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REVIEW

Advances in and Algorithms for the Treatment of Relapsing-Remitting Multiple Sclerosis

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Abstract Treatment options in relapsing-remitting multiple sclerosis have increased considerably in recent years; currently, a dozen different preparations of disease-modifying therapies are available and some more are expected to be marketed soon. For the treating neurologist this broad therapeutic repertoire not only greatly improves individualized management of the disease, but also makes choices more complex and difficult. A number of factors must be considered, including disease activity and severity, safety profile, and patient preference. We here discuss the currently existing options and suggest treatment algorithms for managing relapsing-remitting multiple sclerosis.

Key Words Relapsing-remitting multiple sclerosis · Disease-modifying therapy · Treatment decisions · Treatment algorithm

Since the emergence of interferon-β and glatiramer acetate (GA) in the early and mid-1990s the treatment of relapsing-remitting multiple sclerosis (RR-MS) was rather simple for many years, the 2 compound classes being the only approved therapies. In recent years, however, numerous options with very different mechanisms of action, efficacy, and safety profiles, and also differing features concerning patient convenience, have entered the market. For the treating neurologist, as well as the patient, the resulting options are becoming increasingly challenging. We here summarize the current disease-modifying therapies (DMTs) in terms of efficacy and safety profile and propose a treatment algorithm. Several new drugs are imminently emerging and will be subject to another review in this issue and thus not be discussed in detail here [1, 2].

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Currently Approved Drugs for RR-MS: First-line DMTs

IFN-β

In 1993, subcutaneous IFN-1β (Betaseron/Betaferon: Bayer HealthCare Pharmaceuticals, Berlin, Germany and later also Extavia: Novartis Pharma, Basel, Switzerland) was the first preventive drug approved for RR-MS and has since been the mainstay of RR-MS treatment [3]. Several similar preparations have been marketed since, namely intramuscular IFN-1βa (Avonex: Biogen, Cambridge, MA) [4], subcutaneous IFN-1βa (Rebif: Merck, Darmstadt, Germany) [5], and, more recently, pegylated IFN-1βa (pegIFN-1βa; Plegridy: Biogen, Cambridge, MA) [6]. They differ mainly in terms of application route and frequency (s.c. *vs* i.m.; once-daily to once every other week; different application devices). Across studies, efficacy is roughly 30 % in terms of decrease in annualized relapse rate. Comparative data between IFNs are scarce and overall do not show meaningful differences with regard to efficacy [7]. The mechanisms of action probably relate to a multitude of cell-based functions, including induction of regulatory mediators [e.g., interleukin (IL)-10 and IL-4, and others], decreasing proinflammatory cytokines (e.g. IFN-γ, IL-17, tumor necrosis factor-α, osteopontin, and others), and modulating cell trafficking across the blood–brain barrier [8]. The safety profile is quite favorable in terms of severe adverse effects. However, many patients complain about the relatively frequent influenza-like symptoms and injection site reactions.

GA

GA followed IFN-1β in 1995 as the second DMT approved for the prevention of MS relapses and is marketed as Copaxone: Teva Pharmaceuticals, Petah Tikva, Israel, initially as once-daily subcutaneous injections [9], and more recently as a 3 times weekly regimen [10]. GA is a mixture of polypeptides derived from 4 amino acids and its mechanisms of action may include a shift from a T helper 1 cell-driven immune response to a T helper 2 cell-driven one by interacting with CD4+ and CD8+ T cells, as well as antigen-presenting cells [11]. GA does not induce influenza-like symptoms but cutaneous side effects such as lipoatrophy at the injections site is common [12]. As with the IFNs, it has a favorable safety profile in terms of severe side effects. GA showed beneficial effects on Expanded Disability Status Scale progression, but only trends without reaching formal significance. Even though there is a lack of well-controlled data on pregnancy-related risks for all DMTs, some data suggest that GA may have the best safety profile among the first-line DMTs with regard to this common patient need. Copaxone received the most favorable Food and Drug Administration (FDA) pregnancy label (category B), but data are considered insufficient and further research seems necessary [13].

Dimethyl Fumarate

Dimethyl fumarate (DMF; formerly known as BG-12) is the first oral DMT approved in 2013 by both the FDA and European Medicines Agency (EMA) for first-line therapy. The compound, marketed as Tecfidera: Biogen, Cambridge, MA, originates from dermatology, namely psoriasis treatment with fumarate esters. It is given in 2 daily doses. Its mechanism of action has not been completely revealed and is still a matter of discussion. Cytokine modulation and neuroprotective effects mediated via the nuclear factor E2-related factor are likely to play an important role [14, 15], as well as hydroxycarboxylic acid receptor 2-regulated invasion of neutrophils into the central nervous system (CNS) [16]. The formulation as delayed-release DMF was found to be superior to placebo [17–19] and noninferior to the active comparator GA, in 2 large controlled phase III trials [20]. The latter showed a numerically superior effect against the active comparator, although this did not achieve significance (51 % relapse risk reduction compared with placebo for DMF *vs* 31 % relapse risk reduction compared with placebo for GA). The safety profile includes nonsevere, but potentially unpleasant, side effects such as gastrointestinal irritations and flush symptoms, which in the majority of patients tend to diminish and abate over time; however, there are also more severe, though very rare, side effects. Much attention has been paid to the news that fumarates (used in a similar but differing formulation in psoriasis [21, 22]) can, in general, be associated with the occurrence of JC virus (JCV)-induced progressive multifocal leukencephalopathy (PML). PML is a relevant issue, especially in natalizumab treatment (see below), but lately also occurred in patients with MS treated with DMF. One patient from an extension of one of the phase II studies developed PML after long-term low lymphocyte counts, suggesting that lymphocyte counts could be a risk marker [23]. A recent case of PML in DMF in RR-MS, however, apparently developed the infection in the absence of low lymphocyte counts, thus questioning their relevance for risk management [24]. These cases are certainly of concern but in light of the large number of treated patients worldwide, DMF is generally still viewed as a very useful and safe first-line DMT and has become one of the most commonly prescribed DMTs in RR-MS [25, 26].

