

# Recent Advances in the Management of Multiple Sclerosis

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## ABSTRACT

Over the last few decades, there have been significant advances in the diagnosis and management of multiple sclerosis (MS), and treatment options for MS have broadened dramatically. The advent of disease-modifying therapies (DMTs) has changed the clinical and social burden of this disease. First-line therapies, e.g., interferon beta (IFNB) and glatiramer acetate (GA), are safe, but only partially effective, and in several cases, they are poorly tolerated by patients. Pharmacological and non-pharmacological interventions, such as nursing support, auto-injector devices, and patient education programs, may enhance adherence to injected drugs. Comparison studies have demonstrated a substantial equivalence of efficacy between IFNB and GA. Monitoring patient response to first-line therapies and improving their tolerability represent the primary objectives in the management of treated patients. Second-line therapies, such as natalizumab or mitoxantrone, are indicated for those patients with breakthrough disease despite first-line treatment, or with a rapidly evolving course of MS. Safety concerns of second-line drugs and the lack of long-term safety data require accurate patient selection and monitoring during treatment. Oral treatments and other monoclonal antibodies will be available in the next few years to improve our armamentarium for the treatment of MS. The present review provides a description of the latest advances in the available therapy for the management of MS and describes the state of promising therapies currently under study.

**Keywords:** multiple sclerosis, interferon beta, glatiramer acetate, natalizumab, mitoxantrone, oral drugs, monoclonal antibodies

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## INTRODUCTION

Multiple sclerosis (MS) is a lifelong demyelinating disease that typically affects young adults, usually presenting between the ages of 15 and 50 years, with a female predominance at ratios of a 2–3:1 over men. It is widely believed to be an autoimmune disorder triggered by some environmental factors in genetically predisposed subjects.

In the past, symptomatic treatment was the mainstay of therapy for patients with MS. Improved diagnostic criteria and the availability of effective therapy in the last decade have emphasized the importance of early diagnosis and treatment. Six disease-modifying therapies (DMTs) have been approved for the treatment of patients with MS: three formulations of interferon beta (IFNB), including subcutaneous 250 µg of IFNB-1b every other day (Betaseron, Bayer, USA; Betaferon Schering, UK), intramuscular 30 µg of IFNB-1a once weekly (Avonex, Biogen, UK), and subcutaneous 44 µg of IFNB-1a 22 three times a week (Rebif, Serono, UK); subcutaneous 20 mg of glatiramer acetate (GA) once a day (Copaxone, Teva, UK); the immunosuppressive agent mitoxantrone (Novantrone, Wyeth, UK); and the monoclonal antibody natalizumab (Tysabri, Biogen, USA).

## LONG-TERM EXPERIENCE WITH IMMUNOMODULATORY THERAPIES

Four multicenter, phase III, randomized clinical trials (RCTs) consistently demonstrated that IFNB and GA reduce

the relapse rate and slow the progression of disability in patients with relapsing MS [1–4]. The development of new demyelinating lesions, as seen on magnetic resonance imaging (MRI), also decreased [5–8]. Evidence of persisting clinical and MRI efficacy over time was confirmed by extension phases of original RCTs, as well as by post-marketing surveys [9–14].

The long-term data from the extension phases of the phase III RCTs, performed using IFNB formulations and GA, are

**Table 1.** Long-term Data on Immunomodulatory Treatment

| Treatment                        | Length of double-blind phases | Length of follow-up (years) | Patients lost at long-term follow-up (%) |
|----------------------------------|-------------------------------|-----------------------------|--|
| IFNB-1b 250 µg sc, eod [9]       | 5 years                       | 16                          | 12                                       |
| GA 20 mg, sc, od [10]            | 30 months                     | 10                          | 27                                       |
| IFNB-1a 22 or 44 µg sc, tiw [11] | 2 years                       | 8                           | 32                                       |
| IFNB-1a 30 µg, im, ow [12]       | 2 years                       | 8                           | 43                                       |

IFNB, interferon beta; GA, glatiramer acetate; sc, subcutaneous; im, intramuscular; eod, every other day; od, once daily; tiw, three times a week; ow, once weekly.

shown in **Table 1**. To date, the 16-year long-term follow-up of an original North American IFNB-1b pivotal trial represents the longest follow-up evaluation of any MS therapy [9]. Patients remaining on long-term IFNB-1b treatment had a slower progression of disability than those having received treatment only for a short period. The finding that IFNB is effective in slowing the progression of disability has been also confirmed by two 8-year follow-up studies of patients originally enrolled in the phase III trials of intramuscular IFNB-1a and subcutaneous IFNB-1a [10, 11].

