**Abstract**

Etanercept was the first specific anti-cytokine approved for the treatment of rheumatoid arthritis (RA). Its clinical efficacy and safety has been demonstrated by several clinical trials in early as well as established disease. Etanercept, along with other tumour necrosis factor inhibitors (TNFi), have revolutionised management of RA and dramatically improved disease activity, function, quality of life and mortality for these patients. It is structurally distinct from other TNFi and thus has desirable profiles for immunogenicity, drug survival and infection rate. With the increasing number of etanercept biosimilars, there will likely be a resurgence of their prescription. This article reviews the pharmacology, efficacy, and safety of the etanercept reference product, and its biosimlars, in the context of RA treatment.

**Keywords:** Etanercept, Enbrel, rheumatoid arthritis, anti-TNF, efficacy, safety, pharmacology, biosimilar, SB4, GP2015.

**Introduction**

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects approximately 1% of the population [[1](#_ENREF_1)]. It is characterised by synovial as well as systemic inflammation and, if inadequately treated, has potential to cause disability, reduced quality of life, loss of work capacity and substantial economic impact [[2](#_ENREF_2)]. Before the turn of the century, a third of RA patients stop work due to the disease within two years of onset [[3](#_ENREF_3)], with a total cost to the economy of around £4 billion per year in the UK [[4](#_ENREF_4)]. Furthermore, patients with severe RA have increased mortality with life expectancy reduced by 10 years on average [[5](#_ENREF_5)].

Management of RA has changed dramatically in the past few decades, from controlling symptoms to modifying disease progression. Glucocorticoids are rapidly effective in controlling symptoms but are associated with significant dose-dependent toxicity. Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) such as methotrexate (MTX) - the most widely used anchor drug - were the first viable long-term treatment, commonly used with glucocorticoids as bridging therapy. As RA management improved, these drugs were introduced earlier in the disease course and often in combination [[6](#_ENREF_6)]. However, a significant proportion of patients could not achieve or maintain an adequate response, and many could not tolerate treatment due to adverse effects and toxicities [[7](#_ENREF_7)].

Progress in the understanding of RA pathophysiology led to the development of biologic DMARDs (bDMARDs) that selectively targeted proinflammatory cytokines, such as tumour necrosis factor (TNF). TNF has both proinflammatory and immunoregulatory functions, mediated via ligand interaction with two receptors, TNF receptor (TNFR) I and II, which activate different pathways. In RA, dysregulated production of TNF mediates synovial proliferation and produces other pro-inflammatory cytokines, prostaglandins and metalloproteinases [[8](#_ENREF_8)]. Approved in 1998, etanercept (Enbrel®) was the first specific anti-cytokine therapy for RA. It, along with other TNF inhibitors (TNFi) and anti-cytokine bDMARDs, formed an effective second-line for those with inadequate response to csDMARDs [[6](#_ENREF_6)] and dramatically improved mortality for RA patients [[9](#_ENREF_9), [10](#_ENREF_10)]. Patent expirations have since seen the introduction of two etanercept biosimilars in the European Union (EU). Unlike other TNFi, etanercept is structurally distinct and consequently has many unique pharmacological properties. The aim of this article was to review firstly the pharmacology, efficacy, and safety of the etanercept reference product in the context of RA treatment, and secondly the etanercept biosimilars.

**Pharmacology**

Etanercept is a soluble fusion protein consisting of two human 75kD TNFR II, each linked to a Fc portion of human immunoglobulin G1 (Figure 1) [[11](#_ENREF_11)]. It is administered via subcutaneous injection and is absorbed slowly, reaching peak concentrations 2 to 3 days later. The drug is widely distributed, including into the synovium, and is eliminated slowly with a half-life of 70 to 100 hours in RA patients [[12](#_ENREF_12)]. The pharmacokinetics of etanercept does not appear to be affected by age, gender, ethnicity, cardiac or renal failure [[12](#_ENREF_12)], but may be influenced by certain genetic polymorphisms [[13](#_ENREF_13)].



Figure 1. Etanercept structure in comparison with other TNF inhibitors. TNFR2, TNF receptor 2; Fc, fragment crystallisable region.

Functioning as a decoy receptor, etanercept binds to both TNF-α and TNF-β (lymphotoxin-α) with much greater affinity than endogenous soluble TNF receptors, thereby preventing their interaction and the consequent pro-inflammatory cascade. This is unique from other TNF inhibitors that are variants of anti-TNF antibodies (Table 1). Unlike the monoclonal antibodies (mAbs), etanercept binds less avidly to transmembrane TNF (tmTNF) which may potentially explain both its comparative lack of efficacy in inflammatory bowel diseases and lower risk for reactivation of latent tuberculosis (TB) [[14-16](#_ENREF_14)].

