

Questions and Answers in 2008 about Biologics in Rheumatoid Arthritis

It is my pleasure to present the Dunlop-Dotteridge Lecture for 2008.

This has been an exciting decade for advances in the treatment of rheumatoid arthritis (RA). There are, however, many questions remaining about the use of our therapies in the treatment of this disease.

Are tumor necrosis factor (TNF) inhibitors effective?

The answer is a resounding yes. There have been multiple randomized trials as part of the development programs of the 3 approved anti-TNF therapies. There has been a consistency of response with all 3 therapies, whether used as monotherapy or in combination with methotrexate (MTX). If one uses the Disease Activity Score 28 (DAS28) remission as an endpoint, response rates with infliximab, etanercept, or adalimumab range from the low 30% to low 40% range, with a placebo response that ranges from 6% to 21% (Table 1)¹⁻⁴.

Is the combination of MTX plus anti-TNF therapy better than anti-TNF monotherapy?

Again, a resounding yes. There have been several trials of combination anti-TNF therapy plus MTX versus anti-TNF therapy alone. The first large study to examine this question was the Tempo trial², in which 686 patients were randomized to receive etanercept 50 mg per week, monotherapy MTX (with a rapid dose escalation to 20 mg per week), or the combination of MTX and etanercept. American College of Rheumatology (ACR) response rates of patients in the combination arm were an ACR20 of 85% and ACR50 of

69%, as compared to 76% and 48% with etanercept monotherapy, and 75% and 43% with MTX therapy, respectively. A study of early RA examined adalimumab in a similar design and confirmed the etanercept experience that combination treatment was superior to not only MTX but to anti-TNF therapy as monotherapy⁴. In this study, combined adalimumab and MTX achieved ACR50 response in 62% of the patients as compared to 46% with MTX and 41% with adalimumab alone. DAS remission was seen in 43% of the combination patients, 21% of the MTX group, and 23% of the adalimumab group. Why there is increased response with the combination of MTX plus biological therapies is unclear. A pharmacokinetic interaction exists with infliximab and adalimumab when combined with MTX. An increase in serum concentrations is observed when these 2 monoclonal antibodies are combined with MTX. With etanercept, rituximab, and abatacept, there is no increase in drug concentrations when combined with MTX.

One of the great challenges in rheumatology is the selection of appropriate patients to receive these therapies. We do not yet have reliable predictors of which patients will or will not respond on anti-TNF therapy or other biologics. Clinical, demographic, serologic, and radiographic data have not defined which patients will or will not respond on treatment. In one study, investigators reported that a lack of change in C-reactive protein after one dose of infliximab predicted those patients who did not respond on infliximab therapy at Week 12⁵. In this study, 86% of patients who failed to reduce the CRP by 20% did not meet response criteria at Week 12. To date, many biomarker and genomic studies have been inconclusive and underpowered. One of our major goals as we move forward is to incorporate both biomarkers and genetic studies in clinical trials so we can address this issue of response markers.

What about longterm therapy with these agents?

There have been several longterm studies with both etanercept and adalimumab and they both report sustained clinical response over time^{6,7}. One should be cautious in interpreting the efficacy and retention data from these open studies, since patients who are doing well remain in the study. Patients also remain for a variety of other reasons, including access to treatment and medical care; and there is a financial incentive for investigators to retain patients in clinical trials.

Table 1. Disease Activity Score 28 remission (< 2.6) as an endpoint. Response rates with infliximab, etanercept, or adalimumab plus methotrexate (MTX) versus placebo and MTX.

	Anti-TNF + MTX	Placebo + MTX
ASPIRE ¹	31 (6 mg/kg)	15
Infliximab, %	21 (3 mg/kg)	
TEMPO ²	37	14
Etanercept, %		
ARMADA ³	39	6
Adalimumab, %		
PREMIER ⁴	43	21
Adalimumab, %		

What about the response rate in those patients who withdrew from study?

We examined the response rates of the patients who withdrew from the longterm study of adalimumab⁷. There was improvement in clinical status as measured by the DAS response at the last study unit in the majority of patients who withdrew. Of the patients who withdrew, only 8% did so due to lack of efficacy. Discontinuation rates in these longterm studies therefore may not serve as a surrogate of drug inefficacy.

Patients in these longterm studies have also been able to either discontinue or significantly reduce the doses of corticosteroids, nonsteroidal antirheumatic drugs, and MTX therapy.

What about dose modifications?

One study sought to determine if patients who were incomplete responders to a loading dose of infliximab of 3 mg per kg would respond to a dose escalation⁸. Patients received infliximab (3 mg/kg) first in an open study with MTX. At Week 22, if the joint counts had not decreased by 20%, patients entered a double-blind study in which the infliximab dose was increased by increments of 1.5 mg per kg. Thirty percent of the patients required dose escalation. Over 70% of the patients who underwent dose escalation subsequently had a clinical response.

We studied etanercept in 2 different higher-dose studies. In the first monotherapy study, etanercept 50 mg was compared to etanercept 100 mg as monotherapy in patients with active RA⁹. There was no significant difference in clinical response to etanercept between patients who received 50 mg and those who received 100 mg. In a second study, we asked whether a higher dose of etanercept would induce better clinical response in patients who had active disease despite chronic etanercept (50 mg per week) plus MTX¹⁰. In this 12-week double-blind randomized trial, 100 mg etanercept plus MTX achieved a DAS28 response in 46% of patients, and among those who continued taking 50 mg etanercept per week plus MTX, a DAS28 response was achieved in 35%, which was not statistically significant.

With adalimumab the 80 mg dose was no better than the 40 mg dose, and both were better than the 20 mg dose³. The approved and marketed dose of adalimumab is 40 mg.

