

Guidelines



BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy

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Executive summary

The 2000 BSR recommendations on eligibility for anti-TNF agents had a limited evidence base [1], but were accepted unchanged in the first National Institute of Health and Clinical Excellence (NICE) guidelines [2]. This included the criteria of a 28-joint version of the disease activity score (DAS-28) being >5.1 on two occasions 1 month apart in patients having failed on two DMARDs (one being MTX), and a drop in DAS-28 of 1.2 to demonstrate response. The updated BSR guidelines in 2005 did not consider that there was sufficient evidence to enable a change in eligibility or response criteria [3]. An editorial

in 2006 discussed the shortcomings of these guidelines, and established an agenda for their regular review [4]. Updated NICE anti-TNF in RA guidelines have been published recently [5] and have left eligibility criteria unchanged. Response criteria have become more exacting, not only requiring initial evidence of response, but also 6-monthly assessments demonstrating maintenance of response for patients to remain on therapy [5]. The arguments over the cost-effectiveness of anti-TNF therapy in RA will be revisited in 2010, and it is important that robust evidence-based arguments improve the current NICE guidelines on biological therapies in RA, and ensure the identification of those patients who are most likely to gain benefit, in a manner that NICE deems to be cost-effective.

A scope for the guidelines was agreed by the BSR RA Biological Guidelines Group (BSRBG) in 2007. The following questions were posed and answers sought by conducting detailed literature searches.

- (i) Should DAS-28 be the disease activity measure on which to make decisions about eligibility? If so:
 - (a) should other eligibility criteria also be included beyond DAS-28?
 - (b) should the cut-off be at high disease activity [>5.1 according to European League Against Rheumatism (EULAR) criteria]?
 - (c) should there be a minimum number of repeated measures prior to treatment?; and
 - (d) how should response to treatment be judged?

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- (ii) Should there be a minimum number of conventional DMARDs that have resulted in an inadequate response before introducing biological therapy?
- (iii) If DAS-28 is retained and the threshold for access to biological therapies lowered, what would be the increase in use of biological therapies?

The recommendations

Recommendation 1: biological therapies are recommended as options for the treatment of adults who have the following characteristics.

- (i) active RA as measured by DAS-28 >3.2 with at least three or more tender and three or more swollen joints; and
- (ii) have undergone trials of two DMARDs, including MTX (unless contraindicated). A trial of DMARDs is defined as at least two DMARDs usually given concurrently over a 6-month period, with 2 months at standard doses, unless significant toxicity has limited the dose or duration of treatment. (Level IIa evidence, Grade of recommendation B.)

Recommendation 2: treatment with biological therapies in RA should be continued only if there is evidence of an adequate response to treatment following the first 6 months of continuous treatment. An adequate response is defined as a good or moderate EULAR response. (Level IV evidence, Grade of recommendation C.)

Recommendation 3: after initial response, anti-TNF treatment in RA should be monitored with assessment of DAS-28 no less frequently than 6-monthly. Anti-TNF therapy should be withdrawn if an adequate response is seen (as defined in Recommendation 2) despite 6 months of continuous therapy. (Level IV evidence, Grade of recommendation C.)

Summary of justification for above recommendations

The detailed justification for these recommendations is included in the full version of these guidelines, available at *Rheumatology* online (<http://www.rheumatology.org.uk>).

Although there are problems with DAS-28, it remains a popular way of assessing disease activity, and should be retained until better alternatives can be validated. The BSRBG felt that low levels of DAS-28 should be considered to truly reflect RA disease activity, and that the presence of at least three swollen and tender joints should be a requirement for eligibility to initiate biological therapy, irrespective of their DAS-28, consistent with the NICE anti-TNF guidelines for the treatment of PsA [6, 7] and eligibility criteria in influential clinical trials, such as FIN-RACo [8]. Although there are attractions to including other measures of disease activity and progression in eligibility criteria, such as radiological deterioration, it was felt that there was insufficient evidence to justify this at

present. The arguments for reducing the DAS-28 threshold are:

- (i) NICE RA management guidelines recommend that newly diagnosed active RA should be treated with combination treatment and steroids from the start of the disease [9]. Patients on combination therapies, particularly where corticosteroids are included, should have a lower threshold than a DAS-28 >5.1 for determining that disease suppression is inadequate;
- (ii) data from observational cohorts shows that RA with sustained DAS-28 between 3.2 and 5.1 still translates into radiological progression, functional decline and loss of work in a manner not dissimilar to that in more active disease; and
- (iii) analyses of international databases have shown that the lower the baseline DAS-28, the greater the chance of achieving DAS-28 remission score (<2.6). Other *post hoc* analyses of randomized controlled trials (RCTs) or observational databases, including a study of the BSR Biologics Register [10], have supported equal, if not greater, efficacy in patients with moderate as opposed to severe baseline disease activity.

Published evidence shows that prior to going onto anti-TNF therapy, there is a high correlation between the DAS-28 pre-assessments and baseline scores, so that patients have an unnecessary wait of 1 month prior to being able to start anti-TNF therapy [11]. EULAR response criteria are evidence based and validated, whereas the NICE response criteria are not, and are simplifications of the EULAR response criteria. The NICE criterion for response should therefore be replaced by the EULAR response criteria [12]. Recommendation 1(ii) seeks consistency with the NICE RA Management Guidelines on use of combinations of DMARDs with MTX as the anchor drug and steroids in early active RA [9]. Decreasing the threshold for eligibility to go onto anti-TNF from a DAS-28 of 5.1 to 3.2 is likely to increase the use of biological therapies of RA patients from 6 to 8–12% if specialists behave like their colleagues in other European countries that use similar criteria. However, this use of biological therapies may decrease by following NICE RA Management Guidelines, by treating active disease aggressively from symptom onset [9].

The guidelines will be reviewed in 2012.

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