British Society for Rheumatology Response to Appraisal Consultation Document - Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed [ID537]

Introduction

The British Society for Rheumatology (BSR) exists to promote excellence in the care of people with rheumatic and musculoskeletal disorders (RMDs) and to support those delivering it. Its membership is drawn from wide range of healthcare professionals involved in the care of people with RMDs, including rheumatologists, nurses, allied health professionals, GPs and academics. BSR aims to improve standards of care in rheumatology and secure a high priority for rheumatology services across the UK.

Response

We thank the Appraisal Committee for the opportunity to comment on the recent appraisal consultation document issued June 2015. Our comments are focussed on three main areas:

1. On-going access to bDMARDs in patients with severe, active rheumatoid arthritis
2. Removal of access to bDMARDs for patients with intolerance and/or contra-indications to methotrexate
3. Lack of access to bDMARDs in patients with moderate disease

Access to bDMARDs in severe, active rheumatoid arthritis.

We are pleased that NICE have recognised the value that bDMARDs add to the care of patients with active, severe rheumatoid arthritis and are relieved that NHS patients will continue to have access to these life-changing therapies. We accept that only patients at highest risk of progressive joint damage should receive these therapies, and agree that active synovitis despite combination cDMARD therapy is a clinically useful indicator of poor outcome for those with severe disease. This represents a stricter eligibility threshold than previous MTAs but is in line with the modern treatment of rheumatoid arthritis and national (NICE, BSR) and international (EULAR) guidelines.

Removal of access to bDMARDs for patients with intolerance and/or contra-indications to methotrexate

We are concerned that the committee '*was not persuaded that biological DMARDs were a cost-effective use of NHS resources when used as monotherapy'*. The removal of access to bDMARDs for patients who cannot take methotrexate is disappointing and represents a significant change to routine clinical practice, contradicting previous NICE technology appraisals (TA 130, TA186, TA195, TA247) and introducing significant variation from current NICE guidance on the management of RA (CG79).

Observational national registry data (both UK and elsewhere) suggest that a number of patients are unable to take methotrexate and receive bDMARDs as monotherapy [1, 2]. This decision will adversely impact many patients' quality of life. When not contraindicated, alternative strategies include co-prescription with other DMARDs[3,4], although there is evidence that once patients have responded to biologic therapy methotrexate may be withdrawn without loss of efficacy[5].

There are broadly two groups of patients that cannot receive methotrexate:

i) those in whom methotrexate is contra-indicated (including concurrent lung or liver disease, those with previous methotrexate-pneumonitis, and men/women planning a pregnancy);
ii) those in whom methotrexate causes unacceptable side-effects.

Both groups of patients would suffer unnecessarily if access to bDMARDs as monotherapy was withdrawn. Clinicians and patients would potentially find themselves in the unenviable position of not accessing bDMARDS, thereby suffering with progressive, disabling disease, or living with significant side-effects to therapy. Patients planning a family will be particularly affected, as current guidance suggests withdrawal of methotrexate at least 6 months before conception, for men and women. Removal of access to licensed bDMARDs as monotherapy will therefore mean patients living with active, disabling RA at a time when stable disease control is most desired. These are entirely avoidable scenarios and would represent a significant regressive step in the management of patients with rheumatoid arthritis. The ICER for bDMARDs in combination with methotrexate in patients at higher-risk of progressive disease is considerably lower than the base case ICER (£25,300 vs £41,600; Table 1 of Assessment Group Report, May 2015). We note however that the Assessment Group has not provided an equivalent ICER for those patients receiving bDMARD monotherapy at highest risk of progressive disease (Table 2 of Assessment Group Report, May 2015). We invite the committee to accept that monotherapy will be similarly more cost effective for those at highest risk of progression, and to recommend that bDMARDs should normally be prescribed in combination with methotrexate and should only be prescribed as monotherapy in those who are either intolerant or have a significant contraindication to methotrexate.

Lack of access to bDMARDs in patients with moderate disease

We consider it is an appropriate use of NHS resources to prescribe biologic drugs only for those who are most likely to have significant benefit. As discussed above we agree with the revised stricter eligibility criteria of active synovitis despite combination cDMARD therapy in those with a DAS>5.1. However, we also consider that failure of tight control in patients with moderate disease is a poor prognostic indicator.

