RHEUMATOLOGY

Rheumatology 2018;57:vii5–vii10
doi:10.1093/rheumatology/key059

20 years of experience with tumour necrosis factor inhibitors: what have we learned?

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Abstract

TNF inhibitors are biologic DMARDs approved for the treatment of active RA in mid-1990s. They still represent a valuable therapeutic option to control the activity, disability and radiographic progression of the disease. In the context of TNF inhibitors, there are currently several molecules and different administration routes that provide optimal treatment personalization, allowing us to respond to a patient's needs in the best possible way. The increasing use of TNF inhibitors has not only improved the management of RA, but it has also helped in our understanding of the pathogenetic mechanisms of the disease. This review focuses on the basis of this targeted therapy and on the knowledge gained from their use about therapeutic effects and adverse events. Effectiveness analysed from drug registries and safety issues are presented together with recent data on infections (in particular, *Mycobacterium tuberculosis* and hepatitis B), cancer (lymphoma, skin cancers) and cardiovascular risk.

Key words: effectiveness, long-term experience, rheumatoid arthritis, safety, TNF inhibitors

Rheumatology key messages

- Biologics have revolutionized the way we treat RA.
- TNF inhibitors were the first biologics used both in randomized controlled trials and in clinical practice.
- TNF inhibitors are effective and safe and represent a valid option for RA.

Introduction

The last 20 years have seen a revolution in the therapeutic approach to RA. The aim of therapy has gone from the control of symptoms to the treat-to-target strategy based on a combined approach focusing not only on symptom control, but also on prevention of structural damage, normalization of function and social participation [1]. Part of this revolution is due to improvement in the use of conventional synthetic DMARDs (csDMARDs) as soon as the diagnosis is made but also the efficacy that targeted therapies have demonstrated in randomized clinical trials (RCTs) and registries.

Neutralizing the effect of TNF in RA has been the first targeted approach and one of the most successful so far. This short review summarizes the role played by TNF in RA and what the use of TNF inhibitors (TNFis) has taught us about the articular and extra-articular manifestations of a complex and systemic disease such as RA.

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Submitted 11 August 2017; revised version accepted 8 February 2018

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The TNF-dependent cytokine cascade

The inflammatory milieu in the synovial compartment in RA is regulated by a complex network of cytokines and chemokines, leading to induction and maintenance of the inflammatory response by activating endothelial cells and attracting immune cells to the synovial compartment. Activated fibroblasts, together with activated T and B cells, monocytes and macrophages, ultimately trigger osteoclast generation that leads to bone erosion [2–4].

This knowledge led some groups in the late 1980s and early 1990s to use pro-inflammatory cytokines as a therapeutic target. Brennan *et al.* [5] performed a pivotal experiment in 1989, blocking cytokines produced in cultures of rheumatoid synovium using antibodies [6] demonstrating that the blockade of TNF-α downregulated most of the other pro-inflammatory cytokines. This assumption was confirmed in animal models and also *in vitro* and *in vivo*, using patients' serum samples and blood [7].

Table 1 Currently available TNFis for RA

TNF inhibitor	Molecule type	Year of release	Half-life, days	Route of administration	Monotherapy approval
Adalimumab (ADA)	Human mAb IgG1	2003	14	Subcutaneous	Yes
Certolizumab pegol (CZP)	Humanized Fab fragment conjugated to a polyethylene glycol	2009	14	Subcutaneous	Yes
Etanercept (ETN)	Fusion protein of TNF receptor 2 and IgG1 Fc component	2000	4–6	Subcutaneous	Yes
Golimumab (GLM)	Human mAb IgG1	2009	14	Subcutaneous	No
Infliximab (IFX)	Chimeric mAb IgG1	1999	8–10	Intravenous	No

Fab: fragment antigen binding.