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| Table 1. Overview of biologic DMARDs used in the treatment of rheumatoid arthritis. |
| Drug class | Drug (year approved) | Structure | Dose and route | Indications |
| TNF inhibition | Etanercept (1998) | Soluble fusion protein of two 75kD TNF receptors each linked to human IgG1 Fc tail | SC injection of 25 mg twice weekly or 50 mg once weekly | RA, PSO, PsA, AS, nr-axSpA |
| Infliximab (1999) | Chimeric mouse/human IgG1 anti-TNF monoclonal antibody | IV infusion of 3 mg/kg at weeks 0, 2, 4, then every 8 weeks; up to 7.5 mg/kg if necessary | RA; higher dose for PSO, PsA, AS, UC,CD |
| Adalimumab (2002) | Fully human IgG1 anti-TNF monoclonal antibody | SC injection of 40 mg every 2 weeks  | RA, AS, nr-axSpA, PsA; different dosing for uveitis, PSO, HS, UC, CD |
| Certolizumab pegol (2009) | Humanized Fab fragment that lacks an Fc portion, bound to polyethylene glycol (PEG) | SC injections of 400 mg loading at weeks 0, 2, 4 and followed by 200 mg alternate weeks | RA, PsA, AS, nr-axSpA |
| Golimumab (2009) | Fully human IgG1 anti-TNF monoclonal antibody | SC injection of 50 mg once a month (100mg/month for body weight>100kg) | RA, PsA, AS, nr-axSpA; different dosing for UC |
| T-cell co-stimulation blocker | Abatacept (2005) | Fusion protein of the extracellular domain of human CTLA-4 and human IgG1 Fc tail | IV infusion of 500–1000 mg, depending on bodyweight, at weeks 0, 2, 4, then every 4 weeks; or SC injection 125mg weekly | RA, PsA |
| B-cell depletion therapy | Rituximab (2006) | Chimeric human/mouse anti-CD20 monoclonal antibody | IV infusion of 1000 mg 2 weeks apart | RA; difference dosing for NHL, CLL, GPA |
| IL-6 inhibition | Tocilizumab (2010) | Humanized antibody against membrane-bound and soluble IL6 receptorα (IL6Rα) | SC injection 162mg once weekly | RA, GCA |
| Sarilumab (2017) | Fully human monoclonal antibody against membrane-bound and soluble IL6Rα | SC injection 200mg alternate weeks | RA |
| IL-1 inhibition | Anakinra (2001) | Recombinant non-glycosylated version of human IL1 receptor antagonist | SC injection of 100 mg daily | RA (limited efficacy) |
| TNF, tumour necrosis factor; IL, interleukin; RA, rheumatoid arthritis; PSO, psoriasis; PsA, psoriatic arthritis; AS, ankylosing spondylitis; nr-axSpA, non-radiographic axial spondyloarthritis; UC, ulcerative colitis; CD, Crohn’s disease; NHL, non-Hodgkin lymphoma; CLL, chronic lymphocytic leukaemia; GCA, giant cell arteritis; GPA, granulomatosis with polyangiitis; HS, hidradenitis suppurativa; CAPS, Cryopyrin-Associated Periodic Syndromes |

As with all biologic drugs, immunogenicity is an important concern. Neutralizing anti-drug antibodies (ADA) can block the drug binding to its target, and both neutralizing and non-neutralizing ADA can form immune complexes with the drug, thereby reducing drug levels. Presence of ADA is associated with reduced clinical efficacy and increased frequency of adverse effects [[17](#_ENREF_17), [18](#_ENREF_18)]. Over 40% of patients treated with adalimumab or infliximab develop ADA [[19](#_ENREF_19)]. In contrast, ADA against etanercept were not consistently detected [[20](#_ENREF_20), [21](#_ENREF_21)] and were not found to be associated with reduced clinical response even when present [[17](#_ENREF_17)]. This may have several explanations: When bound to TNF, etanercept forms smaller immune complexes compared to adalimumab or infliximab, which may reduce uptake by antigen-presenting cells [[22](#_ENREF_22)]. In addition, non-endogenous amino-acid sequences promote ADA formation, which accounts for immunogenicity of the chimeric antibody infliximab. Only the fusion part of the etanercept protein can contain foreign epitopes whilst the TNF binding area does not, which might explain its apparent low immunogenicity [[23](#_ENREF_23)]. Concomitant use of csDMARDs reduces ADA formation [[18](#_ENREF_18)] and will be discussed in further detail later.