Data from the open-label extension study on the original cohort of the phase III trial of GA showed that the mean Expanded Disability Status Score (EDSS) in ongoing treatment patients was significantly lower than that in patients withdrawing from the study [12].

### Treatment in the early stage of the disease

In 85% of young adults who develop MS, onset is an acute, clinically isolated syndrome (CIS) of the optic nerves, brainstem, or spinal cord [15]. It is known that axonal damage and brain atrophy occur even in CIS patients, the appearance of these conditions being linked to inflammation [16–18]. Available data from RCTs indicate that DMTs are most effective when started early [19].

Therefore, early treatment is warranted for patients with CIS that is suggestive of MS. A beneficial effect of treatment was noted in all subgroups based on gender, age, clinical presentation (monofocal or multifocal), presenting syndrome, previous treatment with steroids, and baseline brain MRI parameters [20–22]. The main data on clinical trials performed on a CIS population are shown in **Table 2**. IFNB therapy can reduce the risk of converting to clinically definite MS by 30–50% [21, 23, 24]. GA showed a 45% risk reduction of developing definite MS in comparison to placebo [25]. Results from a 5-year, open-label extension of the original study on intramuscular IFNB-1a in a CIS population also showed that the cumulative probability of the development of clinically definite MS was significantly lower in the group initially randomized in the active arm [26].

A positive effect on later disability levels has been reported by the 5-year follow-up study of subcutaneous IFNB-1b [27].

**Table 3.** Head-to-head Studies Comparing Immunomodulatory Treatments

| Study         | Treatments   | Duration of study | No. Of patients | Primary outcome   |
|---------------|--|-------------------|-----------------|---|
| EVIDENCE [28] | IFNB-1a 44 µg, sc, tiw vs. IFNB-1a 30 µg, im, ow                         | 6 months          | 677             | Proportion of relapse-free patients                         |
| INCOMIN [29]  | IFNB-1b 250 µg, sc, eod vs. IFNB-1a 30 µg, im, ow                        | 2 years           | 188             | Proportion of relapse-free patients                         |
| REGARD [30]   | IFNB-1a 44 µg, sc, tiw vs. GA 20 mg, sc, od                              | 2 years           | 764             | Time to first relapse                                       |
| BEYOND [31]   | IFNB-1b 500 µg, sc, eod vs. IFNB-1b 250 µg, sc, eod vs. GA 20 mg, sc, od | 2 years           | 2244            | Hazard ratio for multiple relapses                          |
| BECOME [32]   | IFNB-1b 250 µg, sc, eod vs. GA 20 mg, sc, od                             | 2 years           | 75              | Mean number of combined active lesions per scan per patient |

IFNB, interferon beta; GA, glatiramer acetate; sc, subcutaneous; im, intramuscular; eod, every other day; od, once daily; tiw, three times a week; ow, once weekly.

**Table 2.** Overview on Clinical Trials with Immunomodulatory Agents Performed on CIS Patients

| Study        | Treatment               | Duration of double-blind phases (years) | Percentage of conversion to definite MS |
|--------------|-------------------------|---|---|
| CHAMPS [23]  | IFNB-1a 30 µg, im, ow   | 2–3 <sup>a</sup>                        | Active 35                               |
|              |                         |   | Placebo 50                              |
| ETOMS [24]   | IFNB-1a 22 µg, sc, ow   | 2                                       | Active 34                               |
|              |                         |   | Placebo 45                              |
| BENEFIT [21] | IFNB-1b 250 µg, sc, eod | 2                                       | Active 28                               |
|              |                         |   | Placebo 45                              |
| PRECISE [25] | GA 20 mg, sc, od        | 3                                       | Active 25                               |
|              |                         |   | Placebo 43                              |

<sup>a</sup>The trial was stopped after a preplanned interim efficacy analysis. IFNB, interferon beta; GA, glatiramer acetate; sc, subcutaneous; im, intramuscular; eod, every other day; od, once daily; tiw, three times a week; ow, once weekly.

Early treatment reduced the risk for progression of disability by 40% in comparison to delayed treatment.

### Head-to-head studies on immunomodulatory therapies

After the introduction of DMTs in the daily clinical setting, there has been much debate about the relative efficacy of different formulations of IFNB and GA. The principal findings from the head-to-head studies performed to date are reported in **Table 3**.

