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TNF Inhibitor Therapy for Rheumatoid Arthritis

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Abstract

Immunotherapy has improved considerably the treatment outcomes in rheumatoid arthritis (RA). Tumor necrosis factor (TNF)-α antagonists have been widely used for the treatment of RA such as infliximab, etanercept, adalimumab and the recent two new TNF-α inhibitors - certolizumab pegol and golimumab. Infliximab, a chimeric monoclonal antibody, binds with high affinity and specificity to human TNF and cancels out its biologic activity. Etanercept is also monoclonal antibody, but it is a solute protein. Adalimumab is a recombinant human IgG monoclonal antibody specific for human TNF-α. Infliximab, when used in combination with methotrexate (MTX), provides significant, clinically relevant improvement in physical function and quality of life, inhibits the progressive joint damage, and sustains improvement in the signs and symptoms of patients with RA. Etanercept monotherapy is effective and safe for patients with RA. Combination therapy with etanercept and MTX reduces disease activity, decreases total joint score progression, slows the pace of joint destruction, and improves function more effectively than does either monotherapy. Adalimumab with or without MTX also relieves the signs and symptoms of RA. Certolizumab pegol and golimumab expand the therapeutic schedule for patients with RA. All the TNF-α inhibitors have similar efficacy in clinical treatment, but they have distinct clinical pharmacokinetic and pharmacodynamic properties that must be considered when selecting a drug for therapy. The common adverse events of these TNF-α antagonists include adverse reactions, infections, injection-site reaction and so on. And these adverse events are mostly mild or moderate and the incidence is low. Some patients show a lack of response to anti-TNF-α therapies, either due to the lack of drug efficacy or following the development of adverse events. These patients may discontinue the first drug and switch to a second anti-TNF-α agent. The shortage of clinical response to one agent may not predict deficiency of response to another. This review mainly addresses the latest development of these biological agents in the treatment of RA, including clinical efficacy, physical function, radiographic progression and adverse events.

Keywords: Rheumatoid arthritis; Immunotherapy; Biological agent

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by progressive joint destruction. As their joints deteriorating, patients suffer pain and loss of function, often accompany with decreasing quality of life and increasing mortality [1]. Depending on the severity of the disease at onset, the risk of disability can be as high as 30%, and mortality can be increased by as much as 52%, frequently as a result of infection or circulatory disease [2].

RA treatment aims to minimize disease activity thereby prevents or controls joint damage and diminishes the risk of other serious co-morbidities such as heart disease and stroke. It is absolutely necessary that early intervention in patients with confirmed RA to preserve joint function [3-5].

Non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids are used to control pain and inflammatory process [6]. After defined the diagnosis of RA, patients are given disease-modifying antirheumatic drugs (DMARDs), which reduce signs and symptoms of the disease, and can inhibit in radiographic progression [6]. While many RA patients do respond to DMARDs, a large proportion of RA remained active despite such treatments. The approach of targeting cytokines has dramatically improved the success in the treatment of RA. Five TNF-α inhibitors are available, infliximab, etanercept, adalimumab [7-10], golimumab and certolizumab pegol, in the clinical application.

This paper focuses on how these agents have developed in the aspect of their effects on symptoms (evaluated by American College of Rheumatology [ACR] response criteria), structure (in the light of the erosion, joint-space narrowing, and Sharp scores), and physical function (based on standardized questionnaires such as the Health Assessment Questionnaire [HAQ]).

Tumor necrosis factor-α antagonist

TNF-α is an important cytokine that mediates inflammation in RA. Elevations of TNF-α level have been observed in synovial fluid and the synovium of patients with RA [11]. TNF-α plays a very central role in driving a inflammation and associated bone degradation [12]. Because it has an influence on various cell in synovial membrane, such as synoviocytes, macrophages, chondrocytes and osteoclasts, which can produce metalloproteinas, collagenase, stromelysin and so on, result in local inflammation and pannus formation, eventually lead to further erosion of cartilage and bone destruction. Introduction of TNF-α inhibitors revolutionize RA treatment options and bring about the development of further biologic DMARDs [13]. The effects of a TNF-α blockade are partially dependent on synovial TNF-α expression and in filtration by TNF-α-producing inflammatory cells [14]. The progress of biotechnology contributes to the development of biological agents such as anti-TNF-α monoclonal antibodies as a strategy for the treatment of chronic inflammatory disease.

