New oral drugs for the treatment of multiple sclerosis

Multiple sclerosis is an inflammatory demyelinating and neurodegenerative disease of the CNS. Over the past two decades, multiple sclerosis has gone from being an essentially untreatable condition to one for which there are an increasing number of highly effective treatments that suppress relapses (episodes of new neurological symptoms that evolve over hours to days). There has been less success treating the progressive component of multiple sclerosis – characterized by an unremitting, albeit usually slow, accrual of neurological deficit – and while trials have shown some early promise (for example simvastatin at phase 2 (Chataway et al, 2014) and ocrelizumab at phase 3 (Montalban et al, 2015)), there are currently no licensed treatments to treat progressive multiple sclerosis.

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Inflammatory demyelinating lesions in the white matter of the CNS are the most readily identified pathological hallmark of multiple sclerosis, and their development leads to symptomatic relapses. However, it is increasingly recognized that grey matter lesions may be as, and perhaps more, extensive than those in white matter (although they are much more difficult to see using magnetic resonance imaging), and multiple sclerosis-associated brain atrophy can be substantial. It is now clear that clinical outcomes in multiple sclerosis represent a complicated interplay of immune-mediated inflammation and neurodegeneration. Current disease-modifying treatments for multiple sclerosis have been assessed based on their ability to suppress white matter lesion formation and licensed based on their effect on relapses.

Treatments for multiple sclerosis

Most treatments that are now used in multiple sclerosis were first developed for use in other conditions. Given the significant role that the immune system plays in multiple sclerosis, it is unsurprising that most have been developed to suppress inflammation. There are now three licensed oral agents for the treatment of relapsing-remitting multiple sclerosis: dimethyl fumarate (Tecfidera, Biogen Idec), fingolimod (Gilenya, Novartis) and teriflunomide (Aubagio, Genzyme) (*Table 1*). These are all at least as, and probably more, effective as the first-line injectable agents (beta-interferon and glatiramer acetate) and are more convenient to administer, but they require more blood test monitoring, pharmacovigilance and neurological oversight.

Fingolimod

Fingolimod was the first oral agent to be approved by the National Institute for Health and Care Excellence (2012) for use in people who had not responded adequately to treatment with beta-interferon and is a good example of the change in our practice that has arisen as a result of the introduction of such drugs.

Beta-interferon is usually started as an outpatient, is commonly associated with 'flu'-like symptoms after injections and occasionally local injection site reactions, and 6-monthly

Table 1. Current oral disease-modifying treatments approved by the National Institute for Health and Care Excellence (NICE) for use in multiple sclerosis

Agent	Year approved by EMA	Dosing	Reduction in annualized relapse rate *vs* placebo*	First-line use?	Side effects
Fingolimod (Gilenya)	2011	0.5 mg once daily	50%	No, for second-line use if treatment failure	Deranged liver function tests, lymphopenia, rare macular oedema, heart block and basal cell carcinoma, very rare progressive multifocal leucoencephalopathy
Teriflunomide (Aubagio)	2013	14 mg once daily	30%	Yes but not for highly active disease	Diarrhoea, alopecia, nausea, deranged liver function tests, potentially teratogenic
Dimethyl fumarate (Tecfidera)	2014	240 mg twice daily	45%	Yes but not for highly active disease	Flushing, gastrointestinal symptoms, lymphopenia, deranged liver function tests, very rare progressive multifocal leucoencephalopathy

**to nearest 5%, from NICE appraisal. EMA = European Medicines Agency*

full blood counts are monitored (to look for lymphopenia) and liver function tests. In contrast, because of potentially fatal (although rare) first dose heart block, fingolimod is started with 6-hourly electrocardiogram monitoring, and if treatment is missed for more than a day in the first 2 weeks, or 3 days after this, then treatment is restarted with the same cardiac monitoring protocol.

Blood tests are undertaken every 3 months to assess lymphocyte counts (which are reversibly reduced as a result of the mechanism of action of fingolimod) and liver function. Other side effects of fingolimod that require active assessment include macular oedema (particularly in patients with diabetes), which is screened for even in asymptomatic people after 3 months on treatment, and regular skin inspection for basal cell carcinoma (now recommended yearly).

Dimethyl fumarate and teriflunomide

Dimethyl fumarate (National Institute for Health and Care Excellence, 2014a) does not require particular first dose precautions, but requires more frequent blood test monitoring than beta-interferon (for liver dysfunction and suppression of lymphocytes).

Similarly teriflunomide (National Institute for Health and Care Excellence, 2014b) is straightforward to start, but initially requires frequent blood monitoring (every 2 weeks for the first 6 months) as a result of potential adverse effects on liver function, and it can also suppress white blood cell counts. While the authors recommend that all women taking any disease-modifying treatments avoid conception, there are specific concerns about pregnancy in women taking teriflunomide which has a clear teratogenic warning. Moreover it may persist in the body for years, and it may take up to 2 years to drop to a level where it is thought safe to attempt conception, although it can be actively removed with cholestyramine.

Side effects

While the interferons and glatiramer acetate seem essentially free of long-term serious side effects, experience with natalizumab (Tysabri) (given by monthly intravenous infusion) highlights the need for care when adopting new agents wholesale. Since the pivotal trials (Polman et al, 2006), it is known that there is a clear risk of developing progressive multifocal leucoencephalopathy, which is fatal in about 20% and associated with severe persistent neurological disability in about 30% of people who develop it (Baldwin and Hogg, 2013).

Progressive multifocal leucoencephalopathy is caused by reactivation of the John Cunningham virus infection in the CNS and depends both on the duration of treatment and whether immunosuppressive treatments (such as mitoxantrone) have previously been used. In those who are John Cunningham virus seropositive (about half the population), and who have not previously taken an immunosuppressant, the estimated risk of developing progressive multifocal leucoencephalopathy within 2 years of starting treatment with natalizumab is ~0.06%, rising to ~ 0.52% beyond 2 years (McGuigan et al, 2016). Prior immunosuppressant use appears to at least double the risk of developing progressive multifocal leucoencephalopathy (McGuigan et al, 2016).

There are now a handful of reports of progressive multifocal leucoencephalopathy in people taking fingolimod (European Medicines Agency, 2015a) or dimethyl fumarate (European Medicines Agency, 2015b), albeit seemingly much less often than in those taking natalizumab, but with the caveat that oral disease-modifying treatments have been in widespread use for less time.

Conclusions

While the introduction of oral disease-modifying treatments for multiple sclerosis provides very welcome additional options, along with more convenient administration, they require greater monitoring and a clear commitment from people taking them to fully engage with and share responsibility for this. All clinicians treating people with multiple sclerosis need to be much more aware of the medications they are taking, as starting and stopping these new oral disease-modifying treatments is not necessarily as straightforward as injectable agents, and they may have significant drug interactions and side effects that require urgent review. Alongside the addition of highly active infusion treatments for multiple sclerosis which are not discussed here (alemtuzumab and natalizumab), this has major implications for the configuration of multiple sclerosis services which need to be safe and effective. It is truly a new dawn for multiple sclerosis therapeutics. **BJHM**

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KEY POINTS

- As of July 2016, three oral agents are licensed in the UK for use as disease-modifying treatments in relapsing-remitting multiple sclerosis.
- These oral agents are all at least as, and probably more, effective at suppressing multiple sclerosis relapses as the first-line injectable treatments.
- They can have significant side effects, and require more blood test monitoring, pharmacovigilance and neurological oversight than first-line injectable agents.
- There are currently no medications licensed in the UK for the treatment of progressive multiple sclerosis.

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