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REVIEW

Managing MS in a changing treatment landscape

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Abstract Increasing options are dictating the development of new algorithms to provide guidance in the treatment of people with multiple sclerosis (MS). There is a wealth of evidence on the safety and efficacy of interferon-beta and glatiramer acetate, which have been used in Europe and in the United States for more than 10 years. The spectrum of approved indications for these conventional disease modifying therapies includes the treatment of relapsing-remitting MS, secondary progressive MS, and the clinically isolated syndrome. Beyond these therapies we already have the recently introduced antibody natalizumab and, in some countries, the immunosuppressive agent mitoxantrone. Oral therapies are expected in the near future, with the sphingosin-1-phosphate receptor modulator fingolimod approved in the US and the EU and the purine nucleoside analogue cladribine in Australia and Russia. The evidence on all of these conventional and novel therapeutics is reviewed in this paper to provide an overview of the changing landscape of MS treatment.

Keywords Multiple sclerosis · Interferon-beta · Glatiramer acetate · Mitoxantrone · Natalizumab · Fingolimod · Cladribine

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Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS), often with progression of disability over time. The majority of patients with MS begin with relapsing-remitting MS (RRMS), a disease course characterized by unpredictable clinical relapses and remissions. This is often followed by disability progression outside of relapses, defined as secondary progressive MS (SPMS). Most patients who eventually develop RRMS will initially have presented with a single demyelinating event, a clinically isolated syndrome (CIS). However, MS is not always suspected at the time of the attack, and not all patients with CIS will develop RRMS. A minority ($\sim$15%) of patients begin with primary progressive MS (PPMS) with disease progression from onset, or progressive relapsing MS (PRMS), characterised by disease progression from onset but with superimposed acute relapses, with or without recovery [1].

The pathophysiology of MS, though not fully understood, includes early inflammatory cell infiltration of the CNS affecting primarily the white matter [2]. Axonal

damage, resulting in permanent clinical disability, starts from the earliest stages of the disease [3, 4]. Parameters including magnetic resonance imaging (MRI) data and the number of attacks in the first two years partly predict long term outcome in MS patients [5–9]. This provides a rationale for early intervention with disease modifying therapies (DMTs), aiming to reduce relapses and resulting residual disabilities and to prevent or delay the onset of progressive disability. Making use of the advances in MRI techniques, the modified McDonald criteria now enable earlier diagnosis of MS [10, 11], thus facilitating early treatment. The evidence on conventional DMTs and immunosuppressive agents that have been used in the US and Europe for many years and also on selected, recently approved or past phase III novel therapeutics will be reviewed in this paper to provide an overview of the changing landscape of MS treatment.

Conventional DMTs with broad experience

Interferon-beta and glatiramer acetate

Interferons are naturally occurring immunomodulatory cytokines, among which interferon-beta (IFN-β) shows a range of anti-inflammatory activities. The relevant mechanisms for the effects of IFN-β in MS are believed to involve inhibition of T-cell activation and proliferation, apoptosis of autoreactive T-cells, induction of regulatory T-cells, inhibition of leukocyte migration across the blood–brain barrier, and modulation of cytokine production toward a more anti-inflammatory profile [12]. In 1993 IFN-β 1b (Betaseron® in the US, Betaferon® in Europe) was the first DMT to be approved for the treatment of RRMS, and additional IFN-β preparations have since become available for clinical use: IFN-β 1a for intramuscular (im) or subcutaneous (sc) use (Avonex® and Rebif®, respectively), and IFN-β 1b as Extavia® (also sc). Glatiramer acetate (GA, Copaxone®) is a random polymer of glutamic acid, lysine, alanine, and tyrosine. In the context of MS, a number of potential immunological mechanisms have been discussed for GA, including the generation of suppressor cells, induction of tolerance, expansion of regulatory T-cell populations, alterations of antigen presenting cells [13], and neuroprotective autoimmunity [14].

