Oral treatment for multiple sclerosis

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Summary

Background The armamentarium for the treatment of relapsing-remitting multiple sclerosis (RRMS) is increasing rapidly. Several oral treatments have shown benefit and will generate much interest because of the convenience of such administration. However, availability of convenient oral drugs will not necessarily translate into clinical effectiveness and safety. Here, we provide an interim report about the mechanisms of action, and efficacy and safety results that have been reported since January, 2010, for five new oral drugs. Additionally, we draw attention to issues that neurologists and patients will encounter when considering the use of new oral drugs.

Recent developments Positive results have been reported for five new oral drugs for RRMS—fingolimod, cladribine, teriflunomide, laquinimod, and dimethyl fumarate—in phase 3 studies; a few new oral drugs are likely to be approved for RRMS soon.

Where next? Emerging oral treatments are ushering in a new era in the treatment of MS, providing not only new treatment options but also new challenges. Since data for some of the new drugs have not been reported in peer-reviewed journals yet and safety profiles are not yet fully developed, opinions about the use of these new oral drugs in practice are preliminary and tentative. Practice will evolve with time as information and experience accumulates. Of importance will be results from comparator trials, information about management of patients with breakthrough disease, results from long-term safety studies, and results of studies to assess the potential for neuroprotective effects of the new drugs.

Introduction

The armamentarium for the treatment of multiple sclerosis (MS) is fast increasing. Positive results have been reported for five new drugs in phase 3 studies; two of these drugs have been reviewed by regulatory agencies, and the other three will be reviewed within the next year. Therefore, a few new oral drugs are likely to be available soon for patients with relapsing-remitting MS (RRMS). This striking development will bring new options to patients, and will lead to both opportunities and challenges for the treatment of MS.

The need for oral drugs for patients with MS is obvious; before the approval of the first oral drug for MS in September, 2010, all approved disease-modifying treatments (DMTs) required injection or intravenous infusion. The first-line drugs—interferon beta-1a (administered intramuscularly; Avonex, Biogen Idec, Weston, MA, USA), interferon beta-1a (administered subcutaneously; Rebif, Merck Serono, Geneva, Switzerland), interferon beta-1b (administered subcutaneously; Betaseron, Bayer Schering, Leverkusen, Germany), and glatiramer acetate (administered subcutaneously; Copaxone, Teva, Petah Tiqva, Israel)—have been the most used treatments for MS. More effective drugs with greater toxicity—natalizumab (Tysabri, Biogen Idec) and mitoxantrone (Novantrone, EMD Serono, Rockland, MA, USA)—have been used largely as second-line treatments (administered by intravenous infusion) for patients who either did not respond satisfactorily to first-line drugs or did not tolerate injections. Although the first-line Injectable DMTs have shown excellent safety profiles, they have low efficacy—ie, about 30% reduction in annual relapse rate (ARR). Compliance is poor in many patients because of the low efficacy and frequent injections. Although second-line treatments are generally thought to have greater efficacy, there are many safety concerns.

Results of phase 3 trials have been reported for cladribine and fingolimod (FTY720). Fingolimod was approved for RRMS by the US Food and Drug Administration (FDA) in September, 2010, and by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) in January, 2011. Cladribine received a negative EMA and FDA response and the sponsor will be stopping development of oral cladribine for MS. Phase 3 trials of teriflunomide, laquinimod, and dimethyl fumarate (BG-12) have been completed, and positive results were reported for teriflunomide and laquinimod at academic meetings, and for dimethyl fumarate in press releases.

Despite the continuously evolving information about new MS drugs, we believe the reported data are adequate to provide an overview of the most recent developments for the five oral drugs that have shown efficacy in phase 3 trials. We describe the new challenges and complexities of these drugs, and draw attention to gaps in our knowledge that suggest the need for further research.

