Optimizing Treatment with Biologics

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ABSTRACT. Disability and joint damage in rheumatoid arthritis (RA) occur rapidly and early in the course of the disease. Disease activity is predominantly responsible for the disability in the early stages of RA. Nonreversible joint damage increases disability later in the course of RA. In recent years, several strategies that employed combination therapies with conventional disease modifying antirheumatic drugs (DMARD) were studied with the aim of rapidly bringing the disease under control. The ultimate goal was to alleviate symptoms and slow or halt the progression of joint damage. The introduction of highly efficient biologic agents allows introduction of a number of new strategies, including early administration of a biologic agent alone or in combination with high-dose methotrexate. Other options for the use of biologic therapies include the use of biologic agents for moderate disease, and early use of a biologic agent for induction of remission and subsequent treatment with a conventional DMARD. A strategy for tight control of disease with targeted outcomes for decision-making may offer further improvement in disease control irrespective of the treatment approach. The remarkably improved outcomes that can be achieved by initiating aggressive therapy early, with close monitoring of disease progression and modification of ineffective therapeutic strategies, support the use of biologics in the optimal management of RA. (J Rheumatol 2007;34 Suppl 80:16-24)

Key Indexing Terms:
BIOLOGIC THERAPY RHEUMATOID ARTHRITIS THERAPY

INTRODUCTION

There have been significant changes in the management of rheumatoid arthritis (RA) in the past 20 years. The goal is no longer simply symptom control, but rather prevention of structural damage and functional decline. New agents and new strategies are making this goal ever more achievable[1,2].

The introduction of tumor necrosis factor (TNF) inhibitors was a key step in the evolution of RA management. Use of these agents in combination with conventional disease modifying antirheumatic drugs (DMARD), in particular methotrexate (MTX), has emerged as an effective and targeted therapeutic strategy that directly alters the biological processes underlying synovial RA inflammation and progressive structural destruction.

Various strategies have been proposed to optimize the use of biologic therapies in RA, and will be reviewed in this article. They are:

1. Early use of biologic agents: (a) Monotherapy: TNF inhibitors vs MTX. (b) Monotherapy: Early versus later use. (c) Combination therapy: addition of TNF inhibitors to MTX. (d) Combination therapy: first-line therapy with TNF inhibitors and MTX.
2. Combination therapy (TNF inhibitor + MTX) in established disease.
3. TNF inhibitors in moderate versus severe disease.
4. Tight control of disease activity.
5. Induction and maintenance: TNF inhibitors followed by conventional DMARD.
6. Switching between TNF inhibitors: (a) Scientific rationale. (b) Clinical experience.
7. Switching between biologic therapies: (a) TNF inhibitors to abatacept. (b) TNF inhibitors to rituximab.

1. Early Use of Biologic Agents

The use of TNF inhibitors early in RA has been shown to provide symptomatic relief and slow the rate of joint destruction, compared to use of these agents later in the course of the disease.

Monotherapy: TNF inhibitors versus MTX. The Early RA trial compared etanercept monotherapy with MTX monotherapy in patients with RA ≤ 3 years' duration. Results showed similar American College of Rheumatology (ACR) responses after one and 2 years of therapy. However, radiographic progression (total Sharp scores

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and erosion scores at 6 months and 2 years) was significantly less with etanercept[3,4].

Similarly, the PREMIER study demonstrated that adalimumab monotherapy in early RA (< 3 years' duration) was significantly more effective than MTX in slowing the rate of radiographic progression, despite comparable clinical responses [ACR, DAS28, and Health Assessment Questionnaire (HAQ)][5].

The authors of the PREMIER study suggest that the results of these 2 trials may reflect 2 separate mechanistic pathways: one that mediates improvement in signs and symptoms, and is similarly responsive to both TNF inhibition and MTX therapy; and another that mediates joint damage, and is more responsive to TNF inhibition[5].

Monotherapy: early versus later use. There is a considerable body of evidence to support the early use of conventional DMARD therapy in RA: the majority of studies demonstrate a quantitative benefit in clinical outcome[6]. "Earlier is better than later" holds true for TNF inhibitor therapy, as well. A post hoc analysis of data from 2 trials (the Early RA trial[3] and a longterm etanercept safety trial[7]) compared improvement in disability with etanercept in patients with recent onset (≤ 3 years) and established disease (mean duration 12 years)[8]. Etanercept monotherapy significantly improved disability scores in both groups. However, at 3 years, a significantly greater proportion of patients with recent-onset RA (26%) achieved a HAQ score of zero than did patients with established RA (14%).

