Editorial

Updating the British Society for Rheumatology guidelines for anti-tumour necrosis factor therapy in adult rheumatoid arthritis (again)

Because of the significant cost implications of biological treatment, most UK rheumatologists are willing to accept limitations in the use of these drugs. They are, however, aware of the increasing literature on biological treatment and are concerned about the rigid nature of the guidelines. Guidelines cannot be static and must be adjusted according to new information so that they can best meet the needs of our patients. No government is likely to allow unlimited access to anti-tumour necrosis factor (anti-TNF) drugs for rheumatoid arthritis (RA) unless these drugs suddenly become inexpensive. We have data in abundance for the efficacy and safety of anti-TNF drugs, but ‘cheap’ is not an adjective we will be able to apply to them for the foreseeable future. In the meantime, UK clinicians see patients with active RA in whom their clinical instinct says that anti-TNF therapy is indicated, yet they fail to fulfil the current British Society for Rheumatology (BSR) guidelines. Is there a case for modifying the eligibility criteria without breaking the NHS bank?

In 2003 the process to update the original 2001 BSR RA anti-TNF guidelines began [1]. Uniquely for NICE, these guidelines were incorporated unchanged into their Health Technology Appraisal [2]. At the time, it was felt that there was little evidence for changing many of the eligibility criteria, and the document concentrated on an update on safety issues. In April 2004 the guidelines were presented in draft form at the BSR Annual General Meeting and feedback was invited. The limited comments from BSR members and from the drug companies suggested slight changes in content, but no disquiet about the eligibility criteria. In 2005 the updated anti-TNF guidelines for adult RA were published in this journal [3]. In the time lag between these events, many more data have emerged on the appropriate use of disease-modifying anti-rheumatic drugs (DMARDs) and anti-TNF drugs.

Furthermore, other national societies and representative bodies have published anti-TNF guidelines. Many of these are less restrictive than those produced by the BSR:

(i) The Irish Rheumatology Society has suggested that anybody with persistent, active RA (which is undefined) should be eligible for anti-TNF therapy. It is suggested that assessments take place on two occasions a month apart, though this is not mandatory (and probably therefore unlikely to happen). Anti-TNF therapy should be considered after the failure of one DMARD, usually methotrexate. Treatment should be withdrawn if it is not efficacious, but the method of estimating this is largely left to the clinician (see http://www.isr.ie/for details).

(ii) The American College of Rheumatology 2002 update of the Guidelines for the Management of Rheumatoid Arthritis suggest that an inadequate response to 3 months of maximal therapy of methotrexate should render the patient eligible for consideration of anti-TNF therapy (see Fig. 1, p. 329 [4]). An inadequate response is not defined, so this is left to the discretion of the treating rheumatologist.

(iii) The Dutch have guidelines that suggest the failure of one DMARD and a disease activity score (DAS) of $>3.2$ is sufficient to consider anti-TNF treatment [5].

(iv) A consensus statement on biological treatments by national experts from the US and Europe has recently been updated, and continues to advise that biological treatments should be considered after the failure of one DMARD (usually) in patients with (undefined) active RA [6]. Norway and Denmark follow this recommendation, and a recent survey showed that 47.9% of Norwegian and 41.3% of Danish patients on anti-TNF would not meet the BSR criteria [5].

It is understandable in this climate that colleagues feel that the 2005 BSR guidelines already look dated, unduly restrictive and out of kilter with the approaches of other national and international guidelines.

At a recent meeting of the Clinical Affairs Committee of the BSR, it was decided that this area is so important to our patients, and changing so rapidly, that the BSR RA anti-TNF guidelines needed a further overhaul, mainly to address the increasing evidence base for changing eligibility criteria. Not only does this need to be done as soon as possible, but it was also agreed that this should be revisited on an annual basis. In this editorial we summarize the issues, and invite comments and feedback from colleagues at this relatively early stage of development.