Fingolimod

Fingolimod modulates sphingosine-1-phosphate (SIP) receptors and has strong immunoregulatory features. The lysophospholipid SIP is crucial in many cellular processes. Although S1P1, S1P2, and S1P3 receptors are abundant in diverse tissue types, S1P4 is located on lymphoid and haemopoietic cells, whereas S1P5 is mainly...
expressed in the CNS. Fingolimod is phosphorylated immediately after oral administration and the phosphorylated form interacts with all S1P receptor subtypes except S1P2.23–25 How phosphorylated fingolimod exerts its specific effects in MS has not been fully elucidated.26 However, S1P1 receptor internalisation in lymphocytes seems to be a crucial step. This process does not reduce lymphocyte activation but inhibits egress of T cells and B cells from lymph nodes.27 Fingolimod reduces the number of circulating memory T cells, including interleukin-17-producing T cells (Th17 cells) by more than 90%.28 Th17 cells are thought to be essential mediators of inflammation in MS and interleukin 17 might be elevated in individuals who are not responsive to interferon beta.29

Because fingolimod is lipophilic, it easily enters the CNS, where it can bind to several S1P receptor subtypes on different cell types, possibly leading to poorly understood neuroprotective or reparative effects.24,27 Although highly active in ameliorating experimental autoimmune encephalitis, fingolimod is ineffective in genetically engineered mice lacking S1P1 receptors on astrocytes, suggesting that the benefits in MS could be mediated by an effect of the drug on astrocytes.30

Data from clinical trials have indicated that fingolimod is a highly effective treatment for RRMS. In a 6-month phase 2, proof-of-concept randomised trial, 281 participants with active relapsing MS (255 completed the trial) were given a single dose of placebo or fingolimod 1·25 mg/day or 5·0 mg/day.14 The numbers of gadolinium-enhancing (GdE) MRI lesions were reduced in the fingolimod groups compared with placebo (1·25 mg, p<0·001; 5·0 mg, p=0·006). The relative reduction in ARR was 53% in the high-dose fingolimod group and 55% in the low-dose group.

Results of two phase 3 studies in patients with RRMS (FREEDOMS,13 a placebo-controlled 24-month trial, and TRANSFORMS,12 a 12-month trial with comparator interferon beta-1a) showed efficacy and an acceptable safety profile. The FDA approved fingolimod as first-line treatment for RRMS, whereas the EMA restricted its use for second-line treatment or active disease.

1272 patients with relapsing MS participated in the FREEDOMS study13 and 1033 completed the follow-up. Compared with placebo, ARR (the primary endpoint) was reduced by 60% in the fingolimod 1·25 mg group (p<0·001) and by 54% in the 0·5 mg group (p<0·001). Over 24 months, fingolimod significantly postponed the time to first relapse and resulted in a larger proportion of patients remaining relapse-free than in the placebo group. Fingolimod also significantly reduced the cumulative probability of the 3-month confirmed progression according to the expanded disability status scale (EDSS; hazard ratio vs placebo 0·68 in the high-dose fingolimod group and 0·70 in the low-dose fingolimod group). Additionally, superiority of both fingolimod doses compared with placebo was confirmed in all secondary MRI-related endpoints.

There were no differences in the number of patients with adverse events in the different study groups. However, adverse events leading to interruption of the study drug were more common with the higher dose of fingolimod than with the lower dose or placebo. Adverse events related to fingolimod included bradycardia and atrioventricular conduction block during the start of fingolimod, macular oedema, elevated liver enzyme levels, lymphocytopenia, and hypertension.14

1292 patients with active RRMS were enrolled in the TRANSFORMS study,12 another phase 3 trial. The duration of the core study was 12 months. Participants were randomly assigned in a double-blind manner to fingolimod 1·25 mg/day or 0·5 mg/day, or interferon beta-1a once a week (intramuscularly).12 ARR (the primary outcome measure) was 0·33 in the interferon beta-1a group, 0·20 in the high-dose fingolimod group, and 0·16 in the low-dose fingolimod group (both