Combination therapy: addition of TNF inhibitors to MTX. The addition of biologic therapy to MTX in patients not fully responsive to MTX has been shown to provide substantial clinical benefit. The ATTRACT study investigated the effect of infliximab plus MTX in patients with active RA despite treatment with MTX[9-11]. At 102 weeks, radiographic progression was significantly less ($p < 0.001$) in the infliximab plus MTX group than in the MTX-only group[11]. A subanalysis revealed comparable results in patients with early RA (< 3 years' duration): those treated with infliximab plus MTX showed significantly less radiographic progression than those treated with MTX alone[12]. Further, patients with early RA who received MTX alone showed almost 3-fold more radiographic progression than all patients who received MTX alone[12] (Figure 1).

A 2-year controlled trial of immediate or one-year delayed addition of infliximab to MTX also supports the early addition of TNF inhibition to MTX therapy[13]. Patients had erosive early RA (< 3 years' duration) and were taking MTX at the time of enrollment. At 2 years, patients who received one year of MTX alone followed by one year of combination therapy showed significantly greater structural damage than patients who received infliximab plus MTX for the full 2 years of the study.

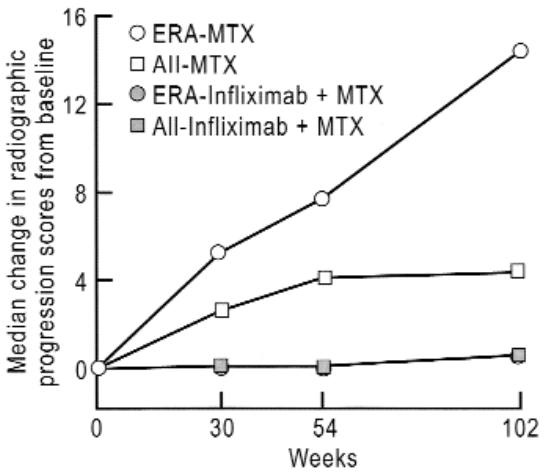

Figure 1. Two-year results from the ATTRACT study subanalysis[12]. Median change in total radiographic score from baseline to Week 102 for all patients with RA (All) versus patients with early RA (ERA; disease duration ≤ 3 yrs) who were randomized to MTX only (MTX) or infliximab plus MTX (Infliximab + MTX). From Breedveld FC, et al. Ann Rheum Dis 2004;63:149-55, with permission.

A retrospective analysis of the DE019 adalimumab study showed similar results with adalimumab added to MTX in patients partially responsive to MTX[14]. Clinical and radiographic outcomes were substantially improved with the combination compared with MTX alone in both early RA (≤ 2 years' duration) and established disease (> 2 years' duration). There was, however, a marked trend toward greater efficacy in patients with early RA.

These studies show that early addition of biologics in patients with insufficient response to MTX yields better outcomes than delayed use. It seems reasonable, therefore, to initiate biologics before failure of a multiplicity of conventional DMARD.

Combination therapy: first-line therapy with TNF inhibitors and MTX. The infliximab ASPIRE trial was the first study to investigate the use of combination treatment as first-line therapy in early RA[15]. MTX-naive patients with early RA (≤ 3 years' duration) who received infliximab plus MTX showed significantly less radiographic progression and greater improvement in physical function after 54 weeks than patients who received MTX alone.

Similarly, a subanalysis[16] of the TEMPO trial[17,18] showed that in patients with early RA (≤ 3 years' duration) the response to etanercept plus MTX was significantly greater than the response to MTX alone in terms of ACR, Disease Activity Score (DAS), and HAQ scores. DAS remission was achieved in 19%, 34%, and 43% of patients treated with MTX, etanercept, and combination therapy, respectively.

