Review

Disease-modifying drugs in multiple sclerosis: new oral options

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Practice Points

- Multiple sclerosis, clinically represented by relapsing-remitting, secondary progressive and primary progressive subtypes, is an autoimmune CNS disease, characterized by multifocal lesions with inflammation and neurodegeneration involving white and gray matter.
- Disease-modifying drugs (DMDs) are used to treat the course of multiple sclerosis, with a predominant effect on inflammation (clinical relapses and MRI activity); however, marginal impact on neurodegeneration is conceivable. After the current parenteral drugs, some oral DMDs are approaching the market: fingolimod, BG-12, laquinimod and teriflunomide.
- Fingolimod, agonist and finally functional antagonist of sphingosine 1-phosphate receptors, is an oral DMD able to induce lymphocyte entrapment in the lymphoid organs. Reducing lymphocyte trafficking is a strategy to control CNS inflammation and, consequently, clinical relapses.
- BG-12 is an oral anti-inflammatory and potential neuroprotective DMD, because it activates the Nrf2 transcriptional pathway, which protects against the oxidative stress that contributes to myelin and axonal damage.
- Laquinimod is an oral modulator of inflammation. It influences Th1/Th2 balance, lymphocyte migration and antigen presentation, but also seems to act as a protective drug against axonal damage and brain atrophy.
- Oral antimetabolites such as cladribin and teriflunomide can control CNS inflammation by lymphocyte depletion. Cladribin, an analog of deoxyadenosine that is resistant to adenosine deaminase, induces preferential and sustained $CD4^+$ T-cell depletion via apoptosis, due to disrupted DNA synthesis and repair. Teriflunomide reduces T-lymphocyte proliferation, largely dependent on pyrimidine synthesis, by blocking the dihydroorotate dehydrogenase activity.

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- In the future, DMDs will be taken by an easier oral route compared with the parenteral, with better adherence and similar or higher control of multiple sclerosis inflammatory activity. However, caution is still needed regarding safety issues and planning appropriate surveillance against side effects is mandatory.

SUMMARY Multiple sclerosis is characterized by multifocal CNS lesions with perivenular inflammation, demyelination, axonal transection, neuronal degeneration and gliosis. Proinflammatory $CD4^+$ and $CD8^+$ T cells reactive to CNS myelin antigens mediate the initial phases of lesion formation. Other T-cell subsets, B cells, monocyte-macrophages and natural killer cells have been implicated in both effector and regulatory mechanisms. Inflammatory processes predominate in early disease, whereas progression of neurological disability reflects neurodegeneration. A number of disease-modifying drugs with immunomodulatory (e.g., IFN-β, glatiramer acetate and natalizumab) or immunosuppressant properties (e.g., mithoxantron) have been employed over the past two decades, in order to reduce the relapse rate. Unfortunately, they are limited by parenteral use. Recently, some new oral compounds have been developed reaching similar or higher control of disease activity, improving quality of life and increasing adherence. In this article, an update of main emerging oral disease-modifying drugs will be provided, including clinical trials design, mechanisms of action and safety aspects.

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the CNS, resulting from variably combined inflammation and neurodegeneration, characterized by recurrent neurological deficits (clinical relapses) often associated with dynamic MRI activity and leading to disability over time. Both T and B lymphocytes are believed to play a key role in inflammatory processes acting in the pathogenesis of the disease, including the activation of autoreactive T cells, subsequent migration of T cells into the CNS, initiation of the inflammatory cascade, production of CNS-directed antibodies and possibly direct axonal damage [1,2]. Parameters including MRI data and the number of relapses in the first 2 years partly predict long-term outcome in MS patients [3,4]. The nonconventional imaging techniques have demonstrated the importance of cortical pathology and gray matter atrophy as factors influencing an unfavorable course of the disease because, by contrast to white matter, gray matter atrophy is more relevant in MS and correlates with disease phenotype and disability to a greater extent [5]. Several drugs are currently approved as disease-modifying treatments (DMTs) in relapsing-remitting MS (RR-MS), but it is generally accepted that there are no drugs with a strong impact on disability progression. No drugs are approved as DMTs in primary progressive MS and only a few are administered in secondary progressive MS forms. Among the conventional DMTs, all used by the parenteral route in the last two decades, are IFN-β-1a and -1b, acting predominantly on inflammation by inhibiting T-cell activation and proliferation, inducing Treg activation, regulating endothelial adhesion molecules involved in blood–brain barrier permeability and shifting cytokine production toward an anti-inflammatory profile [6].

