

British Journal of Hospital Medicine: New oral drugs for multiple sclerosis

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Multiple sclerosis (MS) is an inflammatory demyelinating and neurodegenerative disease of the central nervous system. Over the past two decades, MS has gone from 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 MS - characterised by an unremitting, albeit usually slow, accrual of neurological deficit - and while recent 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 MS.

Inflammatory demyelinating lesions in the white matter of the central nervous system (CNS) are the most readily identified pathological hallmark of MS, and their development leads to symptomatic relapses. However, it is increasingly recognised that grey matter lesions maybe as, and perhaps more, extensive than those in white matter (but they are much more difficult to see using magnetic resonance imaging [MRI]), and MS-associated brain atrophy can be substantial: It is now clear that clinical outcomes in MS represent a complicated interplay of immune mediated inflammation and neurodegeneration. Currently available MS disease modifying treatments (DMTs) have been assessed based on their ability to suppress white matter lesion formation and licensed based on their effect on relapses.

Most treatments that are now used in MS were first developed for use in other conditions, and given the significant role the immune system plays in MS, it is unsurprising that most have been developed to suppress inflammation. There are now three licensed *oral* agents for the treatment of relapsing-remitting MS: dimethyl fumarate [Tecfidera], fingolimod [Gilenya] and teriflunomide [Aubagio] (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 greater blood test monitoring, pharmacovigilance and neurological oversight.

Fingolimod [Gilenya] was the first oral agent to be approved by National Institute for Health and Care Excellence (NICE; www.nice.org.uk/Guidance/ta254) 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 we monitor with six-monthly full blood counts (to look for lymphopenia) and liver function tests. In contrast, because of potentially fatal (though 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 two weeks, or three days after this, then treatment is restarted with the same cardiac monitoring protocol. We undertake blood tests every three months to assess lymphocyte counts (which are reversibly reduced due to mechanism of action of fingolimod) and liver function. Other side effects of fingolimod that require active assessment include macular oedema (particularly in diabetics), which we screen for even in asymptomatic people after three months on treatment, and regular skin inspection for basal cell carcinoma (now recommended yearly, www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002202/WC500104528.pdf).

Dimethyl fumarate [Tecfidera] (www.nice.org.uk/guidance/ta320) does not require particular first dose precautions, but also requires more frequent blood test monitoring than beta-interferon (for liver dysfunction and suppression of lymphocytes). Similarly

Teriflunomide [Aubagio] (www.nice.org.uk/guidance/ta303) is also straightforward to start, but initially requires frequent blood monitoring (every 2 weeks for the first 6 months) due to potential adverse effects on liver function, and it can also suppress white blood cell counts. While we recommend that all women taking any DMTs avoid conception, there are specific concerns about pregnancy in women taking teriflunomide which has a clear teratogenic warning (www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002514/WC500148682.pdf). Moreover it may persist in the body for years, and it may take up to two years to drop to a level where it is thought safe to attempt conception, although it can be actively removed with cholestyramine.

While the interferons and glatiramer acetate have proven to be essentially free of long-term serious side effects, experience with natalizumab [Tysabri] (given by monthly IV infusion) highlights the need for care when adopting new agents wholesale. Since the pivotal trials (Polman et al. 2006), we now know that there is clear risk of developing progressive multifocal leucoencephalopathy (PML), which is fatal in about 20% and associated with severe persistent neurological disability in about 30% of people who develop it (Baldwin et al. 2013). PML is due to reactivation of the John Cunningham virus (JCV) infection in the central nervous system (CNS) and depend both on the duration of treatment and if immunosuppressive treatments (such as mitoxantrone) have previously been used. In those who are JCV sero-positive (about half the population), and who have not previously taken an immunosuppressant, the estimated risk of developing PML 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 PML (McGuigan et al. 2016). There are now a handful of reports of PML in people taking fingolimod

(http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/12/news_detail_002447.jsp&mid=WC0b01ac058004d5c1) or dimethyl fumarate (http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/10/news_detail_002423.jsp&mid=WC0b01ac058004d5c1), albeit seemingly much less often than in those taking natalizumab, but with the caveat that oral DMTs have been in widespread use for less time.

In conclusion, while the introduction of oral DMTs for MS brings 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. It means that all clinicians treating people with MS need to be much more aware of the medications they are taking, as starting and stopping these new oral DMTs 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 MS which are not discussed here (alemtuzumab and natalizumab), this has major implications for the configuration of MS services which need to be safe and effective. It is truly a new dawn for MS therapeutics.

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Table 1: Current oral DMTs approved by NICE for use in MS.

Agent	Year of approval by EMA	Dosing	Reduction in annualized relapse rate compared with placebo (to nearest 5%, NICE appraisal)	1st line use?	Side effects
fingolimod (Gilenya)	2011	0.5 mg od	50%	No, for 2 nd line use if treatment failure	Deranged LFTs, lymphopenia, rare macular oedema, heart block and BCC, very rare PML
teriflunomide (Aubagio)	2013	14 mg od	30%	Yes but not for highly active disease	Diarrhoea, alopecia, nausea, deranged LFTs, potentially teratogenic
dimethyl fumarate (Tecfidera)	2014	240 mg bd	45%	Yes but not for highly active disease	Flushing, gastrointestinal symptoms, lymphopenia, deranged LFTs, very rare PML

BCC = Basal cell carcinoma

EMA = European Medicines Agency

LFTs = liver function tests

NICE = National Institute for Health and Care Excellence

PML = progressive multifocal leucoencephalopathy