We are therefore concerned that:
'The Committee was not persuaded that the exploratory analysis for the moderate active group was as applicable to this group as to the severe active group.'
We consider this conclusion to be unreasonable. The ICER from the exploratory analysis for the moderate group was only slightly higher than for the severe active group (£28,500 vs £25,300).
For patients in the moderate group who have the 'fastest HAQ progression', the ICER of £28,500 falls within the cost effective range set by NICE.

In order to understand the magnitude of the problem in those with moderate DAS scores, we commissioned a further independent analysis of the ERAS database. In the whole ERAS database (1465 patients) there were 602 patients with a high HAQ progression defined as $\geq$0.06 p.a. This may be an overestimate because of a number of patients with low data points

who had HAQ progression rates as high as 1.5 or 2 that may have biased the analysis. Nevertheless we analysed the data to determine the number of moderate patients who had rapid HAQ progression. There were 120 patients treated with methotrexate who *always* had a DAS score between 3.2 and 5.1; there was only a modest rise in the average HAQ of 0.017 p.a. in this group. However, even in this cohort 39 patients (32.8%) had an average HAQ progression of ≥0.06 p.a. We also evaluated the cohort of patients with a *mean* DAS score between 3.2 and 5.1 - a total of 868 patients. There were 319 patients in this group who had rapid HAQ progression of ≥0.06 p.a. (36.8% of those with a mean DAS of 3.2 to 5.1 and 53% of all patients in the whole ERAS database with rapid HAQ progression). This data is in keeping with published evidence that the majority of damage occurs in patients with moderate disease[6].

These data explain the reason for many European countries allowing patients with a DAS >3.2 to be eligible for bDMARDs[7] and emphasise the fact that many patients defined as 'moderate' have a rapidly progressive course. They constitute a major clinical problem and should be considered for bDMARDs if they fail combination therapy. Rheumatologists in England and Wales would want to have the same clinical freedom as many European countries and prescribe bDMARDs to any patient with a DAS score of >3.2 who has failed combination cDMARDs. We would welcome the committee recommending this clinical freedom. However, we recognise that the committee wish to identify those who will have the fastest HAQ progression.

Some risk factors for progression were identified in the ERAS study.[8] However, more recent studies have found that one of the most useful predictors of progression is the anti-cyclic citrullinated peptide antibody (CCP or ACPA) that was unavailable during the data collection for ERAS. Several studies have now evaluated ACPA in predicting outcome in patients with rheumatoid arthritis. It is now clear that in addition to persistent active synovitis despite combination therapy,

i) persistent elevation of inflammatory markers,
ii) erosions on x-ray and
iii) a positive ACPA

are strong predictors of progressive disease.[9-15]

In clinical practice, rheumatologists target those who have all three factors for more aggressive therapy. The patients with a DAS 3.2 to 5.1 with these criteria who have failed combination therapy and steroids will have the fastest HAQ progression with an ICER calculated by the assessment group of £28,500. Although it is unlikely that these criteria will include all those with a moderate DAS who have progressive disease, it would identify the cohort of patients described by the Assessment Group with an ICER in the cost effective range.

There are additional data to indicate that long term costs will be reduced. In addition to the introduction of biosimilar drugs, there is increasing data to indicate that once patients are in remission, the dose of the bDMARD may be reduced in the majority of patients without loss of efficacy [16-18] and many rheumatologists in the UK now follow EULAR guidelines[19] and consider dose reduction in their treatment protocols. This practice has not been included in the Assessment Group analysis. We therefore invite the committee to reconsider their decision regarding patients with moderate disease, and recommend biologic treatment for those with a DAS score of 3.2 to 5.1 who have failed combination therapy and who have radiographic erosions, raised inflammatory markers and a positive ACPA (CCP). These are very strict criteria, and more demanding than those with a DAS>5.1, but we believe this to be a reasoned and measured response in this group of patients and is fully supported by published evidence.

Conclusions

In conclusion, whilst we welcome the preservation of access to biological therapies in severe, active rheumatoid arthritis we invite the committee to re-consider its decision to remove access to bDMARD monotherapy in patients with severe active disease who are unable to take methotrexate. We also recommend the committee accepts that active synovitis in higher-risk patients is a predictor of poor outcome in patients with moderately active disease, and that bDMARDs, especially for those patients with several risk factors for progressive disease, would represent a cost-effective therapy for the NHS.

[redacted] and [redacted]

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