<table>
<thead>
<tr>
<th></th>
<th>Fingolimod (FREEDOMS)13</th>
<th>Cladribine (CLARITY)10</th>
<th>Teriflunomide (TEMSO)19</th>
<th>Laquinimod (ALLEGRO)16</th>
<th>Laquinimod (BRAVO)21</th>
<th>Dimethyl fumarate (DEFINE)22</th>
</tr>
</thead>
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Results of phase 3 trials have been reported for cladribine (Moventra, Merck Serono, Geneva, Switzerland) and fingolimod (Gilenya, Novartis, Basel, Switzerland). Phase 3 trials of teriflunomide (Sanofi-Aventis, Paris, France), laquinimod (Teva, Petah Tiqva, Israel), and dimethyl fumarate (Biogen Idec, Weston, MA, USA) have been completed. The data in this table should be interpreted with caution because most have not been peer reviewed yet13—22 and some of the differences might be related to different patient characteristics or differences in trial methods rather than to differences in treatment effect. Efficacy results for fingolimod 0·5 mg/day, cladribine 3·5 mg/kg, teriflunomide 14 mg/day, laquinimod 0·6 mg/day, and dimethyl fumarate 240 mg twice a day are presented. EDSS=expanded disability status scale. *An additional one patient in four was free of gadolinium-enhancing T1 lesions compared with the placebo group.

Table 1: Completed placebo-controlled phase 3 trials of oral treatments for patients with multiple sclerosis
p<0·001 compared with interferon beta-1a). Secondary MRI outcome measures—ie, the number of GdE lesions, new or enlarged T2 lesions, and brain volume measures—confirmed significant differences in favour of fingolimod. No differences in the number of adverse events between study groups were noted. Serious adverse events and events leading to interruption of treatment, however, arose most frequently in the high-dose fingolimod group. Two patients died during treatment with high-dose fingolimod—one patient from disseminated primary varicella zoster infection and the other from herpes simplex encephalitis.

Results from a 1-year extension of TRANSFORMS have been reported. 882 participants completed 24 months of follow-up. Persistent reductions in ARR were shown in patients treated continuously with fingolimod, whereas in those who were initially given interferon beta-1a, the ARR was significantly lower after switching to fingolimod than in the initial year of the trial. 12

Fingolimod has been shown to be a promising new treatment for patients with relapsing MS. 22,31 Its effects on circulating lymphocytes are reversible, showing cell counts returning to normal within 4–6 weeks after cessation of treatment. Although fingolimod was better than an established first-line treatment, 32 specific safety issues have been identified—eg, the risk of herpes virus dissemination, macular oedema, long-term consequences of elevated blood pressure, and the risk of cancer.33 These potential risks should be carefully considered. Long-term safety data are warranted.34

Further trials, including one in patients with primary progressive MS (PPMS), are underway. Results from FREEDOMS II (ClinicalTrials.gov number NCT00355134), in which about 1000 patients with RRMS were randomly assigned to placebo or fingolimod 0·5 mg/day, are expected in time for presentation at the annual meeting of the European Committee for Treatment and Research in Multiple Sclerosis in autumn, 2011. Investigators of the INFORMS study (NCT00731692) are randomly assigning about 650 patients with PPMS to placebo or fingolimod 0·5 mg/day and results are expected in early 2014.

Cladribine

The synthetic purine nucleoside analogue cladribine (2-chloro-2’-deoxyadenosine) enters the cell through purine nucleoside transporters and is phosphorylated by deoxycytidine kinase.34,35 Lymphocytes have fairly high concentrations of this enzyme and low levels of 5’ nucleotidase, leading to a preferential accumulation in lymphocytes.35,36 Cladribine nucleotide accumulation disturbs DNA synthesis and repair mechanisms, resulting in lymphocyte depletion and longlasting lymphopenia. The drug mainly targets CD4+ T cells, CD8+ T cells, and B cells.37 Because cladribine can penetrate the CNS, it interacts with cells in both the peripheral circulation and the CNS.38 Therapeutic efficacy and safety of cladribine have been assessed in several autoimmune disorders and the parenteral formulation of cladribine is used as first-line treatment for hairy cell leukaemia.39

