Advances in the treatment of rheumatoid arthritis and the spondyloarthropathies

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The 70th Annual Scientific Meeting of the American College of Rheumatology (ACR) took place in Washington, DC, USA, from November 10–15, 2006. More than 13,000 attendees, a record number, which included over 9500 scientists, registered for the meeting. Approximately 2000 abstracts were presented, along with a number of state-of-the-art lectures and topical symposia. While it is not feasible to review all of the important findings from this meeting, an attempt will be made to highlight selected abstracts. This article will focus on the advances in the treatment of rheumatoid arthritis (RA) and spondyloarthropathies (SpA), while a follow-up article will discuss treatment of connective tissue diseases.

Treatment of rheumatoid arthritis

Early treatment of RA with disease-modifying antirheumatic drugs (DMARDs) improves the clinical outcomes in patients with recent onset of RA [1]. Indeed, multiple clinical trials have demonstrated that even a brief delay in starting DMARD therapy can negatively impact radiographic outcomes [2]. Undifferentiated arthritis (UA) is an early presentation of arthritis that does not fulfill criteria for a more definitive diagnosis [3]. The PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment (PROMPT) trial was a randomized, double-blind, placebo-controlled study of 110 patients with UA, treated with methotrexate (15 mg/week) or placebo [4]. The disease activity score (DAS) was calculated every 3 months and the dose of methotrexate increased as needed to achieve a DAS score of 2.4 or less. After 12 months, medication was tapered off and patients followed for a period of 30 months. The outcome measures were the fulfillment of ACR criteria for RA and radiographic progression. After 30 months, a total of 22 of 55 patients in the methotrexate group had progressed to develop RA, compared with 29 of 55 in the placebo group ($p = 0.04$). Furthermore, those treated with methotrexate had less radiographic progression. Although these findings support the concept of a window of opportunity in the treatment of RA, it must be realized that approximately 40–50% of patients with UA go into lasting remission, 28–43% remain undifferentiated and only 17–32% progress to RA [3]. The benefits of methotrexate were only seen in anticyclic citrullinated peptide-positive subjects and, therefore, support the important role of these antibodies in the diagnostic armamentarium for early RA.

The TIght Control Of Rheumatoid Arthritis (TICORA) study compared sustained, tight control of disease activity with routine outpatient care in the management of RA [5]. In this trial, patients assigned to intensive management were followed on a monthly basis. After the third month, treatment was increased according to protocol to achieve a DAS of 2.4 or less. Subjects in the routine care group were started on monotherapy and medications changed at the discretion of the rheumatologist. This study concluded that an intensive management strategy of targeting persisting disease activity using a step-up DMARD protocol was superior to routine clinical care, over a period of 18 months, in patients with early RA. Patients from this trial were invited for follow-up visits 5 years after initial enrolment. Assessment of 73 patients (of 111 in the original trial), 39 from the intensive treatment group and 34 from the routine group, revealed that several disease activity measures, including DAS and ACR response rates, remained lower in those assigned to the intensive treatment group [6].

In the Treatment of Early Aggressive Rheumatoid arthritis (TEAR) study, 96 patients with early RA (mean duration of 11 months) were randomized to receive step-up therapy (as used in the TICORA trial) or early combination therapy with methotrexate, sulfasalazine and hydroxychloroquine [7]. Treatment was escalated in either group if a DAS of 3.2 or less was not achieved. Measures of disease activity, quality of life and physical function as well as radiographic outcomes were recorded at 12 months. Interestingly, in this study, the use of early triple therapy did not appear to provide any additional benefit when compared with step-up therapy.

Treatment with antitumor necrosis factor-α blockers

The use of antitumor necrosis factor (TNF) therapy has significantly improved functional outcomes of patients with RA. A consensus statement in 2001 predicted that TNF antagonists may become first-line agents in the treatment of RA [8]. In 2005, the Behandel-Strategieen (BeSt) study reported that early therapy of RA with a combination that included prednisone or infliximab resulted in earlier functional improvement and less radiographic damage after 1 year when compared with sequential monotherapy, step-up combination therapy or step-down therapy [9]. Of the 508 patients enrolled in this trial,

