TNF therapy for spondyloarthropathy: can we marshal the argument?

‘Health Authorities and Primary Care Groups and Trusts should not wait for guidance from NICE.’

Lord Hunt, House of Lords, 3 April, 2001.

There is an unmet need for effective disease-modifying treatments in the spondyloarthropathies (SPAs). Comprehensive evidence is presented in this issue [1] and published elsewhere [2] for the use of anti-TNF therapy in this group of diseases. Unfortunately, the SPAs represent a group of overlapping entities that have received less attention from pharmaceutical developers in comparison to the ‘single’ heterogeneous diagnosis of rheumatoid arthritis (RA). In patients with RA, routine assessment of interventions and their outcomes has proved a powerful means of justifying biological therapies. In addition, the effectiveness of disease-modifying antirheumatic drugs (DMARDs), such as sulphasalazine and methotrexate, is widely accepted. Patients with SPAs suffer badly by comparison, for two reasons. First, a historical lack of cooperation and coordination has delayed the acceptance of internationally recognized criteria for evaluating the effectiveness of treatment and its long-term benefits. Secondly, once physiotherapy, NSAIDs and localized therapies (e.g. injections) are exhausted, treatment options become extremely limited. There is little convincing evidence that traditional systemic therapies have a predictable disease-modifying effect on the axial, peripheral joint and extra-articular manifestations of the SPAs. Best evidence suggests that NSAIDs modify radiological progression of ankylosing spondylitis (AS) axial disease [3, 4], but have no effect on other indices. Many DMARDs (e.g. sulphasalazine, bisphosphonates, gold, cyclophosphamide, cyclosporin, methotrexate, azathioprine, thalidomide and leflunomide) have been evaluated in relatively small uncontrolled studies, but none has emerged as a standard treatment that can be used with confidence to treat all manifestations of the SPAs. The lack of significant benefits from such studies probably explains the pharmaceutical industry’s historical reluctance to assess therapies for the SPAs in large controlled trials.

In recent years, however, studies in animal models [5] and clinical studies of articular [6] and extra-articular inflammation [7] in patients with SPAs have provided convincing evidence that TNF-α has a pivotal pathological role. In addition, we now know that patients with SPAs not only experience pain and disability similar to that found in RA [8], but also have increased mortality [9] and reduced quality of life [10]. The prevalence of SPAs (1–2%) is similar to that seen in RA [11] and accounts for a significant socio-economic burden [12]. These discoveries have now resulted in greater attention being paid to the improvement of therapy for the SPAs. This may supply the motivation for clinical trials of anti-TNF drugs to be funded, allowing the extension of their marketing authorities to include the spondyloarthropathies.

Recommendations on how we evaluate AS [13] have now been made, and a consensus conference [14] has drawn on experience gained from RA to recommend criteria for the use of anti-TNF therapy. Patients should:

- have no contra-indications to anti-TNF therapy (as per RA);
- fulfil the New York diagnostic criteria for AS;
- have active disease determined by a BASDAI score >4 for at least 4 weeks and an expert opinion that they have active disease;
- have failed to respond to standard therapy; and
- be assessed after 6–12 weeks, and continue treatment if there is a significant response defined by an improvement of 50% or 2 units of the BASDAI and expert opinion that there has been a response.

Whereas these recommendations might appear to offer a way forward for patients with AS, there is no clear evidence or agreement on what is the effective standard therapy, for how long anti-TNF treatment should be continued, what is an effective dosage, and whether it should be used in combination. Moreover, AS is only one of the SPAs.

In contrast to the situation in RA, the measures used to assess response to anti-TNF therapy in AS are uniformly subjective and rely on patients reporting improvement. The objective measure of acute-phase response is a poor indicator of persistent inflammation in the SPAs, and alternative objective assessments of inflammation, such as MRI scanning, have not been widely evaluated [15, 16] and have additional cost implications. Radiographic progression cannot be used as a basis for inferring response until 2 yr has elapsed [17]. Having to continue anti-TNF in all patients for 2 yr before the response could be determined would considerably increase the cost of their use.

