2: 55.8% Group 3: Numerical results unavailable
Westhovens et al. 2009	5 year extended phase IIb study of abatacept 10mg/kg following 1 year of variable dose abatacept or placebo (N = 419)	5 year results ACR20 82.7%
Genovese et al. 2005 ATTAIN	6 month randomised double-blind, Phase III trial Group 1: Abatacept + DMARDs Group 2: Placebo + DMARDs	6 month ACR20 Group 1: ACR20 50.4% Group 2: ACR20 19.5%

Author	Duration, type of study, treatment, number of patients (N)	Main results
Emery et al. 2010 ADJUST	Randomised, double-blind, placebo controlled phase II trial Group 1: Abatacept Group 2: Placebo	1 year results Group 1: 46% developed RA, mean change from baseline to year1 in total GmTSS = 0 Group 2: 67% developed RA, mean change from baseline to year1 in total GmTSS = 1.1
Westhovens et al. 2009 AGREE	12 month double-blind study followed by 12 month open label treatment with abatacept and MTX Group 1: Abatacept and MTX Group 2: Placebo and MTX	At 1 year: Group 1: ACR50 64.7% Group 2: ACR50 50.2% At 2 years Group 1: ACR50 74.1% Group 2: ACR50 67%

Legend: ACR20 – American College of Rheumatology 20% response criteria; ACR50 – American College of Rheumatology 20% response criteria; CTLA4 – cytotoxic T lymphocyte associated antigen 4; DMARDs – disease modifying anti-rheumatic drugs; GmTSS – Genant-modified total Sharp score; MTX – methotrexate; N – number of patients; RCT – randomised controlled trial.

Abatacept has also been shown to be superior to infliximab [52]. Long term data shows abatacept efficacy to be maintained at 5 [53] and 7 years [54] of follow up. IV abatacept is similarly effective in patients who have an inadequate response to anti-TNF [55],[56], with an ACR20 response rates of 50.4% vs. 19.5% at 6 months, and achievement of DAS28 remission of 10% vs. 0.8% (P<0.001) [55].

Few studies have investigated abatacept monotherapy. An IV dose ranging study showed abatacept monotherapy to be effective compared with placebo, albeit with lower ACR responses compared to other studies of abatacept combination therapy [49]. Abatacept has been shown to maintain efficacy after dose reduction [47]. Its effect also persists after drug withdrawal [48], [57-58].

A weekly SC preparation of abatacept (125mg) is now available, and has been shown to have a similar efficacy and side effect profile to the IV regime. This option has cost saving implications and provides greater flexibility to patients in that they can administer their own treatment. A phase III study showed SC abatacept to be non-inferior to IV abatacept [59]. A head to head

study comparing SC abatacept to SC adalimumab, both in combination with MTX, did not show inferiority [60]. SC abatacept monotherapy has been shown to be as effective as MTX monotherapy and less effective than abatacept and MTX combination therapy [57].

A Cochrane systematic review of over 2900 patients treated with abatacept showed that, in comparison to placebo, patients on abatacept were 2.2 times more likely to achieve an ACR50 response at one year [risk ratio (RR) 2.21, 95% CI 1.73 to 2.82] with a 21% (95% CI 16% to 27%) absolute risk difference between groups. The number needed to treat to achieve an ACR50 response was 5 (95% CI 4 to 7) [61].

Other meta-analyses of abatacept in combination with MTX also show this treatment to be more effective than MTX monotherapy, and of comparable efficacy to other biologic DMARDs (bDMARDs) at 24 weeks, when ACR20/50/70, DAS28 < 2.6 (remission) and Health Assessment Questionnaire (HAQ) change from baseline response rates are assessed [25], [62]. An exception was tocilizumab appearing more effective at reducing DAS28 scores. This however, is likely due to the fact that tocilizumab has a specific effect on reducing CRP levels used in calculating DAS28 scores [62]. Both IV and SC abatacept seem to have slightly better safety outcomes in comparison to TNF blockers and tocilizumab, however, these differences were not statistically significant [25]. Serious adverse events were increased when abatacept was given in combination with other biologics (RR 2.30, 95% CI 1.15 to 4.62) [61].

