NICE appraisal consultation document for alemtuzumab [ID539]

Response from the Multiple Sclerosis Trust and UK Multiple Sclerosis Specialist Nurse Association

9th January 2014

Please find below comments from the MS Trust and UKMSSNA in relation to the Appraisal Consultation Document (ACD) for alemtuzumab, published in December 2013. The ACD states that the Appraisal Committee is minded not to recommend alemtuzumab for the treatment of relapsing-remitting multiple sclerosis (MS).

Our submission will address the following areas, as set out in the ACD, namely:

a) Has all of the relevant evidence been taken into account?
b) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
c) Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
d) Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

We do not believe that there are any points relating to item D. All our points relate to the first three items for consideration.

The MS Trust and UKMSSNA are extremely disappointed that the Committee is minded not to recommend alemtuzumab for adults with relapsing-remitting multiple sclerosis. Our interpretation of the ACD is that the Committee's concerns centre around two main aspects:

- unable to support a recommendation for alemtuzumab in rapidly evolving severe (RES) or highly active despite treatment (HA) subgroups (4.9, 4.22)

- unable to determine the cost effectiveness of alemtuzumab compared with other disease-modifying treatments (4.22)

Our comments focus on these two major issues.

1. Rapidly evolving severe and highly active despite treatment subgroups

The MS Trust and UKMSSNA is particularly concerned that the Committee is unable to support a recommendation for alemtuzumab in rapidly evolving severe (RES) or highly active despite treatment (HA) sub-groups.

With regard to RES and HA, we have commented in previous technology appraisal submissions to NICE that these are artificial sub-groups created to facilitate licensing of natalizumab and fingolimod. In clinical practise, these sub-groups overlap and represent the upper end of a spectrum of disease activity in relapsing-remitting MS, characterised by more frequent and more disabling relapses which may not be controlled by initial treatment with beta interferon drugs or glatiramer acetate. Failure to reduce the number and severity of relapses has a devastating impact both in the short and long term.

High disease activity relapsing-remitting MS should be a priority treatment group for disease modifying treatments. These are precisely the patients who have the most to gain from the very effective reduction in relapse rates and stabilisation (and in some cases reversal) of disability seen with alemtuzumab which would offset the greater risk of side effects. This is the group of patients for whom clinicians have been prescribing alemtuzumab off-licence and clinical experience has shown it to be a very effective treatment for these people. Furthermore, the ERG's own exploratory analyses of the cost effectiveness of treating HA and RES sub-groups found that alemtuzumab dominated both fingolimod and natalizumab treatments (3.31).

As the treatment paradigm for relapsing remitting MS evolves, there is greater clinical emphasis on induction therapy, dampening down inflammation with a goal of eliminating all evidence of disease activity, both clinical and MRI. Early treatment is therefore key, particularly when there is evidence of aggressive disease. The trade-offs between clinical benefit and burden of potential side-effects and ongoing monitoring may also be more acceptable for patients who have experienced more of the impact of relapses.

The Committee heard from specialists about the importance of offering alemtuzumab ‘at an earlier rather than a later stage in the disease’ (4.4) and also to those ‘for whom other disease-modifying treatments have not been effective’ (4.4). The exclusion of RES and HA sub-groups from the guidance effectively leaves the very groups who might most benefit from the treatment ineligible. This would not serve the interests of people with relapsing-remitting MS. Given, this, we are surprised that the Committee did not at least request further consideration and analysis of clinical benefit for these sub-groups.

No head-to-head trials have compared natalizumab or fingolimod directly with alemtuzumab, but indirect comparison indicates that alemtuzumab has a similar efficacy to these two drugs (3.8). The most substantial use of alemtuzumab off-licence has been in place of natalizumab and fingolimod.

2. Economic model

Our interpretation of the ACD is that the Committee's concerns centre on uncertainty over the manufacturer's economic model and felt it was unable to determine the cost effectiveness of alemtuzumab compared with other

disease modifying treatments (4.22). The Committee has presented a series of questions for the manufacturer but has not been clear about the implications of the results of the additional analyses or what further evidence this is expected to provide.

