Anti-TNF-α therapy for ankylosing spondylitis

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Management of the inflammatory symptoms of ankylosing spondylitis has been revolutionized by use of TNF inhibitors. Although three TNF inhibitors have been approved by the US FDA, none has proven to be superior for treatment of ankylosing spondylitis. Our knowledge of TNF and its receptors suggests that there should be differences in the mechanism of the inhibitors. In addition to long-term safety data and structural modification information, knowledge of the effect of TNF inhibition on extra-articular manifestations of the disease is needed.

Ankylosing spondylitis (AS) has a prevelance of 0.2–1% and affects more than 350,000 patients in the USA [1]. It is a chronic condition that most often manifests as inflammatory spinal pain, enthesitis and peripheral arthritis. Several extra-articular changes in the eye, gastrointestinal tract, cardiovascular system and lungs can also occur in this disease. The onset of nocturnal back pain and morning stiffness typically occurs between 15 to 35 years of age, and the severe deformity and disability can result within the first 10 years [2]. AS is more common and often more severe in males. It is a disease that substantially impacts quality of life.

The etiology of this inflammatory process is unknown, although a strong association with HLA-B27 is recognized. This association suggests a role of altered immunity in disease pathogenesis. Identification of the key mediators of inflammation occurring secondary to this aberrant immune response is essential for the development of a treatment strategy. Although no treatment cures AS, the use of TNF blockers has revolutionized the management of symptoms that are refractory to conventional treatment.

Tumor necrosis factor

There are both transmembrane and soluble forms of TNF. TNF is initially expressed on the cell surface as a transmembrane homotrimer with a small domain in the cytoplasm [3]. A TNF-converting enzyme (also known as TACE or ADAM 17) can cleave the extracellular portion to generate a soluble homotrimer. Both the transmembrane and the soluble forms of TNF are biologically active, but have important differences in their activity.

The potent cytokine TNF-α is primarily produced by monocytes and macrophages, but also by B cells, T cells and fibroblasts [4]. TNF-α exerts its pleiotropic effects through binding to two receptors, the type 1 TNF receptor (also known as p55 and CD120a) and the type 2 TNF receptor (also known as p75 and CD120b), which are found on nearly all human cells, including immune, inflammatory and endothelial cells. Transmembrane and soluble forms of TNF differentially bind the p55 TNF receptor and the p75 TNF receptor [2].

An interaction of soluble TNF and the p55 TNF receptor is sufficient for the induction of inflammatory arthritis, by providing anti-apoptotic and inflammatory signals through nuclear factor κB. It also has a critical role in granuloma formation. In the absence of p55 TNF receptor signaling there is a decrease in macrophage survival [5].

The transmembrane form of TNF is superior to the soluble form in activation of the p75 TNF receptor, which signals to induce apoptosis [6]. The degree of inflammatory gene modulation is unclear. Of note, TNF signaling heterogeneity and modulation of proinflammatory gene expression can occur through influence of other cytokines, such as interferons [7].

The importance of TNF-α as a mediator of inflammation in AS is supported by elevation of this cytokine, both in the serum and sacroiliac biopsy specimens of AS patients [8,9]. Three potent neutralizers of TNF bioactivity have been developed and are approved for treatment of AS. Although there are differences in their molecular structures, their binding specificities and the manner in which they neutralize TNF, no agent is regarded as superior for treatment of this condition.

The role of TNF inhibitors in the treatment of AS has been defined by clinical trial data. Pain, physical function, spinal stiffness, spine

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mobility, patient global assessment, structural damage, quality of life (short form [SF]-36) and acute-phase reactants (erythrocyte sedimentation rate [ESR], C-reactive protein) are common end points that are measured in AS studies. For the purposes of clinical trials, the activity of disease in AS is generally defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and functional status by the Bath Ankylosing Spondylitis Disease Functional Index (BASFI), with increased levels indicating more severe disease. Although spinal mobility and hip function is often measured by the Bath Ankylosing Spondylitis Meterology Index (BASMI), this tool does not have well-established measurements, so it is often used with other relevant measures, such as chest expansion or occiput-to-wall. The Asessment in Anklosing Spondylitis (ASAS) response criteria are defined as an at least 20% improvement and absolute improvement of at least ten units on a 1–100 scale in at least three of the following: patient global assessment, pain visual analog scale, BASDAI and BASFI.

