Relative Efficacies: Antimalarials to Abatacept – The Choice Is Ours

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ABSTRACT. Early diagnosis and treatment of rheumatoid arthritis (RA) are important in order to halt disease progression and joint destruction, and minimize loss of function. Individually, the disease modifying antirheumatic drugs have demonstrated similar efficacies in radiological and clinical outcomes. However, various combination therapies have been shown to improve therapeutic outcomes for patients who fail to respond adequately to monotherapy. With the introduction of the cytokine inhibitors and the development of newer biologic therapies, a number of treatment options are available for patients with RA. The efficacies of the various treatment strategies are reviewed. (J Rheumatol 2009;36 Suppl 82:17-24; doi:10.3899/jrheum.090127)

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Rheumatoid arthritis (RA) is a chronic, inflammatory disorder associated with significant morbidity and requiring longterm, and potentially lifelong, treatment. Early diagnosis and treatment are integral to the management of RA, with the goal of reducing and controlling symptoms of joint pain and inflammation, minimizing loss of function, and reducing joint damage and disability. The traditional disease modifying antirheumatic drugs (DMARD), such as methotrexate (MTX), remain the standard of care in patients with newly diagnosed RA. However, the introduction of the biologic therapies over the past decade has revolutionized the treatment of RA. The relative efficacies of the currently available treatments for RA are reviewed.

THE IMPORTANCE OF EARLY TREATMENT

With the introduction of more effective medications for the treatment of RA with more favorable toxicity profiles, management strategies have evolved toward earlier use of these agents. Delaying therapy even a few months from the onset of symptoms has been shown to decrease the ability of the traditional single-drug strategy to induce remission in early RA[1]. In the FINnish Rheumatoid Arthritis Combination therapy (FIN-RACo) trial, 195 patients with recent-onset RA (median duration 6 months) were randomly assigned to treatment with either a combination of DMARD (sulfasalazine, MTX, hydroxychloroquine, and prednisolone) or a single DMARD with or without prednisolone[1]. For patients treated using a single DMARD, a 4-month delay in treatment had a significant effect on remission.

In the Hydroxychloroquine in Early Rheumatoid Arthritis (HERA) study, patients with disease duration of less than 2 years were randomly assigned to treatment with hydroxychloroquine or placebo – with a 9-month placebo run-in period. Patients who received hydroxychloroquine experienced significantly greater improvements in joint, pain, and physical function indexes at 9 months[2]. Three years later, these differences were maintained in those who had received placebo for 9 months and were then switched to an active drug[3]. Whether this difference is stable or is magnified because of the initial delay is not known and was not addressed by the study.

In a metaanalysis of results from 13 trials of cytokine antagonists, Nixon, *et al* found that patients treated earlier in the duration of RA disease had a higher probability of achieving a 50% improvement in American College of Rheumatology criteria (ACR50) versus those in whom treatment was delayed[4].

COMBINATION DMARD THERAPY

O'Dell and colleagues were among the first to popularize the benefits of combination therapy with traditional DMARD[5,6]. The combination of doxycycline and MTX was also studied in 66 patients with early seropositive RA who had not previously been treated with a DMARD. ACR20 and ACR50 responses were higher among patients who received a combination of doxycycline 20 mg or 100 mg and MTX than among those treated with MTX monotherapy[7]. Response was not affected by dose of doxycycline.

The best responses observed to date with combination therapy involving traditional DMARD were seen in a 2002 study of MTX, sulfasalazine, and hydroxychloroquine in the treatment of RA[6]. The triple combination of MTX, sulfasalazine, and hydroxychloroquine resulted in

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a better response than the double combination of MTX and either of the other 2 drugs. After 2 years of treatment, patients receiving the triple combination therapy achieved an ACR20 response of 78%, compared with 60% for MTX plus hydroxychloroquine ($p = 0.05$) and 49% for MTX plus sulfasalazine ($p = 0.002$). A similar trend was seen for ACR50 response, which was achieved by 55%, 40%, and 29% of patients in each of the 3 groups, respectively. The ACR20 and ACR50 responses achieved with triple combination therapy were the highest among patients who had not been exposed to prior MTX therapy – 83% and 67%, respectively. While impressive, these results have not been assessed in other clinical trials. One study has shown a benefit of combination MTX and sulfasalazine[8]. However, at 18 months, ACR20 was achieved in only 29% of patients.

