



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

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Introduction and objectives

Why do we need RA Guidelines for eligibility for the first biological therapy?

Biological therapies represent a huge advance in the management of RA. They are monoclonal antibodies or soluble receptors that specifically block mediators of inflammation or autoimmunity (cytokines, receptors and cells). Biological therapies have the following major advantages over conventional DMARDs:

- (i) their development followed an increased understanding of pathogenesis of inflammatory arthritis;

- (ii) their target is highly specific, with the mode of action easier to elucidate than with traditional DMARDs;
- (iii) their use in clinical practice has added to the confidence of health-care professionals and patients to be able to satisfactorily control disease resistant to conventional therapies, and remission of disease is an increasingly realistic aim; and
- (iv) for anti-TNF drugs, and some of the newer biological drugs, their action is usually rapid, with good symptom control, and significantly greater slowing of radiological progression than conventional DMARDs [1].

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Consequently, it is important that these drugs are available to patients with inflammatory arthropathies, who fail to respond to conventional DMARD therapy, and that the best use is made of them. A drawback of biological therapies is that they are expensive compared with conventional DMARDs, and thus their unrestricted use would be unaffordable. Deciding what constitutes a cost-effective use of biological therapies has been a source of considerable debate. In the UK, the National Institute of Health and Clinical Excellence (NICE), professional and patient representative bodies and the pharmaceutical industry have interpreted the available evidence very differently. All parties agree that there is a need to make these drugs available to those patients most likely to

respond to them, where alternative therapies are inappropriate, and in a fashion that makes the best use of limited National Health Service (NHS) resources.

In making the original recommendations in the year 2000 on eligibility to receive anti-TNF agents and on how to determine response to these therapies, the BSR was mindful of a limited evidence base to inform which patients were the most appropriate, and also did not want to be seen to be profligate with the public purse [2]. They recommended a simplification of the European League Against Rheumatism (EULAR) classification of disease activity and response criteria using the 28-joint version of the disease activity score (DAS-28). The first NICE guidelines on anti-TNF in RA uniquely accepted the BSR eligibility recommendations unchanged. This included the eligibility criteria of a 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. These criteria became enshrined in UK rheumatology practice [3]. The BSR published updated guidelines for anti-TNF therapy in adult RA in February 2005 [4], but did not consider that there was sufficient evidence to enable a change in eligibility or response criteria. An editorial in *Rheumatology* in 2006 discussed the shortcomings of these guidelines, and established an agenda for their regular review [5]. Updated NICE anti-TNF in RA guidelines have been published recently [6] 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 the maintenance of response to enable patients to remain on therapy [6]. The arguments over the cost-effectiveness of anti-TNF therapy in RA will be revisited in 2010, and it is important that professional, patient and pharmaceutical companies have robust evidence-based arguments to 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. Currently, NICE only allow the use of adalimumab, etanercept and infliximab as first-line biological therapies after inadequate responses to conventional DMARDs. However, other anti-TNF therapies (golimumab, certilzumab pegol), and other biological therapies such as tocilizumab, will be considered by NICE in the near future, and may be licensed for first-line biological use. Rituximab may also eventually be granted a licence for use after an inadequate response to conventional DMARDs. Therefore, these guidelines are referred to as 'Guidelines for Eligibility for First Biological Therapy' in the hope that the choice for RA patients will broaden, and eligibility criteria should be the same for all first-line biological therapies deemed by NICE to be appropriate for use after an unsatisfactory response to conventional DMARDs.

NICE published guidelines on the management of RA in February 2009 [7]. However, very few of the recommendations include biological therapies, acknowledging that only a minority of RA patients are exposed to these

drugs. Furthermore, the NICE guidelines were not able to contradict current Single or Multiple Technology Appraisals, whereas BSR guidelines do not face the same constraints. There is still a place for BSR biological therapy guidelines.

What are the objectives of these guidelines?

A scope for the guidelines was agreed by the BSR Biological Group (BSRBG) in 2007, and addressed the following areas, with a view to producing recommendations on the appropriate use of biological therapies in RA. In seeking to determine whether evidence is available to suggest that the current (2005) eligibility and response criteria can be modified, 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?
- (ii) If DAS-28 is used, should other eligibility criteria also be included beyond DAS-28?
- (iii) If DAS-28 is retained, should the cut-off be at high disease activity (>5.1 according to EULAR criteria) to justify the use of biological therapy?
- (iv) If DAS-28 is retained, should there be a minimum number of repeated measures prior to treatment on which to base decisions on eligibility for treatment?
- (v) If DAS-28 is retained, how should we judge response to treatment?
- (vi) Should there be a minimum number of conventional DMARDs that have been deemed to have resulted in an inadequate response before introducing biological therapy?
- (vii) If DAS-28 is retained and the threshold for access to biological therapies lowered, what would be the increase in use of biological therapies?

It is inappropriate to consider the role of biological therapies in disease management without considering the global approach to providing a high-quality service for patients with RA. These biological therapy guidelines should be read in the context of the available and much broader RA management guidelines, such as the NICE guidelines [7] and the BSR and British Health Professionals in Rheumatology (BHPR) guidelines [8, 9]. Furthermore, in order to be eligible to go onto a first biological therapy, a patient should not have any contraindications to the drug. Safety aspects of the biological therapies will be updated in other BSR and BHPR guidelines that will be published in the near future.

