The British Society for Rheumatology

BSR Statement

[redacted], [redacted] BSR, [redacted]
[redacted], [redacted] [redacted] and
[redacted], [redacted] BSR, [redacted], [redacted]

Background

The British Society for Rheumatology is the professional organisation for rheumatology, musculoskeletal medical and long term conditions. The Society currently has 1360 members including Consultants, Trainees, Fellows, non-clinical scientists, retired members, international members, Heads of Departments and GP's. Our sister organisation, the British Health Professionals in Rheumatology, has 460 Allied Health Professional members including specialist nurses, physiotherapists, podiatrists and occupational therapists.

We support clinicians at all levels to deliver the highest quality Rheumatology care - in the UK and abroad - by providing:

- An authoritative voice collectively representing Rheumatology in the formulation and implementation of policy at local, regional, national and international levels
- An information service providing continuous updates on developments in Rheumatology practice as well as a comprehensive knowledge archive and evidence base
- A professional network linking our members across all boundaries to continuously improve professional practice and clinical standards
- A learning hub which gives our members access to a wide range of learning opportunities, in a variety of formats, to help them develop their clinical and professional knowledge
- An annual scientific meeting to advance knowledge and practice
- Education courses to further professional development
- Clinical guidelines on a wide range of musculoskeletal conditions

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- A register to monitor long-term safety of biologic agents for patients with rheumatoid arthritis
- An international peer-reviewed journal covering the full spectrum of rheumatological conditions

The Society is a longstanding stakeholder with NICE, having regularly supplied submissions to technology appraisals and other consultations based on advice and input from internationally renowned experts in the specific areas under review, and is recognised as the leading voice in rheumatology in the UK.

BSR produced guidelines on eligibility for the first biologic in 2001, informing the first NICE anti-TNF guidelines for rheumatoid arthritis (RA), and a subsequent update to the guidelines did not find any evidence to change these (1). BSR has been keen to ensure access to these highly effective and innovative medications, whilst also being good guardians of the public purse. The BSR eligibility criteria were adopted by NICE, have continued to be used up to now, and are summarised in the scope. Although they have served a purpose, we believe they no longer adequately capture those patients who would gain greatest benefit from their first biologic, and should be modified. Furthermore we have comments to make on the sequencing of biologics. As clinicians we will focus on clinical aspects, leaving health economic considerations largely up to other experts and the committee.

The scope covers some key principles of high quality management of rheumatoid arthritis (RA), in keeping with NICE Guidelines CG79 (2). There are other points which require emphasis. The sooner patients are seen by specialist teams after disease onset, and the sooner patients can be put onto conventional disease modifying anti-rheumatic drugs (DMARDs) with short term steroids to reduce disease activity, the greater the chances of achieving remission, with delay in going onto DMARDs a good predictor of poor long term outcomes (3). Furthermore, monthly follow ups and measurement of disease activity, with action taken to suppress active disease, can ensure excellent outcomes (2). The National Audit Office (NAO) report in 2009 demonstrated that only 10% of patients in the UK go onto conventional DMARDs within 3 months of symptom onset (4). Just doubling this proportion of patients to 20% was calculated by the NAO to initially increase costs to the NHS by £11 million over five years due to higher expenditure on drugs and the associated costs of monitoring people with the disease (after around nine years, earlier treatment could become cost neutral to the NHS). This increase in earlier treatment

could, however, result in productivity gains of £31 million for the economy due to reduced sick leave and lost employment. On average, this could also increase quality of life by four per cent over the first five years, as measured by quality adjusted life years (QALY) gained (4). This makes implementation of the recommendations in CG79 all the more important, because of their substantial cost saving potential. A Best Practice Tariff will be commencing in April 2013 to financially incentivise hospitals to see patients with early inflammatory arthritis (EIA) within 3 weeks of referral, and start DMARDs where appropriate within a further 3 weeks, then follow patients up regularly to measure and decrease their disease activity (5). A national HQIP audit on EIA and RA will start later in 2013, with measures of delays in getting patients onto DMARDs, and benchmarking between units to improve services.