The Tight Control for Rheumatoid Arthritis (TICORA) study showed what can be achieved with conventional combination therapy[9]. The aim of the study was not to assess differences in the drugs used, but rather to assess differences in approaches to the use of available treatment options. Patients were randomly assigned to either intensive therapy (every month), or routine/nonintensive therapy (about every 3 months). At the 18-month assessment, 84% of patients undergoing intensive therapy had achieved an ACR50 response, compared with only 40% in the group that received routine therapy ($p < 0.0001$). The strategy of intensive outpatient management substantially improved disease activity, radiographic disease progression, physical function, and quality of life at no additional cost.

Clinical improvements have also been achieved with the addition of intramuscular gold to MTX treatment. In the Methotrexate and Gold (METGO) study, patients with a suboptimal response to MTX were randomly assigned to intramuscular treatment with gold or placebo in addition to their treatment regimen[10]. Of the patients who received combination therapy including gold, 61% achieved an ACR20 response, compared with 30% of patients who received placebo ($p = 0.014$). An ACR50 response was achieved in 26% and 4% of patients who received gold and placebo, respectively.

COMBINATION THERAPIES WITH ANTI-TUMOR NECROSIS FACTOR AGENTS

The development of the cytokine antagonists, particularly the anti-tumor necrosis factor (TNF) agents, has represented a tremendous advance in the treatment of RA. In the metaanalysis by Nixon, *et al*, the combination of MTX with either an anti-TNF agent or an interleukin 1 (IL-1) inhibitor was found to further increase the efficacy of each therapy[4]. The anti-TNF agents were found to be equally effective, with greater efficacies than the IL-1 inhibitor.

Infliximab. In the Behandel Strategieën (BeSt) trial[11], 508 patients were randomly assigned to one of 4 treatment strategies: sequential monotherapy, step-up combination therapy, initial combination therapy with tapered high-dose prednisone (COBRA), or initial combination therapy with infliximab. Patients who received initial combination therapy with prednisone or infliximab achieved clinical remission [Disease Activity Score 28 (DAS28) 1.6 or lower] significantly faster than patients who received sequential monotherapy or step-up combination therapy. As well, functional status, as assessed by changes in scores on the Health Assessment Questionnaire (HAQ), improved more rapidly in patients treated with initial combination therapy. However, after 2 years of treatment, functional and clinical outcomes were comparable among the 4 groups.

In the Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE), MTX-naïve patients were randomly assigned to treatment with MTX plus the addition of infliximab 3 mg/kg, infliximab 6 mg/kg, or placebo[12]. After one year of treatment, a significantly greater number of patients who received the combination of MTX and infliximab at either dose achieved better ACR20 (66% for 6 mg/kg; 62% for 3 mg/kg), ACR50 (50% for 6 mg/kg; 46% for 3 mg/kg), or ACR70 (37% for 6 mg/kg; 33% for 3 mg/kg) responses compared with patients who received MTX alone. However, reasonably good results were seen even among the patients who received MTX monotherapy, with 54%, 32%, and 21% achieving ACR20, ACR50, and ACR70 responses, respectively.

The Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) randomly assigned 428 patients with active RA, despite continuous treatment with MTX for 3 months or longer, to continue on MTX alone or to undergo one of 4 regimens of infliximab: 3 or 10 mg/kg every 4 or 8 weeks[13,14]. The addition of infliximab to MTX resulted in a sustained reduction in the signs and symptoms of RA that was significantly greater than the reductions associated with continued MTX. Significantly more patients in the combination groups achieved ACR20, ACR50, or ACR70 responses than in the MTX monotherapy group at Weeks 30[13] and 54[14].

Etanercept. As a monotherapy, etanercept has demonstrated efficacy similar to that of MTX monotherapy for the treatment of RA. In a trial of 632 patients with early RA, those assigned to etanercept treatment thrice weekly had a more rapid rate of improvement than those who received weekly MTX therapy, with significantly more patients achieving ACR20, ACR50, and ACR70 responses at 6 months[15]. However, at one year, ACR responses were not significantly different between the 2 groups.