Who is the target audience for these guidelines?

These guidelines are directed at all organizations and to health-care professionals involved in determining the eligibility of patients to go onto biological therapies, and involved in making best use of NHS resources. They may also provide a model for other countries in their approach to determining eligibility to go onto anti-TNF.

Clinical situations covered by these guidelines

These guidelines provide the best practice approach to the evidence-based use of biological therapies in RA.

What are the areas that the present guidelines do not cover?

These guidelines do not cover the eligibility of patients with other inflammatory arthropathies or diseases to go onto biological drugs.

How have the patients' and other stakeholders' views been incorporated into the guidelines?

We approached the National Rheumatoid Arthritis Society for patient representation on the BSRBG. The final draft of the guidelines has been circulated to patient representative bodies for comment, and feedback has been incorporated where appropriate. Drafts of the guidelines were also circulated at the BSR Annual General Meeting in Glasgow in April 2009, and feedback considered, and incorporated where appropriate.

What is the evidence to support these guidelines?

The guidelines are referenced throughout, and where new research has been performed to inform the guidelines this is included in detail in the text. Comprehensive literature searches were performed by members of the BSRBG to seek evidence to determine whether changes to current NICE eligibility criteria could be justified. Searches were conducted using MEDLINE, CINAHL, Cochrane, PUBMED and EMBASE. MEDLINE is widely recognized as the premier source for bibliographic coverage of the medical literature, and CINAHL for nursing literature. A manual search from the references cited by generated articles was also used. All searches were performed for literature up to May 2009. Abstracts were read for relevant evidence from the annual conferences of British Society for Rheumatology, EULAR and ACR up to May 2009. Evidence was graded according to the strength of literature to support each statement, using the grading suggested by the Royal College of Physicians of London (<http://www.rcplondon.ac.uk/college/ceeu/conciseGuidelineDevelopmentNotes.pdf>) and the document was prepared in accordance with the principles outlined in the Appraisal of Guidelines Research and Evaluation (AGREE) guidelines (www.agreecollaboration.org).

How will these guidelines be piloted and introduced?

The recommendations on eligibility to commence, and stay on, biological therapies will be presented to NICE at subsequent multiple and single technology appraisals of the drugs. It will not be possible to introduce them unless agreement is secured with NICE. The recommendations will also be used to promote the further development of an evidence base to support their incorporation into NICE guidelines, particularly if they are not accepted into these guidelines.

How often will these guidelines be reviewed?

The guidelines will be revisited either in 3 years, or prior to the next round of relevant NICE multiple and single technology appraisals (whichever is sooner), unless substantial new evidence becomes available in the meantime.

How will these guidelines be publicized and implemented?

The full guidelines will be published on the BSR web site, and sent to all BSR members and Primary Care Trusts. A summary of the guidelines will be published in *Rheumatology*, with web links to the full guidelines. Implementation will depend on negotiations with NICE.

Cost implications and conflicts of interest

A detailed health economic analysis is beyond the scope of these guidelines, but the approach to determining eligibility criteria for biological drugs has been influenced by the methodology adopted by NICE to determine cost-effectiveness. Comments are made on implications of the recommendations on any likely change in the frequency of prescribing biological drugs. No funding has been received to assist with the development of these guidelines, and individual conflicts of interests of authors are disclosed. These guidelines have been developed with complete editorial independence. The conflicts of interest of contributors are listed at the end of this document.

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.)

Justification for the above recommendations: defining eligibility criteria

Should DAS-28 be the disease activity measure on which to make decisions about eligibility?

It is important to be able to assess disease activity, and there are a variety of ways of achieving this. In clinical trials, it is necessary to have reliable and valid measures, but in clinical practice these tools have become increasingly influential. Studies have been published which show that careful documentation of disease activity improves outcomes, providing that escalation, or cautious reduction, of treatment is performed according to the level of disease control. These studies have led to recommendations in the NICE RA Management Guidelines that support the use of regular measures of disease activity in clinic, and appropriate action when necessary [7]. NICE also demand measures of disease activity to determine eligibility to commence anti-TNF therapies, and remain on them.

The most popular of these instruments is the DAS, which was developed in order to provide a quantifiable measure of RA disease activity [10, 11]. The DAS acknowledges that measurement of disease activity in RA is not straightforward, and cannot rely on a single score. For example, measures of disease activity that are perceived entirely by the patient, such as joint tenderness, may be influenced by a large number of variables that do not reflect objective disease activity (e.g. pain thresholds, depression, fibromyalgia, degenerative change [5]). Even laboratory measures such as ESR and CRP are non-specific and may reflect disease other than active RA (e.g. intercurrent infection, and in the case of ESR, age, gender, haemoglobin levels, polyclonal gammopathies, etc.). In early disease, even in the presence of multiple swollen small joints, such as in the hands and feet, the acute phase markers may not be elevated. Consequently, the DAS is derived from a combination of information on swollen joints, tender joints, the acute phase response and general health on a visual analogue

scale. Since it was originally created in 1993, the DAS has been found to show a greater power than other indices or single variables to discriminate low from high disease activity [12]. Furthermore, good correlation over time between DAS and increased joint damage has been found [13]. The DAS-28 is a modified version of the original DAS, based on the same four variables, but in order to increase clinical utility, it has a reduced joint count of 28 swollen and tender joints. One of the limitations of the DAS-28 is that joints of the feet and ankles are not included. Despite this reduction in the number of joints counted, the DAS-28 has a high correlation with the original DAS, and has been validated to a similar degree [14].