Abatacept has been shown to significantly improve health-related quality of life. Clinically meaningful and significant improvements of Short Form 36 questionnaire (SF-36) scores have been shown [52], [55], [63]. HAQ scores also statistically improve at 6 and 12 months assessments in abatacept vs. placebo groups [49], [51], [55]. These improvements have been sustained in 5 year follow up data [53]. Patient reported outcomes for SC abatacept have been similar [57], [59-60].

Abatacept significantly slows radiographic progression with 50% reduction in Genant modified total Sharp scores (GmTSS) (radiographic score assessing for the disease associated damage) compared to baseline [49]. This has been corroborated by other studies at short and long term follow up [48], [64].

Cost-effectiveness

Provided that TNF blockers are used as first biologic agents, abatacept has a similar cost-effectiveness to rituximab or a second anti-TNF, when used as a second line biologic agent [65]. There were 6.09 QALYs gained with abatacept compared with 4.76 QALYs gained with csDMARDs. The incremental ICER

was estimated to be £ £23,357 per QALY gained for abatacept compared with csDMARDs [39].

Safety

Abatacept is well established as a relatively safe biologic for RA treatment. RCTs confirm that the incidence of AEs for placebo and IV abatacept treatment groups is similar. The same is true for serious adverse events (SAEs). Acute infusion reactions occur at less than 10%. The most common adverse events have been headache, nasopharyngitis, nausea and cough [49], [51], [55-56], [63], [66]. AEs and SAEs occur at similar frequencies between IV and SC abatacept [59]. Injection site reactions were distinct to the SC groups but with no difference in occurrence rates between SC abatacept and SC placebo. Long term safety data [67] with 4 years of follow up data has shown SC abatacept to have a similar safety profile to IV abatacept.

National/International Guidelines on Use

According to NICE [40], EULAR [41] and ACR [42] guidelines, abatacept can be used as first line biologic, preferentially in combination with MTX or other csDMARDs. NICE however, specifically stipulate that abatacept should not be used as a monotherapy due to its greater efficacy when given as a combination therapy. Abatacept treatment is licensed as a monotherapy in the USA.

B CELL DEPLETION THERAPY - ANTI-CD20

Rituximab (Rituxan™, Genentech and Biogen – USA, Canada & Japan; Mabthera™, Roche - Europe)

Mechanism of Action

B cells have been shown to be involved in chronic rheumatoid synovitis and the production of rheumatoid factor, a well-recognized prognostic factor for aggressive RA [68].

Rituximab is a genetically engineered mouse-human chimeric anti-cluster of differentiation (CD) 20 monoclonal antibody. CD20 is a phosphoprotein that is highly expressed by naïve, mature, and memory B cells, but not by early B cell precursors and antibody-producing plasma cells.

CD20 is not present on stem cells and therefore B cells may be depleted by rituximab without preventing their regeneration, whilst potentially eliminating

the autoantibody-producing clones. CD20^{+} B cell depletion in RA is complete at 1 month after the start of a single treatment dose, and is sustained for several months [69]–[72]. Peripheral B cells repopulate to almost baseline levels 6-10 months after treatment [73-74].

The three mechanisms by which rituximab achieves B cell depletion [75 - 76] are:

a. Antibody dependent cell mediated cytotoxicity and phagocytosis, in which natural killer cells, macrophages, and monocytes are recruited through their Fcγ receptors bound to surface CD20. This induces CD20+ B cell lysis.

b. Complement dependent cytotoxicity induced by rituximab bound to surface CD20 and binding C1q. This results in activation of the complement cascade and generation of the membrane attack complex, causing CD20+ B cell lysis.

c. Promotion of CD20+ B cell apoptosis.

Structure, Dose and Pricing

Rituximab is a chimeric molecule consisting of human IgG1 kappa constant regions and small variable light and heavy chain regions from the anti-CD20 murine antibody fragment, which is reactive to human CD20.