Two clinical trials have directly compared the efficacy and tolerability of different IFNB formulations: the EVIDENCE and the INCOMIN studies [28, 29]. Both of these studies showed that high-dose and frequent administration of subcutaneous IFNB was more effective than intramuscular IFNB-1a once weekly.

More recently, three head-to-head comparison studies have compared the efficacy of GA to that of two different formulations of IFNB: the REGARD trial [30], which compared GA vs. subcutaneous IFNB-1a thrice weekly, and the BEYOND [31] and the BECOME [32] trials, which compared GA to subcutaneous IFNB-1b every other day. The conclusion from these head-to-head-studies showed that the

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efficacy of GA is comparable to that of IFNB on some clinical and MRI outcomes. Nevertheless, the suggestion that the control of the blood–brain barrier by GA might be delayed with respect to IFNB [33] seems to be confirmed by these comparative studies.

The major strength of these recent studies (REGARD and BEYOND) was the very large sample size, which was greater than the overall population enrolled in the pivotal trials [30, 31]. On the other hand, there is also a major concern: the low number of relapses observed during the two trials may have compromised the power for detecting some between-group differences. At the time of enrollment, patients in the head-to-head studies had much lower disease activities than those enrolled in the pivotal trials. These data indicate that the population actually eligible for enrollment into MS clinical trials is quite different from the populations used in RCTs over a decade ago.

Finally, as it has been demonstrated that the efficacy of GA is comparable to that of IFNB, switching between immunomodulatory treatments may represent an interesting approach in case of treatment failure or intolerability [34, 35]. The scientific rationale for switching to other monotherapies is strongest for patients treated with IFNB with persistently high titers of anti-IFNB antibodies [36].

### Response to immunomodulatory therapies

Great variability is present in terms of disease activity among patients during treatment with IFNB. A relevant number of subjects treated with IFNB or GA continue to experience clinical bouts and disease progression. An early identification of patients with poor responses to immunomodulators and a prompt switch to another DMT is warranted to avoid the accumulation of fixed disability over time. Nevertheless, there are some difficulties in detecting these patients, primarily because a clear and shared clinical definition for the lack of response does not exist [37, 38]. MRI changes during IFNB therapy could be useful in identifying patients who respond to treatment. Recent studies suggest that MRI parameters considered during treatment (i.e., the presence of gadolinium-enhanced lesions or the accumulation of new hyperintense lesions in T2-weighted sequences) might be useful in defining the patient response status to IFNB [39–42]. These data support the routine use of MRI in monitoring subclinical disease activity during treatment, even in the absence of a clinical worsening.

### Improved tolerability with injectable immunomodulatory therapies

Patient compliance is an important issue for any long-term treatment. Several studies demonstrated that every third MS patient discontinued IFNB treatment within 3–5 years and that 10–20% of discontinuation occurred within the first 3–6 months [43–46]. To maintain adherence to injective DMTs, it is necessary increase their tolerability as much as possible.

IFNB treatment is generally well-tolerated long term; side-effects, such as flu-like symptoms, injection-site reactions,

headache, and fatigue, are more frequent during the first months of treatment and gradually subside; however, in some patients, these side-effects persist or are intolerable, leading to discontinuation of IFNB by treated patients [43].

Approaches aimed at reducing the proportion of subjects discontinuing IFNB encompass both pharmacological and non-pharmacological interventions. The clinical relevance of IFNB-related systemic side-effects can be minimized by dose escalation and concomitant symptomatic therapy.

As IFNB-related side-effects are dose–response related [1], treatment may be started at 25% of the recommended dose and increased by 25% increments weekly to every other week; the titration may be prolonged for those patients experiencing more severe side-effects [47]. Using paracetamol or other non-steroidal anti-inflammatory drugs prior to or following injection may reduce the incidence of flu-like symptoms. It has been demonstrated that gradual dose escalation associated with ibuprofen treatment diminished flu-like symptoms to rates comparable with the placebo group in the pivotal trial [48]. Oral prednisone (10–20 mg/day) has been reported as helpful in some refractory cases: one study performed on 71 relapsing–remitting (RR)-MS patients starting IFNB-1b treatment showed that systemic side-effects were minimal in subjects receiving low doses of steroids compared to those receiving only paracetamol [49].

Preinjection use of topical anesthetics (such as lidocaine) or steroids (1% hydrocortisone) may reduce the severity of site reactions and injection-related pain [47]. Presently, the wider availability of autoinjector devices with smaller needles may reduce injection-related trauma and pain and local skin reactions, improving treatment compliance [50]. In addition, it has been reported that patients using self-injected intramuscular IFNB-1a experienced less fear when using the smaller needle [51].