Consequently, DAS-28 is well established as a measure of disease activity, and was accepted by the BSR in 2000 as the standard to determine eligibility to commence anti-TNF, and subsequently by NICE in the first and the current RA anti-TNF guidelines. The disadvantages of DAS-28 are summarized in Table 1. This illustrates that DAS-28 is open to substantial criticism. The greater challenge is to suggest an alternative. Having no eligibility criteria would not be acceptable to the public purse, and would invite wide variation in clinical practice. Alternatives would have to be an index relying on a number of measures of disease activity, such as the Clinical Disease Activity Index [15], and the Simplified Disease Activity Index [15]. Although they are easier to use in clinics because they are simple additive scales and do not rely on complex calculations, these are not as well established as DAS-28.

On balance, the BSR Biological Group (BSRBG) concluded that, despite the inherent problems with DAS-28, this measure of disease activity should be retained in the next version of the BSR RA biological therapies guidelines, but ongoing research should seek to find a more satisfactory alternative. It was felt that reducing the thresholds for eligibility was more important than replacing the DAS-28. Because of the problems inherent in the DAS-28, it was felt that if evidence could be found to reduce the threshold, it would be necessary to ensure

TABLE 1 The disadvantages of DAS-28 (with references where appropriate)

Developed from a single clinic.
Requires a calculator, unlike other additive scales (e.g. Simplified Disease Activity Index [15]).
Relies on subjective measures, such as joint tenderness and the patient's global health visual analogue scale.
Joint tenderness receives twice the weighting of joint swelling in the calculation, even though the latter should be more objective than the former.
Relies on patient global assessment but not on physician global assessment.
Ignores the feet and ankles.
Patients with comorbidities such as fibromyalgia and OA may score highly [19].
Traditionally, it is calculated using the ESR, which is influenced by a large number of non-inflammatory mechanisms (a CRP version is available, although not as widely used [20]).
A high score in early disease usually represents active disease, but may not do so in established disease [21].
Some patients with early active disease, particularly affecting small joints of the hands and feet, may not have a particularly elevated DAS-28 despite disabling problems [21].
The DAS-28 cut-off of 5.1 does not reflect the ability of a patient to respond or benefit from therapy [22].
It can differ in weighting RA disease activity variables compared with the physician's assessment [22].

that low levels of DAS-28 should truly reflect RA disease activity. It was felt that demonstrating 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 (see the next section on 'If DAS-28 is retained, should this be <5.1 to justify the use of biological therapy?' for more details) as this is consistent with the NICE anti-TNF guidelines for the treatment of PsA [16, 17] and has been used as eligibility criteria in some influential clinical trials, such as Finland RA-Combination study (FinRACo) [18].

If DAS-28 is used, should other eligibility criteria also be included beyond DAS-28?

The DAS-28 as a single determinant of eligibility to commence biological therapy has been criticized as it can differ in weighting RA disease activity variables compared with physician's assessment [22]. Other international guidelines have accepted the limitations of DAS-28, and allow patients to qualify for biological therapy if other criteria are fulfilled. A good example of this is the French RA anti-TNF guidelines [23]. The British and French guidelines share some features in common. Both require patients to fulfil the ACR 1987 classification criteria for RA, and a demonstration of persistent disease activity with a DAS-28 > 5.1 on two occasions at least 1 month apart (following the EULAR classification of high levels of disease activity [24, 25]). However, this is where the similarities end. The French guidelines acknowledge that a more sophisticated approach than just relying on DAS-28 is required to determine who is not doing well on conventional DMARDs. They extend their eligibility criteria to include patients with:

- a DAS-28 < 5.1 who have ongoing signs of inflammation [defined as a DAS-28 > 3.2 with more than three synovitic joints, an elevated ESR (>28 mm/h) or CRP (>15 mg/dl)] despite >0.1 mg/kg/day of prednisolone or equivalent; and
- evidence of progressive radiological damage despite conventional DMARDs.

The BSRBG acknowledged the clinical value of these additional criteria. The NICE RA Guidelines recommend aggressive combination therapy, including steroids, for active RA from the onset of disease [7]. Patients on such aggressive regimens may have a DAS-28 < 5.1 and yet still have very active disabling disease. Some of these patients may be corticosteroid dependent despite combinations of conventional DMARDs. In addition, corticosteroid use may reduce the DAS-28 < 5.1, yet still not control disease satisfactorily. The NICE RA Management Guidelines recommend that attempts should be made to remove corticosteroids whenever possible, including the tactic of using biological drugs [7].

The BSRBG decided that in the absence of sufficient data to justify a corticosteroid dependence eligibility criterion similar to the French guidelines, efforts would concentrate on trying to support a reduction in the baseline DAS-28 threshold for eligibility to commence

biological therapy. If evidence could be found to support a reduction of the DAS-28 threshold to ≥ 3.2 being sufficient to go onto biological therapy (in keeping with EULAR guidelines for moderate disease activity [24, 25]), this would probably capture most of those patients who were corticosteroid dependent. Furthermore, this level of DAS-28 would act as a more sensitive measure of persistent disease activity despite conventional DMARDs, and suggest the need to intervene with biological therapy, rather than relying on the more crude demonstration of X-ray progression. The BSRBG, however, recognized the deficiencies of the DAS-28 and that joint swelling is:

- a more objective marker of inflammation than joint tenderness, or patient global VAS;
- a more specific marker of synovitis than an ESR; and
- commonly used in clinical trials as a marker of disease activity and eligibility to enter the trial [18].

