

Bioboosters in the treatment of rheumatic diseases: a comprehensive review of currently available biologics in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis

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Abstract: Immunologic research has clarified many aspects of the pathogenesis of inflammatory rheumatic disorders. Biologic drugs acting on different steps of the immune response, including cytokines, B- and T-cell lymphocytes, have been marketed over the past 10 years for the treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA). Randomized controlled trials (RCTs) of anti-cytokine agents in RA (including the anti-tumor necrosis factor alpha (TNF α) drugs infliximab, etanercept, adalimumab, golimumab, certolizumab, anti-interleukin (IL)-1 anakinra, and anti-IL-6 tocilizumab) demonstrated a significant efficacy compared to traditional therapies, if combined with methotrexate (MTX), as measured by ACR 20, 50 and 70 response criteria. The new therapies have also been demonstrated to be superior to MTX in slowing or halting articular damage. RCTs have shown the efficacy of anti-TNF α in AS patients through significant improvement of symptoms and function. Trials of anti-TNF α in PsA patients showed marked improvement of articular symptoms for psoriasis and radiological disease progression. More recent studies have demonstrated the efficacy of B-cell depletion with rituximab, and T-cell inactivation with abatacept. All these drugs have a satisfactory safety profile. This paper reviews the different aspects of efficacy and tolerability of biologics in the therapy of RA, AS, and PsA.

Keywords: anti-TNF, anti-cytokine agents, rituximab, abatacept, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis

Introduction

Over the past 30 years research results have identified many of the immune mechanisms responsible for the pathogenesis of different inflammatory rheumatic disorders including rheumatoid arthritis (RA),¹ ankylosing spondylitis (AS)² and psoriatic arthritis (PsA),³ and have provided the groundwork to develop innovative drugs (biologics) which act on different areas of immune response pathways.

Given the central role exerted in the immunopathogenesis of inflammatory rheumatic disorders by the cytokine tumor necrosis factor alpha (TNF α), a trimeric protein encoded within the major histocompatibility complex and mainly produced by macrophages and lymphocytes, TNF α -inhibitors were developed by pharmaceutical companies throughout the 1990s.⁴ Between 1998 and 2002 three drugs – etanercept (Enbrel®; Immunex Corp., Seattle), infliximab (Remicade®; Centocor, Malvern, PA) and adalimumab (Humira®; Abbott Lab. IL) – were approved by the United States Food and Drug Administration (FDA) for use in

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the treatment of RA. Since then all three drugs have been approved for the treatment of AS and PsA also. In 2009 a fourth anti-TNF α agent, golimumab (Simponi[®], Centocor[®]; Ortho Biotech Inc.), came on the market as a possible treatment for these disorders.

The introduction of etanercept, infliximab, and adalimumab revolutionized the treatment of RA despite concern over their efficacy, tolerability and safety.⁵ Over the 10 years the three drugs have been available they have played a crucial role in the treatment of RA, AS, and PsA. and maintained reassuring safety profiles. Moreover, they are increasingly used in the treatment of pathologic conditions such as Behçet's disease, adult-onset Still's disease and sarcoidosis.

Biologics directed against other targets of inflammatory immune response have been developed and marketed for the treatment of RA. These include anakinra (Kineret[®]; Amgen, Thousand Oaks, CA, USA), a recombinant non-glycosylated homolog of the human interleukin (IL)-1 receptor antagonist; certolizumab pegol (Cimzia[®]; UCB Pharma), a humanized, pegylated TNF α inhibitor; tocilizumab (Actemra[®]; Roche), the first IL-6 receptor-inhibiting monoclonal antibody; abatacept (Orencia[®]; Bristol-Myers Squibb Co.), a T-cell co-stimulation modulator; and rituximab (Rituxan[®]; Genentech and Biogen Idec), an anti-CD20-positive B-cells.

Methods

A systematic review of the literature, using PubMed, EMBASE and Cochrane Library databases, was performed to identify English-language articles related to phase III randomized controlled trials (RCTs) of at least 12-week duration on the efficacy and safety of etanercept, infliximab, adalimumab, and golimumab in RA, AS and PsA. In addition, the results of long-term extension, open-label studies of RCTs were analysed. The same search was performed for anakinra, rituximab, abatacept, tocilizumab and certolizumab concerning their efficacy in the treatment of RA. The literature review was extended to June 2009.

Mechanism of action of biologics

Currently approved biologic therapies for RA can be divided in anti-cytokine targeted drugs (including the TNF α inhibitors infliximab, adalimumab, etanercept, golimumab and certolizumab), the anti IL-1 anakinra, the anti IL-6 tocilizumab, and the lymphocyte-targeted agents such as the T-cell co-stimulatory inhibitor abatacept and the B-cell inhibitor rituximab.

Anti-cytokine targeted drugs

TNF α inhibitors

Infliximab

Anti-TNF α infliximab is an immunoglobulin G1 (IgG1) antibody composed of a variable region of a murine antibody grafted to a constant region of human antibody. It binds to soluble and cell membrane-bound TNF α with high affinity, halting the interaction between the TNF α and its receptor.⁶ The drug is administered by intravenous infusions at the dose of 3 to 5 mg/kg scheduled at weeks 0, 2 and 6 and every 8 weeks thereafter. The infusion intervals may be shortened to 6 weeks if needed.

