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Review

Clinical application and evaluation of anti-TNF-alpha agents for the treatment of rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic progressive autoimmune disease that dramatically impairs quality of life. A number of compounds are available to treat RA, but they vary in effectiveness. Thus, no optimal treatment strategy has been defined. Currently, disease-modifying anti-rheumatic drugs (DMARDs) and anti-tumor necrosis factor-alpha (anti-TNF-α) agents are considered the treatments of choice. For patients with inadequate responses to DMARD therapy, one recommended therapeutic alternative is anti-TNF-α therapy. Anti-TNF-α agents are effective and have rapid onset of action compared with DMARDs. Elucidating the differences in effectiveness of anti-TNF-α compounds has important clinical implications. By comparing the efficacy, safety and use principle of different treatment options, this review focuses on providing important information about three anti-TNF-α compounds (etanercept, infliximab, and adalimumab) to help define optimal treatments for RA patients.

Keywords: rheumatoid arthritis; anti-tumor necrosis factor-alpha; etanercept; infliximab; adalimumab; methotrexate

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Introduction

Rheumatoid arthritis (RA) is a chronic progressive autoimmune disease that is related to erosion of articular cartilage and subchondral bone, deformity, and impaired quality of life[1]. Disability and joint damage occur rapidly and early in the course of RA[1]. With the development of biologics, all of this can be achieved to some extent. Biologics such as interleukin 1 (IL-1) receptor antagonists (anakinra) and anti-tumor necrosis factor-α (anti-TNF-α) agents (etanercept, infliximab, and adalimumab) are generally well tolerated.

Among these biologics, TNF-α inhibitors have been used successfully to treat RA patients. Anti-TNF-α therapy leads to substantial functional improvement in the vast majority of patients and down-regulates inflammatory cytokines stimulated by TNF-α. The use of methotrexate (MTX) in combination with three such agents has dramatically improved the treatment of severe RA[2–6]. Studies have established that combination therapy can provide greater therapeutic benefits than single-drug regimens. Due to the safety and efficacy of combination therapy, various combination therapies are widely used in the treatment of RA patients. Clinical trials, however, indicate that a significant number of RA patients do not respond to these therapies. With the increased number of therapeutic options, the optimal therapeutic strategy for RA patients needs to be defined. This review describes the efficacy and safety of different anti-TNF-α-based therapies and investigates the optimal therapeutic strategy to help optimize everyday clinical practice. The American College of Rheumatology (ACR) efficacy response criteria is used to assess clinical response. This review analyzes the ACR response rates [20% (ACR20), 50% (ACR50), and 70% (ACR70), respectively] of different therapeutic strategies against RA.

The properties of three anti-TNF-α agents

TNF-α is a cytokine that plays an important role in joint inflammation. The effects of a TNF-α blockade are partially dependent on synovial TNF-α expression and infiltration by TNF-α-producing inflammatory cells[7]. Infliximab, etanercept and adalimumab have been available since 1999[8]. They bind and block TNF-α by different mechanisms, and etanercept additionally binds to lymphotoxin[9]. Despite their quite short histories, many studies have been published concerning these agents. Anti-TNF-α therapy leads to substantial functional improvement in the vast majority of patients and down-regulates inflammatory cytokines stimulated by TNF-α. The basic properties of infliximab, etanercept and adalimumab, which are typically used to treat RA, are briefly described in Table 1. The mechanisms of action, efficacy and safety of these com-

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Table 1. Basic properties of infliximab, etanercept and adalimumab.

