Abstract

The identification of tumor necrosis factor-alpha (TNF-α) as an important mediator in the pathogenesis of rheumatoid arthritis (RA) led to the development of TNF inhibitors (TNFIs), which has ushered in a revolution not only in therapies for RA, but other rheumatic diseases as well. Treatment strategies for RA will continue to evolve as new agents are developed and as new data become available. This article provides a summary of clinical studies with TNFIs conducted in RA patients and reported over the previous 18 months based on a PubMed search using the terms TNFIs (with their individual generic names) and RA.

Rheumatoid arthritis (RA) is one of the most common types of inflammatory arthritis, affecting 1% to 2% of adults in Western countries. The disease itself is associated with joint inflammation and destruction, which leads to major decrements in health-related quality of life, functional limitations, work disability, and more importantly, an increased risk of cardiovascular disease that may reduce life expectancy by 3 to 18 years.

The therapeutic landscape in the management of RA has witnessed revolutionary changes over the past decade. Researchers are making a combined effort to develop new immune-modulatory agents, specifically biological agents, which block the pro-inflammatory cytokines present in RA. The tumor necrosis factor inhibitors (TNFIs) were the first of the biologic drugs to be accessible, illustrating successful translation of bench side theory to clinical practice. Since the conduction of the first randomized, double blind, placebo-controlled trial with infliximab in RA patients in 1993, several approaches using differently engineered proteins have been developed.

This review highlights the major clinical studies published over the last year (between January 2010 and June 2011) pertaining to advances in the use of TNFIs in the management of RA. To identify clinical trials to be discussed here, a PubMed search was performed using the query terms of “TNF inhibitors” and “rheumatoid arthritis” with the search limited to previous 18 months. The US Food and Drug Administration (FDA) approved no new TNFIs during the previous year for the treatment of RA. Therefore, only those selected papers about the clinical trials conducted in RA patients with infliximab (INF, n = 2), etanercept (ETA, n = 2), adalimumab (ADA, n = 1), and golimumab (GM, n = 1) will be summarized here (no clinical study was found for certolizumab when the search was limited to the most recent 18 month period).

Infliximab

There is a large body of evidence supporting the effectiveness of TNFIs including INF for both established and early RA patients, which makes remission an achievable goal in increasing percentage of patients with the introduction of early, intensive goal-steered therapy. However, the optimal protocol for cost-effective and safer use of these agents has remained largely unanswered. In particular, the question of whether a patient with RA in prolonged remission could discontinue TNFIs has often been asked.

Historically, the first study addressing the potential for remission without the use of TNFIs was reported by Quinn and co-workers from Leeds, UK. In that double-blind study, 20 previously untreated RA patients with less than 1 year of disease duration and poor prognosis were randomized to receive either methotrexate (MTX) plus INF
combination therapy or MTX monotherapy for 12 months. Treatment was discontinued after 12 months, and patients were followed for an additional 12 months according to standard clinical care. In the INF group, 1 year after stopping the drug, disease activity remained below remission levels in 70% of patients. While DAS28 similar between the treatment groups, function and quality of life percentage changes remained significantly better in the INF group.

In October 2010 issue of Rheumatology (Oxford), the same research group reported the outcomes of those 20 RA patients, 8 years following remission induction regime.5 After the double blind period, all of the patients continued MTX therapy in a step-down protocol and were allowed further disease modifying anti-rheumatic drugs (DMARDs) at the discretion of the treating physician. At 8-year follow-up, data were available for 18 patients (one in each group had died), and disease activity was significantly lower in the group given INF-MTX combination compared with those given MTX-alone during the first year (median DAS-28 2.7 vs. 4.3, p = 0.02). Furthermore, half of the patients in the combination group were in remission (with DMARDs) while none in the placebo-MTX group were. Despite some of the shortcomings of the study, such as small sample size and lack of radiographic data, this study shows that a remission induction regime with an INF-MTX combination for 1 year in early RA can improve long-term outcomes.

The second study, RRR (remission induction by Remicade in RA), addressing the same question as the above-mentioned study, was from Japan.7 As stated by the investigators, this study was partially based on the economical motives specific to Japan where the majority of patients have to pay 30% of their medical expenses and, unsurprisingly, want to know whether it is possible to discontinue TNFIs during the disease course. In this multicenter observational study, Tanaka and coworkers evaluated the possibility of discontinuing INF treatment in a cohort of 114 RA patients after they had achieved low disease activity (DAS28 < 3.2) for more than 24 weeks. All of the patients were given concomitant MTX and the attending physician determined the dose for each patient. The primary end-point was the percentage of patients maintaining low disease activity (LDA) 1 year after discontinuing INF. During the 1-year period after stopping treatment with INF, 55% of the patients still had LDA. Furthermore, 43% achieved remission for more than 1 year after discontinuation of INF. The observed chance of flare was 45% at 1 year, while majority of those who flared reached LDA within 24 weeks after re-treatment with INF. Comparison of the patients who achieved remission and who relapsed reveals that patients who were younger and had a shorter disease duration had a higher chance of achieving biologic free remission. The results of this study are somehow less striking than the 1-year data of the British study (remission rate at 1-year following discontinuation of INF 43% vs. 70%) described above.5 The most important difference between the populations enrolled in the two studies is mean disease duration, 0.5 years in British study vs. 5.9 years in RRR study, which might explain relatively lower rate of remission observed in RRR study. However, analysis of the data also shows that such a benefit is not only limited to those having early RA, since even patients whose disease duration was more than 10 years successfully remained without INF for 1 year.

