CLINICAL INVESTIGATION

Emerging oral disease-modifying therapies in multiple sclerosis: a review of the latest clinical evidence

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Over the last two decades, patients have relied on the use of self-injectable disease modifying agents for the treatment of multiple sclerosis. The need for frequent injections has affected treatment up take and adherence. Fingolimod, the first oral disease modifying agent to be licensed in Europe and the United States, has been shown to be effective in reducing relapse rates in comparison to placebo and once weekly low dose interferon β-1a (Avonex®) in relapsing remitting multiple sclerosis. Four other oral agents, currently in Phase III trials, have also shown promising results. Over the next few years, physicians may have up to five oral agents to choose from all of which may compete with currently available therapies in terms of efficacy, tolerance and ease of administration. However their cost, side effect profile and lack of long term efficacy and safety data are likely to limit their use in the short term. Despite the advantages of oral disease-modifying therapies, it is likely that currently available agents will continue to be the mainstay of treatment for the foreseeable future with the emerging oral therapies providing effective second line therapy.

Keywords: annualized-relapse rate • clinically active • clinically isolated syndrome • primary progressive • rapidly evolving • relapsing • relapsing remitting • secondary progressive • self-injectable disease modifying treatments

Multiple sclerosis (MS) is a chronic immune-mediated disease of the CNS, which affects approximately 0.1% of Caucasians of north and central European ancestry [1]. It presents in a variety of symptoms including visual impairment, limb weakness, sensory disturbance, balance and postural problems, sphincter dysfunction, cognitive impairments, pain and fatigue [2]. The cause of MS remains unknown but it appears that there are two distinct, but possibly linked, pathological mechanisms that underpin the clinical course of the disease [3]. In the majority of patients, the illness runs an initial inflammatory relapsing remitting (RR) course where predominantly T cell- (and to a lesser extent B cell-) mediated demyelination and subsequent axonal destruction result in acute loss of function which is followed by varying degrees of recovery. Over time, a phase of neurodegeneration ensues and manifests clinically in a progressive acquisition of disability. Once a critical level of axonal loss is reached, the course of the illness becomes secondary progressive (SP) in approximately 65% of all patients with RRMS [4]. MRI demonstrates frequent new lesion formation with contrast enhancement during the RR phase and progressive atrophy of both grey and white matter with less contrast enhancement during the SP phase [5]. The major goals of current treatments include a reduction in the number of relapses and the prevention of physical and cognitive disability. Current treatments have shown some impact on the initial immune-mediated process and therefore have the most benefit in the early RR phase [6]. As yet, no treatments have had any significant impact on the neurodegenerative process in the progressive stages of MS.

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Over the last 14 years the mainstay of first-line treatment for active RRMS has been self-administered injectable disease-modifying therapies (DMTs). Physicians can chose from four brands of IFN-β (Avonex®, Betaferon®, Extavia® and Rebif®) or glatiramer acetate (Copaxone®) (Table 1). No robust, long term (≥2 years) comparison trials have demonstrated which, if any, of these drugs is the 'best' [7]. Treatment is indicated in patients with clinically active disease as defined by two clinically significant relapses in the preceding 2 years [101]. In patients with RRMS, DMTs reduce relapses by approximately a third [8–11]. The side effects of these DMTs are mainly mild and include flu-like symptoms and injection site reactions. Almost two decades of experience with these medications has provided reliable long-term safety data. However, the need for regular injections has been a major drawback. Patients must bear the pain and potential fear of needles as well as injection site reactions and the cost and inconvenience of drug storage and administration. As a result, some decline treatment whilst others fail to adhere to its regime [12]. Rates of adherence with self-injectable DMTs have been reported to be between 75 and 80% [13,14]. Many patients therefore welcome the convenience of oral therapies which may well improve treatment take-up and adherence.