In the 1990s, a significant reduction in EDSS progression compared with placebo and a reduction in the number of GdE lesions was shown in the first study of cladribine use in patients with progressive MS. 40 Parenteral forms of cladribine were further assessed,38,41 and overall the results of these studies showed a significant effect on MRI disease activity, irrespective of the route of administration or dosing regimen.42

The CLARITY study was the first completed phase 3 trial of an oral DMT for RRMS and included 1326 patients.38,42 Two or four short courses of oral cladribine or placebo were administered during the first year of the randomised controlled trial, and two short courses were given in the second year. Cladribine resulted in a significantly lower ARR than in the placebo group (0·14 in the 3·5 mg/kg group, 0·15 in the 5·25 mg/kg group, and 0·33 in the placebo group; p<0·001 for low-dose or high-dose group vs placebo). Additionally, both cladribine doses resulted in a significantly lower probability of EDSS progression, confirmed after 3 months. Cladribine also resulted in significant reductions in the number of active MRI brain lesions (Δ=-1·6% in the 3·5 mg group and 31·5% in the 5·25 mg group vs 1·8% in the placebo group) and herpes zoster (eight patients in the 3·5 mg group and 12 patients in the 5·25 mg group vs none in the placebo group). Serious infections were noted in 1·6% of patients in the placebo group, 2·3% in the cladribine 3·5 mg/kg group, and 2·9% in the cladribine 5·25 mg/kg group. Neoplasms arose in six (1·4%) patients in the cladribine 3·5 mg/kg group and four (<1%) in the 5·25 mg/kg group, but in none of the patients in the placebo group. Neoplasms included leiomyomata (n=5), cervical carcinoma in situ (n=1), melanoma (n=1), ovarian carcinoma (n=1), pancreatic cancer (n=1), and myelodysplasia (n=1).38 Post-hoc subgroup analyses of the CLARITY study data showed that cladribine was effective in patients with high RRMS activity, and in those who did not respond well to treatment with first-line injectable DMT.43

Oral cladribine is being assessed in three multicentre phase 2b and phase 3 randomised controlled trials in patients with relapsing forms of MS—the CLARITY extension study (NCT00641537), ONWARD (add on to interferon beta; NCT00436826), and ORACLE–MS (patients with clinically isolated syndrome; NCT00725985). Although the results of studies with oral cladribine have shown substantial efficacy, the drug did not achieve regulatory approval in the USA (FDA) and Europe (EMA). After the rejection of marketing authorisation applications, Merck Serono has decided to
Teriflunomide

Teriflunomide is the active metabolite of leflunomide, which is approved for use in patients with rheumatoid arthritis. It reduces the activity of the mitochondrial enzyme dihydroorotate dehydrogenase, which is crucial in pyrimidine synthesis. T-lymphocyte proliferation largely depends on pyrimidine synthesis. However, because the drug induces only a small degree of lymphocytopenia, these processes only partly account for its effects. The results of a phase 2 trial of teriflunomide in patients with relapsing MS showed a reduction in active lesions on brain MRI scans.

The findings of initial efficacy in the phase 3 TEMSO trial were presented as abstracts at the annual meeting of the American Academy of Neurology this year. TEMSO was a 2-year randomised controlled trial in 1088 patients with active RRMS. Participants were randomly assigned to once-daily placebo or teriflunomide (7 mg or 14 mg).

Both teriflunomide doses significantly reduced the primary endpoint ARR, with a reduction in relative risk compared with placebo of 31.2% for the lower dose (p=0.0002) and 31.5% for the higher dose (p=0.0005). 12-week confirmed EDSS worsening was reduced by 29.8% with teriflunomide 14 mg (p=0.029). The superiority of the drug versus placebo was confirmed for a range of MRI endpoints. Several MRI outcomes favoured the 14 mg dose. For example, compared with patients in the placebo group, reduction in new lesion formation in the 7 mg group was 39%, compared with a 67% reduction in the 14 mg group. Both teriflunomide doses were quite well tolerated, showing safety profiles that were consistent with earlier reports. Diarrhoea, nausea, and abnormal liver enzymes were associated with teriflunomide.