The BSRBG therefore felt that if arguments could be formulated to support a reduction in the threshold value DAS-28 required to be eligible to commence anti-TNF therapy, it would be necessary to demonstrate that the patient had at least three swollen joints as assessed by an experienced health-care professional, in addition to the level of DAS-28 deemed to be appropriate for the recommendation.

If DAS-28 is retained, should the cut-off be at high disease activity (>5.1 according to EULAR criteria) to justify the use of biological therapy?

The following are arguments in favour of a reduction in DAS-28 < 5.1 to be eligible to go onto biological therapies.

- (i) As was argued above, the NICE RA Management Guidelines recommend that newly diagnosed active RA should be treated with combination treatment and steroids in some form or another from the start of the disease [7]. This means that a patient who, for example, is on a Combinatietherapie Bij Reumatoide Artritis (COBRA) regimen [26] with full doses of MTX plus SSZ, and who has tapered the corticosteroids down to 10 mg, but still has a DAS-28 of, say, 4.2, is continuing to do badly with inadequate suppression of disease activity. Although combinations of conventional disease-modifying drugs can be just as effective in suppressing disease activity as anti-TNF therapies, they are not as good at slowing, or even reversing radiological progression [1] and this eventually translates into disability [27]. Consequently, 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. This approach would be consistent with the NICE RA Management Guidelines, particularly the recommendations on the use of combination therapy with steroids in newly diagnosed active RA (Recommendation

TABLE 2 Changes in DAS-28, HAQ and employment over 2 years of follow-up of patients with varying baseline DAS-28s

Year 1 DAS, <i>n</i> = 302	DAS scores in Year 2, %			HAQ scores in Year 2, %		Employment status in Year 2, %	
	DAS <3.2	DAS 3.2–5.1	DAS >5.1	HAQ 0–<1.25	HAQ ≥1.25	Still working	Stopped working
<3.2	69	20	11	77	23	82	18
3.2–5.1	25	56	19	39	61	77	22
>5.1	10	46	44	17	83	74	26

R16, p. 128 [7]), and only to continue long-term treatment with glucocorticoids when all other treatment options (including biological drugs) have been offered (Recommendation R24, p. 141 [7].)

- (ii) It is also important to consider the outcome of patients with DAS-28 <5.1, who have ongoing moderate disease activity, in order to determine the response of this group of patients, and whether these differ from those with more severe disease. In other words, are patients who currently do not qualify for first biological therapy in the UK experiencing a disease course resulting in as much disability as those who are eligible? This would suggest that the current UK criteria are discriminating against patients with moderate disease activity.

The Early Rheumatoid Arthritis Network (ERAN) has been collecting data on patients with newly diagnosed RA since 2002. Data on 302 RA patients, enrolled in 13 ERAN centres, were available over a 2-year follow-up period, of whom 170 (56%) were in employment at Year 1 [28]. Between Years 1 and 2, 95% of these cohorts were treated with non-biological drugs, as DMARD monotherapy 65%, combination therapy 26% and NSAIDs/analgesics alone 4%. Table 2 shows the change in DAS-28 and HAQ scores, and employment status after a further year of DMARD therapy, according to their DAS-28 status at Year 1. All outcomes were worse on a continuous scale for incremental increases in Year 1 DAS status. Within the Year 1 DAS range 3.2–5.1, there was a significant difference in Year 2 HAQ and employment outcome in patients with baseline scores 3.2–4.1 vs those with a score of 4.2–5.1. These data demonstrate that RA patients with moderate disease activity after 1 year of DMARD treatment, yet not eligible for anti-TNF therapy in the UK (i.e. with a DAS-28 score 3.2–5.1), have a poor outcome after a further year of non-biological therapy, with only 25% achieving a low DAS status (<3.2), 39% achieving a low HAQ (score 0–1.13) and 22% having to stop work [28].

The Early Rheumatoid Arthritis Study (ERAS) is a UK-based nine-centre inception cohort started in 1986, where patients with disease onset of <2 years and DMARD naïve were followed prospectively. The details of an analysis of ERAS data in patients with moderate disease activity are available elsewhere [29]. In summary, routine clinical and radiographical data were collected at

disease presentation and annually for up to 20 years. The analysis addressed the outcome of those patients with less severe disease according to DAS when compared with those with high DAS in an era before the introduction of anti-TNF drugs. Outcome data were examined at 5 years on all patients who had a DAS-28 at both 3 and 5 years (*n* = 820). A total of 721 (88%) were treated with conventional DMARDs, 210 of whom had at least two DMARDs including MTX. At 3 years, DAS-28 was 3.2–5.1 in 33% and >5.1 in 47%. The remaining patients with a DAS-28 <3.2 were not included in this analysis. Table 3 shows 3-year DAS groups (*n* = 163) by 5-year HAQ (quartiles), 5-year X-ray damage (Larsen), orthopaedic surgery and 5-year work status (in 96 patients who were employed at baseline). Although higher 3-year DAS-28 was more frequently associated with being in the worst HAQ group at 5 years, and higher rates of replacement joint surgery and work loss by 5 years, none of these outcomes achieved significantly different odds ratios between the disease activity groups.