A cycle of rituximab consists of two 1000 mg IV infusions given two weeks apart. The cost of a single cycle of rituximab is £3492.6 in the UK (excluding VAT, BNF 70) [10], with an annual cost of £6,985.2. This does not include the administration related costs. The need for further rituximab courses should be evaluated 24 weeks following the previous course. Retreatment should be given at that time if residual disease activity remains, otherwise retreatment should be delayed until disease activity returns. However, clinicians are looking into establishing the pattern of RA relapse specific to every patient, to be able to administer the rituximab course before they flare.

Efficacy [Table 3]

A case report in the late 1990s documented that remission of coexisting RA occurred in patients with non-Hodgkin lymphoma who were treated with rituximab [77]. A small open label study of rituximab, albeit with concomitant steroid and cyclophosphamide, in patients with RA was the first to show the efficacy of rituximab [70]. All five patients included in this study met the ACR50 criteria six months post rituximab, and three patients also met the ACR70 criteria. An extension to this initial open label study [78], and further small, independent, open label studies also provided evidence of rituximab

being an effective treatment for RA with ACR20-70 responses in the majority of patients [184, 194].

Table 3. Anti-CD20

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Emery et al. 2006 DANCER	24 week RCT of rituximab 2x500mg (N = 124) vs. rituximab 2x1000mg (N = 192) vs. placebo (N = 149)	Week 24: ACR20 55% vs. 54% vs. 28% (P<0.0001). ACR50 33% vs. 34% vs. 13% (P<0.001)
Cohen et al. 2006 REFLEX	24 week RCT of rituximab + MTX (N = 311) vs. placebo + MTX (N = 209)	At 24 weeks - ACR20: 51% vs. 18%, ACR50: 27% vs. 5%, ACR70: 12% vs. 1%.
Finckh et al. 2007	6 months prospective cohort study of rituximab (N = 50) vs. alternative TNFi (N = 66)	Mean decrease in DAS28 at 6 months: -1.61 vs. -0.98
Emery et al. 2010 SERENE	48 week RCT of rituximab 2x500mg (N = 167) vs. rituximab 2x1000mg (N = 170)	ACR20 55.7% vs. 57.6%, ACR50 32.9% vs. 34.1%, ACR70 12.6% vs. 13.5%
Hubbert-Roth et al. 2010 MIRROR	48 week RCT of different rituximab recurrent dosing regimens. Group 1:2x500mg + 2x500mg Group 2:2x500mg + 2x1000mg Group 3:2x1000mg + 2x1000mg	Group 1+2 at week 48: ACR20 64% Group 3 at week 48: ACR20 72%

Legend: ACR 20 – American College of Rheumatology 20% response criteria; ACR 50 – American College of Rheumatology 50% response criteria; ACR 70 – American College of Rheumatology 70% response criteria; DAS 28 – disease activity score 28 joints; MTX – methotrexate; RCT – randomised control trial; TNFi – tumour necrosis factor inhibitor.

A RCT (DANCER) to evaluate the efficacy of rituximab in RA patients, who were non-responders to MTX, showed rituximab to be more effective than placebo in controlling symptoms of arthritis, with 54% of patients achieving ACR20 responses at week 24 [80]. Similar efficacy of rituximab was reported in patients with a prior inadequate response to anti-TNF (REFLEX) [81]. Evidence from further independent RCTs supported the evidence of efficacy of rituximab in RA (72, 80, 81) and also that its efficacy was longstanding, lasting up to a year after initial treatment course [70] [82].

Rituximab in combination with MTX has been found to be more effective than rituximab monotherapy [83]. Other csDMARDs given in combination, including leflunomide, were also effective and safe [84].

A study (TAME) comparing rituximab (2 x 500 mg) with a TNF inhibitor (adalimumab), to MTX with rituximab, and MTX alone did not show increased infection rates in the TNF inhibitor group; however there was no difference in efficacy between the two groups, therefore this combination therapy is not currently recommended [85]. An open label study of rituximab (2 x 500 mg) with either etanercept, infliximab, adalimumab or abatacept did not show increased infection rates [86]. There was some evidence of increased efficacy with the combination of rituximab and another biologic agent; however, as this study did not have a control arm and patients' characteristics varied, no generalizable conclusion can be drawn.