Infliximab treatment for ankylosing spondylitis

Infliximab is a chimeric monoclonal antibody (mAb) with murine variable regions and human IgG1 and κ constant regions. The size (149 kDa) and structure of infliximab are similar to those of naturally occurring antibodies [10]. Infliximab is not known to bind to any antigen other than TNF, and is capable of blocking all receptor binding sites on TNF [11]. It binds with high affinity to soluble and membrane-bound TNF-α and inhibits its effect by blocking TNF-α-receptor interactions. It is cytotoxic for TNF-expressing cells.

The currently approved dose of infliximab for AS is an initial 5 mg/kg body weight baseline intravenous infusion, followed by repeat administration 2 and 4 weeks later. It is then given every 6–8 weeks thereafter. Its efficacy and safety in the treatment of AS was evaluated in a randomized, placebo-controlled trial of 279 patients with active AS that was suboptimally controlled by at least one NSAID [12]. Patients were randomly assigned to receive infusions of placebo (n = 78) or 5 mg/kg infliximab (n = 201) at weeks 0, 2, 6, 12 and 18. The primary end point in this study was the proportion of patients with a 20% improvement response according to the ASAS International Working Group criteria (ASAS20 responders) at week 24. After 24 weeks, 61.2% of patients in the infliximab group were ASAS20 responders compared with 19.2% of patients in the placebo group ($p < 0.001$). Patients receiving infliximab also showed significant improvements in secondary outcomes: BASDAI, BASFI, BASMI, chest expansion and physical component summary score of the SF-36. All adverse events were of mild or moderate severity, and were reported by 82.2% of patients receiving infliximab and by 72.0% of patients receiving placebo.

In 194 patients in the infliximab group and 72 patients in the placebo group, pre- and post-gadolinium T1 and short-τ inversion recovery (STIR) MR images of the spine were acquired at baseline and 24 weeks, and evaluated by two independent readers blinded to treatment and sequence [13]. Approximately 80% of the patients had at least one active spinal lesion at baseline, as assessed by MRI. Improvement in the MRI Activity Score after 6 months was significantly greater in the patients who received infliximab (mean 5.02, median 2.72) than in those who received placebo (mean 0.60, median 0.0; $p < 0.001$). Almost complete resolution of spinal inflammation was observed in most patients who received infliximab, irrespective of baseline activity. However, it is unclear whether long-term structural modification is provided by TNF inhibitors.

Etanercept treatment for ankylosing spondylitis

Etanercept is a fusion protein of the extracellular domain of the p75 TNF receptor (CD120b) and the hinge and Fc domains of human IgG1 given subcutaneously as a weekly 50 mg dose. Etanercept binds equally well to both TNF-α and lymphotoxin (LTα; TNF–β), but forms a 1:1 complex with the TNF trimer, thus leaving a binding site open. The p75 TNF receptor has fast rates of association and dissociation with TNF and is not cytotoxic [14].

The efficacy of etanercept for patients with active AS was evaluated in a 24-week, randomized, placebo-controlled study with an open-label extension [15,16]. In the first trial, patients were treated with either etanercept 25 mg (n = 138) or placebo (n = 139) subcutaneously twice weekly for 24 weeks. The primary outcome measures were the percentages of patients achieving the ASAS20 response at weeks 12 and 24. The ASAS20 was achieved by 59% of patients in the etanercept group and by

28% of patients in the placebo group ($p < 0.0001$) at week 12, and by 57% and 22% of patients, respectively, at week 24 ($p < 0.0001$). All secondary outcome measures, including individual ASAS components, acute-phase reactant levels and spinal mobility measures were also significantly improved. In the trial extension, patients continuing etanercept treatment had a sustained response for almost 2 years, with 74% achieving ASAS20 response after 96 weeks of etanercept treatment. Patients who had received placebo in the preceding double-blind trial also had improvement, with 70% of patients attaining an ASAS20 response after 24 weeks of etanercept treatment and 78% achieving an ASAS20 response after 72 weeks. Improved spinal mobility was seen in both groups.