Glatiramer acetate (GA), a random polymer of glutamic acid, lysine, alanine and tyrosine, has been shown to reduce the frequency of relapses in patients with RR-MS. Daily subcutaneous injection of GA reduces relapse rate, MRI activity and disease burden [7,8]. Several potential immunological mechanisms have been hypothesized for GA such as induction of tolerance, expansion of Treg populations, alterations of antigen-presenting cells [9] and neuroprotective mechanisms [10].

Clinical trials conducted in the earliest stages of MS, such as the first demyelinating episode (referred to as clinical isolated syndrome according to the McDonald Criteria [11]), have accumulated evidence that supports early initiation of disease-modifying drugs in order to reduce

the risk of conversion to clinically definite MS. For example, results of the ETOMS, CHAMPS and, most recently, the BENEFIT trials demonstrated that early initiation of IFN-β is effective in delaying conversion to clinically definite MS [12,13].

The results of the PreCISe study, a placebo-controlled trial of GA in clinically isolated syndrome, are similar to those of previous trials with IFN-β, in which conversion to clinically definite MS was delayed [14].

On average, all injectable DMTs have demonstrated a beneficial effect on decreasing annual relapse rates by approximately 30% when compared with placebo. Nevertheless, the caution to compare efficacy across clinical trials provides limited ascertainment of therapeutic superiority [15]. Moreover, the mechanisms by which treatments can reduce accumulation of disability still remain a matter of debate.

Second-line drugs of intravenous use, with more recent experience, are the monoclonal anti-VLA-4 integrin natalizumab and the anthracenedione derivative mithoxantron. Both drugs have reached high control of clinical relapses with a trend in reduction of disability progression (68% reduction of relapse rate at 1 year and 54% reduction of disability progression over 2 years in the placebo-controlled AFFIRM study for natalizumab; 60% reduction of relapse rate and 64% reduction of disability progression for 2 years' administration of mithoxantron in the MIMS trial) [16,17].

Nevertheless, critical issues have been raised about their safety in the long term, consisting of the risk of progressive multifocal encephalopathy (PML) for natalizumab [101] and acute leukemia for mithoxantron [18], so most MS specialists are no longer using mithoxantron.

Lastly, the new oral drugs represent an emerging option for the treatment of MS patients and this review will highlight recent promising data in this field.

Among them, fingolimod has been recently approved and marketed in the USA, southern America, Europe and Australia, whereas cladribin's approval remains limited to Russia and Australia, due to negative opinion by the EMA. Another molecule that reached approval in the USA and Europe is dimethyl fumarate (BG-12), while laquinimod and teriflunomide are close to later stages of development and also will likely come to market.

New oral drugs for MS treatment

■ Lymphocyte trafficking inhibitors

Fingolimod

Fingolimod (FTY720, Gilenya™, Novartis AG, Basel, Switzerland), approved by the US FDA in September 2010 and by the EMA in January 2011 to treat patients affected by RR-MS, is the first oral DMT developed. Fingolimod was identified in the early 1990s from an extensive chemical derivatization program of myriocin, an immunosuppressant isolated from the entomopathogenic fungus *Isaria sinclairii* [19]. Fingolimod's mechanisms of action in MS are not completely understood. The main accepted mechanism is the immunologic effect, specifically the inhibition of lymphocyte egress from lymph nodes and interruption of their recirculation to the CNS, an event known to be responsible for disease features such as relapses and MRI activity. Fingolimod is a prodrug reversibly phosphorylated to fingolimod-P, the active moiety, which binds with high affinity to several subtypes of sphingosine 1-phosphate (S1P) receptors; S1P1, S1P3, S1P4 and S1P5, but not S1P2 [20]. The fingolimod-P interaction with S1P1 expressed by lymphocytes has the functional consequence of a mixture of agonistic and functional antagonistic effects within the immune system, accounting for the immunologic mechanism of action of this drug.

Downregulation of S1P1 expression on lymphocytes by fingolimod makes them unresponsive to the lymph nodes' efferent lymphatic S1P gradient required for egress, rapidly reducing lymphocyte counts in thoracic duct, peripheral blood and spleen [21,22].

Nevertheless, redistribution of lymphocytes from blood to lymph nodes does not produce lymphoadenopathy, because the percentage of lymphocytes in blood is only approximately 2% of the total lymphocyte count in the body [23]. The drug can also reduce naive and memory B cells, because they are physiologically trafficking through secondary lymphoid organs and therefore can be entrapped, while increasing the number of natural killer cells, which are not usually moving along the same pathway [24]. Fingolimod's efficacy data in RR-MS can be derived from critical studies: a 2-year, placebo-controlled Phase III study (FREEDOMS) [25], a 1-year Phase III study (TRANSFORMS) [26] with an active comparator (IFN-β-1a) and a >4 year Phase II extension [27]. All these studies

showed benefit of fingolimod on relapse rate and MRI lesion activity.