Whilst self-injectable DMTs are a reasonable option for many patients with RRMS, such treatments are less effective when the illness runs a different clinical course. Their modest impact on relapse rate may not be sufficient for some patients with more severe MS where the disease remains active despite the use of such treatments or when the illness runs a rapidly evolving severe course. For those patients, the humanized monoclonal antibody natalizumab (Tysabri®) [102], which reduces relapse rates by 68% [15], is a reasonable alternative (Table 1). However, this agent is used with caution due to its serious side effects which include hypersensitivity reactions [15], malignant melanoma [16,17] and progressive multifocal leukoencephalopathy (PML), a CNS viral infection which often results in death or severe disability [18]. The risk of developing PML is thought to be approximately one in 1000 [19] but varies depending on treatment duration and possibly prior exposure to immunosuppression [20]. This risk is only deemed acceptable in those with severe RRMS and this treatment may therefore not be a viable long-term option especially if the risks increase with prolonged use. The emergence of PML has reminded clinicians of the difficulties of balancing risk and benefit that these drugs pose. Mitoxantrone (Novantrone®) is used in some countries in the treatment of aggressive RR or rapidly progressive MS but its risks are significant and included immunosuppression, malignancy and cardiac toxicity (Table 1) [21]. There is currently no treatment available for patients with primary progressive MS [4]. In patients who present with clinically isolated syndromes, IFN-β reduces the conversion rate to MS from 45–50 to 28–35% over 2–3 years [22–25]. However, at best, only a marginally significant gain in disability prevention has been demonstrated [25]. Glatiramer acetate is presumed to have a similar effect [26].

For the first time an oral treatment, fingolimod, has been licensed in both the USA and Europe for patients with RRMS. Four other oral therapies show promising efficacy and tolerability and may have an impact in patients where current treatments fail (Table 1). This article reviews the evidence for the most promising emerging oral agents.

Fingolimod (Gilenya®)

By preventing T lymphocytes re-circulating from lymphoid organs, fingolimod prevents autoaggressive T-cells damage in the CNS whilst allowing lymphocytes to remain functional in the lymphoid compartment [27]. It acts as a high-affinity agonist at the G protein-coupled sphingosine 1-phosphate receptor-1 (S1P-1) on lymphocytes. This causes aberrant internalization of S1P-1 and renders the cells unresponsive to the signal by serum sphingosine 1-phosphate to egress from the lymphoid organs. Fingolimod crosses the blood-brain barrier and has been found to modulate myelin-producing oligodendrocyte membrane dynamics and survival responses that are directly relevant for myelin integrity [28] and modulates multiple neuroglial cell responses, resulting in enhanced remyelination [29].

Several Phase III trials in patients with active RRMS have evaluated the efficacy of either fingolimod 0.5 or 1.25 mg daily. FREEDOMS [30] involved 1033 patients over 2 years and found fingolimod to significantly reduce the annual relapse rate to 0.18 with 0.5 mg and 0.16 with 1.25 mg compared with 0.40 with placebo, resulting in a relative relapse risk reduction of 54 and 60%, respectively. Risk of disability progression and MRI-related markers of disease activity and progression (number of new or enlarged lesions on T2-weighted images, gadolinium-enhancing lesions, and brain-volume loss) were also significantly reduced. Further studies are ongoing to gain more data into both the efficacy and safety of the drug. The 24-month FREEDOMS extension study [103] is expected to complete in August 2011. FREEDOMS II [104] is an ongoing, Phase III 2-year placebo-controlled study of fingolimod 0.5 mg, similar to FREEDOMS, that involved a further 1000 patients. The study is expected to publish data in late 2011 and its extension [105] is expected to complete in 2013.

Whilst the FREEDOMS trials provide data in a large number of patients over 4 years, they do not allow direct head-to-head comparison with current

DMTs. TRANSFORMS was a 1-year Phase III trial in 1153 patients with RRMS that directly compared two doses of fingolimod with IFN-β-1a (Avonex) [31]. The annualized relapse rate was significantly lower in both groups receiving fingolimod (0.20 in the 1.25 mg group and 0.16 in the 0.5 mg group) than in the interferon group (0.33). The study reported a relative relapse risk reduction of 52% (0.5 mg) and 39% (1.25 mg) compared with Avonex. Other relapse related measures, including proportion of patients who remained relapse free, time to first relapse and MRI measures of disease activity significantly favored fingolimod but there was no significant difference in disability progression. A total of 882 patients completed the 12-month extension phase [32] during which time those on Avonex were reassigned to fingolimod. The trial found 71–73% of the patients who received continuous fingolimod for 2 years to have remained relapse free compared with only 60% of those patients who were first treated with Avonex and then switched to fingolimod.