The conclusion from this analysis was that the majority of RA patients with a DAS-28 of 3.2–5.1 at 3 years have only marginally better functional, radiological and orthopaedic outcomes at 5 years when compared with those with a DAS-28 >5.1 [29]. These results suggest that current DAS thresholds for eligibility to commence anti-TNF therapy may not differentiate between groups in terms of functional, radiological, orthopaedic and occupational outcomes, and consequently patients with a lower DAS-28 should be entitled to anti-TNF if they are not showing a satisfactory response to conventional DMARDs.

The British Rheumatoid Outcome Study Group was a multicentre, randomized, observer-blinded, controlled trial of 466 patients with established RA (>5 years), on stable therapy for at least 6 months, who were randomized to adequate symptom control/shared care setting (SCSC) or aggressive treatment/hospital setting (ATH). All were reviewed annually by a rheumatologist [30]. The primary outcome after 3 years was the HAQ. Patients in the SCSC arm began the trial with mean disease duration of 12.6 years and a DAS-28 of 4.12, with the figures for the ATH arm being 12.5 and 3.96, respectively. After 3 years, the DAS-28 had improved in the SCSC arm to 3.96, but the HAQ had gone from 1.25 to 1.40 (a significant deterioration, *P* = 0.04) (Fig. 1). In the ATH arm, the DAS-28 had also improved to 3.82, but the HAQ had deteriorated from 1.31 to 1.45 (also a significant deterioration, *P* = 0.04).

TABLE 3 A comparison of functional, radiological, orthopaedic and occupational outcomes in patients with ongoing moderate or severe disease activity

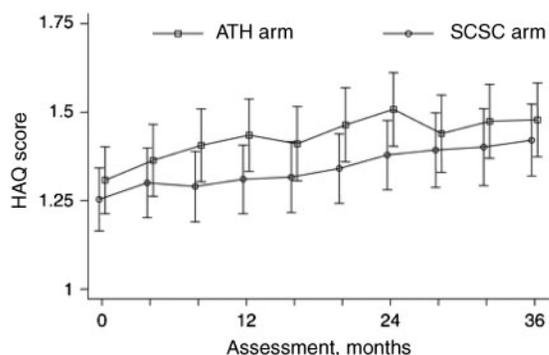
DAS-28 at 3 years	Total, <i>n</i>	HAQ 5 year (<i>n</i> = 163), %			
		≤0.25	0.25–0.75	0.76–1.5	>1.5
3.2–5.1	63	13	14	37	37
>5.1	100	5	12	30	53

DAS-28 at 3 years	Total, <i>n</i>	Larsen score 5 year (<i>n</i> = 123)			
		<2	2–8	9–25	>25
3.2–5.1	50	10	18	26	46
>5.1	73	11	11	37	41

DAS-28 at 3 years	Total, <i>n</i>	Major joint replacement 5 year (<i>n</i> = 163)	
		0	≥1
3.2–5.1	63	95	5
>5.1	100	89	11

DAS-28 at 3 years	Total, <i>n</i>	Work loss 5 year (<i>n</i> = 73)	
		Same job	Stopped due to RA
3.2–5.1	34	65	35
>5.1	39	54	46

All the values are expressed in percentages.

Fig. 1 Change in HAQ over 36-month follow-up in RA patients in the adequate SCSC or ATH arms of the British Rheumatoid Outcome Study Group trial.

Both groups showed radiological deterioration over 3 years for new erosions and Larsen score. In conclusion, two groups of well-established RA patients on conventional DMARD treatments followed up over 3 years showed significant increases in HAQ and radiological progression, despite having persistent DAS-28 < 5.1. This suggests that the conventional DMARD strategies were inadequate to suppress disease progression,

despite DAS-28s well below the level needed for current eligibility for anti-TNF. These findings strengthen the case for considering anti-TNF medication in patients with DAS-28 < 5.1.

A study from Leeds based on data from the Yorkshire Early Arthritis Register looked at patients with early RA (<1 year of disease), who were treated with initial dose-escalated MTX, and subsequent addition of SSZ and HCQ by 6 months if they had a poor response [31]. Changes in HAQ over months 6–12 were compared between groups in whom DAS-28 was persistently high (>5.1), moderate (>3.2 and ≤5.1) or mild (<3.2). Change in HAQ exceeding two published values of the minimum clinically important difference (MCID) (0.22 and 0.38) was determined in each group. A total of 151 patients were studied. Looking at absolute change, 23.4% of patients with mild DAS-28 deteriorated, compared with 33.3% of moderate and 41.5% of persistently high DAS-28. For MCID of 0.22, the proportions of patients deteriorating were 14.9, 25.1 and 34.1%, respectively. For an MCID of 0.38, the proportions were 14.9, 20.6 and 14.6%. The authors conclude that a high DAS-28 was generally associated with a greater degree of functional decline, but persistent moderate elevation of DAS-28 was associated with important functional deterioration in at least 20% of early RA patients following a modern step-up protocol over a short time period. This supports the argument

that a significant proportion of patients with moderate DAS-28 do not have benign disease based on their functional decline, and may benefit from more aggressive therapy.