Teriflunomide

The most recently approved first-line DMT, teriflunomide, is also an oral drug, the once-daily pill Aubagio: Genzyme, Cambridge, MA. It is the active metabolite of its parent drug leflunomide that has been in use for rheumatoid arthritis since 1998 [27]. Teriflunomide's main mechanism of action is thought to be inhibition of the enzyme dihydroorotate-dehydrogenase and the subsequent inhibition of pyrimidine synthesis. Consequently, this reduces the activity of proliferating (blasting) lymphocytes. It is not supposed to affect homeostatically proliferating hematopoietic cells [28, 29]. Efficacy was superior to placebo and comparable to intramuscular IFN-1βa [30–32]. Safety issues include nausea, diarrhea, hair thinning, and elevations in liver enzymes. Drug-related deaths or safety signals of the magnitude of PML have not so far been observed for teriflunomide. However, leflunomide's safety profile is relevant for teriflunomide and some rare serious side effects have been observed with this predecessor drug, including 3 cases of PML (in > 2 million patient-years of leflunomide use). Two patients had previously been treated with other immunosuppressants [33, 34], and there is limited information on the third [35]. A safety concern relevant for many young female patients with MS is the probable teratogenic potential of leflunomide and teriflunomide. For leflunomide, animal studies have demonstrated teratogenicity, prompting great caution with the use of teriflunomide in females with child-bearing potential and a wish to have children. For teriflunomide, pregnancy outcomes were retrospectively evaluated in the global pharmacovigilance database following patients included in clinical phase II and phase III trials and did not indicate a teratogenic potential [36]. Overall, teriflunomide is expected to become a mainstay in disease-modifying treatment of RR-MS [37].

Currently Approved Drugs for RR-MS: Second-line DMTs

Fingolimod

Fingolimod (Gilenya: Novartis Pharma, Basel, Switzerland) was the first approved oral drug for RR-MS treatment and was initially approved by the FDA in 2010 as a first-line therapy and in 2011 by the EMA as a second-line therapy. It is a first-in-class modulator of lymphocyte migration that binds to the sphingosine-1-phosphate (S1P) receptor on lymphocytes and prevents their egress from lymphatic tissue. It therefore ultimately blocks their invasion into the brain [38, 39]. As fingolimod, as a lipophilic substance, accumulates in fatty tissues, including the CNS and S1P receptors, found on CNS-residing glia cells, direct neuroprotective properties of fingolimod have been suggested [40–42]. While preclinical studies and consistently beneficial effects of fingolimod on atrophy development in phase II and III trials support such an effect, fingolimod failed to show efficacy in primary progressive MS, the pathology of which is thought to be dominated by neurodegeneration [43]. In RR-MS the FREEDOMS and TRANSFORMS studies showed superiority not only to placebo [44–47], but also to the active comparator intramuscular IFN-1βa [48]. Fingolimod significantly reduced the relapse rate by 38 % and 50 % (for 1.25 mg and 0.5 mg daily, respectively) compared with IFN-1β, and several magnetic resonance imaging (MRI) measures consistently favored fingolimod. Both the EMA and FDA approved the drug for second-line use while a considerable proportion of subjects had not been pretreated with another DMT. There are no other direct controlled prospective comparisons to other DMTs, but a recent retrospective database analysis could show that patients switching from IFNs to fingolimod experienced fewer relapses than those switching from IFNs to GA [49]. Furthermore, as efficacy for first-line therapeutics has consistently been around a 30 % reduction in relapse rate (as was the IFN-1β arm in TRANSFORMS), it is generally believed that fingolimod is more efficacious than the IFNs, GA, and teriflunomide (and probably also to DMF, according to indirect comparisons [50]). While controlled prospective studies comparing fingolimod to the other second-line drugs natalizumab and alemtuzumab are completely lacking, a comparison between several placebo-controlled trials, as well as findings from the MSBase registry, lead most to view fingolimod as less effective than the other 2 treatments [51]. There are several safety issues, including cardiac side effects, that result from off-target effects on S1P receptors on cardiomyocytes, with bradycardia and atrioventricular conduction block, and 1 possible fatality after the first dose in the postmarketing phase. Several cases of herpes virus encephalitis (including 2 deaths) and cryptococcal meningitis have been reported in the pivotal studies (including patients treated at a higher dose than later approved) and in postmarketing [52]. Two cases of hemophagocytic syndrome with fatal outcome have been reported recently. In the absence of immunity, varicella zoster virus infections occur with increased frequency but can be prevented by appropriate vaccination before embarking on fingolimod therapy [53]. Finally, there have been several cases of PML under fingolimod, mostly after a switch from natalizumab treatment (where PML risk is a much greater issue), and 3 cases on fingolimod monotherapy [54].