The PREMIER study[5] investigated the use of adalimumab plus MTX versus the 2 agents alone in MTX-naive patients

with early aggressive RA (≤ 3 years' duration). At 2 years, combination therapy was superior to both MTX and adalimumab in all outcomes measured. There was significantly less radiographic progression ($p < 0.002$) among patients in the combination treatment arm at both Year 1 and Year 2 (1.3 and 1.9 Sharp units, respectively) than in patients in the MTX arm (5.7 and 10.4 Sharp units) or the adalimumab arm (3.0 and 5.5 Sharp units). After 2 years of treatment, 49% of patients receiving combination therapy exhibited disease remission (DAS28 < 2.6), compared with 25% in each of the monotherapy arms (both $p < 0.001$).

The results of these studies clearly show that in early RA first-line therapy with a TNF inhibitor and MTX in combination is more effective than either agent alone. Most healthcare providers and payers are at present reluctant to support such an approach, largely because of the cost, but further studies may demonstrate its cost-effectiveness. In the ASPIRE trial, investigators evaluated the effect of infliximab therapy on the employment status of patients with early RA[19]. At Week 54 actual employment rates among patients receiving infliximab plus MTX versus MTX alone were not different. However, patients in the infliximab plus MTX group had a higher probability of maintaining their employability.

A recent followup publication on the FIN-RaCo study[20] suggests that results analogous to those with TNF inhibitors may be seen with conventional DMARD: that is, combination therapy is more effective than monotherapy. In the FIN-RaCo trial[21], patients with early RA (< 2 years' duration) received single DMARD or combination DMARD therapy for 2 years. Patients in the combination DMARD group achieved significantly better remission rates (by ACR and DAS28 criteria) than patients in the single-DMARD group. Combination DMARD patients also exhibited a much slower rate of radiographic progression[20]. Further studies are needed to compare aggressive early therapy with combinations of conventional DMARD versus combinations of biologic agents plus conventional DMARD.

2. Combination Therapy (TNF Inhibitor + MTX) in Established Disease

TNF inhibitors in combination with MTX have been shown to be effective in patients with established RA who have failed conventional DMARD. In the ARMADA trial, 147 patients with active RA despite MTX therapy completed 4 years' treatment with adalimumab plus MTX: 43% achieved clinical remission (DAS28 < 2.6). Of 196 patients who were treated for 2 to 4 years, 38% achieved clinical remission[22].

In the TEMPO trial, etanercept plus MTX yielded significantly better results (clinical, radiographic, and patient-reported results) than monotherapy with either agent in patients with established RA despite MTX