Non-pharmacological interventions, including correct information about treatments and their effects, patient involvement in decisions about treatment, and effective support when problems occurred, are essential to enhancing adherence to therapy. Recently, it has been reported that MS support programs may help patients in ameliorating their coping with and adherence to treatment. One multicenter, prospective, observational study performed on 1095 patients receiving IFNB-1b treatment showed that the availability of some services, such as assistance from specialist nurses, the MS-Gateway website, and the availability of autoinjector devices, may improve the quality of life over a 12-month timeframe [52]. The 1-year interim results of the study showed that the majority of patients used more than one support element, but the use of the specialist nurse program was more appreciated by patients than other services, suggesting an important contribution of patient education to adherence.

Tolerability and adverse events were similar between different formulations of IFNB [28, 29]. Head-to-head studies (IFNB vs. GA) reported that patients treated with IFNB were more likely to experience flu-like symptoms and liver enzyme

elevation; in contrast, injection-site reaction occurred more frequently with GA, as well as systemic reactions, such as dyspnea, chest pain, or tightness [30–32, 53]. In the recently published data from the BEYOND study, lipotrophy occurred only in patients treated with GA [53].

## IMMUNOSUPPRESSANT AGENTS

There is convincing pathological and MRI evidence suggesting that an inflammatory process is responsible for neurodegeneration and disease progression [18, 54]. Therefore, immunosuppressive therapy may have an important role in MS, especially in patients with a rapidly worsening course or in those who do not respond to first-line treatment. Immunosuppression may also be useful even in the early phase of the disease, when it may avoid the process of epitope spreading and may prevent early structural damage [55–57]. The induction strategy involves the initial use of an immunosuppressive agent for a short period of time, followed by maintenance treatment with a first-line therapy [58].

The only approved immunosuppressant agent, mitoxantrone (MTX), is an anthracycline antineoplastic that intercalates with DNA causing single- and double-strand breaks. It also impairs DNA repair via inhibition of topoisomerase II. The rationale of its use in MS is that MTX induces a rapid immunosuppression on proliferating cells, especially B and T lymphocytes, and selectively decreases the secretion of some pro-inflammatory cytokines. Results from clinical trials have demonstrated the beneficial effect of MTX in patients with either RR or secondary progressive MS while in the inflammatory phase [59–61]. MTX treatment reduces relapse rate and MRI activity, and slows down disease progression when used at a dose of 8–12 mg/m<sup>2</sup> for 6–12 months and 12 mg/m<sup>2</sup> every 3 months for up to 24 months [59–61]. A delayed beneficial effect even after MTX treatment discontinuation has recently been suggested, showing that only a small number (14%) of patients had disability progression once the drug was suspended [62].

Despite its efficacy, the toxicity of MTX limits more widespread use in MS [63]. Nausea, vomiting, recurrent infection, and gonadal dysfunction are relevant adverse effects. An increased risk of cardiac toxicity has been reported to be associated with MTX exposure at the highest cumulative dose of <140 mg/m<sup>2</sup>. A higher incidence of therapy-related acute leukemia than previously estimated has been recently reported in patients receiving MTX as a single-agent therapy [64, 65].

Cyclophosphamide (CYC), an alkylating agent related to nitrogen mustards, strongly suppresses both cell-mediated and humoral immunity through its effects on T and B lymphocytes. It is commonly used to treat several autoimmune disorders, including immune-mediated neuropathies. Although off label, CYC is also used to treat rapidly deteriorating MS [66, 67]. As for MTX, given the limited tolerability; given the limited tolerability and potentially

severe side-effects of CYC, identification of patients with a favorable benefit/risk profile is essential.

## MONOCLONAL ANTIBODIES

Monoclonal antibodies (mAbs) allow precise targeting of molecules involved in the immunopathogenesis of MS [68]. Only one monoclonal antibody is approved for the treatment of MS, although three mAbs have already passed phase II trials and many more are in preclinical development.

Natalizumab, a humanized monoclonal antibody that binds the alpha4–beta1 integrins, is the first mAb approved as a monotherapy for the treatment of relapsing MS [69]. Actually, it is indicated as a second-line treatment for patients who have breakthrough disease despite treatment with IFNB and GA, or for treatment-naïve patients with rapidly evolving severe MS [70]. Stringent recommendations for appropriate patient selection are warranted for safety reasons, given some cases of progressive multifocal leukoencephalopathy, an opportunistic demyelinating infection caused by the human polyomavirus JC virus [71].

