Novel Therapies For Ankylosing Spondylitis

Walter P. Maksymowych, FRCP(C), FACP, FRCP(UK)

Address
Alberta Heritage Foundation for Medical Research, University of Alberta, 562 Heritage Medical Research Building, Edmonton, Alberta T6G 2S2, Canada.
E-mail: walter.maksymowych@ualberta.ca

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Recent interest in therapeutic developments for ankylosing spondylitis has focused primarily on two anti-tumor necrosis factor-α therapies, infliximab and etanercept, with several reports establishing their efficacy in pivotal phase III trials. Open extension analyses of earlier controlled trials have also shown that efficacy is maintained for at least 3 years, that monotherapy is adequate, and that treatment is well tolerated with few serious infections. Treatment is associated with reduction in sick leave and days spent in hospital. Despite induction of antinuclear antibodies and anti-ds DNA antibodies, clinical sequelae are rare. Reduction in magnetic resonance imaging parameters of inflammation and serologic biomarkers of cartilage turnover suggest that these agents may be disease-modifying though direct evidence from plain radiographic studies is still lacking. Conventional second line therapies typically used in rheumatoid arthritis have also been examined and while leflunomide appears to possess limited efficacy, there may be a case for re-examining the value of methotrexate.

Introduction

The past year has witnessed an acceleration of major reports that constitute significant advances in the therapy for ankylosing spondylitis (AS). These have included pivotal phase III as well as additional clinical trials that have unequivocally established the efficacy of anti-tumor necrosis factor-α (anti-TNFα) therapies for AS, open extension studies of earlier clinical trials that have provided further reassurance regarding their safety, and miscellaneous studies addressing their cost-benefit, effects on work disability, and predictors of response. Although interest has been intensely focused on the use of anti-TNFα therapies, access to such therapy for patients with AS is presently restricted in most countries and it is, therefore, gratifying that investigators continue to show interest in agents such as methotrexate, leflunomide, and bisphosphonates. In keeping with the tradition of evaluating novel agents first shown to be beneficial in rheumatoid arthritis (RA), the past year has also witnessed the first reports of anakinra in patients with AS.

Pivotal Trials of Anti-TNFα Therapies in AS

Two multicenter, double-blind, randomized, placebo-controlled trials (DB-RCT) in patients with AS have been reported, one study evaluating etanercept and the other infliximab. The former study recruited 277 patients who were randomized to etanercept 25 mg twice weekly (n = 138) or placebo (n = 139) for 24 weeks [1••]. Patients were allowed to continue receiving second line therapy with hydroxychloroquine, sulfasalazine, or methotrexate at stable dosages. The primary outcome was the proportion of patients achieving the Assessments in AS Working Group 20% response (ASAS20) at 12 weeks. Treatment groups were well matched at baseline and it is noteworthy that a third was receiving second line therapy. The mean disease duration was 10.1 and 10.5 years for the etanercept and placebo groups, respectively. Retention of patients during the 24 week study was high (91% and 86% for etanercept and placebo groups, respectively). The ASAS20 response was achieved by 59% of etanercept versus 28% of placebo patients at 12 weeks. At 24 weeks the corresponding response rate was 57% versus 22%. Differences between treatment groups were significant as early as week 2 and were maintained over the 24 weeks of the study. Partial remission defined as a value of less than 20 units (on a 100 mm visual analogue scale) for each of patient's global assessment, pain, Bath AS Functional Index (BASFI), and inflammation was achieved by 17% of etanercept versus 4% of placebo patients at 24 weeks. Concomitant treatment with second line agents did not affect the outcome of the study. Significant differences in favor of etanercept were also noted for all the individual components of the ASAS response criterion (patient global, pain, physical function, and inflammation), acute phase reactants, Bath AS Disease Activity Index (BASDAI), and spinal mobility measures (modified Schober, chest expansion, occiput to wall) at 12 and 24 weeks. The frequency of adverse events was similar in both treatment groups with only injection site reactions, upper respiratory tract infection, and accidental injury being more common in etanercept treated patients. There were seven study discon-

tinuations resulting from adverse events in the etanercept group, two of which were because of exacerbations of inflammatory bowel disease. Three patients who received etanercept and one patient in the placebo group experienced serious adverse events because of infection though no tuberculosis or opportunistic infections were noted during the study. Flares of inflammatory bowel disease occurred in similar numbers of patients in both treatment groups, although somewhat more placebo patients ($n = 8$) had a flare of uveitis as compared with etanercept treated patients ($n = 3$). A sub-study of 40 patients also demonstrated regression of inflammatory spinal lesions scored by magnetic resonance imaging (MRI) [2]. A brief report has described sustained efficacy and safety over 18 months in the open label extension phase [3].