In the Phase III FREEDOMS study, RR-MS patients were randomized to oral fingolimod 0.5 mg or 1.25 mg daily or placebo for a 2-year period [25]. A relative reduction of approximately 52% in relapse rate was seen for patients taking fingolimod, in both treatment-naive patients and those previously treated with DMTs. A reduction in the risk of increased disability and a benefit in MRI-related efficacy end points were also shown and no significant differences in efficacy appeared between the two fingolimod arms. The 12-month Phase III TRANSFORMS study has been conducted in RR-MS patients comparing fingolimod 0.5 mg and 1.25 mg daily with IFN-β-1a, administered at 30-mg intramuscularly weekly [26]. Patients treated with fingolimod 1.25 and 0.5 mg showed lower annualized relapse rates (0.20 and 0.16, respectively vs 0.33 for placebo) together with less MRI-enhancing lesions and brain volume loss. Progression of disability was not significantly influenced, but it has been reported that a non-negligible proportion of patients is completely relapse free.

In Phase II and III MS studies, fingolimod decreased the peripheral blood lymphocyte count starting within hours of the first dose, reaching 20–30% of baseline (mean: 500–600/mm^3) within several weeks [26].

Because fingolimod causes lymphocyte redistribution rather than depletion, the lymphopenia is reversible. In the FREEDOMS study, when fingolimod was discontinued, the mean lymphocyte count rose within several days and reached the normal range (0.8 × 10^9/l) within 6 weeks [28]. Fingolimod affects both T cells and B cells, with small or even absent effect on granulocytes, monocytes, eosinophils, erythrocytes and platelets. T cells are likely affected more than B cells [29], and CD4$^+$ T cells are affected more than CD8$^+$ T cells, decreasing the blood CD4:CD8 ratio [30]. Fingolimod preferentially impairs recirculation of IL-17-producing T cells (Th17 cells) [31], which have been implicated in MS pathogenesis and response to IFN-β therapy [32]. A matter of concern has been whether lymphocyte trafficking inhibitors might increase the risk of infection, but the previously discussed clinical trials seem to support the relatively safe profile of fingolimod.

Serious infections were reported in 2.6 and 1.7% of patients on fingolimod 1.25 mg and in 1.6 and 0.2% of patients on fingolimod 0.5 mg in the FREEDOMS and TRANSFORMS studies, respectively, with two fatal herpes virus infections on fingolimod 1.25 mg. Headache, nasopharyngitis and fatigue were reported in more than 10% of patients in the Phase III trials FREEDOMS and TRANSFORMS [25,32]. Other side effects are probably related to the widely distributed S1P receptors specifically in myocardial tissue, liver and macula.

Bradycardia and atrioventricular conduction blocks are well-documented side effects of fingolimod and pretreatment ECG is recommended in order to rule out subjects at major risk, as well as 6-h heart rate monitoring during the first dose administration. The first dose administration of fingolimod often results in a decrease in heart rate, due to the drug's agonistic properties on S1P receptors on the sinus node and atrial cells [33]. There is one case of delayed heart rate abnormalities, a case of asystole 21 h after the first dose, described by Espinosa *et al.* in 2011 [34], and one case of unexpected death in the first 24 h of treatment, but no reports of arrhythmias after longer periods except for a recent report by Lindsey *et al.* in 2012 [35].

Other side effects are represented by minor increases in blood pressure persisting on therapy and asymptomatic liver enzyme elevations [25]. Macular edema, mostly reversible within 1–6 months after discontinuation of therapy [36], occurred in 0.8% of patients on fingolimod, most of whom received fingolimod 1.25 mg [25]. Malignancies are another area of suspicion. While there was no significant report of malignancies in the FREEDOMS trial [25], eight cases of localized skin cancer occurred in fingolimod treated patients in the TRANSFORMS trial [26] with further new cases in the extension study [37]. Overall, the benefit:risk profile was better for the 0.5 mg dose in both trials.

■ Oral anti-integrin agents

Firategrast

Firategrast is an orally bioavailable α4β1/α4β7 integrin antagonist that reduces trafficking of lymphocytes into the CNS. Looking at its mechanism of action, a putative role as an oral analog of the parenteral natalizumab may be conceivable for the future. A multicenter Phase II, randomized, double-blind, placebo-controlled, dose-ranging study (protocol number A4M105038) was performed in 343 patients

