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Dear Mr. Powell

NRAS Response to the Assessment Report by West Midlands Health Technology Assessment Collaboration in regard to adalimumab, Etanercept, Infliximab, Rituximab and abatacept for the treatment of rheumatoid arthritis, after the failure of a TNF inhibitor

Thank you for the opportunity to respond to the above Technology Assessment Report. At this point I would like to state that NRAS supports and endorses the submissions from the BSR and RCN.

I think it is important to place on record that I have found the work of preparing for this submission profoundly dispiriting in the light of the work done for NICE in the last few years and particularly the last 18 months, as three important and clinically effective drugs for RA have been consecutively turned down at various stages. I feel this despair both personally, as I have nowhere to go should my current TNF fail (I am sero-negative and anti-ccp negative), and on behalf of all those in the UK represented by my charity, and I have previously submitted many patient testimonials from people who feel the same way.

Switching to a second TNF

I talk to rheumatology health professionals from all over the UK on a regular basis and am well aware that current clinical practice is to put someone who has failed their first TNF onto a second TNF, because this is likely to give that patient the best chance of a good response, keeping Rituximab in the bag as a further option should a second TNF fail, (providing Rituximab is a suitable option). The evidence for this approach is reinforced by patients who are successful on a second TNF being able to get on with their lives, but more than this anecdote, are data from the BSRBR (Hyrich et al. Outcomes after switching

from one Anti-TNF to a second) which paper states “in conclusion, these data from a large unselected population of RA patients suggest that based on treatment continuation rates, there is a strong case for switching patients to a second Anti-TNF agent when failure to respond to the first agent occurs. In fact our findings showed that more than 70% of patients continued on a second agent for at least 6 months.”

The Assessment Group have used data from the BSRBR in their modeling, however, these patients have a long disease duration (10 years + with irreversible joint damage) and patients who have been diagnosed in recent years will move onto biologics much more quickly with much less damage, making data comparison much more problematic.

Diagnosed at young or middle age, despite the shortened life expectancy in RA, it is vital that people have sufficient choice of biologics in their pathway, once they reach that stage, as they will have many years of life to live. There is absolutely no doubt at all in the minds of any of the 580,000 people with RA in England that one Anti-TNF + Rituximab for some (sero-negative and MTX intolerant sub groups excluded), is a totally inadequate choice, given the number of effective biologic treatments licensed. Where is the sense and the logic in enabling the most severely ill to access biologic therapy to improve their disease control and quality of life if at some point in the future, you are going to undo all the good that this has done, by returning them to ‘supportive care’ when they could continue to do well on other biologic therapies?

Rituximab

Rituximab is an effective treatment for sero-positive patients who can take methotrexate. This leaves a large sub-group of patients who are sero-negative and/or methotrexate intolerant for whom Rituximab is not a suitable option. This confers major disadvantage to this group of patients which cannot be justified under any circumstances.

The range of interval sizes between doses seems to be wide. Talking to our members who are on Rituximab, many are now receiving infusions on a 6 monthly basis, whereas others are able to go for longer. How has NICE gathered and interpreted data on this since their economic modeling first time round?

We certainly agree that Rituximab should remain an available option post TNF failure and as individual disease phenotyping becomes more sophisticated, may in time, for some, be more suitable as a first line biologic.

Abatacept

We were extremely disappointed that this effective therapy was turned down on first application. It represents, along with certolizumab, tocilizumab and golimumab, a real alternative to Rituximab following failure of first TNF, particularly for the sub-groups mentioned above. The long term data shows increasing efficacy with good safety profile and we would urge NICE to reconsider their initial decision.

Failure of HAQ score to reflect health utility – QoL

The argument against using HAQ has been substantially discussed by all stakeholders in their various submissions under this MTA in that it fails to reflect the full utility benefit of treatment and is well made in the BSR submission. If I may remind the appraisal committee of a quote from the BSR submission from last August, " the importance of including clinical response as well as disability, is reflected in the study by Brennan ad colleagues (Brennan A, Bansback et al, 2007). They modeled the clinical response to the disability/utility improvement rather than using average improvement in HAQ scores. They also differed from the BRAM in modeling the concept of withdrawal unless an adequate clinical response was achieved. The result of this study indicated that using a second Anti-TNF after failure of the first drug was cost effective using the current parameters accepted by NICE."

