Update on the treatment of ankylosing spondylitis

Walter P Maksymowych

Heritage Medical Research Building, University of Alberta, Edmonton, Alberta, Canada

Abstract: Non-steroidal anti-inflammatory agents (NSAIDs) remain the mainstay of treatment for ankylosing spondylitis (AS) though one recent trial suggests that continuous as opposed to on-demand use may be superior in preventing progression of structural damage. One particular NSAID, which is a highly selective cyclo-oxygenase 2 inhibitor, etoricoxib, may be superior to standard NSAIDs for AS. Second-line agents typically used for rheumatoid arthritis appear to lack efficacy. Salazopyrin is only moderately effective in the subgroup of AS patients with concomitant peripheral arthritis and not in those with purely axial disease. A recent trial showed that there is no greater efficacy in patients presenting early in their disease course. Three anti-tumor necrosis factor alpha agents, infliximab, etanercept, and adalimumab, are now available for the treatment of AS, the latest being adalimumab. All possess similar clinical efficacy in phase III trials with response rates of about 60%. Imaging studies using magnetic resonance show substantial amelioration of inflammatory lesions in the spine and sacroiliac joints. There is as yet no evidence that any of these agents prevent progression of structural damage. One study that evaluated etanercept demonstrated no impact on damage progression. Increasing evidence points to the superiority of the two monoclonal antibodies, infliximab and adalimumab, over etanercept for the treatment of extra-articular manifestations typically seen in AS such as acute anterior uveitis and inflammatory bowel disease. All three agents can be used as monotherapy and concomitant methotrexate appears to offer no advantages although insufficient doses have been used to date. Future studies should target patients earlier in their disease course as well as those with adverse prognostic factors such as elevated serum metalloproteinase 3 levels and radiographic evidence of spinal ankylosis.

Keywords: infliximab, etanercept, adalimumab, ankylosing spondylitis, NSAIDs

Ankylosing spondylitis (AS) is a common inflammatory joint disorder affecting the axial skeleton, peripheral large joints, certain entheses (attachments of tendons and ligaments to bone) and extra-articular sites such as the anterior uvea. It is increasingly becoming more amenable to treatment, particularly since the introduction of anti-tumor necrosis factor alpha (anti-TNFα) therapies. Advances in therapy have been made possible by the availability and international standardization of clinical outcome measures and increasing recognition that magnetic resonance imaging (MRI) constitutes a valuable outcome tool for the objective evaluation of disease activity. The primary objectives in the management of AS are to reduce symptoms of pain and stiffness, to improve and/or maintain function and mobility, to prevent disability, to improve quality of life and to prevent structural damage. Over the past few years, there have been several notable advances in the use of both standard therapies for AS, such as non-steroidal anti-inflammatory agents (NSAIDs), as well as the further development of anti-TNFα therapies, the latest agent introduced into clinical practice being adalimumab. Finally, several consensus documents have been published outlining approaches to treatment in AS.

Correspondence: Walter P Maksymowych
562 Heritage Medical Research Building, University of Alberta, Edmonton, Alberta T6G 2S2, Canada
Tel +1 780 407 1964
Fax +1 780 407 6055
Email walter.maksymowych@ualberta.ca

Nevertheless, several key issues remain to be resolved and these are highlighted later in this review.