A second phase III DB-RCT of an anti-TNFα therapy for AS recruited 279 patients who were randomly assigned in a 3:8 ratio to receive infusions of placebo or infliximab 5 mg/kg at weeks 0, 2, 6, and every 6 weeks thereafter [4]. Study details have as yet been reported in abstract form only. The primary outcome was the ASAS20 Response Criterion at 24 weeks and this was met by 61.2% of patients receiving infliximab versus 19.2% of patients on placebo. A significant benefit over placebo was noted as early as week 2 and maintained over the 24 week study period. ASAS partial remission was noted in 22.4% of patients receiving infliximab versus 1.3% on placebo. Significant improvement was also noted in disease activity (BASDAI), function (BASFI), spinal mobility (BASMI), night pain, patient global, and the physical component summary score of the short-from 36 (SF36). Serious adverse events were reported in seven infliximab treated patients (3.5%) versus two patients (2.7%) who received placebo though none of these events led to discontinuation of study medication. Frequency of infusion reactions was similar in both treatment groups (2.7%) and there were no cases of tuberculosis.

A third phase III multicenter RCT has been reported although only 84 patients were recruited [5]. Patients were allowed to remain on stable second line therapy. Significantly more etanercept patients than placebo patients (60% vs 23.1%) were ASAS20 responders at week 12. The primary efficacy endpoint and study group differences were not significantly affected by the concomitant use of disease modifying antirheumatic drugs. Significant improvement in the etanercept group was evident by week 2, the earliest assessment time point, and was sustained thereafter to week 12. Scores for etanercept patients improved by 43% on the spinal inflammation and back pain measures, 37% on patient global assessment of disease activity, and 35% on the functional impairment index compared with 15%, 6%, 13%, and 3% improvements, respectively, for placebo patients. The etanercept treated patients also had significantly greater improvements in acute phase reactants and spinal flexion. Virtually all patients completed the study with only one serious adverse event being reported in the etanercept group that was likely unrelated to study drug. Frequency of adverse events was similar apart from an increased frequency of injection site reactions in etanercept treated patients.

The results of these studies provide unequivocal evidence in support of the short term efficacy and safety of anti-TNFα agents for the symptomatic treatment of patients with AS. Response rates of 60% have been consistently noted in active treatment groups as compared with 20% to 25% for placebo treated patients. More substantial clinical responses as defined by the ASAS50 response criterion have been consistently noted in 40% of actively treated patients. Clinical benefit is apparent by 2 weeks and appears to be maximal by 12 weeks as indicated by plateauing of the ASAS20 and ASAS50 response rates at 12 weeks. The normalization of acute phase reactants and improvement in spinal mobility measures is unprecedented amongst therapeutic agents used to date for the treatment of AS.

Anti-TNFα Therapies—Open Extension Analyses

Several reports have now provided 2- to 3-year follow-up data from the first DB-RCTs of anti-TNFα therapies in AS.

Braun *et al*. [6] have described the results of a second year extension of an original 3 month DB-RCT that recruited 69 patients for treatment with placebo or infliximab. The primary endpoint was the proportion of patients achieving at least 50% improvement from baseline in disease activity (BASDAI) at week 102. Concomitant disease modifying antirheumatic drugs and oral corticosteroids were not permitted. Nonsteroidal antiinflammatory drug (NSAID) use was allowed and the dose could be reduced but not increased over the baseline level. Of the 54 patients (78%) that completed the study up to week 54, 52 patients chose to continue with the second year and 49 completed the entire 102 week study. A response rate of approximately 50% was maintained over 2 years in the analysis of the complete intention-to-treat population. Similar and stable response rates were also noted for secondary endpoints such as function (BASFI) and metrology (BASMI). This was accompanied by sustained improvement in quality of life (SF36) and acute phase reactants (erythrocyte sedimentation rate, C-reactive protein [CRP]). By week 102, 25% of patients had achieved partial remission which included two more patients than those that achieved remission at week 54. Of interest, there was a further improvement in spinal mobility between weeks 54 and 102. However, peripheral arthritis was reported in six patients that represented an increase of five patients from the number reported at week 54. Six patients (12%) reported serious adverse events during the second year of the study though four were considered unrelated to study drug, while the other two represented an infusion reaction and musculoskeletal pain. There were three discontinua-