Burden of Illness (p.32 - 3.2.20)

The TAR acknowledges the huge burden of this disease, identifying that "it is also clear that informal caregivers shoulder a considerable burden in terms of foregone paid employment, leisure activity and personal health".

NRAS undertook a Mapping Project (NRAS Mapping Project, Bosworth & Oliver, 2007) which was published in 2007 and followed the journeys of 22 RA positive patients from symptoms to 3 years of disease, mapping costs not only to the NHS but costs to the individual. I attach some of the patient maps which I think the Appraisal Committee will find of interest as they chart the 'real' journeys which people experience, rather than an idealized medical model which often doesn't reflect the reality for the patient and their family. The average age of the participants in this project was 49, 7 had to take early retirement/job losses directly attributed to their RA within the time of this study, 6 had to make significant reductions in their work hours directly attributed to their RA, 13 participants during the period of our study had taken > 2 weeks' sick leave, 10 participants had inpatient or emergency admissions and 6 participants were registered disabled (incapacity benefit). This was a random selection of typical patients from across the UK who met the inclusion criteria for the study, which were: diagnosis of sero-positive RA and a diagnosis for 3 years or less.

Some of the key results of this piece of work made it clear (reinforced last year by Kings Fund and NAO Reports), that delays in referral or receiving diagnosis/treatment can result in significant costs both to the NHS and the individual. The indirect costs are high and borne silently by the individual with RA and their family, and for those calculating the direct costs of RA, the assumptions of healthcare costs fail to adequately capture the wide use of healthcare resources – patients are admitted and often managed through a range of medical specialities. Some individuals can be identified as heavy consumers of healthcare resources early on in their disease, regardless of costs of drug therapies.

Specifically in regard to work related costs, at the end of December, NICE themselves called for more help for people to remain in work, by issuing guidance:

“Professor Mike Kelly, Public Health Excellence Centre Director, NICE said: "Long-term sickness absence and incapacity for work is a massive issue, and around 175 million working days are lost in Britain each year due to sickness absence; the associated cost of this is reaching £100 billion - more than the annual NHS budget.

The guidance from NICE aims to help employers and employees work together to ensure that when someone is off work due to genuine illness, the right support is available as early as possible, so they can return to work as soon as they can.”

We are delighted that NICE are now openly recognizing the enormous burden to society of people losing their jobs due to illness and want to ensure that the right support is available to help keep people active and working as long as possible. However, we would challenge their assertion that only a third of employed patients cease work due to their disease. A lot of data on this subject is now available and we know that in fact The seriously disabling nature of this condition means that 42% of RA patients are registered disabled within 3 years, and 80% are moderately to severely disabled within 20 years of diagnosis.[1 & 2] Our own research (RA and Work – a National Picture, NRAS 2007) showed that of the people who lost their jobs due to the RA, one third had lost them within 1 year of diagnosis which is appalling.

Increasingly RCTs in RA are reflecting work, whether paid, voluntary or work in the home, as an endpoint. We and other stakeholders are calling for health professionals to consider work as an important outcome measure of treatment.

Surely, it is increasingly incredible that the full burden of disease is not being reflected in the health economic modelling.

50% Efficacy of DMARDS following return to DMARDS post TNF failure

We have challenged this point with the Appraisal Committee previously, but feel the necessity to do so once more. We understand that the TAR looks at DMARDs which have not already been failed (rather than DMARDs which have already been failed) as comparators, eg. Azathioprine, Ciclosporin, Gold etc.