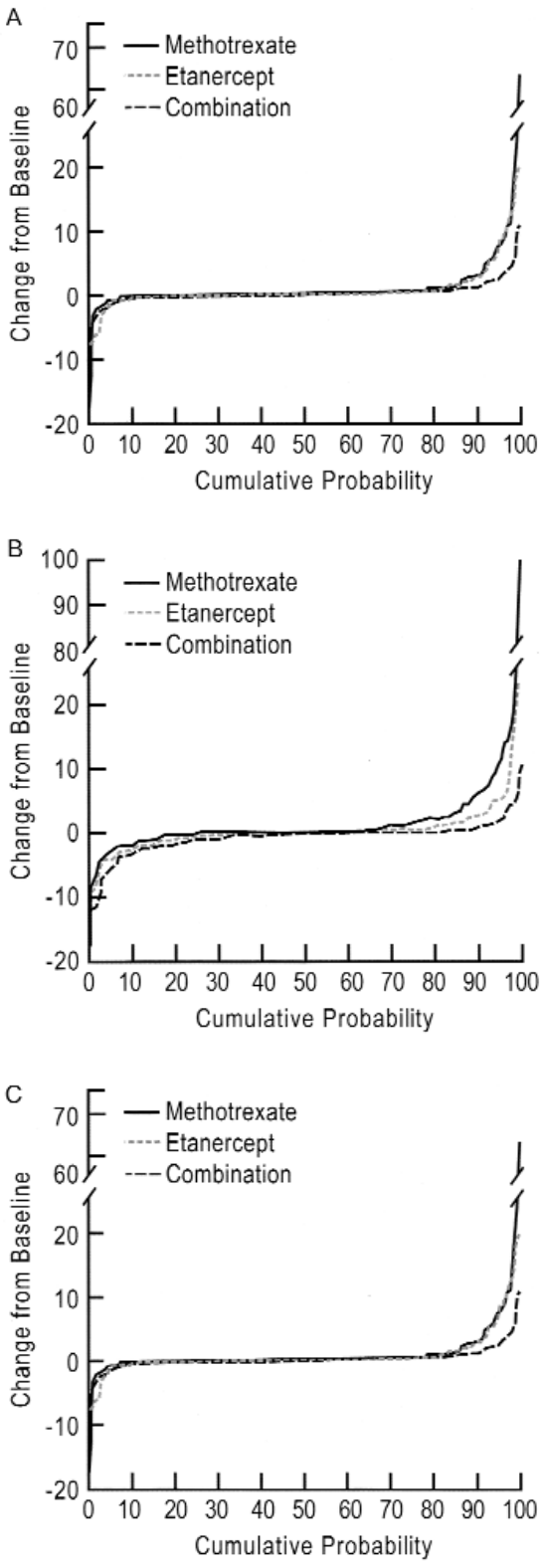

Figure 2. Two-year results from the TEMPO study[18]. Cumulative probability distribution of total Sharp scores (A), erosions (B), and joint space narrowing (C) over 2 years of treatment with MTX, etanercept, or combination of etanercept plus MTX. From van der Heijde D, et al. Arthritis Rheum 2006;54:1063-74, with permission.

treatment[17,18,23]. Interestingly, cumulative probability plots of the radiographic data (Figure 2) show that the proportion of patients without radiographic progression did not differ significantly between the combination and MTX-only groups. However, the *rate* of progression was slower in the combination therapy group, suggesting that the subset of patients that would progress taking MTX alone would particularly benefit from combination therapy.

3. TNF Inhibitors in Moderate versus Severe Disease

For ethical and legal reasons, studies with new and costly therapies are usually reserved for patients with either severe or unresponsive disease. As experience with TNF inhibitors increases, however, it is becoming apparent that treatment of moderate RA with these agents provides greater clinical benefit than treatment of severe disease. In patients treated with adalimumab plus MTX for up to 4 years, patients with moderate disease (DAS28 < 5.1) achieved clinical remission (DAS28 < 2.6) after an average of 6 months, while those with severe disease (DAS28 ≥ 5.1) required an average of 9 months[24]. Patients achieving remission within the first year tended to have lower baseline disease activity as measured by DAS28.

A retrospective analysis of data from 4 etanercept trials, involving patients with early RA (< 3 years' duration) and late, DMARD-refractory RA showed similar results[25]. The percentage of patients who achieved clinical remission (DAS28 < 2.6) at 6 months was significantly higher in patients with moderate disease (DAS28 > 3.2 but ≤ 5.1) than in patients with severe disease (DAS28 > 5.1), regardless of disease duration ($p < 0.001$). Similarly, a subgroup analysis of radiographic progression in RA patients with moderate disease despite MTX showed that patients treated with adalimumab had substantially less radiographic progression at one year than those treated with placebo[26].

Randomized controlled trials have long been considered the "gold standard" for assessing the safety and efficacy of new agents. However, results from clinical trials do not necessarily reflect the results one might expect or achieve in clinical practice. RA patients in clinical practice generally have less severe disease than patients in clinical trials[27]. If TNF inhibitor therapy of moderate disease provides greater benefits, it behooves clinicians to extend the use of these agents to patients with less severe disease.

4. Tight Control of Disease Activity

The TICORA (Tight Control of Rheumatoid Arthritis) trial was a controlled study of a therapeutic strategy aiming for sustained, tight control of disease activity[28]. Patients were randomized to receive either intensive management or routine care. Intensive management included monthly outpatient assessments, objective assessment of disease activity, intraarticular corticosteroid injections, and targeting of persistent disease activity by means of a strict protocol for the escalation of standard DMARD therapy in patients with DAS > 2.4. Patients in the routine-care group saw a rheumatologist every 3 months and had their therapy adjusted at the discretion of the physician after a clinical examination.

At 18 months the mean decrease in DAS was significantly greater in the intensive-management group than in the routine-care group (–3.5 vs –1.9; $p < 0.0001$). Compared with routine care, patients treated intensively were significantly more likely to have a good response (by ACR and EULAR criteria) or be in remission (DAS < 1.6, 65% vs 16%; $p < 0.0001$)[28].