Adalimumab and golimumab

These agents are both fully human monoclonal antibodies which act by binding to the human TNF α with high affinity inactivating the cytokine.⁶ Similarly to infliximab, it prevents TNF α from binding to its receptor and kills cells that express TNF α through antibody-dependent and complement-dependent cytotoxicity.⁶⁻⁸ Adalimumab is given as a 40 mg subcutaneous injection every 2 weeks. Golimumab has been licensed as 50 mg monthly subcutaneous injections.

Etanercept

Etanercept is a fusion protein made up of two recombinant p75 TNF receptors fused with the Fc portion of a human IgG1. Etanercept binds specifically to TNF α and blocks its interaction with cell surface receptors.⁶ The drug is given by subcutaneous injection 50 mg once weekly or 25 mg twice weekly.

Certolizumab pegol

This is a novel TNF α inhibitor consisting of a Fab fragment of a humanized monoclonal anti-TNF α antibody specifically bound to two 20-kDa molecules of polyethylene glycol (PEG) that do not interfere with TNF α binding properties. PEG is a bulky, hydrophilic, inert molecule that increases the pharmacokinetic half-life.⁶ The lack of Fc region may avoid potential Fc-mediated effects including complement- or antibody-dependent, cell-mediated cytotoxicity or apoptosis.⁹ The monoclonal antibody and the receptor analog bind to circulating TNF α and block its interaction with membrane receptors.⁶ Certolizumab pegol has been licensed at a dose of monthly 400 mg subcutaneous injections.

Anakinra

Anakinra is a recombinant non-glycosylated homolog of the human IL-1 receptor antagonist (IL-1Ra) that competitively

inhibits binding of IL-1 with its receptor.¹⁰ The recommended dose is 100 mg/day by subcutaneous injection.

Tocilizumab

Tocilizumab is a humanized monoclonal antibody targeting the IL-6 receptors, it acts by binding to IL-6 receptors and interfering with signal transmission leading to reductions in inflammatory mediator production.¹¹ The drug has been licensed in the USA and Europe at a dose of 4 mg/kg monthly infusions.

Lymphocyte-targeted drugs

Abatacept

Abatacept is a soluble, fully human fusion protein consisting of the extracellular domain of human cytotoxic T-lymphocyte associated-antigen 4-IgG1 fusion linked to the modified Fc (hinge CH2 and CH3 domains) portion of human IgG1. Abatacept blocks the activation of T-cells by binding to co-stimulatory proteins present on antigen-presenting cells (APCs) (CD80/86 on APCs and CD28 on T-cells).¹² The drug is administered intravenously every 4 weeks at a dose of 10 mg/kg.

Rituximab

Rituximab is a genetically engineered chimeric mouse–human monoclonal antibody that selectively depletes the CD20+ peripheral B cell sub-population. The surface antigen CD20 is expressed throughout B cell differentiation but it is not found on hemopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues. The CD20+ B cells depletion occurs via multiple mechanisms including antibody dependant cellular toxicity, complement mediated lysis and induction of apoptosis.⁶ The standard treatment for RA consists of 2 infusions of 1000 mg each with a 2-week interval. Patients can be re-treated after 6 months.

Anti-cytokine therapies in RA

Anti-TNF α agents

Anti-TNF α have been successfully employed in RA resistant to long-standing, traditional disease modifying anti-rheumatic drugs (DMARDs) and in patients with early disease who are naïve to DMARDs, mainly methotrexate (MTX). The efficacy has been evaluated mostly according to the American College of Rheumatology 20 (ACR 20) response criteria as primary end-point.¹³ In other studies the primary end-point was the inhibition of radiological progression, mainly evaluated with the modified total Sharp score and erosions score.¹⁴ Table 1 summarizes the list of published

RCTs with the results of efficacy of anti-TNF α agents early and late RA. Overall, 9821 RA patients were recruited in 21 RCTs: 4 of infliximab, 7 of etanercept, 5 of adalimumab, 2 of golimumab, and 3 of certolizumab.^{15–37} Of these, 16 were conducted in late RA, predominantly of non-responders to MTX (6779 enrolled patients),^{15,16,19–21,23–26,28–31,33–37} and 5 in early RA with recruitment of 3042 patients.^{17,18,22,27,32} Infliximab was always employed in association with MTX, while the other anti-TNF agents have been evaluated as associated with MTX, sulfasalazine (SSZ), previously prescribed DMARDs, or as monotherapy.

A careful analysis of the results in late RA shows that the primary end-point of ACR 20 response was significantly higher compared to controls in all trials of anti-TNF combined with MTX with a percentage of responders ranging from 45.5% to 86%. This large difference is explained by the higher response rates observed in RCTs including patients previously treated with DMARDs (excluding MTX).^{26,29} The percentage of responders in all but 2 remaining RCTs was rather homogeneous ranging between 45.5% and 62%. Similar results were observed concerning the ACR 50 and ACR 70 improvement. Interestingly, in several RCTs of anti-TNF efficacy in late RA patients were randomized to receive the active drug associated with MTX or in monotherapy.^{21–24,31,32–34,36} Examining the results related to monotherapy arms – etanercept, adalimumab, golimumab and certolizumab – demonstrated a significant efficacy compared to controls receiving placebo alone or previous DMARDs excluding MTX, but no significant differences were observed between anti-TNF monotherapy arms and controls treated with placebo and MTX.

The efficacy of anti-TNF in early RA is supported in the results of RCTs.^{17,18,22,27,32} In comparison with controls receiving placebo and MTX, the proportion of patients achieving the primary end-point of ACR20 improvement was significantly higher in active treatment arms if the study drug was associated with MTX, but not in monotherapy.