with RR-MS who had ≥2 relapses in the previous 24 months, ≥1 relapse or documented gadolinium (Gd) enhancement on MRI in the previous 12 months and ≥5 T2 lesions on brain MRI. They were randomized to receive different dosages of firategrast (either 150, 600 or 1200 mg) or placebo. The primary outcome was cumulative number of new Gd-enhancing brain lesions during the treatment, while secondary efficacy outcomes included additional MRI and clinical measures including relapse rate. Safety assessments included JC virology, neurological symptoms and review of MRIs for evidence of PML. The primary outcome was statistically significant for the 900/1200 mg firategrast group versus placebo: the adjusted cumulative mean rate of Gd^+ lesions was 2.69 versus 5.31 ($p = 0.0026$; 49% decrease). A significant decrease in new T2 lesions was observed in the 900/1200 mg group ($p = 0.009$). A nonsignificant trend for fewer relapses with increasing dose was also observed. Firategrast was generally well tolerated at all dose levels. The frequency of all adverse events was not increased in treated patients versus placebo except for urinary infections with the higher doses. No PML cases were identified [38].

■ Immunomodulators with potential neuroprotective role

Dimethyl fumarate

BG-12, an oral formulation of dimethyl fumarate (DMF), has been supposed to have dual neuroprotective and anti-inflammatory effects on CNS. BG-12 and its metabolite, named monomethyl fumarate, behave as activators of the Nrf2 transcriptional pathway [39], which is involved in phase 2 detoxifying enzyme gene expression and oxidative stress response [40].

CNS macrophages are oxygen and nitrogen free radical producers and they can contribute to demyelination and axonal injury in experimental autoimmune encephalomyelitis and MS [41]. Transcription factors such as NF-κB that upregulate the expression of many genes that could be implicated in experimental autoimmune encephalomyelitis and MS can be activated by free radicals [42], and increased free radical activity or deficiencies in antioxidant enzymes have been reported in MS patients compared with healthy individuals [43].

Activation of the Nrf2 pathway means protection against oxidative stress-induced neuronal death [44], maintenance of blood–brain barrier integrity [45] and support of myelin integrity in the CNS [46]. BG-12 can also induce the expression of phase 2 detoxification enzymes in astroglial and microglial cells [47].

In addition, data coming from *in vitro* studies have shown that BG-12 leads to the switch of the T-helper response from the Th1 to Th2 phenotype and inhibits expression of cytokines and adhesion molecules implicated in the inflammatory response [48].

A pilot study has been conducted in RR-MS patients using an oral formulation of fumaric acid (Fumaderm®, Biogen Idec Gmbh, Ismaning, Germany), previously successfully tested in psoriasis [49], and the results showed reduction in the number and volume of Gd-enhancing (GdE) lesions on brain MRI scans compared with baseline [50].

On the basis of these preliminary findings, a multicenter, randomized, double-blind, placebo-controlled Phase IIb study has been conducted [51]. The population included 257 patients, aged 18–55 years, with RR-MS, randomly assigned to receive 120 mg once daily (n = 64), 120 mg three-times daily (n = 64) or 240 mg three-times daily (n = 64) BG-12, or placebo (n = 65), for 24 weeks. During the subsequent 24-week safety extension period, patients treated with placebo received BG-12 240 mg three-times daily. The primary end point was total number of new GdE lesions on brain MRI scans at weeks 12, 16, 20 and 24. Additional end points included the cumulative number of new GdE lesions (weeks 4–24), new or enlarging T2-hyperintense lesions, new T1-hypointense lesions at week 24 and the annualized relapse rate. Safety and tolerability were also assessed. Treatment with BG-12 240 mg three-times daily reduced the mean total number of new GdE lesions by 69% from week 12–24 compared with placebo (1.4 vs 4.5; $p < 0.0001$). It also reduced the number of new or enlarging T2-hyperintense ($p = 0.0006$) and new T1-hypointense ($p = 0.014$) lesions compared with placebo. BG-12 reduced annualized relapse rate by 32% (0.44 vs 0.65 for placebo; $p = 0.272$). Adverse events were more common in patients treated with BG-12 than in the placebo group and included abdominal pain, flushing and hot flush.

Two Phase III studies are underway in order to determine safety and efficacy of oral DMF in RR-MS. The first study, DEFINE, is a

double-blind study in which 1011 patients have been randomized 1:1:1 to receive oral DMF 240 mg three-times daily, twice daily or placebo, completed in January 2011. The second, CONFIRM, is a study comparing two dosages of oral DMF and subcutaneous GA 20 mg once daily. A total of 1232 RR-MS patients have been enrolled to receive 1:1:1:1 oral DMF 240 mg three-times daily, twice daily, GA or placebo [52]. The DEFINE trial showed that twice daily administered BG-12 reduces the risk of relapse at 2 years by 49%, compared with placebo, and by 50% if given three-times daily ($p < 0.0001$). The reduction of annual relapse rate was 53 and 48% for BG-12 *bis in die* and *ter in die*, respectively ($p < 0.001$). The risk of confirmed 12-week disability progression was reduced by 38% in the twice-daily-treated arm and by 34% in the three-times treated patients [53]. A strong effect on MRI end points has been detected, particularly on the mean number of new or newly enlarging T2 lesions, with a reduction by 85% with BG-12 *bis in die* and 74% with *ter in die* [54].