It is of interest that more than two-thirds of patients who were treated intensively needed to escalate oral treatment to achieve good control, and about half ended the trial on triple therapy with MTX, sulfasalazine, and hydroxychloroquine. Patients in the intensive-management

Table 1. Results from TICORA (Tight Control for Rheumatoid Arthritis) trial[28]. Change in disease activity, radiographic damage, physical function, and quality of life between 0 and 18 months. Data are mean (SD) unless otherwise indicated. From Grigor C, et al. Lancet 2004;364:263-9, with permission.

	Intensive Group, n=53	Routine Group, n=50	Difference (95% CI)	p*
Disease Activity Score	–3.5 (1.1)	–1.9 (1.4)	1.6 (1.1 to 2.1)	<0.0001
Joint swelling count	–11 (5)	–8 (5)	3 (1 to 5)	0.0028
Joint tenderness count	–20 (9)	–12 (12)	8 (4 to 12)	0.0003
Patient global assessment	–51 (30)	–21 (34)	30 (17 to 24)	<0.0001
Assessor global assessment	–58 (22)	–34 (28)	24 (14 to 34)	<0.0001
Pain score	–45 (24)	–20 (31)	25 (14 to 36)	<0.0001
Erythrocyte sedimentation rate	–30 (28)	–12 (24)	18 (8 to 28)	0.0007
C-reactive protein	–30 (53)	–14 (40)	16 (-3 to 34)	0.09
Health Assessment Questionnaire	–0.97 (0.8)	–0.47 (0.9)	0.5 (0.2 to 0.8)	0.0025
Short-form-12: physical summary score	9.3 (12)	40 (11)	5.3 (0.8 to 9.8)	0.021
Short-form-12: mental health summary score	10.9 (16)	6.0 (18)	5.0 (-1.6 to 11.6)	0.138
Erosion score†	0.5 (0-3.375)	3 (0.5-8.5)	NA	0.002**
Joint space narrowing†	3.25 (1.125-7.5)	4.5 (1.5-9)	NA	0.331**
Total Sharp score†	4.5 (1-9.875)	8.5 (2-15.5)	NA	0.02**

NA: not applicable. * Student t test. † Median (IQR) increase in score. ** Mann-Whitney test.

group also used more MTX and received more intra-articular steroid injections[28].

It is important to note that the effect of intensive management on radiographic progression was less striking than the effect on clinical disease activity, and (the authors point out) less impressive than radiographic results obtained in trials with TNF inhibitors. Patients in the intensive group had reduced progression of erosion scores and total Sharp scores, but no difference was seen in the progression of joint space narrowing[28] (Table 1). This suggests that combinations of conventional DMARD, even when part of an intensive management program, are less effective than TNF inhibitors in reducing radiographic progression.

The CAMERA (Computer-Assisted Management of Early Rheumatoid Arthritis) trial also showed that intensive treatment and monitoring may be more clinically beneficial than "routine care"[29]. Patients were randomized to intensive or routine treatment with MTX. Patients in the intensive-management group were seen more frequently in clinic; dosages were adjusted based on predefined criteria and tailored to achieve remission; and a computer assisted program was used to determine dosage changes more objectively. Results showed that more patients in the intensive-management group achieved remission than in the routine-care group (20% vs 5%; $p < 0.0001$). Median area under the curve results for all clinical variables [erythrocyte sedimentation rate, morning stiffness, visual analog scale (VAS) for pain, VAS for general well-being, number of swollen joints, number of tender joints] were significantly better in the intensive-management group than in the routine-care group ($p < 0.05$). Patients in the routine-care group used more nonsteroidal antiinflammatory drugs than the intensive-management group.

These studies support the use of targeted outcomes to improve management in RA. The TICORA results did not, however, really address the question of tight control in RA since the 2 arms of the study had quite different treatment algorithms. The question of timeframes must also be considered: in TICORA, treatment escalations were initiated after only 3 months of therapy. This may not be enough time to achieve low disease activity.

Perhaps the most important issue that must be addressed in future studies is the dissociation between (very good) clinical responses and (poorer) radiographic responses seen with DMARD therapy. It is possible that different targeted cutpoints will be required for biologic therapy versus conventional DMARD therapy.

5. Induction and Maintenance: TNF Inhibitors Followed by Conventional DMARD

The efficacy shown by TNF inhibitors in controlling disease activity has led to a new concept in RA management: induction therapy with biologic agents, followed by maintenance therapy with conventional DMARD. This approach has been supported by studies of infliximab in early RA.