tions because of adverse events of which two were because of infusion reactions and one came after an exacerbation of pre-existing pancreatitis that was considered unrelated to study drug. For the entire 2 year study, 14 patients discontinued therapy because of adverse events. The overall discontinuation rate (8%) during the second year of the study was lower than that seen during the first year of the study (22%) and also lower than that observed during the second year of the anti-TNFα trial in RA with concomitant therapy (ATTRACT; 17%), the pivotal phase III trial of infliximab in RA. The 3-year follow-up data has also been reported in abstract form [7]. The response rate for disease activity continues to remain at 50% with few patients withdrawing from therapy. Treatment continues to be well tolerated with no serious infections, tuberculosis, or systemic lupus. A preliminary report has also described the consequences of treatment discontinuation in this patient cohort [8]. By 4 months, over 90% of patients had experienced a relapse of disease necessitating reinstitution of infliximab therapy.

One additional study of 30 AS patients recruited to a DB-RCT of etanercept in AS followed-up patients after treatment discontinuation until disease relapse (mean of 27 weeks) [9]. Twenty-six fulfilled the relapse criteria whereupon etanercept treatment was re-instituted and patients were followed-up for 2 years. Twenty-three completed year 1 and 21 completed year 2. Almost 60% of patients achieved a reduction in disease activity (BASDI) of at least 50% after the first year that was maintained into the second year. Treatment was well-tolerated with no serious infections.

The impact of infliximab on days of sick leave and days in hospital has also been studied during a 2-year follow-up of the German infliximab in AS DB-RCT [9]. Questions related to sick leave and hospital admission were asked every 3 months for the previous 3 month period. The percentage of patients admitted to hospital was significantly reduced from 41% in the year prior to the start of the trial to 10% after 1 and 2 years of treatment. This corresponded to a reduction in the mean inpatient days from 11.1 days before infliximab to 0.6 days after 1 year and 2.9 days after 2 years of treatment. This was associated with substantial cost saving. A significant reduction in the frequency of sick leave from 57% to 36% of all employed patients was noted at year one. This was reduced further to 14% in the second year of treatment. There was also a reduction in the mean number of days of sick leave for each patient from 31.3 to 12.5 at year 1 and 4.7 days at year 2. This again was associated with substantial cost saving for sick leave [10]. A 2-year follow-up study compared the humeral immune response induced by infliximab in RA and AS [11••]. Infliximab was given in a dose of 5 mg/kg every 6 or 8 weeks depending on the clinical response. Antinuclear antibodies (ANA) were examined at six monthly intervals by an in-direct immunofluorescense technique using Hep-2 cells and sera were considered positive at a titre of greater than or equal to 1/160. Anti-ds DNA was analyzed by radioimmunoassay and a titre of greater than or equal to 5 IU/mL was interpreted as a positive result. Organ specific autoantibodies were also examined, including antismooth muscle, antimitochondrial, antiliver and kidney microsomes, antithyroid peroxidase, antithyroglobulin, and antiadrenal autoantibodies. Infliximab led to a significant induction of ANA and anti-ds DNA auto-antibodies in 86.7% and 57% of RA patients and in 85% and 31% of AS patients, respectively. The incidence of antiphospholipid autoantibodies was significantly higher in RA patients (21%) and AS patients (27%) than in the control group of RA patients receiving methotrexate but not infliximab. Most anti-ds DNA and antiphospholipid autoantibodies were of the immunoglobulin (Ig) M isotype and were not associated with infusion side effects, lupus-like manifestations, or infectious disease. It was noteworthy that induction of anti-ds DNA autoantibodies was evident as late as 24 months after the onset of infliximab treatment. No AS patient developed an organ specific autoantibody during infliximab therapy. Two patients discontinued therapy because of septic pericarditis in one patient and a severe anaphylactic reaction in the other.

These follow-up studies are reassuring in that more prolonged therapy beyond short term controlled trials appears to be associated with maintenance of efficacy and acceptable safety. Survival on therapy appears to be much greater than has been noted with existing therapies for AS. Though a high proportion of patients develop ANA and anti-ds DNA autoantibodies are evident in up to a third of infliximab treated patients over 2 years, this does not appear to be of clinical relevance. There is also emerging evidence that prolonged therapy with anti-TNFα agents may significantly reduce the burden of illness and, specifically, work disability. Furthermore a cost effectiveness study of treatment with infliximab suggests that the cost of treatment may be partly offset by reductions in the cost of disease and improvement in patient's quality of life [12].

