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DIFFERENT EFFECTS OF BIOLOGICAL DRUGS IN RHEUMATOID ARTHRITIS

Fabiola Atzeni\textsuperscript{1}, Maurizio Benucci\textsuperscript{2}, Salvatore Salli\textsuperscript{3}, Sara Bongiovanni\textsuperscript{1}, Laura Boccassini\textsuperscript{1}, Piercarlo Sarzi-Puttini\textsuperscript{1}.

\textsuperscript{1}Rheumatology Unit, L. Sacco University Hospital, Milan, Italy; \textsuperscript{2}Rheumatology Unit, Department of Internal Medicine, San Giovanni di Dio Hospital, Florence, Italy; \textsuperscript{3}Internal Medicine and Geriatric Unit, University of Palermo, Palermo, Italy.

\textbf{Running title:} Biological drugs in RA

\textbf{Corresponding author:}

Piercarlo Sarzi-Puttini, MD,

Consultant and Director,

Rheumatology Unit,

L. Sacco University Hospital, Milan,

20127 Milano,

Italy.

E-mail: sarzi@tiscali.it; atzenifabiola@hotmail.com
ABSTRACT

Biological drugs have brought new hope to patients with rheumatoid arthritis (RA) in whom previously existing treatments could not control inflammation, joint destruction, or the progression of disability. The five currently available TNF blockers are approved for treating RA patients, but they have different structures, morphology, pharmacokinetic properties, and activity. Randomised clinical trials (RCTs) have shown that they improve the signs and symptoms of both early and long-standing RA and other inflammatory arthritides, prevent radiographic progression, and improve the patients’ health-related quality of life. However, they are more effective in combination with methotrexate (MTX) than alone. Combined treatment is generally well tolerated, and seems to be relatively safe in the short term, as confirmed by RCTs, long-term observational studies and in clinical practice. Patients who fail to respond or develop adverse effects/events can be successfully treated with a second TNF antagonist. However, in the case of primary failure, it is possible that biological agents with a different mechanism of action may be more successful. Tocilizumab alone or in combination with MTX is more effective than MTX monotherapy in reducing disease activity over 24 weeks. Abatacept is well tolerated and retains its efficacy over time, as does rituximab in non-responders to other anti-TNF drugs. Finally, although these drugs improve the quality of life of RA patients, they considerably increase direct medical costs.

Key words: Anti-TNF agents; biological drugs; rituximab; anti-IL6; abatacept
Introduction

Rheumatoid arthritis (RA) is characterised by joint inflammation and destruction, and leads to functional limitations, working disability, and a poor quality of life [1]. It has an estimated adult prevalence of 0.8% worldwide, and is more common in females. Synovial inflammation can cause erosive changes that are generally irreversible and often occur early in the disease process [1].

Pro-inflammatory cytokines such as tumour necrosis factor alpha (TNFα) and interleukin(IL)-1β play a key role in the pathogenesis of RA [2]. The synovial membrane of RA patients is hyperplastic, highly vascularised, and infiltrated by inflammatory cells. When activated by an antigen, CD4+ T lymphocytes stimulate monocytes, macrophages, and synovial fibroblasts to produce IL-1, IL-6, and TNF; they also secrete matrix metalloproteinases (MMPs) as a result of cell-surface signalling by CD69 and CD118, and the release of soluble mediators such as interferon (IFN)-γ, IL-1, IL-6, IL-17, and TNF. Activated CD4+ T cells stimulate B cells by means of cell-to-cell contacts, and bind α sub 1 and β sub 2 integrin, CD 40 ligand, and CD28 to produce immunoglobulins (Ig), including rheumatoid factor (RF) [2,3]. They also express the receptor activator of NF-κB (RANK), which stimulates osteoclastogenesis via the RANK ligand (RANKL). Activated macrophages, lymphocytes, and fibroblasts can also stimulate angiogenesis, which is responsible for synovial hypervascularity [2-4]. Synovial endothelial cells are activated and express adhesion molecules that promote the recruitment of inflammatory cells. B cells produce the rheumatoid factor (RF) antibody that induces the formation of immune complexes at the sites of synovial inflammation, the activation of complement and leukocyte infiltration by the downstream products of complement activation (especially the soluble C5a anaphylatoxin), and the subsequent recruitment of the other components of the membrane attack complex [5]. B cells can act as highly efficient, antigen-presenting cells (APCs): they process and present antigenic peptides to T cells, which subsequently proliferate and switch on their pro-inflammatory action [2,5]. Furthermore, activated B cells can synthesise cytokines such as IL-4, IL10, etc., as well as membrane-associated molecules that provide non-specific help to adjacent T cells [2].
**Rheumatoid arthritis therapy**

