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REVIEW ARTICLE

Aspects of TNF inhibitor therapy in rheumatoid arthritis

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Abstract Treatment outcomes in rheumatoid arthritis (RA) have improved considerably with the use of biological therapies. Since the discovery of the role of tumor necrosis factor (TNF) alpha in the pathogenesis of the disease, three TNF inhibitors, infliximab, etanercept and adalimumab, have become widely used for the treatment of RA. More recently, two newer TNF inhibitors—certolizumab pegol and golimumab—have become available, increasing the armamentarium of therapy. With improved therapies, treatment strategies have also changed, with the aims now being to achieve and maintain remission. This article addresses some of these aspects of treating RA, reviewing the studies on these two newer TNF inhibitors, certolizumab pegol and golimumab, and those addressing the induction of remission or low disease activity with TNF inhibitors and maintenance with less intensive treatment.

Keywords Certolizumab · Remission · Rheumatoid arthritis · Golimumab · TNF inhibitor

Introduction

Treatment of rheumatoid arthritis (RA) has been revolutionised by the use of biological therapies. The discovery of the role of cytokines, in particular tumor necrosis factor (TNF) alpha, in the pathogenesis of RA has pioneered the 'bench to bedside' development of the first TNF inhibitor, infliximab (IFX), in the 1980s. Since then, there have been major advances in the understanding of the disease itself and the development of newer biological agents and novel strategies for treating RA. This article addresses some of the recent advances in TNF therapy in RA, including therapy involving the two newer TNF inhibitors, golimumab and certolizumab, as well as various aspects of RA treatment strategies.

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Immunology

Tumor necrosis factor alpha (TNF-α) is a cytokine that is central to the inflammatory cascade. It has pleiotropic effects driving the immune response, with powerful modulatory effects on many aspects of cellular and humoral immunity [1, 2], and plays an important role in the persistence of early RA [3]. These functions include cell activation, cell proliferation and cytokine and chemokine production as well as the sequelae of these functions, such as cell recruitment, inflammation, immune regulation, angiogenesis and extracellular matrix degradation. Effects on cartilage and bone erosion are due to the TNF-driven production of matrix-degrading enzymes and osteoclastogenic factors, such as RANKL [4].

Newer TNF inhibitor therapies

There are currently three established TNF inhibitors—infliximab, a chimeric monoclonal antibody, adalimumab, a fully human monoclonal antibody and etanercept, a soluble receptor antibody. Two newer monoclonal antibodies targeting TNF have been developed and marketed recently, golimumab and certolizumab pegol, adding to the armamentarium of biological therapies available for patients with RA.

Golimumab (GLM), a fully human monoclonal antibody, binds both soluble and transmembrane TNF, thereby preventing binding to TNF receptors and inhibiting TNF activity. This full-length bivalent immunoglobulin G monoclonal antibody is administered by subcutaneous injections (50 or 100 mg) every 4 weeks.

Certolizumab (CZP) is a humanised monovalent Fab antibody fragment covalently linked to polyethylene glycol (PEG). Partly because of its structure, it has a different mechanism of action and kinetics to other TNF inhibitors [5]. The PEG portion is a bulky hydrophilic inert molecule that increases the plasma half-life of the drug. Because it has no Fc region, it does not activate complement or initiate complement-dependant cell lysis or antibody-dependant cytotoxicity in vitro or kill cells with membrane-bound TNF. The recommended dose for adults with RA is 400 mg (given as two subcutaneous injections of 200 mg) initially and at weeks 2 and 4, followed by 200 mg every other week.

Three randomised double blind controlled trials of CZP and four recent GLM studies have evaluated the efficacy and safety of these biological agents for treating RA patients. These studies will be outlined in the following sections; those those with outcome measures reported at 6 months are summarised in Table 1.