To summarize, currently approved anti-TNF agents for early and late RA therapy significantly improve the disease when combined with MTX. This conclusion is reinforced by the results of RCTs examining the proportion of patients with early RA achieving the clinical remission defined as Disease Activity Score (DAS) 28 score < 2.6. In the PREMIER study,³² 115 of 268 (43%) patients receiving combined adalimumab and MTX achieved clinical remission after 1 year of treatment compared to 63 of 274 (23%) patients receiving adalimumab monotherapy and 54 of 257 (21%) patients receiving MTX, with a statistically

Table 1 American College of Rheumatology (ACR) 20/50/70 response rates in randomized controlled trials of efficacy of anti-TNF agents in patients with rheumatoid arthritis compared to controls

Author/ref	Drug	Study duration (weeks)	Late RA patient no.	Early RA patient no.	Combined DMARD/ monotherapy (patient no.)	Treatment arm ACR 20/50/70 (%)	Control arm (patient no.)	Control arm ACR 20/50/70 (%)	P value
Maini et al, ¹⁵ Lipsky et al ^{16a}	IFX	54	428	0	MTX (340)	53/29/10	Placebo + MTX (88)	17/8/2	<0.001
St. Clair et al ¹⁷	IFX	54	0	1049	MTX (767)	62/46/32	Placebo + MTX (282)	53/32/21	<0.001
Quinn et al ¹⁸	IFX	54	0	20	MTX (10)	80/80/70	Placebo + MTX (10)	20/0/0	<0.05
Abe et al ¹⁹	IFX	14	147	0	MTX (100)	61/30/10	Placebo + MTX (47)	11/4/0	<0.001
Weinblatt et al ²⁰	ETN	24	89	0	MTX (59)	71/39/15	Placebo + MTX (3)	27/3/0	<0.001
Moreland et al ²¹	ETN	24	234	0	Monotherapy (154)	59/40/15	Placebo (80)	11/5/1	<0.001
Bathon et al ²²	ETN	54	0	632	Monotherapy (415)	61/41/22	MTX (217)	59/40/20	ns
Klareskog et al ^{23/} van der Heijde et al ²⁴ (TEMPO Study)	ETN	52/104	682	0	MTX (231) Monotherapy (223)	85/69/43 (52 wks) 86/71/49 (104 wks) 70/48/24 (52 wks) 75/54/27 (104 wks)	Placebo + MTX (228)	75/43/19 71/42/21	<0.01 <0.01 ns ns
Keystone et al ²⁵	ETN	16	420	0	MTX (367)	55/29/8	Placebo (53)	19/6/2	<0.001
Combe et al ²⁶	ETN	24	260	0	SSZ (101) Monotherapy (103)	74/52/25 74/47/21	SSZ (50)	28/14/2	<0.01 <0.01
Emery et al ²⁷	ETN	52	0	542	MTX (274)	86/71/48	Placebo + MTX (268)	67/49/28	<0.001
Weinblatt et al ²⁸	ADA	24	271	0	MTX (209)	70/55/27	Placebo + MTX (62)	14.5/8/5	<0.001
Furst et al ²⁹	ADA	24	636	0	Previous DMARDs (318)	53/29/15	Previous DMARDs + placebo (318)	35/11/3.5	<0.001
Keystone et al ³⁰	ADA	52	619	0	MTX (419)	59/39/23	Placebo + MTX (200)	24/9.5/4.5	<0.001
Van de Putte et al ³¹	ADA	26	544	0	Monotherapy (434)	52/25/14	Placebo (110)	19/8/2	<0.001
Breedveld et al ³²	ADA	104	0	799	MTX (268) Monotherapy (274)	69/59/47 49/37/28	Placebo + MTX (257)	56/43/28	<0.001 ns
Kay et al ³³	GOL	52	172	0	MTX (137)	61/31/12	Placebo + MTX (35)	13/2/0	0.001
Keystone et al ³⁴	GOL	52	444	0	MTX (178) Monotherapy (133)	60/35/17 35/19/11	Placebo + MTX (133)	28/13.5/5	0.001 ns
Keystone et al ³⁵	CZP	52	982	0	MTX (783)	61/40/21	Placebo + MTX	14/8/4	<0.001
Fleischmann et al ³⁶	CZP	24	220	0	Monotherapy (111)	45.5/23/5.5	Placebo (111)	9/4/0	<0.001
Smolen et al ³⁷	CZP	24	619	0	MTX (492)	57/32.5/16	Placebo + MTX (127)	9/3/1	<0.001

*Results of the first study and its blinded extension phase.

Abbreviations: ADA, adalimumab; CZP, certolizumab pegol; DMARD, disease-modifying anti-rheumatic drugs; ETN, etanercept; GOL, golimumab; IFX, infliximab; MTX, methotrexate; SSZ, sulfasalazine.

significant difference ($P < 0.001$). This finding has recently been supported by the COMET trial,²⁷ designed to compare combination therapy ETA + MTX with MTX alone in terms of frequency of clinical remission as the primary endpoint of the study. At 52 weeks, 132 of 265 (50%) patients of the combined-therapy group and 73 of 263 (28%) of controls achieved DAS 28 remission with a statistically significant difference ($P < 0.0001$).