The AFFIRM [69] study demonstrated that the efficacy of natalizumab was very high, with a 68% reduction in relapse rate and a 54% reduction in the risk of sustained disability progression over 2 years. There was also a decrease of 92% for gadolinium-enhanced lesions, in addition to a reduction of 83% for new or enlarging T2-hyperintense lesions. Recently, a retrospective analysis of the AFFIRM study confirmed the effectiveness of natalizumab, showing that, over a 2-year period, 37% of patients on natalizumab were free of combined (i.e., clinical and radiological) disease activity, against only 7% of patients on placebo [72].

Other mAbs are currently under study [68]. Alemtuzumab is a humanized anti-CD52 antibody able to induce leukopenia via complement-dependent and antibody-mediated cytotoxicity, as well as via apoptosis. Encouraging results of a comparative trial of alemtuzumab vs. IFNB-1a in relapsing MS patients were reported in terms of reductions in relapse rate and MRI activity [73]. Daclizumab is a humanized mAb that blocks the interleukin 2  $\alpha$ -chains (CD25) on activated T lymphocytes, preventing the release of pro-inflammatory cytokines that lead to an amplification of lymphocyte proliferation. A strong inhibition of new gadolinium-enhanced lesions and an improvement in clinical disability were recently observed in a phase II clinical trial in MS patients with inadequate response to IFNB [74]. Rituximab is a chimeric mouse–human antibody that targets CD20, an antigen expressed by cells of the B-cell lineage. It depletes B cells from peripheral blood and decreases the number of B cells in cerebrospinal fluid. A phase II trial showed a marked reduction in new enhancing lesions and in clinical relapses after two infusions separated by an interval of 2 weeks, with a sustained efficacy for 48 weeks [75].

## EMERGING ORAL DRUGS

All therapies currently available for MS are parenterally administered; thus, the search for alternative oral treatments

**Table 4.** Ongoing Phase III Trials on Oral Agents as Monotherapy in Relapsing-Remitting MS Patients

| Study              | Treatments                                    | Duration of double-blind phases (years) | Main efficacy outcome                   |
|--------------------|---|---|---|
| CLARITY            | Cladribine 1.75 or 3.5 mg/kg/year vs. placebo | 2                                       | Reduction in annualized relapse rate    |
| FREEDOMS           | Fingolimod 1.25 or 0.5 mg/day vs. placebo     | 2                                       | Reduction in annualized relapse rate    |
| DEFINE             | BG00012 480 or 720 mg/day vs. placebo         | 2                                       | Proportion of relapsing subjects        |
| TEMSo <sup>a</sup> | Teriflunomide 7 or 14 mg/day vs. placebo      | 2                                       | Disability progression assessed by EDSS |
| ALLEGRO            | Laquinimod 0.6 mg/day vs. placebo             | 2                                       | Number of confirmed relapses            |

<sup>a</sup>TOWER study duplicates TEMSO trial, but without MRI.  
EDSS, Expanded Disability Status Score.

is warranted. The safety profile represents the most important factor in the future use of these oral drugs. Five oral treatments are already in phase III development; a panel of currently ongoing trials on oral drugs is provided in **Table 4** [76]. Moreover, the potential combinations of oral drugs with IFNB or GA are being tested in some current trials.

Cladribine is a chlorinated purine analogue that impairs the cellular metabolism of lymphocytes and monocytes, with preferential depletion of CD4 cells. Preliminary 2-year results from the CLARITY study, a randomized, double-blind, placebo-controlled, phase III trial performed on relapsing MS patients, have recently been presented at the 25th AnnualECTRIMS meeting [77]. Oral cladribine showed a significant reduction of 58% in the annualized relapse rate for the low-dose group and a reduction of 55% for the high-dose group with respect to placebo. The percentages of patients that were relapse-free over the 2-year study period were as follows: 80% with the low-dose regimen, 79% with the high-dose regimen, and 61% in the placebo group. Patients treated with oral cladribine also showed more than a 30% reduction in the risk of disability progression over the 2-year study period and a reduction of at least 70% in the mean number of gadolinium-enhanced lesions for both dose regimens of active drug [77].

The most common side-effects reported were headache, nasopharyngitis, upper respiratory tract infections, nausea, and lymphopenia. Four cases of malignancies were also reported (melanoma, pancreatic cancer, ovary cancer, and uterine cervical carcinoma) [78].