**Clinical efficacy in rheumatoid arthritis**

The efficacy of etanercept in both early and longstanding RA has been shown by several controlled trials and open label extensions (table 2). The most common clinical outcome measures used in these trials were the ACR20, ACR50, ACR70 responses [[24](#_ENREF_24)] and remission (DAS<1.6 and DAS28<2.6) [[25](#_ENREF_25)]. Etanercept recipients had improved responses at all follow-up time points compared to placebo [[26](#_ENREF_26)]. Furthermore, when added to traditional csDMARD treatment, etanercept combination therapy (with MTX or sulfasalazine (SSZ)) gave consistently better ACR responses and remission rates than either MTX [[11](#_ENREF_11), [27](#_ENREF_27), [28](#_ENREF_28)] or SSZ [[29](#_ENREF_29)] alone.

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| Table 2. Randomised controlled trials of etanercept in rheumatoid arthritis. |
| Study | Number of participants | Disease duration | Treatment groups | Study duration | Outcomes assessed |
| Moreland 1999 [[26](#_ENREF_26)] | 246 | mean 12 years | ETN 10mg twice/week ETN 25mg twice/weekPlacebo twice/week | 6 months | Primary endpoint: ACR20, ACR50ACR 70, tender/swollen joint counts, pain VAS, physician/patient global, duration morning stiffness, HAQAdverse events |
| Weinblatt 1999 [[11](#_ENREF_11)] | 89 | mean 13 years | ETN 25mg twice/week + MTXPlacebo twice/week + MTX | 6 months | Primary endpoint: ACR20ACR50, ACR70tender/swollen joint counts, pain VAS, physician/patient global, duration morning stiffness, HAQAdverse events |
| Bathon 2000 [[30](#_ENREF_30)] | 632 | <3 years | ETN 10mg twice/week + placeboETN 25mg twice/week + placeboPlacebo twice/week + MTX | 1 year | Primary endpoint: ACR-N, change in modified Sharp score ACR20, ACR50, ACR70Adverse events |
| Keystone 2004 [[31](#_ENREF_31)] | 420 | mean 8.9 years | ETN 50mg once/week + placeboETN 25mg twice/weekPlacebo twice/week (then ETN 25mg twice/week after 8 weeks) | 16 weeks | Primary endpoint: ACR20ACR50, ACR70Serum drug levels |
| Klareskog (TEMPO) 2004 [[27](#_ENREF_27)] | 686 | 6m to 20 years | ETN 25mg twice/week+ MTXETN 25mg twice/week + placeboPlacebo twice/week + MTX | 3 years | Primary endpoint: ACR-N AUC; modified total Sharp scoreACR20, ACR50, ACR70, DAS, DAS remission, HAQAdverse events |
| Combe 2006 [[29](#_ENREF_29)] | 260 | mean 6.6 years | ETN 25mg twice/week + placeboPlacebo twice/week + SSZETN 25mg twice/week+ SSZ | 2 years | Primary endpoint: ACR20ACR50, ACR70, DAS44-ESR, morning stiffness durationHAQ, EQ-5D VASAdverse events |
| Emery (COMET) 2008 [[28](#_ENREF_28)] | 542 | 3m to 2 years | ETN 50mg once/week + MTXPlacebo once/week + MTX | 2 years | Primary endpoints: DAS28 remission (< 2.6), change in van der Heijde modified total Sharp scoreHAQ, employment statusAdverse events |
| ETN, etanercept; SSZ, sulfasalazine; MTX, methotrexate; AUC, area under the curve; ACR-N, American College of Rheumatology N index of improvement; VAS, visual analogue scale; HAQ, Health Assessment Questionnaire;  |

However, there were mostly no differences in ACR response or remission rate when etanercept monotherapy was compared to a csDMARD (MTX [[27](#_ENREF_27), [30](#_ENREF_30)] or SSZ [[29](#_ENREF_29)]) alone; although it did provide a more rapid response to treatment than MTX [[30](#_ENREF_30)]. Etanercept combination therapy (with MTX or SSZ) showed consistently better clinical responses than etanercept monotherapy [[27](#_ENREF_27), [29](#_ENREF_29), [32](#_ENREF_32)]. This synergistic effect was also evident for radiographic progression.

Several different scores for radiographic change were used across the studies. In monotherapy trials, etanercept recipients had smaller changes from baseline when compared with those on csDMARD. Furthermore, more participants in the etanercept group had no progression of their joint damage at three years [[27](#_ENREF_27)]. Patients on etanercept combination treatment had significantly smaller change from baseline in radiographic scores at most time points than either csDMARD or etanercept monotherapy. For most people on etanercept combination therapy, radiographic damage appeared to be arrested [[33](#_ENREF_33)].

Combination vs monotherapy

The greater efficacy of etanercept combination therapy, compared to etanercept monotherapy, is also seen with most other bDMARDs [[34](#_ENREF_34)]. This observation is important as real-life data has shown that at least a third of patients receiving a bDMARD are doing so as monotherapy [[35](#_ENREF_35)].