When given as an add-on to MTX, etanercept therapy has been shown to result in rapid, sustained improvements in ACR20, ACR50, and ACR70 responses[16]. In a 24-week, double-blind trial, 89 patients with persistently active RA despite treatment with MTX were randomly assigned to treatment with etanercept or placebo while continuing to receive MTX. After 24 weeks, 71% of patients treated with etanercept in addition to MTX achieved an ACR20 response compared with 27% of those receiving MTX monotherapy ($p < 0.001$)[16]. In the Trial of Etanercept and Methotrexate With Radiographic Patient Outcomes (TEMPO), disease activity was also better controlled by a combination of etanercept 25 mg twice weekly plus MTX up to 20 mg/week, than by either agent alone after 3 years of treatment[17].

In the COmbination of Methotrexate and ETanercept in Active Early Rheumatoid Arthritis (COMET) trial, 542 outpatients with early moderate to severe RA of 3 to 24 months' duration and no history of MTX were randomly assigned to treatment with etanercept plus MTX or MTX monotherapy[18]. After one year of treatment, 50% of patients in the combination group had achieved remission, defined as a DAS28 of 2.6 or lower, compared with 28% of the patients receiving MTX monotherapy ($p = 0.001$). Radiographic nonprogression, defined as total Sharp score of 0.5 or less, was achieved by 80% in the combination group and 59% in the MTX monotherapy group ($p < 0.001$)[18].

Adalimumab. As monotherapy, adalimumab has shown some efficacy for the treatment of RA that fails to respond to traditional DMARD therapy. In a 26-week double-blind, placebo-controlled trial, 544 patients who had previously failed to respond to DMARD therapy were randomly assigned to treatment with adalimumab monotherapy at one of 4 dosages (20 mg every other week, 20 mg weekly, 40 mg every other week, or 40 mg weekly) or placebo[19]. Among this population of inadequate responders to DMARD therapy, adalimumab monotherapy resulted in significant improvements in ACR20, ACR50, and ACR70 responses. However, as with the other biologics, the efficacy of adalimumab in monotherapy is generally comparable with that of MTX monotherapy. In the PREMIER study, patients who received adalimumab monotherapy achieved similar, or slightly lower, ACR20, ACR50, and ACR70 response rates at one and 2 years of treatment compared with those who received MTX monotherapy[20]. Patients who received a combination of 2 agents performed better on all outcomes than those who received either monotherapy.

In the Anti-TNF-Research Study Program of the Monoclonal Antibody D2E7 in RA (ARMADA) trial, 271 patients who had previously failed one to 4 DMARD and had inadequate response to MTX were randomly assigned to adalimumab 20 mg, 40 mg, or 80 mg or placebo every other week, in addition to continued stable dosage of MTX[21]. At 24 weeks, all the combinations of adalimumab resulted in a significantly higher proportion of patients who achieved ACR20 and ACR50. As well, significantly more patients treated with the 40 mg or 80 mg doses of adalimumab in combination with MTX achieved an ACR70 response compared with those treated with MTX monotherapy.

Golimumab. The new anti-TNF agent golimumab has been studied for the treatment of RA, alone or in combination with MTX. In a multicenter, double-blind, placebo-controlled trial, 637 MTX-naïve patients with active RA were randomly assigned to treatment with MTX in addition to either placebo or one of 3 doses of golimumab[22]. Combination therapy resulted in a higher proportion of patients achieving ACR20. Therapy with the biologic agent alone did not result in greater efficacy than MTX monotherapy in this group of MTX-naïve patients.

Golimumab has also been studied in patients with active RA despite previous MTX therapy. In the GO-FORWARD study, 444 patients were randomly assigned to MTX, golimumab 100 mg subcutaneously plus placebo capsules, golimumab 50 mg plus MTX, or golimumab 100 mg plus MTX[23]. Results were consistent with those of other anti-TNF therapies, with significantly higher ACR20, ACR50, and ACR70 response rates seen in the combination therapy groups than in the MTX placebo group. Patients who received golimumab with placebo did slightly better than those who continued MTX placebo. However, this result was not statistically significant, reinforcing the overall impression that the anti-TNF agents do work better in combination with MTX, even in those who have already shown an inadequate response to MTX.