Before the advent of biological drugs, RA was treated with non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs), all of which were started after the patients had fulfilled the American College of Rheumatology (ACR) criteria: i.e., in patients with late-onset disease. However, since then, the European League Against Rheumatism (EULAR) has recommended that DMARD treatment be started as soon as possible after RA has been diagnosed, with the primary therapeutic aim of obtaining remission (especially in the case of early RA), although a low level of disease activity may be an appropriate alternative, especially in patients with long-standing RA [6-8]. Conventional DMARD treatment may be clinically and functionally effective, but does not always suffice to halt joint destruction [6,7]. The treatment target should preferably be reached within three months and definitely attained within a maximum of six months. Methotrexate (MTX) is considered the anchor drug in RA. An inadequate response to a first-line DMARD at an optimal or maximally tolerated dose may be followed by switching to an alternative DMARD, such as sulfasalazine or leflunomide, or a DMARD combination [8]. If the treatment target is not achieved using the first DMARD strategy, combined treatment with a tumour necrosis factor (TNF) inhibitor (adalimumab, certolizumab, etanercept, golimumab or infliximab) and MTX should be started [9,10] (Table I).

Intensive regimens using combinations of traditional DMARDs, or of one traditional DMARD and biological agents, not only induce a clinical response, but also prevent joint damage [8]. However, since about 30% of patients treated with an anti-TNF agent fail to achieve a 20% improvement in the ACR criteria, and even more of them experience the loss of efficacy or adverse events during treatment [11], switching to a second TNF inhibitor has become established practice although, in the case of primary failure, it is possible that other biological agents with different mechanisms of action (such as rituximab, abatacept and tocilizumab) may be more successful.
Tumour necrosis factor alpha and anti-TNF drugs

TNF-α is a key cytokine in the pathogenesis of RA. It induces macrophages and other cells to secrete pro-inflammatory cytokines such as interleukin (IL) IL-1, IL-6 and IL-8, leads to T-cell activation, and causes endothelial cells to express adhesion molecules [3,4]. TNF-α is involved in the differentiation and maturation of osteoclasts (the main cells involved in arthritic bone destruction), and stimulates fibroblasts, osteoclasts and chondrocytes to release proteinases, which destroy articular cartilage and bone [2,3,12].

TNFα is synthesised as pro-TNF (26 kDa), which is bound to the membrane and released upon the cleavage of its pro-domain by the TNF-converting enzyme (TACE) [12,13]. TNFα acts via two distinct receptors (TNFR-1 and TNFR-2), although its affinity for TNFR-2 is five times higher than its affinity for TNFR-1. Understanding the role of TNFα in the pathogenesis of RA has been important for the development of drugs capable of controlling its clinical signs and symptoms, and halting its radiographic progression. Five TNF blockers have been approved in Europe for treating RA patients (the three monoclonal antibodies infliximab [IFN], adalimumab [ADA] and golimumab [GLM], the recombinant TNF receptor etanercept [ETN], and the pegylated certolizumab [CTZ] [14], but they have different structures, morphology, pharmacokinetic properties and activity.

Monoclonal antibodies

IFN, ADA and GLM are full-length, bivalent immunoglobulin G (IgG) monoclonal antibodies (mAbs) [14-17]. IFN is an intravenously administered, chimeric IgG 1K monoclonal antibody, consisting of a constant human region and variable murine regions, that specifically binds human TNFα with an association constant of 1010 M⁻¹[15]. After initial parenteral administration, its serum half-life is approximately 8.9 days, and is maintained by dosing every eight weeks thereafter. Intravenous administration ensures that maximum serum concentrations are reached within one hour. The infusion of IFN induces a rapid and clinically highly efficacious TNF blockade, with a remission rate of 30-40% after a single dose [15].
ADA and GLM are fully human mAbs [16,17]. ADA only binds TNFα (not the other members of the TNF family) and has a dual mechanism of action: it neutralises TNFα and rapidly removes it from the circulation. The standard dose of ADA is 40 mg subcutaneously (s.c.) every other week, and it can be used alone or in combination with DMARDs. After administering a single 40 mg dose to a healthy adult, it reaches a maximum serum concentration of 4.7 k 1.6 g/ml within 131 ±5 hours [16].

Like ADA, GML is a fully human monoclonal antibody but has different light and heavy chain amino acid sequences that are similar to those of IFN [17]. It is administered s.c. every four weeks, and the median time to reach maximum serum concentrations ranges from two to six days in both healthy subjects and in RA patients [17]. Its mean maximum serum concentration after a 50 mg dose is approximately 2.5 μg/ml, and its estimated median terminal half-life is approximately two weeks [17]. This is similar to ADA.