One explanation is the effect of csDMARD in reducing production of ADA. Presence of ADA is associated with reduced clinical efficacy and increased frequency of adverse effects [[17](#_ENREF_17), [18](#_ENREF_18)]. ADA positivity was associated with over three times higher odds of drug discontinuation, and nearly four times greater odds of hypersensitivity reactions [[18](#_ENREF_18)]. Concomitant use of csDMARDs reduces odds of ADA by 68%. However, etanercept does not appear to induce neutralising ADA as discussed earlier. This suggests that csDMARDs may have additional effects beyond their effects on immunogenicity. csDMARDs may have different mechanisms of action from TNFi which act in synergy. Exploratory pharmacodynamic studies have shown that when MTX was combined with adalimumab, many more biological pathways were inhibited than with either agent alone [[36](#_ENREF_36)].

Comparison with other treatment options

There are only a few head-to-head randomised control trials (RCTs) of bDMARDs in RA (table 3), with no direct comparisons of efficacy involving etanercept. A phase IV RCT evaluated the rate of cardiovascular events of tocilizumab against etanercept, with or without csDMARDs [[37](#_ENREF_37)]. This study was published in abstract form at the time of writing, and reported a small and non-significant increase in major adverse cardiovascular events (HRa 1.05; 0.77 to 1.43) in the tocilizumab group. However the average follow-up period was relatively short at 3.2 years. The etanercept group had less elevated low-density lipoprotein (LDL) levels and numerically lower numbers of adverse events, serious infections and gastrointestinal perforations.

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| Table 3. Head-to-head trials of biologic and targeted synthetic DMARDs in rheumatoid arthritis. |
| Study  | Number of participants | Study duration | Conclusion |
| Biologic DMARDs | EXXELERATESmolen 2016 [[38](#_ENREF_38)] | 915 | 2 years | Certolizumab pegol plus MTX is not superior to adalimumab plus MTX.Adverse events were similar between the treatment groups. |
| ORBITPorter 2016 [[39](#_ENREF_39)] | 295 | 1 year | Rituximab is non-inferior to TNF inhibitor treatment (adalimumab or etanercept).AEs and SAEs were similar between the treatment groups. |
| ADACTAGabay 2013 [[40](#_ENREF_40)] | 325 | 24 weeks | Tocilizumab monotherapy is superior to adalimumab monotherapy.More patients in the tocilizumab group had increased LDL-cholesterol, increased ALT concentrations, and reduced platelet and neutrophil counts. |
| MONARCHBurmester 2016 [[41](#_ENREF_41)] | 369 | 24 weeks | Sarilumab monotherapy is superior to adalimumab monotherapy.AEs and SAEs were similar between the treatment groups. The mean increase in ALT was greater in the sarilumab group. Neutropenia was more common in the Sarilumab group. |
| AMPLEWeinblatt 2013 [[42](#_ENREF_42)] | 646 | 2 years | Abatacept plus MTX is similarly efficacious to adalimumab plus MTX.There were fewer discontinuations due to AEs, SAEs and serious infections in the abatacept group. There were fewer injection site reactions. |
| ENTRACTEGiles 2017 [[37](#_ENREF_37)] | 3080 | 5 years | The tocilizumab group had a small, non-significantly raised hazard of major adverse cardiovascular events than those receiving etanercept.Tocilizumab recipients had greater elevations in total cholesterol, LDL-cholesterol and triglycerides. The overall rate of AEs, serious infections and gastrointestinal perforations was numerically higher for tocilizumab. |
| Targeted synthetic DMARDs | ORAL-StrategyFleischmann 2017 [[43](#_ENREF_43)] | 1146 | 1 year | Tofacitinib plus MTX (but not tofacitinib monotherapy) is non-inferior to adalimumab plus MTX.More patients developed SAEs in either tofacitinib groups, but discontinuations due to AEs were higher in the adalimumab group. |
| RA-BEAMTaylor 2017 [[44](#_ENREF_44)] | 1305 | 1 year | Baricitinib plus MTX was superior to adalimumab plus MTX.Radiographic progression was similar between baricitinib and adalimumab. Rates of AEs (including infections and serious infections) were similar. |
| AE, adverse events; SAE, serious adverse events; MTX, methotrexate; ALT, alanine aminotransferase; LDL, low-density lipoprotein. |

A Cochrane network meta-analysis of RCTs found that etanercept, adalimumab and infliximab had similar efficacy [[45](#_ENREF_45)]. In observational studies, analysis of the BSR biologics register reported that etanercept had comparable efficacy to infliximab [[46](#_ENREF_46)]. Similarly, report from the Swedish SSATG registry found no differences in clinical response or quality of life improvement between bDMARD agents including TNFi, abatacept, rituximab and tocilizumab [[47](#_ENREF_47)]. However in the DANBIO registry, etanercept recipients had 50% higher odds of ACR50 response and 78% higher odds of ACR70 response, compared to those receiving infliximab, whilst response rates were similar to adalimumab [[48](#_ENREF_48)]. Both SSATG and DANBIO registries found etanercept to have the best drug survival of all TNFi agents [[47](#_ENREF_47)].