Certolizumab pegol. Certolizumab pegol is the first PEGylated anti-TNF therapy to be studied for the treatment of RA. In the RAPID 1 trial, 992 patients previously treated for 6 months or longer with MTX were randomly assigned in a 2:2:1 ratio to treatment with three 400 mg doses of certolizumab pegol every 2 weeks, followed by certolizumab pegol either 200 mg or 400 mg, or to a group receiving placebo every 2 weeks[24]. MTX therapy was continued as usual. At Week 24, the ACR20, ACR50, and ACR70 response rates were significantly higher among patients who received the combination of MTX and certolizumab at either dose, compared with those who received MTX alone. The RAPID 2 trial, with 634 patients with active RA, was essentially the same[25]. Again, significantly more patients who received a combi-

nation of MTX and certolizumab achieved ACR20, ACR50, or ACR70 responses compared with those who received MTX alone. These results are consistent with those of the other anti-TNF therapies.

COMBINATIONS WITH NON-ANTI-TNF BIOLOGIC THERAPIES FOR THE TREATMENT OF RA

Abatacept. In the Abatacept in Inadequate responders to Methotrexate (AIM) trial[26], 652 patients with active RA despite MTX treatment were randomly assigned to either abatacept or placebo in addition to their existing MTX. At one year, ACR response rates were significantly higher among patients treated with abatacept combination therapy versus those treated with MTX monotherapy, with ACR20 response rates of 73.1% versus 39.7%, ACR50 response rates of 48.3% versus 18.2%, and ACR70 response rates of 28.8% versus 6.1%, respectively ($p < 0.001$ for all comparisons). In the open-label extension phase of the AIM trial, 539 patients continued to receive abatacept[27]. At 2 years, the ACR70 response rate demonstrated sustained efficacy in the group that had originally received abatacept. By 2 years, the group that had originally received placebo and were then given abatacept in the open-label phase had caught up to this ACR70 response rate.

In the Abatacept study to Gauge Remission and joint damage progression in MTX-naïve patients with Early Erosive rheumatoid arthritis (AGREE), 509 patients with early RA (2 years' duration or less) and no previous treatment with MTX were randomly assigned to treatment with abatacept plus MTX or MTX monotherapy[28]. At one year, 41.4% of patients treated with the combination of abatacept and MTX had achieved clinical remission, defined as DAS28 less than 2.6, compared with 23.3% in the group receiving MTX monotherapy. Radiographic nonprogression, defined as a change in total Sharp score of 0 or less, was achieved in 61% of patients treated with combination therapy and 53% of patients treated with MTX monotherapy.

The efficacy of abatacept monotherapy has also been evaluated in a phase 2a trial of RA patients with an inadequate response to DMARD[29]. In this pilot, dose-finding, double-blind, placebo-controlled trial, 214 patients with RA were randomly assigned to treatment with one of 2 costimulatory molecules, abatacept or belatacept (0.5 mg/kg, 2 mg/kg, or 10 mg/kg), or placebo. Patients received 4 infusions on Days 1, 15, 29, and 57. On Day 85, dose-dependent increases in ACR20 responses were seen in the abatacept and belatacept groups compared with the placebo group. ACR20 responses were achieved by 23%, 44%, and 53% in patients receiving abatacept 0.5 mg/kg, 2 mg/kg, and 10 mg/kg, respectively, and by 34%, 45%, and 61% of patients receiving belatacept 0.5 mg/kg, 2 mg/kg, and 10 mg/kg, respectively. ACR20 response was achieved in 31% of patients who received placebo.