Several studies of teriflunomide are in progress. TENERE (NCT00883337) is a randomised controlled active-group trial for the comparison of teriflunomide 7 mg/day and 14 mg/day versus interferon beta-1a (subcutaneous injection) in about 300 patients with RRMS. TOWER (NCT00751881) is a randomised, placebo-controlled trial for the comparison of teriflunomide 7 mg/day and 14 mg/day versus placebo in about 1100 patients with RRMS. TOPIC (NCT00622700) will compare the effect of teriflunomide 7 mg/day and 14 mg/day with placebo in the prevention of conversion to clinically definite MS in patients with clinically isolated syndrome.

Thus, much additional information will accumulate about the use of teriflunomide in patients with RRMS and firm conclusions cannot be drawn until data have been reported in a peer-reviewed manner. An important issue about the use of teriflunomide in clinical practice will be the risk profile. Although safety seemed to be excellent in the TEMSO study, rare cases of fatal liver failure with leflunomide have been reported, as well as one case of progressive multifocal leukoencephalopathy in a patient with systemic lupus erythematosus who was treated with leflunomide. In addition, the well recognised teratogenic effects of leflunomide create challenges with the widespread use of DMTs in women of childbearing age with MS.

Laquinomod

Laquinomod is a derivative of linomide (roquinimex). Linomide effectively prevented progression of experimental autoimmune encephalitis and preliminary clinical data have suggested efficacy in MS. However, a phase 3 trial had to be stopped because of unforeseen safety concerns. Laquinomod seems to be much better tolerated than is linomide. It induces a cytokine shift towards T-helper-2 (Th2) and Th3 cytokines, without inducing much immunosuppression.

Results of two phase 2 studies showed that laquinomod reduced MRI-monitored disease activity, according to assessment of the number of GdE T1 lesions and new T2 lesions, in patients with RRMS. The results of the first clinical trial showed a 44% reduction (p=0.0498) in the number of active lesions at weeks 0–24 with laquinomod 0.3 mg compared with placebo. In the second study, the 0.6 mg dose resulted in a reduction of 40% (p=0.0048) in the number of GdE T1 lesions in the last 4-monthly scans compared with placebo, whereas the 0.3 mg dose did not show evidence of efficacy.

239 (93%) patients completed an extension of the phase 2b trial. The number of GdE T1 lesions was reduced in patients switching from placebo to either dose of the active drug (52%, p=0.0006), confirming the efficacy results of the core study.

The preliminary results of the phase 3 ALLEGRO study were presented at the annual American Academy of Neurology meeting in 2011. The effects of laquinomod compared with placebo in 1106 patients with relapsing MS, given either an oral daily dose of laquinomod 0–6 mg or placebo, were reported at this meeting. The ARR was reduced by 23% from 0.395 in the placebo group to 0.304 in the laquinomod group (p=0.0024). Additionally, the cumulative probability of 3-month confirmed EDSS worsening was reduced by 36% (p=0.0122). Laquinomod reduced the mean cumulative number of GdE lesions by 37% (p=0.0003). The mean cumulative number of new T2 lesions was reduced by 30% (p=0.0002). Moreover, laquinomod was associated with a 33% reduction in the loss of brain volume over 2 years (p<0.0001). Laquinomod was safe and well tolerated. The most commonly reported adverse events were gastrointestinal side-effects and back pain. The incidence of liver enzyme elevation was higher in laquinomod-treated patients; however, these elevations were transient, asymptomatic, and reversible.
In a second phase 3 study, BRAVO (NCT00605215), laquinimod 0.6 mg was compared with placebo and interferon beta-1a (intramuscular injection) in about 1200 patients with RRMS. The primary endpoint, reduction in ARR for laquinimod versus placebo, was not significant, although significant reductions in EDSS progression (33.5%, p=0.044) and loss of brain volume (27.5%, p<0.0001) were reported in a press release.13 Meaningful conclusions about the effects of laquinimod can be drawn after full presentation of the trial data and peer-reviewed publication.