To date there are no published studies in RA comparing the newer targeted synthetic DMARDs (tsDMARDs) with etanercept, but trials have been performed with the similarly effective adalimumab. In MTX combination therapy, the Janus kinases (JAK) 1 and 3 inhibitor, tofacitinib, was non-inferior to adalimumab combination therapy (ACR50 at 6 months, 46% vs 44%, respectively) [[43](#_ENREF_43)]. When each were combined with MTX, the JAK 1 and 2 inhibitor, baricitinib, was superior to adalimumab for its primary end point, ACR20 at 12 weeks (70% vs 61%), and remained so at 52 weeks. Radiographic progression was similar at 24 weeks [[44](#_ENREF_44)].

**Safety and tolerability**

The same Cochrane meta-analysis referenced above reported significantly fewer withdrawals related to adverse events among patients taking etanercept than those taking adalimumab or infliximab in RCTs [[45](#_ENREF_45)]. This was supported by another meta-analysis which found that, compared to controls, etanercept recipients in RCTs had the lowest risk of drug discontinuation due to adverse events of all TNFi agents [[34](#_ENREF_34)]. None of the TNFi agents had significantly higher risk of all adverse events compared to controls. The risk of serious adverse events was not statistically different between controls and each TNFi, except certolizumab pegol (RR 2.24; 95%CI 1.38 to 3.63). When comparing injection site reactions, etanercept had the highest pooled risk of all TNFi compared with controls (RR 4.46; 95%CI 3.13 to 6.36) [[34](#_ENREF_34)].

Infection

Meta-analysis of RCTs showed that the incidence rate (per 100 patient-years) of serious infections among TNFi was lowest for etanercept (4.1) [[49](#_ENREF_49)]. Serious infections are defined as those requiring hospitalization and/or treatment with parenteral antibiotics. Abatacept (3.0), rituximab (3.7) and tofacitinib (3.0) were found to have numerically smaller incidence rates of serious infections [[49](#_ENREF_49)]. Longer-term observational results were varied with regard to infections. Studies of low to moderate risk of bias generally showed small or non-significantly increased risk of serious infections for TNFi as a group compared with csDMARDs [[50](#_ENREF_50)]. However, etanercept individually did not have higher risk of serious infections than csDMARDs [[50](#_ENREF_50), [51](#_ENREF_51)].

One infection of particular interest for TNFi is TB, since TNF is important in clearing mycobacterial infections. In animal models, infliximab but not etanercept exacerbated chronic TB because of better penetration of mAbs into the granuloma [[52](#_ENREF_52)]. As discussed earlier, etanercept is less able than the mAbs to bind tmTNF, which is expressed by activated macrophages and T lymphocytes and is essential in protecting against TB infection [[53](#_ENREF_53)]. In RCTs, TNFi treatment significantly increased risk of TB compared with controls (OR 2.29; 95%CI 1.09 to 4.78), with no reported differences between the TNFi agents [[54](#_ENREF_54)]. Observational studies also found that TNFi recipients had higher risk of TB compared to csDMARDs (HR range 2.7 to 12.5) and to the general population (HR range 12.4 to 34.9) [[50](#_ENREF_50)]. When compared with etanercept, however, risk of TB was higher with infliximab (OR 13.3; 95%CI 2.6 to 69.0) and adalimumab (OR 17.1; 95%CI 3.6 to 80.6) in a French population. This was confirmed by a Taiwanese study comparing adalimumab against etanercept (incidence rate ratio 1.83; 95%CI 1.19 to 2.77) [[55](#_ENREF_55)]. Nevertheless, all patients should be screened for TB prior to commencing TNFi [[56](#_ENREF_56)], regardless of the agent.

There may also be a higher risk of herpes zoster reactivation in patients on TNFi compared with csDMARDs (HR 1.4; 95%CI 1.1 to 1.8). Interestingly, etanercept (HR 0.62; 95%CI 0.40 to 0.95) and adalimumab (HR 0.53; 95%CI 0.31 to 0.91) were associated with lower risk compared to infliximab [[57](#_ENREF_57)].