- (iii) Although anti-TNF therapies represent a significant advance in the management of patients with severe active RA, less is known about their effectiveness in patients with milder degrees of disease activity resistant to traditional DMARD therapy. 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) [32–34]. This may be because patients with a lower baseline DAS-28 have a shorter distance to drop to achieve these levels, or that patients with a lower DAS-28 have a disease that is likely to be more responsive to anti-TNF therapy than those with very high levels of disease activity. Furthermore, despite the fact that patients in a 2005 cohort were being treated with anti-TNF agents had lower baseline disease activity than an earlier 2000/2001 cohort (mean DAS-28 of 5.3 vs 5.9; $P < 0.001$), the improvement in DAS-28 at 12 months assessment was greater in the 2005 cohort (2.2 vs 1.8; $P < 0.001$) [35]. The fraction with a good EULAR response increased from 28 to 50%. The authors concluded that from 2000 to 2005, significantly improved treatment response to anti-TNF therapy was seen in clinical practice, despite a lower threshold of baseline disease activity levels. Other studies of etanercept and adalimumab from *post hoc* analyses of randomized controlled trials (RCTs) or observational databases, have supported equal if not greater efficacy in patients with moderate as opposed to severe baseline disease activity in terms of decreased disease activity and radiological outcomes [36–40].
- (iv) A new analysis was performed for these guidelines on data from the BSR Biologics Register to compare the response with anti-TNF therapy, defined as change in HAQ score over a 12-month period,

between RA patients with high DAS-28 (>5.1) and moderate DAS-28 (>3.2 – 5.1) [41]. In summary, patients were selected if they had received treatment with standard doses of at least two DMARDs and had either a DAS-28 at registration of >5.1 (high DAS-28) or between 3.2 and 5.1 (moderate DAS-28). Change in HAQ over the first 12 months of enrolment was compared first between anti-TNF-treated and -untreated patients in each DAS group, and then between treated patients in the moderate and high DAS groups. Results were adjusted for age, gender, disease duration, baseline HAQ and DAS-28 score, number of previous DMARDs and steroid use. The analysis included 4687 and 224 anti-TNF-treated patients in the high and moderate DAS groups, respectively. Change in HAQ was compared with 344 and 300 biologic naïve patients with high and moderate DAS-28, respectively, despite two DMARDs, including MTX. Anti-TNF-treated patients tended towards lower age and higher mean DAS-28 and HAQ scores at baseline, but had similar disease duration. They had also failed on average one more DMARD than the group not given anti-TNF treatment. The mean adjusted change in HAQ over 12 months was similar in anti-TNF-treated patients with moderate and high disease activity at baseline: moderate -0.26 (95% CI -0.35 , -0.16), high -0.28 (95% CI -0.34 , -0.23), mean difference -0.03 (95% CI -0.14 , 0.08) (Table 4).

In conclusion, after accounting for baseline differences in disease activity and severity, patients with moderate DAS-28 scores at the start of anti-TNF therapy experience a similar improvement in HAQ score over the first 12 months of therapy compared with those patients with a DAS-28 > 5.1 [41].

- (v) Other national and international guidelines that use the DAS-28 as a determinant of eligibility, have set

TABLE 4 A comparison of the change in HAQ over 12 months in patients with mild and severe disease activity on and off anti-TNF

Treatment group	Baseline DAS-28			
	>3.2 – 5.1		>5.1	
	DMARD ($n = 300$)	Anti-TNF ($n = 224$)	DMARD ($n = 344$)	Anti-TNF ($n = 4687$)
HAQ baseline, mean (s.d.)	1.43 (0.76)	1.78 (0.61)	1.87 (0.63)	2.05 (0.55)
HAQ 12 months, mean (s.d.)	1.45 (0.78)	1.51 (0.75)	1.85 (0.63)	1.71 (0.72)
Mean change in HAQ, 95% CI	0.03 (-0.02 , 0.07)	-0.27 (-0.34 , -0.21)	-0.01 (-0.06 , 0.03)	-0.35 (-0.36 , -0.33)
Adjusted mean change in HAQ, 95% CI	Ref.	-0.26 (-0.35 , -0.16)	Ref.	-0.28 (-0.34 , -0.23)
Adjusted mean change in HAQ, 95% CI		Ref.		-0.03 (-0.14 , 0.08)

Ref: referent against which the comparison is made.

a threshold of >3.2, along with a failure to respond to conventional DMARDs (e.g. EULAR consensus guidelines [42], Dutch, Spanish and Swedish guidelines [43]).

If DAS-28 is retained, should there be a minimum number of repeated measures prior to treatment, on which to base decisions on eligibility for treatment?

- (i) 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. Having had a DAS-28 > 5.1 at pre-assessment, there was a 97.2% chance that patients would also have a DAS-28 > 5.1 at baseline [44]. The paper concludes that, by dictating that patients have two DAS assessments 1 month apart, patients have an unnecessary wait of 1 month prior to being able to start anti-TNF therapy, during which they continue to suffer from ongoing active disease.
- (ii) A further paper has demonstrated that the baseline DAS-28 is critical in determining whether patients are classified as responders or non-responders to anti-TNF therapy. Patients with scores just >5.1 are more likely to be classified as non-responders than those with a DAS-28 substantially >5.1 [45]. The paper recommends that several measures of DAS-28 should be taken in a pre-assessment period, with the highest DAS-28 being recorded as the baseline, reflecting the disease activity at its worst.

If DAS-28 is retained, how should we judge response to treatment?