1. Is pre-assessment necessary? The 2005 guidelines continued the requirement that a patient should have a DAS of $>5.1$ on two occasions a month apart [1, 3]. The rationale was to select patients with ongoing active disease, as opposed to those experiencing a single flare. In real life, our nursing colleagues often state that this is a cruel delay of the inevitable, in that virtually everybody who fulfils the criteria at 1 month prior to baseline continues in a similar vein at baseline. Furthermore they may deteriorate over the month’s delay, and their carers are reluctant to intervene (with steroid injections, for example) in case this jeopardizes their chances of fulfilling the criteria at the second visit. In an audit of 175 patients in Derby and Cannock, it was shown that the DAS did show a small but significant increase over the pre-assessment month, and that 98.3% of patients fulfilled the entry criteria at both assessments [7]. As the drugs are used earlier in the course of the disease, patients with more recent onset disease would be expected to have more fluctuating DASs. These patients might be particularly penalized by the current pre-assessment requirements. We are not aware of any other guidelines suggesting pre-assessment. Is there sufficient evidence and opinion to replace this approach with a single assessment?

2. Is it necessary to have failed two DMARDs? There are increasing data to support the efficacy of all three anti-TNF drugs in DMARD-naïve RA patients [8–10], but it is difficult to argue for the cost-effectiveness of this approach, particularly when methotrexate is so cheap and very effective for many patients. There is also more evidence for the successful early use of combinations of conventional DMARDs, such as the COBRA trial, the FIN-RACo study and TICORA [11–13]. This raises the
It may be that conventional DMARD combinations are being underused, and should be tried before the initiation of anti-TNF therapy. This concept is supported by the findings of the BeSt study in which conventional DMARD approaches (monotherapy or step-up delayed combination therapy) were significantly less effective than a more intensive COBRA-style induction protocol with respect to radiological and functional outcome over 1 yr [15]. Furthermore, in the same study, clinical, functional and radiological outcome was statistically indistinguishable (with the exception of new erosions in non-erosive patients) at 12 months in the intensive COBRA-style treatment group and the infliximab group. These findings might argue for the introduction of more stringent eligibility criteria, requiring a failure to respond to a more intensive combination strategy than in the current guidelines. This would contrast even more markedly with the criteria from other societies and representative bodies which are lax in comparison. Ultimately the decision of where to impose eligibility reflects contrasting perspectives of health care, with a humanitarian view (treat all with the best drugs available, i.e. lax criteria) and a political view (imposing health economic factors leading to strict criteria), placing conflicting priorities on the BSR and its members. Perhaps individual members are best left to balance these conflicts on their own, and guidelines should retreat from prescriptive definitions of ‘activity’, ‘response’ and requirements for preceding therapy?

Currently in the UK, if newly diagnosed RA patients cannot tolerate their first two DMARDs, they may only have a few months of disease before they are eligible to go onto anti-TNF. Even if DMARD toxicity is not a problem, patients may have a minimum of 6 months of disease before they can go onto anti-TNF. Is this an adequate approach for our patients? Should the guidelines be more specific about combinations of DMARDs that should be tried before anti-TNF? Is there a case for stating that failure of methotrexate alone should constitute eligibility for anti-TNF, which is the suggestion in some other guidelines? Are we moving towards an all-encompassing set of guidelines for managing RA to assist in the complex decision to start anti-TNF therapy? Or are the current BSR guidelines an acceptable compromise as they stand, where more specific recommendations would fail to encompass the complexity and diversity of the individual patient?

3. Is a DAS28 of more than 5.1 an appropriate eligibility criterion? This question begs several further questions. Should the DAS be retained but set at a different level? As was mentioned above, other national societies and representative bodies use a much lower level of 3.2, or set no specified level at all. This equates to the original cut-off between the European League Against Rheumatism (EULAR) criteria for low and moderate disease activity [16]. A recent study of the opinions of 35 experts set the cut-off slightly higher at 3.6 [17]. Should this be adopted in the absence of a clear evidence based approach?

Should the DAS be replaced with something else? DAS is a rather unwieldy tool that requires a calculator. Patients with fibromyalgia may score highly on the DAS [18], and secondary osteoarthritis from long-standing RA will raise the score for non-inflammatory reasons. A DAS of 5.1 in a patient with early RA indicates very active disease, whereas in a patient with long-standing destructive disease the same score may represent remission from inflammatory disease. Alternatives to the DAS include simpler disease activity scores that have been shown to be reliable and valid, such as the Simplified Disease Activity Index (SDAI) [19, 20]. This score does not rely on a complex mathematical formula, but is determined by simple numerical summation. This would increase the clinical utility. The SDAI is sensitive to change (essential in sequential measures for the efficacy of anti-TNF) and has been validated in several studies [17]. Would we be better off using this index?