Infliximab

Infliximab is a recombinant IgG1 monoclonal antibody specific for TNF-α, which hinders the cytokine from triggering the cellular TNF receptor complex [15]. Infliximab must be given by intravenous

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infusion and has a terminal half-life of 8 to 10 days. Hence it is administered every 4 to 8 weeks and the dosage lies between 3 to 5 (to 10) mg/kg.

The efficacy of infliximab with MTX has been demonstrated in several trials (Table1). Patients receiving combination therapy achieved obviously higher median improvements in ACR-N than those in the MTX plus placebo group [16-18]. In addition, the clinical efficacy is similar in different dosage of infliximab group [16-18]. In terms of radiographic image, the combination of infliximab and MTX prevented the radiographic progression and led to lasting clinical amelioration [16]. Infliximab treatment inhibited progression of joint damage even in patients take low of MTX in the RISING study [18]. Compared with the MTX-only-treated patients, both erosions and joint space narrowing obviously reduced from baseline in the infliximab plus MTX-treated patients except infliximab 3 mg/kg every 8 weeks. There were fewer newly eroded joints per patient in the infliximab plus MTX treatment groups than in the MTX-only group [17]. The studies by St Clair EW illustrated that HAQ scores accelerated more in the group conducted infliximab than in the group receiving MTX alone [16].

The most common adverse events found in clinical trials of infliximab included infusion reactions, infection. The therapy of infliximab might increase the risk of malignancies tumors and cardiovascular [19]. The incidence of serious infections, acute infusion reactions, and death was similar between patients treated with infliximab plus MTX and those adopted MTX only [17]. Among the serious infections, pneumonia, tuberculosis occurred more frequently in the infliximab-treated patients than in those treated with MTX alone [16,19].

Etanercept

Etanercept is a genetically engineered protein consisting of two molecules of the extracellular domain of TNF receptor II (p75) and the Fc portion of IgG1 [20]. Owe to its half-life of approximately 3-5.5 days, etanercept is administered subcutaneously (s. c) either weekly (50mg) or twice a week (25mg) [21].

The superiority of the combination therapy of etanercept plus MTX over etanercept or MTX monotherapy in patients with RA has been demonstrated (Table 2) [22-24]. The 2-year data from the TEMPO study confirmed that apparently larger proportion of patients treated with combination therapy achieved the clinical response than that receiving either monotherapy [22]. Moreover, the combination-treated patients had predominantly lower erosion change scores (-0.67) than patients treated with etanercept alone (0.39) or MTX alone (3.25) [25]. Therefore, treatment with a combination of etanercept and MTX halted joint damage and patients achieved disease remission [25]. Sustained efficacy and decreased rate of radiographic progression gained in patients with early aggressive RA who use long-term treatment with etanercept [26]. Patients adopted combination therapy enhanced greatly in function status than in group of monotherapy [27]. Additionaly, etanercept 50 mg once weekly is an optimal in most patients with RA. Increasing the dosage of etanercept from 50mg once a week to 50 mg twice a week in suboptimal responders did not dramatically improve response rates [28]. There was no obvious improvement between etanercept as monotherapy at 50 mg twice weekly and 25 mg twice weekly with regard to the safety and efficacy [29].

Injection-site reactions and hypertension were more common with etanercept than with MTX or with combination therapy [22]. These events were mostly mild or moderate. Nausea and vomiting were more often concerned with MTX than with etanercept or combination therapy. No significant differences were seen among the groups in the incidence of serious adverse events (infectious and noninfectious) [22].

In summary, etanercept was benefit for patients with RA. But the combination of etanercept with MTX is superior to a montherapy with each drug. The combination regimen can reduce disease activity, slow radiographic progression and improve function. Furthermore, the treatment with etanercept plus MTX was well-tolerated and did not increase serious adverse events.

