Ankylosing Spondylitis – A Major Advance in Management : Light at the End of the Proverbial Tunnel

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For decades, patients with ankylosing spondylitis have been waiting for more than just counseling, nonsteroidal anti-inflammatory drugs, and the advice to stop smoking and to follow an exercise programme. Over these same years, the exercise programmes have become more sophisticated, with well-structured hydrotherapy, inpatient rehabilitation, and a standard exercise regimen for patients to follow at home.[1] However, there had been only one meaningful addition to the drug armamentarium over the past decade with the advent of the cyclooxygenase II inhibitors. This new class of nonsteroidal drugs was safer than conventional agents and had an equivalent or better efficacy profile.[2] Nevertheless, there was only minimal evidence[3] that any of these management modalities could alter the underlying course of the disease or modify disease activity to the extent that patients could fully participate in social and professional activities. In other words, a "magic bullet" directed towards the pathogenetic mechanism of the disease was still lacking.

Furthermore, disease-modifying drug was available for ankylosing spondylitis, and virtually every agent known to work in rheumatoid arthritis and other rheumatologic conditions was shown to be a failure for patients with ankylosing spondylitis. Indeed, methotrexate, azathioprine, cyclophosphamide, gold, and other agents were all shown at different times to be ineffective. Sulphasalazine had a weak effect on the peripheral joint disease in patients with ankylosing spondylitis (rarely a major problem), but the spinal signs and symptoms continued unabated.[4]

Developments in the understanding of the pathogenesis of ankylosing spondylitis in the last few years have translated into dramatic improvement for many patients. Tumour necrosis factor-α (TNF-α) was known to be a pivotal cytokine in the immunoinflammatory cascade.[5] AntiTNF agents were developed, and both etanercept and infliximab were quickly shown to have great success in the management of rheumatoid arthritis.[6,7] However, this condition was often adequately treated by methotrexate. For example, a study of etanercept versus methotrexate in early rheumatoid disease reaffirmed not only the enhanced efficacy that resulted from the antiTNF agent, but also, the rather dramatic effect of aggressive methotrexate therapy.[8]

Thus, it was with enormous enthusiasm that patients and clinicians turned to the antiTNF agents in the hope that they would be effective in treating ankylosing spondylitis. Infliximab had already been shown to be effective in Crohn's disease,[9] which was encouraging because many patients with ankylosing spondylitis also have intestinal inflammation. Mielants, Veys, and colleagues in Belgium reported that some 60% of patients with ankylosing spondylitis had Crohn's-like lesions on biopsy of the iliocolonic junction, even for patients who had not received nonsteroidal therapy or other agents that could "irritate" the bowel.[10] Many of these patients did not have other symptoms consistent with intestinal inflammation. In addition, bowel inflammation has been observed in the transgenic B27 rat model.[11] It is known that 5 to 10% of patients with ankylosing spondylitis have concurrent symptomatic inflammatory bowel disease.[12]

Psoriasis is also an important condition that is observed in 10 to 15% of patients with ankylosing spondylitis. Both etanercept[13] and infliximab[14] have been shown to be effective in this skin condition, which is additional support for using these agents to treat patients with ankylosing spondylitis.

A third condition that occurs with ankylosing spondylitis is inflammatory eye disease. Early concerns were raised that there had been some spontaneous episodes of uveitis occurring in patients with other rheumatologic and nonrheumatologic disorders who were treated with etanercept.[15] This provided us with a caveat regarding the use of this agent in patients known to be susceptible to uveitis. In our own database of over 6,400 patients with ankylosing spondylitis, 40% have had one or more episodes of uveitis.[16]

In terms of the systemic features of ankylosing spondylitis, one of the outstanding issues relates to fatigue.[17,18] In a major publication on etanercept and ankylosing spondylitis,[19] the drug was shown to be efficacious but apparently had no effect on fatigue when a nonvalidated fatigue questionnaire was used. However, later in our work with etanercept using a validated outcome instrument, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI,[20] we showed that etanercept improved fatigue as well as the other disease symptoms.[21]

In recent years, results from pilot studies and well-controlled investigations began to appear, with data supporting the use of etanercept or infliximab for the management of ankylosing spondylitis. In the near future, adalimumab, the third anti-TNF agent now available for rheumatoid arthritis, will be evaluated in ankylosing spondylitis, and physicians will have to decide which would be the preferred agent for treating patients with ankylosing spondylitis.

At this stage, we can summarise the situation as follows:

Both etanercept and infliximab have been shown to be efficacious in short-term studies of ankylosing spondylitis by improving function, metrology, and sense of well-being, while at the same time, reducing disease activity and evidence of bone oedema from magnetic resonance imaging.[19,22-24] However, the results of long-term studies are more relevant to clinical practice, and these studies are currently ongoing.

From a patient's point of view, one cannot readily differentiate between the attributes of self-administered subcutaneous etanercept at home or intravenous infliximab in the clinic. Anecdotally, it does seem that many patients prefer regular contact with physicians or nurse specialists, and therefore, the "hassle" associated with an intravenous bolus of infliximab appears not to be of much concern. Of course, in terms of safety, it is perhaps preferable to have more frequent contact with any patient receiving a biologic agent so they can be monitored for adverse events.

Both etanercept and infliximab are expensive, but data on their cost-effectiveness over the long term are forthcoming.[25] The goal of treatment is not only to decrease pain, sleep disturbance, morning stiffness, and peripheral joint swelling, but also to enhance patients' well-being, improve employability, and maintain physical function over years and decades. Patients are often 20 to 30 years old when they are diagnosed with ankylosing spondylitis. Prior to the arrival of the antiTNF agents, we knew that these patients would lose 5 to 10 years of productivity in the labour force. When all of these hidden and not-so-hidden costs are taken into consideration, the drugs will likely be considered cost effective.

Ankylosing spondylitis is typically viewed as the prototypic spondyloarthropathy – a name given to the group of conditions with sacroiliitis, ascending spinal disease, psoriasis (to a varying degree), inflammatory bowel disease, and inflammatory eye disease. The majority of patients with ankylosing spondylitis do not escape from these other inflammatory disorders. Indeed, as intimated above, 40% of patients with ankylosing spondylitis have inflammatory eye disease, 10 to 15% have inflammatory skin disease (psoriasis), and 60% have symptoms consistent with inflammatory bowel disease.

Infliximab is effective in the treatment of patients with Crohn's disease,[9] while etanercept is not.[26] Given that many patients with ankylosing spondylitis will also have associated bowel, skin, and eye inflammation, infliximab may offer a more holistic approach to treatment. Debate will continue as to what extent intestinal inflammation plays a role in maintaining the ongoing inflammatory rheumatological disorder. If the bowel is involved, then reducing inflammation (be it overt or covert) within the bowel wall should benefit patients.

The ultimate goal is to provide patients with therapeutic agents that will "turn off" the ankylosing spondylitis by halting its progression after early diagnosis. Perhaps intervention with an antiTNF agent in teenagers with early ankylosing spondylitis will have this effect. Patients with ankylosing spondylitis can be recognised readily with the help of family history (eg, early maternal onset of ankylosing spondylitis greatly increases the risk of disease in teenage offspring).

Future studies should address the following questions:-

1. How important is early diagnosis and treatment with antiTNF therapy?
2. For how long should a patient receive antiTNF therapy?
3. Will long-term use of biologics such as antiTNF agents be safe, or will hidden problems become apparent?
4. Should all patients be offered anti-TNF therapy or only those with Bath Ankylosing Spondylitis index scores exceeding 4?

These and other considerations invite early attention and investigation.

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