Adalimumab treatment for ankylosing spondylitis

Adalimumab is a recombinant humanized monoclonal anti-TNF-α antibody that is administered subcutaneously, usually as a 40 mg dose every other week. It binds to human TNF-α with high affinity, thus preventing the cytokine from binding to its receptors.

Its efficacy was shown in a large multicenter, randomized, double-blind, placebo-controlled study to evaluate a subcutaneous injection of adalimumab (n = 208) compared with placebo (n = 107) for 24 weeks [17]. The primary efficacy end point was an ASAS20 response at week 12. Secondary outcome measures included the ASAS20 at week 24 and multiple measures of disease activity, spinal mobility and function, as well as ASAS partial remission. At week 12, 58.2% of adalimumab-treated patients achieved an ASAS20 response, compared with 20.6% of placebo-treated patients ($p < 0.001$). More patients in the adalimumab group (45.2%) than in the placebo group (15.9%) had at least a 50% improvement in the BASDAI at week 12 ($p < 0.001$). Significant improvement in the ASAS40 response and the response according to the ASAS5/6 criteria at weeks 12 and 24 were also demonstrated. The ASAS40 and ASAS5/6 are considered better outcome measures than the ASAS20 [18].

Management of ankylosing spondylitis

An individualized combination nonpharmacologic and pharmacologic treatment is necessary for all AS patients [19]. The nonpharmacologic approach should be offered to AS patients at the time of diagnosis and throughout the course of their disease. It includes physical therapy, exercise, education and lifestyle modification. Although home exercise is better than no exercise, the addition of supervised group physical therapy may be more effective [20].

NSAIDs and cyclo-oxygenase (COX)-2 selective inhibitors are the cornerstone of medical therapy in patients with AS, and should be initiated in all patients with pain and stiffness. Anti-inflammatory selection is based on gastrointestinal risk factors. TNF inhibitors are first-line for severely symptomatic spondylitis unresponsive to the NSAIDs or COX-2 inhibitors.

If peripheral arthritis symptoms predominate, sulfasalazine can be combined with NSAIDs. This combination can result in reduction in morning stiffness and ESR [21]. However, sulfasalazine therapy is not sufficient for spondylitis symptoms. Other DMARDs, such as methotrexate, cyclosporine and azathioprine, have been used in AS but demonstrated significant improvement in physical function, pain, spinal mobility, enthesitis and patient- and physician-rated global assessments. There is some evidence to support the use of thalidomide and pamidronate in the treatment of AS, however, use of these agents is not standard of care and needs additional clinical trials [22,23]. There are no clinical trial data to support the use of oral systemic corticosteroids [24].

Use of surgical intervention is usually dictated by neurologic compromise, substantial instability or severe pain, since there are many known challenges to surgical procedures done on the ankylosed, fragile joints of an AS patient. With lack of these symptoms, atlantoaxial and atlanto-occipital subluxation may be monitored over a long period before surgery is recommended [25]. The main role of total hip arthroplasty is for pain relief [26].

Additional TNF considerations

In addition to functional improvement, TNF inhibition has been suggested to have additional beneficial bone and cardiovascular effects. TNF inhibition has been suggested to improve bone mineral density [27]. TNF inhibition studied in 26 patients with AS showed a modest, but sustained, increase in serum HDL-C levels, which may have a favorable effect in reducing the cardiovascular risk in these patients [28].

The extra-articular manifestations of AS are well recognized and have additional TNF management considerations. Eye inflammation, especially acute anterior uveitis, has a likelihood of 1:4 in AS [29]. The prognosis of uveitis is usually good with topical treatment, but, if chronicity develops, patients might benefit from additional immunosuppressive therapy [30]. A meta-analysis of four placebo-controlled and three open-label studies showed that anterior uveitis occurs less frequently in patients treated with TNF-α-blocking agents [31]. There is some evidence that infliximab is more effective than etanercept in the treatment of recalcitrant uveitis [32]. The role for TNF inhibition in subclinical gut inflammation, which has a higher incidence in AS patients with peripheral arthritis, is unknown. Remission of joint inflammation, however, is associated with a disappearance of the gut inflammation [33]. The role of TNF inhibition for changing the outcome of valvular disease, apical fibrosis, pulmonary interstitial infiltrates, pleural thickening and secondary renal amyloidosis seen in AS patients is unknown.