120 patients were started on infliximab (3 mg/kg body weight) and methotrexate (25 mg/week). The dose of infliximab was then increased or decreased based on whether the C-reactive protein (CRP) was greater or less than 2.4. When remission was achieved (DAS < 2.4), infliximab and methotrexate were tapered off. Data presented at the meeting demonstrated that 3 years after initiation of therapy, 51% of patients who had discontinued infliximab remained in clinical remission [10]. Remarkably, 15% of patients continued to be in clinical remission and had no radiographic progression despite having stopped all antirheumatic drugs. These findings support the notion that early aggressive therapy or induction therapy may alter the course of early RA. This conclusion, however, contrasted with findings from a 15-center, randomized, double-blind Finnish trial of 99 DMARD-naive patients, treated with methotrexate, sulfasalazine, hydroxychloroquine and prednisolone, in combination with either infliximab or placebo infusions [11]. The ACR criteria for remission were used to assess outcomes at 6 and 12 months. Adding infliximab during the first 6 months to the above regimen did not appear to increase the likelihood of remission. A long-term follow-up of a larger cohort of patients with clinical and radiographic outcomes might be necessary to determine the position of anti-TNF therapy in early treatment of RA.

High levels of TNF-α have been found in patients with heart failure and may also play a role in atherosclerosis. Despite the disappointing results of anti-TNF-α therapy in congestive heart failure, there is now ample evidence to suggest that these agents may reduce cardiovascular risk in patients with RA. A retrospective analysis compared the incidence of cardiovascular disease in 8073 RA patients treated with anti-TNF agents (3782 etanercept, 2812 infliximab and 1479 adalimumab) with a cohort of 1807 subjects with active RA requiring DMARD therapy [12]. Myocardial infarction and cerebrovascular accident (CVA) rates were calculated per 1000 person-years from registration, based on events that led to hospitalization or death. Analysis at 6 months suggested that anti-TNF therapy did not increase the risk of MI. The risk for CVA was also reduced in the short term. An observational study from Sweden compared the mortality in RA patients treated with anti-TNF therapy (etanercept, infliximab or adalimumab) with that of a standard RA population [13]. Of a total 1534 patients, 949 received anti-TNF therapy. Overall mortality and cardiovascular mortality was estimated, with adjustments made for age, sex, disease severity markers and baseline comorbidities. Treatment with TNF inhibitors was associated with a reduced overall mortality among RA patients under 80 years of age, mainly due to a lower cardiovascular mortality.

Since their approval, a major concern with the use of anti-TNF therapy has been an increased risk of infections due to TNF suppression. A recent meta-analysis of RA patients treated with infliximab and adalimumab demonstrated a significant increase in risk for serious infections [14]. Solomon and colleagues assessed the association between initiation of anti-TNF therapy and the risk of serious bacterial infection [15]. The number of serious bacterial infections requiring hospitalization in a large cohort of RA patients (15,597 courses of therapy equivalent to 5676 patient-years of exposure) started on DMARDS or anti-TNF therapy was monitored over a period of 8 years. No increase in serious bacterial infections was found among users of anti-TNF-α therapy compared with those on methotrexate. Glucocorticoid use, however, was associated with a dose-dependent increase in such infections. These results contrasted with the findings of a study by Saag and colleagues that compared the rate of infection in RA patients treated with anti-TNF therapy (n = 2393; post-index observation time: 3894 person-years) with patients treated on methotrexate alone (n = 2933; post-index: 4846 person-years) [16]. In this study of 187 patients, the multivariable-adjusted risk for hospitalization with a bacterial infection was significantly higher among patients receiving anti-TNF than among those receiving only methotrexate.

The meta-analysis by Bongartz estimated that the risk for malignancies was also increased in patients receiving higher doses of infliximab and adalimumab [14]. A prospective study from France reported on cases of lymphoma in patients treated with anti-TNF agents over a period of 2 years [17]. In an estimated 30,000 patients treated with anti-TNF therapy, 16 cases of lymphoma were identified (nine cases with infliximab, four with adalimumab and three with etanercept). When compared with the national population, no increase in the incidence of lymphoma was detected in patients treated with anti-TNF agents, except for a slight increase in risk for Hodgkin's lymphoma in men, a finding already reported in RA patients treated with methotrexate. A study from the USA reported on incident cases of cancer among 13,001 subjects, participating in a study of RA outcomes over a period of approximately 7 years compared with overall population rates using the US National Cancer Institute Surveillance, Epidemiology, and End Results data bank [18]. This study also concluded that biologic therapy was unassociated with major cancers, including lung cancer and lymphoma, during 49,000 patient-years of observation. Melanoma and other skin cancers did, however, appear to occur more frequently among biologic users.