Advances in the use of NSAIDs

Although these agents have been the cornerstone of pharmacological intervention for AS since their introduction in the 1950s, there are still many questions that pertain to their appropriate use. Several NSAIDs are available with differences in chemical structure, dosage, pharmacology, half-life and adverse effects. It is not known if there are differences in efficacy between NSAIDs, particularly when used in the long term, although it is generally accepted that aspirin is of limited efficacy in AS. Their principal mode of action centers on the inhibition of cyclo-oxygenase, and NSAIDs vary in their ability to suppress expressed cyclo-oxygenase-1 (COX-1) versus the inducible form of the enzyme cyclo-oxygenase-2 (COX-2) which is highly regulated and increased in inflammatory tissues. The latter is also constitutively expressed in the kidney, spleen and osteoblasts. Two recent studies suggest that there may be an advantage to using NSAIDs that are selective for COX-2, not only from the perspective of the suppression of inflammation but also the prevention of structural damage progression. One study of a COX-2 selective, etoricoxib, recruited 387 patients that were randomized to etoricoxib 90 mg or 120 mg daily, naproxen 1,000 mg daily, or placebo, for 6-weeks followed by an extension phase to week 52 whereby placebo patients were randomly allocated to either naproxen or etoricoxib therapy (van der Heijde, Baraf, et al 2005). It is important to note that the dose of naproxen is that which is typically used by rheumatologists in the treatment of AS. More patients discontinued for lack of efficacy in the placebo (47.3%) and naproxen (22.2%) groups than in those on etoricoxib (7.8% and 9.8% for the 90 mg and 120 mg groups, respectively). Discontinuation for adverse events was similar across groups. The primary end points were patient's assessment of spinal pain (0–100 mm visual analogue scale (VAS)), patient's global assessment of disease activity (0–100 mm VAS) and the Bath AS functional index (BASFI) (0–100 mm VAS). In addition to observing a statistically significantly greater improvement in all 3 primary end points in the 90 mg and 120 mg etoricoxib as compared to placebo treatment groups, the etoricoxib groups in combination also demonstrated statistically significantly greater improvement when compared to naproxen for all 3 primary end points. The Assessments in AS International Working Group 20% response rates (ASAS 20) were 64.7%, 64.8%, 52.5%, and 20.4% in the 90 mg etoricoxib, 120 mg etoricoxib, naproxen, and placebo groups, respectively. Maintenance of treatment effect was evaluated in the 6 to 52-week period of the study and this showed that both etoricoxib groups demonstrated significantly greater effects compared with the naproxen group for all 3 primary end points with no loss of treatment effect over time. There were no significant differences in the incidence of overall clinical adverse events, drug related clinical adverse events, laboratory adverse events, serious adverse events or discontinuations due to adverse events among all 4 treatment groups. However, 5 serious cardiovascular thrombotic events occurred in the extension phase and these were all noted in etoricoxib treated patients. Three patients receiving etoricoxib and 4 receiving naproxen experienced peptic ulcer bleeds. To determine whether the differences between the etoricoxib and naproxen groups were clinically meaningful a 6-week comparison of the percentage of patients with a good to excellent response in each group was performed in a post-hoc analysis. The results corroborated those of the primary end points with significantly more patients reporting a good to excellent response in the combined 90 and 120 mg etoricoxib treatment groups in comparison with the naproxen group. This, together with the differences in discontinuation rates and the ASAS 20 responses, generally supports the conclusion that treatment with etoricoxib is more efficacious than treatment with either naproxen or placebo.

A recent active comparator trial of a second COX-2 selective agent, celecoxib, is also of particular interest (Wanders et al 2005). This was a 2-year extension of a 6-week randomized, double-blind, clinical trial that compared celecoxib, ketoprofen, or placebo, with patients then being randomly allocated to receive either continuous treatment with celecoxib at 100 mg twice daily or on- demand for a period of 2-years. Patients could increase this dosage to 200 mg twice daily or could switch to another NSAID while maintaining the same treatment strategy. The primary end point was structural damage progression measured over 2-years using the modified Stoke AS Spine Score (mSASSS) (Creemers et al 1994). This was evaluated by one observer who was blinded to the treatment strategy and temporal order of the radiographs. The primary objectives of the study were to determine whether continuous use of NSAIDs might be more effective in controlling the disease process leading to a reduction in structural damage progression. The study group comprised 215 patients, 111 of whom were randomized to continuous treatment and 104 to on-demand treatment. In the continuous treatment group, 96 completed the study, 68 on celecoxib and 28 taking a different NSAID. In the on-demand group, 86 completed the study, 67 on celecoxib and 19 on a