Adalimumab

Adalimumab is a monoclonal antibody of recombinant immunoglobulin (IgG1) containing only human sequences of peptides. It is an antagonist of TNF, which prevent the binding of TNF-α to its receptors [6]. It has a half-life of 10–20 days and can be used as monotherapy or in combination with several other DMARDs, preferably MTX [30,31]. The recommended dose of adalimumab is 25 mg s. c twice a week.

Treatment with adalimumab plus MTX was found to be statistically superior to placebo plus MTX according to the ACR20/50/70 response rates at week 26 (Table 3) [32]. If patients received

First author	Groups	Disease duration	ACR20	ACR50	ACR70	vdH-S score (Mean + SD)
St.Clair EW et al. [16]	IFX 3mg/kg + MTX IFX 6mg/kg + MTX Placebo + MTX	54week	62.4 66.2 53.6	45.6 50.4 32.1	32.5 37.2 21.2	0.4 ± 5.8 0.5 ± 5.6 3.7 ± 9.6
Maini RN et al. [17]	IFX 3mg/kg + MTX q8week q4week IFX10mg/kg + MTX q8week q4week Placebo + MTX	102week	 42 40 48 40 16	 21 30 36 20 6	 10 21 20 10 1	 1.02 ± 7.13 1.03 ± 11.65 1.14 ± 4.92 -0.42 ± 6.10 12.59 ± 20.05
Takeuchi T et al. [18]	IFX 3mg/kg + MTX IFX 6mg/kg + MTX 10mg/kg + MTX	54week	75.8 78.8 82.7	60.6 58.7 66.3	37.4 42.3 43.3	

IFX = infliximab; MTX = methotrexate; ACR = American College of Rheumatology; vdH-S = van der Heijde modification of the total Sharp score.

Table1: Comparison of clinical and radiographic response to infliximab plus MTX.

First author	Groups	Disease Duration	ACR20	ACR50	ACR70	DAS28 <2.6(%)	TTS (mean)
Van der Heijde D et al. [22]	ETN + MTX ETN MTX	100 week	86 75 71	71 54 42	49 27 21	42.4 22.4 18.9	-0.56 1.10 3.34
Kavanah A et al. [23]	ETN + MTX ETN MTX ETN + MTX ETN MTX	24 week 54 week	 81,0 70.8 62.2	 83.8 88.5 50.0	 82.6 66.7 63.2		 -1.35 -0.19 2.82
Kameda H et al. [24]	ETN + MTX ETN	24 week	90.4 63.8	64.4 47.8	38.4 26.1	27.4 10.1	

ETN = etanercept ; DAS = Disease Activity Score; DAS28 = DAS in 28 joints; TTS = Total Sharp Scores

Table 2: Comparison of clinical and radiographic response to etanerceptplus MTX and monotherapy.

adalimumab+MTX in early RA, they would achieve rapid clinical and functional improvements [32]. Adalimumab regimens decreased risk of radiographic disease progression [33]. In an open-label extension study of 5 years, the addition of adalimumab led to greater inhibition of structural damage compared with patients who continued with MTX monotherapy (Table 3) [34]. The PREMIESR study confirmed that treatment with adalimumab plus MTX is initiated early, it contribute to higher improvements in clinical, functional, and radiographic responses as compared with the treatment with MTX alone or adalimumab alone [35].

In addition, adlimumab plus MTX ameliorated physical function for patients with RA [33,36].

Adalimumab had good tolerance generally. The research demonstrated that the rate of adverse events (both serious and nonserious) was similar in the adalimumab and placebo groups, although the proportion of patients reporting serious infections was higher in patients receiving adalimumab (3.8%) than that in placebo (0.5%) (P<0.02), and was the highest in the patients adopted 40mg every other week [33]. The common adverse events were injection site reactions, serious infections such as military tuberculosis, cellulitis [35]. However, adalimumab were safe and well tolerated. These adverse events were not serious and severe side effects were relatively seldom.

Golimumab

Golimumab is a human anti-TNF-α monoclonal antibody that was generated and affinity matured in an in-vivo system [37]. Golimumab has a high affinity and specificity for human TNF-α and effectively neutralizes TNF-α bioactivity in vitro [38].