Laquinimod

Laquinimod is a novel synthetic compound whose mechanism of interference with the pathophysiology of MS has not been completely elucidated. It seems to act as a modulator of the Th1/Th2 cytokine balance, as observed in an experimental autoimmune encephalomyelitis model, and it shows increased potency and an improved safety profile compared with its predecessor linomide, whose previous Phase III trials had stopped due to serious cardiopulmonary toxicity [55]. In addition, there are new insights on laquinimod's potential neuroprotective mechanism. Laquinimod has been found to penetrate the CNS, acting on resident cells (mainly astrocytes) via interference with the NF-κB pathway, decreasing lymphocyte adhesion to the endothelium and migration into CNS, as well as interfering with antigen presentation, resulting in reduced demyelination and axonal damage [56].

Two Phase II studies have demonstrated that laquinimod reduces MRI-monitored disease activity, as assessed by GdE T1 lesions and new T2 lesions, in patients with RR-MS. The first clinical trial showed a 41% reduction in mean cumulative number of active lesions at weeks 0–24 (as measured with a triple dose of Gd) in patients on laquinimod 0.3 mg as compared with those on placebo [57]. In the second study, conducted with a single dose of Gd, the 0.6 mg dose demonstrated a reduction of 40% in the mean cumulative number of GdE T1 lesions in the last 4-monthly scans (weeks 24–36) compared with placebo [58]. Laquinimod was found to be well tolerated, with only 5.5% of the patients assigned to the 0.6 mg dose prematurely discontinuing treatment. Reversible elevations of liver enzymes were found, without concomitant elevations of bilirubin or manifestations of hepatic insufficiency. Upon completion of the 36th week of the placebo-controlled study, patients were enrolled into a double-blind active extension of the trial (LAQ/5063), in which actively treated patients continued their original treatment and placebo patients were randomly switched to either 0.3 or 0.6 mg daily doses of laquinimod for a further 36-week period. The extension phase of the study was designed to determine whether the effects seen in the placebo-controlled phase of the study were sustained for patients on laquinimod and reproducible in patients originally randomized to placebo and switched to 0.6 or 0.3 mg laquinimod in the active extension, as well as to obtain data regarding long-term safety and tolerability.

No differences emerge between high and low doses during the extension phase when the relapse rate reduction is considered. There were no changes in disability during the trial period for any of the cohorts, perhaps attributable to the short duration of the trial period.

The safety and tolerability profile of both doses confirmed the good profile that emerged in the placebo-controlled phase. The incidence rate of the transient, self-limited liver enzyme elevation that had occurred during the placebo-controlled phase appeared to decrease in the extension phase. Elevations of liver enzymes led to early termination in three patients. Liver enzymes returned to normal values in all three individuals. In addition, no new safety signals emerged during the extension phase.

Two Phase III trials have been conducted. The first, ALLEGRO, is a double-blind study that recruited 1000 patients with RR-MS who were randomized to receive laquinimod 0.6 mg or placebo once daily for 24 months. The study demonstrated a significant reduction in annualized relapse rate compared with placebo and showed a significant reduction in disability progression, consisting of a reduction of 48% of the risk for 6-month confirmed Expanded Disability Status

Scale progression. The proportion of patients with confirmed Expanded Disability Status Scale progression after 2 years was 9.8% for laquinimod and 14% for placebo (p = 0.038). The severity of relapses seems to be reduced, because the need for intravenous steroids decreases, as does hospitalization for relapses, in the laquinimod-treated sample [59]. The second Phase III randomized, double-blind, parallel-group, placebo-controlled study, BRAVO, compared the effect of daily oral laquinimod 0.6 mg with placebo and with IFN-β-1a (Avonex®) administered intramuscularly once a week. The primary outcome of the annual relapse rate reduction was not significant, but significant seems to be the 33.5% reduction in Expanded Disability Status Scale progression and the 27.5% decrease in loss of brain volume. Even in these last two clinical trials, laquinimod confirms its safety profile, with most reported adverse events represented by gastrointestinal disturbances and back pain [60].