different NSAID. Withdrawal from treatment was therefore similar in both groups. Complete sets of radiographs were available for 76 patients on continuous treatment and 74 in the on-demand group. There were no statistically significant differences in baseline characteristics of the 2 treatment groups although patients in the on-demand group had higher scores for global pain, spinal pain, night pain, patient global and baseline mSASSS radiograph damage score. The mean daily dose of celecoxib was 243 mg in the continuous treatment group, and 201 mg in the on-demand group and this difference of 42 mg was statistically significant. The probability plot for radiographic progression over 2-years showed that a greater proportion of patients in the on-demand group (45%) compared with the continuous treatment group (22%) demonstrated radiographic progression. In fact, the curve for radiographic progression in the on-demand group was to the left of the curve for the continuous treatment group along the entire range, reflecting an overall higher level of radiographic progression. The mean score for progression at 2-years was 0.4 mSASSS units in the continuous treatment group and 1.5 mSASSS units in the on-demand group, which was statistically significant ($p = 0.002$). Disease activity was stable over time in both groups and although somewhat higher in the on-demand group, the differences were not statistically significant. When analysis was confined to patients with a complete set of radiographs, time averaged values for pain at night and physician's global assessment were significantly worse in the on-demand treatment group. Regression analysis showed that differences in signs and symptoms at either baseline or during treatment could not explain the between-group differences in radiographic progression. There were no significant differences in adverse events between the two groups.

The authors of this study concluded that the effects of NSAIDs on structural damage progression were independent of their effects on disease activity but there are some potential pitfalls to their conclusions. Perhaps the most important relates to the differences in baseline characteristics between the two groups. Although not significantly different, the on-demand group had consistently higher parameters for disease severity measures, which included the mSASSS radiographic damage score. The latter is of particular relevance as baseline radiographic damage has been identified as the only predictor of subsequent radiographic damage in a longitudinal analysis of AS patients (van der Heijde et al 2004). Consequently the differences between the two groups might reflect inadequate randomization so that patients in the on-demand group had a more severe category of disease. Moreover, time averaged values for pain at night and physician's global were also significantly worse in the on-demand treatment group supporting the tenet that inadequate randomization may be a better explanation for the observed differences in primary outcome. On the other hand, there is biological plausibility for the study findings in that COX-2 is constitutively expressed in osteoblasts and both COX-2 knock-out mice and mice treated with COX-2 inhibiting drugs had reduced callous formation after a fracture (Zhang et al 2002). Moreover NSAIDs have been shown to reduce the risk of heterotopic bone formation after hip arthroplasty by 50 to 65% (Neal et al 2000).

These two studies raise the question as to whether there is a therapeutic advantage to the use of NSAIDs that are selective inhibitors of COX-2 in the management of patient with AS. Immunohistochemical analysis comparing synovial tissue samples obtained from patients with AS, osteoarthritis (OA), rheumatoid arthritis (RA) and psoriatic arthritis showed the highest COX-2 expression in samples from patients with AS (Siegle et al 1998). This, together with a role for COX-2 in the process of ossification, argues in favor of using these agents for the treatment of AS. On the other hand, COX-2 plays an important role in vascular homeostasis by sustaining vascular prostacyclin production and there is a concern that sustained COX-2 inhibition might increase the risk of vascular thrombosis. Moreover, many patients with AS maintain good symptomatic control with the use of an on-demand strategy and patients generally are reluctant to use medications continuously, particularly in view of the widespread media exposure to the harmful effects of treatment with agents such as rofecoxib. A compromise proposal might be to recommend continuous NSAID therapy if radiography of the spine shows syndesmophytes and/or ankylosis but to use the lowest dose that controls the patient's symptoms, eg, celecoxib 100 mg twice daily.

Second-line agents

The lack of efficacy of second-line agents typically used in RA, including methotrexate, has been a major disappointment in AS. Two large randomized, multi-center, placebo-controlled trials have shown that the efficacy of salazopyrin is confined to those AS patients with concomitant peripheral arthritis (Dougados et al 1995; Clegg et al 1996). A recent systematic review of 11 trials with a total of 895 patients treated for period ranging from 12-weeks to 3-years show that differences between salazopyrin and placebo in a pooled analysis were statistically significant only in erythrocyte sedimentation rates (ESR) and the severity of spinal stiffness