A 2-year multicenter study evaluating two dosages of IFN-β 1b was the first randomized, double-blind, placebo-controlled trial demonstrating clinical efficacy of a DMT in the treatment of RRMS. Compared to placebo, 250 µg IFN-β 1b sc every other day significantly reduced the clinical relapse rate by 34%, the median number of T2 active lesions by 83%, and the median volume of MRI T2 disease burden by 17.3% [15–17]. The results of this and the other pivotal clinical trials with IFN-β and GA in RRMS and SPMS, summarized in Table 1, have previously been evaluated for the development of clinical practice

Table 1 Results of pivotal randomized, double-blind, placebo-controlled trials with IFN-β 1b, IFN- β 1a and GA in RRMS and SPMS (modified from [18])

Condition	Study	Active agent	Dosage	Patients	Percentage reduction compared to placebo				Reference
					Clinical attack rate	MRI attack rate	EDSS progression	MRI T2 BOD	
RRMS		IFN-β 1b sc	250 µg EOD[a]	372	*34**	83*	ns	17.3*	[15, 16]
RRMS		IFN-β 1a im	30 µg/wk	301[b]	18[†]	33[†]	*37*[†]	ns	[22]
RRMS	PRISMS	IFN-β 1a sc	44 µg 3x/wk[a]	560	*32**	78*	30[†]	14.7*	[23, 24]
RRMS		GA sc	20 mg/d	251	*29**		ns		[25]
RRMS		GA sc	20 mg/d[c]	249	33[†]	*35**	ns	8.3*	[26]
SPMS	EU SPMS	IFN-β 1b sc	250 µg EOD	718	31*	78*	*22**	13*	[20]
SPMS	NA SPMS	IFN-β 1b sc	250 µg EOD	939	43*	66*	*ns*	10.5*	[21]
SPMS	IMPACT	IFN-β 1a im	60 µg/wk	436	33*	45.6*	*ns*	(na)	[27]
SPMS	SPECTRIMS	IFN-β 1a sc	44 µg 3x/wk[a]	618	31*	(na)	*ns*	11.3*	[28, 29]

PRISMS Prevention of relapses and disability by interferon beta-1a subcutaneously in multiple sclerosis, *IMPACT* International Multiple Sclerosis Secondary Progressive Avonex Clinical Trial, *SPECTRIMS* Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-beta-1a in MS, *BOD* burden of disease, *EOD* every other day, *wk* week, *d* day, *ns* not significantly improved, *na* not available in this form

Primary endpoints in italic font

* Significantly improved ($p < 0.01$), [†] marginally improved ($0.01 < p < 0.05$)

[a] Study included an additional treatment arm with lower dosage, data not shown

[b] Only 172 patients completed 2 years on medication

[c] 9 months treatment duration

guidelines [18, 19]. Across the trials in RRMS patients, IFN-β and GA demonstrated a reduction of the clinical and the MRI attack rates with less consistently demonstrable benefit on measures of disease severity. Both IFN-β 1a and IFN-β 1b showed significant reductions of the attack rates and MRI burden of disease in SPMS patients, but only the European trial with IFN-β 1b met its primary endpoint and showed a significant reduction in the confirmed 1-point Expanded Disability Status Scale (EDSS) progression rate in this setting [20]. Compared to the failed North American study [21], patients in this European trial were in an earlier phase of SPMS and had more active relapsing disease. In the US guidelines, the data from these pivotal studies resulted in a Type A recommendation for IFN-β for patients who have RRMS or SPMS and are still experiencing relapses, and a Type A recommendation for GA for RRMS patients [18].

Some head-to-head trials and long-term follow-up data have since added to the evidence on DMTs in the RRMS setting: The inferior results for standard doses of IFN-β 1a im compared to IFN-β 1a sc and IFN-β 1b sc in the EVIDENCE[1] [30] and INCOMIN[2] trials [31], respectively, may reflect a dose–response effect, although dose escalating studies for IFN-β 1a im (IMPACT[3] [27]) and recently for IFN-β 1b (BEYOND[4] [32]) showed no additional improvement at higher doses. While it is possible some patients may achieve an adequate response with lower doses of IFN-β, subgroup analysis has not revealed any predictive criteria to allow such individualised treatment decisions. More recent trials comparing GA with IFN-β 1b sc (BEYOND [32], BECOME[5] [33]) and IFN-β 1a sc (REGARD[6] [34]) have shown lower relapse rates overall than in the pivotal trials with these agents, but did not reveal clinically important differences in efficacy. Follow-up for a mean of 21.1 years after enrollment in the original IFN-β 1b pivotal study in RRMS, with an ascertainment rate of 98.4% of patients, established long term safety and tolerability in the group of patients who stayed on IFN-β 1b 250 μg [35].