Swiss [87] and Swedish [88] cohort data analysis has shown that switching seropositive RA patients to rituximab rather than to an alternative anti-TNF therapy, once initial anti-TNF therapy has failed, leads to better outcomes.

Rituximab retreatment is relatively safe and efficacious [89]–[92]. Rituximab is licensed for treatment every 6 months in the UK, and every 4 months in the USA. There is no consensus on whether treatment should be given at fixed six monthly intervals, or rather guided by when patients begin to have symptoms. An open label study has shown that there is no significant difference in the efficacy and safety of rituximab when comparing the fixed 6 month interval administration, with the administration guided by patients' flare [93]. Other studies however showed that better clinical outcomes, with no significant difference in safety, were reported with the 6 month fixed retreatment courses [82], [91], [94-95].

A Cochrane systematic review of RCTs, including over 2700 patients, on rituximab (two 1000 mg doses) in combination with MTX compared with MTX monotherapy has shown that the ACR50 response rates were statistically significantly improved in the rituximab and MTX combination therapy groups, compared with MTX alone from 24 to 104 weeks. The RR for achieving an

ACR50 at 24 weeks was 3.3 (95% CI 2.3 to 4.6). A proportion of 29% of patients receiving rituximab combination therapy achieved ACR50 compared to 9% of controls. The number needed to treat (NNT) was six (95% CI 4 to 9). At 24 weeks, the RR for achieving a clinically meaningful improvement in HAQ scores (> 0.22) for patients receiving rituximab combined with MTX compared to patients on MTX alone was 1.6 (95% CI 1.2 to 2.1) [96]. Other meta-analyses continue to provide evidence that rituximab is an effective treatment for patients with active RA [97], [98].

Studies on patient reported outcomes have consistently shown rituximab to improve degree of disability (HAQ-DI), levels of fatigue (FACIT-F) and patients' perception of physical and mental health (SF-36) [99]–[101].

Rituximab is effective at reducing radiographic progression [196, 217–219] and joint damage, as assessed by MRI [105]. Pooled results from meta-analyses show 57% of patients receiving rituximab in combination with MTX had no radiographic progression compared to 39% of patients taking MTX alone [96].

Though overall similar in cost-effectiveness, rituximab is more cost-effective than abatacept or a second anti-TNF agent in RA patients who have failed one anti-TNF drug [65], [106], [107]. This is partly due to the fact that rituximab has lower than average treatment costs compared to other biologics [108].

Safety

Rituximab is well established as a relatively safe biologic for RA treatment. RCTs confirm that the incidence of AEs is similar between placebo (70-88%) and rituximab (73-85%) active treatment groups [70], [80], [81], [87]. The same is true for SAEs, ranging from 3-10% for placebo to 5-15% for rituximab groups. The most common adverse events tend to be headache, respiratory tract infection, nasopharyngitis, nausea and arthralgia. Rituximab can cause infusion reactions therefore premedication with steroid and antihistamine is required. Infusion reactions typically occur during the first infusion and can include urticaria, hypotension, angioedema and bronchospasm. Symptoms can be minimised by reducing infusion rates or stopping the infusion until the symptoms resolve. Immunoglobulin levels need to be checked regularly, as these can fall following rituximab treatment and potentially increase the risk of infection.

According to a Cochrane systematic review of patients treated with rituximab in different RCTs, a greater proportion of patients receiving rituximab in combination with MTX developed AEs after their first infusion, compared to those receiving MTX monotherapy and placebo infusions (RR 1.6, 95% CI 1.3

to 1.9). No statistically significant differences were noted in the rates of SAEs [96].

Progressive multifocal leukoencephalopathy (PML) is a life-threatening demyelinating infection of the brain caused by the JC (John Cunningham) virus in immunosuppressed individuals [109]. Very rare cases of PML (documented as <1/10,000 patients in the rituximab summary of product characteristics (SPC), [110]) have been reported following the use of rituximab. Analysis of an American inpatient database from 1998 to 2005 estimated the rate of PML in patients with RA being 0.4 per 100, 000 discharges, compared with 0.2 for the general population [111].