Even if the need for combined therapy with MTX to achieve a significant beneficial effect on clinical signs and symptoms of RA seems to overshadow the decisive therapeutic role of anti-TNF drugs, the evidence supports the use of the traditional therapies to halt or slow down the radiological disease progression. Indeed, RCTs and their open-label extension study results have provided a consistent body of evidence on the effectiveness of anti-TNF agents in halting the joint erosive process of RA, mainly evaluated using the modified total Sharp score. Joint damage expressed by the radiographic appearance of new erosions has been strongly associated with uncontrolled disease activity as reflected by the number of persistent tender and swollen joints, raised acute-phase reactants and functional scores.^{38,39}

Interesting data emerged from Lipsky's study of infliximab in patients with late RA.¹⁶ A significant reduction of radiographic progression was observed in the combined infliximab-MTX group compared to the control group receiving MTX alone ($P < 0.001$) after a 54-week follow-up period. The radiological progression was observed to slow down independently of the clinical response. This result was maintained at week 102.⁴⁰

In the ASPIRE trial on early RA,⁴¹ designed to evaluate the impact of therapy on the radiological outcome, the mean change of modified Sharp score after 54 weeks was significantly less in the 641 patients receiving infliximab and MTX compared with the 363 control patients treated with MTX alone. The correlation between the disease activity and the radiographic progression was observed in patients treated with MTX alone but not in those receiving infliximab. This dissociation is probably related to the inhibition of circulating and local synovial production of TNF α exerted by infliximab but not by MTX, and represented the rationale for treatment with anti-TNF drugs in an early phase of the disease.⁴² These data were supported in a controlled MRI study of a small cohort of patients with early RA; those receiving infliximab associated with MTX showed no new erosions at week 54.¹⁸

Three studies have provided evidence relating to the inhibition of joint damage progression in patients with

RA treated with etanercept. In Bathon's study, 72% of patients receiving etanercept had no increase in the erosion score compared to 60% of the MTX group ($P = 0.007$).²² In the TEMPO trial,²³ 682 patients with late RA were randomly allocated to receive either MTX (228 patients), etanercept (223 patients) or combined etanercept and MTX (231 patients) for 1 year. The mean change of Sharp score was significantly lower in the combination therapy group compared with MTX or etanercept ($P < 0.0001$ and $P = 0.0006$ respectively). A significant inhibition of disease progression resulted also in etanercept monotherapy group compared to MTX alone group ($P = 0.0077$). The study was extended to 2 years duration and at the end of follow up 86% of patients receiving combination therapy had no progression of erosions with significant difference compared with either monotherapy (etanercept 75%; MTX 66%; $P < 0.05$) and etanercept versus MTX ($P < 0.05$).²⁴ Finally, in the COMET trial 80% of combined etanercept and MTX therapy group (246 patients) and 59% of those treated with MTX alone had no radiographic progression ($P < 0.0001$).²⁷

The efficacy of adalimumab to inhibit the radiographic progression of RA has been assessed in two trials. The primary end point of Keystone's study was the inhibition of radiographic progression in late RA as expressed by change of modified Sharp score.³⁰ After 52 weeks, patients taking adalimumab plus MTX had a significantly lower change of Sharp and erosion scores compared to those treated with MTX alone ($P < 0.001$ for each comparison). The co-primary end point of the PREMIER study was the mean change of modified total Sharp score in 799 patients with MTX-naïve early RA randomized to receive adalimumab plus MTX, adalimumab monotherapy, and MTX monotherapy.³² The evaluation of radiographic progression at 1 and 2 years showed a significant lower Sharp score change in patients treated with combination therapy compared to those receiving adalimumab or MTX monotherapy ($P = 0.002$ and $P < 0.001$ respectively). Similarly to infliximab studies, although the clinical response was not significantly different between the two arms treated with monotherapy, patients receiving adalimumab alone had significantly less progression compared to MTX alone ($P < 0.001$).

Two RCTs of certolizumab pegol in RA included as secondary end-point the radiographic progression inhibition.^{35,37} In the RAPID I study, a 52-week trial of patients with late RA, certolizumab pegol combined with MTX was significantly more effective than placebo plus MTX treatment.³⁵ At the end of the follow up mean Sharp score changes were 0.2 and 0.4 (for certolizumab pegol 200 mg and 400 mg, respectively)

in the active treatment arm and 2.8 in controls ($P < 0.001$). In the RAPID 2 study the mean changes of Sharp and erosion scores at 24 weeks were significantly less in the active treatment arm compared to controls treated with MTX alone (Sharp score: 0.2 vs 1.2; $P < 0.001$; Erosion score: 0.1 vs 0.7; $P < 0.01$).³⁷

No data on disease progression for patients treated with golimumab were available while preparing this manuscript. In addition, several studies on both RA and AS have demonstrated that switching to another anti-TNF α agent may improve symptoms of the disease where the first biologic used did not.^{43–46}

In recent years an increasing interest has emerged about the role of anti-TNF α therapy in preventing accelerated atherosclerosis and consequent cardiovascular events associated with a higher mortality rate in patients with RA.⁴⁷

Atherosclerosis and RA pathogenesis share several immunologic mechanisms, such as elevated circulating levels of TNF α , which play an important role in the inflammatory process leading to endothelial dysfunction, which is the first clinically measurable step of vascular wall damage.^{48,49} Moreover, TNF α seem to influence atherogenesis through its release of adipokines including leptin, resistin and adiponectin.^{50,51}