These uncertainties undermine the arguments in favour of making resources available to offer anti-TNF therapy to patients with AS. Furthermore, health resource providers have learnt from the use of this treatment in RA that randomized controlled trials (RCTs) do not always anticipate the demand for continued treatment, which has considerably exceeded the figure predicted from RCTs by the National Institute for Clinical Excellence (NICE) [18]. Observational studies may be more realistic [19]. Clearly, patients entering RCTs are not representative of patients who attend rheumatology departments and the outcome of such studies will therefore underestimate the true clinical need.

By applying the EULAR consensus criteria prospectively to 126 of our own sequential AS patients, we have estimated that 56% have a BASDAI >4 [unpublished data, J. Packham], and other departments have estimated similar percentages (50–67.5%) [20–22]. A BASDAI greater than 4 and spinal pain greater than 4/10 could be considered as more discriminating criteria for active AS. In our sequential AS patients, 83% of those with a BASDAI greater than 4 had pain greater than 4/10. Based on an estimate of AS prevalence of 0.1% and RA data that 35% of patients are not suitable for anti-TNF, 18,000 AS patients in the UK could benefit from anti-TNF therapy at an annual cost of £180 million. This economic cost could not be met from current local health resources, and health providers are under no legal obligation to ensure these treatments are funded and made available unless NICE recommends their use in early 2006. Despite political protestations that patients will not be deprived of effective therapy, the reality in the UK is that bureaucratic barriers and hurdles prevent clinicians from introducing these therapies. Individual patients’ needs have to be justified on a case-by-case basis to health commissioners, and clinicians who implement therapy without approval risk ostracism and censure.
For the time being, SPA patients and their clinicians find themselves in a void created by competing motives and responsibilities:

Broadening the use of anti-TNF drugs might improve patient care but the SPAs were not a priority when these therapies were initially developed and a successful application to the regulatory authority for a new (or extended) marketing authorization would require a series of expensive RCTs.

The low prevalence of the SPAs provides no financial incentive for the pharmaceutical industry, whose primary motive is to generate profit for its shareholders, to fund further research. The Health Technology Appraisal programme to which NICE must work is determined by the Department of Health. NICE accepts it has a backlog and is trying to catch up, but is unable at present to appraise new drugs or new indications within a timescale appropriate to the needs of clinicians (and patients). In the meantime, the funding of drugs that are awaiting appraisal (or reappraisal) is bound to display inconsistency.

The Department of Health has devolved responsibility for this problem. It has devised a mechanism by which new medicines can be appraised, and has given primary care trusts (PCTs) full responsibility for deciding priorities beyond those that relate to central health-care targets, using the money from their existing budgetary allocation pending a recommendation from NICE.

PCTs are working to priorities that are largely set by the Department of Health, and are relatively inexperienced in local priority setting. They depend on whatever medical and pharmaceutical advice they can employ to guide their judgements on the allocation of funds for new medicines, and are likely to adopt a cautious approach to requests from secondary care. They are entitled to reject requests on grounds of non-affordability, provided they can be seen to have followed due process in their evaluation.

Clinicians who divert funds from their RA patients to equally deserving SPA patients not only deny RA patients appropriate therapy but risk severe criticism for using NICE funding for an unauthorized purpose.

One way to break the deadlock might be to recommend an approach that has been used in Glasgow to evaluate the clinical effectiveness of new (and expensive) medicines [23]. Based on preliminary evidence of clinical efficacy and safety, a case is made for limited funds to support a pragmatic outcome study in a limited number of selected patients, allowing collection of data on clinical effectiveness. This can then be used to support the extension of funding to allow larger numbers of patients to be treated. Such an approach would allow a proactive response to new scientific data, while we await definitive research and/or clear guidance from NICE.

The unfortunate reality is that NICE is unlikely to recommend the use of anti-TNF therapy for AS and other SPAs according to the present European guidelines—a BASDAI score greater than 4 is not a sufficiently discriminating criterion. The Scottish Medicines Consortium has already recently ruled that infliximab should not be recommended for the treatment of AS within Scotland. To justify the very considerable cost of these drugs, we need more objective measures of eligibility for, and response to, anti-TNF therapy. This is the enigma to which the rheumatology community in the UK must seek a solution that is both timely and persuasive.

The authors have declared no conflicts of interest.

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References