A UK pilot study attempted induction of remission using MTX with or without infliximab in patients with early (symptoms < 12 months), poor-prognosis RA[30]. The primary endpoint was synovitis measured by magnetic resonance imaging (MRI). Clinical observations continued to 24 months. At one year, all MRI scores were significantly better in the infliximab plus MTX group, and there were no new MRI erosions.

ACR50 and ACR70 response rates at one year were significantly greater in the infliximab plus MTX group than in the MTX-only group (80% vs 40% and 70% vs 30%, respectively; $p < 0.05$), and the infliximab plus MTX group had greater functional benefit ($p < 0.5$ for all comparisons). At 2 years there were no significant differences between groups in the DAS28, ACR response, or radiographic scores, but the differences in HAQ and RA Quality of Life scores were maintained[30] ($p < 0.05$; Figure 3).

The authors of the pilot study concluded that if larger studies confirm these data, this approach may provide a solution to the economic issues associated with the early use of biologic agents. It is not reasonable or realistic to expect any healthcare system to fund life-long use of agents as expensive as the new biologic therapies, in a disease as prevalent as RA. Remission induction protocols, however, may offer the potential for these drugs to be

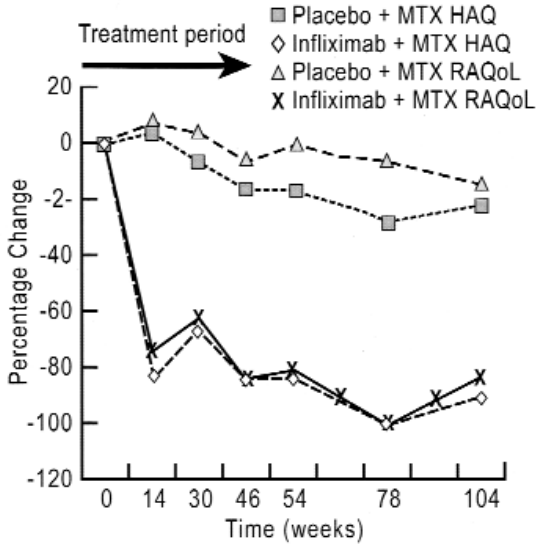

Figure 3. Very early treatment in early poor-prognosis RA: patients were treated with MTX with or without infliximab for 12 months and clinical observation continued to 24 months[30]. Figure shows percentage change in the median functional (HAQ) and quality of life (RAQoL questionnaire) scores over time in the infliximab plus MTX group and the placebo plus MTX group. From Quinn MA, et al. Arthritis Rheum 2005;52: 27-35, with permission.

used for a limited (affordable) period, at a time when they have the best chance of making a difference[30].

The BeSt study[31-33] evaluated the efficacy of 4 of the most frequently used RA treatment strategies in a head-to-head comparison: sequential monotherapy, step-up combination therapy, initial combination therapy with tapered high-dose prednisone, and initial combination therapy with infliximab. Tri-monthly therapy adjustments were dictated by calculation of the DAS, with the goal of achieving and maintaining a DAS44 ≤ 2.4.

At one year, 74% of patients treated with infliximab plus MTX achieved a low disease activity state (DAS44 ≤ 2.4). After a median of 12.6 months, 50% of infliximab plus MTX treated "responders" (patients who had not needed any escalation of therapy) were able to discontinue infliximab because of low disease activity; 8% required reintroduction of infliximab within one year[31].

At 2 years, the proportion of infliximab plus MTX treated patients who achieved DAS44 ≤ 2.4 increased to 82%, and 54% of patients initially treated with infliximab plus MTX had tapered their treatment to MTX monotherapy. Radiographic progression was halted in 93% of infliximab plus MTX treated patients after one year and was maintained in the responders up to 2 years[31-33]. For additional discussion of the BeSt study, please see "Treatment of recent onset rheumatoid arthritis: Lessons learned from the BeSt study" elsewhere in this supplement[34].

The data available to date suggest that rapid control of inflammation by means of induction therapy confers benefits in function, quality of life, and structural damage. A number of unanswered questions require further investigation: How early must induction therapy be initiated to provide longterm benefit? And will this approach create problems in terms of generating human antichimeric antibodies? Further controlled studies in patients with very early disease are currently being planned.