No conclusive data are available on the efficacy of anti-TNF therapies to reverse the endothelial dysfunction in patients with RA.⁵² However, the leading causes of mortality in RA are cardiovascular events, and data from British and Swedish registries show a significant reduction in cardiovascular events and mortality in patients receiving anti-TNF compared to those treated with traditional DMARDs.^{53–56}

Safety of TNF α inhibitors

Overall, the safety profile of TNF α inhibitors mainly evaluated in terms of infection, and malignancy occurrence is satisfactory. Results from RCTs of all 5 approved biologics indicate that there are no differences between active treatments and controls in terms of withdrawals due to adverse events, minor and severe infections, and malignancy onset.^{57,58} However, severe bacterial and opportunistic infections have been repeatedly reported in clinical practice treated patients.⁵⁹ It is difficult to interpret the sporadic cases, especially if we consider that RA itself is associated with a higher risk of infections.⁶⁰ Post-marketing surveillance reports and data from Swedish, British, Japanese, and German registries indicate a moderate increase in relative risk (ranging from 1.43 to 4.48) of serious infections in patients treated with etanercept, infliximab and adalimumab

with no differences among the three drugs.^{61–66} The risk seems higher during the first year of treatment and decreases over time.⁶³

An increased risk of tuberculosis (TB) was initially observed in patients receiving infliximab, adalimumab and to a lesser extent in those receiving etanercept.^{67,68} The risk has been reduced following adalimumab dose reduction and the introduction of screening procedures to detect previous contacts with mycobacterium tuberculosis by tuberculin skin test, QuantiFERON-TB Gold test and recommendations for chemo-prophylaxis.^{69,70} Several reports have confirmed the validity of the recommendations for TB screening with a probability of developing the disease 7 times lower when procedures were followed correctly.⁶⁹ In a recent report from a French registry the authors found an increased risk of TB in patients receiving anti-TNF monoclonal antibody infliximab or adalimumab and to a lesser extent in those treated with etanercept.⁷¹ However, these findings are of limited value due to the absence of correct chemoprophylaxis.

As TNF α exerts an important role in host defence and in the pathobiology of cancer through its action on natural killer cells and CD8 lymphocyte-mediated killing of tumor cells, an increase in malignancy occurrence has been considered as a possible adverse event of TNF α blockade.^{72,73}

An association between anti-TNF and lymphoma was first reported in 2002,⁷⁴ but the role exerted by therapy is uncertain owing to the well-known increased incidence of lymphoma in patients with RA.^{75,76}

A recent meta-analysis of RCTs of infliximab and adalimumab reported a significantly higher occurrence of solid tumors in patients receiving the active drug compared to placebo.⁷⁷ These results are yet to be replicated.^{78,79}

Data from a Swedish register and 1 Japanese, 1 Canadian and 3 US Healthcare databases^{45–50} seem to exclude an increased frequency of all malignancies in patients receiving anti-TNF α agents compared to the general population and those taking traditional DMARDs.^{61,62,80–84}

In a recent systematic review of RCTs of anti-TNF infliximab, adalimumab, etanercept treatment for RA, AS and PsA we did not find an increased frequency of malignancies in the study drug arms compared to placebo.⁸⁵ However, we evidenced findings consistent with defective cancer screening procedures as indicated by around 1 in 4 malignancies occurring within 12 weeks from the start of therapy for both groups. Therefore, we suggested more comprehensive cancer screening procedures with respect to those currently used based only on the detection of “positive history or current diagnosis of cancer”.⁸⁵

Because the incidence of demyelinating disorders recorded in patients taking anti-TNF, especially etanercept, is not higher than in general population, their use should be avoided in subjects with suspected pre-existing demyelinating disorders.⁸⁶

Anti-TNF in different co-morbid conditions

Due to study design and the wide spectrum of RCT participation criteria, the results do not cover many situations that may be encountered in real-life practice. Patients with rheumatic inflammatory disorders, particularly RA, may present with concomitant co-morbidities or therapies possibly precluding anti-TNF therapy.

Several reports have provided useful information on the safety of anti-TNF use in people older than 65 years,⁸⁷ on the absence of interaction of etanercept with diabetes and hypertension therapies,⁸⁸ and on the two frequently used drugs warfarin and digoxin.^{89,90} In around 5% of patients exposed to certolizumab pegol a prolonged activated partial thromboplastin time was recorded, indicating that anti-TNF should be used with care in patients with hemorrhagic disorders or receiving concomitant anticoagulants.³⁷

Elevated levels of TNF α in patients with heart failure suggested the rationale for performing 2 studies of infliximab and etanercept in patients with this condition.^{91,92} The studies were stopped early due to the inefficacy of both drugs and the increased mortality in patients receiving higher dose of infliximab. These results suggest avoiding the use of anti-TNF in patients with New York Heart Association class III and IV heart failure.⁹³

Limited data from small clinical series and 1 phase II pilot study indicate that anti-TNF are safe for patients with chronic hepatitis C virus (HCV) infection with no increase in serum levels of alanine aminotransferase or viral load as well as for HIV-infected subjects.^{94,95} The use of TNF-inhibitors in patients with hepatitis B virus (HBV) infection seems more problematic. Case reports of fulminant hepatitis and an increase in viral load have been published in HBV-positive patients receiving anti-TNF drugs.^{96,97} Antiviral therapy with lamivudine associated with TNF-inhibitor seems to prevent the worsening of hepatic function and viral replication.^{94,95} These findings have been recently replicated in a small, French clinical series.⁹⁸