There are two points to make here:

1) Like the BSR, we do not believe that NICE can claim that there is a 50% efficacy of effect when a patient who has failed on TNF is returned to standard DMARD therapy and fully support the BSR’s argument in this respect.
2) In current clinical practice, Azathioprine, Ciclosporin and Gold are drugs which are rarely used since the advent of biologics. The first two are drugs which patients would be extremely likely to be unwilling to go onto if there were more viable, modern alternatives. It therefore makes no sense to me as a patient, to suggest putting me onto outdated drugs with little chance of response and high likelihood of failure/ unwanted side effects.

The real cost of palliative care

I set out in my last submission (Aug. 2009) that I felt that the Committee had under-estimated the cost of palliative care. Patients who are inadequately controlled and receiving ‘supportive’ care will:

- Visit their GP much more frequently
- May be hospitalised from time to time due to inability to cope with severity of disease, symptoms and disability
- Will become increasingly disabled as their bones erode
- Will require more frequent surgery
- Will risk job loss and will lose their job more than controlled patients
- Will be more likely to claim benefits
- Will be a greater burden to social care costs
- Will have greater impact on their family who are more likely to also suffer job loss to become 'carers'
- Incur worse health economic outcomes
- Be less able to self manage adequately
- Have a significantly worse quality of life
- Have higher morbidity and mortality

We think that there is general lack of awareness that about 50% of people with RA die of cardiovascular disease and that there is significantly increased morbidity and mortality due to upper-gastrointestinal disease as a result of treatment for RA.

There is also a lack of awareness that associated co-morbidities in these patients reinforce each other, impacting on disability, and that the number of co-morbidities in each patient is in itself an independent risk factor for premature death and by the time patients get to this stage, there is a high likelihood of co-morbidity.

The NICE RA Guidelines specifically recommend that steroids should not be used long term which would be the case with supportive care. We would consider it unethical to put people onto 'supportive care' using long term steroids which is contrary to NICE RA Guidelines, when there are other, effective drugs available.

Loss to UK PLC of research revenue

In establishing the Office of Life Sciences, the Government clearly signaled the importance of the pharmaceutical industry to building the Britain of the future by ensuring that this country offers an attractive environment for life sciences companies to do business. The Office, under Lord Drayson's leadership has set out a blueprint which has the potential to transform the UK for the life sciences industry, in particular:

- creation of an 'Innovation Pass' that will give patients faster access to cutting edge medicines;
- Introduction of measures to ensure the NHS leads the way in the uptake of ground breaking and cost-effective medicines and technologies.

I am not advocating on behalf of the pharmaceutical industry, but I would like to ask NICE how they square the above in the light of figures released over the new year which showed a decline in the number of clinical trials conducted in the UK. The figures from the Department of Health show the number of mid-stage, late-stage and post-approval clinical trials fell from 728 in 2008 to 470 in 2009, its lowest level in the past decade. Early-stage trials fell to 210, the lowest in five years. The UK's share of

global clinical trials has fallen from 6 per cent in 2002 to 2 per cent in 2007, and as a citizen of the UK, who wants this country to prosper and lead in this area, this does concern me. According to Financial Times bureaucracy, low recruitment rates and slow uptake of new drugs are pushing pharma companies to undertake more research in other countries in Europe and North America, as well as in low-cost developing nations. The NHS/NICE's negative attitude towards industry and reluctance to pay for drugs are also cited as reasons for the decline. It is also noticeable that whereas the UK was usually the first European country to launch a new drug, this is no longer the case.

In summary, I can only re-iterate with the utmost passion, the need for a whole range of biologic therapies to be available to treat people adequately over the lifetime of their disease.

Yours sincerely,

[redacted]

Enclosures (with hard copy) : Client Maps 7, 10, 16 and 19

References:

1 Albers,J, Kuper, H & van Reil, P et. al., Socio-economic consequences of rheumatoid arthritis in the first years of the disease, Rheumatology, 1999;38:423-430

2 Barrett,EM, Scott DGI, Wiles NJ & Symmons DPM, The impact of rheumatoid arthritis on employment status in the early years of disease:a UK community-based study; Rheumatology, 2000;39:1403-1409

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