Fingolimod is a structural analogue of sphingosine with a very innovative mechanism of action: it downmodulates sphingosine 1-phosphate receptors on lymphocytes, inhibiting recirculation of pro-inflammatory T cells, and in neural cells/astrocytes, and reduces astrogliosis and neurodegeneration. A 6-month, placebo-controlled, phase II study consisting of 281 patients with relapsing MS showed that oral fingolimod at doses of 1.25 and 5 mg significantly reduced inflammatory disease activity as measured by MRI (up to 80%) and clinical relapses (more than 50%) [79]. In the 2-year extension phase of this study, patients previously treated with oral fingolimod continued their originally assigned treatment; those on placebo were re-randomized to fingolimod with dosages of 1.25 or 5 mg [80]. More than 80% of patients remained gadolinium-enhanced lesion free: 81% and 87% (low- and high-dose arms, respectively) in the con-

tinuously-treated group, and 79% and 91% in the switched group (low- and high-dose arms, respectively). Out of patients on continuous 1.25 and 5 mg fingolimod treatments, 75% and 77% were relapse free at month 24, respectively. Common side-effects included dose-dependent transient arrhythmias, increased mean arterial blood pressure, nasopharyngitis, dyspnea, headache, diarrhea, nausea, and clinically asymptomatic elevations of alanine aminotransferase levels. Three cases of skin cancer were also reported at the 24-month follow-up period.

Dimethyl fumarate, also known as BG00012, is an oral derivative of fumaric acid, a chemical intermediate in the tricarboxylic acid cycle for organic acid biosynthesis (i.e., the Krebs cycle). The exact mechanism of action is still unclear; however, it seems to be attributable to the induction of an immune deviation, with the skewing of Th1 into a Th2 cytokine pattern. Furthermore, it seems to be able to activate the Nrf2 pathway in cellular defense against toxic, metabolic, and inflammatory damage.

A randomized, double-blind, placebo-controlled, phase II study showed that treatment with oral fumarate at a dose regimen of 240 mg three times daily reduced the mean total number of gadolinium-enhanced lesions by 69% from week 12 to week 24 in comparison to placebo [81]. It also reduced the number of new or enlarged T2-hyperintense and new T1-hypointense lesions when compared to placebo. The most common side-effects were hot flushing and abdominal pain.

Teriflunomide is a de novo pyrimidine synthesis inhibitor with antiproliferative activity on lymphocytes. A placebo-controlled, phase II trial demonstrated a 61% reduction in comparison to placebo in the cumulative mean number of combined unique active lesions [82]. The duration of two dose regimen treatments (7 mg and 14 mg daily, respectively) was 36 weeks. Common side-effects of oral teriflunomide included liver enzyme increase, nasopharyngitis, paresthesia, alopecia, back pain, diarrhea, and arthralgia.

Laquinimod is a new quinoiline-3-carboxamide derivative that has shown an improved safety profile in comparison to its predecessor compound, linomide. Indeed, a phase III clinical trial was interrupted because of severe adverse events (myocardial infarction, pericarditis) [83]. It is still unknown how laquinimod interferes with disease pathophysiology; however, it may induce the Th1–Th2 shift.

A 36-week, placebo-controlled, phase II trial showed a reduction of 40.4% in the mean cumulative number of gadolinium-enhanced lesions in patients treated with the higher dose (0.6 mg/day), whereas no significant effects using the lower dose (0.3 mg/day) were observed [84]. The incidence of adverse events was similar in the three groups (placebo, lower, and higher doses). Both doses of oral laquinimod were well tolerated, with some transient and dose-dependent increases in liver enzymes.

## CONCLUSIONS

There is a growing availability of drugs that are active against MS, with comparable or greater efficacy than the current standard agents. The possibility of switching between DMTs, the algorithm of their administration (i.e., escalation, induction), and the time of using new agents present challenges for neurologists. Sequential or combination treatments may lead to a synergistic effect, improving the benefit/risk ratio. In this regard, monoclonal antibodies and new oral agents seem to be novel promising therapeutic options. Positive advances in MS treatment should finally be provided by new agents specifically designed to target immunopathological dysfunctions at different MS stages.

**Funding:** Dr. Pozzilli has received honoraria for consultancy or speaking from Sanofi Aventis, Biogen, Bayer Schering, and Novartis, in addition to research grants from Sanofi Aventis and Merck Serono.

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