To date, the only comparison between 2 biologics in the treatment of RA has been between abatacept and infliximab in the Abatacept or infliximab vs placebo, a Trial for Tolerability, Efficacy and Safety in Treating rheumatoid arthritis (ATTEST)[30]. Schiff, *et al* enrolled 431 RA patients with an inadequate response to MTX and no prior treatment with an anti-TNF agent in a randomized, double-blind, placebo-controlled trial. Patients were randomly assigned to abatacept, infliximab, or placebo, in addition to background MTX treatment, and assessed at 6 months for reductions in mean DAS28. Patients in the abatacept and infliximab groups were then followed for a further 6 months to assess DAS28 and ACR response. At 6 months, patients in the placebo group were switched to abatacept but were not included in the one-year analysis. Changes in DAS28 at 6 months were greater in the abatacept and infliximab groups than in the placebo group ($p < 0.001$; Figure 1). The one-year data showed a trend toward increasing efficacy for abatacept beyond 6 months, while the efficacy of infliximab remained unchanged or decreased over time. The one-year safety data also suggested a more favorable risk-benefit profile for abatacept versus infliximab. However, the study was not powered to detect a difference between the 2 biologics.

Rituximab. Rituximab has also been compared with MTX, alone or in combination with either MTX or cyclophosphamide[31]. In a 24-week randomized, controlled trial, 161 patients who had previously failed to respond to multiple DMARD, including MTX, were assigned to one of four 17-day treatment groups: MTX alone, rituximab alone, rituximab plus cyclophosphamide, or rituximab plus MTX. All patients also received a 17-day course of corticosteroids. A significantly higher proportion of patients treated with rituximab achieved an ACR20, ACR50, or ACR70 response compared with MTX alone. The combinations of rituximab with either cyclosphosphamide or MTX were equally effective and better than rituximab alone.

The Dose-ranging Assessment International Clinical Evaluation of Rituximab in RA (DANCER) trial enrolled patients with active RA despite previous treatment with DMARD, including biologic agents[32]. A total of 465 patients were randomly assigned to one of 9 treatment groups: placebo, rituximab 500 mg, or rituximab 1,000 mg, with each group also taking either placebo glucocorticoids, or intravenous methylprednisolone premedication, or intravenous methylprednisolone premedication plus oral prednisone for 2 weeks.

Significantly more patients who received either infusion of rituximab achieved ACR20, ACR50, or ACR70 responses compared with those who received the placebo. The ACR20 response was independent of glucocorticoid treatment used.

Anakinra. As a monotherapy, the IL-1 inhibitor anakinra has demonstrated improvements in clinical response in patients with RA. Among patients with severe RA who were randomly assigned to placebo or anakinra monotherapy at a dose of 30 mg, 75 mg, or 150 mg, 43% of patients receiving anakinra 150 mg achieved ACR20 at 6 months, compared with 27% of patients who received placebo ($p = 0.014$)[33]. Even more significant results have been achieved when anakinra was combined with MTX. In a study of 899 patients with active RA who had been taking a stable dose of MTX for a minimum of 8 weeks, patients were randomly assigned to treatment with either anakinra 100 mg or placebo in addition to their MTX. Among patients who received the combination therapy, 38% achieved an ACR20 response compared with 22% who received placebo[34].

Tocilizumab. To date, the only biologic agent to demonstrate greater efficacy in monotherapy versus MTX is tocilizumab. In the Actemra versus Methotrexate double-Blind Investigative Trial In mONotherapy (AMBITION), 570 patients with active RA who had not previously failed a DMARD therapy were randomly assigned to either tocilizumab 8 mg/kg every 4 weeks or MTX 7.5 mg/week, titrated to a dose of 20 mg/week within 8 weeks[35]. At 24 weeks, the tocilizumab-treated group had a higher proportion of ACR20, ACR50, and ACR70 responders than the group that received MTX monotherapy (ACR20 70% vs 53%, $p < 0.001$; ACR50 44% vs 34%, $p = 0.0023$; ACR70 28% vs 15%, $p = 0.0002$).

SWITCHING STRATEGIES IN THE TREATMENT OF RA

Switching from one to another anti-TNF agent. There are currently 3 commercially available anti-TNF agents: infliximab, etanercept, and adalimumab. Clinical trial evidence suggests that these therapies are equally effective. Despite the good clinical responses achieved with the anti-TNF agents, a substantial proportion of patients with RA have persistent disease or continued flares of disease activity. In these cases, switching to an alternative anti-TNF agent may be discussed.