To determine whether early treatment with DMTs following a CIS in patients with abnormal MRI scans can delay the second clinical event and therefore a diagnosis of clinically definite MS (CDMS), four large-scale placebo-controlled clinical trials were conducted. In the CHAMPS[7] study, weekly injections of 30 μg IFN-β 1a im resulted in a significant reduction of the cumulative probability of the development of CDMS within 2 years (35 vs. 50% for placebo) and significant benefits concerning the volume of brain lesions, new or enlarging lesions, and gadolinium-enhancing lesions at 18 months [36]. The rate of conversion to CDMS was reduced from 45 to 34% for once-weekly treatment with 22 μg IFN-β 1a sc in the ETOMS[8] trial, and the time to a second exacerbation was significantly delayed (569 vs. 252 days) [37]. In the BENEFIT[9] study, treatment with IFN-β 1b 250 μg sc every other day delayed time to CDMS by 363 days and decreased the risk for CDMS within 2 years by 50% [38, 39]. In the PreCISe[10] trial GA 20 mg/d reduced conversion to CDMS by 45% with the time to conversion significantly prolonged from 336 to 722 days [40]. Together, these trials have shown that early treatment with well-established DMTs consistently reduces the cumulative probability of developing CDMS in CIS patients with MRI abnormalities at presentation. Extension studies and long-term follow up data have since demonstrated persisting differences in conversion to CDMS based on the original treatment allocation [41–43]. Despite the convincing and persisting benefits in relapse activity, CIS studies have not shown an effect in preventing early disability, probably reflecting the low level of accumulation of disability at this stage of the disease.

While benefits have been demonstrated across the range of relapsing forms of MS, unfortunately neither IFN-β nor GA have shown convincing efficacy in PPMS. In two single-centre placebo controlled trials in PPMS patients, treatment with IFN-β did not result in reduced disability progression [44]. The secondary outcome pre-specified in the protocol of one of these trials did, however, show that at 2 years the numbers of active lesions on brain MRI scan in the IFN-β group of patients were significantly lower than in the placebo arm [44]. The placebo-controlled 3-year trial investigating GA in PPMS was stopped after an interim analysis showed no discernible effect on time to sustained accumulated disability. A post-hoc analysis, however, did suggest a benefit in male patients with more rapid progression [45]. In the failed PPMS trial investigating selective B-cell depletion, there was a delay in time to confirmed disease progression in rituximab-treated patients

[1] Evidence for Interferon Dose–Response: European-North American Comparative Efficacy.

[2] Independent comparison of interferon.

[3] International MS secondary Progressive Avonex Controlled Trial.

[4] Betaferon efficacy yielding outcomes of a new dose.

[5] Betaseron versus Copaxone in MS with triple-dose gadolinium and 3T MRI endpoints.

[6] Rebif versus Glatiramer acetate in relapsing MS disease.

[7] Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study.

[8] Early treatment of Multiple Sclerosis.

[9] Betaferon in newly emerging Multiple Sclerosis for initial treatment.

[10] Early glatiramer acetate treatment in delaying conversion to clinically definite Multiple Sclerosis in subjects presenting with a clinically isolated syndrome.

below 51 years of age and/or with gadolinium-enhancing lesions [46].

Second-line drugs with limited experience

Mitoxantrone

Mitoxantrone (MX) is a synthetic anthracenedione derivative for intravenous use that interacts with topoisomerase II and causes single and double strand breaks by intercalating the DNA. Originally developed as a cytotoxic for the treatment of adult acute myeloid leukaemia, studies in animal models of MS provided evidence for immunosuppressive effects of MX, targeting proliferating macrophages, B- and T-lymphocytes [47, 48]. Experimental evidence suggests that MX acts via short-term induction of cell lysis at high concentrations [47, 49] and long-term induction of programmed cell death in antigen-presenting cells at lower concentrations [50].

The efficacy of MX in MS has been evaluated in four randomised controlled clinical trials. A placebo-controlled study in RRMS patients showed a reduction of disability progression (79%) and relapse rate (60%) for treatment with monthly infusions of MX 8 mg/m^2 over 1 year [51]. A double-blind trial comparing 13 infusions of MX 12 mg/m^2 or methylprednisolone 1 g over 32 months in patients with highly active MS and rapid disease progression confirmed its efficacy in reducing relapse rates and brain MRI activity [52]. In a trial comparing six cycles of monthly treatment with methylprednisolone 1 g with or without MX 20 mg in MS patients with very active progressive disease, the addition of MX resulted in an 86% decrease in the proportion of patients with enhancing lesions and a reduction in EDSS disability progression and relapse rate by 84 and 77%, respectively [53]. In the largest study ($n = 194$), the double-blind, placebo-controlled MIMS[11] trial evaluating MX doses of 5 and 12 mg/m^2 every 3 months in rapidly progressive relapsing MS and SPMS patients, administration of the drug for 2 years led to a reduction of the progression of disability and the annualised relapse rate by 64 and 60%, respectively, in the 12 mg/m^2 group [54]. Based on these last two trials, MX (Novantrone®) was approved for the treatment of SPMS, progressive relapsing MS or worsening RRMS in the United States in 2000 and later in some European countries.