■ Antimetabolite treatments

Cladribine

Cladribine (2-chlorodeoxyadenosine) is an analog of deoxyadenosine that is resistant to adenosine deaminase, an enzyme that metabolizes adenosine and deoxyadenosine to inosine and deoxyinosine [61]. It acts as a prodrug and must be phosphorylated by intracellular deoxycytidine kinase to form the active moiety 2-chloro-2′-deoxy-β-D-adenosine triphosphate, which is incorporated into DNA. Deactivation of 2-chloro-2′-deoxy-β-D-adenosine triphosphate via dephosphorylation is catalyzed by enzymes of the 5′ nucleotidase family. Thus, in cells such as lymphocytes, which have a high intracellular ratio of deoxycytidine kinase to 5′ nucleotidase, the active form of cladribine accumulates, resulting in disruption of DNA repair and synthesis, cell cycle arrest and apoptosis [62].

Cladribine induces preferential and sustained depletion of $CD4^+$ T cells, less pronounced dose-dependent reductions in $CD8^+$ T cells and $CD16^+/CD56^+$ lymphocytes [63]. According to the hypothesis that a targeted T-cell depletion should be useful to suppress inflammation in MS, safety and efficacy of parenteral cladribine in patients with RR-MS or progressive MS forms have been evaluated in three double-blind placebo-controlled Phase II trials [64–66]. These studies showed the ability of cladribine to suppress clinical and MRI activity, with a possible encouraging, although not confirmed, action on disease progression. Later, an oral formulation of cladribine was evaluated in a Phase III, placebo-controlled study, CLARITY, in which RR-MS patients were randomized to receive cumulative doses of 3.5 or 5.25 mg/kg cladribine or placebo, with treatment administered in two or four short courses for the first 48 weeks, then in two short courses starting at week 48 and week 52 [67]. For both cladribine dosages, a significant reduction of the annualized relapse rate at 96 weeks was shown (0.14 and 0.15 for patients with 3.5 and 5.25 mg/kg cladribine, respectively, compared with 0.33 for the placebo group), equivalent to relative reductions of 58 and 55%, respectively. The reduction in the annualized relapse rate occurred as early as 12–16 weeks [68] and was independent of patients' baseline demographics (e.g., sex and age) and prognostic markers (e.g., disease duration, MRI parameters, relapse history and prior disease-modifying drugs) [69]. A significantly higher proportion of cladribine recipients (3.5 or 5.25 mg/kg) compared with placebo remained relapse free at 96 weeks (80 and 79, respectively vs 61%; $p < 0.001$) [67,70].

In the cladribine arms, a significant reduction in the number of GdE T1 lesions, active T2 lesions and combined unique lesions on MRI was detected, together with a significant reduction in the risk of 3-month sustained progression of disability (hazard ratios of 0.67 and 0.69, respectively). A recent paper by Cook *et al.* summarizes safety and tolerability issues of cladribine coming from the CLARITY study [71]. Lymphopenia was the most commonly reported adverse event in patients treated with cladribine tablets during the CLARITY trial, as expected considering its mechanism of action. The incidences of infections were 48.3% with cladribine and 42.5% with placebo, with 99.1 and 99% rated mild-to-moderate by investigators. Herpes zoster infections, all dermatomal, developed in 2.3% cladribine recipients, whereas no cases occurred in the placebo group. There was one case of exacerbation of a pre-existing chronic tuberculosis infection in a 5.25 mg/kg young Tunisian female recipient, who died. This patient presented three episodes of pancytopenia due to myelodysplasia and cladribine likely contributed to the worsening of the tuberculosis infection. Three isolated cases of malignancy were reported in cladribine-treated patients during the study; a fourth was reported

during the poststudy surveillance. The incidence of malignancies did not exceed the expected rate in a population standardized for country, gender and age [67]. In animal studies, cladribine has been shown to be teratogenic and, although there is no evidence of teratogenicity in humans, the effect of this treatment during pregnancy remains to be fully established [71]. Oral cladribine (Movectro), already approved in Australia and Russia for RR-MS, received a negative opinion from the EMA in September 2010, with the main concerns that led to refusal represented by a suspected increased number of patients with cancer compared with the control group. The committee also noted that the degree of benefit and the most appropriated dosage for treatment have not been fully established. Although the clinical trials still in progress continue, new trials will not be performed and Merck-Serono has decided not to pursue any longer the global approval process for cladribine tablets [72].

Teriflunomide

As reported by Breedveld *et al.*, teriflunomide is an inhibitor of the dihydroorotate dehydrogenase [73].

Dihydroorotate dehydrogenase is the rate-limiting enzyme in *de novo* pyrimidine synthesis, because it is the only enzyme located at the outer surface of the inner mitochondrial membrane [74]. In the phases with no proliferation, lymphocytes can retrieve the pyrimidines needed for phospholipid and glycoprotein synthesis from physiologic catabolic processes. However, when proliferation starts, *de novo* synthesis of pyrimidines becomes mandatory to fuel the synthesis of new DNA.