The TNF-antagonist mAbs have different IgG isotypes, in Fc regions that drive effector functions such as complement fixation, and Fc receptor–mediated biological activities [14-17].

CZP is a recombinant, humanised antibody Fab fragment conjugated to polyethylene glycol (PEG), an inert hydrophilic molecule that increases the drug’s pharmacokinetic half-life [18]. CTZ is a potent neutraliser of human TNF, and has a half-life of 14 days. It is a Fab1 fragment of an IgG1 mAb but lacks effector functions because it does not have the Fc region and therefore cannot activate complement or initiate complement-dependent cell lysis or antibody-dependent cytotoxicity. In patients with RA, it is administered at doses of 200 or 400 mg by means of an s.c. injection every two weeks. Its safety profile is comparable to that of the other anti-TNF agents, with the major adverse events being due to infections [18].

ETN is a fully human, recombinant molecule that consists of two soluble TNF receptor (TNFR) subunits (p75) fused to the Fc portion of human IgG1. It binds and neutralises soluble and membrane-bound TNFα, as well as the related lymphotoxin molecule TNFβ [19]. Its dimeric structure means that it can bind to two molecules of TNFα and is 50-1000 times more efficient at
neutralising TNFα activity in vitro than the monomeric soluble TNF receptor. It has greater affinity for TNF than IFN, and binds circulating and membrane-bound TNF in order to reduce the amount of inflammatory cytokines available for receptor binding [19]. It has a shorter serum half-life and higher clearance rate than IFN or ADA, and is administered by means of an s.c. injection of 25 mg twice weekly or 50 mg once a week [19].

**Clinical efficacy and safety**

All anti-TNF drugs are highly effective in both early and established RA, as has been shown by a number of randomised clinical trials (RCTs) and extension studies [15-19]. Furthermore, large-scale observational and registry studies have evaluated their use and long-term efficacy in clinical practice. Their efficacy was first demonstrated in patients with established RA who had previously failed on traditional DMARDs.

They are much more effective when combined with another DMARD, particularly MTX, and their use in early RA relieves symptoms and slows joint destruction. Rapid and aggressive treatment of early RA, if possible based on the disease activity score (DAS), is crucial for obtaining good clinical results in many patients [15-19]. Combined first-line therapy with a TNF inhibitor and MTX is more effective than either agent alone, particularly in terms of halting radiographic progression [15-19].

All of the published studies took the well-known and validated ACR 20, 50 and 70 response criteria into consideration, but quantifying radiographic changes is also important when evaluating the response of RA patients to anti-TNF drugs. A number of studies have described modified Sharp scores after 12 months, and shown the ability of anti-TNF agents to inhibit the progression of structural joint damage [14], due to the rapid and prolonged suppression of inflammation, and an acceptable safety profile.

The rapid onset of efficacy of anti-TNF drugs is due to their pharmacokinetic and pharmacological characteristics, but only those of CTZ have been studied in detail. RCTs have found that significant improvements in the signs and symptoms of RA (based on the ACR20 criteria) can be observed as
early as after one week of treatment with CTZ in some patients [18], and that its effectiveness is maintained over a 52-week treatment period. Furthermore, a post hoc analysis of RCTs (RAPID 1) suggests a strong positive association between early response and long-term outcomes. In particular, 64% of patients who achieved an ACR20 response by week 12 could be divided into two groups: “week 6 responders” (patients who achieved an ACR20 response by week 6 that was confirmed after 12 weeks and “week 12 responders” (patients who achieved an ACR20 response by week 12 but not by week 6). The rapid response of the former group was associated with a greater probability of a long-term response than in the case of week 12-14 responders [20]. These findings were followed by an algorithm showing that patients who clinically improved by week 12 were more likely to show a low level of disease activity after 52 weeks than patients with a later and smaller response. Consequently, long-term responses can be estimated early during therapy with CTZ [21].

Published data show that ETN, ADA and IFN are clinically efficacious in early RA patients who are MTX naïve, incomplete MTX responders, or DMARD failures [15,16,19], CTZ is effective in DMARD failures and incomplete MTX responders [19], and GLM is effective in incomplete MTX responders and in patients failing to respond to TNF agents [17]. There do not seem to be any significant differences in the efficacy and safety of these drugs, although the pivotal trials of each agent were obviously carried out at different times and there may have been differences in their patient populations. Consequently, the only way of deciding whether one biological agent is superior to another is to compare the medications directly.

