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21st February, 2013

Dear Lori,

NRAS Response to Review - Multiple Technology Appraisal
Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab for the treatment of rheumatoid arthritis (review of TA guidance 130, 186, 224, 234 and part review of TA guidance 225 and 247) [ID537]

Thank you for the opportunity to contribute to the above review.

The National Rheumatoid Arthritis Society (NRAS) was launched in 2001 and in a relatively short space of time has become established as the voice in the UK for people with rheumatoid arthritis (RA). NRAS provides a one-stop shop, offering support, information, education and advocacy for all people in the UK with RA, their carers and families. We campaign in England and the Devolved Nations to raise awareness of the disease and ensure fair access to services and treatment for all. We also support health professionals who treat people with RA.

NRAS has provided the principal expert patient in virtually all NICE Technology Appraisals (TAs) since 2003 and has been involved with all the above appraisals. As we are not appraising new treatments in this review, the key issues we wish to explore are those of eligibility criteria and sequencing of drugs.

Background
The original eligibility criteria set by the British Society for Rheumatology (BSR) were entirely appropriate at the time when NICE was formed and we were at the early stages of introducing the Anti-TNFs and comparatively little was known about the long-term effects. Now, a decade later and with substantial Registry and further research data available to us these criteria are no longer appropriate and we need to address the patients who are being failed and damaged by continued adherence to this guidance.

However, we appreciate that it would be financially unsustainable to simply ask that the Disease Activity Score (DAS) criteria be reduced to an arbitrary figure such as 3.2 for everyone at the current time. We have therefore reviewed the relevant data and spoken to a number of our medical advisors and the BSR about what we think would be a feasible and acceptable alternative path. We have also, of course, spoken to patients and include a number of their stories to illustrate the difficulty faced by both patients (and clinicians treating them) who fall in this middle ground between DAS 3.2-5.1 and are failing on treatment, yet not quite meeting the criteria to get onto biologics.

Moderate active disease
The case for widening access to biologics for some patients with moderate rheumatoid arthritis is substantial. For instance, we know that patients in the DAS 3.2-5.1 bracket suffer joint damage[i] and that conventional disease-modifying anti-rheumatic drugs (DMARDs) are less effective at controlling

moderate disease than when used in combination with a biologic[ii]. Research indicates that patients with moderately active disease have a 21.4% chance of suffering severe joint damage[iii].

Indeed, outcomes of people with moderate disease may not be better than those classed as having severe RA[iv], with data from Early Rheumatoid Arthritis Clinics indicating that only 25% of those with moderate disease, using conventional DMARDs, achieve a low DAS score, 39% achieve a low HAQ and 22% have to stop work[v].

In light of the fact that people with moderate disease respond just as well to biologics as those with severe disease[vi], we believe it is unacceptable to deny all people in this category access to biologics. A recent survey of UK patients conducted by NRAS found that 24 per cent of respondents felt current practices in the UK delayed their access to a biologic treatment[vii] and illustrative case studies submitted by NRAS members with moderate disease (see appendix 2), also demonstrate the wide-ranging emotional and physical impacts and further strengthen the case for amending the eligibility criteria.

NRAS's Chief Medical Officer, Professor David GI Scott (President of the BSR 2002-04) and former medical adviser Dr Andrew Bamji (President of the BSR 2006-08) both strongly support a reduction in the criteria to access biologics. Dr Bamji says the following:

"I support NRAS calls for a lowering in the threshold for access to biologics. The original 5.1 threshold was an arbitrary figure chosen by the BSR group which set up the guidelines on which the NICE recommendations were based; I chaired this. Research has moved things on and there are undoubtedly people who might benefit from biologics despite not reaching the current threshold."

"However – there will be a substantial cost implication to this. Given that other research continues to show that 'ordinary' DMARDs are still being delayed inappropriately, the way to offset the potential cost hike would be to include biologics in a global RA treatment guideline which forces initiation of combination therapy (2 DMARDs and steroids) at an early stage; the benefit from early introduction may reduce the need for later biologics by virtue of increasing efficacy."