6. Switching Between TNF Inhibitors

TNF inhibitors have revolutionized the standards and goals of treatment in RA. Infliximab, etanercept, and adalimumab have all been shown to provide substantial (and quite comparable) benefits in terms of clinical and radiographic outcomes[10,17,35]. Despite this, treatment failure is observed in up to one-third of patients due to lack of efficacy or to adverse events[36,37]. Switching to a second or even third TNF inhibitor has become common practice. The question is whether there is a scientific and/or clinical rationale for this practice. Increasingly, the answer seems to be yes.

Switching between TNF inhibitors: scientific rationale. Infliximab, etanercept, and adalimumab are similar, but not identical. They differ in terms of molecular structure, mechanism of action, pharmacokinetics, and efficacy in diseases other than RA. Infliximab and adalimumab (monoclonal antibodies) bind soluble and membrane-bound TNF and induce neutralizing antibodies, but differ markedly in their pharmacokinetics. Etanercept (a fusion protein) binds TNF and lymphotoxin α, and does not induce antibodies[38,39]. Unlike infliximab and adalimumab, etanercept is not effective in granulomatosis disorders such as Crohn's disease and Wegener's granulomatosis[40,41]. The differences between the TNF inhibitors in molecular structure and modes of action provide a solid scientific rationale for switching agents in the event of treatment failure.

Switching between TNF inhibitors: clinical experience. Some 2 dozen reports have been published on switching TNF inhibitors in RA[42,43]. These include open-label, observational trials, retrospective studies, and analyses of clinical registry databases. A number of issues make interpretation of the results problematic, not the least of which is the lack of randomized, controlled trials. In most of these studies sample sizes are small, methodologies are often inadequately described, and study durations are short. Concomitant medications and outcome measures used to evaluate efficacy vary widely. As important, little consideration is given to the question of regression toward the mean: the tendency of patients with very active disease to improve without additional therapeutic intervention. Nonetheless, the aggregate data and increasing clinical experience suggest that patients with RA may benefit from switching TNF inhibitors[42,43].

Unanswered questions about switching between TNF inhibitors that require further investigation include the effects and significance of primary nonresponse (NR) compared with secondary NR (that is, patients who never had a response to the previous agent versus those who lost their initial response)[43]. In patients switched from infliximab to adalimumab, higher response rates were observed in the secondary NR group than in the primary NR group (71% vs 43%)[44]. In patients switched from infliximab to etanercept, response rates were higher in the primary NR group compared to the secondary NR group (67% vs 56%)[45].

It also remains unclear whether the magnitude of the response to a second or third TNF inhibitor is significantly different from the response to the first agent, and whether the order in which the agents are used has any influence on efficacy. A Danish national registry[46] suggests that patients switching due to lack of efficacy had a better clinical response to the second agent than the first. Patients switching because of adverse effects responded equally well to the first and second treatments and had a low risk of discontinuing the second treatment because of adverse effects.

Available data suggest that switching TNF inhibitors is effective in the management of RA. More rigorous, randomized, placebo-controlled studies are needed to address unresolved issues.

7. Switching Between Biologic Therapies

Despite the demonstrated clinical efficacy of TNF inhibitors, a substantial proportion of patients with RA do not achieve significant clinical responses to these agents. Abatacept and rituximab, 2 additional biologic therapies approved in the US in late 2005 and early 2006, offer new treatment options for TNF inhibitor-resistant patients.

Switching between biologics: TNF inhibitors to abatacept. Abatacept is the first in a new class of agents for the treatment of RA that selectively modulate a specific co-stimulatory signal required for full T cell activation. Phase II trials have shown abatacept to be safe and effective in RA as monotherapy and in combination with MTX[47-49]. In the larger Phase III trial known as AIM (Abatacept in Inadequate Responders to Methotrexate), patients with active RA despite MTX received either placebo or abatacept for 12 months[50]. At one year, ACR responses for abatacept plus MTX vs MTX alone were ACR20 73.1% vs 39.7%; ACR50 48.3% vs 18.2%; and ACR70 28.8% vs 6.1% ($p < 0.001$ for all). Patients receiving abatacept plus MTX showed statistically less worsening of the median joint erosion score than those receiving MTX alone (0.0 vs 2.7; $p = 0.029$). However, median changes in the joint space narrowing scores and total scores were similar between the 2 treatment groups.