Eligibility criteria

Even with optimal management, approximately 15% of RA patients in England require biological therapies because their disease does not respond adequately to DMARDs. The current eligibility criteria of a DAS>5.1 on two occasions a month apart is too restrictive in clinical practice. Guidelines on more appropriate eligibility criteria were published by BSR in 2010 (6). The principle arguments for modifying current criteria are:

1. Measuring disease activity on two occasions a month apart painfully delays the inevitable need for biologics in 97.2% of patients (7). Patients with psoriatic arthritis only require a single assessment of disease activity, putting RA patients at an unfair disadvantage (8). RA patients should have a single assessment of disease activity having failed to respond to two DMARDs.
2. Moderate RA with DAS28 between 3.2 and 5.1 is not benign disease, with outcomes not much better than those with persistent disease activity greater than 5.1 (6).
3. Treating moderate RA with biological therapies produces outcomes that are just as good as, if not better than, those in severe RA (6,9).
4. England and Wales are now the only countries in Europe to restrict biologic drugs to severe disease; the criteria in other countries in Europe is a DAS28>3.2. (10)
5. NICE RA management guidelines advocate the use of combinations of DMARDs and short term steroids in active RA (2). One sign that the DMARDs are working is if the steroids can be gradually withdrawn. Some patients may

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have a DAS28 between 3.2 and 5.1, but if their steroids were withdrawn this would lead to a DAS28 > 5.1. It would be inhumane in clinical practice to have to decrease or withdraw steroids in order for patients to fulfil the criteria to commence their first biologic. CG79 states that long term steroids should be avoided wherever possible, using biologics where necessary in order to achieve this (2). Patients with a DAS28 > 3.2 in spite of intensive DMARDs should have access to biologics.

Methods for decreasing the need for biologics

A concern about decreasing the threshold for using biologics is that this will increase their use and the overall cost. Some countries with a threshold of DAS28>3.2 for using biological therapies in patients not responding to conventional DMARDs such as Sweden, Holland and Spain may use up to twice the levels of biological therapies compared with the UK (10). However, if CG79 was implemented as stated above, there is increasing evidence to show that making best use of conventional DMARDs and short term steroids would decrease the need for biological therapies. Trials of intensive conventional therapy from the start of disease have been shown to potentially halve the need to use biologics. One example is the recently reported tREACH trial. Combination therapies (methotrexate, sulfasalazine and hydroxychloroquine) were better than methotrexate monotherapy, and led to a 50% decrease in the need to use biological therapies. Bridging therapies with oral or intramuscular steroids showed no differences between these strategies (11). The UK TEAR study (12) found the outcome of combination therapy was similar whether the drugs were initiated together or added sequentially for persistent disease (12) – the importance is to monitor regularly and treat aggressively until in remission.

Methotrexate is usually advocated as the anchor drug of choice, to which other conventional DMARDs are added. If oral methotrexate is not tolerated or the response is not adequate, subcutaneous injections of the drug can be used (13). This improves tolerability, and increases efficacy. Glucocorticoids are powerful suppressors of signs and symptoms of RA, and have disease modifying effects, at least in early RA (6). These effects probably persist after discontinuation of therapy (13). Standard care is to induce and maintain remission with IM or oral glucocorticoids until the DMARDs take effect.

RECOMMENDATION

Suggested revised eligibility criteria

Because further data has been added since the publication of the BSR guidelines on eligibility for the first biological therapy (6), but mindful of the need to maintain downward pressure on the costs of these drugs, we suggest the following eligibility criteria, in keeping with CG79:

Biological therapies are recommended as options for the treatment of adults who have the following characteristics:

1. *a single assessment of active RA as measured by a DAS28>3.2.*
   This is especially important in patients who are unable to be weaned off oral steroids or monthly intramuscular injections of steroids without their disease flaring.
2. *have undergone trials of at least two DMARDs used in combination, including methotrexate orally or subcutaneously (unless contraindicated), as well as a treatment with oral or intramuscular steroids, with two months at standard doses, unless significant toxicity has limited the dose or duration of treatment of the DMARDs*

Response criteria should be based on the EULAR validated criteria for good or moderate response (6).