- (i) It has been demonstrated that over time anti-TNF drugs in UK practice are being used earlier in the disease course, and with DAS-28 closer to 5.1 than was initially the case when these drugs first became available [46]. This has also increased the number of patients with a DAS-28 moderate response at 6 months assessment (DAS < 5.1, change in DAS-28 < 1.2 but > 0.6—see Table 5), but this does not fulfil the NICE response criteria (i.e. it is less than the required drop in DAS-28 of 1.2). The EULAR response criteria are evidence based and validated, whereas the NICE response criteria are not and are simplifications of the EULAR response criteria. It is consistent with NICE methodology to accept the evidence-based response

criteria. The NICE criterion for response should, therefore, be replaced by the EULAR response criteria [46].

- (a) A further paper has shown that assessment of response at 6 months is more appropriate than at 3 months, because some patients who fail at 3 months will go on to meet response criteria at 6 months [47]. The BSRBG therefore endorses the current NICE policy.
- (b) The BSRBG is aware that, in clinical practice, anti-TNF drugs often have to be temporarily stopped; for example, because of infections or elective operations. These interruptions in treatment may result in a reversible deterioration in disease control and should therefore be taken into account when assessing both initial and ongoing response to therapy. It is therefore recommended that any decision about withdrawal of therapy due to lack of efficacy should only be made after 6 months of continuous treatment.

Should there be a minimum number of conventional DMARDs that have been deemed to have resulted in an inadequate response before introducing biological therapy?

- (i) NICE RA management guidelines recommend that patients with a recent onset of active RA should commence combination DMARDs (including MTX, one other DMARD and corticosteroids in some form or another) [7], and should have monthly disease activity measured and acted upon if it remains high. Corticosteroids should be counted as DMARDs, as evidence exists suggesting that they modify the course of the disease when given orally [7]. The steroids in very early arthritis (STIVEA) trial suggests that intramuscular corticosteroids may be protective in very early undifferentiated inflammatory arthritis from developing established RA [48]. However, whereas current NICE RA management guidelines advocate aggressive combination therapy from the start of treatment for active disease, the BSRBG acknowledged that there are patients with well-established disease who may have been on sequential conventional DMARD monotherapy, and these patients should not be denied access to biological therapy if their disease is not adequately suppressed. Therefore, a modification was made to the recommendation to encourage rheumatologists to use combinations of DMARDs, in keeping with NICE RA Management Guidelines, but not to make this a prerequisite before access to biological therapy [Recommendation 1(ii), p. 3].
- (ii) Although there is evidence for infliximab leading to anti-TNF therapy-free remission when used in DMARD naïve patients [49, 50], and other anti-TNF agents can work well with MTX in DMARD naïve patients, there is no evidence to suggest that this approach is cost-effective.

TABLE 5 The EULAR response criteria

Change in DAS-28	DAS-28		
	>5.1	≤5.1 and >3.2	≤3.2
>1.2	Moderate	Moderate	Good
>0.6 and ≤1.2	None	Moderate	Moderate
≤0.6	None	None	None

- (iii) The ACR guidelines on anti-TNF therapy argue that patients with poor prognostic RA should be offered access to anti-TNF therapy as a first-line DMARD, but again there is no cost-effectiveness data attached to this recommendation [51].
- (iv) Conventional DMARDs are much cheaper and may be very effective in many patients. A health economic analysis commissioned by NICE for the current guidelines found that first-line use of anti-TNF therapies was not cost-effective [52]. Until reliable biomarkers are identified that predict patients with a poor prognosis, who will do badly on conventional DMARDs but well on anti-TNF therapies, the BSRBG felt that an argument cannot be made for the use of anti-TNF therapy prior to a trial of conventional DMARDs.
- (v) A question that requires further research is how long to trial combinations of conventional DMARDs until it is decided that anti-TNF therapy is indicated. On the one hand, unsuppressed inflammation can lead to irreversible damage. On the other, conventional DMARDs and steroids are considerably cheaper than anti-TNF therapy and, when used aggressively enough in clinical practice, can suppress disease activity to satisfactory levels. The BSRBG decided to follow the current NICE guidelines and recommend a trial of at least 6 months of combination DMARDs.

If DAS-28 is retained, and the threshold for access to biological therapies lowered, what would be the increase in use of biological therapies?

It has been estimated that 6% of RA patients are currently on anti-TNF in the UK [53]. If this is compared with prevalence rates in countries that currently allow patients to go onto anti-TNF with a DAS-28 > 3.2, the rates in Spain, Sweden and Holland are 8, 11 and 12%, respectively [53]. This would suggest that decreasing the threshold in the UK may increase the use of biologics by 25–100%. However, this cannot be looked at in isolation. If the NICE RA management guidelines are followed [7], and patients with recently diagnosed active disease are commenced on combination therapies with steroids in some form or another, this may decrease the number of patients who find conventional DMARDs inadequate for controlling their disease, by treating patients during the window of opportunity, during which aggressive management has a good chance of controlling the disease in the short term, and limiting the damage in the long term. The health economic model that was commissioned for the NICE guidelines showed that the most cost-effective strategy for early RA was a step-down combination therapy. In part, the increased cost-effectiveness was due to a decreased chance of patients going onto anti-TNF therapy after the failure of conventional therapy when compared with sequential monotherapy in the model (see Appendix C at www.rcplondon.ac.uk/pubs/brochure.aspx?e=271 for the details of the model).