Anti-TNFα Therapies—Predictors of Response

In view of the substantial costs associated with treatment, identification of predictors of response might prove helpful in selecting patients for treatment. One report analyzed data from two placebo-controlled randomized trials with infliximab (n = 69) and etanercept (n = 30) [13]. Various demographic, clinical, and laboratory variables, as well as MRI parameters, were examined for their ability to predict a major clinical response defined as a 50% improvement or more of the initial disease activity score (BASDAI) after 12 weeks of treatment. Step-wise, multivariate logistic regression analysis was performed to control for disease duration and baseline function. Univariate analysis showed that shorter disease duration, better function,

younger age, elevated erythrocyte sedimentation rate, and CRP, were predictive of response. The multivariate model showed that disease duration, baseline function (BASFI), disease activity, and CRP were the best predictors of response. In particular, patients with a disease duration of greater than 20 years and/or functional disability score of 6.5 or more (0–10 scale) were much less likely to respond. Most patients who achieved a major clinical response at 12 weeks had already demonstrated some improvement (BASDAI 20% response) after 2 to 3 weeks. However, a preliminary report has suggested that the presence and extent of acute inflammatory lesions as detected by MRI may not be of value in predicting a major clinical response to anti-TNFα agents [14]. These observations are not surprising and most likely reflect the likelihood that patients with shorter disease duration and better functional status have less structural (irreversible) damage and more acute inflammation as a basis for their symptoms. Although measures of spinal mobility (BASMI) and radiologic damage (BASRI) were not predictive of response to treatment, these instruments have low discriminatory properties and poorly reflect variance in function. This study also suggests that most patients who are likely to respond are already demonstrating improvement within the first 2 to 3 weeks of therapy. Disease activity was less helpful in predicting response compared with disease duration, functional status, and acute phase reactants. However, there were insufficient numbers of patients with extra spinal manifestations such as peripheral arthritis and enthesitis to address a more complete spectrum of disease activity. Although pooling of data from two trials using different anti-TNFα agents may obscure differences between these drugs, a separate analysis of predictive variables by therapeutic agent did not reveal any significant differences. It is still too early to conclude that anti-TNFα agents should not be offered to older patients with longstanding disease and higher BASFI until more data becomes available from phase III trials. However, the rapid response to therapy and attainment of maximal responses by 12 weeks suggests that a 3 month trial of treatment is sufficient in evaluating responses to these agents in routine clinical practice.

Anti-TNFα Therapies—The Preliminary DCART Response Criterion

The ASAS working group has proposed that several domains be included in a core set that would be evaluated in trials of potential disease controlling antirheumatic therapies (DCART) in addition to those domains included in the ASAS20 response criterion that was derived from the analysis of controlled trials of NSAIDs in AS. In particular, it was proposed that acute phase reactants and spinal mobility be added to a core set for disease controlling therapies. One report analyzed the data from two DB-RCTs of anti-TNFα agents in AS for Boolean-type improvement criteria that best discriminated patients on active therapy from those on placebo [15]. The American College of Rheumatology Response Criteria for RA are an example of Boolean-type improvement criteria. The discriminant properties of the DCART improvement criteria were first examined in a data set from an infliximab DB-RCT [16] and then validated in a second data set from an etanercept DB-RCT [17]. In both trials, the patients were selected using the same inclusion and exclusion criteria. Two sets of criteria performed best, namely, the ASAS 40% response and 20% improvement in five of six domains that included pain, function, patient global, inflammation, acute phase reactants, and spinal mobility. The ASAS 40% improvement criterion has the advantage of setting a high threshold but only in patient reported outcomes while the latter improvement criterion might be considered to have more face validity. It is important to note that the criteria are preliminary and will require further analysis in much larger data sets from the phase III trials.

Anti-TNFα Therapies and Biomarkers

Serologic biomarkers reflecting pathologic processes such as degradation of collagen, synthesis of extracellular matrix, and production of tissue degrading enzymes, have been shown to possess independent predictive validity for structural damage in patients with RA. They can therefore be used to evaluate the disease modifying properties of new therapeutic agents, particularly where plain radiographic evidence of structural damage is not yet apparent. Plain radiographic instruments for monitoring disease progression in AS demonstrate limited sensitivity to change so that at least 2 years are required before significant change can be demonstrated in patients receiving standard therapies. There is, therefore, considerable interest in using such biomarkers as surrogates for structural damage in patients with AS. Two recent reports have demonstrated that infliximab therapy leads to a significant reduction in serum levels and synovial expression of metalloproteinase-3, commensurate with changes in disease activity (BASDAI) that is particularly evident in patients with concomitant peripheral arthritis [18,19••]. A preliminary report has also shown that etanercept decreases serologic levels of an epitope of type II collagen generated de novo by cleavage with collagenase [20]. Increased levels of an epitope denoting newly synthesized aggrecan molecules was also noted, suggesting increased synthesis of cartilage matrix. The predictive validity of these biomarkers for structural damage has not yet been examined in longitudinal studies and so the significance of these observations remains to be established.