Cardiotoxicity, characterized by decreased left-ventricular ejection fraction (LVEF) in ~12% and/or potentially fatal congestive heart failure in ~0.4% of patients, is a major limitation of MX treatment [55, 56]. An assessment for cardiac signs and symptoms and LVEF evaluations by appropriate methodology, such as multi-gated radionuclide angiography (MUGA), are therefore recommended prior to the initial and subsequent doses of MX. Patients with a LVEF below the lower limit of normal at baseline or during MX therapy should not receive MX [57]. The risk of cardiotoxicity increases with cumulative MX dose, and the lifetime dose is generally restricted to 140 mg/m^2. As MX-induced cardiotoxicity may occur months to years after termination of therapy, patients should be monitored for late occurring cardiotoxicity by annual quantitative LVEF evaluation after stopping MX treatment.

Therapy-related acute leukaemia (TRAL) occurs in up to 0.8% of MS patients treated with MX [55], with drug-induced cleavage of DNA by topoisomerase II mediating the formation of chromosomal translocation breakpoints in mitoxantrone-related acute promyelocytic leukaemia [58]. MX treatment has an age- and dose-related effect on the reproductive capacity with 26% of MX-treated patients reporting chemotherapy-induced amenorrhea (CIA) in the retrospective FEMIMS[12] study [59]; use of estroprogestinic drugs may reduce the risk of CIA. Recent evidence suggests that ABC-transporter gene-polymorphisms may be pharmacogenetic surrogate markers for response and drug-related adverse events in MX-treated MS patients [60], possibly representing a step towards personalized therapy.

In an attempt to minimise toxicity while exploiting its efficacy over conventional DMTs, various small trials with MX have been conducted under the concept of a more aggressive, "induction therapy" approach for patients with highly active RRMS [61]. A multicentre, single blind controlled trial compared a 6-month induction therapy of monthly MX 20 mg combined with methylprednisolone 1 g, followed by high-dose IFN-β 1b over 3 years with a treatment regimen without MX. Time to worsening of EDSS by at least 1 point was significantly delayed in patients receiving MX, and the annualized relapse rate was reduced by 61.5% [62]. Induction therapy with MX followed by GA maintenance therapy resulted in a trend toward decreased clinical disease activity and major effects on MRI measures of disease burden and severe tissue injury when compared to GA alone [63]. Beneficial effects of MX induction therapy were also reported in several observational studies [64–67]. MX appears to be ineffective in PPMS [68].

Natalizumab

Natalizumab is a recombinant, humanized monoclonal antibody directed against the α4 subunit of the integrin Very Late Antigen (VLA)-4 on the surface of lymphocytes. Natalizumab blocks the interaction of VLA-4 with its

[11] Mitoxantrone in Multiple Sclerosis.

[12] Fertility and Mitoxantrone in MS.

ligand, vascular-cell adhesion molecule 1 (VCAM-1), on the surface of vascular endothelial cells in brain and spinal cord blood vessels, thus reducing the adhesion and migration of lymphocytes into the brain. Blocking of VLA-4 also limits migration through the extracellular matrix by limiting binding of VLA-4 to fibronectin [69]. Prevention of lymphocytic infiltration has been shown in vivo to halt the cellular autoimmune driven destruction of myelin in an animal model of MS [70].

The safety and efficacy of natalizumab in the treatment of RRMS was evaluated in two phase III studies. In the placebo-controlled AFFIRM[13] study, natalizumab (300 mg IV once every 4 weeks) reduced the rate of clinical relapse at 1 year by 68% and the risk of 24 week sustained progression of disability by 54% over 2 years [71], with reductions of 81 and 64% respectively for patients with highly active disease [72]. The accumulation of new or enlarging hyperintense lesions over two years, as detected by T2-weighted MRI, was reduced by 83% for natalizumab versus placebo [71]. The 2-year SENTINEL[14] study evaluated this natalizumab regimen as add-on to continued IFN-β 1a in patients relapsing under IFN-β 1a treatment [73]. In this setting, add-on natalizumab resulted in a 24% reduction in the relative risk of sustained disability progression compared to IFN-β 1a alone, a reduction in annualized relapse rates of 54 and 55%, respectively, at 1 and 2 years, and an 83% reduction in new or enlarging lesions on T2-weighted MRI. In the subgroup of patients with highly active disease despite IFN-β 1a treatment, natalizumab reduced the risk of disability progression by 58% and relapse rate by 76% [72]. Natalizumab effects were sustained with low annualised relapse rates and stable disability scores confirmed in the open-label STRATA extension study evaluating the long-term safety of natalizumab in participants of these and other controlled studies [74, 75].