The safety and efficacy of abatacept in patients with active RA and an inadequate response to at least 3 months of TNF inhibitor therapy were evaluated in the ATTAIN (Abatacept Trial in Treatment of Anti-TNF Inadequate Responders) trial[51]. Patients received either placebo or abatacept, in addition to at least one DMARD. At 6 months, ACR responses for abatacept versus placebo were ACR20 50.4% versus 19.5% ($p < 0.001$); ACR50 20.3% versus 3.8% ($p < 0.001$); and ACR70 10.2% versus 1.5% ($p = 0.003$). Significantly more patients in the abatacept group than in the placebo group had a clinically meaningful improvement in physical function, as reflected by an improvement from baseline of at least 0.3 in the HAQ disability index (47.3% vs 23.3%; $p < 0.001$).

The data available to date suggest abatacept is an effective and well tolerated addition to the RA armamentarium. It shows good results in terms of quality of life and physical function measurements and offers patients resistant to TNF inhibitors a viable therapy option. Areas that will require further investigation include longterm safety and durability of response (abatacept studies have been ≤ 12 months in duration) and the effect of abatacept on structural damage (AIM is the only abatacept trial to date that has addressed radiographic progression).

Switching between biologics: TNF inhibitors to rituximab. Rituximab is a genetically engineered chimeric monoclonal antibody that targets CD20+ B cells[52]. It was initially approved by the US Food and Drug Administration for the treatment of non-Hodgkin's lymphoma[53]. Recently, clinical trials have shown it to be effective in RA as monotherapy and in combination with MTX, in patients who are MTX-resistant and TNF inhibitor-resistant[54-57].

The REFLEX (Randomized Evaluation of Long-Term Efficacy of Rituximab in RA) trial is a 2-year Phase III study to evaluate the safety and efficacy of rituximab and MTX in combination in patients with active RA who have an inadequate response to one or more TNF inhibitors. A primary safety and efficacy evaluation at 24 weeks showed that a single course of rituximab with concomitant MTX therapy provided significant and clinically meaningful improvements in disease activity[56]. Significantly more ($p < 0.0001$) rituximab-treated patients than placebo-treated patients demonstrated ACR20 (51% vs 18%), ACR50 (27% vs 5%), and ACR70 (12% vs 1%) responses and moderate to good EULAR responses (65% vs 22%). All ACR response parameters were significantly improved in rituximab-treated patients, who also had clinically meaningful improvements in fatigue, disability, and health-related quality of life (demonstrated by FACIT-F, HAQ DI, and SF-36 scores, respectively).

At 24 weeks, rituximab-treated patients in the REFLEX trial showed a trend toward less progression in radio-graphic endpoints[56]. At Week 56, the mean change in the total Genant-modified Sharp score in the placebo group was 2.31, compared to 1.00 in the rituximab group ($p = 0.0043$). Significant differences were also observed in changes of erosion score and joint space narrowing score. In addition, the proportion of patients with no change in erosion score was significantly higher in the rituximab group compared to the placebo group (61% vs 52%; $p = 0.0445$)[57].

These preliminary findings suggest that rituximab therapy was associated with significant inhibition of structural damage. It is important to point out, however, that the trial allowed rescue therapy between Weeks 16 and 24 (with 40% of placebo-treated patients and 13% of rituximab-treated patients entering the rescue protocol at or after Week 16), and included intravenous and oral steroids for the first 2 weeks in both the placebo and rituximab groups[56,57].

Clinical trials with rituximab in RA have demonstrated a small increase in serious infections (but not opportunistic infections, including tuberculosis). There have also to date been no safety signals regarding malignancies. However, more longterm data will be required before any firm conclusions can be drawn about the longterm safety of rituximab in RA[53].

Conclusions

Optimizing treatment with biologics may yield better

outcomes. Key points include:

1. Combination therapy (biologic agent + MTX) is more effective than either agent alone, whether in early or established disease.
2. Early use of biologic agents is more effective than use later in the disease course.
3. Patients with moderate disease have better outcomes following treatment than patients with severe disease.
4. Tight control of disease activity (by means of aggressive therapy and close monitoring) achieves better outcomes than routine care.
5. Combination therapy (biologic agent + MTX) early may induce remission and allow longterm therapy with MTX only.
6. Abatacept and rituximab offer alternative options for patients resistant to TNF inhibitors.

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