These limited data suggest a need for HBV and HCV testing in patients requiring anti-TNF drugs. A few data indicate that anti-TNF agents increase the risk of cytomegalovirus and herpes virus infections.^{99–101}

Finally, although there is a lack of prospective studies on a large number of cases, the limited data available indicate anti-TNF are safe during pregnancy with no increased risk of adverse pregnancy outcome or fetal toxicity.¹⁰²

Anti-TNF immunogenicity

Patients newly positive for antinuclear antibodies (ANA) have been recorded in all studies of anti-TNF. This finding has been observed in around 60% of patients taking infliximab with 10% to 15% positivity for anti-double-stranded DNA, and to a lesser extent in those taking etanercept (11% ANA+; 4% DNAds+), adalimumab (12% ANA+; 4% DNAds+),⁵⁹ golimumab (21% ANA+; 1% DNAds+),³⁴ and certolizumab (17% ANA).³⁷ Of note, these antibodies have a low clinical relevance and cases of drug-induced lupus have rarely been described.¹⁰³

In addition, all the currently approved anti-TNF agents stimulate the production of antibodies against themselves including the human anti-human antibodies (HAHA) neutralizing etanercept and adalimumab, and human anti-chimera antibodies (HACA) directed against infliximab. Antibodies against a single drug have been recorded with a frequency of around 10% for infliximab, 3% for etanercept, 8% for adalimumab, 6.5% for golimumab, and 5% to 6% for certolizumab.^{59,34,37} Overall, the development of these antibodies contributes to the drug failure and infliximab infusion reactions.^{57,104}

Anakinra

Anakinra was approved in 2001 by the FDA for RA patients whose systems have resisted one or more DMARDs. In the first published 24-week RCT, 472 patients refractory to traditional DMARDs were randomized to receive subcutaneous injections of anakinra monotherapy at a daily dose of 30, 75, or 150 mg and compared to placebo.¹⁰⁵ A statistically significant ACR 20 improvement compared to placebo was achieved by patients taking 150 mg/day (43% vs 27%; $P = 0.014$).¹⁰⁵ The radiologic progression evaluated by the total Larsen score was significantly lower in anakinra groups compared to placebo independent of the clinical response. The 48-week extension of this study confirmed the relatively modest effects of anakinra on disease activity with ACR 20, 50, and 70 response rates of 42%, 18% and 3%, respectively.¹⁰⁶ The efficacy of anakinra to reduce the radiological progression of RA was replicated 2 years later in a 48-week RCT using the Genant and Larsen scores.¹⁰⁷ Anakinra has also been studied in combination therapy with MTX. In a 24-week RCT, 419 RA patients with active

disease despite MTX therapy were randomized to receive anakinra at doses of 0.04, 0.1, 0.4, 1.0 or 2.0 mg/kg daily with MTX or placebo plus MTX. Only group receiving 1.0 mg/kg daily achieved a significant ACR 20 improvement compared to placebo (42% vs 23%; $P = 0.018$).¹⁰⁸ Similar modest efficacy, with an ACR 20 improvement of 38% compared 22% of placebo group ($P < 0.001$), was recorded in a RCT of anakinra combined with MTX in 506 RA patients resistant to MTX.¹⁰⁸ In all RCTs of efficacy and in 2 further studies designed to evaluate the safety in RA patients with different comorbidities, anakinra demonstrated a good tolerability and safety,^{110,111} but, due to its limited efficacy, it is usually underemployed with respect to anti-TNF in clinical practice.

Tocilizumab

The efficacy of the anti-IL-6 receptor antibody tocilizumab in patients with active RA despite MTX treatment was first evaluated by the CHARISMA Study Group in a 16-week RCT.¹¹² The primary end-point was the proportion of patients achieving a ACR 20 response. Patients were randomized to receive monthly intravenous tocilizumab at doses of 2, 4 or 8 mg/kg as monotherapy or combined with MTX, or placebo plus MTX. Compared to placebo, a significant response was achieved by groups receiving 4 or 8 mg/kg either in monotherapy (4 mg/kg: 61%; 8 mg/kg: 63%; placebo: 41%; $P < 0.05$) or combined therapy (4 mg/kg + MTX: 63%; 8 mg/kg + MTX: 74%; $P < 0.001$). At these two dosages the ACR 50 and ACR70 responses were also significant compared to placebo. These results were confirmed in the OPTION study enrolling 623 RA patients, with an ACR 20 response in 59% of patients of active drug treatment and 265 in those of placebo arm ($P < 0.0001$).¹¹³ Two RCTs have also provided the evidence of a significant efficacy of tocilizumab compared to traditional DMARDs on RA disease activity and radiological progression.^{114,115} Finally, the RADIATE trial evaluated the efficacy of tocilizumab in 499 RA patients who have failed at least 1 anti-TNF agent.¹¹⁶ After 24 weeks, both the patients receiving 8 mg/kg or 4 mg/kg had 50% and 30% ACR 20 responses, respectively, compared to 10 of the placebo arm ($P < 0.001$). The results of RCTs of tocilizumab raise some concerns about the safety related to liver function tests and serum lipid levels. In around 5% of patients, elevation of alanine aminotransferase serum levels was observed and more than 20% of patients had elevation of serum cholesterol. In addition, severe grade 3 neutropenia was recorded in 4% of patients.^{112–116} The drug has been only recently marketed in the US, in Japan, and in

European countries. Therefore, post-marketing data useful to assess more precisely the efficacy and safety of tocilizumab are lacking.