(Chen and Liu 2005). There was only one trial in which salazopyrin showed benefit in primary outcome analyses that included back pain, chest expansion, occiput to wall test and patient global (Nissila et al 1988). In this trial, patients had the shortest disease duration and the highest level of ESR at baseline plus the greatest proportion with concomitant peripheral arthritis. There was, therefore, hope that this agent might be effective when used very early in the disease course. This was examined in a multi-center, randomized, placebo-controlled trial in which 230 patients were treated with either salazopyrin 1 gram twice a day or placebo for 24-weeks (Braun, Zochling et al 2006). Only patients with inflammatory back pain (IBP) and features of spondyloarthritis according to the European Spondyloarthropathy Study Group (ESSG) classification criteria were eligible for the study and patients could not have a symptom duration of more than 5-years. In addition to IBP, 47% of patients had peripheral arthritis and 50% had enthesitis at baseline. Only 13% showed radiographic changes fulfilling the modified New York criteria for AS. The same number of patients (n = 17) withdrew from both treatment arms by 24-weeks. There was no major difference in the primary outcome, the Bath AS disease activity index (BASDAI), between treatment groups although the median dose of NSAID was markedly lower in the salazopyrin group than in the placebo group (28 mg versus 88 mg diclofenac or equivalent/day). Subgroup analysis according to presence or absence of peripheral arthritis at baseline showed that in contrast to earlier studies patients with IBP but no peripheral arthritis treated with salazopyrin had a significantly greater reduction in the BASDAI compared to those treated with placebo. There was no significant difference in any outcome parameter between treatment groups in those patients with concomitant peripheral arthritis. This study, therefore, dispelled the hope that patients with early disease might be more responsive to salazopyrin therapy and also challenges current treatment recommendations that salazopyrin should be considered for those AS patients with concomitant peripheral arthritis (Braun, Baraliakos et al 2003; Maksymowych et al 2003). Further placebo-controlled trials of salazopyrin for AS are likely not warranted.

Anti-TNFα therapies

Anti-TNFα therapies represent a major advance in the treatment of AS (Table 1). Three agents are currently available, a chimeric monoclonal IgG1 antibody to TNFα, infliximab, a recombinant 75 kd TNFα receptor IgG1 fusion protein, etanercept, and a human monoclonal antibody to TNFα, adalimumab.

Etanercept

The first pivotal phase III study of these agents in AS showed that etanercept was superior to placebo, significant differences being apparent as soon as 2-weeks and ASAS 20 responses being observed in 57% of etanercept treated patients as compared to 22% of those on placebo (Davis et al 2003). A substudy also revealed improvement in MRI features of spinal inflammation although this was limited to evaluation of only the lower thoracic and lumbar spine (Baraliakos, Davis et al 2005). In the open-label phase, placebo patients switched to etanercept achieved similar responses to those seen in patients originally randomized to etanercept and prolonged follow up over 4-years has shown that the response to treatment is sustained (Davis, van der Heijde, Braun et al 2005). A recent report addresses the impact of etanercept on radiographic progression of structural damage in the spine over 2-years (van der Heijde, Landewe et al 2006). This is the minimum period of time required to demonstrate significant change in a group of AS patients on standard therapies who might constitute a comparator group (Wanders et al 2004). Since anti-TNFα therapies have now been shown to be highly effective for the treatment of AS, it is ethically inappropriate to conduct 2-year placebo-controlled trials that would be required to evaluate structural damage progression in randomly allocated treatment groups and a proposed solution has been the comparison of damage progression in patients on active therapy with a historical cohort of AS patients, particularly those who would otherwise meet the inclusion criteria for clinical trials of anti-TNFα therapies (van der Heijde, Landewe et al 2005). Such a comparison has shown no impact of etanercept on structural damage progression (van der Heijde, Landewe et al 2006). Definitive conclusions should not be drawn because the historical cohort analyzed in this study was very different from patient cohorts recruited to trials of anti-TNFα therapy and simple comparisons based on subgroups stratified by a limited number of inclusion criteria do not adequately address differences in disease characteristics between observational and clinical trial cohorts. It has been shown that physicians place equal or greater emphasis on disease characteristics other than those that typically constitute primary inclusion criteria for clinical trials (eg, BASDAI greater than or equal to 4) (Pham et al 2006). Moreover, monoclonal anti-TNF antibodies have a different mechanism of action from etanercept and it would be erroneous to assume that findings observed with the latter agent would necessarily also be observed with the former two agents.

