Anti-TNF drugs in ankylosing spondylitis: the present and future

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Evaluation of: van der Heijde D, Schiff MH, Sieper J *et al.*: Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. *Ann. Rheum. Dis.* (2008) (Epub ahead of print).
In contrast to the situation in rheumatoid disease where a variety of inexpensive disease-modifying agents exist (e.g., methotrexate), no such agent modifies disease in ankylosing spondylitis. Therefore, the arrival of anti-TNF drugs has been an enormous contribution. All the anti-TNF agents are efficacious in this condition, and this article reviews data regarding adalimumab in ankylosing spondylitis. In the future, we will need to define which anti-TNF agent should be considered the drug of choice for which type of disease. Important outstanding issues exist, such as should anti-TNF be given very early, following symptom onset, in order to turn off the disease process rather than merely suppress symptoms? The long-term will certainly see more anti-TNF agents, and the hope remains that as the choice increases, the price will reduce. In societal terms, this class of drug is cost-effective, given there are patients who can continue with work and return to the workplace after a few weeks or months of treatment.

Van der Heijde and colleagues have recently published their long-term follow-up data of adalimumab efficacy in the management of ankylosing spondylitis, maintained for up to 2 years [1]. In essence, this was a follow-up of the initial randomized, double-blind placebo-controlled 24-week study.

Initially, patients received adalimumab 40 mg every other week or placebo for 24 weeks, and then subjects were switched to adalimumab 40 mg weekly. Efficacy focused on 20% improvement in the assessment in spondylarthritis international measures, ASsessment in Ankylosing Spondylitis (ASAS) [2] 20, ASAS 40 and ASAS partial remission, together with changes in ASAS 20 components. For example, 65% were ASAS 20 responders, while 51% met the ASAS 40 criteria and 34% achieved ASAS-defined partial remission.

From baseline to the end of year 2, the Bath Ankylosing Spondyltis Disease Activity Index (BASDAI) [3], an expression of disease activity and a component of ASAS, improved from 6.3 to 2.4, and the Bath Ankylosing Spondylitis Functional Index (BASFI) [4] improved from 5.2 to 2.9.

Adaliumumab was well-tolerated, and there were no cases of serious infection, TB, congestive heart failure, lupus-like syndrome, demyelinating disease or malignancy.

Certainly, the degree of maintained improvement has been impressive. It is generally accepted that a BASDAI score of over 4 (0–10 scale) or a BASFI score of similar dimensions represents severe disease and, often, inability to work. By contrast, figures of 2.4 and 2.9, respectively, suggest that patients have had only mild-to-moderate disease activity, were functioning well and, thus, likely to have been able to return to work and enjoy everyday activities.

With regards to 'value for money' in societal terms, the benefit of adalimumab seems worthwhile. Inevitably, the results of such a study leave us with a series of further questions that need to be considered.

We now have impressive data supporting the use of adalimumab in the management of ankylosing spondylitis, comparable with the improvement seen with etanercept and infliximab. Ideally, we would have access to large multicenter comparative studies, comparing outcome with these different anti-TNF agents, on a head-to-head basis. Such studies would need to be dramatically large to allow the clinician to determine which of the three anti-TNF agents should be used in general, and in which specific subset of disease.

There are certain features that all three anti-TNF agents have in common, such as enormous cost, relative safety and impressive efficacy, but there are differences and we need to know more regarding these, particularly with the advent of new anti-TNF agents that are under study at various stages, some of which are close to the marketplace.

If anything, the situation is even more urgent with ankylosing spondylitis than with rheumatoid disease. The latter responds well to methotrexate, a drug that costs very little per week,

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whereas effectively there are no disease-modifying agents in ankylosing spondylitis. Indeed, we know that gold, methotrexate, azathioprine sulfasalazine, penicillamine and other agents that are well-respected in terms of the management of rheumatoid arthritis are useless in ankylosing spondylitis [5]. We also know that TNF has a relatively central role in terms of disease pathogenesis in ankylosing spondylitis, and it is not surprising that all the anti-TNF agents, to date, are efficacious in this disease.

However, we know less regarding the response of specific clinical features of spondylarthritis to the different anti-TNF agents. For example, if an individual patient has uveitis, which anti-TNF drug should be chosen for that individual, and what should be chosen regarding inflammatory bowel disease, extreme fatigue, the very young and the old or those with heart involvement. These and other difficult issues need to be addressed.

Furthermore, we need to establish whether anti-TNF therapy can prevent disease rather than merely suppressing disease activity once it has occurred. It is very easy to define the ideal study given what we know regarding the epidemiology of this condition. For example, we have shown that women with young-onset disease are at high risk of having a son or daughter who are destined to develop disease [6]. Careful attention to such families would allow us to address the *HLA-B27* status of offspring of such mothers and, with appropriate ethical approval, conduct a study to follow such *HLA-B27*-positive children with magnetic resonance imaging and, at the first sign of inflammatory disease, introduce anti-TNF therapy in order to determine whether the disease can be 'turned off' by what is an aggressive and expensive, but safe and probably efficacious, approach to management.

Clearly, there would be ethical considerations, but in my experience, most families would be anxious to see such a formal study carried out. It seems likely that the pharmaceutical industry would be prepared to fund such research.

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Bibliography

1. van der Heijde D, Schiff MH, Sieper J *et al.*: Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. *Ann. Rheum. Dis.* (2008) (Epub ahead of print).
2. van der Heijde D, Calin A, Dougados M *et al.*: Selection of specific instruments for each domain in core set for DC-ART, SMARD, physical therapy and clinical records keeping in ankylosing spondylitis. Progress report of the ASAS working group. *J. Rheumatol.* 26, 951–954 (1999).
3. Garrett SL, Jenkinson TR, Whitelock HC, Kennedy LG, Gaisford P, Calin A: A new approach to defining disease status in ankylosing spondylitis: The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). *J. Rheumatol.* 21, 2286–2291 (1994).
4. Calin A, Garrett SL, Whitelock HC *et al.*: A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index (BASFI). *J. Rheumatol.* 21, 2281–2285 (1994).
5. Calin A, Taurog J (Eds): *The Spondylarthritides*. Oxford University Press, Oxford, UK, p1–353 (1998).
6. Calin A, Brophy S, Blake D: Impact of sex on inheritance of ankylosing spondylitis. Authors reply to letter. *Lancet* 355, 1098 (2000).

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