There is no current data on the use of fingolimod in patients with clinically isolated syndromes, progressive MS or as an adjunct to self-injectable DMTs. However, the INFORMS study [106] is currently recruiting patients with primary progressive MS and is expected to complete in December 2013.

A total of 2,600 patients have been treated with fingolimod over the last 10 years [107]. Pooled data from the Phase II and III trials [33] found that the overall incidence of adverse effects (AEs) leading to study drug discontinuation and of serious AEs was similar in the fingolimod 0.5 mg and placebo arms but serious AEs were higher in the 1.25-mg arm. Most AEs were dose dependent [30,31] and included elevation of liver enzymes, transient bradycardia on treatment initiation, lower respiratory tract infections, macular oedema and a slight reduction in forced expiratory volume in one second (FEV_1). The malignancies reported in the various trials (malignant melanoma, breast cancer *in situ*) were of similar proportions in all treatment groups [33]. Of most concern were two deaths during the TRANSFORMS trial [31]. Both occurred in the high dose group and were associated with lymphopenia. One was caused by disseminated primary varicella zoster infection in a patient who was exposed to a child with chicken pox whilst receiving a course of corticosteroids [31]. The second death was caused by herpes simplex encephalitis [31]. The incidence of serious herpes infections was higher in the 1.25 mg group than the 0.5 mg [33] but the overall incidence was low. In view of the increased side effect profile without significant increase in efficacy of the increased dose, only the 0.5 mg dose has been licensed.

In September 2010 after a long consultation period the US FDA approved the use of fingolimod for RRMS [108]. In March 2011, the European Committee for Medicinal Products for Human Use (CHMP) licensed fingolimod as a second line agent for patients that continue to experiences frequent relapses (at least one per year) despite the treatment with IFN-β or glatiramer acetate (for ≤1 year) and for patients with rapidly evolving severe RRMS [109]. One criticism of the European license is that none of the published trials include data on the specific use of this agent in patients with aggressive disease or in those who have failed first line treatment and it is therefore unclear if the efficacy of fingolimod is comparable to those of the currently available alternatives (mainly natalizumab). This may make it difficult for clinicians to recommend the use of fingolimod to patients with severe disease. It is also worth noting that although the evidence supports the use of fingolimod in patients who currently qualify for first-line self-injectable DMTs (that is, active but not aggressive RRMS), it has not been licensed for use in this patient group in Europe.

Following its European licensing, the use of fingolimod needs to be reviewed by the individual national health agencies before funding can be granted. In the UK an appraisal will begin in July and a decision is expected in the latter part of this year. Fingolimod is currently being marketed in the US at an annual cost of US$44,000 (EUR€35,000) per year. This compares to the yearly cost of self-injectable DMTs in the UK of between £5,823 (€6783) and £8502 (€9904), and £14,730 (€17,159) for natalizumab [110], which excludes the associated costs of administration and monitoring. In the more stringent European market the high cost of fingolimod may limit its use.

Teriflunomide

Teriflunomide is a metabolite of leflunomide, a drug that has been used to treat inflammatory conditions such as rheumatoid arthritis. Teriflunomide interferes with the activity of rapidly dividing cells including activated T cells. It inhibits pyrimidine synthesis by binding to the enzyme dihydro-orotate dehydrogenase, which is the fourth enzyme in the *de novo* synthesis pathway of pyrimidines [34].

A number of clinical trials have shown teriflunomide to have promising results in reducing relapses both as monotherapy and as an adjunct to first line treatment. It has also been shown to have some impact on disability progression. TEMSO [35] was a Phase III trial in which 1088 patients with RMS were randomized to receive either teriflunomide 7 or 14 mg or placebo. At 2 years the drug significantly increased the time to first relapse in both active treatment groups

Table 1. Oral disease-modifying agents currently in clinical trials and licensed MDTs used for the treatment of multiple sclerosis.