Malignancy

In meta-analyses of RCTs, pooled incidence of all malignancies for TNFi recipients was low at 0.8%. However, their risk was higher than the placebo group (OR 3.3; 95%CI 1.2 to 9.1), especially for those receiving higher doses [[58](#_ENREF_58)]. It is worth noting that this meta-analysis included only nine RCTs. No increased risk was reported in meta-analysis of early RA trials [[59](#_ENREF_59)]. There were no reported differences between the TNFi agents. Despite the signal for higher risk of malignancy in RCTs, observational studies have reassuringly shown that patients on bDMARDs did not have increased risk for malignancies in comparison to the general population or to patients on csDMARDs [[50](#_ENREF_50)]; individual analyses of etanercept also did not reveal any increased risk [[51](#_ENREF_51), [60](#_ENREF_60)].

The link between RA and lymphoma, particularly non-Hodgkin, was well documented before the advent of bDMARDs [[61](#_ENREF_61), [62](#_ENREF_62)]. Increased rates of lymphoma have been attributed to RA severity [[63](#_ENREF_63), [64](#_ENREF_64)], but concerns remained for the immunosuppressants used in its treatment. Patients with more severe disease are more likely to receive more immunosuppressive treatment, and this channelling bias has been used to explain risk found with DMARDs. In fact some have suggested that treatment reduces lymphoma risk associated with otherwise uncontrolled disease [[65](#_ENREF_65)]. Compared with the general population, the adjusted hazard ratios for TNFi recipients ranged from 2.3 to 2.7 [[66](#_ENREF_66), [67](#_ENREF_67)]. However no increased risk was found when they were compared with patients on csDMARDs [[67](#_ENREF_67), [68](#_ENREF_68)].

No increased risk was reported for solid cancers, individually or as a group, in patients on bDMARDs compared with csDMARDs [[50](#_ENREF_50)]. One study reported an increased risk of non-melanoma skin cancer in TNFi recipients compared to the general population (HR 1.7; 1.7 (1.4 to 2.0) [[69](#_ENREF_69)], but when compared with csDMARDs only one (HR 1.4; 95%CI 1.2 to 1.7) [[70](#_ENREF_70)] out of four studies of low to moderate risk of bias [[68](#_ENREF_68), [69](#_ENREF_69), [71](#_ENREF_71)] found an increased risk.

**Biosimilar etanercept**

Biologic drugs are large, complex molecules produced by recombinant DNA and mammalian cell lineages through highly refined processes that are affected by the cell line and their environment [[72](#_ENREF_72)]. This creates the specific protein-folding and complex three-dimensional structures that are key to their ability to bind antigen. Although the amino-acid sequence may be identical, each manufacturer will use a unique cell line and production process, therefore copies cannot be identical to the reference product (RP) [[73](#_ENREF_73)]. Such “biosimilars” are defined as biological agents that are similar in terms of structure, quality, safety and efficacy to an already licensed RP. With etanercept’s EU patent expiring in 2015, many manufacturers have invested in developing etanercept biosimilars.

Biosimilar approval does not require the manufacturer to re-establish efficacy, which reduces the number and size of clinical trials required, thereby decreasing financial cost. Instead they go through a series of studies to demonstrate that there are no clinically meaningful differences from the RP. This involves comprehensive comparison firstly of structure and function through analytical and in vitro studies, then in vivo animal studies and, finally, abridged clinical studies of pharmacokinetics, pharmacodynamics, immunogenicity, safety and efficacy [[74-76](#_ENREF_74)].

At the time of this review, two etanercept biosimilars are approved in the EU for use in RA, SB4 (Benepali®) and GP2015 (Erelzi®); indication for the latter was extrapolated from a plaque psoriasis trial [[77](#_ENREF_77)]. Only SB4 and HD203 have published phase III trials in RA [[78](#_ENREF_78), [79](#_ENREF_79)]. Table 4 lists completed and ongoing phase III trials of etanercept biosimilars.