TNF represents an important host defence molecule and the first cytokine appearing after injuries. Other pro-inflammatory mediators are produced much later and mostly depend on the prior release of TNF [8]. TNF-α blockade has been shown to have clinical benefits: a reduction in cytokine blood levels and their decreased access to the brain can explain a lower level of fatigue and mood improvement, a decrease in local TNF levels normalizes the pain threshold and probably the most relevant factor is connected with the reduction of leucocyte trafficking to the joints, mediated by a reduction in both chemokine expression and adhesion molecules [9].

Among the TNFis, five drugs have been approved, one for i.v. use (infliximab) and four for s.c. administration (adalimumab, certolizumab pegol, etanercept and golimumab). Etanercept is a recombinant human TNF dimeric receptor fusion protein**,** while the others are mAbs or fragments of mAbs. The main features of TNFis currently available for RA treatment are shown in Table 1. Biosimilars of infliximab and etanercept have also been available since 2013 and 2016, respectively.

TNFis: what did RCTs teach us?

The first formal randomized phase II double-blind trial with TNFi was conducted in 1994. Results of a single infusion of infliximab, compared with placebo, provided the first favourable evidence that a specific cytokine blockade can be effective in active RA [10] and this was later corroborated by repeated dosing trials [11, 12]. A larger multicentre double-blind trial confirmed that infliximab was significantly better than placebo in all measures of disease activity and the clinical response was greater in infliximab groups compared with MTX alone [13]. In the same years similar data were also published for etanercept [14–16]. The main limitation of these first trials is related to the type of patients enrolled: first experiences with TNFis refer to a population with a long-standing severe joint disease. Years later, the availability of Early Arthritis Clinics, the attention paid to an early diagnosis of RA, knowledge of the treat-to-target strategy and the chance to use more effective treatments allowed us to carry out trials with TNFis in patients who presented the disease at an early stage.

Today, clinical, functional and structural results represent the main outcomes in the management of RA. The simultaneous achievement of these three outcomes, defined as comprehensive disease control [17], has been shown to be associated with significant improvement in a patient's work-related outcome, quality of life, pain and fatigue, but also with a reduction of health care–related costs and a decreased mortality rate. This is the main reason why current recommendations state that the treatment of RA should focus on achieving clinical remission to inhibit disease progression and improve physical function, or at least reach low disease activity [1, 18], which is reflected quite well by the achievement of a 70% improvement in ACR criteria. However, such a stringent response is difficult to obtain in patients with established disease, even during clinical trials [19].

Indeed, there is considerable evidence that treating arthritis early is much better than treating it late [20]. In the OPTIMA trial, patients with very short disease duration, treated with MTX with incomplete disease control, received an additional TNFi (adalimumab), showing a much greater response than in previous trials that used long-standing disease populations [21]. In general, all biologic DMARDs (bDMARDs) showed enhanced efficacy when combined with MTX in particular and, among other csDMARDs, with leflunomide [22–25]. Current recommendations state that addition of a bDMARD should be considered when the treatment target has not been achieved with the first csDMARD strategy. This approach is particularly necessary when poor prognostic factors are present [18]. The use of TNFi is strongly supported by the availability of long-term registry data concerning their use, as we will discuss later. The progression of structural damage is strongly inhibited by a biologic monotherapy rather than by MTX monotherapy, despite not being as effective as combined treatment. The combination of a biologic with MTX has shown clinical and functional superiority compared with monotherapy with a biologic or with MTX alone [26, 27]; nevertheless, a substantial number of patients do not tolerate csDMARDs [28]. A recent meta-analysis showed that etanercept monotherapy is as effective as monotherapy with anti-IL-6 (tocilizumab) [29].