Treatment	Reduction in ARR	Potential use	Delivery	Main side effects	Annual cost	Evidence	Ongoing trials	Ref.
Fingolimod	54% compared with placebo at 2 years	USA: RRMS Europe: second-line RRMS and severe, rapidly progressive RRMS	Oral once daily	Viral infections, lymphopenia and malignancy	UK£30,000	FREEDOMS	FREEDOMS extension, FREEDOMS II	[30,103,104]
	52% compared with Avonex® at 1 year					TRANSFORMS	TRANSFORMS II	[31,32]
Cladribine	54–58% at 2 years	Currently in Phase III trials	Short courses at intervals	Infections, bone marrow suppression and malignancies	Unknown	CLARITY	CLARITY extension, ORACLE, ONWARD	[44,116–118]
Teriflunomide	31% at 2 years	Currently in Phase III trials	Oral once daily	Possible teratogenicity	Unknown	TEMSO	TOWER, TENERE, TOPIC, TERACLES	[35,111–113,115]
Laquinimod	23% at 2 years	Currently in Phase III trials	Oral three-times daily	Mild rise in inflammatory markers and liver enzymes	Unknown	ALLEGRO	ALLEGRO extension, BRAVO	[112,124,125]
Dimethyl fumarate	53% at 2 years	Currently in Phase III trials	Oral three-times daily	Abdominal pain, flushing, MS relapse and headache	Unknown	DEFINE	DEFINE extension, CONFIRM, EXPLORE	[121,122,129,130]
IFN-β-1a (Avonex)	~30% at 2 years	RRMS SPMS, CIS	im. once weekly	Injection-site reactions, flu-like symptoms and transient liver derangement	£8502	The Multiple Sclerosis Collaborative Research Group trial CHAMPS		[8] [24]
INF-β-1a (Rebif®)	~30% at 2 years	RRMS SPMS CIS	sc. three-times per week	Injection-site reactions, flu-like symptoms, transient liver derangement	22 µg: £7513 44 µg: £8512	PRISMS ETOMS		[9] [23]
INF β-1b (Betaferon®)	~30% at 2 years	RRMS SPMS CIS	sc. alternate days	Injection site reactions, flu-like symptoms, transient liver derangement	£7259	IFN-β Multiple Sclerosis Study BENEFIT		[10] [25]
Glatiramer acetate (Copaxone®)	~30% at 2 years	RRMS CIS	sc. daily	Injection-site reactions, flushing and lipoatrophy	£5823	Copolymer 1 Multiple Sclerosis Study PreCISe		[11] [26]

ARR: Annualized relapse rate; CIS: Clinically isolated syndrome; im.: Intramuscular; iv.: Intravenous; PML: Progressive multifocal leukoencephalopathy; RRMS: Relapsing remitting multiple sclerosis; sc.: Subcutaneous; SPMS: Secondary progressive multiple sclerosis.

Table 1. Oral disease-modifying agents currently in clinical trials and licensed MDTs used for the treatment of multiple sclerosis (cont.).

Treatment	Reduction in ARR	Potential use	Delivery	Main side effects	Annual cost	Evidence	Ongoing trials	Ref.
Natalizumab (Tysabri®)	68% at 2 years	USA: RRMS Europe: second-line RMS and severe rapidly progressive RRMS	iv. four-times weekly	PML, allergic reactions, infection fatigue and depression	£14,730	AFFIRM		[15]
Mitoxantrone	Reduction in relapses and disability progression	Unlicensed Worsening, RRMS or SPMS	iv. one or three monthly	Infection, leukemia, cardiac and hepatic toxicity	£3600	MIMS		[21]

ARR: Annualized relapse rate; CIS: Clinically isolated syndrome; im.: Intramuscular; iv.: Intravenous; PML: Progressive multifocal leukoencephalopathy; RRMS: Relapsing remitting multiple sclerosis; sc.: Subcutaneous; SPMS: Secondary progressive multiple sclerosis.

relative to placebo. Patients in the active treatment groups showed an annualized relapse rate of 0.370 and 0.369 compared with 0.54 in the placebo group resulting in a statistically significant 31% reduction in relapse rates compared with placebo. Secondary endpoints showed that the risk of sustained disability progression was significantly reduced by 29.8% with the 14 mg dose, with a trend to a reduction of 23.7% with the 7 mg dose. MRI lesion volume was also significantly reduced by 39.4% in the 7 mg group and by 67.4% in the 14 mg group. There was no increase in serious AEs and no increase in serious opportunistic infections and the most common side effects were mild and included mild hair thinning, diarrhea, nausea and mild liver enzyme derangement [35]. Animal models [36] had found leflunomide to have teratogenic potential and it was therefore advised that both women and men receiving teriflunomide should avoid reproduction whilst exposed to the drug. One patient who became pregnant during the TEMSO study went on to deliver a healthy baby [35].

