Daclizumab: another option for highly active relapsing-remitting MS

Tarek Gaber FRCP, Clare Shippen MRCP

Daclizumab provides clinicians with a new treatment option for patients with relapsing-remitting multiple sclerosis. Here the authors consider its benefits compared with other multiple sclerosis drugs and its likely place in therapy.

The publication of NICE guidance for the use of daclizumab in relapsing-remitting multiple sclerosis in April 20171 is the latest in a series of appraisals of the efficacy and cost effectiveness of the multiple sclerosis (MS) disease modifying treatment (DMT). The current guidance for the use of this group of drugs enables neurologists, commissioners and patients to have explicit recommendations about the most appropriate way to utilise such a valuable resource.

Having a clear definition for the different stages / scales of relapsing-remitting MS presentations is a clear priority for NICE. The definitions used in previous guidelines may differ from the ones used when recruiting patients for some of the most important trials. NICE recognised this dilemma and suggested a compromise to enable treating neurologists to use a uniform method to classify their patients (Table 1). Using this classification, the current guidance is summarised in Table 2.

The Association of British Neurologists (ABN) adopted a more pragmatic approach in their 2015 guidelines2 (published before the approval of daclizumab). The ABN classified the available DMTs into two broad categories. Category 1 includes all available DMTs with the exception of monoclonal antibodies and category 2 includes the two monoclonal antibodies – alemtuzumab and natalizumab.

The ABN guidelines consider the safety and experience most neurologists have using the two standard DMTs – interferon and glatiramer – as a justification for their continued use as a first-line management. Other practical issues such as patient preference, especially considering method of administration and potential side-effects, are important factors when choosing first- or second-line treatment. Category 2 drugs, alemtuzumab and natalizumab, are considered for highly active disease. The ABN recommendations are designed to allow treating neurologists more flexibility and a personalised approach to manage a particular clinical scenario.

Daclizumab

Three monoclonal antibodies, alemtuzumab, natalizumab and now daclizumab, are uniquely effective for the management of the most aggressive and feared type of relapsing-remitting MS: rapidly evolving severe disease.

Daclizumab is one of the oldest monoclonal antibodies used in clinical practice. It was the first humanised monoclonal antibody approved anywhere in the world when it was approved in 1997 for the prevention of acute rejection of kidney transplants by the Food and Drug Administration in the USA. The interest in daclizumab waned because of lack of demand until relatively recently when its efficacy in MS management was demonstrated.3

Pharmacokinetics

Daclizumab is a therapeutic humanised monoclonal antibody that binds to CD25 on the alpha unit of the high-affinity IL-2 receptor. This binding prevents IL-2 signaling through the high-affinity receptor and increases the availability of IL-2 expressing the intermediate-affinity

Table 1. Definitions used by NICE to describe different patterns of MS relapses

<table>
<thead>
<tr>
<th>Active relapsing remitting multiple sclerosis</th>
<th>At least two clinically significant relapses in the previous two years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly active disease despite previous treatment:</td>
<td></td>
</tr>
<tr>
<td>• no response after at least 1 year of treatment with a disease-modifying therapy, and:</td>
<td></td>
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<tr>
<td>• at least 1 relapse in the previous year while on therapy, and at least 9 T2 hyperintense lesions on cranial MRI, or</td>
<td></td>
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<tr>
<td>• at least 1 gadolinium-enhancing lesion, or</td>
<td></td>
</tr>
<tr>
<td>• unchanged or increased relapse rate in the previous year compared with the previous 2 years.</td>
<td></td>
</tr>
<tr>
<td>Rapidly evolving severe multiple sclerosis:</td>
<td></td>
</tr>
<tr>
<td>At least 2 relapses in the previous year and at least 1 gadolinium-enhancing lesion at baseline MRI.</td>
<td></td>
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</tbody>
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Comment

receptor. Therapeutic effects are hypothesised to be secondary to inhibition of activated T cells and expansion of natural killer cells resulting in selective immunomodulation without causing depletion of lymphocytes. 4

Efficacy
The NICE technology appraisal was based on two large and well designed randomised controlled trials: SELECT comparing daclizumab with placebo, and DECIDE comparing daclizumab with interferon beta.