Drug	Molecular structure	Dosage	Administration route	Adverse effects
INF	Chimeric monoclonal antibody	3 mg/kg/8 week administered at weeks 0, 2, 6, and 8 and every 8 weeks thereafter	Intravenous	Severe infection; injection site reaction; hypotension; headache
ADA	Humanized monoclonal antibody	40 mg every 2 weeks	Subcutaneous	Infection; tuberculosis, malignancy; serious infection; demyelinating disease, SLE
ETA	Fusion protein of soluble TNF receptor and Fc portion of immunoglobulin	25 mg twice a week	Subcutaneous	Nausea; abdominal; pain; injection reaction; headache; back pain; increased cough; vomiting; asthenia; arthralgia; hypertension; rash; diarrhea; pain

INF: infliximab; ADA: adalimumab; ETA: etanercept

pounds have been demonstrated in clinical trials, which allow physicians to use them more effectively.

The efficacy, drug continuation rates and safety of infliximab have been assessed in trials[2, 9–11]. The mechanism of action of infliximab is shown in Figure 1. Infliximab should be used in patients with active disease who have not responded adequately to at least two disease-modifying anti-rheumatic drugs (DMARDs) including MTX (unless contraindicated)[12]. Frequently administered doses of infliximab may result in high peak serum concentrations[9]. Patients receiving infliximab are more likely to discontinue therapy because of side effects, which are occasionally severe, as well as infections and infusion reactions[8]. However, infliximab has been found to have a relatively acceptable toxicity profile[3]. Characteristics of infliximab that may influence patient persistence include a preferred administration method and less frequent needle sticks compared with subcutaneous agents[13].

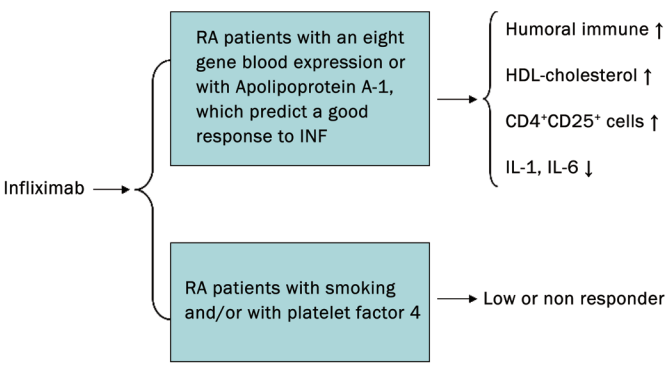

Figure 1. The mechanism and impact of infliximab.

Treatment of RA with infliximab is thought to induce the humoral immune response against organ-specific or non-organ-specific antigens in RA patients[10] and inhibit IL-1 and IL-6 gene expression in human osteoblastic cells[14]. Anti-inflammatory therapy with infliximab improves HDL-cholesterol anti-oxidative capacity in RA patients[2]. Research indicates that smoking has a negative effect on RA patients treated with infliximab[15]. Analysis of whole blood gene expression profiles of RA patients can be used to build a robust predictor of the response to infliximab therapy, in which an eight-gene blood expression profile predicts the response to infliximab in RA patients. For example, a significantly higher number of CD4+CD25+ cells were found in the responder group compared to the non-responder group at baseline[16]. Apolipoprotein A-1 was predictive of a good response to infliximab, whereas platelet factor 4 was associated with non-responders[17].

Adalimumab exerts its therapeutic effects by blocking the interaction of TNF-α with the p55 and p75 receptors[18] and decreasing mean white blood cell counts, platelet counts, and neutrophil percentages[4]. Responses to adalimumab are rapid, with 22.2% of patients achieving an ACR20 response within 24 hours[19]. After 52 weeks of administration, patients did not develop new erosions and suffered lower rates of radiographic progression[4]. Adalimumab is effective and well tolerated not only in RA patients that were previously treated with etanercept and/or infliximab[20] but also in difficult-to-treat patients with active RA[5]. Adalimumab is very effective at inhibiting the progression and reducing the signs and symptoms of structural joint damage. Adalimumab improves physical function in active RA patients who previously had an incomplete response to MTX[4]. Patients receiving adalimumab are more likely to discontinue therapy because of side effects and injection reactions[8].