Certolizumab pegol

Two randomised controlled studies, RAPID 1 [6] (982 patients) and RAPID 2 [7] (619 patients) have assessed the efficacy of CZP in methotrexate (MTX) non-responders. The drug formulation in the two studies differed, with patients in RAPID 1 [6] receiving lyophilised CZP and those in RAPID 2 [7] receiving a liquid formulation. In both studies, RA patients were randomised 2:2:1 to receive CZP 400 mg every 2 weeks for 4 weeks with a subsequent dose of 200 or 400 mg every 2 weeks, or given placebo. All patients continued background MTX therapy. Significant improvements were seen in clinical responses as well as in reduction in radiographic progression at week 24 in both studies and at week 52 in RAPID 2 (see Table 1). In RAPID 1, the American College of Rheumatology 20% improvement criteria (ACR 20) at 24 weeks were 58.8 and 60.8% for the CZP 200 and 400 mg groups, respectively, versus 13.6% in the placebo group ($p < 0.001$). The mean change from baseline in the modified Total Sharp Score (TSS) at 52 weeks was 0.4 and 0.2 Sharp units for the CZP 200 mg and CZP 400 mg groups, respectively, versus 2.8 Sharp units for the placebo group ($p < 0.001$ by rank analysis). Similarly, in RAPID 2, the ACR 20 responses at week 24 were 57.3 and 57.6% in the CZP 200 mg and CZP 400 mg groups versus 8.7% in the placebo groups ($p \leq 0.001$). Radiographic progression was also significantly less, with a mean change in modified TSS of 0.2 and −0.4 for patients receiving CZP 200 and 400 mg, respectively, versus 1.2 in those on placebo ($p \leq 0.01$ and $p < 0.001$ by rank analysis for the CZP 200 and 400 mg groups, respectively). Acceptable safety profiles were demonstrated, although higher incidences of infection and TB were reported in both trials.

In the 24 week FAST4WARD study [8] (220 patients) CZP 400 mg was administered subcutaneously every 4 weeks and compared to placebo in patients who had previously failed to respond to treatment with one or more disease-modifying antirheumatic drugs (DMARDs). Background DMARDs, including MTX, were discontinued. The ACR 20, 50 (50% improvement) and 70 (70% improvement) responses were 46, 23 and 6%, respectively, in the group receiving CZP versus 9, 4 and 0% in the placebo group. Significant and clinically meaningful improvements were also seen in patient-reported outcomes, including physical function [measured by the Health Assessment Questionnaire Disability Index (HAQ-DI)], quality of life [measured by the Health Related Quality of Life (HRQoL)] and fatigue scores.

Golimumab

The efficacy of GLM has been assessed in several different patient groups. In the GO-BEFORE [9] study, 637 patients with active RA who were MTX naive were randomised to receive MTX ($n = 160$), GLM 50 mg plus MTX ($n = 159$), GLM 100 mg plus MTX ($n = 159$) or GLM 100 mg monotherapy ($n = 159$). The primary endpoint was the percentage of patients achieving an ACR 50 response at week 24. Although the primary endpoint (ACR 50) by intention-to-treat analysis (ITT) was not achieved; the modified ITT analysis (excluding the three patients who were randomised but discontinued the study before receiving any treatment) showed that treatment with GLM 50 mg weekly plus MTX achieved a statistically greater response than treatment with MTX alone, namely, 40.5 versus 29.4%, respectively ($p = 0.038$).

In MTX incomplete responders, 172 patients in a phase II study of GLM [10] were randomised for the first 16 weeks to placebo, GLM 50 mg every 4 weeks, GLM 50 mg every 2 weeks, GLM 100 mg every 4 weeks or GLM 100 mg every 2 weeks. Background MTX treatment was continued. By week 16, 61% of the patients in the combination GLM plus MTX dose groups had achieved an ACR 20 compared to 37% of patients receiving placebo plus MTX ($p = 0.010$). After 16 weeks, patients on the placebo arm received IFX 3 mg/kg every 8 weeks. Patients on injections of GLM at 2-weekly intervals had the

Table 1 Randomised controlled trials of certolizumab pegol and golimumab in rheumatoid arthritis