We recognise that a key responsibility of the Committee is to establish whether a new treatment represents a cost-effective use of NHS resources. Our own reading of the ACD, both from the summaries of the manufacturer's submission and the ERG comments, would suggest that certain changes made by the ERG to the economic model resulted in alemtuzumab dominating (being less costly and more effective than interferon beta-1a) with a cost saving of £852 per QALY gained (3.28). Further manipulation of the economic model generated ICERs per QALY gained of £1013 to £8336 (3.29), elsewhere described as mostly below £10,000 (4.22). This falls well within the NICE QALY threshold of £20,000-30,000.

However, further manipulating the economic model to create a worst case scenario generated an ICER of £1,200,000 (4.22). In all the NICE technology appraisals for multiple sclerosis disease modifying drugs, the health economics of MS have proved very difficult to model. How do the assumptions behind this worst case scenario reflect a real world situation? Should an extreme outcome of this sort be disregarded or should it disallow evidence which clearly demonstrates value for money to the NHS?

The Committee acknowledges that alemtuzumab's administration schedule and reduction in relapse rates represents a "step change in the treatment of relapsing-remitting multiple sclerosis" (4.14). Furthermore, the Committee concluded that "on the basis of improvements in sustained accumulation of disability at 6 months in the trials and in relapse rates, alemtuzumab was a more clinically effective treatment for relapsing-remitting MS than subcutaneous interferon beta-1a" (4.8). The ERG's own analyses in different scenarios found that alemtuzumab dominated or gave ICERs of less than £10,000 compared to interferon beta 1a. On the face of that evidence, that the drug is clinically effective and cost-effective, that is has a positive effect on health outcomes and delivers value for the health service, it seems perverse that NICE would not recommend the drug for use in the NHS.

3. People with relapsing-remitting multiple sclerosis currently have very limited treatment options. The committee heard from both clinical and patient experts about the importance of access to a range of medicines, particularly for those who are unable to tolerate current treatments which are associated with significant side effects as well as injection site reactions.

   Despite the overall efficacy of current treatments for preventing MS relapses, any one of them can simply fail to work in a particular patient, or cause debilitating side effects. Clinicians lack tools to predict who would respond well to a specific therapy.

   Four of the five current first line treatments (Avonex, Betaferon, Extavia and Rebif) have the same mechanism of action. If a patient fails to respond to one of these drugs or develops side effects, glatiramer acetate is the only alternative treatment with a different mechanism of action.

All of the current first line treatments are self-injected. Through supporting people who are taking the current first line treatments, the MS Trust is aware that the requirement for long-term injections places a burden on them and in some cases leads to a decision not to start treatment, delays initiating treatment or results in reduced adherence. Self-injecting is painful, results in anxiety and stress; can lead to skin reactions and complications at injection sites; may be difficult for people whose manual dexterity is limited, requiring help from carers and families; and imposes restrictions on a number of aspects of general living.

Alemtuzumab has a unique administration schedule, it acts in a different way to the current disease modifying drug therapies, and has a different profile of side effects. It will significantly enhance the range of treatments available to people with relapsing-remitting MS, providing a genuine alternative to the current therapies.

Conclusion

As stated in the ACD, clinical specialists considered that in clinical practice, alemtuzumab would be used instead of other disease modifying treatments and preferably at an earlier rather than a later stage in the disease (4.4). Alemtuzumab would also be offered to people for whom other disease modifying treatments have not been effective and for whom there are no other treatment options currently recommended. Alemtuzumab has efficacy greater than current first line treatments (beta interferon drugs, glatiramer acetate and teriflunomide), and approximately equivalent, or greater, efficacy than fingolimod and natalizumab. The Committee heard from clinical experts (4.4) that alemtuzumab is "not for everyone" and acknowledges that some people are willing to accept the risks of alemtuzumab treatment and adhere to the monitoring schedule (4.7). The committee concluded that alemtuzumab would be a valuable treatment option for selected patients.

Research evidence demonstrates the importance of active, early treatment of relapsing-remitting MS to prevent axonal damage and avoid irreversible disability. The European Commission has licensed alemtuzumab for active relapsing-remitting MS, defined by clinical or MRI features. The difficulty in calculating cost effectiveness of MS drugs is well recognised, particularly as the trial data does not address the long term benefits of treatment.

The MS Trust encourages the Committee to recognise that alemtuzumab would be an important addition to the small range of available disease modifying therapies for MS.

As with other disease modifying therapies, alemtuzumab should be prescribed by neurologists, with commencement of therapy and ongoing monitoring provided by specialist MS nurses.