National/International Guidelines on Use

British and European guidelines [40], [41], [112] on the use of rituximab in RA state that rituximab can be used in adult patients with seropositive RA who are eligible for biologic treatment and have had an inadequate response to one or more anti-TNF medications, or are unable to take anti-TNF due to a contraindication. Evidence thus far has shown rituximab to be more efficacious in seropositive patients; but despite this, British NICE guidelines recommend its use as a second line biologic treatment in all RA patients.

American (American College of Rheumatology, ACR) 2015 guidelines [42] now state that rituximab can be used as first line biologic, if appropriate, after csDMARD monotherapy failure. Rituximab can be used if patients have a history or solid organ malignancy or non-melanoma skin cancer within the past 5 years [110].

INTERLEUKIN 1

Anakinra (Kineret™, SOBI)

Mechanism of Action

IL1 is a pro-inflammatory cytokine produced abundantly by synovial cells. Early studies of tissue samples have observed a far greater proportion of cells produce IL1 rather than TNF [113]. Experimental studies suggested this cytokine played an important role in promoting tissue inflammation and remodelling. In addition, IL1 is the principal mediator of bone and cartilage destruction. It stimulates the release of matrix metalloproteinases inhibiting cartilage repair and activates osteoclast augmenting bone resorption [114],

[115]. Experimental models have demonstrated that IL1 blockage produces significant but often modest anti-inflammatory effects and potent inhibition of cartilage and bone damage [116].

Structure, Dosing and Pricing

Anakinra is a recombinant, non-glycosylated form of human IL1-receptor antagonist that inhibits the activity of IL1. It is administered by SC injection at a dose of 100 mg once daily. It costs £20.47 per day in the UK (excluding VAT, BNF70) [10], equivalent to £7450 per annum.

Efficacy [Table 4]

Several RCTs reviewed anakinra with MTX compared to MTX monotherapy and demonstrated significantly greater ACR responses. This was often rapid and associated with significantly less radiographic progression [117], [118].

Table 4. Anakinra

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Cohen et al. 2004	24-week double-blind, randomised, placebo-controlled trial. Group 1: Anakinra 100mg SC daily + MTX (N = 250) Group 2: Placebo + MTX (N = 251)	ACR20 at week 24: Group 1: 38%, P<0.001 Group 2: 22%

Legend: ACR 20 – American College of Rheumatology 20% response criteria; MTX – methotrexate; N – number of patients; SC – subcutaneously.

However, indirect comparisons based on meta-analyses of placebo-controlled trials found anakinra to be less effective than anti-TNF therapy. The comparison of the two agents revealed a non-significant RR of ACR50 response of 0.67 (95% CI 0.38 to 1.17), favouring anti-TNF but concluding that anakinra was inferior to first generation TNF inhibitors [119], [120].

A subsequent meta-analysis found anakinra to be less effective than TNF inhibitors, although this was only statistically significant for comparisons with adalimumab and etanercept [121].

A subsequent study, designed to determine if there were any additive or synergistic effects of combination therapy with anti-TNF (etanercept), did not find any benefit and reported increased safety concerns [122].

Other agents targeting IL1, including anti-IL1 antibodies, anti-IL1 receptor and IL1 "TRAP" (consisting of IL1 receptors and an Fc subunit), have all failed to show clear efficacy in RA [123], [124].

Safety

A Cochrane review showed that, at doses of 50–150 mg/day, the rates of injection site reactions were 71% for the anakinra-treated groups vs. 28% for placebo [125]. One of the disadvantages of this biologic agent is the frequency of administration (daily). A meta-analysis of RCTs indicated a significantly increased risk of serious infections with high doses of anakinra [126], however no difference was found in the Cochrane review. Neutropenia can occur with the potential for resolution on temporary discontinuation and re-challenge of anakinra [127].