Trial	Prior treatment	Treatment regimen	Number of patients	Disease duration (years)	Follow-up (months)	Clinical outcomes at 6 months				Radiographic outcome (mean change from baseline)	
						ACR 20	ACR 50	ACR 70	Remission (%) (DAS 28 < 2.6)	6 months	12 months
FAST4WARD, Fleischmann et al. [8]	DMARD IR	MTX + placebo	109	10.4	6	9.3	3.7	0			
		CZP 400 mg/4 weeks	111	8.7		45.5*	22.7*	5.5			
RAPID 1, Keystone et al. [6]	MTX IR	MTX + placebo	199	6.2	12	13.6	7.8	3.0		1.3*,b	2.8*,b
		CZP 200 mg/2 weeks + MTX	393	6.1		58.8*	37.1*	21.4*		0.2*,b	0.2*,b
		CZP 400 mg/2 weeks + MTX	390	6.2		60.8*	39.9*	20.6*		0.2*,b	0.4*,b
RAPID 2, Smolen et al. [7]	MTX IR	MTX + placebo	127	5.6	6	8.7	3.1	0.8	0.8	1.2[c]	
		CZP 200 mg/2 weeks + MTX	246	6.1		57.3*	32.5*	15.9	9.4	0.2**,c	
		CZP 400 mg/2 weeks + MTX	246	6.5		57.6*	33.1*	10.6	8.5	−0.4*,c	
GO-BEFORE, Emery et al. [9]	DMARD IR (MTX naive)	MTX + placebo	160	1.2	6	49.4	29.4		28.1		
		GLM 100 mg/4 weeks +placebo	159	1.8		51.6	32.7 (33.1[a])		25.2		
		GLM 50 mg/4 weeks + MTX	159	1.0		61.6	40.3 (40.5[a])		38.4		
		GLM 100 mg/weeks + MTX	159	1.3		61.6	36.5 (36.5[a])		37.7		
GO-FORWARD Keystone et al. [11]	MTX IR	MTX + placebo	133	6.5	6	27.8	13.5	5.3	6		
		GLM 100 mg/+placebo	133	5.9		35.3	19.5	11.3	12		
		GLM 50 mg + MTX	89	4.5		59.6*	37.1	20.20*	20.2		
		GLM 100 mg + MTX	89	6.7		59.6*	32.6	14.6	22.5		
GO-AFTER Smolen EULAR [15]	TNF IR	DMARD + placebo	155	8.65–9.8		16.8	5.2	5.2			
		GLM 50 mg/4 weeks + DMARD	153			34.00*	18.3*	18.3*			
		GLM 100 mg/4 weeks +DMARD	153			43.8*	20.3*	20.3*			

DMARD Disease-modifying antirheumatic drug, *MTX* methotrexate, *CZP* certolizumab pegol., *GLM* golimumab, *IR* incomplete response, *TNF* tumor necrosis factor, *ACR20* American College of Rheumatology 20% improvement criteria, *ACR50* ACR 50% improvement criteria, *ACR70* ACR 70% improvement criteria van der Heijde modification, *DAS28* Disease Activity Score using 28 joint counts

* $p < 0.001$ vs. MTX and placebo, ** $p \leq 0.01$ vs. MTX and placebo

[a] Modified intention-to-treat analysis

[b] Modified Total Sharp Score

[c] van der Heijde-modified Total Sharp Score

frequency decreased to once every 4 weeks, while patients receiving injections every 4 weeks continued with this dose through to 52 weeks. Increases in ACR 20, 50 and 70 responses at week 52 were seen in all patients groups on GLM.

The efficacy of GLM in patients with active RA despite stable dose MTX therapy has also been evaluated in the GO-FORWARD study [11]. In this study, 444 patients were randomised to receive MTX ($n = 133$), GLM monotherapy ($n = 133$), GLM 50 mg plus MTX ($n = 89$) or GLM 100 mg plus MTX ($n = 89$). The percentage of patients achieving the co-primary endpoints, an ACR 20 response at week 14 and change from baseline based on the HAQ-DI at week 24 was greater in the combination therapy group than in the group receiving MTX alone. At week 24, the ACR 20 responses were also significantly greater with combination therapy groups—59.6% in each of the GLM plus MTX groups versus 27.8% in that receiving MTX alone ($p < 0.001$) (Table 1).