Table 1 Summary data for phase III pivotal trials of anti-TNFα therapies for AS

Study	Patient no	Disease duration	Primary endpoint	Primary endpoint Active	Primary endpoint Placebo	Secondary endpoints	Secondary endpoints Active	Secondary endpoints Placebo
Davis et al (2003)	Etanercept = 138 Placebo = 139	10-years 10-years	ASAS 20 response at 12-weeks	59%	28%	BASDAI ASAS 50 CRP	–40.6% 43% –68.4%	–7.6% 8% –5%
Van der Heijde et al 2005	Infliximab = 201 Placebo = 78	8-years 13-years	ASAS 20 response at 24-weeks	61.2%	19.2%	ASAS 40 ASAS partial remission ASAS 5/6 BASDAI BASFI	47% 22.4% 49% –43.9% –29.8%	12% 1.3% 8.0% –6.2% 0%
Van der Heijde et al 2006	Adalimumab = 208 Placebo = 170	11-years 10-years	ASAS 20 response at 12-weeks	58.2%	20.6%	ASAS 40 ASAS partial remission ASAS 5/6 BASDAI BASFI	39.9% 20.7% 48.6% –41.3% –68.8%	13.1% 3.7% 13.1% –12.7% –14.3%

Infliximab

An earlier double-blind, placebo-controlled, randomized trial of infliximab in 70 patients with AS conducted in Germany, established this agent as being efficacious in the treatment of the signs and symptoms of AS (Braun et al 2002). A substudy of 20 patients who had MRI examination of the spine also showed improvement in spinal inflammation (Braun, Pham et al 2003). Open-label follow up has demonstrated sustained responses over 3-years and withdrawal of treatment leads to disease relapse within 4-months in the majority of patients (Braun, Baraliakos, Brandt et al 2005; Baraliakos, Listing et al 2005). A pivotal phase III placebo-controlled study of infliximab in AS recruited 279 patients of whom 201 received infliximab 5 mg/kg at 0, 2 and 6-weeks, followed by every 6-weeks thereafter for 2-years (van der Heijde, Dijkmans et al 2005). Placebo patients received open-label infliximab after 24-weeks. An ASAS 20 response was observed in 61% of infliximab patients as compared to 19% of placebo patients by 24-weeks. The significant difference between treatment groups was evident as early as week 2. Treatment was well tolerated with similar proportions of serious adverse events, infusion reactions and serious infections between the two treatment groups. Patients in this trial also had MRI evaluation conducted at baseline and 24-weeks. Patients in the infliximab group had a significantly greater improvement in spinal MRI activity score from baseline to week 24 than the patients in the placebo group (Braun, Landewe, et al 2006). The dose of infliximab examined in most controlled and open-label studies of this agent in AS has been the same dose that was originally developed for the treatment of Crohn's disease. A recent Canadian randomized, placebo-controlled trial has examined a dose of 3 mg/kg, using the same dosing regime that has been developed for the treatment of RA (Inman et al 2006). Preliminary findings indicate a similar ASAS 20 response rate in the active treatment group.

Adalimumab

Several recent studies have focused on the evaluation of adalimumab in the treatment of AS. A preliminary open-label trial of adalimumab in AS recruited 14 patients refractory to NSAIDs who received 40 mg on alternate weeks over 52-weeks (Haibhel et al 2006). An ASAS 20 response was seen in 70% of patients with 50% reporting a substantial response (ASAS 50). Significant improvement was also noted in function, nocturnal pain and patient global. A further increase in the percentage of ASAS 20 responders to 86% was noted at week 20, after an increase in dosage to weekly therapy. This was accompanied by a reduction in sacroiliac joint and spinal inflammation observed on MRI. A phase III pivotal, multi-center clinical trial of adalimumab 40 mg on alternate weeks in AS has now been reported (van der Heijde, Kivitz et al 2006). This trial recruited 315 patients with AS refractory to NSAIDs and second-line agents such as methotrexate and salazopyrin, of whom 208 were randomized to adalimumab 40 mg on alternate weeks and 107 to placebo for 24-weeks. After the week 12 assessment, patients not achieving an ASAS 20 response were eligible for early escape therapy with adalimumab. By week 24, only 27% of patients were still on placebo with the remainder having entered the early escape protocol and received open-label adalimumab. In contrast, only 39% of patients originally randomized to adalimumab entered the early escape protocol. A significantly greater ASAS 20 response was observed in adalimumab treated patients (58.2%) as compared to those

