Editorial

Anti-tumour necrosis factor therapy for ankylosing spondylitis—unresolved issues

The management of ankylosing spondylitis (AS) has been revolutionized by the introduction of anti-tumour necrosis factor (TNF) drugs. The long-standing need for an effective treatment for AS seems to have been met at least partially and at a price. There is ample evidence that treatment with infliximab, etanercept and adalimumab reduces pain and stiffness, greatly enhances the sense of well-being and improves functional outcome in patients with long-standing AS [1–3]. Moreover, this symptomatic improvement is accompanied by a significant degree of reduction in spinal inflammation as detected by magnetic resonance imaging [4–6]. There is no doubt then that, for the first time ever, the outlook for people with AS is radically better. But, in spite of such good news it is clear that much important groundwork has not been done—for good reasons—so that critical, unresolved questions remain. The answers to these are all the more critical for a treatment which carries substantial real and potential risk and huge cost. Some of these questions concern the best ways to use biologic treatments, others the balance between cost and benefit. It is no surprise that in a disease that has been all but untreatable research has not focused on these issues in the past but there is no time to lose now in resolving them.

The balance of cost and benefit hangs on the kind of long-term benefit biologic treatment confers and the likely necessary duration of treatment. Chief amongst these unanswered questions is: does TNF blockade modify the disease? In recent years the term ‘disease modification’, used in rheumatoid arthritis, has come to refer principally to radiographic progression as a marker of biological change in the affected sites [7]. However, no such clear understanding exists in AS. Disease modification in AS encompasses a combination of spinal movement and function, well-being, comorbidities and radiographic progression including prevention of ankylosis, all reflected in changes from that which would be expected in work capacity, independence and recreational ability. A positive trend towards improvement in spinal measurements (Bath Ankylosing Spondylitis Metrology Index) with anti-TNF therapy has been demonstrated [1, 3] but the changes are not dramatic. Inevitably, as these are relatively insensitive measures, this question will take time to answer. Small but important changes in functional state, reflected by the Bath Ankylosing Spondylitis Functional Index (BASFI) have been consistently demonstrated in AS patients treated with anti-TNF therapy as having significant improvements in patient health-related quality of life [8]. Any impact on work and recreation is not yet clear in spite of this being a crucial indicator of true disease modification. Listing et al. [9] showed that infliximab treatment for 2 yrs in a small cohort of patients (n = 49) led to a reduction in the number of hospital in-patient days and days of sick leave. More recently, van der Heijde et al. [10] showed that infliximab treatment significantly improved the daily productivity of patients with active AS and also reduced workday loss among employed patients with AS. However, no significant improvement in employment status was observed and not many unemployed patients returned to work. This area needs further prospective evaluation. A trend towards deceleration of X-ray progression after treatment with anti-TNF therapy has been reported [11, 12]. However, these were small study samples of short duration. MRI studies have shown a reduction in inflammatory spinal changes [4–6] within a short time of starting anti-TNF treatment. Persistence of inflammation, however, has been seen in a proportion of patients continuing treatment [4, 5]. MRI may not be the perfect tool but its potential use as a predictor of outcome needs urgent clarification. It is clear that the correlation between symptomatic response to treatment and changes in MRI scanning are at best suboptimal. More importantly, it remains unclear whether lesions demonstrable on MRI scanning correlate with subsequent ankylosis and/or socioeconomic outcomes. It is clear that modifying both the biology and outcome of AS is the prime objective of treatment but that both a consensus of what constitutes ‘disease modification’ and essential research to demonstrate it are still lacking.

Who should we treat?

It seems inescapable that treatment with potent, expensive and potentially hazardous anti-inflammatory agents should be aimed at individuals with active inflammation, troublesome and restricting symptoms and a poor prognosis. But how accurately can we identify these patients? A simple measure of inflammatory activity is a surprisingly good start but our understanding of the natural history of AS is incomplete. Do all patients progress radiographically and can progress be halted? Is progression linear or episodic? What early features sensitively predict deformity, job loss and long-term suffering? This background of uncertainty renders questions as to patient selection and what real outcomes can be expected answerable only with large numbers of patients observed in a standardized way over several years. This is not a task for single units or small focused trials but rather for large-scale multi-centre collection and collation of facts. Data from clinical trials indicates that all patients, even those with ankylosis, may respond [3]. A recent report from Leeds, UK [13] estimated that almost two-thirds (64%) of their patients with AS met the British Society for Rheumatology (BSR) eligibility criteria for anti-TNF therapy [14]. If more than half of people with AS are to receive anti-TNF treatment we need to be sure that the potential risks and cost are worthwhile for them all rather than only an identifiable subgroup.

Access to treatment

Access to anti-TNF drugs within the UK is still not easy and many primary care trusts (funding bodies) await recommendations from the national institute for clinical excellence (NICE) before committing funds. Hence, the outcome of NICE’s appraisal is eagerly awaited by patient groups and the rheumatology community. In a recent survey of consultant rheumatologists’ in the UK [15], it was observed that 33% of the respondents had no access to anti-TNF drugs to treat AS and psoriatic arthritis. Amongst those who did, the ability to freely prescribe according to the BSR guidance was limited to only 25% of the consultants and the others could do it only under some circumstances.

Should we treat AS early?