Etanercept, a fusion protein of the soluble TNF receptor and Fc portion of immunoglobulin, was marginally more effective than MTX in reducing the symptoms of RA[12] but was no more effective than MTX for slowing the radiographic progression of joint destruction in a 1-year trial, as determined by the primary radiographic endpoint[21]. However, for the second consecutive year, the situation was reversed[6]. For patients with long disease durations and who are unresponsive to MTX

treatment[12] or not adequately responding to sulfasalazine[22], etanercept is a more effective alternative. The safety profile of etanercept is superior because of its limited range of doses[8]. It is generally safe and well tolerated by elderly RA patients, and no serious risks have been reported for subjects aged ≥65 years[23]. Elderly RA patients treated with etanercept experience significant improvements in disease activity and function without incurring additional safety concerns[24]. Elderly RA patients treated with etanercept exhibit rapid improvements in functional status during controlled studies, and these improvements are sustained during open-label extension trials[25]. Studies with RA patients showed that treatment with etanercept elicits a lower frequency of anti-etanercept antibodies[26] compared with the frequency of anti-infliximab antibodies elicited by infliximab therapy[27]. Patients receiving etanercept are less likely to discontinue because of side effects but are more likely to experience injection site reactions[8]. With etanercept treatment, there are rarely life-threatening adverse events, but injection site reactions are quite common[28, 29].

Due to the different safety profiles of these three anti-TNF-α compounds, some patients are forced to change therapeutic strategies. The safety profiles of the three agents are compared in Table 2, and the efficacy of the agents in terms of ACR20, ACR50, and ACR70 response rates are shown in Table 3.

The evaluation of anti-TNF-α agents

Perhaps because of differences in the sites of action and molecular structure of these three anti-TNF-α agents, individual patients have differential responses. RA patients who experience treatment failure with one anti-TNF-α agent, due to either inefficacy or toxicity, are frequently switched to a second anti-TNF-α agent to determine if the new agent is more effective. Many concerns have been raised about switching between anti-TNF-α agents. Researchers have found that patients who fail to respond to TNF-α antagonist therapy can be switched to another TNF-α antagonist with improved response rates[35–37]. Infliximab is a possible alternative for patients who do not adequately respond to etanercept. Conversely, treatment with etanercept has similar clinical efficacy for patients who discontinued infliximab therapy due to adverse events[36]. For these patients, etanercept maintains the clinical benefit achieved by infliximab[38]. Etanercept provides a well-tolerated and effective treatment option for some patients even when infliximab therapy has been ineffective[39]. Response rates of first-time anti-TNF-α switchers are somewhat below those of anti-TNF-α-naive RA patients, while the markedly inferior response rates of second-time switchers suggest other therapeutic options should be considered in this situation[40].

One study suggests that failure to respond to infliximab and etanercept may predict failure to respond to adalimumab[41]. Some studies have investigated why certain RA patients fail to respond to anti-TNF agents and how antibodies against anti-TNF agents influence response after switching between anti-TNF agents. One study showed that patients who develop anti-infliximab antibodies are more likely to develop anti-adalimumab antibodies than anti-TNF-naive patients. It has been suggested that a second anti-TNF agent should be offered to RA patients who fail to respond to anti-TNF therapy in the

Table 2. Different continuation rates of infliximab, etanercept and adalimumab therapy.

Drugs	Continuation rate (<year 1)	Continuation rate (year 2)	Persistence rate	Major reason of discontinuation
INF	78.0% (284 days)[30]	Not available	78.0%[30]	Due to adverse events patients suffer severe side effects[8]
ADA	70.8% (258 days)[30] 60%[32]	60.9%[31]	70.8%[30]	Due to adverse events patients suffer injection site reactions[8]
ETA	72.8% (256 days)[30] 74%[32] 76%[33]	61%[33] 63% (10 mg)[6] 74% (25 mg)[6]	72.8%[30]	Due to lack of efficacy patients suffer injection site reactions[8]

INF: infliximab; ADA: adalimumab; ETA: etanercept

Table 3. Efficacy of infliximab, etanercept and adalimumab in terms of ACR20, ACR50, and ACR70 response rates.

