Beta interferons and glatiramer acetate for treatment of MS: TA guidance 2018

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A recent NICE technology appraisal has updated the 2002 guidelines on the use of beta interferons and glatiramer for the treatment of multiple sclerosis. Initial draft guidance in December 2017 proposed not recommending the use of glatiramer and other beta interferons apart from interferon beta-1b (Extavia) as interferon beta-1a and glatiramer were deemed to be not cost effective. Many clinicians and patients disagreed with that conclusion and NICE has duly agreed to revisit the data, integrating best supportive care measures rather than relying completely on a head-to-head comparison with the newer medication options.

The NICE 2002 guidance did not endorse unlimited use of both drugs, instead patients with relapsing-remitting MS or secondary progressive MS with relapses were able to access these treatments under the Department of Health Risk Sharing Scheme (RSS). The scheme was established to ensure that the drugs supplied to patients by the NHS were monitored annually for 10 years with regards to their effectiveness. Prices would fall if the drugs were less effective than anticipated, and alternatively, an increase in price would be permitted if they were more effective than anticipated. The RSS was fully accepted by the British neurology community, and more than 5000 patients were recruited between 2002 and 2005. As the RSS has now ended, a reappraisal by NICE was needed.

In the last decade, NICE has also recommended several other options for treatment of relapsing-remitting MS such as alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab and teriflunomide. Recommendations for these medications were provided from trials generally comparing the new medications with the standard disease-modifying agents, beta interferons and glatiramer. In general, the literature demonstrated the beneficial outcomes of the newer medications.

Currently all patients with active relapsing-remitting MS are considered early for treatment. This is an individual decision for each patient, considering the risks and benefits of each potential treatment. According to Association of British Neurologists (ABN) guidelines (2015), most patients are likely to start on a newer MS treatment such as dimethyl fumarate or fingolimod. These are the more effective drugs for this category of patients and have the advantage of being oral formulations. However, there is still a role that beta interferons or glatiramer can play in certain patients who may be more risk averse, concerned regarding side-effects of other medications and who have a less aggressive form of MS.

Pathophysiology

Multiple sclerosis is characterised by an autoimmune inflammation due to activation of pro-inflammatory T cells that act on the central nervous system. This then leads to neurodegeneration. Both beta interferons and glatiramer acetate have beneficial effects in multiple sclerosis via immune-modulation; however, they act via different mechanisms.

Beta interferons (IFNβ)

Interferons are naturally occurring anti-inflammatory cytokines. The action of IFNβ is complex and not fully understood. It appears that IFNβ increases expression of pro-inflammatory cytokines, reduces transfer for inflammatory cells across the blood-brain barrier and increases nerve growth factor production. As the first disease-modifying agent for MS, interferon beta has an iconic status and was described as ‘the drug that changed our understanding of MS’. First to market in 1995 was interferon beta-1b (Betaferon), followed by two formulations of interferon beta-1a (Avonex and Rebif).

Glatiramer acetate

Glatiramer acetate is a synthetic molecule that inhibits the T cell response to several myelin antigens. It also acts as a T cell antagonist and promotes increased secretion of anti-inflammatory cytokines that can migrate across the blood-brain barrier. It was first approved by the United States Food and Drug Administration (FDA) in 1996 for relapsing-remitting multiple sclerosis, in 2009 for clinically isolated syndrome (CIS). The manufacturer advises avoidance in pregnancy because of the lack of epidemiological data, having said that, the drug was safe in animal models. It was given a licence for use in the United Kingdom in 2000, but was not officially recommended for the use on the NHS by NICE until the recent review.
Recommendations
The recommendations from this appraisal conclude that interferon beta-1a (Avonex/Rebif) and glatiramer (Copaxone) can continue to be used as an option for relapsing-remitting MS. Interferon beta-1b (Extavia) can also be used in relapsing-remitting MS, and also in patients with secondary progressive MS with continuing relapses. These are only recommended and deemed cost effective if they are provided by a discount patient access scheme. This does not affect any patients who were taking these medications prior to publication of this appraisal.

Evidence
This appraisal considered evidence from four meta-analyses of clinical trials. Three of these analyses were performed by the company providing the medication and the fourth meta-analysis was performed by the appraisal group. These company analyses were subject to some limitations, including issues with methodology and omission of relevant trials. There was also a discrepancy in the statistical approach compared with the appraisal group's own meta-analysis. Therefore NICE focused on results from its own analysis to establish the recommendations. The appraisal also considered data from the 10-year follow-up from the Department of Health Risk Sharing Scheme, which included all patients on either beta interferons or glatiramer after the initial NICE appraisal was published.

These results showed that all treatments (glatiramer, interferon beta-1a and 1b) were similarly effective in reducing the annual relapse rate (between 0.66–0.72), with no treatment being statistically superior. All agents delayed disability progression compared with placebo, displaying similar rates of time to disability progression. Adverse events occurred with all treatment options compared with placebo, however, all these treatments have well established tolerability profiles.

Within the data collected for the RSS, all treatments slowed disease progression. Given the prolonged data collection in these patients, it was noted that the treatment efficacy was not constant and waned after the first two years.

Conclusions
The recommendations from this appraisal ensure that beta interferons and glatiramer will remain available for clinicians and for patients with relapsing-remitting MS. Patients can then make their own decision on treatment. Although newer agents may be more effective in treatment of MS, there are patients for whom these established treatments are the most suitable option. Given the extensive clinical experience MS teams have with beta interferons and glatiramer, they continue to be prescribed widely and are a useful option in the complex management of relapsing-remitting MS.

Maintaining these treatment options will help patients who have concerns regarding potential side-effects or have other medical comorbidities, which could preclude them from the newer alternative agents. Newer agents also require regular monitoring with blood and urine testing, which can be inconvenient; for glatiramer no safety monitoring is required. Patients who have adverse reactions to other recommended therapies also have more options to choose from.

Another important aspect of the continued recommendation for the use of glatiramer is its use in pregnancy. Currently glatiramer is considered a safer option during pregnancy compared to other DMARDs, although its use during this period should only be recommended if the benefit to mother outweighs any risk for the foetus.

This appraisal also recommended the use of interferon beta-1b (Extavia) for patients with secondary progressive MS but who continue to have relapses; this is the only treatment currently recommended by NICE for this specific clinical scenario.

Retaining the variety of treatment options for patients with relapsing-remitting MS is valuable. It promotes the ability of patients to be involved in a shared decision making process to choose which disease-modifying treatment will be most suitable for their specific circumstances.

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Declaration of interests
No conflicts of interest were declared.

References