A recent study from Glasgow of early RA compared step-up therapy with parallel triple therapy of MTX, SSZ and HCQ with steroid injections [54]. If the DAS-28 was ≥ 3.2 , therapy was intensified according to protocol. The two treatment arms had mean symptomatic disease duration of 10 and 13 months (well beyond the accepted window of opportunity of 3–4 months [43]), and 85% had radiological erosions. Despite these unpromising baseline characteristics, both groups had excellent clinical responses that are equivalent to those achieved by early use of anti-TNF. At 12 months, the mean DAS-28 had dropped by 4.0 and 3.3 in the step-up and parallel triple therapy arms, respectively, with DAS-28 remission in 45 and 33%. A DAS-28 good EULAR response was achieved in 60 and 41%, respectively, and overall the HAQ dropped from 2.0 to 1.1. This demonstrates what is achievable in UK clinical practice when NICE RA management treatment guidelines are followed. The Glasgow group would almost certainly have achieved even better results if they had seen patients sooner in their disease course, in keeping with NICE recommendations.

It would be reassuring if conventional treatment strategies led to sustained benefit, and enabled patients to maintain good disease control without the need to necessarily go onto biological therapies. Four-year follow-up data from the BeSt study has been published [55]. In patients who went onto sequential monotherapy, 39% needed to go onto infliximab and MTX at some stage during the follow-up period. However, in the sequential step-up combination therapy, only 11% went onto anti-TNF, and the figure for the COBRA regimen (combination therapy with tapered steroids) was 20%. Forty three per cent of patients were in remission at 4 years, and 13% in drug-free remission. Of patients on sequential monotherapy, sequential step-up combination therapy, and COBRA regimen, respectively, 19, 6 and 12% were still on infliximab at year 4. These data suggest that combination therapies are superior to monotherapies in decreasing the chances of patients needing to go onto biological therapies, and this approach is in keeping with NICE RA Management Guidelines.

For two intensive early treatment regimens, FinRACo and COBRA, 11-year follow-up data are now available. The FinRACo study studied early active RA (<2 years of symptoms) with a combination DMARD group (MTX, sulfasalazine, HCQ and prednisolone) compared with monotherapy (sulphasalazine with or without prednisolone) [56]. After 2 years of follow-up, the mean DAS-28 in the combination group was 2.2, and 3.1 in the monotherapy arm. After 11 years, the figures were 2.5 and 2.7, respectively. The overall HAQ decreased from 0.86 to 0.36 at 11 years. The COBRA study looked at active RA patients with <2 years of symptoms, who were randomized to MTX, SSZ and tapered oral steroids vs SSZ alone [57]. After 11 years of follow-up, the overall DAS-28 had dropped from 5.8 to 3.0, with very similar outcomes for both arms of the trial. The overall HAQ decreased from 1.4

to 1.0. Both studies may have had even better long-term outcomes if they had been compliant with NICE RA Management Guidelines with earlier interventions. FinRACo achieved better outcomes than COBRA, with greater differences in the combination and monotherapy arms. This may have been because patients in FinRACo had less active disease at baseline than in COBRA. Despite delays in therapy, and differences in baseline disease activity, both studies demonstrate that early use of DMARDs, particularly in combination, can maintain long-term control of disease, with sustained DAS-28 < 3.2 in the majority of patients.

In summary, 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 with combinations of conventional DMARDs and steroids closer to symptom onset.

The BSRBG felt that the process of putting these guidelines together had exposed areas that required further research, and these are included in Appendix 1.

Summary and conclusions

The BSRBG has presented evidence to demonstrate that the threshold for treating RA with biological drugs should be decreased from 5.1 to 3.2 on the DAS-28. The following points support such a move:

- (i) the NICE RA Management Guidelines recommend intensive use of combinations of conventional DMARDs and steroids in early active disease. A DAS-28 of 5.1 is too high to identify those patients who are not showing a satisfactory response to such regimens;
- (ii) patients with persistent DAS-28 levels of between 3.2 and 5.1 have outcomes that are not dissimilar to those with persistent levels >5.1;
- (iii) patients with a DAS <5.1 have a disease activity response to anti-TNF therapies that is as good as, if not better than, patients with a DAS-28 > 5.1; and
- (iv) an analysis of BSRBR data suggests that patients treated with a DAS-28 < 5.1 have just as good an improvement in HAQ as those with a DAS-28 > 5.1, suggesting that this is a cost-effective use of anti-TNF.

This approach is likely to increase the use of biological therapies, but this increase may be attenuated by the implementation of the NICE RA management guidelines on treating early active disease intensively.

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Appendix 1: research recommendations

- (i) More objective measures of disease activity, such as ultrasound, MRI scans or biomarkers, should be explored to determine whether they can replace or enhance the reliability and validity and of eligibility to go onto biological drugs, and assess response, when compared with the DAS-28.
- (ii) The optimal use of conventional DMARDs, alone or in combination should be determined, in order to decide whether or not further attempts, to control the disease satisfactorily with conventional DMARDs, are likely to be helpful, before establishing a patient on biological drugs.
- (iii) Predictors of response to biological drugs should be determined, so that the drugs can be better targeted to those patients who are most likely to respond.
- (iv) The impact of biological therapies on non-articular manifestations, such as the cardiovascular system, should be determined. If they increase both duration as well as quality of life, this should be taken into account in health economic analyses of the cost-effectiveness of the drugs.