Lymphocyte-targeted drugs

Rituximab

Although the role of B-cells in the immunopathogenesis of RA is not completely understood, these cells are responsible for the production of autoantibodies directed against the Fc portion of IgG with rheumatoid factor formation and actively participate to the synovial inflammatory process.⁶ In an open-label study, all 5 RA patients resistant to traditional DMARDs who were treated with rituximab in association with cyclophosphamide achieved a sustained ACR 70 response.¹¹⁷ This finding provided the rationale to design a phase II RCT of rituximab efficacy in MTX-resistant RA patients to evaluate the proportion of patients achieving a ACR 50 response as primary end point.¹¹⁸ A total of 161 patients were randomized to receive MTX alone, rituximab alone, rituximab plus cyclophosphamide or rituximab plus MTX. After 24 weeks, groups receiving rituximab either combined with MTX or cyclophosphamide had a significantly higher ACR 50 response compared to MTX alone ($P = 0.0005$) and at week 48 65% of patients in the rituximab plus MTX group maintained the ACR50 response ($P < 0.001$).

A phase IIb trial on 465 MTX-resistant RA patients substantially confirmed the previous results.¹¹⁹ In the REFLEX trial the efficacy and safety of rituximab plus MTX in patients with active RA with an inadequate response to at least 1 anti-TNF drug was evaluated.¹²⁰ Rituximab was given at the optimal dose of 1 course of 2 infusions of 1000 mg each at baseline and after 2 weeks, preceded by intravenous methylprednisolone 100 mg. At 24 weeks, ACR 20 response was reached by 51% of 308 patients receiving rituximab plus MTX and in 18% of 209 controls treated with MTX plus placebo ($P < 0.0001$). The ACR 50 and ACR 70 responses were also significantly higher in the study drug arm (27% vs 5% for ACR 50 and 12% vs 1% for ACR70; $P < 0.0001$ for both comparisons). No differences were observed between the study drug arm and placebo for all types of adverse events. In addition, due to its mechanism of action on B lymphocytes, rituximab does not seem to enhance the reactivation of latent TB and may constitute a valid alternative therapeutic choice to anti-TNF in high-risk patients.^{118–120}

Rituximab combined with MTX was significantly more effective than anti-TNF switching in a prospective study of 116 RA patients who had failed the first TNF α inhibitor.¹²¹

These data led to the approval of combined rituximab plus MTX for the treatment of RA patients with inadequate response to at least 1 anti-TNF agent.

Abatacept

Phase II and IIb trials provided the evidence of efficacy of monthly infusions of abatacept 10 mg/kg in RA by inhibiting the CD80/CD86 co-stimulatory signal expressed on antigen-presenting cells which in turn prevents the full activation of T-cell CD28+. ^{122,123} Four phase III trials of efficacy and safety of abatacept have been published. ^{124–128} The effectiveness of abatacept combined with MTX was evaluated in comparison with MTX in the AIM study, ¹²⁵ with infliximab in the ATTEST study, ¹²⁸ and in patients with inadequate response to at least 1 anti-TNF in the ATTAIN study. ¹²⁷ In all 3 studies the combination therapy abatacept plus MTX was significantly superior to comparators, a mean of 60% and 70% of patients showing ACR 20 response after 6 and 12 months, respectively. However, abatacept was not superior to infliximab in the ATTEST study, despite the anti-TNF being used at the dose of 3 mg/kg. ¹²⁸

As observed in the extension phase of AIM trial, abatacept was effective in halting the progression of radiological joint damage. ¹²⁹

The results of phase III trials and of the ASSURE study, ¹³⁰ designed to evaluate the safety of abatacept in RA, show that abatacept has a good safety profile. However, because it has only recently available in clinical practice, data from post-marketing surveillance are lacking.

Biologics in ankylosing spondylitis and psoriatic arthritis

Traditional DMARDs have been demonstrated inefficacious in the treatment of AS and for a long time AS has remained an orphan disease. ¹³¹ Due to the evidence of the crucial role of TNF α in the pathogenesis of both AS and PsA, ^{132,133} anti-TNF α agents have strongly changed the quality of life and the prognosis of patients with the two diseases. The available results from RCTs of efficacy of anti-TNF infliximab, etanercept, adalimumab and golimumab in patients with AS are summarized in Table 2.

The therapeutic role of anti-TNF in AS was assessed primarily through the evaluation of efficacy on symptoms defined as 20% or greater improvement of Assessments in Ankylosing Spondylitis Working Group (ASAS) response, ¹⁴³ and the degree of inflammation as expressed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). ¹⁴⁴

In addition, inflammation has been investigated with magnetic resonance imaging studies and over time other efficacy outcome measures have been evaluated such as radiographic disease progression, health-related quality of life, and cost-effectiveness. ^{145–149}

Two controlled studies of infliximab, ^{134,135} 5 of etanercept, ^{136–140} 1 of adalimumab, ¹⁴¹ and 1 of golimumab ¹⁴² have provided the evidence of efficacy and safety of anti-TNF in the treatment of active AS. Overall, these drugs gave similar results, around 60% of the patients showing significant clinical response compared to placebo. The study sub-analysis results have demonstrated the efficacy of anti-TNF on extra-spinal manifestations of AS including enthesitis, dactylitis and anterior uveitis. Moreover, extension studies of infliximab, etanercept and adalimumab trials have also shown the sustained efficacy of the treatments over time. ^{150–154} Interestingly, TNF α inhibition is effective in reducing the symptoms also in patients with total spinal ankylosis. ¹⁵⁵

Whether anti-TNF α therapy is capable of preventing disease progression and spine ankylosis is under debate. Data are scanty and controversial, and are derived from short-term sub-analyses of the blinded phase of RCTs or evaluation of the radiological outcome in open-label extension studies. ^{156,157} Further, the long duration of AS, the selection of patients and the use of a historical control group have probably negatively influenced the results, and properly designed studies on patients with early onset AS should be planned.