Laquinimod might exert a neuroprotective effect. This hypothesis is supported by the beneficial effects noted in the cuprizone mouse model, in which laquinimod protected against oligodendrocyte and secondary axonal damage,15 and by the positive results of clinical trials in patients with brain atrophy.

**Dimethyl fumarate**

BG-12, an oral formulation of dimethyl fumarate, is metabolised to monomethyl fumarate. Both dimethyl fumarate and its primary metabolite monomethyl fumarate induce activation of the nuclear factor E2-related factor-2 pathway, which protects against oxidative-stress-related neuronal death and damage to myelin in the CNS. Several neuroprotective and anti-inflammatory mechanisms have been attributed to the drug—ie, the expression of phase 2 detoxification enzymes in astroglial and microglial cells and a drug-induced shift towards a more anti-inflammatory cytokine profile (induction of Th2-type cytokines) and adhesion molecule expression.18,33,42,52

In a pilot study in patients with RRMS, an oral formulation of fumaric acid (Fumaderm, Biogen Idec, Ismaning, Germany), approved in Germany for the treatment of psoriasis, reduced the number of GdE lesions on brain MRI scans.19 Subsequently, three doses of BG-12 were tested against placebo in a phase 2b study in 257 patients with RRMS.19 Compared with placebo, BG-12 at 240 mg three times a day reduced the number of GdE lesions from week 12 to 24 by 69% (p<0.0001). The numbers of new or enlarging T2-hyperintense and new T1-hypointense lesions were also reduced (p=0.0006 and p=0.014, respectively).

Two phase 3 trials of dimethyl fumarate have been initiated. The DEFINE study enrolled about 1200 patients and its preliminary results were announced in a press release.20 The primary endpoint was the proportion of patients who relapsed during 2 years of follow-up. According to the news release, BG-12 at 240 mg either twice or three times a day met this primary study endpoint. A 49% reduction in the proportion of patients who relapsed occurred with BG-12 given twice a day compared with placebo; the ARR was reduced by 53%, number of GdE lesions by 90%, and new or enlarging T2 lesions by 85%. The cumulative probability of 3-month confirmed EDSS worsening was reduced by 38%. No new significant safety issues were reported.20

The second study (CONFIRM; NCT00451451) is in progress, with results expected before the end of 2011. Roughly 1200 patients with RRMS have been randomly assigned to four groups: BG-12 240 mg twice a day, BG-12 240 mg three times a day, glatiramer acetate, or placebo. The primary endpoint is ARR at 2 years.

Results from DEFINE, although preliminary, are encouraging, because of the extensive experience with the long-term safety of Fumaderm. Results of randomised trials have shown benefits of Fumaderm in psoriasis. Adverse events, including gastrointestinal side-effects and facial flushing, are common at treatment onset. About a third of patients discontinue or interrupt treatment. Results of observational studies in the past 14 years have not shown serious or permanent adverse events, however. Availability of long-term safety data distinguishes BG-12 from fingolimod, teriflunomide, and laquinimod. There might be much interest in BG-12, depending on full results from the DEFINE study, and results from the CONFIRM study.