receiving placebo (20.6%) at week 12, the difference already being significant by week 2. This is the only phase III trial that included patients with total spinal ankylosis and 50% (3 of 6) of the adalimumab treated patients achieved an ASAS 20 response at week 12 compared with 0% (0 of 5) of the placebo treated patients. Significant improvement was also observed in measures of spinal mobility (Bath AS Metrology Index) and enthesitis (Maastricht AS enthesitis score (MASES)) at weeks 12 and 24. A highly significant improvement was also observed in the acute phase reactant C-reactive protein and the physical and mental summary scores of the SF-36 Quality of Life instrument. The overall incidence of adverse events was significantly higher in the adalimumab treated patients, although this was primarily due to an increased incidence of injection site reactions. There were no other statistically significant differences in the incidence of any other adverse events between treatment groups and no serious infections were reported in the adalimumab treated group. A smaller, randomized, placebo-controlled trial of adalimumab 40 mg on alternate weeks was conducted in Canada and recruited 82 patients (Maksymowych, Rahman et al 2005). The design of the study was similar to the multinational trial in that it included an early escape option for patients failing to achieve an ASAS 20 response at week 12. Efficacy at week 12 was similar to that observed in the multinational trial and comparable to that observed in trials of other anti-TNF agents. MRI evaluation was conducted at baseline, 12 and 52-weeks and inflammation was scored using the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI index (Maksymowych et al 2005a, 2005b; Lambert et al 2006). At week 12, decreases of 54% and 53% were noted in adalimumab treated patients for the spinal and sacroiliac joint SPARCC MRI scores, respectively, which were significantly different from placebo (9.4% and 12.7%, respectively). The response in adalimumab treated patients was maintained to 52-weeks and placebo patients switched to open label adalimumab treatment by week 24 experienced similar reductions in spinal and sacroiliac joint inflammation by week 52. Interestingly, similar large reductions in spinal and sacroiliac joint SPARCC scores were noted even in adalimumab-treated patients who were ASAS non-responders at 12-weeks.

Recent studies have examined the impact of anti-TNFα therapies on the extra-articular features of AS, particularly acute anterior uveitis (AAU). One study pooled data from both controlled and open-label studies of infliximab and etanercept in AS (Braun, Baraliakos, Listing et al 2005). The incidence of AAU per 100 patient years was 15.6 in placebo patients as compared to 3.4 and 7.9 in infliximab and etanercept treated patients respectively. For all anti-TNFα treated patients, the incidence was 6.8 per 100 patient years. This suggests that both infliximab and etanercept might be effective in suppressing flares of uveitis. On the other hand, 2 recent observational studies indicate that etanercept does not appear to reduce flares of uveitis and, in fact, several patients have developed flares whilst on treatment (Cobo-Ibanez et al 2006; Guignard et al 2006). In contrast, both infliximab and adalimumab were shown to reduce flares of uveitis, suggesting that monoclonal antibodies to anti-TNFα may be more effective in depressing flares of acute anterior uveitis. This is reminiscent of data observed from clinical trials of anti-TNF agents in agents with Crohn's disease. Both infliximab and adalimumab have been shown in pivotal phase III trials to ameliorate the activity in patients with Crohn's disease whilst etanercept has proven to be ineffective (Sandborn et al 1997; Targen et al 1997; Hanauer et al 2006). In fact, studies have reported flares of Crohn's and other granulomatous disorders in patients whose spondylitis responded to treatment with etanercept (Oh et al 2005; Gonzalez-Lopez et al 2006). Additional data in both pulmonary and ocular sarcoidosis also attests to the efficacy of infliximab in the treatment of granulomatous inflammation in contrast to etanercept (Utz et al 2003; Baughman et al 2005, 2006).

In conclusion, all three available anti-TNFα agents appear to have similar efficacy for the articular manifestations of AS with clinical responses being observed in 60% of patients. There is mounting evidence that the two available monoclonal antibodies, infliximab and adalimumab, are superior in treating extra-articular features such as AAU and inflammatory bowel disease. There is no evidence at this time that any anti-TNFα agent is disease modifying with respect to prevention of structural damage progression and one study evaluating etanercept in fact showed no effect. Because 40% of AS patients do not respond to anti-TNFα therapies, it has been suggested that the addition of methotrexate might be beneficial by analogy with the considerable improvement in efficacy consistently observed with all three anti-TNFα agents in trials of RA. One study of 123 AS patients examined the combination of methotrexate 12.5 mg weekly in addition to infliximab 5 mg/kg over 54-weeks (Breban et al 2005). However, there was no treatment group difference in ASAS 20 response rate.