In the open-label Research in Active RA: Adalimumab Trial (ReACT), the efficacy and safety of adalimumab were compared between RA patients who had previously failed to respond to treatment with etanercept and/or infliximab therapy and those who had no history of anti-TNF treatment[36]. Patients were given adalimumab 40 mg subcutaneously every other week for 12 weeks, in addition to their current DMARD, with the exception of anti-TNF therapies, which had been discontinued prior to the trial. Of the 6,610 patients enrolled in ReACT, 899 had received prior treatment with etanercept and/or infliximab. All of the subgroups responded well to treatment with adalimumab, with a somewhat higher response observed in patients who had not previously been treated with an anti-TNF medication. Among those with a history of prior anti-TNF treatment, responses were similar, regardless of whether patients had discontinued treatment because of loss of efficacy or because of intolerance.

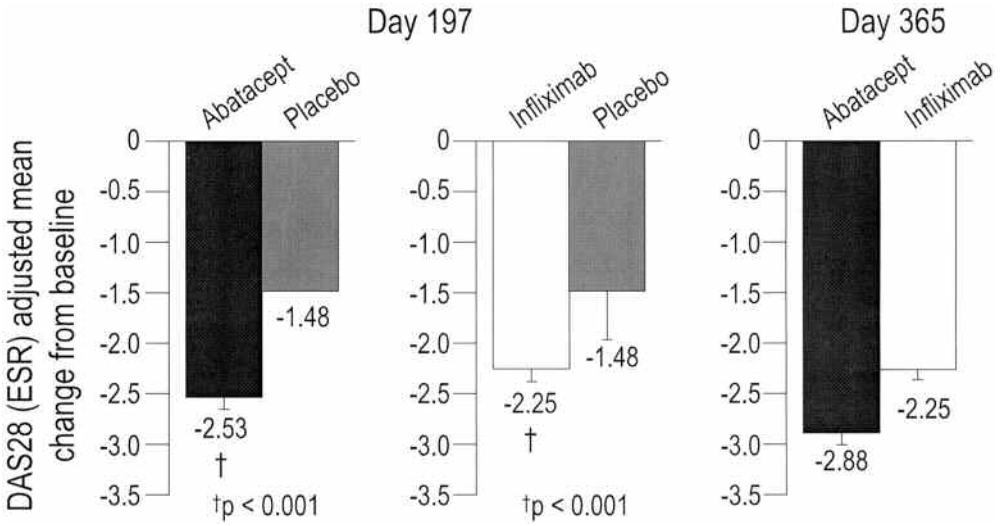

Figure 1. Mean change from baseline in Disease Activity Score 28 (DAS28) at Days 197 and 365 in the ATTEST trial[30]. ESR: erythrocyte sedimentation rate. Reprinted from Ann Rheum Dis 2008;67:1096-103, with permission.

The value of switching to an alternative anti-TNF therapy after failing to respond to one therapy was supported by Bharadwaj, *et al* in a study presented at the 2008 European League Against Rheumatism annual meeting[37]. In this retrospective analysis of patients who had failed treatment with at least one anti-TNF therapy, switching to a second or third anti-TNF therapy resulted in ACR20 response rates of 50% and 30%, respectively.

The randomized, double-blind, placebo-controlled GO-AFTER trial examined the efficacy of the anti-TNF agent golimumab in patients with active RA despite previous treatment with an anti-TNF therapy[38]. A total of 461 patients were randomly assigned to treatment with golimumab 50 mg, golimumab 100 mg, or placebo. Golimumab reduced the signs and symptoms of RA, as demonstrated by higher ACR20 and ACR50 responses, and improved physical function, as shown by improvements in DAS28.

Despite evidence suggesting an improved response with a second anti-TNF agent when the first agent does not elicit an adequate response, the likelihood that a patient will adhere to treatment declines with each subsequent switch in therapy. Drug survival was analyzed among 488 patients (68% with RA) in a Spanish registry previously treated with more than one anti-TNF medication[39]. The probability of a patient continuing treatment with a second or third anti-TNF therapy was significantly reduced.