Restoring well-being and preventing long-term damage and disability are laudable objectives of treatment. Currently, however, only the first is a demonstrably realistic prospect in AS. Nonetheless, the possibility that early treatment could lead to
the avoidance of the awful medium to long-term consequences of disease or even ‘switch it off’ altogether would radically change the balance between advantage and disadvantage. Some evidence that early treatment may indeed do just this in rheumatoid arthritis has emerged [16, 17]. In one study of AS patients [18], remission of symptoms following anti-TNF therapy occurred in fewer patients with increasing disease duration (35% of patients with disease duration <10 yrs, 24% in those with AS for 10–20 yrs, none in those with AS for >20 yrs). Short-term treatment would clearly be an almost ideal approach and ‘switching off’ disease must still represent the ultimate objective of treatment. Although in one study treatment with etanercept in individuals with early onset AS (onset <18 yrs of age) improved signs and symptoms for at least 24 weeks [19], it remains unclear whether early treatment with biologic drugs will reduce disease progression.

In practice, early treatment is effectively prohibited by the long delay between the onset of symptoms and diagnosis for most patients—which may be up to 11 yrs [20]—and by the present guidance [14, 21], which requires a secure diagnosis based on the modified New York criteria [22]. These require clear-cut radiographic changes at the sacroiliac joints which may take several years to develop; hence opportunities to treat in the ‘pre-radiographic’ stage are effectively precluded. MRI scanning is helpful in diagnosing sacroiliitis earlier than conventional radiography [23]. There is, therefore, an ‘unmet need’ to be able to diagnose AS early, irrespective of the value of early biological therapy. The use of MRI scanning in the detection of sacroiliitis might be one part of meeting this need. Clear criteria for the diagnosis of inflammatory (IBP) as distinct from mechanical back pain and increased awareness of AS amongst general practitioners might be others. New candidate criteria for IBP have recently been proposed [24]. These may be especially helpful as the diagnosis of AS is often missed or markedly delayed especially in the primary care setting [25]. In a recent survey of general practitioners in Norfolk, UK (submitted for publication) only 5% could identify all eight features known to be indicative of IBP, with 17% able to identify fewer than four features.

Hence, there is a need to develop adequate screening criteria that would aid primary care physicians for early referral of patients with IBP from the community along with robust criteria which will allow early diagnosis.

How long should treatment continue?

The prospect of indefinite anti-TNF therapy, with associated costs and risk of toxicity (both short- and long-term) is a source of real concern, amplified by the fact that patients with AS are likely to start treatment at a young age. To answer this question fully, both the natural history of AS and the long-term maintenance of drug efficacy need to be appreciated. Continuous anti-TNF therapy has been shown to maintain clinical response for up to 5 yrs [26, 27]. On the other hand, one study showed that most patients with AS who stopped anti-TNF therapy after 3 yrs relapsed within the next year [28].

‘How long’ to treat is inseparable from ‘how’ to treat. Now that the first tranche of clinical effectiveness data are in, experimental drug regimens need to be investigated. Might lower doses, on-demand usage, or less frequency of dosing work? Although the recommended (licensed) dose of infliximab for the treatment of AS is 5 mg/kg, two recent reports [29, 30] (involving small numbers of patients treated with 3 mg/kg) have highlighted the clinical effectiveness of lower doses for most patients. Intermittent use seems effective in some conditions, especially Crohn’s disease, [31] and in some patients with AS treatment at increased intervals may be acceptable. Plainly, expecting to continue biological treatment life-long is not presently justified. Therefore, stopping after pre-determined treatment periods seems inevitable. The clinical issue is that the effects of doing so are monitored on a large scale and that evidence-based treatment strategies can be developed.

Will the benefits of treatment justify the costs?

Healthcare costs are an integral element of decision making about treatment, so it is critical to assess what, if any, costs might be saved by an annual investment in treatment of £10 000 or more. The costs associated with having AS are difficult to quantify but increase steeply with increasing severity of disease [32]. Withdrawal from work is three times higher in patients with AS compared with the general population [33], while others do not achieve what might reasonably be expected in their careers [34]. A proportion of patients require hospital care for joint replacement surgery, spinal surgery, osteoporosis, cardiovascular morbidity, symptom severity or disability. Perhaps the greatest of all these costs—to both the patient and society at large—are those associated with work disability. We need to know the extent to which biologic treatment might mitigate these costs.

Clearly, the key element in cost mitigation overall is targeting the potentially ‘expensive’ patients with a bad prognosis. There are some data to indicate that AS patients with shorter disease duration, younger age, a lower BASFI [18], raised inflammatory markers [35] and greater amounts of spinal inflammation on MRI at presentation [36] have better responses to anti-TNF therapy. However, these observations do not imply that patients who do not have these features do not respond or are not worthy of treatment. Only large-scale data collection on patients receiving and not receiving TNF blockade therapy can put the monetary cost and value of treatment into a usable perspective.

Conclusion

The introduction of TNF blockade treatment for AS has huge and undeniable value. There is now an urgent need to optimize its effectiveness, safety and value for money by gathering prospective large-scale data. In our view this should involve setting up a large, broadly based AS inception cohort with long-term follow up. In particular data collection should address the following issues:

(i) Assessment of efficacy and disease modification (spinal movement and function, well-being, work and recreational status, co-morbidities and radiographic progression including prevention of ankylosis).
(ii) Determining optimum treatment regimens.
(iii) The impact of anti-TNF treatment on AS-related complications and mortality.
(iv) The costs and benefits of treatment.
(v) Development of criteria for early diagnosis and bad prognosis.

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