Based on the AFFIRM and SENTINEL trials natalizumab (Tysabri®) was approved for the treatment of patients with rapidly evolving severe RRMS and patients with ongoing disease activity despite IFN-β.

With the development of effective biologic agents resulting in a treatment paradigm shift in other diseases, notably rheumatology, it has been discussed whether the ultimate goal of therapy, freedom from disease activity and even disease improvement, may be achieved in MS treatment, too. In a post-hoc analysis of the AFFIRM study, the proportion of patients who were free of disease activity according to combined clinical and radiologic criteria over 2 years was shown to be fivefold greater in the natalizumab group than in the placebo group. Considering those with highly active disease at baseline (defined as two relapses and MRI evidence of disease activity in the year pre-treatment), 27% of natalizumab-treated versus 2% in the corresponding placebo group were disease-free at 2 years [76]. Another post-hoc analysis of AFFIRM reported a significant increase in the cumulative probability of achieving a sustained improvement in disability for natalizumab treatment [77].

There were few notable side effects in the natalizumab trials. However, two patients receiving combined natalizumab and IFN-β in the SENTINEL trial developed progressive multifocal leukoencephalopathy (PML) [78, 79], a rare opportunistic infection with the ubiquitous John Cunningham virus (JCV) previously seen only in severely immuno-compromised patients. Natalizumab-associated PML has since been reported in MS patients receiving natalizumab monotherapy [80], and as of February 2, 2011, there were 95 confirmed cases [81]. The pathogenesis of natalizumab-associated PML remains unclear. One hypothesis that natalizumab reactivates and mobilizes the virus from bone marrow cells carrying JCV [82] has since been refuted by other groups [83, 84]. Another hypothesis involves natalizumab-related compromised brain immunosurveillance, yet does not explain why PML occurs in some patients but spares the majority [85].

Affected patients most commonly present with changes in cognition, personality, and motor performance. The diagnosis of PML in patients with the typical clinical picture is based on characteristic MRI data and the detection of JCV DNA by quantitative polymerase chain reaction (PCR) in the cerebrospinal fluid (CSF) [86, 87]. PML is characterised by a marked clinical deficit with relatively little radiological change. In contrast to PML in other settings, contrast enhancement occurs in a quarter of cases with natalizumab-associated PML. Spinal manifestations are rare but have been demonstrated at autopsy. Compared to the radiological changes of MS, grey matter localisation and large confluent granular T2-weighted lesions are more frequent [88].

Recent evidence suggests that both prior immunosuppressive treatment and a treatment duration of >2 years on natalizumab increase the risk of PML, resulting in a range from 1 in 5,000 for immunosuppressive-naïve patients with less than 2 years on natalizumab to 1 in 200 for patients with more than 2 years of natalizumab exposure and prior immunosuppressive therapy [89]. To date there is no reliable means of predicting individuals remotely or immediately at risk of developing PML while on therapy. Several parameters have been discussed as potential predictive markers for natalizumab-associated PML. These include CD4+/CD8+ cell counts [85], adaptive mutations in the capsid protein of JCV [90], and JCV load in urine, plasma or peripheral blood mononuclear cells [82, 83, 91]. Screening

[13] Natalizumab safety and efficacy in relapsing remitting Multiple Sclerosis.

[14] Safety and efficacy of natalizumab in combination with Avonex.

for JCV in CSF by monthly lumbar puncture has been suggested [92]. Functional immunoassays to stratify patients' risk for natalizumab-associated PML, among them cellular energetics as parameter of cellular immune response, are currently being validated [93]. None of these approaches has yet gained widespread acceptance. A promising new option may be a recently developed enzyme-linked immunosorbent assay (ELISA) which was used to determine the presence of anti-JCV antibodies in serum samples collected 16–180 months prior to the diagnosis of PML in natalizumab-treated patients [94]. Based on the finding that all 17 available samples tested seropositive, the clinical utility of this assay for stratifying MS patients for higher or lower risk of developing PML is currently being investigated. 6-month drug holidays that have been discussed in order to reduce the risk of PML have resulted in increases in annualized relapse rates, EDSS scores and MRI activity in patients with very active RRMS [95].