Although PsA has long been considered a benign disease, several follow-up studies have demonstrated an aggressive course with development of articular erosions and deformities in around 50% of the cases. ¹⁵⁸ PsA management is strictly related to the severity of the disease. Mild monoarticular or oligoarticular peripheral variants of PsA are usually treated with local injection therapy and non-steroidal anti-inflammatory drugs, eventually associated with short-term, low-dose corticosteroids. ¹⁵⁹ Non-responders and patients with polyarthritis at onset require a more aggressive therapy with second-line drugs, including SSZ, MTX, cyclosporine and leflunomide. Immunopathologic studies have provided evidence of the central role exerted by TNF α in the pathogenesis of both PsA and psoriasis. ^{133,160} Based on this rationale the efficacy of anti-TNF α drugs has been evaluated in patients with PsA using different clinical outcome measures, including the ACR Response Criteria (including DIP and CMC joints), the Psoriatic Arthritis Response Criteria (PsARC) and the DAS. ^{133,161} The radiologic progression of the disease has been assessed using the modified Sharp score. ¹⁴ Moreover, in all studies the response

Table 2 Clinical response evaluated by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Assessments in Ankylosing Spondylitis Working Group (ASAS) response criteria scores in randomized controlled trials of anti-TNF α drugs in patients with ankylosing spondylitis

Author/ref.	Drug	Study duration (weeks)	Patient no.	Treatment arm patient no.	Control arm patient no.	Treatment arm BASDAI 50% improvement	Control arm BASDAI 50% improvement	P value	Treatment arm ASAS 20/50/70 (%)	Control arm ASAS 20/50/70 (%)	P value
Braun et al ³⁴	IFX	12	70	35	35	53%	9%	<0.0001	71/50/20	24/7/1	<0.0001
Van der Heijde et al ³⁵	IFX	24	279	201	78	51%	11%	<0.001	61/47/22	19/12/1	<0.001
Gorman et al ³⁶	ETN	16	40	20	20	80% ^a	30%	0.004	NA	NA	
Brandt et al ³⁷	ETN	24	30	14	16	57%	6%	0.004	79/43/33	25/12.5/0	<0.01
Davis et al ³⁸	ETN	24	277	138	139	See legend ^b	See legend ^a	<0.0001	57/40/21	22/8/2	<0.0001
Calin et al ³⁹	ETN	12	84	45	39	See legend ^b	See legend ^a	<0.0001	60/49/24	23/10/10	<0.001
Van der Heijde et al ⁴⁰	ETN	12	356	305	51	60%	20%	<0.001	71/68/59	39/22/20	<0.05
Van der Heijde et al ⁴¹	ADA	24	315	208	107	42%	15%	<0.001	45/39/22	12/13/6	<0.001
Inman et al ⁴²	GOL	24	356	278	78	46%	15%	<0.001	60/43/42	22/15/11	<0.001

^aData on percentage of patients achieving BASDAI 50% improvement are not available. The significance between study drug and placebo arms was calculated by the difference of change of BASDAI score from baseline.

Abbreviations: IFX, infliximab; ETN, etanercept; ADA, adalimumab; GOL, golimumab; NA, not available.

of skin disease has been evaluated with the Psoriasis Area and Severity Index (PASI).¹⁶²

The anti-TNF α agents approved for use in PsA and psoriasis include etanercept, infliximab, adalimumab, and golimumab.

A 24-week phase III trial of infliximab, 200 PsA patients unresponsive to previous therapies were randomized to receive infliximab 5 mg/kg or placebo.¹⁶³ An ACR 20 response was recorded in 54% of patients in the active drug arm and in 16% of patients in the placebo arm ($P < 0.001$). ACR 50 and ACR 70 responses were observed in 36% and 15% of the infliximab group and in 4% and 2% of placebo ($P < 0.001$ for both comparisons), respectively. Compared to placebo arm, the reduction of PASI was also significant ($P < 0.001$). The extension phase of this study confirmed the durable efficacy of the drug after 2 years and its disease-modifying action, with a significant reduction of radiological disease progression.^{164,165} Similar results were obtained in 2 RCTs of etanercept,^{166–168} in 1 trial of adalimumab,^{169,170} and in 1 of golimumab.¹⁷¹

To summarize, anti-TNF α enabled good control of PsA clinical manifestations, with inhibition of disease progression and marked improvement of psoriasis. Moreover, in patients with peripheral disease, anti-TNF α induce the disease clinical remission in up to 25% of patients.¹⁷² These drugs have also been demonstrated to be cost-effective in the treatment of PsA.¹⁷³

Conclusion

Overall, biologics have had a great impact on the therapy of RA, AS and PsA. They effectively control symptoms and change the clinical course of these diseases by inhibiting joint damage and greatly improving patient quality of life. Importantly, data from RCTs and post-marketing surveillance confirm the good safety profile of these agents.

Disclosures

The authors disclose no conflicts of interest.

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