Recently approved biologics

There were several reports on the efficacy and long-term safety of rituximab and abatacept. Rituximab was recently approved in the USA and Europe for the treatment of RA in patients with an inadequate response to anti-TNF therapy. The Randomized Evaluation of Long-Term Efficacy of Rituximab (REFLEX) trial, a Phase III study of rituximab plus methotrexate in active RA patients with an inadequate response to anti-TNF therapy, demonstrated a significant improvement in disease activity in those treated with

rituximab compared with those treated with methotrexate alone at 24 weeks [19]. Keystone and colleagues reported on radiographic outcomes from the ongoing REFLEX trial [20]. At week 56, a significant decrease in the radiographic damage, as measured by the Genant–Sharp score was noted in the rituximab and methotrexate group when compared with the methotrexate-only group. This represents the first evidence that rituximab can inhibit joint damage in patients with an inadequate response to TNF inhibitors. Interestingly, even subjects who were ACR 20 nonresponders at week 24 appeared to have decreased radiographic progression, suggesting that radiographic progression may be independent of clinical response. The same authors presented an abstract on the ongoing open-label extension study to assess the long-term safety and efficacy of rituximab in active RA patients with an inadequate response to a TNF inhibitor [21]. Patients who had demonstrated an improvement in the initial Phase II/III trial but had residual disease activity (more than eight tender and swollen joints) were eligible for repeat courses of rituximab at 6 months. Results were available for 155 patients. A higher proportion of patients achieved clinical responses, as measured by the ACR 20, 50 and 70 and DAS (less than 2.4) criteria, after the second course. Additionally, rituximab was well tolerated, with no evidence of an increase in the rate of infections or overall incidence of adverse events (including infusion reactions). An imprecise association has been described between the risk of relapse following rituximab therapy and depletion of peripheral B-cell populations. Emery and colleagues suggest that minimal residual disease flow cytometry, a process that detects B cells up to 2 logs below levels identified by conventional analysis, may allow for prediction of response rates [22]. The same authors suggest that peripheral blood B-cell expression does not always reflect synovial B-cell expression. Indeed, optimal clinical responses to rituximab seem to occur when both these compartments are depleted. Furthermore, they demonstrated that without synovial B-cell depletion, it is difficult either to achieve or maintain a good clinical response [23]. A small observational study of 78 active RA patients, who had received anti-TNF therapy after rituximab therapy, revealed rates of serious infections that were similar to rates prior to anti-TNF therapy [24].

The clinical benefits of abatacept have been previously reported [25–27]. Results of the 2-year long-term extension of the Abatacept Trial in Treatment of Anti-TNF INadequate (ATTAIN) responders and Abatacept in Inadequate responders to Methotrexate (AIM) trials, Phase III studies of abatacept in patients with inadequate response to anti-TNF and methotrexate in RA, respectively, demonstrated continued and possibly increased efficacy of abatacept over time [28,29]. Similarly, the 2-year data of the Abatacept Study of Safety in Use with other Rheumatoid arthritis thErapies (ASSURE) trial, abatacept use in patients with active RA in clinical practice receiving background DMARD therapy that included patients with comorbidities, demonstrated a consistent safety profile [30]. An abstract presented by Genant and colleagues estimated that 56 and 50% of patients had no progression of structural joint damage after 1 and 2 years of abatacept therapy, respectively [31].

Agents in the pipeline

The impressive results observed with the anti-TNF therapies and the promising outlook of the newer biologic agents described above have created additional momentum to develop novel agents for the treatment of RA. Some of these agents are summarized in **Table 1**.

Spondyloarthropathies

Treatment of ankylosing spondylitis

Methotrexate has not demonstrated consistent efficacy in the treatment of axial disease in ankylosing spondylitis (AS) [32]. In an open-label study of 20 patients, methotrexate (20 mg weekly given as subcutaneous injections) did not show a benefit for the axial symptoms in patients with active AS beyond the expected placebo response [33].

Previous trials have established the efficacy and safety of etanercept and infliximab in the treatment of AS [32]. The results of long-term therapy with etanercept and infliximab in AS patients were presented at this meeting. Sieper and colleagues indicated that the improvements in measures of clinical efficacy and disease activity, including spinal mobility, were sustained after 148–160 weeks of etanercept therapy [34]. Similarly, efficacy of infliximab in AS was shown to be maintained after 5 years of treatment [35]. The recommendation for a higher dose of infliximab in AS (5 mg/kg body weight compared with the 3 mg/kg used in RA) is based on a small study of patients with undifferentiated SpA that showed a superior effect with a dose of 5 mg/kg compared with 3 mg/kg body weight [36]. A recent trial of 22 patients with AS had reported that infliximab at a dose of 3 mg/kg body weight may be effective for treatment of AS [37]. Results of a larger study of 80 subjects (40 placebo and 40 infliximab) were presented at the meeting. This study supported the notion that infliximab at 3 mg/kg may be effective in reducing the signs and symptoms of active AS [38].