Taken together, these two studies imply that remission free from biological agents can be more easily obtained in patients with early RA than in those with more established disease, but remission after discontinuation of INF is still possible even in patients with long established RA.

**Etanercept**

Studies of the various TNFIs administered in combination with MTX in patients with longstanding RA with active disease despite MTX treatment have demonstrated that these agents provide considerable benefit.4 Although the ETN plus combination therapy produced significantly better response than ETN monotherapy in RA patients unresponsive to DMARDs other than MTX,8 the only study investigating ETN plus MTX combination therapy compared to ETN monotherapy in RA patients resistant to MTX failed to show greater efficacy of combination therapy.9 With an aim to clarify whether the continuation or discontinuation of MTX at the institution of ETN is a better option for patients resistant to MTX, Japanese researchers conducted Japanese Etanercept Study on Methotrexate Resistance (JESMR), a prospective randomized, open-label, multi-center study. The prior year saw the publication of 24-week results of this 2-year study.10 Patients who decided to start treatment with ETN were randomized to continue (combination therapy) or discontinue to MTX (switching to ETN monotherapy). Patients had to have active RA with six or more tender and six or more swollen joints and either ESR greater than 28 mm/h or CRP greater than 2 mg/dl. All patients were required to have taken 6 or more mg of MTX per week for at least 3 months. The co-primary endpoints were good response according to the EULAR criteria and the ACR50 response rate at week 24. In this study, the EULAR good response rate at week 24 was significantly higher in patients receiving combination therapy than ETN monotherapy (52.1% vs. 33.3%, p = 0.0001).

Furthermore, the superiority of the good response rate in the combination group compared to monotherapy was evident as early as week 4 and was sustained thereafter. Although the co-primary endpoint, ACR50 response rate, was higher in the combination group than in the ETN monotherapy group (64.4% vs. 47.8%), it did not reach statistical significance. Thus, similar to the experience obtained with other TNFIs, this study demonstrated that addition of ETN is preferable to switching to ETN for RA patients who are resistant to MTX. Although the results
of this study seem to be contrasting with the results of the ADORE study, the lack of efficacy in ADORE might be due to the relatively short observation period (16 weeks) and the gradual dose reduction of MTX in that study.

Several lines of evidence support the new treatment paradigm, which recognizes the potential window of opportunity for therapeutic intervention in early RA. Some studies have evaluated the effectiveness of TNFIs in early disease, which provides evidence that early use of TNFIs may have a specific effect on the process that sustain underlying inflammation. One such study is the Combination of Methotrexate and Etanercept in Early RA (COMET), which aimed to evaluate the effects of early intensive therapy with combined treatment on clinical remission and radiographic progression of early RA. The COMET trial is a double blind, randomized, multinational, 2-year study that enrolled 542 patients with active early RA. The trial consisted of two 12-month treatment periods, with patients randomized into the following four groups: 1. etanercept 50 mg plus methotrexate for 24 months; 2. combination therapy for 12 months followed by etanercept alone for 12 months; 3. methotrexate alone for 12 months followed by combination therapy for 12 months; and 4. methotrexate for 24 months. The 1-year results of this study revealed that 50% of patients in the combined-treatment group and 28% in the methotrexate-only group achieved a DAS28 remission, a statistically significant difference. The rate of radiographic non-progression was 80% in the combined-treatment group and 59% in those on methotrexate only, also a statistically significant difference. Last year, results were published from the second year of the COMET trial that established how continuation of and alterations to the initial combination and monotherapy regimens affected long-term outcomes. For the year-2 analysis, 222 patients who completed the first year on ETN plus MTX were randomized either to continue the combination or to switch to etanercept monotherapy. From the control arm, 189 patients who completed 1 year on MTX monotherapy were either continued on methotrexate only or begun on MTX plus ETN. The primary end points after a second year of treatment were the same as the original end points: remission and radiographic non-progression. At the end of year 2, the remission rate in the non-responders imputation analysis was 46% in patients who were on the combined regimen for the entire 2 years and 24% in patients who received MTX alone throughout. The remission rates were between these two rates for patients who were switched from both drugs to ETN alone after 1 year (a 38% remission rate), and for those switched from MTX only to both drugs after 1 year (37% remission rate). Radiographic non-progression was also greatest (90%) in the patients who got received drugs for 2 years and was lowest (68%) in those who received methotrexate only for 2 years. These data highlight the importance of early intensive treatment with ETN, which can help stop progressive joint damage and provide the opportunity to maintain remission.