Standard Care vs Biologic Therapies

A small number of studies have been undertaken in patients who were either methotrexate naive or had limited exposure to methotrexate. ERA (14) and TEMPO (15) studied etanercept, PREMIER (16) studied adalimumab, AMBITION (17) studied tocilizumab and GO-BEFORE (18) studied golimumab but this compound is currently only licensed in combination with methotrexate. The ERA and PREMIER studies were in early disease. Other than the response to tocilizumab which was superior to methotrexate monotherapy, monotherapy with the remaining biologic drugs was similar to methotrexate.

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The best clinical responses were in the studies that had a combination of the biologic drug with methotrexate. Over 40% of methotrexate naive patients achieved an ACR 70 response following treatment with a combination of methotrexate and either etanercept or adalimumab in the TEMPO and PREMIER studies (15,16). However, other data do not support the use of a biologic drug when initiating methotrexate. The recently published US TEAR trial in early RA found that at weeks 48 and 102 the DAS28 was similar in patients randomised to either triple therapy (methotrexate, sulfasalazine, hydroxychloroquine) or methotrexate with etanercept. There were slight differences in radiographic progression in favour of the etanercept arm, but the significance of this is unclear (19). This suggests that making best use of conventional drugs is broadly similar in outcomes over two years to first line biologic, and is much more cost effective. The Swefot trial where patients with early RA were randomised after three months of methotrexate to either triple therapy or infliximab and methotrexate also had similar clinical outcomes at two years, although the infliximab patients had better disease control at 12 months, and better radiological results at 24 months, but at substantially higher costs (20). The authors concluded that in patients who fail on methotrexate monotherapy, combination therapy with conventional DMARDs is appropriate. Taken together, the TEAR and SWEFOT studies suggest making best use of conventional DMARDs is almost equivalent to, but substantially cheaper than first line or early introduction of biologics.

Sequencing of Biologic drugs

Although combination with methotrexate improves outcome, a significant minority of patients are either unable to tolerate methotrexate or have a contraindication often as a result of concomitant pulmonary or liver disease. Abatacept, infliximab and golimumab are only licensed for use in combination with methotrexate so if co-administration of methotrexate is contraindicated, this would exclude these drugs but the other anti-TNF inhibitors and tocilizumab may be considered.

Anti-TNF drugs have been used in most patients as the initial biologic drug because they were the first drugs to be licensed. The only head to head studies between the drugs in this scope compared abatacept with either infliximab (21) or adalimumab (22) and found no significant differences in outcomes. Meta-analyses indicate little differences between the drugs. One recent meta-analysis (23) concluded that all biologics had the same efficacy and although another recent meta-analysis (24) found a slight advantage with etanercept, the differences between the compounds was small. Patient preference for frequency and route of administration may

influence the choice of treatment. Patient access schemes may also influence prescribing. Some units have adopted a policy of taking advantage of the three months free certolizumab on the patient access scheme, but then negotiated with local commissioners that patients failing to respond to this should be allowed a second anti-TNF.

For patients failing on conventional therapies, there is no clear evidence for the strategy in deciding on the best biologic for each patient. Studies with biomarkers have so far been unhelpful. There have been few direct comparative studies to guide prescribing. Differing trial design prevents a useful comparison but indicates that treatment with methotrexate is preferable. However, these data do not support limiting the first choice of biologic to an anti-TNF drug.

RECOMMENDATION

Until there is data to support specific indications of biologic drugs, we would argue for the clinical freedom to prescribe either a TNF inhibitor, an IL-6 inhibitor or a T cell inhibitor as initial biologic therapy based on the clinical assessment of each patient.

Long term outcomes

As discussed above prompt and effective treatment of rheumatoid arthritis leads to significant productivity gains for the economy as a result of reduced sick leave and lost employment. This relates not only to the patient but to the family and carers who may have to give up productive employment to care for their relative or partner. This was illustrated in a study of patients with early RA prior to the introduction of biologic dugs (25). RA had an impact on one of the socio-economic items measured in almost all patients, and was a major impact in 58%. Work disability was 4-15 times higher than in the general population. After 3 years, 42% of the patients were registered as work disabled. Other economic benefits from effective treatment of RA include cost savings from reduced hospital admissions including the reduction in orthopaedic surgery for hand surgery and joint replacements (26), and the financial benefits from a reduction in morbidity and mortality resulting from improved cardiovascular disease (27, 28).

RECOMMENDATION

We would recommend that socio-economic benefits are included in the health economic analysis in this appraisal.

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