SB4 and the etanercept RP 50mg weekly were compared in a double-blind RCT of 596 biologic-naïve patients with active RA despite MTX. The primary end-point (ACR20 at week 24) using the per-protocol set (PPS) was 78.1% for SB4 and 80.3% for the RP. The adjusted difference between the two drugs (-2.22; 95%CI -9.41 to 4.98) was within the equivalence margin of ±15%. ACR50 (46.6% vs 42.3%) and ACR70 (25.5% vs 22.6%) were again equivalent between SB4 and RP, respectively. Adverse events were reportedly similar. However, the trial publication did not report drug safety in as much detail as SB4’s European Public Assessment Report (EPAR) by the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) [[80](#_ENREF_80)]. In particular, there was a signal for higher incidence of hepatobiliary disorders with SB4 compared to RP etanercept (17 vs 0 adverse events), including four events of cholelithiasis, three of liver disease disorder, three of chronic cholecystitis, two of bile duct stone, and one event each of biliary colic, cholangitis, cholecystitis, gall bladder perforation and hypertransaminasaemia [[80](#_ENREF_80), [81](#_ENREF_81)]. Six events from four subjects were reported as serious adverse events. The authors subsequently reported that baseline biliary risk factors were more common in the SB4 group, and concluded that the difference in incidence of hepatobiliary events was not treatment related [[82](#_ENREF_82)]. ADA incidence was reported to be lower with SB4 (0.7% vs 13.1%). However ADA incidence rate for the RP was inconsistent with reports from existing literature (0% to 6%) [[83](#_ENREF_83)]. Several important questions were raised for the validity of SB4’s lower apparent immunogenicity, particularly with regard to the ADA assay used [[84](#_ENREF_84)]. This was echoed in the EPAR, which concluded that the immunogenicity of SB4 was ‘uncertain because of the low drug tolerance of the ADA assay that led to a low sensitivity and a potential bias’ [[80](#_ENREF_80)].

GP2015 25mg twice weekly was compared with its RP in 531 patients with plaque psoriasis (EGALITY study). The difference in its primary endpoint, 75% reduction in the Psoriasis Area and Severity Index (PASI75) after 12 weeks, was equivalent to the RP (73.4% vs 75.7%) [[77](#_ENREF_77)]. The incidence of adverse events was comparable (59.8% vs 57.3%). HD203 was approved by the Korean Ministry of Food and Drug Safety but withdrawn a year later. In brief, its primary end point (ACR20 at 24 weeks) using PPS was similar between the HD203 and RP groups (83.5% vs 81.4%). Adverse events and immunogenicity were comparable [[78](#_ENREF_78)].

It is worth noting that clinical outcomes in biosimilar trials are often better than the original RP trials. For example, PASI75 response of the etanercept RP in the EGALITY study (76%) was higher than in previous studies (47% to 49%) [[85](#_ENREF_85), [86](#_ENREF_86)]. This may indicate differences in study populations. Many recruitment sites for biosimilar trials were from countries where participants may receive better healthcare if enrolled in a trial, thereby incentivising trial engagement but possibly introducing bias. It is also possible that the greater response rates are due to these participants having less severe disease. Nevertheless, the introduction of etanercept biosimilars provides an opportunity to greatly increase patient access to treatment and emerging real-world data will reassure clinicians of their equivalence.

A further source of concern is the safety of switching to biosimilars. Of the six proposed etanercept biosimilars (table 4) only SB4 and GP2015 have published switching data [[87](#_ENREF_87)], with the latter only in plaque psoriasis. In the open label extension of the phase III SB4 trial, etanercept RP recipients switched to SB4 for a further 48 weeks. Efficacy, safety and immunogenicity were no different between switched and non-switched patients at the end of the study period [[88](#_ENREF_88), [89](#_ENREF_89)]. In the EGALITY study, patients with plaque psoriasis were randomized to either etanercept RP or GP2015 for 12 weeks and then re-randomized to either continue current treatment or to undergo repeated switching between treatments. Repeated switching had no impact on efficacy, safety or immunogenicity, although the study was not powered for the latter end point [[77](#_ENREF_77)].

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| Table 4. Completed and ongoing phase III etanercept biosimilar trials as of Sept 2017. |
| Biosimilar (Sponsor) | number randomised | Comparison | primary end point | AE | ADA |
| SB4 (Samsung Bioepis) [[79](#_ENREF_79)] | 596 | SB4 vs ETN50mg weekly | 78.1% vs 80.3% ACR20 at 24 wks | 55.2% vs 58.2% | 0.7% vs 13.1% |
| HD203 (Hanwha Chemical) [[78](#_ENREF_78)] | 294 | HD203 vs ETN25mg twice weekly | 83.5% vs 81.4%ACR20 at 24 wks | 76.9% vs 78.1% | 7.0% vs 2.5% |
| GP2015 (Sandoz)[[90](#_ENREF_90)] | 376completed June 2017 | GP2015 vs ETN50mg weekly | DAS28-CRP change at 24wks | NA | NA |
| CHS-0214 (Coherus Biosciences)[[91](#_ENREF_91)] | 647completed May 2016 | CHS-0214 vs ETN50mg weekly | ACR20 at 24 wks | NA | NA |
| TuNEX (TSH Biopharm)[[92](#_ENREF_92)] | 91Trial ongoing | ENIA11 vs ETN25mg twice weekly | ACR20 at 24 wks | NA | NA |
| LBEC0101 (LG Life Sciences)[[93](#_ENREF_93)] | 372Trial ongoing | LBEC0101 vs ETN 50mg weekly | DAS28 at 24 wks | NA | NA |

The safety of switching to biosimilars looks most promising at present, but results from ongoing studies for SB4 (BIO-SPAN [[94](#_ENREF_94)]), GP2015 (EQUIRA [[95](#_ENREF_95)]), LBEC0101 [[96](#_ENREF_96)] and CHS-0214 [[91](#_ENREF_91)]) are awaited. Reports from these and further pharmacovigilance studies are required to provide sufficient long-term real-world data.