**Challenges in MS treatment**

In less than 20 years, the number of approved DMTs for MS increased from none to eight, and this number is likely to continue to increase within the next few years. This advance presents not only opportunities and options, but also challenges for treatment. Probably the most important challenge is whether current DMTs, alone or in combination, are capable of completely arresting the MS process. With more potent drugs, such as natalizumab or alemtuzumab (which is still in development and not discussed here), the notion of disease-free status has emerged41,54,55 and DMTs are now compared in terms of their ability to inhibit clinical disease activity or MRI evidence of disease activity. However, whether disease-free status, using current definitions, correlates with pathology-free status or predicts absence of later disability is not clear. None of the existing or emerging drugs has been shown convincingly to slow progressive neurodegeneration, although results of studies showing reduced atrophy rates with treatment in patients with RRMS are encouraging. Other challenges relate to how the newer drugs should be used relative to the time-tested injectable drugs, how DMTs should be sequenced, whether the DMTs should be used after initial induction with potent immunosuppressant agents, whether drugs should be used in combination, and how benefit-to-risk ratios for individual drugs will be compared. Answers to these challenges will be informed by complete description of study results in peer-reviewed journals, clinical experience as it accumulates, and by findings from future research studies. The following represent an initial framing of some of the main questions.

**How will neurologists choose treatments?**

As oral therapies are approved and marketed, development of strategies to define which patients should be treated with which drugs will be necessary.
Reliable biomarkers that can be used to predict how an individual patient with MS will respond to a particular drug are lacking. Until methods become available for personalised decision making, only general risk–benefit analyses can be done and applied to subgroups of patients rather than to individuals. Comparison of drugs between different trials is inevitable (table 1) because there are few randomised trials in which the various drugs have been compared directly. However, data such as those shown in table 1 should be interpreted with caution. Part or most of the observed differences might be a result of patient differences between studies or of differences in trial methods used.56

Convenience and patient preference are likely to gradually diminish use of the injectable drugs as first-line treatment and lead to an increase in the use of oral preparations, although the long-term safety profile of interferon beta preparations and glatiramer acetate, and the fact that many patients have done well on the injectable drugs for many years, will slow this trend. Most patients will probably start treatment with a drug that is associated with fairly low risks, either an ABCR (Avonex, Betaseron, Copaxone and Rebif) injectable or a new oral drug that seems safe. Patients will be monitored for breakthrough disease activity, and when this occurs treatment will be escalated to one of the more potent but riskier drugs, such as natalizumab or fingolimod.

Patients not using DMTs

For patients who in the past have used DMTs, but have discontinued because of side-effects or perceived lack of efficacy, the new oral drugs offer an attractive alternative, especially if patients have had disease activity while off DMTs. Some patients who are not using a DMT because of mild disease might elect to use convenient oral drugs with favourable safety profiles. However, with the exception of dimethyl fumarate and teriflunomide (data derived from experience with leflunomide), data for long-term safety are lacking.

Patients with the first episode of demyelinating disease who do not yet meet diagnostic criteria for MS (clinically isolated syndrome) present a special challenge in the new era. Use of the ABCR injectable drugs in this setting is supported by the results of large-scale randomised controlled trials.57–60 and trials in patients with clinically isolated syndrome are in progress for some of the newer drugs. With or without clinical trials, the oral drugs will be used increasingly in patients with clinically isolated syndrome.

For treatment-naive patients with MS, use of oral drugs as first-line treatment will correspond strongly with perceived safety, although peer-reviewed data are lacking and the safety of drugs that have had only minimal long-term use in people is unclear.61 Whether fingolimod should be used in treatment-naive patients with MS is still being discussed. The National Institute for Health and Clinical Excellence stated that fingolimod was not recommended for the treatment of patients with RRMS in the UK. The extent of the effect in the subgroups defined by the marketing authorisation raised doubts; the committee assumed an underestimation of the incremental cost-effectiveness ratio.61

Patients using first-line injectable drugs

If a patient on interferon beta or glatiramer acetate is tolerating treatment and shows minimal MS activity, there is no compelling reason to change treatment. An exception might be a patient who is doing well on interferon beta but has persisting interferon-beta-neutralising antibodies or who lacks upregulation of myxovirus resistance protein A with injections.62 In that setting, treatment with interferon beta seems unlikely to provide benefit, but the neurologist might be reluctant to discontinue DMTs. For patients using injectable drugs who have breakthrough disease, are needle-phobic, or do not tolerate injectable drugs because of side-effects, the new oral drugs offer attractive alternatives.