Although therapeutic beneficial effects of TNF-inhibition have been demonstrated, there clearly are potential side effects to be considered in patients treated with anti-TNF agents. The infections, including sepsis and tuberculosis, malignancies, demyelinating disorders/neuropathy and infusion/injection and hypersensitivity reactions, are important adverse effects of TNF-inhibition that AS patients should be educated about [34]. The injection site reactions of mild-to-moderate severity occur, and are managed with antihistamines, injection of hydrocortisone or, less commonly, cessation of therapy. TNF inhibitors should be avoided in patients with advance heart failure since in large Phase II and Phase III trials with TNF-α antagonists they have shown trends towards a poorer prognosis in this population. TNF-α inhibitors are also associated with the formation of autoantibodies, although these autoantibodies are rarely associated with any specific clinical syndrome. Rare cases of aplastic anemia, pancytopenia and vasculitis have also been described with anti-TNF therapy [35].

Conclusion

AS is a chronic disorder with significant disability that results from spondylitis, arthritis, enthesitis and extra-articular inflammation. Treatment requires both a pharmacologic and nonpharmacologic approach. Exercise, including formal physical therapy and education, is important for all AS patients. NSAIDs and COX-2 inhibitors should be initiated for all patients with pain and stiffness. Sulfasalazine has a role for unresponsive peripheral arthritis. TNF inhibitors are important for the management of persistently symptomatic spinal disease. Clinical trial data demonstrate that all US FDA-approved TNF inhibitors – infliximab, etanercept and adalumimab – have resulted in a significant improvement in AS patients' quality of life and functionality. However, long-term safety and disease modification data are still needed for TNF inhibitors.

Executive summary

Treatment of ankylosing spondylitis has been revolutionized by TNF-inhibitors

- NSAIDs and cyclo-oxygenase (COX)-2 inhibitors are often substandard for controlling inflammatory symptoms.
- Traditional DMARDs are ineffective for axial disease.
- Clinical data support use of TNF inhibitors as first-line therapy for spondylitis unresponsive to NSAIDs or COX-2 inhibitors.

There are three FDA-approved TNF inhibitors for treatment of ankylosing spondylitis

- With the exception of anterior uveitis, no TNF inhibitor has proven to be superior for treatment of ankylosing spondylitis.
- It is recognized that the effects of soluble and transmembrane TNF are different.
- Clarification of the anti-TNF effect, whether primarily by apoptosis of macrophages or downregulation of inflammatory mediators is needed to better understand differences in these pharmaceutical agents.

Conclusion

- In addition to nonpharmacologic interventions, TNF inhibition has a very important role in the symptomatic management of ankylosing spondylitis.

Future perspective

- Superiority between TNF-inhibitors for treatment of spondylitis, peripheral arthritis and extra-articular features, such as inflammatory eye disease, pleuropulmonary disease, valvular disease and secondary renal amyloidosis are needed.
- Long-term structural modification and safety data for TNF inhibition in ankylosing spondylitis patients are needed.

TNF exerts a pleiotropic effect through transmembrane and soluble forms, which interact with two different forms of the receptor, p55 and p75. Although there may be a differential ability of infliximab, etanercept and adalumimab to modulate apoptosis and the anti-inflammatory cascade, no TNF inhibitor is currently regarded as superior for treatment of spondylitis and peripheral arthritis in AS. Infliximab may be superior for treatment of AS eye disease. There may also be benefits of TNF inhibition on bone and cardiovascular health. The role of TNF inhibition for subclinical GI disease, pleuropulmonary disease, valvular lesions and secondary renal amyloidosis is unknown. An understanding of these lesions' response to TNF-inhibition should better elucidate their pathophysiology. Additionally, the long-term safety and disease modification data will be instructive. Although TNF inhibition appears to be very promising in the treatment of AS, the benefits of therapy must be carefully weighed with potential risks, which can be quite severe.

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