Clinical and structural efficacy is similar across all types of bDMARDs: when a patient does not achieve the treatment target with a bDMARD (plus MTX), any other

Table 2 Main European registries of patients with inflammatory arthritis treated with bDMARDs

Registry	Country	Date	Number of patients treated with TNFis
LORHEN [35]	Italy	1999	~5200
GISEA [36]	Italy	2005	~12 500
BSRBR	UK	2001	~11 700
RABBIT	Germany	2001	~7600
BIOBADASER	Spain	2000	~5400
ARTIS	Sweden	1999	~7300
DANBIO	Denmark	2000	~3000

bDMARD can be used [18]. Moreover, the sequential use of TNFis after an initial lack of response seems to provide similar outcomes to biologics with different mechanisms of action, at least in clinical trials [30–32].

The appearance of antidrug antibodies is another pivotal aspect regarding efficacy and treatment persistence, in particular related to a secondary non-response to bDMARDs. Currently no evidence has been provided to support routine testing for antidrug antibodies and it has been shown that combination therapy with a low dose of MTX can reduce the incidence of immunogenicity, which explains the better result obtained using a combination therapy [12, 33].

TNFis in real life: data from registries

Registries are a precious tool to monitor and survey commercial drugs in the long run. Their follow-up allows us to identify side effects and serious events not previously observed in RCTs. In the past decade, several registries of patients with RA have been established, as presented in Table 2 [34].

Effectiveness

TNFis have been demonstrated to be effective and well tolerated in a great proportion of patients from RCTs [37], but in clinical practice, primary and secondary failures of TNFi strategies have been shown to affect between a third and half of treated subjects, in particular patients with long-standing disease [38, 39]. A poorer EULAR clinical response has been shown to be associated with the number of DMARDs previously used. Non-response is strongly predicted by a high level of disability and a daily corticosteroid dose >5 mg/day, whereas a good response is associated with the concomitant use of MTX, male gender and higher 28-joint DAS (DAS28) scores at baseline [40].

Moreover, TNFi therapy is effective in both high and moderate disease activity [41], with higher rates of remission in the latter. Predictive factors in patients with high disease activity were pointed out by the analysis of the Italian Lombardy Rheumatology Network (LORHEN) registry, showing that lower age at the first TNFi and the absence of comorbidities independently predict the EULAR response, while male gender is a positive response predictor for both groups [42]. These findings could be explained by the potential effects of TNFis on the neuroendocrine axis, which include higher levels of anti-inflammatory androgens in the synovial tissue of males compared with females [43]. The effectiveness of a TNFi therapy in reducing RA-related disability has also been confirmed in patients with highly active and long-standing RA: patients can achieve a good functional recovery even after years. Starting TNFi therapy not only reduced disability from moderate to mild, but patients who achieved clinical remission during the follow-up are recovering from disability, regardless of disease duration [44].

Patients who suboptimally respond to a TNFi or fail to maintain an initially good response over time may benefit from switching to a second TNFi after failure of the first one, although their probability to achieve a EULAR response is slightly lower than that observed in patients who start TNFi treatment [45, 46].

TNFis have different molecular structures, sites of action and dosing regimens, so for these reasons, switching to a second TNFi has become common clinical practice. Results from the British Society for Rheumatology Biologics Register-RA showed that 73% of patients switching to a second TNFi were still on treatment after a mean of 15 months of follow-up [47], and data from the Spanish registry indicated a similar drug survival of the first and second TNFi [48], confirming data from RCTs [49]. The reason for stopping the first TNFi does not predict the response to the second one, but the DAS28 score at the beginning of the second TNFi treatment is a significant predictor of EULAR response [45]. Various reports suggest that the rate of response to the third drug is significantly lower and that changing the target may be more useful: for this reason, prescribing a third switch of TNFi does not seem to be cost effective [50]. Moreover, increasing age and comorbidities, in particular cardiovascular risk factors and infections, are associated with reduced chances of receiving a TNFi in clinical practice [51].