Groups	3 mon ACR20	3 mon ACR50	3 mon ACR70	6 mon ACR20	6 mon ACR50	6 mon ACR70	12 mon ACR20	12 mon ACR50	12 mon ACR70	24 mon ACR20	24 mon ACR50	24 mon ACR70
INF				92%[34]	58%	16%	71%	42%	15%	83%	60%	19%
ADA	60%[20]	33%		63%[20]			54%[31]	41%	26%	49%	37%	28%
ETA				78%[33]	46%	22%	77%	46%	26%	67%	45%	22%
							77%[6]	47%		75%	54%	27%

Mon: month; INF: infliximab; ADA: adalimumab; ETA: etanercept

absence of anti-biological antibodies[42]. Further investigation is needed to determine the efficacy of this therapeutic option.

Therapeutic strategy of combination treatment with MTX

TNF-α antagonists are generally effective in the treatment of RA. However, some RA patients do not respond or fail to maintain their clinical response over time. At present, many clinical trials have shown that combination therapies are effective in treating several inflammatory disorders. In patients who are naive to MTX or who have not previously failed MTX treatment, TNF blockade in combination with MTX is significantly more effective than MTX monotherapy against early RA[12, 31, 33, 43]. For patients with early or established RA, treatment with the combination of anti-TNF-α drugs and MTX has produced increased clinical remission rates associated with greater control of radiographic progression compared with traditional DMARD or MTX monotherapy[44].

Infliximab plus methotrexate

Accumulated evidence from controlled trials has demonstrated that combination treatment with infliximab and MTX is more effective than single-drug regimens. The ACR response rate is higher for infliximab combined with MTX than for MTX alone. Patients receiving the combination treatment show lower radiographic progression, higher remission rates and improved efficacy compared to patients receiving MTX alone[21]. Infliximab plus MTX can produce a significantly higher number of responders[36]. The combination treatment can inhibit radiographic progression across all disease activity states[45], irrespective of the levels of traditional predictors[46]. It was. found that patients with greater joint damage at baseline showed lower disease progression with infliximab plus MTX therapy compared with MTX monotherapy[46]. RA patients who received initial combination therapy with infliximab have earlier functional improvement, slower progression of radiographic joint damage and fewer side effects than patients who received monotherapy[47]. Even in patients without clinical improvement, treatment with infliximab plus MTX provided significant benefits against the destructive process[48]. The use of infliximab along with optimal doses of MTX significantly retards the progression of radiographic changes in patients with persistently elevated disease activity[46]. Studies with RA patients have shown that the prevalence of anti-infliximab antibodies increases over time[27], and this phenomenon can result in deceased infliximab effectiveness. However, the immunogenicity of infliximab can be significantly reduced in combination with MTX[49].

Some studies have shown that there is an increased risk of serious infections when infliximab is combined with MTX[12, 21]. Some researchers suggest that infliximab in combination with MTX should be limited to early RA patients with clinical and biological signs of aggressive disease, such as an insufficient response to MTX alone or the presence of rapidly progressing erosions[50].

Adalimumab plus MTX

After 12 months of therapy, more patients receiving combination therapy with adalimumab plus MTX exhibit an ACR50 response than patients receiving MTX or adalimumab alone (62% *vs* 46% and 41%, respectively). For patients with early aggressive RA, combination therapy is significantly superior to monotherapy in improving signs and symptoms of disease, inhibiting radiographic progression and promoting clinical remission[31]. Patients receiving adalimumab plus MTX demonstrate significant and rapid improvement in disease activity compared with those receiving placebo plus MTX[28]. Through 24 weeks of treatment, there were statistically significant decreases in serum levels of the cartilage destruction marker pro-matrix metalloproteinase (pro-MMP) compared to baseline with adalimumab plus MTX therapy[28].