Over the last few years, the number of RA patients treated with TNFα antagonists has increased dramatically [10], and only a few differences in their efficacy and safety have been discovered. IFN, ETN and ADA have been in clinical use for years and there is an extensive amount of post-marketing data available, whereas more post-marketing information about CTZ and GLM is needed for the purposes of comprehensive pharmacovigilance. The unresolved issues are the long-term safety of TNFα antagonists and their high cost.
Although there are no published guidelines suggesting the best strategy to adopt after a first anti-TNF failure, switching from one TNF inhibitor to another has become common practice for patients who fail or are unable to tolerate their initial treatment [11]. As the drugs have a similar mechanism of action, it is difficult to understand the differences in patient response, but it has been suggested that they may be due to differences in bioavailability, the stability of the drug/TNF complex, the development of anti-drug antibodies, and possibly, treatment compliance [15-19]. The most frequent reason for discontinuing both first- and second-line treatments is the lack of efficacy but, regardless of the reason and the sequence of the administered drugs, disease activity is reduced after switching. Discontinuation of the second drug because of adverse events is almost always seen in patients who discontinued the first one for the same reason. Survival on second biological treatment is longer than on the first, but shorter than what is observed in non-switchers. RA patients can be successfully treated with a second TNF antagonist, especially those who have experienced secondary failure or adverse events with the first; in the case of primary failure, it is possible that other biological agents with different mechanisms of action (such as rituximab, abatacept and tocilizumab) may be more successful [11].

**Anakinra**

Anakinra, a recombinant non-glycosylated form of human IL-1RA (rhIL-1RA) produced in *Escherichia coli*, has been approved for the treatment of patients with RA who are unresponsive to DMARDs [22]; its efficacy and safety (alone or in combination with DMARDs) have been demonstrated in a number of RCTs [23,24]. A significantly higher percentage of patients treated with a combination of anakinra and MTX fulfilled the ACR criteria for 20%, 50% and 70% improvement than patients who were treated with MTX plus placebo [23]. The most frequently reported adverse events are injection site reactions and infections [22-24]. However, the efficacy of anakinra alone or in combination has been poor in clinical practice, and it is currently rarely used to treat RA.
**Rituximab, abatacept and tocilizumab**

Other European-approved biological agents for treating moderate-severe RA include abatacept, rituximab, and tocilizumab (Table I).

*B cell depletion therapy: rituximab*

Rituximab (RTX) is a chimeric mouse/human monoclonal antibody against the B cell-specific antigen CD20, a tetraspan membrane protein that is first expressed in the early pre-B cell stage and that remains present in mature B cells [5]. It depletes B cells *in vivo* by means of various mechanisms: cell-mediated cytotoxicity, complement-mediated lysis, and apoptosis. It is administered by means of an intravenous infusion, and is effective and relatively safe in patients with established RA [5,25]. It is licensed for the treatment of RA in combination with MTX, and in patients who fail to respond to, or are unable to tolerate TNF antagonists, and has been shown to inhibit the progression of structural damage over two years and after long-term treatment [25,26]. Sustained control of disease activity can be achieved by means of repeated courses, but the optimal dose and schedule of re-treatment have not yet been established [25]. One prospective cohort study of 318 RA patients found that when the reason for switching to RTX was the ineffectiveness of a TNF inhibitor, disease improvement was significantly better than when using an alternative anti-TNF agent [27]. Prolonged RTX therapy causes B cell depletion, and so it is necessary to consider immunoglobulin status and the role of immunoglobulins in the occurrence of infections [28].

*Abatacept*

Abatacept (ABA) is a novel agent that works by inhibiting the “second signal” needed for T cell activation and thus by secondarily inhibiting the “downstream” generation of cytokines, including TNF, IL-1, and IL-6 [29]. Its clinical efficacy is comparable with that of anti-TNF agents and it has an excellent safety profile: it is associated with fewer severe adverse events, and can be used in patients with co-morbidities
precluding the use of anti-TNF agents [14]. It is administered by means of a loading dose and a dose based upon the patient's weight. The rapid infusions do not require pre-medication, and lead to few adverse reactions. Responders may show an improvement after as little as one month, and this affects all of the ACR core components by month 4 [29]. Clinical response tends to be maintained over time, with little evidence of tachyphylaxis or antibody-mediated drug resistance. It has also been shown that ABA increasingly and significantly inhibits the progression of structural damage in patients receiving treatment for two years [30], and it may have an increasing disease-modifying effect over time in the majority of patients who respond to treatment.

ABA is clinically beneficial in RA patients who have previously failed on TNF inhibitor treatment, but should be considered first-line therapy in patients with early RA who incompletely respond to MTX [31,26].