Teriflunomide targets the proliferating fraction of lymphocytes only, in a semi-selective way, because it is a high-affinity inhibitor of the enzyme dihydroorotate dehydrogenase, crucial for pyrimidine synthesis [75], and therefore it could be useful in MS treatment using the mechanism of lymphocyte depletion. Its effectiveness and safety have been evaluated in clinical trials.

A 2-year Phase III clinical program with teriflunomide monotherapy versus placebo in patients with relapsing MS or progressive MS with relapses (the TEMSO trial, sponsored by Sanofi-Aventis) has been completed [76]. A large sample of 1088 patients with RR-MS or progressive relapsing MS received placebo, teriflunomide 7 mg/day or teriflunomide 14 mg/day for 108 weeks (randomization 1:1:1). There was a significant reduction in the annualized relapse rate with both doses (relative risk reductions in the 7 and 14 mg groups vs placebo were 31.2 [p = 0.0002] and 31.5% [p = 0.0005]). The relative risk for sustained progression was significantly reduced (by 29.8% vs placebo) for patients treated with 14 mg, but not for the others (p = 0.0279). This Phase III study also confirmed the MRI results obtained in the Phase II study [77].

In the TEMSO study, MRI scans performed at baseline and at weeks 24, 48, 72 and 108 found a significant relative risk reduction of 47.7 and 69.4% for both doses, respectively ($p < 0.001$) in the number of combined unique active lesions per scan (2.463, 1.288 and 0.754 in the placebo, 7 and 14 mg groups, respectively). The proportion of adverse events related to treatment was similar in all the three groups. Beside these two trials, other Phase II studies had the aim to evaluate teriflunomide used as an add-on therapy to either IFN-β or GA [78]. The first double-blind, placebo-controlled Phase II study randomized RR-MS patients on stable doses of IFN-β (n = 117) to receive teriflunomide 7 mg/day, teriflunomide 14 mg/day or placebo, in addition to IFN-β, for 6 months. Looking at T1 Gd MRI activity, teriflunomide, used as add-on drug to IFN-β, significantly improved disease control. Teriflunomide as adjunctive therapy to GA was evaluated in another double-blind, placebo-controlled Phase II trial with a similar 24-week duration. One hundred and twenty three GA-treated patients were randomized to placebo, teriflunomide 7 mg/day or teriflunomide 14 mg/day in addition to GA. The number of GdE T1 lesions was twice as high in the 7 mg group as compared with the placebo (glatiramer only) and 14 mg groups upon entry into the study (see the results presented at the American Academy of Neurology meeting in Toronto in 2010 [79]). Furthermore, teriflunomide added to stable dose of GA significantly reduced the number or the volume of GdE T1 lesions in the brain as compared with GA alone (in 7 mg and 14 mg group, respectively). In addition to the TEMSO study, two further Phase III studies, TOWER and TENERE, are ongoing to investigate the efficacy and safety of teriflunomide 7 mg/day and 14 mg/day versus placebo (TOWER) or IFN-β-1a 44 µg three-times per week (TENERE) in patients with relapsing MS. The aim of the TENERE study is to make a head-to-head comparison over 1 year

of treatment with 'time to failure' as the primary end point, defined as the first occurrence of relapse or permanent study treatment discontinuation for any cause, whichever comes first. This study is still active, not recruiting.

TOPIC is another international, randomized, double-blind, placebo-controlled Phase III study evaluating the efficacy and safety of a 2-year treatment with teriflunomide 7 mg/day and 14 mg/day versus placebo in approximately 780 patients with a first clinical MS relapse (clinical isolated syndrome). The primary outcome is the reduction of time to conversion to MS and this study is expected to be completed in 2015.

Future perspective

From data presented in this review, some main considerations emerge that should be taken into account in the starting new era of oral drug administration in MS.

Since the use of injectable relapse-modifying therapies for MS is well established, the development of oral therapies needs to be placed in the context of a number of ongoing patient management issues. For instance, it is well known that the current medical aim of therapy is to prevent relapses, with the ultimate intention of preventing progressive neurological deterioration, which may or may not occur in the future. This means that therapies may have no beneficial effects to the subject other than a future 'lack of event' and they need to be used for a long time, also in essentially asymptomatic subjects, often with problems in adherence.