### Adalimumab

The only clinical trial published last year regarding the use of ADA in the management of RA was the 5-year results of PREMIER study. The PREMIER study is a randomized, double-blind clinical trial comparing the efficacy of ADA (40 mg every other week) plus MTX combination therapy versus MTX monotherapy or ADA monotherapy in patients with early (disease duration less than 3 years), active RA who were MTX naive. The double-blind, 2-year phase of the study was published in 2006 and demonstrated that, following the second year of treatment, nearly one-half (49%) of patients receiving combination therapy achieved clinical remission, compared with only 25% of patients receiving ADA monotherapy and 25% of patients given MTX monotherapy. The superiority of the combination therapy over each of the monotherapies was also shown by means of radiographic progression.

The previous year witnessed the publication of the results of the additional 3 years of open-label ADA therapy from the same study, allowing an analysis of 5 total years of treatment. Of the 799 patients initially enrolled in the double-blind study, 497 elected to remain in the open-label extension trial, and 354 patients completed 5 years of therapy: 124 who were taking the combination therapy, 115 who were on ADA monotherapy, and 105 patients who were on MTX. Initial randomization to the combination treatment was found to be associated with a greater chance of being in remission from RA, as 61% of the patients initially receiving combination therapy achieved remission (DAS28 < 2.6) after 5 years, compared with 52% of the patients on ADA monotherapy and 56% of those on MTX. In the 5-year radiographic results, fewer patients on the combination therapy progressed (ΔmTSS > 0.5) when radiographic evidence was scrutinized. It was shown that 65% of the patients begun on combination therapy progressed compared with 87% of patients initially begun on ADA and 86% of those patients initially begun on MTX. In summary, patients initially randomized to receive combination therapy with ADA and MTX for 2 years of blinded treatment demonstrated better radiographic, clinical, and functional outcomes over 5 years than those initially randomized to receive either monotherapy, owing in large part to the advantage at which these patients were placed due to the earlier use of ADA plus MTX during the blinded phase of the study.

### Golimumab

Golimumab is one of the latest TNFIs evaluated for its efficacy in double-blind, randomized controlled trials (RCT). The U.S. Food and Drug Administration approved the drug on April 2009 for the treatment of RA based on four phase 3 trials conducted among different RA populations. The GOLimumab FOR Subjects With Active RA Despite MTX
Effect seems to be maintained to 52 weeks. MTX in patients with active RA despite MTX, and this is effective (most effective when used in combination with week 52. Overall, the results of this study dictate that GM and 77.4% of patients in group 4 maintained improvement 78.7% of patients in group 2, 90.6% of patients in group 3, response criteria at week 24, 78.4% of patients in group 1, £ ease activity (DAS28 group 3 and 53% patients in group 4 experienced low dis- activity as measured by DAS28. At week 52, 34% of patients achieved ACR20 response at week 52, 41 patients (30.8%) in group 1, 36 patients (27.1%) in group 2, and 15 patients (16.9%) in group 3 had entered early escape. The findings in the ITT analysis revealed that 44% of patients in group 1, 45% of patients in group 2, 64% of patients in group 3, and 58% of patients in group 4 achieved ACR20 response at week 52. Patients also experienced improvement in disease activity as measured by DAS28. At week 52, 34% of patients in group 1, 31% of patients in group 2, 42% of patients in group 3 and 53% patients in group 4 experienced low disease activity (DAS28 <3.2). Of the patients who met ACR20 response criteria at week 24, 78.4% of patients in group 1, 78.7% of patients in group 2, 90.6% of patients in group 3, and 77.4% of patients in group 4 maintained improvement at week 52. Overall, the results of this study dictate that GM is effective (most effective when used in combination with MTX) in patients with active RA despite MTX, and this effect seems to be maintained to 52 weeks.

Conclusion

Tumor necrosis factor inhibitors transformed RA clinical practice, enabling LDA and remission as an achievable goal for many patients with this debilitating disease. Several clinical studies, including the ones published last year, obviously demonstrated that TNFIs are effective in reducing the signs and symptoms as well as structural damage of RA, particularly when used in combination with MTX. In addition, data obtained from the open-label extension studies suggest that these agents are effective in the long-term with no attenuation of clinical response and, most importantly, no unexpected safety concerns. In general, efficacy outcomes are similar for all agents of this class including the ones recently added to our armamentarium. However, it should be kept in mind that there are still no head-to-head comparative clinical studies to support this view. Although, data to date imply that they are effective in patients with both early and established disease, a growing body of evidence supports the notion that efficacy of disproportionate magnitude is possible with the early institution of these agents. Therefore, clinical practice is beginning to change as a result of paradigm shift that incorporates the increased use of TNFIs in early disease. Furthermore, it has also become more clear that discontinuation of TNFIs after acquisition of low disease activity is a realistic goal in patients with both early and established disease, which is relevant from both clinical and economic perspectives. Finally, despite these encouraging results, there is an ongoing need for clinical studies addressing the unanswered but important issues related with the optimal use of TNFIs in RA, such as predictors of response to these agents, comparative efficacy of individual agents, and switching strategies.

Disclosure Statement

The author has no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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