The case for early aggressive combination therapy (to save on use of biologics)
CG79 needs to be much more widely implemented which recommends earlier referral and commencement on treatment, ideally with combination therapy (more cost effective than monotherapy), followed by tight control[viii]. There is quite a lot of data available now (eg tREACH trial[ix] and a meta analysis reported in the Annals of Rheumatic Diseases in Nov. '12[x]) demonstrating that early RA patients treated with aggressive double or triple combination therapy and prednisolone have both higher remission rates and less radiographic progression than those treated with initial methotrexate monotherapy, even when intensified with prednisolone and if this happens, the need to use biologics reduces significantly.

Barriers to wider implementation
The problem is that there is a resource issue around tight control in many units, guidelines differ (eg EULAR recommends initial use of methotrexate and if that fails adding a biologic) and opinions between consultants on monotherapy versus combination therapy vary widely too. Add to the mix the difficulty of persuading a frightened patient of the need to take multiple potentially toxic drugs and what seems straight forward to achieve is far from it. However better use of combination therapy can be as effective as using biologics and given the financial pressure on the NHS these issues must be addressed.

There are independent reports of significant regional variation in implementation of NICE guidance on RA drugs, with RA patients attending an early arthritis clinic are more likely to receive a treat-to-target

approach[xi]. This is also our experience in talking to patients and health professionals around the UK on a daily basis. We hope that the introduction of a Best Practice Tariff on Inflammatory Arthritis in April 2013 and the HQIP National Clinical Audit on Early RA will both be powerful incentives to drive implementation of NICE Clinical Guideline 79 on RA and gradually reduce these wide variations in practice.

International comparisons on access and use of biologics

We would argue that NICE's restriction of biologics to only those with severe RA is out of step with other countries and more must be done to bridge this gap. For example, the EULAR consensus guidelines, Sweden, The Netherlands and Spain all recommend access to biologics with a DAS threshold of 3.2, and in Slovenia the threshold is 4.2[xii]. Furthermore, overall use of biologic treatments is low across all diseases, with the UK ranked 10th out of 14 countries at between 52% and 79% of the usage in the other countries[xiii], even though the price of biologics in the UK is amongst the lowest in Europe[xiv].

England and Wales is perceived to be an 'outlier' compared to many other countries because of restrictions limiting use of biologics to only those patients with severe disease[xv]. It has been pointed out that NICE guidance is at odds with many published guidelines and standards and there have been consequent calls for the guidance to be changed to allow those patients to access biologics who do not achieve a DAS of under 3.2 after treatment with conventional DMARDS[xvi].

New eligibility criteria

We are aligned with the proposal put forward by the BSR in their submission to NICE in respect of this MTA. Anecdotally, through our helpline and contact with our many groups, members and volunteers across the UK, we are aware of a group of people who are failing to get a DAS score above 5.1, but have persistent disease, and for whom the DMARDs are not working well and simply cannot get off steroids.

I myself fell into that bracket for 20 years and it was only the advent of the Anti-TNFs which I started in 2000, which gave me back a quality of life which enabled me to carry on working, during which time I founded NRAS. If it were not for the advent of biologics, I would certainly be in a wheelchair permanently instead of occasionally and would have had to give up work years ago. I was finally able to get off steroids completely in 2004. I was on a relatively 'so-called' low dose at an average of 5 mg daily, although I did up the steroids (as many do) when I had a flare. However, had I known the damage they would cause me when I first started on them in 1983, I would have done anything to get off them much sooner than I was able to. I have put together a list of the side effects of steroids – Appendix 1 – because I believe the Committee need to be reminded of the side effects of steroids which are many, and we should not be leaving patients who are unable to wean themselves off prednisolone without effective treatment options. We therefore support the following recommendation put forward by the BSR:

"Suggested revised eligibility criteria"

Because further data has been added since the publication of the BSR guidelines on eligibility for the first biological therapy (7), and because 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. active RA as measured by a DAS28 > 5.1, or >3.2 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 and subcutaneously (unless contraindicated), with two months at standard doses, unless significant toxicity has limited the dose or duration of treatment, and trials of steroids (oral or monthly intramuscular).