Switching from an anti-TNF agent to a different biologic agent.

Because of their novel mechanisms of action, the newer biologic agents, such as the costimulatory molecule abatacept or the monoclonal antibody rituximab, may prove to be more effective than switching to an alternative anti-TNF agent when RA patients fail to respond to one anti-TNF agent. As an example, due to its unique mechanism of action, response to abatacept is not expected to be affected by previous treatment with an anti-TNF drug. The Abatacept Trial in Treatment of Anti-TNF INadequate responders (ATTAIN) assessed the efficacy and safety of abatacept in the treatment of patients with RA who had an inadequate response to an anti-TNF therapy[40]. Patients were randomly assigned in a 2:1 ratio to treatment with abatacept or placebo, in addition to at least one other DMARD (normally MTX). Patients had discontinued anti-TNF therapy prior to randomization. After 6 months, ACR20, ACR50, and ACR70 responses were significantly higher in patients treated with abatacept than in those treated with placebo. As well, significant reductions in DAS28 were observed, regardless of the reason for discontinuing the prior anti-TNF treatment[41].

Similar results have been demonstrated with the monoclonal antibody rituximab. In the Randomized Evaluation of Long-Term Efficacy of Rituximab in RA (REFLEX) trial, 520 patients with active RA and inadequate response to one or more anti-TNF therapies were randomly assigned to receive rituximab or placebo – both in addition to MTX therapy[42]. At 24 weeks, significantly more patients in the rituximab group achieved ACR20 and ACR50 responses compared with those in the placebo group. At one year, patients treated with rituximab also had significantly less joint space narrowing than those treated with placebo.

The newer monoclonal antibody tocilizumab demonstrated similar results in the RheumAtoiD ArthritIs Study in Anti-TNF FailurEs (RADIATE) trial. RADIATE randomly assigned 499 patients with moderate to severe RA and prior anti-TNF failure to treatment with tocilizumab 4 mg plus MTX, tocilizumab 8 mg plus MTX, or placebo plus MTX[43]. ACR20, ACR50, and ACR70 responses were significantly higher in the groups treated with tocilizumab than in the group that received MTX alone, irrespective of the number or type of anti-TNF therapy, with a dose-response favoring the 8 mg dose.

Based on the accumulated clinical trial data, consideration should be given to using a biologic agent with a different mode of action for patients who have failed to achieve a response to an anti-TNF inhibitor.

LONGTERM ADHERENCE TO BIOLOGIC THERAPIES

The validity of longterm data collected in randomized, controlled trials of the classic DMARD and of biologic therapies in the treatment of RA has been questioned, due to the high dropout rates[44]. With MTX, blinded treatment of more than 6-month duration is generally associated with dropout rates ranging from 30% to 50%. Reasons for discontinuation include lack of efficacy, adverse events, or reasons of convenience. Patients who receive placebo in randomized trials generally discontinue participation early or are given rescue therapy at some point, which tends to reduce the number of patients available for comparison.

Lower dropout rates may reflect patient expectations as well as treatment benefit, since higher rates of adherence are seen in trials where placebo treatment is given with background therapy, despite a previous failure to respond[44]. Therefore, longterm data from randomized, controlled trials should be examined to determine whether benefits seen in the short term (i.e., within 12 months) are sustained in the long term (i.e., over 24 months) in those who continue with treatment[44].

Longterm data from treatment registries or open-label studies can also offer valuable information, as patients in randomized, controlled trials may not reflect "real-life" patients with early RA. In a recent abstract presented at the 2008 American College of Rheumatology annual meeting, Bykerk and colleagues showed that only 0.7% to 52% of patients in an observational cohort of patients with early RA would have been eligible for inclusion in one of a variety of clinical trials[45].

CONCLUSIONS

The importance of early initiation of remittive DMARD therapy for patients with RA has been confirmed in a number of clinical trials. A number of treatment options are currently available, with the most promising strategies involving combination therapies with the biologic therapies. Clearly, the biologic agents are more effective when given in combination with MTX, even among those who have previously failed to respond to MTX monotherapy. However, data comparing the efficacy of the various biologic agents are limited.

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