Treatment of PML requires immune reconstitution with immediate cessation of natalizumab therapy and removal of the drug. Plasma exchange has been shown to accelerate the clearance of natalizumab [96] and has been routinely used in published case studies [80, 86, 97]. However, immune reconstitution inflammatory syndrome (IRIS) with exacerbation of symptoms and enlargement of lesions on MRI has been observed within a few days to a few weeks of plasma exchange [86]. Strategies to reduce the impact of this by using high dose steroids have been proposed. Attempts have been made to identify an effective antiviral with research being targeted at serotonin receptor antagonists (JCV uses serotonin receptors to infect cells [98]), and at the antimalarial agent mefloquine which inhibits replication of JCV in cells [99]. All these results have been summarized in a proposed treatment algorithm (Fig. 1, modified from [100]).

An analysis of the outcomes in the first 35 cases of natalizumab-associated PML identified in the post-marketing safety evaluation demonstrated that 71% of PML patients survived, mostly younger patients with lower EDSS scores prior to PML and a shorter time from PML symptom onset to diagnosis [101].

Defining the right balance between potency and side effects: oral therapies

Currently available immunomodulatory drugs for the treatment of MS require repeated parenteral administration. Injection-site reactions, needle-phobia, and other injection-related issues have been reported as frequent reasons for non-adherence [102–104], driving the search for effective oral medication.

Fingolimod

Fingolimod, a synthetic analogue of the immunosuppressive fungal metabolite myriocin [105], is a sphingosin-1-phosphate (S1P) receptor modulator for once daily oral

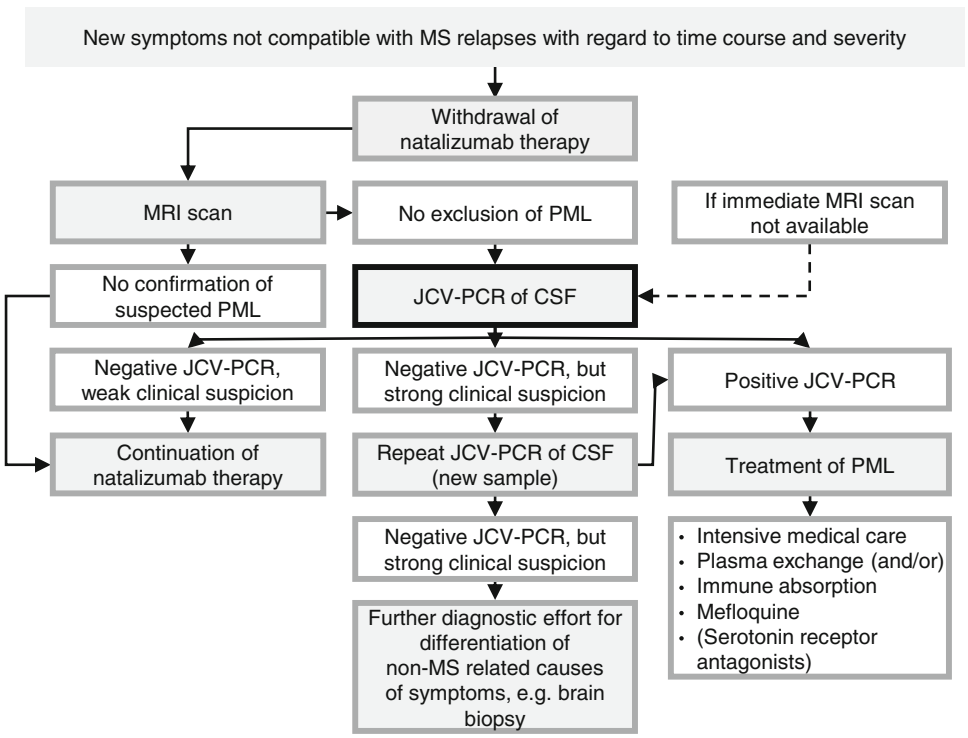

Fig. 1 Algorithm for diagnosis and treatment of natalizumab-associated progressive multifocal leukoencephalopathy. *PML* progressive multifocal leukoencephalopathy, *JCV* John Cunningham virus, *PCR* polymerase chain reaction

administration. In vivo, fingolimod is phosphorylated to yield the biologically active agent that binds to S1P receptors, modulating MS pathology, potentially acting both on the peripheral immune system and at central levels [106]: Fingolimod binding to S1P receptors on lymphocytes prevents their egress from lymph nodes, resulting in a dose-related reduction in the number of circulating lymphocytes and a reduced infiltration of autoaggressive lymphocytes into the central nervous system; preclinical findings suggest that fingolimod may also promote neuroprotective and reparative processes within the central nervous system through modulation of S1P receptors on neural cells.