The efficacy of golimumab had been testified in several different groups (Table 4) [37,39,40]. The combination of golimumab and MTX was significantly better at improving the signs and symptoms of RA and physical funcion [37]. The differece weren't observed in the efficacy of the two golimumab dose group (50 mg and 100 mg) [37]. Though compared individually with the pacebo group, the golimumab in combination with MTX in patients with RA showed greater clinical response , the response rates did not displayed a clear dose-response pattern among the group of golimumab plus MTX (Table 4) [39].

In the multicenter, randomized, placebo-controlled GO-FORWARD study, mean improvement from baseline in HAQ-DI was significantly greater for golimumab 50mg+MTX and 100mg+MTX versus placebo+MTX [41]. On the other hand, golimumab+MTX also elicited a significant better response than placeo+MTX in other efficacy parameters, including disease activity score (DAS28) response. And the combination of golimumab and MTX limit radiographic progression [42].

The safety of golimumab has been demonstrated in different trials. However, adverse events were reported in the process of treatment. The most frequent adverse events in the combined golimumab groups were nausea, headache, and injection sit reaction. Most events were mild or moderate in severity [43].

In general, golimumab, in combination with MTX, can alleviate the signs and symptoms of RA and improve physical function.

Certolizumab pegol

Certolizumab pegol is a humanized anti-TNF-αantibody with high affinity to TNF [44]. In managing patients with RA, the recommended dose of certolizumab pegol is 400 mg (given as two subcutaneous injections of 200 mg) initially and at week 2 and 4, followed by 200 mg every other week.

An international, multicentre, phase 3, randomized, double-blind, placebo-controlled study has assessed the efficacy of certolizumab pegol in MTX non-responders [45]. Compared to placebo treatment, certolizumab pegol plus MTX effectively reduced the signs and symptoms of RA, and inhibited progression of joint damage (Table 5) [45-46] .There were no obvious differences in clinical efficacy between the two certolizumab pegol dose groups [45]. Additionally, treatment with certolizumab pegol monotherapy also provided a rapid, meaningful and durable clinical response and and acceptable dafety profile (Table 5) [47]. Increasing the certolizumab pegol dose from 200 to 400 mg did not give rise to an additional benefit in RA [48]. A research showed that the mean tender joint count (-24.8 versus -24.6) or swollen joint count (-18.6 versus -18.7) was similar between the dose-escalation (200 mg increased to 400 mg every other week) and stable-dose subgroups (400 mg every other week) [49]. The most common adverse reactions included tuberculosis, injection site pain and injection site reaction [46].

As shown above, certolizumab pegol monotherapy or the combination therapy with MTX as an effective treatment provides a rapid, meaningful and durable clinical response and an acceptable safety profile.

Similarity and difference between anti-TNF agents

As is well known, patients with RA have low quality of life. Clinical trials have shown that TNF-α blocking agents, such as etanercept,

First author	Groups	Disease Duration	ACR20	ACR50	ACR70	DAS28 <2.6(%)	TTS (mean ± SD)
Kavanaugh A et al. [32]	ADA + MTX PBO + MTX	Week 26	70 57	52 34	35 17	34 17	
Keystone EC et al. [33]	ADA40mg + MTX ADA20mg + MTX Placebo + MTX	Week 52	58.9 54.7 24.0	41.5 37.7 9.5	23.2 20.8 4.5		0.1 ± 4.8 0.8 ± 4.9 2.7 ± 6.8

ADA = adalimumab

Table 3: Comparison of clinical and radiographic response to adalimumab plus MTX and monotherapy.

First author	Group	Disease Duration	ACR20	ACR50	ACR70	DAS28 (mean ± SD)
Keystone EC et al. [37]	GOLI 50mg + MTX GOLI 100mg + MTX GOLI100mg + placebo Placebo + MTX	Week 24	59.6 59.6 35.3 27.8	37.1 32.6 19.5 13.5	20.2 14.6 11.3 5.3	
Kay J et al. [39]	GOLI + MIX 50mg (every 4 weeks) 50mg (every 2weeks) 100mg (every4 weeks) 100mg (every2 weeks) Placebo + MTX	Week 16	 60.0 50.0 55.9 79.4 37.1	 37.1 23.5 29.4 32.4 5.7	 8.6 14.7 17.6 8.8 0.0	 -1.9 ± 1.3 -1.4 ± 1.3 -1.9 ± 1.5 -1.9 ± 1.1 -0.9 ± 1.0
Weinblatt ME et al. [40]	GOLI 2mg/kg + MTX Placebo + MTX	Week16	58.5* 24.9	34.9 13.2	17.7 4.1	-2.0 ± 1.40 -0.7 ± 1.35