Etanercept plus MTX

Benefits of combined use of etanercept with MTX have been demonstrated in several trials. Patients receiving either the combination of etanercept with MTX or etanercept monotherapy are more likely to achieve a mean ACR20 response at 12 months than patients receiving MTX monotherapy[51]. This combination has greater effects on remission rates, deceased radiographic progression and greater improvement in disability than MTX monotherapy[31, 52]. Furthermore, this regimen provides the highest therapeutic effect in RA patients with moderate disease activity[53]. For patients with active RA and intolerance or unsatisfactory response to MTX, combining etanercept with MTX is an effective way of reducing disability, pain, disease activity, and morning stiffness, and of improving general health[54]. The combination of etanercept and MTX is significantly better at reducing disease activity, improving functional disability, and retarding radiographic progression than MTX or etanercept alone[55]. In terms of safety profiles, the number of patients who withdrew from a study was significantly lower in the combination therapy group than in the MTX monotherapy group[31]. In addition, combination treatment is more effective than etanercept alone or etanercept plus non-MTX, non-biologic DMARDs[56]. There are large differences in the effectiveness of combination therapies with MTX, as shown in Table 4.

Patients receiving infliximab are more likely to require persistent therapy compared to patients receiving adalimumab or etanercept[30]. The effects achieved with etanercept and adalimumab in patients with short-lasting, less severe disease are equivalent to those obtained with first-time MTX treatment[8]. The effect of treatment with etanercept or adalimumab does not differ from that of treatment with MTX[8]. There is high treatment persistence with all of the combination therapies, especially in patients treated with infliximab plus MTX, who had significantly higher persistence rates compared with those treated with adalimumab plus MTX or etanercept plus MTX[30]. TNF-α antagonists in combination with MTX have proven superior to single-drug regimens and are now considered the most effective strategies for treating RA.

Table 4. Efficacy of combination therapy with MTX in terms of ACR20, ACR50 and ACR70 response rates.

Groups	3 mon ACR20	3 mon ACR50	3 mon ACR70	6 mon ACR20	6 mon ACR50	6 mon ACR70	12 mon ACR20	12 mon ACR50	12 mon ACR70	24 mon ACR20	24 mon ACR50	24 mon ACR70
INF+MTX												
3 mg+MTX							62.4%[21]	45.6%	32.5%			
6 mg+MTX							66.2%[21]	50.4%	37.2%			
ADA+MTX												
20 mg+MTX					47.8%[28]	31.9%						
40 mg+MTX				67.2%[28]	55.2%	26%	73%[31]	62%	46%	69%	59%	47%
80 mg+MTX				65.8%[28]	42.5%	19.2%						
ETA+MTX												
10 mg+MTX										61%[6]	35%	19%
25 mg+MTX	75%[55]	42%	22%	80%	59%	36%	85%	69%	43%	72%[6]	49%	29%

Mon: month; INF: infliximab; ADA: adalimumab; ETA: etanercept

The application of other anti-TNF-α drugs

Golimumab

Golimumab is a human anti-TNF-α monoclonal antibody that is generated and affinity matured in an *in vivo* system. Golimumab has high affinity and specificity for human TNF-α and effectively neutralizes TNF-α bioactivity *in vitro*. Golimumab plus MTX effectively reduced the signs and symptoms of RA and is generally well tolerated in patients with inadequate responses to MTX[57]. Golimumab in combination with MTX in patients with active RA significantly reduced the signs and symptoms of RA and improved physical function[58]. The significant decreases in serum E-selectin, IL-18, serum amyloid A, and MMP-9 levels associated with combination therapy with golimumab and MTX may be useful in predicting clinical response[59].