Safety of anti-TNFα agents

Long term observational studies of anti-TNF agents are currently being conducted internationally and in general,

affirm that these agents are well tolerated in real world practice. A pooled analysis of data from placebo-controlled trials of anti-TNF agents in RA has demonstrated a dose dependent increase in the rate of malignancy (Bongartz et al 2006). However, this has not been shown in most longitudinal cohorts of patients receiving these drugs in real world practice (Askling, Fored, Baecklund et al 2005; Askling, Fored, Brandt et al 2005; Askling et al 2006; Setoguchi et al 2006). An increased rate of serious infection has been reported in RA patients receiving anti-TNF therapies in Germany but not in the UK (Listing et al 2005; Dixon et al 2006). A major recent development is a recognition that chronic inflammatory disorders such as RA and AS are strongly associated with increased rates of cardiovascular events and that prolonged therapy with anti-TNF agents may reduce the frequency of these events and thereby improve life expectancy (Jacobsson et al 2005).

Current controversies and future directions

A major resolve question is whether anti-TNF therapies are disease modifying with respect to prevention of structural damage progression. One study conducted with etanercept suggests a lack of impact (van der Heijde, Baraf et al 2005). Data from studies with infliximab and adalimumab are currently awaited. However, even if this data shows a lack of impact, it is important to note that patients recruited to phase III trials of these agents typically have a long disease duration, the mean duration from time of diagnosis typically being greater than 10-years. It is therefore important to conduct further trials in patients presenting much earlier in their disease course. Resolving the question of disease modification is important because cost/benefit considerations have assumed increasing importance and anti-TNFα therapies are still not available in many parts of the world for the treatment of AS. Cost/benefit calculations could also be rendered more attractive if reliable predictors of response could be established. Preliminary data points to baseline disease activity, baseline function, CRP and MRI features of inflammation as potential predictors (Rudwaleit et al 2004; Davis, van der Heijde, Dougados et al 2005). Recent studies have also shown that anti-TNFα therapies are associated with significant changes in certain biomarkers but none have yet been shown to predict response to treatment (Maksymowych, Patra et al 2005; Maksymowych, Poole et al 2005). Further studies of the disease modifying potential of anti-TNFα agents in AS could be rendered more attractive if it were possible to identify a sub-group of patients at much greater risk of structural damage progression. This now appears to be possible as a recent study has demonstrated that a combination of an elevated serum metalloproteinase-3 level together with evidence of pre-existing damage on spinal x-rays is a significant predictor of further damage developing over the course of 2-years (Maksymowych et al 2006). This subgroup of patients should therefore be targeted in future clinical trials assessing the disease modifying properties of new and existing therapies. Combination therapy for AS is an issue that requires further evaluation. In current clinical practice, many patients who achieve good responses to anti-TNFα therapy discontinue their concomitant NSAID therapy. This may be unwise if further studies show that NSAID therapy, and COX-2 selective agents in particular, prevent the development of spinal ossification. Only one study has evaluated concomitant therapy with methotrexate and this study used doses of methotrexate that many rheumatologists would consider inadequate (Breban et al 2005). Further studies should clarify once and for all if methotrexate is efficacious in combination with anti-TNFα therapies.

The past decade has witnessed breathtaking advances in the treatment of AS. There is every reason to believe that the pace of advances will accelerate over the ensuing decade.

Abbreviations

NSAID, Non-steroidal anti-inflammatory agent; COX, Cyclo-oxygenase; Anti-TNFα, Anti-tumor necrosis factor alpha; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; BASMI, Bath ankylosing spondylitis metrology index; ASAS, Assessments in ankylosing spondylitis working group; mSASSS, Modified stoke ankylosing spondylitis spinal score; AAU, Acute anterior uveitis; MASES, Maastricht enthesitis score; SPARCC MRI score, Spondyloarthritis research consortium of canada magnetic resonance imaging score.

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