Despite improved outcomes with established TNF inhibitors, namely, IFX [12], etanercept [13] and adalimumab [14], a percentage of RA patients continue to shown an inadequate response to therapy. In the GO-AFTER study [15], 1461 patients who had previously failed TNF inhibitor therapy were randomised to receive placebo ($n = 155$), GLM 50 mg ($n = 153$) or GLM 100 mg ($n = 153$); all groups continued treatment with their background DMARDs. The primary endpoint, the proportion of patients achieving ACR 20 responses at 14 weeks, was significantly greater in those receiving GLM than in those in the placebo group. Similarly, at week 24, ACR 20 responses were achieved in 34 and 43.8% in the GLM 50 mg and the GLM 100 mg groups, respectively, versus 16.8% in the placebo group ($p < 0.001$).

Both CZP and GLM have therefore been shown to be efficacious in patients with RA who have had an inadequate response to conventional DMARDs. Patients who have failed previous TNF inhibitor therapy have also achieved improved clinical outcomes with GLM therapy. Thus far, the safety profile of these two biological agents has been similar to those of the established TNF inhibitors, with vigilance required for infections, notably tuberculosis. Further information on their clinical safety will emerge from the long-term use of these therapies.

Treatment strategies

The recognition of the importance of early treatment and the use of drugs which target a specific area in the pathogenesis of RA has changed treatment goals to remission or at least a state of low disease activity. The COMET study [16], a randomised, double blind, parallel treatment trial comparing the combination of MTX and etanercept ($n = 274$) with MTX monotherapy ($n = 268$) in patients with active, early and moderate-to-severe RA, respectively, was the first to look at remission as the primary outcome. This study showed that remission was achievable in 50% of patients in the combination therapy group and in 28% in the MTX monotherapy group at 1 year (Fig. 1). Radiographic non-progression was achieved in 80% of patients receiving the combination therapy and in 21% of those with MTX monotherapy. Similar remission rates have been seen in other randomised controlled studies with TNF inhibitors in RA [14, 17].

With the ability to achieve remission or low disease activity, several studies have also addressed treatment strategies akin to those used in oncology, namely, induction with biologics and maintenance with less intensive therapies.

In a study by Quinn et al. [18], 20 DMARD-naive RA patients with a poor diagnosis were randomised to receive MTX monotherapy or combination therapy with MTX and IFX. Greater clinical responses were seen in the combination therapy group than in the MTX monotherapy group, with ACR 50 responses of 78 versus 40% and ACR 70 responses of 67 versus 30%, respectively. Patients in the IFX group developed fewer erosions, based on evaluation of the magnetic resonance imaging scans, at 12 months than those treated with MTX alone. At 1 year after the induction therapy had been stopped, response was sustained in 70% of the patients in the combination therapy group. Furthermore, the functional and quality of life benefits obtained by patients treated with IFX for 1 year

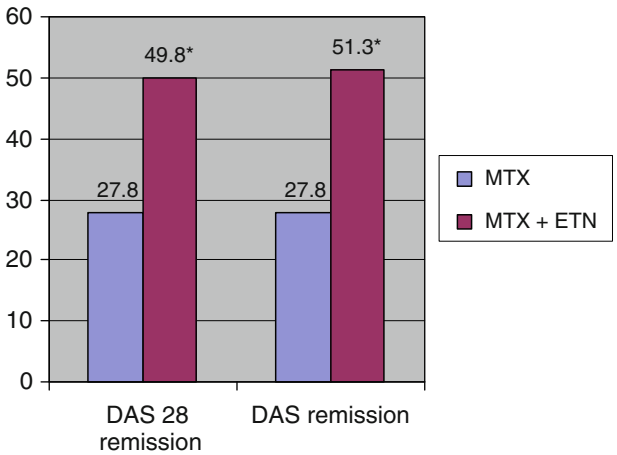

Fig. 1 Percentage of patients achieving remission according to the Disease Activity Score using 28 joint counts (*DAS28*) (primary endpoint) and remission (DAS28) at week 52 in patients receiving methotrexate (*MTX*) versus those receiving the combination therapy of MTX + etanercept (*ETN*) [16] ($p < 0.001$). Source: Presentation by P. Emery at the 2007 meeting of the American College of Rheumatology