SELECT trial
A phase IIb, multicentre, randomised, double-blind, placebo-controlled trial with 621 subjects. 5

DECIDE trial
A phase III randomised, double-blind trial comparing daclizumab with other first-line therapy (interferon beta). In a cohort of 1841 subjects 59% had not received any previous treatment. 6

In these clinical trials, daclizumab reduced relapse rate and delayed accumulation of disability, and was more effective than placebo and interferon. 5, 6

In the DECIDE trial, there was a 45% reduction in relapse rate compared with interferon. In the overall population, daclizumab treatment resulted in a statistically significant delay in disability progression. 6 However, when examining the subgroups of participants with highly active disease and rapidly evolving disease, there was no statistically significant reduction in disability progression. This will continue to be investigated with the extended arm of this trial.

When comparing the above-mentioned data with the alemtuzumab trials results, 7 NICE concluded that alemtuzumab was more beneficial and cost effective than daclizumab in all patient groups. Alemtuzumab was recommended by NICE appraisal guidance in May 2014 for patients with active relapsing-remitting MS. Trials concluded a reduction in the relapse rate of 54.9% and an impact on sustained accumulation of disability with alemtuzumab compared with interferon.

There are different scenarios that may render alemtuzumab unsuitable for clinical use. For example, it is contraindicated in several medical conditions such as HIV. Its side-effects include thyroid disorders, kidney disease and idiopathic thrombocytopenic purpura. The logistics of alemtuzumab administration can be complex as well as it is given by infusion in hospital over five days for the first course then over three days for the next. There is a requirement for monthly monitoring of full blood count, renal function, urinalysis and three-monthly thyroid function tests.

Practicalities of daclizumab use
Daclizumab is given as a once-monthly subcutaneous injection, which can be done at home. This negates the inconvenience of attending hospital, which is often a requirement for other monoclonal antibody therapies.

Generally, daclizumab is well tolerated by patients.

Table 2. A summary of the current NICE guidance for using DMT in relapsing remitting MS (When considering switching drugs, all NHS patients who are on therapy at the date of publication of this guidance should have the option to continue treatment until they and their consultant consider it is appropriate to stop.)

<table>
<thead>
<tr>
<th>Active disease</th>
<th>Highly active disease despite previous treatment</th>
<th>Rapidly evolving severe disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethyl fumarate</td>
<td>An option</td>
<td>No</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>An option</td>
<td>No</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>An option</td>
<td>An option</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>No</td>
<td>An option</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>An option as a second line if alemtuzumab is contraindicated or unsuitable</td>
<td>An option if alemtuzumab is contraindicated or unsuitable</td>
</tr>
<tr>
<td>Interferon beta and glatiramer acetate</td>
<td>Neither interferon beta nor glatiramer acetate is recommended for the treatment of multiple sclerosis (MS)</td>
<td></td>
</tr>
</tbody>
</table>
Cutaneous side-effects such as rash and eczema were the most common side-effects reported in the trials. The therapy can also cause a rise in liver enzymes and hepatobiliary disorders. Serious infections were reported in 4% of patients in the DECIDE trial with no cases of progressive multifocal leukoencephalopathy identified.8

Other side-effects of daclizumab include depression, nasopharyngitis, upper respiratory tract infection, influenza and lymphadenopathy. Due to the risk of hepatic dysfunction, liver function tests are recommended monthly during treatment.

Conclusion
Daclizumab is a welcomed addition to the expanded spectrum of disease modifying treatment in MS. It works via selective immunomodulation of the T cells via the IL-2 pathway. It has been shown in large randomised controlled trials to reduce the relapse rate in patients with relapsing-remitting MS. However, this is not as beneficial and is less cost effective than its main comparator – alemtuzumab.

Until daclizumab’s impact on long-term disease progression is clearer, its main role will be in patients with active disease who have failed other therapies and who have a severe rapidly evolving sub-type of MS.

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Declaration of interests
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References