GOLI = golimumab; *ACR20 responses was observed at week 14

Table 4: Comparison of clinical and radiographic response to golimumab plus MTX and monotherapy.

infliximab, and adalimumab, relieve joint inflammations and slow radiographic progression of joint damage, and improve physical function in advanced RA [50-52]. The availability of newer agents, including certolizumab pegol and golimumab, has increased treatment options for patients with RA. Furthermore, anti-TNF-α agents are more efficacious in promoting the clinical signs and symptoms of RA than MTX alone. Anti-TNF-α agents plus MTX show sustained efficacy and remain more effective than ant-TNF-α monotherapy [53]. Compared with MTX and placebo, the ACR20,50,70 response rates for 1-year treatment with MTX plus any of the TNF inhibitors were 60% versus 25%, 40%versus 10%, and 20% versus 5%,respectivly [54].

However, they have distinct clinical pharmacokinetic and pharmacodynamic properties that must be considered when selecting a drug for therapy [55]. For example, there are obvious differences in the half-lives of the three agents (infliximab, etanercept, adalimumab), with etanercept having the shortest 3-5.5 days and adalimumab having the longest, 2 weeks [21]. Three kinds of biological agents also vary from each other in their dosing regimens [55]. The larger but less frequently administrated dose of infliximab may result in higher peak serum concentrations compared with the smaller but more commonly administrated doses of etanercept and adalimumab, giving rise to higher tissue concentrations [55]. Total efficacies of different biologics were very similar, which have been observated in most of studies and been accepted by many scholars [55]. Nevertheless a recent research indicated that there were significant difference in the efficacy of and adherence to therapy with adalimumab, etanercept, and infliximab [56]. Infliximab had the lowest treatment responsers, disease remission rates, and drug adherence rates. Adalimumab had the highest treatment responses and remission rates, while etanercept had the longest drug survival rates [56] (Table 6).

According to Singh's report [57], patients giving adalimab and infliximab were at remarkably bigger risk versus placebo. Indirect companies revealed that adalimumab was more tend to withdrawls rather than etanercept (OR 1.89, 95%CI 1.18 to 3.04) and etanercept was less likely than infliximab (OR 0.37, 95%CI 0.19 to 0.70). Additionally, there seem to be differences in the risk of tuberculosis (TB) among different biologics, and this might influence which patients went on to receive the biological agent. TB occurred more frequently in monoclonal antibodies-treated patients (that is, infliximab and adalimumab) than in those treated with soluble TNF receptor therapy (that is, entanercept) [58,59]. Additionally, the rate of hospitalised infection for patients treated with other agents was less than for infliximab [60]. Among these biology, the incidence of serious infections was higher in certolizumab pegol group than others. Adalimumab, etanercept and golimumab were associated with a low incidence of treatment discontinuation because of adverse events, while the infliximab was not that [61]. Moreover, all biologic agents increased the risk of infections. So patients should be excluded tuberculosis and should receive pneumococcal, influenza, and hepatitis B vaccinations before they accept the therapy of biologic agents.

Switching between different anti-TNF agents

The patients may discontinue the first drug and switch to a second anti-TNF-α agent because of shortage of drug efficacy. How is the effect of the second biological agents? In a retrospective study [62], some patients (n=20) switch from etanercept to infliximab and some patients (n=73) treated infliximab with no prior TNF therapy. The C-reative protein, swollen and tender joint count, morning stiffness ameliorated in both groups, and there was no statistical difference in the degree of benefit between the groups [62]. On the other hand, infliximab may provide additional clinical profit for patients with an incomplete response to etanercept. Especially, patients taking infliximab revealed better amelioration in HAQ score than those receiving etanercept (Table 7) [63].