Like TNF blockers, anakinra is an anti-cytokine biologic agent. However, unlike TNF agents, invasive opportunist infections are exceptionally rare, suggesting a difference in mechanisms of action between these biotherapies [126]. A 3 year open study reported a higher than expected incidence of melanoma and lymphoma compared with the general population. However due to the presence of additional risk factors and confounders in the RA group included in this study, this risk cannot be attributed to anakinra alone [114].

National/International Guidelines on Use

British NICE guidance [40] does not recommend anakinra for the treatment of RA 'as although there is clinical effectiveness in the short term, the extent of benefit was not sufficient to justify cost'. Anakinra is not specifically mentioned in the abbreviated EULAR recommendations, although the more detailed summary does suggest that some patients may respond to this biologic agent [41]. Anakinra is not recommended for RA treatment by the 2015 ACR guidelines [42].

SMALL MOLECULE INHIBITORS

Janus Kinase Inhibitors [Table 5]

Janus kinase inhibitors, also known as JAK inhibitors, function by inhibiting the activity of one or more of four Janus kinase enzymes (JAK1, JAK2, JAK3, TYK2 (TYrosine Kinase 2). Activation of Janus kinases leads to phosphorylation of cytokine receptors and formation of docking sites for the STAT (Signal Transducer and Activation of Transcription) family of transcription factors. After phosphorylation, the STATs translocate to the nucleus where they bind to deoxyribonucleic acid (DNA) and regulate gene expression [128]. Janus kinase inhibitors interfere with this JAK-STAT signalling inflammatory pathway.

Cytokines that signal through heteromeric receptors containing the gp130 subunit, including IL6 and IL11, primarily utilize JAK1 and JAK2. Type II cytokine receptors that bind IL10, IL19, IL20 and IL22 utilize JAK2 and TYK2 for signalling. Receptors for hormone-like cytokines, such as growth hormone, prolactin and growth factors erythropoietin (EPO), thrombopoietin (TPO), IL3 or GM-CSF use JAK2. Receptors for IFNγ receptor use JAK1 and JAK2, whereas cytokines IL2, IL4, IL7, IL9, IL15 and IL21 signal through gamma chain containing receptors JAK1 and JAK3. Several of these cytokines when dysregulated contribute to the pathogenesis of RA [129]–[131].

Tofacitinib (Xeljanz™, Pfizer)

Tofacitinib is an oral Janus kinase (JAK) inhibitor. Tofacitinib preferentially inhibits signalling through receptors associated with JAK1 and/or JAK3 [129], [130].

There have been six global phase III RCTs investigating tofacitinib in RA patients with a prior inadequate response to DMARDs and/or biologics. Tofacitinib has been shown to be statistically more effective than placebo (P<0.001), at both 5mg and 10mg twice daily dosing regimens, either as monotherapy [130], [132] or with combination csDMARDs [133]–[136]. A head to head study of adalimumab vs. tofacitinib showed similar efficacy [134]. Similar beneficial results were reported in the mean change from baseline in HAQ-DI scores [130], [132]–[136], mean change in TSS [132], [135], and

clinically meaningful change in FACIT-F fatigue scores [132], [133], [135]. The most effective dose was 10 mg administered twice daily. AEs were similar across all studies but with noted rises in low-density lipoprotein (LDL) cholesterol and ALT/aspartate transferase (AST), and falls in neutrophil counts. The most common AEs were upper respiratory tract infections, nasopharyngitis, headache and diarrhoea.