Patients using natalizumab

If a patient is doing well on natalizumab, and is seronegative for JC virus antibodies, there is no compelling reason to change treatment. However, for patients with prolonged exposure to natalizumab who have JC virus antibodies, it seems reasonable to change

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<td>Time to conversion to multiple sclerosis</td>
<td>November, 2015</td>
</tr>
<tr>
<td>TOWER NCT00751881</td>
<td>Teriflunomide 14 mg and 7 mg versus placebo</td>
<td>1110</td>
<td>Annual relapse rate</td>
<td>February, 2013</td>
</tr>
<tr>
<td>FREEDOMS II NCT00355134</td>
<td>Fingolimod 0.5 mg versus placebo</td>
<td>1080</td>
<td>Annual relapse rate</td>
<td>March, 2011</td>
</tr>
</tbody>
</table>


Table 2: Ongoing randomised studies of oral drugs in clinically isolated syndrome and relapsing-remitting multiple sclerosis
from natalizumab to one of the new oral drugs to reduce the risk of progressive multifocal leukoencephalopathy. Although some patients and their neurologists might choose this option, the risk of disease activation after discontinuation of natalizumab is a concern;\(^4\) there are no data for how these patients will do after switching to one of the new oral drugs, and the long-term risks associated with the newer agents are not completely clear.

As a general strategy, the new oral drugs might be an attractive treatment option in many situations, but switching to a new oral drug for convenience only should not generally be recommended at this stage in the absence of complete data and more long-term safety data.

Conclusions and future directions

Several oral drugs have shown benefit in patients with RRMS. Although the available first-line and second-line parenteral compounds have clearly changed the course of MS management over the past two decades, there is room for improvement. Oral drugs will generate significant interest because of the convenience of such administration. However, the availability of oral drugs will not necessarily mean a harmless and convenient treatment. On the basis of the safety and tolerability profiles discussed in this Rapid Review and the lack of long-term safety data, patients will have to be carefully monitored and registries will be needed.

The treatment armamentarium is also likely to change owing to the arrival of other new parenterally administered drugs—eg, alemtuzumab, daclizumab, and ocrelizumab, which are not reviewed here. The role of comparator trials will become increasingly important (table 2), as will information about management of patients with breakthrough disease and the results of long-term safety studies. The studies undertaken to assess the potential for neuroprotective effects of the new drugs will be of great interest because we seek strategies to achieve true disease-free status. Pharmacogenomics might be helpful in identifying which drugs are likely to be beneficial or harmful at the individual patient level. Altogether, the emerging oral treatments will herald the arrival of a new era in the treatment of RRMS, with new options, more convenience, and the potential for better outcomes.

Contributors

JK contributed to the literature search and data gathering, and prepared a first draft of the Rapid Review. RAR contributed to the literature search, drafted portions of the Rapid Review, and contributed to the critical review and revision. CHP contributed to the literature search, review design, gathers and reviewing data, and writing and review.

Conflicts of interest

JK has received consulting fees from Merck Serono, Biogen Idec, and Novartis. Multiple Sclerosis Centre Amsterdam has received financial support for research activities from Bayer Schering Pharma, Biogen Idec, GlaxoSmithKline, Merck Serono, Novartis, Union Chimique Belge, and Teva. In the past 3 years, RAR has received speaker honoraria or consulting fees from Bayhill, Biogen Idec, Genzyme, TEVA Neurosciences, and Weyh Pfizer; and research support from the US National Multiple Sclerosis Society, National Institutes of Health, and Biogen Idec. CHP reports having received consulting fees from Actelion, Biogen Idec, Bayer Schering, Teva, Merck Serono, Novartis, GlaxoSmithKline, Union Chimique Belge, Roche, and Antisense Therapeutics; lecture fees from Biogen Idec, Bayer Schering, Novartis, and TEVA; and grant support from Biogen Idec, Bayer Schering, GlaxoSmithKline, Novartis, Union Chimique Belge, Merck Serono, and Teva.

References