Another research concluded that patients switching to adalimumab had a good clinical response when the therapy of infliximab or etanercept was ineffective [64]. Patients who do not respond to a first anti-TNF drug may also subsequently gain improvements in HAQ score, if switch to a second agent [65]. Patients with RA may be successfully treated with another TNF-α agent, especially those withdrawing for inefficacy and adverse events [66].

The above result revealed that it was useful in switching among different biologic agents.

Conclusion

Biological agents make the treatment of RA into a new era, especially for patients with an insufficient response to DMARDs. Moreover, the strategies target IL-6, IL-1, T cell and B cell, which broaden our

First author	Group	Disease Duration	ACR20	ACR50	ACR70	mTSS (mean)	DAS28 (mean(SD))
Smolen J et al [45]	CZP200mg + MTX CZP400mg + MTX Placebo + MTX	Week24	57.3 57.6 8.7	32.5 32.5 33.1	15.9 10.6 0.8	0.2 -0.4 1.2	-2.27 (1.38) -2.46 (1.31) -0.50 (1.05)
Keystone E et al [46]	CZP200mg + MTX CZP400mg + MTX Placebo + MTX	Week24	58.8 60.8 13.6	37.1 39.9 7.6	21.4 20.6 3.0		-3.3 ± 1.3 -3.4 ± 1.4 -2.4 ± 1.3
Fleischmann R et al [47]	CZP 400mg Placebo	Week 24	45.4 9.3	22.7 3.7	5.5 0.0		-1.5 -0.6

CZP = certolizumab pegol

Table 5: Comparison of clinical and radiographic response to golimumab plus MTX and monotherapy.

	Aadlimumab		Etanercept		Infliximab		P	
	6 months	12 months	6 months	12 months	6 months	12 months	6 months	12 months
EULAR response No. of patients Good Moderate No response	 536 52 33 15	 444 57 30 15	 414 42 39 19	 377 49 39 19	 889 34 38 29	 690 40 39 21	 <0.0001 <0.0001	
DAS28 remission No. of patients Remission LUNDEX corrected	 536 32 26	 444 39 27	 377 33 24	 889 21 17	 690 27 16	 690 27 16	 <0.0001	 <0.0001
ACR response No.of patients ACR50 ACR70	 519 45 24	 426 53 30	 346 45 27	 852 31 14	 852 31 14	 660 38 17	 <0.0001 <0.0001	 <0.0001 <0.0001

EULAR = European League Against Rheumatism

Table 6: Clinical responses after 6 months and 12 months of treatment: values the percent.

Clinical end point	Infliximab	Etanercept
ACR20 response,%	61.5	28.6
ACR50 response,%	30.7	14.3
DAS28		
Mean(SD)	4.0 (1.5)	5.2 (1.6)
% change from baseline	-30.8 (28.6)	-16.0 (24.2)
Patients with DAS28 score<2.6, %	15.4	7.1
Patients with HAQ decrease>0.22, %	61.5	14.3
Patients with HAQ decrease>0.40, %	38.5	0.0

28 patients with an inadequate response to etanercept were randomized 1:1 to discontinue etanercept and receive infliximab 3 mg/kg at weeks 0, 2, 6, 14 and 22, or to continue etanercept 25 mg twice weekly (patients received background methotrexate). Efficacy results at week 16.

Table 7: Switching between different anti-TNF agents.

idea of the therapy on RA. Biological agents can quickly relieve clinical symptoms and delay the bone destruction. When the TNF-α inhibitors apply to clinical practice, the combinations with DMARDs are conducive to ease the symptoms and prevent the bone structural damage and elevate physical function. Besides, the conversion between different agents can reach the same function. Some drugs, such as etanercept, in combination with MTX were better than monotherapy in the long-term efficacy. A higher dosage of certain agents, etanercept, anakinra, rituximab, abatacept, appears to have a better clinical efficacy. Most adverse events of agents are infection-site reactions. Thought large side-effect can be cured by appropriate treatment, they still prevent the clinical remedy. As physicians, we should not only prescribe different treatment according to the patient's symptoms but also need to constantly explore the immune mechanism of RA, and develop new biological agents. In the future, immunotherapy will bring fundamental changes for the patients with RA.

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