RA patients treated with 100 mg of golimumab and placebo capsules produced anti-golimumab antibodies. The study also shows that antinuclear antibodies are produced after treatment with golimumab (50 mg or 100 mg) combined with MTX[58]. The safety profile and tolerability of golimumab are consistent with those of other TNF-α inhibitors[60, 61], and unexpected adverse events or an increased frequency of specific adverse events are not observed[60].

Certolizumab pegol

Certolizumab pegol is a PEGylated Fab' fragment of a humanized monoclonal antibody that binds and neutralizes human TNF-α[62]. Certolizumab pegol is an example of a TNF inhibitor in which PEGylation could potentially optimize the delivery of the neutralizing moiety by specifically targeting the inflamed tissue in RA patients[63]. Certolizumab pegol does not induce apoptosis because certolizumab pegol binds to a different epitope than the other agents, which leads to a different signaling pattern inside cells[62]. Compared to placebo treatment, treatment with 400 mg of certolizumab pegol monotherapy every 4 weeks effectively reduced the signs and symptoms of active RA in patients that previously did not respond to DMARDs compared with placebo[64]. Most adverse events induced by treatment with certolizumab pegol are mild or moderate[64].

The effect of anti-TNF-α drugs on RA patients with concomitant disease

Patients with RA frequently have mood and anxiety disorders, and anti-TNF-α drugs may be useful for improving the mental status of these patients[65]. Anti-TNF-α therapy has been demonstrated to be effective, safe and well tolerated in the setting of hepatic C virus (HCV) infection[66]. Blocking TNF-α could play a protective role in the progression of HCV-related liver fibrosis[67]. Anti-TNF-α therapy combined with periodontal treatment resulted in significant improvement in the periodontal condition, and periodontal therapy had a beneficial effect on the signs and symptoms of RA, regardless of the medications used to treat this condition[68]. Additionally, anti-TNF-α therapy for active RA was highly safe and efficient in a small group of RA patients with coexistent collagen disease[69].

Conclusion

Although other targeted therapies and improved versions of existing drugs are being developed, we have already obtained vast knowledge about anti-TNF-α compounds in clinical practice. Many studies have addressed the efficacy, safety and continuation of anti-TNF-α agents in RA patients and revealed important information. These agents have beneficial effects on the progression of rheumatic diseases at the bone level[14] and lead to a substantial change in the treatment of RA. Treatment with anti-TNF-α drugs other than those recommended are also beneficial[8]. There are no significant differences in effectiveness between infliximab, etanercept and adalimumab[70]. However, differential clinical efficacy for these three agents has been demonstrated in several trials with different RA patient populations. Studies reported that non-responders to one of these compounds often positively respond to another, and TNF-α antagonists in combination with MTX have been

proven effective under certain conditions. Different mechanisms of action of these three compounds may partially explain these findings. Because different compounds and therapeutic strategies have different clinical effects, it is vitally important to determine how to stratify patients prognostically as a means of selecting the most effective anti-TNF treatment with the highest probability of success and lowest potential to produce side effects.

These compounds are beneficial for RA patients, but several side effects are elicited. Serious infections are frequent in daily practice[71]. Patients receiving anti-TNF-α drugs are more prone to experience adverse events, and those using infliximab and adalimumab have higher withdrawal rates[8]. In addition, incorrect therapeutic strategy may also decrease the efficacy of these compounds. For example, the use of infliximab and etanercept in combination with MTX may cause lower titers and lower response rates[72]. For patients with no previous resistance to MTX, the relative efficacy of anti-TNF-α drugs in combination with MTX is much lower compared with that of MTX alone. Etanercept and adalimumab are superior to placebo, but their effects as single agents are similar to that of MTX[8]. For elderly RA patients, there are significantly high numbers of adverse events, including frequent infections[73].

In conclusion, the effects of anti-TNF-α agents in RA patients are complex. The proper selection of anti-TNF-α agents and the optimal therapeutic strategy should be investigated in long-term follow-up studies. We are still awaiting a complete set of clinical and biological criteria capable of classifying RA patients and predicting their responses to different treatments.

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