**Conclusion**

Etanercept reduces disease activity and limits progression of joint damage in RA, with its disease modifying effects optimised by concomitant csDMARDs. In both RCTs and observational studies, etanercept has demonstrated favourable profiles for immunogenicity, drug survival and infections. Although it was the first TNFi approved for RA, there will likely be a renewed enthusiasm for its prescription given the arrival of an increasing number of biosimilars and their reduced financial cost. The approved etanercept biosimilars appear to be equivalent in efficacy and safety. The financial benefits they bring will become increasingly apparent with further reassurance from real-world studies supporting the safety of switching.

**Executive summary**

**Introduction**

* Rheumatoid arthritis (RA) is a chronic inflammatory disease which can cause disability, reduced quality of life and substantial economic impact.
* In RA, dysregulated production of tumour necrosis factor (TNF) mediates synovial proliferation and produces other pro-inflammatory cytokines, prostaglandins and metalloproteinases.
* Approved in 1998, etanercept (Enbrel®) was the first specific anti-cytokine therapy for RA.
* Along with other TNF inhibitors (TNFi), etanercept formed an effective second-line for those with inadequate response to conventional synthetic DMARDs (csDMARDs) and dramatically improved mortality for RA patients.

**Pharmacology**

* Etanercept is a soluble fusion protein consisting of two human TNF receptors linked to a human Fc tail. This is unique from other TNFi that are variants of anti-TNF antibodies
* Etanercept binds to TNF, thereby preventing their interaction endogenous TNF receptors and the consequent pro-inflammatory cascade.
* It binds less avidly to transmembrane TNF, which may explain its lower risk for reactivation of latent tuberculosis (TB).
* Anti-drug antibodies (ADA), which are associated with reduced clinical efficacy and increased frequency of adverse effects, were not consistently detected for etanercept.

**Clinical efficacy in rheumatoid arthritis**

* The efficacy of etanercept in both early and longstanding RA has been demonstrated by several controlled trials and open label extensions.
* Combined with csDMARD, etanercept showed consistently better clinical and radiographic responses than csDMARD monotherapy or etanercept monotherapy.
* Etanercept monotherapy showed similar clinical responses to csDMARD monotherapy, although recipients of the former had less radiographic progression.
* There are no head-to-head trials comparing the efficacy of etanercept with other biologic DMARDs (bDMARDs). However, both network meta-analysis of RCTs and observational studies reported similar efficacy between etanercept and other bDMARDs.

**Safety and tolerability**

* Meta-analyses of RCTs reported significantly fewer withdrawals related to adverse events among patients taking etanercept than other TNFi.
* Etanercept was not associated with higher risk of serious infections than other TNFi or csDMARDs.
* In observational studies, etanercept had lower risk of TB than adalimumab and infliximab.
* Etanercept recipients did not have increased risk for malignancies compared to the general population or to patients on csDMARDs.
* As a group, TNFi did not increase risk of lymphoma compared to csDMARDs.

**Biosimilar etanercept**

* Biosimilars are defined as biological agents that are similar in terms of structure, quality, safety and efficacy to an already licensed reference product (RP).
* Biosimilar undergo expedited regulatory approval by demonstrating no clinically meaningful differences from the RP.
* Currently, two etanercept biosimilars are approved in the EU for use in RA, SB4 (Benepali®) and GP2015 (Erelzi®).
* Biosimilars showed equivalent clinical efficacy compared with RP etanercept.
* Adverse events were reportedly similar, however there may be a signal for increased incidence of hepatobiliary adverse events.
* Immunogenicity was reported to be lower with SB4 but there have been concerns about the assays used.
* Efficacy, safety and immunogenicity were no different when patients were switched between biosimilars and RP, but further pharmacovigilance studies are required to provide sufficient long-term real-world data.

**Conclusion**

* Etanercept reduces disease activity and limits progression of joint damage in RA, with its efficacy optimised by concomitant csDMARDs.
* In both RCTs and observational studies, etanercept demonstrated favourable profiles for immunogenicity, drug survival and infections.
* Although it was the first TNFi approved for RA, there will likely be a renewed enthusiasm for its prescription given the arrival of an increasing number of biosimilars and their reduced financial cost.

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