Table 5. Janus Kinase Inhibitors

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Fleischmann et al. 2012	6-month phase III, RCT parallel-group trial. Group 1: 5mg PO tofacitinib (N = 243) Group 2: 10mg PO tofacitinib (N = 245) Group 3: Placebo (N = 122)	Month 3 ACR20, and mean change from baseline in HAQ-DI results: Group 1: 59.8%, -0.50 Group 2: 65.7%, -0.57 Group 3: 26.7%, -0.19 P<0.001 all groups
Burmester et al. 2013	6-month phase III RCT, placebo-controlled, parallel-group trial. Group 1: 5mg BD PO tofacitinib (N = 133) Group 2: 10mg BD PO tofacitinib (N = 134) Group 3: Placebo (N = 132)	Month 3 ACR20, and mean change from baseline in HAQ-DI results: Group 1: 41.7%, -0.43 Group 2: 48.1%, -0.46 Group 3: 24.4%, -0.18 P<0.001
van Vollenhoven et al. 2013	12-month phase III RCT, placebo-controlled, parallel-group trial. Group 1: 5mg BD PO tofacitinib (N = 204) Group 2: 10mg BD PO tofacitinib (N = 201) Group 3: 40mg SC e.o.w. adalimumab (N = 204) Group 4: Placebo (N = 108)	Month 6 ACR20 (P<0.001), and mean change from baseline in HAQ-DI (P<0.05) results: Group 1: 51.5%, -0.55 Group 2: 52.6%, -0.61 Group 3: 47.2%, -0.49 Group 4: 28.3%, -0.24

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
van der Heijde et al. 2013	24 month phase III RCT Group 1: 5mg BD PO tofacitinib (N = 321) Group 2: 10mg BD PO tofacitinib (N = 316) Group 3: Placebo (N = 160)	Month 6 ACR20 ($P<0.0001$), and mean change from baseline in HAQ-DI, and total SHS results: Group 1: 51.5%, -0.40, 0.12 Group 2: 61.8%, -0.54 ($P<0.0001$), 0.06 ($P<0.05$) Group 3: 25.3%, -0.15, 0.47
Kremer et al. 2013	12 month RCT Group 1: 5mg BD PO tofacitinib (N = 318) Group 2: 10mg BD PO tofacitinib (N = 318) Group 3: Placebo (N = 159)	Month 6 ACR20, and mean change from baseline in HAQ-DI results: Group 1: 52.1%, -0.44 Group 2: 56.6%, -0.53 Group 3: 30.8%, -0.16 $P<0.001$
Lee et al. 2014	24 month RCT, parallel group trial. Group 1: 5mg BD PO tofacitinib (N = 373) Group 2: 10mg BD PO tofacitinib (N = 397) Group 3: Placebo (N = 186)	Month 6 ACR20, and mean change from baseline in HAQ-DI, and total SHS results: Group 1: 71.3%, -0.8, 0.2 Group 2: 76.3%, -0.9, <0.1 Group 3: 50.5%, -0.6, 0.8 $P<0.001$

Legend: ACR 20 – American College of Rheumatology 20% response criteria; BD – twice daily; e.o.w. – every other week; HAQ-DI – health assessment questionnaire – damage index; N – number of patients; PO – oral administration; RCT – randomised control trial; SC – subcutaneously; SHS - Sharp/van der Heijde score.

A meta-analysis of 8 phase II and III RCTs [137] showed that tofacitinib, 5mg twice daily, was associated with statistically significant improvement in

ACR20/50/70 response criteria after 12weeks of treatment when compared to placebo (P<0.00001), and when compared to adalimumab in ACR50 criteria responses (P=0.003). Further systematic review confirmed statistically significant improvement in HAQ scores (P<0.0001) [138].

Tofacitinib is the first oral biologic treatment to receive approval by the Food and Drug Administration of the United States Health and Human services (FDA) for treatment of RA patients with an inadequate response to MTX. In the European Union, tofacitinib has not been approved due to safety concerns and insufficient evidence of consistent reduction in disease activity and radiographic joint damage [139]. This may change however with the release of new data.

CONCLUSION

The therapeutic armamentarium for RA is continuously expanding. In addition to TNF inhibitors, other biologic agents have been shown as effective in treatment of patients with RA, providing opportunities for better disease control in patients who had an unmet need through lack or loss of response to conventional DMARDs or TNF blockage, or intolerance to these therapies. As ever, the cost implications of such treatments can limit which patients have access to these drugs, especially in countries without free at point of access healthcare. Further research in stratifying RA patients based on biomarkers or clinical phenotype will enable a better selection of the most suitable treatment options for a certain RA patient, at a certain stage in their disease course. More head-to-head clinical trials aiming to compare the available biologic agents for RA treatment are required to inform clinicians about differences between the licensed biologic therapies and guide their treatment decisions.

ACKNOWLEDGMENTS

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