So, it is undoubted that oral therapies, which are taken by an easier route, will help patients in long-term adherence, giving the opportunity to avoid injection-related discomfort and offering the important potential to optimize therapeutic outcomes. Moreover, the level of control of disease activity has been shown to be similar or higher compared with the current parenteral immunomodulators. However, whether they can be considered as safe as these previous treatments is not fully established. Therefore, as the disease-modifying drug landscape is becoming more complex due to the conceivable future options of several oral drugs with different mechanisms of action and safety profile, which of them should be chosen, when to start the treatment and which safety investigations should be planned will be a matter of discussion. Current data support the gradual introduction of oral drugs as an option for patients with RR-MS who decline or fail to adequately respond to injectable treatments. Appropriate programs for monitoring adverse events are warranted and the challenge of rational MS treatment will be to stratify patients and identify those suitable for a specific treatment in view of the risk:benefit ratio for any individual compound. A risk:benefit assessment will have to be made, particularly for those agents that have cytostatic or even cytotoxic potential and the main reason is that therapies impairing immune system function can put the user at risk of infections. There is minimal risk of infections with IFN-β and GA. The original reports found no increased risk of infections with natalizumab use, but the emergence of PML and other opportunistic infections in the postmarketing phase has demonstrated that there is impaired immunity in drug recipients and has suggested a rigorous long-term follow-up. Thinking about concerns related to long-term use of natalizumab, some compounds are under development and have been signaled in this review, such as anti-integrin firategrast.

One randomized Phase II trial with this small molecule, an anti-α4β integrin with a shorter half-life than natalizumab, has shown its potential to reduce the number of active MRI lesions in RR-MS without significant adverse events, including PML. Although these are only preliminary data, they may deserve further investigation on firategrast and may encourage the development of other future oral options and safe alternatives to natalizumab.

Among the oral drugs described in this review, fingolimod shows a unique mechanism of action coupled with nonsignificantly impaired immunologic function and a low level of infections, except for two disseminated herpes infections observed. S1P receptor modulation by fingolimod in both the immune system and CNS, producing a combination of beneficial anti-inflammatory and possibly neuroprotective/reparative effects, may contribute to its efficacy in MS. The interaction of fingolimod with S1P receptors in a variety of tissues accounts for many of its off-target adverse events; however, in clinical trials, fingolimod was generally safe and well tolerated, especially for the approved 0.5-mg dose. Anyway, caution is needed regarding the risk of bradycardia, as the possibility for cardiac rate abnormalities to develop at more than 6 h after the first administration is not completely excluded.

These considerations should be kept in mind in the selection of patients, avoiding use of class I β-blockers and assessing cardiac risk, especially in case of concomitant use of antipsychotic or antidepressant drugs. As there are no currently available treatments for MS demonstrated to limit damage directly or improve repair, there is a major unmet medical need in this regard, particularly for purely progressive forms of MS. Further studies are needed to determine whether fingolimod meets this need and may be suitable for all subtypes of MS.

Both teriflunomide and cladribine are immunosuppressive since they inhibit exaggerated proliferation of lymphocytes. However, it appears that cladribine has a higher cytotoxic potential than teriflunomide because toxic cladribine metabolites accumulate in lymphocytes and induce apoptosis. Indeed, teriflunomide does not induce lymphopenia.

Cladribine, which induces lymphopenia, increased the risk of infections overall and of herpetic infections in particular. These issues are a concern as the schemes of administration do not require subjects to automatically attend clinical follow-up frequently and thus infections could become more serious if not managed proactively.

In other words, it is difficult to antagonize cladribine in case something goes wrong, while teriflunomide can be eliminated from the body relatively easily.

At present, teriflunomide is the only one of the previously discussed oral drugs that has been tested in combination with IFN-β and with GA, showing a relatively good risk:benefit profile.

Another critical issue is that, even though several oral products are currently in development, most of them still act with predominant anti-inflammatory properties and there is a lack of therapies for neuroprotection or promising agents for progressive disease.

The possibility that BG-12 and laquinimod are neuroprotective through their proposed mode of action is of particular interest because several lines of evidence have indicated that oxidative stress contributes to the pathological changes of MS. Longer-term (Phase III) studies of BG-12 in larger patient populations are underway to define its place in the future of RR-MS treatment. If these studies show similar relapse rate reductions with BG-12, IFN-β and GA, BG-12 could be a suitable initial treatment for RR-MS. Because of the convenience of an orally administered product, BG-12 could also be an alternative for patients who cannot tolerate or choose not to initiate injectable therapies because of injection-related effects or anxiety. The potentially unique mode of action of BG-12 could also be valuable as a monotherapy or combination therapy.

To summarize, the level of efficacy and method of administration make oral drugs a strong new entry into the MS-modifying therapy scenario. Further data are required on their long-term safety profile, including risk of infections and malignancy and, last but not least, on their influence on pregnancy, in order to establish their placement in the correct therapeutic window and in relation to the existing treatments. Current data support their gradual introduction as an option for patients with RR-MS who decline, opt out of or fail to adequately respond to injectable treatments. Appropriate programs for monitoring adverse events are warranted.

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