Additional reports have sequentially examined serum cytokines in patients receiving infliximab or etanercept in an attempt to identify immunologic markers associated with response to treatment [21,22]. These analyses were mostly uninformative with the exception of baseline TNFα levels which appeared to be higher in responders although a small number of nonresponders preclude firm conclusions.

New Developments in Biologic Therapies for AS

A third anti-TNFα agent, adalimumab, has been examined in patients with AS in a single open-label trial of 14 patients receiving 40 mg on alternate weeks over 12 weeks followed-up by 40 weeks of maintenance therapy [23]. An ASAS 20 response of 70% was evident by 12 weeks with 50% reporting a substantial response (ASAS50). Significant improvement was also noted in individual items comprising the response criterion as well as nocturnal pain and acute phase reactants. A further increase in the percentage of ASAS20 responders to 86% was noted at week 20 after an increase in dosage to weekly therapy. This was accompanied by reduction in sacroiliac joint and spinal inflammation observed on MRI. Treatment was well tolerated with no serious infections.

Two studies have now examined an interleukin-1 receptor antagonist (anakinra) in the treatment of AS [24,25]. Both have been open analyses. One open label study of 20 patients over 24 weeks reported an ASAS20 response in 26% which resembles the placebo response in controlled trials of anti-TNFα therapies [24]. There was no effect on CRP or MRI parameters of inflammation. In contrast, a second open label study of nine patients over 12 weeks reported an ASAS20 response in six patients (67%) together with significant improvement in function (BASFI), CRP, and MRI parameters of inflammation [25]. Controlled trials will be required to resolve these discrepancies.

Conventional Disease-modifying Therapies in AS

Two studies have reported the results of leflunomide therapy in AS [26,27]. An open label study of 20 patients over 24 weeks demonstrated an improvement of at least 50% in disease activity in five patients at 3 months though only 10 patients completed the study [26]. Overall there was no significant benefit at 24 weeks. There was however a significant reduction in the number of swollen joints in the subgroup of 10 patients with peripheral arthritis. A second study was a single center, double-blind, placebo-controlled study of 45 patients over 24 weeks [27]. There was no difference in ASAS20 response rates between the two groups although 11 patients withdrew primarily because of adverse events and few had peripheral arthritis. This agent may have a role in patients with active peripheral arthritis though controlled studies are required.

Thalidomide has been shown to possess anti-TNFα properties by enhancing the degradation of TNFα. A 1-year open label evaluation of 30 Chinese patients with AS demonstrated a response in 80% and significant deterioration was noted 3 months after termination of therapy [28]. Treatment was relatively well tolerated in this Chinese cohort although previous reports have reported a high frequency of drowsiness, constipation, dizziness, and peripheral neuropathy in white subjects.

Methotrexate is used in up to 15% of AS patients refractory to NSAIDs even though there is scant evidence to support its efficacy [1]. A single center, double-blind, study recruited 35 patients who were randomized to methotrexate 7.5 mg weekly or placebo for 24 weeks [29]. Sixty percent had active peripheral arthritis at baseline. Response was defined as a greater than or less than 20% improvement in at least five of seven measures that included morning stiffness duration, patient global, disease activity (BASDAI), function (BASFI), HAQ-S, physical global, physical well being, and no deterioration (> 20%) in these domains. The intention-to-treat analysis at 24 weeks showed a significant difference in response rate of 53% in the methotrexate group and 17% in the placebo group. Analysis of earlier time points showed no significant differences. No comparisons between groups were presented for the individual outcome measures. Peripheral arthritis resolved in 81% and 80% of methotrexate and placebo patients, respectively. Treatment was tolerated with no withdrawals resulting from side effects. This study suggests that further evaluation of methotrexate as a disease-modifying agent in AS should be performed.

Conclusions

Therapeutic developments over the past year continue to be dominated by reports that clearly establish a major role for anti-TNFα therapies in the treatment of NSAID refractory AS. However, these treatments are costly and further work is required to identify major predictors of response. Furthermore, it is presently unclear whether these agents are merely symptom-modifying or capable of ameliorating structural damage. This will likely require long-term studies with assessment of plain radiographic changes and comparisons with historic longitudinal cohorts in view of the low sensitivity to change of radiographic instruments. The relative lack of efficacy of RA disease-modifying agents such as leflunomide again highlights the pathophysiologic differences between AS and RA and the necessity for appropriate clinical trials in AS in preference to their empiric use merely because of their demonstrable efficacy in RA.

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