Phase II studies using teriflunomide in addition to IFN-β-1a [37] or glatiramer acetate [38] revealed acceptable tolerance and safety and showed significant improvements of disease activity as measured by MRI. Overall the safety profile was similar to previous studies.

Besides the TEMSO trial, several Phase III studies are ongoing including TOWER [111], a placebo controlled trial and TENERE [112], which will offer a head-to-head comparison with IFN-β-1a (Rebif). Other Phase III studies are currently evaluating the use of teriflunomide as an adjunct to IFN-β-1a [113] and glatiramer acetate [114] and to assess it efficacy against placebo in patients with clinically isolated syndromes [115]. The results of TOWER study, which are expected in 2012, will support the application for regulatory approval. Should the positive efficacy and safety profile of TEMSO be replicated, the manufactures, Sanofi-Aventis, will be submitting a New Drug Application in the first half of 2012.

Cladribine (Movectro®)

Cladribine is a purine analogue, which is used intravenously in the treatment of chronic lymphocytic and hairy cell leukemia. Intracellular accumulation of the active metabolite of cladribine, which mimics nucleoside adenosine deaminnase, causes disruption of cellular metabolism, inhibition of DNA synthesis and repair, and subsequently apoptosis [39]. It preferentially affects lymphocytes, which are dependent on adenosine deaminase activity to maintain the equilibrium of cellular concentrations of triphosphorylated nucleotides. This results in a rapid reduction in $CD4^+$ and $CD8^+$ T cells and $CD19^+$ B cells whilst sparing other

immune cells [39,40]. It has also been shown to reduce levels of pro-inflammatory cytokines in the serum and cerebrospinal fluid [41].

Research into the use of cladribine has been ongoing since the 1990s and small trials of subcutaneous cladribine showed improvement in frequency and severity of relapses and MRI findings [42,43]. CLARITY [44] was a 2-year, Phase III trial of 1326 patients with RRMS. It randomized patients to three treatment groups: low or high dose cladribine, based on a cumulative total dose of either 3.5 or 5.25 mg/kg body weight, or placebo. The cladribine arms received either two (low-dose arm), or four (high-dose arm) courses of 4/5 days in the first year, and two courses in the second year. The gap between courses was given to allow hematopoetic recovery. Among patients who received cladribine there was a significantly lower annualized relapse rate compared with the placebo group (0.14 in the low-dose arm, 0.15 in the high-dose arm, compared with 0.33 placebo) producing a relative risk reduction of 57.6% in the high-dose arm and 54.5% in the high low-dose arm. The study showed a higher relapse-free rate in the active-treatment arms (79.7% in the low-dose arm, 78.9% in the higher dose arm compared with 60.9% in the placebo arm), a significantly lower risk of 3-month sustained progression of disability and significant reduction in active and the total number of MRI lesions. A 2-year extension study [116] will complete later on this year.

Two further trials are in progress with the aim of broadening the potential use of the cladribine. ORACLE [117] is a Phase III placebo-controlled study, evaluating its use in delaying or prevention conversion to MS in clinically isolated syndrome. ONWARD [118] is a Phase II, placebo-controlled study using cladribine as an adjunct in patients who continue to have active disease despite IFN-β (Rebif).