Safety

RCTs raised a number of safety concerns about an increased risk of infections in patients treated with TNFis. The greatest worry is related to tuberculosis (TB), because the use of TNFis is accompanied by an increased susceptibility to active TB or reactivation of a latent TB infection [52]. In fact, TNF increases the phagocytic capacity of macrophages, enhances intracellular killing of mycobacterium and is also involved in the pathological changes of latent TB infection, especially in maintaining the formation and function of granulomas, which prevents mycobacterium from disseminating into the blood [53, 54]. However, there have been reports indicating the occurrence of other serious infections during the use of TNFis, including opportunistic infections. Large-population RA registries have allowed us to study this aspect more extensively than in RCTs and this may be due to substantial differences in patient enrolment. The incidence of serious infections (the ones that require i.v. antibiotic therapy and/or hospitalization) appear to be quite similar among registries [55, 56]. The most frequent are bacterial skin infections and those involving the lower respiratory tract,

however, a high rate of hospitalization due to pneumonia in RA patients was also found regardless of TNFi treatment [57, 58]. Risk factors for infections include the age at which the biologic drug is started, the baseline ESR and the concomitant use of a high dose of corticosteroids [56, 58]. It has been suggested that monoclonal antibodies carry a higher risk of TB [52], in particular infliximab, but this may be due to the lack of TB screening when TNFis were first introduced. Therapeutic approaches that include intensive screening and surveillance seem to be advisable when TNFis are used. Information about patients' clinical history should be carefully collected and all eligible patients should be appropriately tested in order to assess the risk of TB reactivation [59]. Prophylaxis with a standard anti-TB regimen has been shown to effectively prevent reactivation [60].

Among latent infections, HBV infection represents a major issue in patients with RA on bDMARDs. HBV reactivation can occur not only in HBsAg carriers, but also in HBsAg-negative individuals presenting an occult HBV infection connected to immunosuppression. Therefore, recommendations state that all patients starting bDMARDs should be screened for HBV infection. For HBsAg-positive patients, antiviral therapy should be initiated before any bDMARD therapy, while for patients with resolved HBV infection on a TNFi, simple monitoring without prophylactic treatment is recommended [61].

The increased use of TNFis in clinical practice raised concerns about a possible association with cancer. Data from registries showed that the overall incidence of cancer is similar to that observed in the general population and in patients on csDMARDs [62–64] despite presenting a higher risk of haematological malignancies [63]. However, an increased risk of lymphomas has been attributed to RA itself [65]. In patients on bDMARDs, non-melanoma skin cancer may occur more frequently than in the general population, but there was no increased risk when compared with patients on csDMARDs, suggesting that monitoring skin malignancies may be advisable in RA, irrespective of TNFi treatment [66]. Only one study has shown that patients on TNFi treatment may have an increased risk of melanoma [67]. This finding should be taken into account in patients with a high risk of melanoma due to other reasons.

Among other comorbidities in RA, particular interest has been shown for cardiovascular diseases and correlated risk factors, considering their strong association with the level of disease activity [68, 69]. In a recent analysis from the British Society for Rheumatology Biologics Register, treatment with TNFis has been shown to be associated with a reduced risk of myocardial infarction compared with csDMARDs: this might be attributed to a direct action of TNFi on atherosclerosis and to better overall disease control. TNFi may also reduce cardiovascular risk by changing the lipid profile, insulin resistance and diabetes, resulting in an overall beneficial effect [70].

Conclusions

TNFis were the first bDMARDs used in active RA in RCTs and in clinical practice and have changed the concept of RA from a universally debilitating disease to a goal of remission of symptoms, disability and radiographic progression. The use of TNFis has increased our knowledge of the disease itself, thus improving the way we deal with it.

Supplement: This work was carried out with the unconditional support of Edizioni Internazionali srl, Pavia, Italy.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: R.C. provided expert advice to and received speaker's fees from AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly, Pfizer, Roche, MSD, Novartis, Sanofi and UCB. C.M. provided expert advice to and has received speaker's fees from AbbVie, Bristol-Myers Squibb, Roche, Eli Lilly, Pfizer and MSD. All other authors have declared no conflicts of interest.

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