What about other anti-TNF therapies?

There are 2 additional anti-TNF therapies under development (certolizumab and golimumab). Both these agents have completed several Phase 3 studies and should be available for review by the regulatory agencies over the next 12 months. Certolizumab has recently been approved by the US Food and Drug Administration as a therapy for Crohn's disease.

What about adverse events with anti-TNF therapy?

The risk profile of this class of drugs is highlighted by infection,

including reactivation of tuberculosis, fungal infections, and bacterial sepsis¹¹. Rarely, demyelinating events or lupus-like syndromes can occur. Unusual pulmonary syndromes have been associated with anti-TNF therapy. A worsening of interstitial lung disease has been seen in patients on anti-TNF therapy, but a cause and effect relationship remains to be determined. In addition, a culture-negative granulomatosis process resembling sarcoid has been seen with anti-TNF therapy¹². Primarily observed in the lung, granulomas can also be seen in the bone marrow and skin. Liver toxicity may rarely occur with anti-TNF therapy. Elevations in serum transaminases, which have been seen with all 3 drugs, are generally elevated 1- to 2-fold above the normal range, but occasionally are higher. There have been isolated cases of hepatic failure with anti-TNF therapy, observed primarily in patients with chronic hepatitis B infection. Patients infected with hepatitis B should not receive anti-TNF therapy unless they are also treated with antiviral drugs for their hepatitis B infection.

Anti-TNF therapies have been an important advance in the treatment of RA. They work better when used in combination with MTX and there is an ability to reduce background nonsteroidal and corticosteroid doses. They work in early as well as in longstanding disease and in patients naive to disease modifying antirheumatic drugs (DMARD) and those who have failed multiple DMARD. Response with these therapies occurs early. We do not yet have predictors of either response or lack of response, but those studies are in progress. We have over 10 years' experience with this class of drugs and the safety profile remains very reasonable. These molecules are reasonably well tolerated, but serious adverse events can occur. Tuberculosis and hepatitis B screening prior to initiation of treatment is mandatory. As with MTX and the earlier institution of drug therapy, anti-TNF therapy has changed the course of RA!

What about patients who have active disease despite trials of anti-TNF therapy?

There are now several approaches available for treated patients who continue to have active disease. This includes switching to another anti-TNF therapy or instituting 2 other novel molecules, abatacept or rituximab. With regard to anti-TNF switching, there have been no controlled studies published to date that show switching works. All support for switching is based upon clinical experience and registry data. The rationale for switching is the beneficial effect of anti-TNF therapy on radiographic progression and the fact that there is a rapid indication of clinical response. However, it should be noted that from an evidence-based standpoint, there are no firm data to support switching anti-TNF therapy even though this is now standard clinical practice.

Abatacept has a novel mechanism of action by blocking a costimulation pathway. It has been studied in patients naive to TNF blockers, as well as in those previously on

anti-TNF therapy. In the study in which patients had previously taken anti-TNF therapy, abatacept was superior to placebo: 50% of abatacept patients versus 20% in the placebo group achieved an ACR20 response rate¹³. Rituximab, a monoclonal antibody that depletes the CD20 cell line, has also been approved for RA in patients who previously failed anti-TNF therapy. In the pivotal study in that disease population, 51% of the patients on rituximab plus MTX achieved an ACR20, versus 18% of the patients on placebo plus MTX¹⁴. Both these molecules offer rheumatologists and our patients greater therapeutic options and a greater chance of success.

Are combination biologics a possible approach?

Conceptually the combination would bring either greater efficacy with no increase in toxicity or perhaps allow lower doses of the combination biologics. In studies in which therapeutic doses of biologics in combination have been used, results to date have not been positive. The combinations of anakinra plus etanercept¹⁵ and anti-TNF therapy plus abatacept¹⁶ both showed no greater efficacy, and a 3- to 4-fold increase in infections with combination biologics was observed.

What about the future of drug development in RA?

As we move forward, challenges remain regarding patients who continue to have active disease despite multiple biologic therapies plus MTX. For this group, multiple drugs under development include regimens targeting a variety of proinflammatory cytokines such as inhibitors of interleukin 6 (IL-6), IL-15, IL-17, and IL-18. There are several ongoing studies of other B cell-depleting therapies as well as inhibitors of costimulatory pathways. There is excitement regarding several oral molecules including inhibitors of selected kinases such as the Jak-3 and syk kinase pathways.

One of the great challenges in drug development is the difficulty recruiting appropriate patients for clinical trials. Success in the treatment of RA has made therapeutic studies very difficult to perform. The efficacy of anti-TNF therapy plus MTX has made it increasingly difficult to recruit patients who are anti-TNF therapy-naïve. In addition, there is a limited percentage of patients that do not have some response on anti-TNF therapy so the number of patients available for clinical trials is smaller than a decade ago. Many of the studies are being done in countries in which there is limited access to biologic therapies. In the US many patients enrolling in therapeutic studies are those who are not able to access biological therapies due to financial and insurance constraints. Whether these patients are similar to the overall group of patients in Western Europe and North America is unclear.

Probably the largest group of patients who would benefit from additional therapies are those with a positive response on biologics plus MTX but not yet in remission. This is the

largest group of patients we see at our center. The percentage of patients who are true failures of the biologics and MTX is probably less than 10%. The highest percentage of patients who would benefit from another therapy are those who have active disease despite biologics plus MTX. We are particularly interested in looking at reasonably safe oral molecules that could be added to this combination with the hope that they induce an even better clinical response and might allow us to reduce the dose of the expensive biologic.

The past decade has been met by a great excitement. We have entered a new era in the treatment of RA. Challenges remain for drug development, but the past 10 years have been gratifying for all of us who study and treat patients with RA and most importantly for our patients.

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