Adverse events were of significant concern in the CLARITY trial [44]. They included lymphopenia (21.6% in the low-dose arm and 31.5% in the high-dose arm and 1.8% in placebo arm) and dermatomal herpes zoster (20 patients in the treatment arms, no patients in the placebo arm). In the treatment arms three patients developed severe neutropenia and four patients died compared with two deaths in the placebo arm. One patient in the 5.25 mg/kg group, a 21-year-old female, developed pancytopenia with recurrent bilateral alveolar-interstitial lung infiltrates after receiving her first and only treatment cycle of cladribine tablets (0.875 mg/kg). At 6-months post-treatment, she died from an acute cardiopulmonary arrest considered to be due to severe exacerbation of latent tuberculosis. Cladribine was felt likely to have contributed to the tuberculosis reactivation. Three other patients in the treatment arms died due to metastatic pancreatic carcinoma, myocardial infarct and drowning. Ten patients (1.1%) in the treatment arms developed a neoplasm (none in the placebo arm) of which three were malignant (pancreatic, melanoma and ovarian) and one a cervical carcinoma *in situ*. Like fingolimod, the risks appear to be dose dependent whilst the benefits appear to be equal in both high and low dose groups [44].

Cladribine was licensed in Russia and Australia in 2010. In September 2010 the European CHMP rejected an application on the grounds that the risks of its use outweighed the benefits. Of most concern were the cases of neoplasia and infections seen in the CLARITY trial. The manufacturer Merck Serono appealed this decision but in January 2011 the CHMP rejected the appeal [119] stating that these issues were not resolved and that the risks continued to outweigh the benefits. The FDA had initially rejected the drug in November 2009 and despite being granted priority review status, they issued a response in March 2011 stating it could not grant the application approval in its present form [120]. It stated that whilst the CLARITY trial provided substantial evidence for the effectiveness of cladribine it has requested that Merck Serono provide an improved understanding of the safety risks and overall benefit-risk profile either through additional analyses or further trials. Following further discussions with the FDA, Merck Serono have recently announced they would no longer pursue a global approval for cladribine as a treatment for RRMS [121]. The manufacturer plans to withdraw this drug from Australia and Russia but complete the ongoing clinical trials (CLARITY EXTENSION, ORACLE MS and ONWARD) and proceed with an 8-year observational safety registry (PREMIERE), which follows patients who have participated in previous studies [122].

Laquinimod

Laquinimod is a synthetic compound, structurally related to roquimimex (Linomide®). Roquimimex was found to suppress the appearance of active lesions on MRI [45] but caused serious inflammatory side effects (e.g., serositis andmyocardial infarction) whilst laquinimod appears to be better tolerated in clinical trials. The mechanism of action is not fully understood but it likely affects T cell migration though it does not appear to lead to immunosuppression [46].

A number of trials have shown that laquinimod is efficacious in reducing relapse rates and MRI measures of disease with a reasonable side effect profile. A 24-week Phase II trial [47] of 256 patients found patients receiving laquinimod 0.3 mg three-times

daily to have a 44% reduction in gadolinium-enhancing lesions on MRI compared with placebo although the level of significance in analysis was borderline (p = 0.049). The difference was slightly more pronounced in a subgroup analysis of patients who had active lesions at baseline (52% reduction, p = 0.005). There was no difference in the number of relapses between groups. A further 36-week trial [48] looked at the effect of laquinimod 0.3 or 0.6 mg three-times daily. The 0.3 mg dose had no significant benefit over placebo but patients in the 0.6-mg arm had a 40% reduction in gadolinium-enhanced lesions. In April 2011 the drug's manufacturer Teva announced the results of ALLEGRO, a 24-month Phase III trial [123]. They reported that laquinimod significantly reduces the annualized relapse rate by 23% compared with placebo and states a significant reduction in the risk of disability progression (36%) and brain tissue loss (33%) [124]. An extension phase of this study in currently ongoing [125].

Teva reported a comparable safety profile to placebo with the most common AEs being headache, nasopharyngitis, back pain and a transient rise in liver enzymes [124]. A patient in the Phase II study developed a thrombotic venous outflow obstruction of the liver [48]. However, the patient was found to be heterozygous for Factor V Leiden and no further thrombotic events have been recorded. Meanwhile, a further 24-month, Phase III trial, BRAVO [126], which compares laquinimod to placebo and provides risk benefit data on its uses compared with IFN-β-1a (Avonex) and is due to complete in late 2011.