Is it naïve to propose that any one single instrument is satisfactory to determine which patients should be eligible to go onto anti-TNF? Some patients develop radiological erosions without dramatic disease activity. Others may become increasingly disabled without marked inflammation. Should we have several eligibility criteria, such as active disease (however that is defined), or objective evidence of progressive joint damage (measured by X-rays, ultrasound or MRI), or significant disability (e.g. a HAQ score of more than 1.5)?

4. Is failing to decrease the DAS by >1.2 after 3 months sufficient grounds for withdrawing therapy? Some patients gain benefit from anti-TNF therapy that is not captured by DASs, such as a decrease in fatigue or an increase in well-being. On the one hand genuine non-responders need to be identified so that expensive and unhelpful medication can be stopped, but on the other hand many patients with advanced disease may have a DAS that is relatively fixed by factors related to the chronicity of the disease. In a similar manner to that suggested above, is it naïve to measure drug response with a single index? Should we also include patients who have functional improvement, such as a HAQ score decrease of 0.5 (in keeping with some of the clinical trials [21, 22])? Should consideration also be given to radiological outcomes, as some patients show dissociation of clinical and radiographic response, with some patients failing to meet responder criteria whilst still showing radiological progress [23–25]?

Should anti-TNF medication be more targeted in administration and withdrawal? Perhaps it is early days for suggesting highly sophisticated targeting of anti-TNF therapy, but some informative studies are emerging. A study on infliximab in resistant RA showed that if patients had not shown a significant reduction in C-reactive protein (CRP) after their first infusion, 86% failed to show a clinical or biochemical response by week 12 [26]. In the same study, patients who had a significant reduction in CRP at week 12 despite no clinical improvement were much more likely to go onto clinical improvement by week 24. Would the same apply to the other drugs? Would this allow us to translate these observations eventually into greater targeting of the continued use of anti-TNF in patients?

A study of the use of infliximab in very early DMARD-naïve poor-prognosis patients showed that a ‘hit hard and early withdraw’ regimen achieved sustained and marked benefit when compared with a methotrexate control group [24]. The infliximab arm also showed no advance in MRI metacarpophalangeal damage. Although it is difficult to argue the case for using anti-TNF drugs first-line on the basis of a study that only had 10 patients in each arm, this study demonstrates the need for much more data. A similar inference may be made from the BeSt study in which 50% of the patients in the infliximab arm had stopped the drug at 1 yr because of remission or good response [15]. Should we be calculating prognostic scores (such as the Persistent Inflammatory Symmetrical Arthritis system [27] or other scoring methods [28]) on our patients and targeting the high scorers with early anti-TNF therapy? Could a business case be made for the greater provision of MRI or ultrasound to monitor the response of patients to anti-TNF therapy?

Other potential methods for targeting anti-TNF therapy include estimating cytokine profiles. A patient has been described who failed to respond to infliximab, but showed good efficacy on etanercept. Synovial biopsies showed a high expression of lymphotoxin (TNF-β), which is blocked by etanercept and not infliximab [29]. Would there be value in measuring cytokine profiles in patients so as to be more selective in who receives anti-TNF, and which type of drug?

NICE met in January 2006 to revise the anti-TNF guidelines. Any current deliberations on anti-TNF eligibility are too late
to influence negotiations this time round. What is needed is an ongoing review of the BSR guidelines so that we are in an evidence-based position to appropriately adjust the guidelines in the future, in a way which NICE will find acceptable. Important ammunition in persuading NICE that more RA patients should be eligible for anti-TNF will also rely on strong health economic data. At the moment we can speculate on future savings to the national purse in terms of keeping patients in work, preventing joint replacements, reducing co-morbidities and so on, but we need the hard data that will emerge over the coming years.

It seems clear that one of the functions of the Clinical Affairs Committee needs to be an annual review of the anti-TNF guidelines. If colleagues have comments on any of the above issues we would be grateful if they could be sent to chris.deighton@derbyhospitals.nhs.uk for collation and discussion. Guidelines will never please everybody all of the time. They need to be evidence-based but, where evidence is lacking, they must be informed by the advice and opinions of practitioners who will use them. This will ensure broad acceptability. Most importantly, we need these drugs to reach those patients who are most likely to benefit from them.

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References