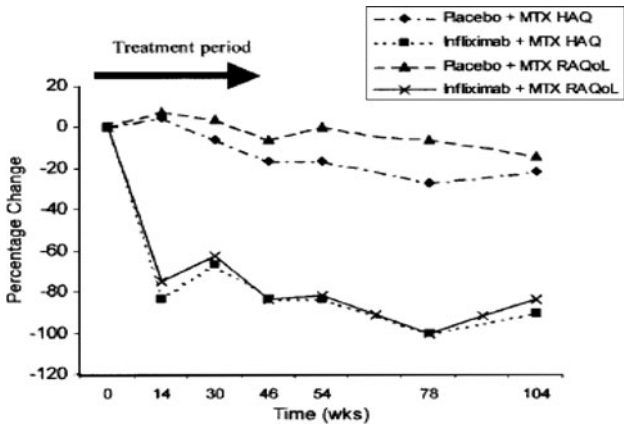

Fig. 2 Percentage change in the median functional and quality-of-life scores over time in RA patients with a poor prognosis. *HAQ* Health Assessment Questionnaire, *MTX*, methotrexate, *RAQoL* rheumatoid arthritis quality of life. Source: Quinn et al. [18]

were sustained at 2 years without further IFX infusion (Fig. 2).

In the BeST study, in which 508 patients with recent onset active RA were randomised into four treatment strategy groups, namely, (1) sequential monotherapy, (2) step up to combination therapy, (3) initial combination therapy with tapered high-dose prednisone and (4) initial combination therapy with IFX, respectively, treatment adjustments were made every 3 months to achieve a DAS ≤ 2.4; if remission was sustained for $\geq$6 months, treatment could be tapered and stopped [19]. An evaluation of the 3-year data from this study reveals that more patients in group 4 have been able to taper and stop all antirheumatic drugs and still maintain a state of remission (17%) than in the other groups (10, 5 and 9%, respectively) [20].

A post hoc analysis of the BeSt study compared the outcomes of 117 patients who started initial MTX + infliximab to those of 67 patients who started MTX + IFX after failing to respond to three or more conventional DMARDs (DAS > 2.4). The median delay to commencing IFX in the latter group was 13 months. The dose of IFX was escalated if the DAS remained >2.4; if the DAS was $\leq$2.4 for $\geq$6 months, the IFX dose was tapered and stopped. Three years after baseline, greater improvements in terms of the HAQ over time and less radiographic progression was seen in the group who received initial MTX and IFX compared to those who received the delayed combination therapy ($p = 0.034$). At 2 years after treatment start, more patients in the initial group than in the delayed treatment group could discontinue IFX after a good response (56 vs. 29%, $p = 0.008$) [21]. These results suggest that the earlier use of combination therapy with IFX resulted in a better HAQ improvement over time, a higher rate of IFX discontinuation and less progression of joint damage.

The ability to discontinue IFX after achieving low RA activity has also recently been studied in the remission induction by remicade in RA (RRR) study [22]. In this study, 114 RA patients who have received IFX therapy and whose DAS28 (erythrocyte sedimentation rate) remained <3.2 (low disease activity, LDA) for 24 weeks consented to discontinue IFX. The average disease duration was 6 years, and the mean DAS28 was 5.5 among all patients. Of the 102 evaluable patients at 1 year, 55% had maintained a DAS28 <3.2 (LDA) and remained off IFX, and 43% achieved a DAS <2.6 (remission) for >1 year after discontinuation of IFX. Disease duration was shorter and the DAS28 lower in the RRR-achieved group than in the RRR-failed group.

Conclusion

The use of biological therapy, including TNF inhibitors, has improved outcomes for patients with RA, with remission being an achievable goal. The availability of newer agents, including certolizumab and golimumab, has increased treatment options for patients with persistent disease activity. Earlier use of these drugs has also allowed rheumatologists to explore new treatment strategies. The potential to discontinue TNF inhibitor therapy after achieving remission is relevant from both clinical and economic perspectives. Much work has recently been done in the area of remission [23] with further research into factors that will predict sustained remission, including remission off TNF therapy, ongoing.

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