Response criteria should be based on the EULAR validated criteria for good or moderate response (7)."

We also support the wider usage of parenteral methotrexate. We have undertaken at least two surveys in recent years about patient use of methotrexate and what has been found on both occasions is that there are many patients who are not offered sub-cut methotrexate early enough, if at all. We would like to hope that more patients are now being offered sub-cut methotrexate when experiencing unpleasant side effects at an early stage. Experience from NRAS's helpline tells us that many people struggle with side effects for quite long periods of time sometimes as they are not due to see their consultant for many months. Our Chief Medical Adviser, Professor David GI Scott, also supports this view, adding the following:

"Subcut methotrexate should be used before calling methotrexate a failure; if this was included there would be some reduction/slowing in the obvious increase in numbers accessing biologics if a lower DAS threshold is accepted by NICE."

Sequencing

The sequencing of the biologic therapies has been an issue for a long time. NICE's current sequence guidance to clinicians on sequencing has been driven in part by the way in which the TAs have historically occurred and in part by price, in recent years influenced by Patient Access Schemes (PAS) which lower the cost to the NHS. We still don't know which biologics are best suited to each patient and this dilemma is driving much important research into biomarkers which we support.

However, there are some disease profiles (sub-sets) and some biomarkers now (Rheumatoid Factor and Anti-Citrullinated Peptide Antibody positivity, or levels of Serum C Reactive Protein at diagnosis for example), which are known clinical indicators, which, given clinical freedom, would influence the choice of one biologic treatment over another. We believe there needs to be some greater freedom and flexibility for patients and clinicians to arrive at the best potential treatment at the time of moving to a first biologic, rather than having to cycle through drugs to arrive at the right solution. More detail on these issues is provided in the BSR submission.

The time is therefore right to comprehensively review NICE's approach to sequencing RA drugs and we note that France, Spain, Poland and Greece all make some provision to allow first-line use of biologics in treating early or aggressive RA, whereas England and Belgium do not allow this[xvii]. NICE's complex treatment algorithm has been criticised on clinical grounds, particularly in relation to methotrexate-intolerant patients, sero-negative patients and for DMARD inadequate responders[xviii] - and we believe these criticisms are still valid and must be addressed.

Given the unmet need in terms of an effective treatment for all, with approximately 30% of patients going onto a biologic being primary non-responders, a percentage of whom then go on to become secondary non-responders after a period of time, it makes better sense economically to try and find

an effective treatment first. The desire for patients and clinicians to have more flexibility in terms of choice of drug, and preferred mode of administration to suit lifestyle, is being reflected by units in some areas coming to specific agreement with the local CCG/PCT to vary the standard NICE sequence of biologic therapies in RA.

We have seen examples of revised biologics pathways which have been accepted by the commissioners and which reflect that important ability to be flexible to meet both patient choice and clinical recommendation and we wholeheartedly support this approach as an interim measure. We believe that as new drugs are introduced in future, and further research on biomarkers is published, the need for flexibility in regard to sequencing of drugs to meet patient choice and clinical need will become even more necessary.

Wider societal costs

We have long held the view that NICE needs to take greater account of wider societal costs when formulating its decisions about access to treatments in the NHS. The cost of sick-leave and work-related disability for RA is officially estimated at around £1.8 billion[xix], although NRAS estimates the total cost to the UK economy in lost productivity to be substantially higher[xx].

Ensuring people are able to stay in work is absolutely vital. Not just in pure economic terms, but also because of the psychological impact on patients. In a survey of our members, 88 per cent of respondents said that having a job helped them cope with the disease with incidences of depression significantly higher among non-workers than workers[xxi].

Another aspect of the disease that is frequently overlooked is impact on the family. Our own research has found that when a person's partner has RA this is likely to have negative impacts for the person on: their domestic responsibilities; their employment choices and the family finances; their social life; their relationship with their partner including their sex life; and their own emotional wellbeing. Children with a parent who has RA are also likely to be affected by this into their adulthood[xxii].

The case for improving access to biologic therapies is even more compelling if NICE takes the additional societal costs of the disease into account.

Yours sincerely,

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