In a phase II proof-of-concept study in RRMS patients, oral doses of fingolimod 1.25 mg and 5 mg once daily significantly reduced the median total number of gadolinium-enhanced lesions on MRI and the annualized relapse rates [107]. During the extension study, patients receiving fingolimod 5.0 mg were switched to 1.25 mg when a benefit-risk assessment indicated that the higher dose offered no efficacy advantage and possibly a less favourable safety profile [108, 109]. For the 24-month phase III FREEDOMS[15] study, RRMS patients were randomized to receive oral fingolimod at doses of 0.5 mg or 1.25 mg daily or placebo [110]. The annualized relapse rate was significantly lower with both 0.5 mg and 1.25 mg fingolimod (0.18 and 0.16, respectively) than with placebo (0.40); this relative reduction of about 58% for fingolimod groups was seen in both treatment-naïve patients and patients previously treated with DMTs. Compared to placebo, patients on fingolimod also showed a reduced risk of disability progression and a benefit in MRI-related efficacy end points, with no significant differences in efficacy between the two fingolimod doses.

The 12-month phase III TRANSFORMS[16] study used the same eligibility criteria to evaluate fingolimod doses of 0.5 and 1.25 mg in RRMS patients in comparison to IFN-β 1a, given at a weekly dose of 30 μg im [111]. Approximately half of the enrolled patients had received prior IFN-β treatment. Compared to the IFN-β group, patients treated with fingolimod 1.25 and 0.5 mg had significantly lower annualized relapse rates (0.20 and 0.16, respectively, vs. 0.33 for placebo), MRI lesion activity and brain volume loss were reduced. A larger proportion of patients remained relapse-free. Progression of disability was not significantly different between treatment groups.

Headache, nasopharyngitis, and fatigue were reported in more than 10% of patients in the phase III trials FREEDOMS and TRANSFORMS [110–112]. Other findings were a transient bradycardia and infrequent atrioventricular conduction blocks after the first dose of fingolimod, minor increases in blood pressure persisting on therapy, and asymptomatic liver enzyme elevations. Macular oedema, mostly reversible within 1 to 6 months after discontinuation of therapy [113], occurred in 0.8% of patients on fingolimod, most of whom received fingolimod 1.25 mg [112]. 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 FREEDOMS and TRANSFORMS, respectively, with two fatal herpes virus infections on fingolimod 1.25 mg. While there was no signal in the FREEDOMS trial [110], eight cases of localised skin cancer occurred in fingolimod treated patients in the TRANSFORMS trial [111] with further new cases in the extension study [114]. Overall, the benefit-risk profile was better for the 0.5 mg dose in both trials.

Based on the results for the 0.5 mg dose in the FREEDOMS and TRANSFORMS trials, fingolimod (Gilenia®/Gilenya®) was recently approved by the FDA for the treatment of patients with relapsing forms of MS, and the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the treatment of adult patients with RRMS with high disease activity for European countries. The placebo-controlled phase III INFORMS trial (Clinicaltrials.gov Identifier NCT00731692) is currently evaluating whether fingolimod 0.5 or 1.25 mg can delay disability progression in patients with PPMS.

Cladribine

Cladribine is a synthetic adenosine deaminase-resistant purine nucleoside analogue with antilymphocytic effects. Its development was based on the observation that an inherited deficiency of adenosine deaminase, an enzyme which metabolizes naturally occurring deoxynucleosides, leads to selective accumulation of toxic deoxyadenosine nucleotides within lymphocytes, resulting in lymphopenia and immunodeficiency [115]. Cladribine induces apoptosis and depletion of both proliferating and quiescent lymphocytes [116], with a preferential and sustained depletion of $CD4^+$ T-cells, less pronounced dose-dependent reductions in $CD8^+$ T-cells, and smaller dose-dependent reductions in $CD19^+$ and $CD16^+/CD56^+$ lymphocytes [117].

Based on the hypothesis that cladribine-induced depletion of lymphocytes could potentially interrupt the cascade of immune events central to the pathophysiology of MS, the safety and efficacy of parenteral cladribine in patients with relapsing or progressive forms of MS was evaluated in three double-blind, placebo-controlled trials [118–120]. Based on the results of these clinical studies, an oral formulation of cladribine was evaluated in the

[15] FTY720 research evaluating effects of daily oral therapy in Multiple Sclerosis.