Anti-IL 6 therapy: Tocilizumab

TCZ is a recombinant humanised anti-IL-6 receptor mAb that prevents the interaction of the membrane-expressed receptor or its soluble counterpart with IL-6, and thus inhibits IL-6 signal transduction [32]. It has been approved in Europe (2009) and the United States (2010) for the treatment of moderate-severe RA in adults who have inadequately responded or been intolerant to previous therapy with one or more DMARDs or TNF antagonists [32].

TCZ seems to be particularly suited to patients with IL-6-driven disease indicated by high C-reactive protein (CRP) levels, chronic disease anaemia, systemic involvement and fatigue. When used alone or in combination with MTX, it has been found to be superior to MTX monotherapy in reducing disease activity over 24 weeks [33,34]. It is also effective in patients who fail to respond or become refractory to anti-TNF drugs [34]. The results of an RCT support the potential of TCZ to suppress radiographic progression, particularly in patients who received TCZ at the start of the trial [35]. A sub-analysis of the ROSE (Rapid Onset and Systemic Efficacy) study evaluating early response showed an improvement in the patients’ overall assessment of disease activity and pain, DAS28, CRP levels and the erythrocyte sedimentation rate (ESR) within seven days of the first
TCZ infusion [36], and the same was observed in the Tocilizumab and DMARDs groups: Achievements in Rheumatoid Arthritis (TAMARA) study, a real-life study from Germany that showed rapid improvement in clinical outcomes such as DAS28 scores, patient measures and CRP by week 1 [37]. These findings provide useful information for practising rheumatologists concerning the time to treatment response. TCZ seems to have an acceptable tolerability profile: the most frequently reported adverse events have been infections [26].

A recent meta-analysis [38] has shown that patients inadequately responding to MTX or anti-TNF agents had the same probability of fulfilling the ACR50 criteria as those taking “non-anti-TNF biological agents” as a whole (odds ratio (OR) 1.30; 95% coefficient of interval (CI) 0.91-1.86). However, a comparison of specific biologicals showed that anti-TNF agents were more likely to lead to an ACR50 response than abatacept (OR 1.52; 95%CI: 1.0-2.28), but not in comparison with RTX and TCZ. In patients inadequately responding to anti-TNF agents, RTX was more likely to lead to an ACR50 response than TCZ (OR 2.61; 95% CI 1.10 to 6.37), but there were no significant differences between RTX, TCZ, ABA and GLM. However, head-to-head trials are necessary to confirm these findings [38].

The choice of biological drugs is not only related to ACR responses, safety and the rapidity of response to the drugs, but it is also related to factors such as how long a medication has been approved, the frequency and mode of administration, co-morbidities, and costs. It has recently been shown that biological drugs significantly increase the quality-adjusted life years (QALYs) gained in comparison with MTX alone as first-line therapy [39], and they have also led to considerable improvements in terms of disease activity and joint damage. However, they have also greatly increased direct medical costs. A systematic review by Schoels et al. [40] has shown that on the basis of society’s willingness to pay incremental cost-effectiveness ratio (ICER) thresholds of US$ 50,000-100,000 in the case of long-standing RA, the combinations of TNF inhibitors with MTX are cost-effective after the failure of conventional DMARD therapy, whereas MTX monotherapy (with
the option of adding biological agents in the absence of a sufficient response) is invariably more
cost-effective than administering both in the first-line treatment of early RA.

Conclusions
There do not seem to be any significant differences in the efficacy and safety of ETN, IFN, ADA, CTZ and GLM. However, the pivotal trials of each agent were obviously carried out at different times, and there may have been differences in the patient populations; there were certainly significant differences in the inclusion and exclusion criteria of many of the trials. Of the anti-TNF blockers, CTZ leads to the most rapid clinical response (evaluable during the first weeks of treatment), and the same is true of TCZ in particular in the case of patients treated early. The efficacy of ABA is maintained over time. RTX is rapidly and lastingly effective in patients failing to respond to anti-TNF drugs. Biological drugs significantly increase the QALYs gained in comparison with MTX alone as first-line therapy.

Take home messages

- Five TNF blockers are available for treating patients with systemic rheumatic disease.
- All anti-TNF drugs are approved for treating RA patients, but they have different structures, morphology, pharmacokinetic properties and activity.
- Patients failing on one anti-TNF agent should be switched to another anti-TNF agent or to a drug with a different mechanism of action
- Rituximab, tocilizumab and abatacept are good alternatives in RA patients failing on anti-TNF agents and/or MTX.
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