In 2006, the US FDA approved the use of adalimumab for AS. A randomized, placebo-controlled, double-blind, Phase III study of adalimumab for AS (Adalimumab Trial evaluating Long-term efficacy and safety for Ankylosing Spondylitis [ATLAS]), conducted in the USA and Europe, demonstrated that adalimumab was efficacious in reducing signs and symptoms of AS [39]. On completion of the 24-week period of the ATLAS trial, all patients were invited to enroll in an open-label extension for an additional 28 weeks [40]. The ASsessment in Ankylosing Spondylitis working group criteria (ASAS 20), the primary outcome measure, was achieved by 46% of patients, suggesting that efficacy was

maintained to week 52. These results were reproduced by a randomized, Phase III study from Canada [41]. Patients were treated with either adalimumab 40 mg (n = 38) every other week or placebo (n = 44) during a 24-week, double-blind period. This was followed by an 80-week open-label period during which all patients received adalimumab. Magnetic resonance imaging of the spine and sacroiliac joint, taken at baseline and weeks 12 and 52, were used to assess inflammation. Adalimumab significantly reduced spinal and sacroiliac joint inflammation in AS patients after 12 weeks of treatment and this improvement was maintained through 52 weeks.

Treatment of psoriatic arthritis

In addition to improving skin and joint manifestations, infliximab and adalimumab have been shown to inhibit radiographic damage in psoriatic arthritis (PsA) patients [42,43]. Elevation in CRP levels has been shown to correlate with the progression of radiographic joint damage in PsA patients. *Post-hoc* analyses of the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT) 2 and ADalimumab Effectiveness in Psoriatic arthritis Trial (ADEPT) were presented at the meeting. They revealed that infliximab and adalimumab inhibit joint damage in PsA, regardless of CRP levels at baseline or during treatment [44,45]. A prospective, open-label trial examined the efficacy and safety of adalimumab in a large number of patients with active PsA, in real-life clinical situations. Patients with an inadequate response to at least one DMARD were treated with adalimumab (40 mg) every other week. Adverse events were monitored for the duration of treatment. Results from analysis of 441 patients, monitored over a 12-week period, suggest that adalimumab is well tolerated, with few cases of serious adverse events [46].

Other spondyloarthropathies

The response to treatment with infliximab appeared to be equally effective in a group of inflammatory bowel disease-associated SpA patients compared with AS patients. Tolerability, autoantibody induction and survival in treatment were also similar in the two groups [47]. A study of over 3000 patients suggests that reactive arthritis after gastrointestinal infection appears to correlate with the severity of gastrointestinal symptoms. In this study, a significant association between human leukocyte antigen-B27 and severity of joint pain in reactive arthritis was also noted [48].

Conclusions

The 2006 Annual Scientific Meeting of the ACR brought together the largest gathering of rheumatologists in the world. The scientific presentations covered a comprehensive range of topics in rheumatology. While the efficacy and safety of anti-TNF agents suggest that they should be considered early in the treatment of RA, AS and PsA, it must be balanced by a careful appraisal of the adverse events and economic impact of using these agents. The identification of several new cytokines offer possibilities for generation of novel therapeutics for the treatment of RA and SpA. The treatment paradigm for these inflammatory arthritides will continue to evolve as the benefits, safety and tolerability of new biologic agents are better understood. Although these advances are exciting and possibly foretell a new era in the field of rheumatology, it must be taken against the backdrop of a looming prediction for a shortage of rheumatologists in the USA by the year 2025 [49].

Table 1. Agents in the pipeline for the treatment of rheumatoid arthritis.

Drug	Description	Company	Development
Golimumab CNTO148	Human monoclonal anti-TNF antibody	Centacor	Phase II
Certolizumab Pegol	PEGylated Fab of an anti-TNF monoclonal antibody	UCB	Phase III
Tocilizumab	Humanized anti-human IL-6 receptor monoclonal antibody	Chugai Pharmaceuticals	Phase III
Denosumab AMG-162	Fully human monocloncal anti-RANKL antibody	Amgen	Phase II
Atacicept	Extracellular portion of the TACI receptor fused to an Fc domain of human IgG	Zymogenetics	Phase IB
Ocrelizumab	Humanized antibody targeting $CD20^+$ B cells	Genentec	Phase I/II
Ofatumumab HuMaxCD20	Human monoclonal IgG1 antibody	Genmab	Phase I/II

Ig: Immunoglobulin; IL: Interleukin; PEG: Polyethylene glycol; RANKL: Receptor activator of NF-κB ligand; TACI: Transmembrane activator and calcium-modulator and cyclophilin ligand interactor; TNF: Tumor necrosis factor.

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