[16] Trial assessing injectable interferon versus FTY720 oral in RRMS.

phase III, double-blind, placebo-controlled CLARITY[17] study: RRMS patients were randomised to receive cumulative oral doses of 3.5 or 5.25 mg cladribine per kilogram of body weight or placebo, with treatment given in two or four short courses for the first 48 weeks, then in two short courses starting at week 48 and week 52 [121]. For both cladribine dosages the annualized relapse rate at 96 weeks was significantly reduced (0.14 and 0.15 for patients with 3.5 and 5.25 mg cladribine, compared to 0.33 for the placebo group), equivalent to relative reductions of 58 and 55%, respectively. In the cladribine treatment arms, there were significantly more relapse-free patients (79.7 and 78.9 vs. 60.9% for placebo), a significant reduction in the risk of 3-month sustained progression of disability (hazard ratios of 0.67 and 0.69, respectively), and significant reductions in the number of gadolinium-enhanced T1 lesions, active T2 lesions, and combined unique lesions on MRI. Lymphocytopenia was reported in 21.6 and 31.5% of patients in the cladribine 3.5 and 5.25-mg group, respectively, compared to 1.8% in the control group. Activation of latent herpes zoster and isolated cases of cancer across different organ systems were observed in patients on cladribine. As expected for a drug with preferentially lymphotoxic effects, myelosuppression is the major dose-limiting effect, and leukopenia, neutropenia and thrombocytopenia may occur. Infections have been reported in patients who have pre-existing immune system disorders [122].

While cladribine (Movectro®) was recently approved in Australia and Russia as a treatment of relapsing-remitting MS, the US FDA issued a complete response letter, requesting an improved understanding of safety risks and the overall benefit-risk profile either through additional analyses or by additional studies. The CHMP of the European Medicines Agency recently confirmed its negative opinion regarding the marketing authorization application for cladribine [123] due to concerns of an increased number of patients with cancer in trials with cladribine. CHMP also noted that the benefits and the most appropriate dosage for treatment had not been fully established in patients who were expected to use the medicine.

Conclusions

For patients with CIS, four large-scale clinical trials have shown that treatment with IFN-β or GA can reduce the early risk of developing clinically definite MS. This evidence has resulted in a move towards early initiation of treatment to reduce the incidence of all relapses from the earliest identifiable stages of the disease.

Several DMTs are currently available for the treatment of relapsing MS. Efficacy has not been established in SPMS without ongoing relapse activity, and to date no DMT has shown convincing efficacy in PPMS.

There are notable differences in the evidence on efficacy and safety of these therapies: The conventional DMTs IFN-β and GA have been used for many years, and there is a wealth of evidence both on their efficacy and especially on their safety. For the immunosuppressive agent mitoxantrone, its potential toxicity may outweigh the clinical benefits early in the course of the disease. The more recently introduced antibody natalizumab appears more effective than conventional DMTs against placebo; however quantifying the advantage is difficult due to differences in patient populations for studies carried out at different times and the lack of direct head-to-head comparisons. The apparent increase in efficacy seen in trials and in clinical practice comes at the risk of potentially lethal adverse effects, limiting its more widespread use. Based on the recognized criteria defined by the American Academy of Neurology [18], experts from a number of European countries, the Multiple Sclerosis Therapy Consensus Group (MSTCG), summarized the evidence on the currently available DMTs in evidence-based recommendations for escalating immunotherapy of RRMS (Fig. 2) [19].

For fingolimod, which will become available for the treatment of RRMS in the near future, its potential adverse effects will have to be balanced against its clinical benefit and the ease of use promised by the formulation for oral administration. Clinicians will then be looking for new treatment algorithms to provide guidance in the changing landscape of management of MS patients.

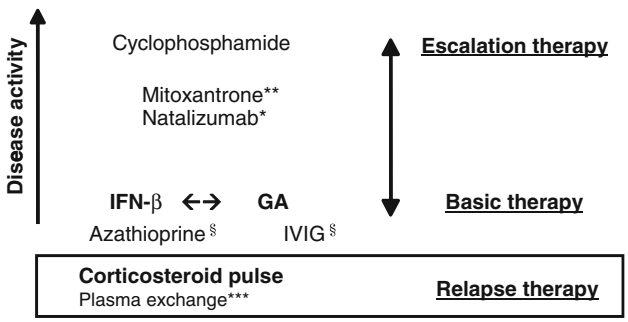

Fig. 2 Escalating immunotherapy of RRMS [19]. *IVIG* intravenous immunoglobulins, *IFN-β* interferon-beta, *GA* glatiramer acetate. *In cases of ≥2 severe relapses per year it may also be used as basic therapy; **Change of these therapies at this stage of escalation not yet formally evaluated; ***Option in severe, steroid-resistant relapses; §Considered in some European countries as second line treatments but not in others

[17] Cladribine tablets treating MS orally.

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