Dimethyl fumarate (BG-12, Panaclar)

Dimethyl fumarate activates the nuclear factor like 2 (Nrf2) transcriptional pathway in mice, which has a role in defending cells against oxidative-stress, induced neuronal death and may play a role in protecting the blood-brain barrier and support maintenance of myelin integrity in the face of inflammatory attack [49]. It has shown some promise in improving MRI outcomes and appears to be well tolerated, but like laquinimod it has failed to demonstrate significant impact on clinical measures. It is also being evaluated in combination with first line treatment.

In a 24-week, Phase II placebo-controlled study of 257 patients [50] who were randomized to receive either placebo or dimethyl fumarate at a dose of 120 mg once daily, 120 mg three-times daily, 240 mg three-times daily or placebo, it was found that in the 64 patients who received 240 mg three-times daily dose, the treatment significantly reduced the number of new gadolinium-enhancing lesions by 69% compared with placebo and reduced the annualized relapse rate by 32% (0.44 in treatment arm, 0.65 in placebo). The most common AEs included abdominal pain, flushing, MS relapse, and headache. There were no significant differences in incidence of infection and only one serious infection occurred (an incident of pelvic inflammatory disease).

The DEFINE study, a 24-month, Phase III, placebo-controlled trial [127] of dimethyl fumarate 240 mg twice- or three-times daily in 1200 patients with RRMS, has recently completed. The drug manufacturer, Biogen-Idec, has recently reported a significant reduction in the proportion of patients who relapsed at 2 years by 49% compared with placebo and a significant reduction in the annualized relapse rate and disability progression by 53 and 38%, respectively [128]. The AEs were similar to those reported in the Phase II trials. Publication of the detailed data is awaited. An extension phase for a further 2 years is ongoing [129] and a further trial [130] comparing the efficacy of dimethyl fumarate against oral placebo or 20 mg of subcutaneous glatiramer acetate is expected to complete in April 2011. The drug is also being evaluated in the treatment of patients that continue to have active disease despite first line therapy [131] in combination with IFN-β or glatiramer acetate

Conclusion & future perspective

The development of oral therapies provides hope to many patients with MS. It offers the potential for superior efficacy, freedom from the inconvenience of regular injections and the possibility of improved adherence. These agents may also offer the possibility of slowing the devastating disability progression seen in many MS sufferers and could prove to have a role when used in addition to current treatments or in patients where the use of current DMTs are not of any proven efficacy. The use of these emerging treatments may be limited by their price, potential AEs as well as the lack of the extensive long-term safety data compared with over a decade of experience of currently used DMTs. One should also be cautious in comparing their effectiveness with established DMTs whist awaiting the results of more head-to-head comparison trials. Despite the advantages of oral DMT's, it is likely that currently available agents will continue to be the mainstay of treatment for the foreseeable future with emerging oral therapies providing effective second line therapy.

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Executive summary

- Currently, first line treatment for patients with active relapsing remitting MS is limited to self-injectable agents (IFN-β and glatiramer acetate). These are well tolerated and reduce the annualized relapse rate by approximately one third compared with placebo.
- Fingolimod demonstrates a reduction in the annualized relapse rate of 54% compared with placebo and has some impact on the risk of disability progression.
- Compared with low dose intramuscular IFN-β-1a (Avonex®), fingolimod demonstrated a relative relapse risk reduction of 52% but rates of progression of disability were similar.
- Fingolimod has been associated with some serious adverse effects including lymphopenia and herpes infections.
- Fingolimod has been approved in the USA for the treatment of relapsing-remitting MS and Europe for the treatment of aggressive MS or where first-line therapies have failed to control relapses.
- Teriflunomide offers a relative relapse risk reduction of 31% compared with placebo and has a promising impact on disability progression with reasonable safety profile and may be of benefit as an adjunct to first line treatment.
- Cladribine has demonstrated a relapse risk reduction of 54–58% compared with placebo but it has not been licensed in the USA or Europe due to concerns regarding its risk-benefit profile.
- Results from the first Phase III trial of laquinimod have shown a modest 23% reduction in annualized relapse rates and an impact on disability progression and a good safety profile.
- Early results from the first Phase III trial suggest that dimethyl fumarate reduces relapse rates and disability progression by 53 and 38%, respectively and full results are awaited.

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