Natalizumab

Natalizumab is a monoclonal humanized antibody binding and antagonizing α4β1-integrin. Thereby it inhibits migration of inflammatory cells across the blood–brain barrier. In 2004, natalizumab was first marketed after accelerated approval was granted in light of the urgent need for more efficient therapy at the time and efficacy not seen before. Data from the AFFIRM study showed a relapse risk reduction of 68 % compared with placebo, significant reduction of sustained disability progression, and significant effects in MRI measures [55]. Results obtained in the AFFIRM trial have been used to discuss natalizumab as a first-line medication (the vast majority of patients had not previously been treated with IFNs or GA), whereas both the FDA and EMA approved the drug for second-line use. A second trial (SENTINEL; natalizumab as an add-on to intramuscular IFN-1βa) was terminated because of 2 cases of PML [56, 57], and approval was withdrawn for some time. After no further cases of PML occurred during the studies, natalizumab was re-approved in 2006 for patients with active MS or those not responding to classical injectable DMTs (IFN-β, GA). Overall clinical experiences, as well as patient registry studies such as the TYSABRI Observational Program or MSBase, confirmed superior efficacy of natalizumab compared with IFN-β or GA [58–60]. Since then, however, > 560 cases of PML have been reported to be associated to natalizumab (as of 4 September 2015, 588 cases out of 142,000 patients treated with natalizumab [61]). The overall risk of PML development under natalizumab seems to be around 2 per 1000, but several factors could be identified that help to stratify the risk: prior immunosuppressant medication, treatment duration > 2 years, and the presence of anti-JCV antibodies as a fingerprint of JCV infection. If all 3 are present, the risk is around 1 per 90; if none is present it is around 1 per 10,000 [62]. Even for some time after the cessation of natalizumab, a certain risk of PML remains and pharmacovigilance should be continued [63, 64]. There are increasing efforts to further refine PML risk stratification, especially for patients that convert to anti-JCV antibody positive status while on natalizumab, using antibody indices in serum and cerebrospinal fluid, as well as other approaches [65–68].

Alemtuzumab

Alemtuzumab is the drug with a new mechanism of action most recently approved for RR-MS by the EMA in 2013 and somewhat later by FDA (actually, the most recently approved substance is pegIFN-β, in 2014). The monoclonal antibody existed for some time and was initially developed for chronic lymphatic leukemia (CLL) as MabCampath: Genzyme, Cambridge, MA. It depletes CD52-positive cells—B and T lymphocytes among others—and the idea of its mechanism of action is that it erases large parts of the circulating memory cells, including those prone to attack the CNS, and then reconstitutes without these cells or at least cells not programmed for attack, and with an increased population of regulatory T cells. Efficacy was shown to be high with a relapse reduction of roughly 50 % compared with the active comparator high-dose, high-frequency subcutaneous IFN-1βa in2 different studies (CARE-MS I and CARE-MS II) [69, 70]. More than the phase III trials for natalizumab and fingolimod, CARE-MS II reflects "real-world" decision making because all patients of the study had been on first-line therapy before entry. The drug induces a sustained deletion of CD52-positive cells, which explains its mode of administration (5 consecutive days of infusions and 3 more infusions 1 year later). Alemtuzumab has never been tested against placebo, making it even more difficult to compare it with other substances. However, most neurologists view alemtuzumab's efficacy at least in the range of that of natalizumab and probably better than fingolimod, but controlled head-to-head studies are lacking. Importantly, efficacy seems to be maintained for years following delivery of 2 annual cycles. Several safety issues are of importance, namely the relatively high rate of developing secondary autoimmune phenomena. Autoimmune thyroiditis has been reported at a rate up to one-third of patients. Even more concerning but less frequent are idiopathic thrombocytopenic purpura and Goodpasture syndrome associated with glomerular basement membrane antibodies. These conditions can develop a while after the first dose of the drug which therefore warrants close and long-term monitoring of the patient (at least 2 years after initiation). Some instances of herpes virus reactivation have been observed (but no encephalitis) so that prophylactic aciclovir treatment is considered obligatory in the first 4 weeks after treatment initiation. Cases of PML have not been reported thus far in patients with MS, but only in hematological and transplantation indications [71–73]. Cases of listeria infections have been reported, some with a severe disease course [74]. Many of the safety issues (especially emergent autoimmune complications) are quite common but appear to follow a known temporal sequence. Usually, they can be dealt with satisfactorily if effective long-term monitoring is in place [75]. Taken together, alemtuzumab is a new approach, broadening the options in severe RR-MS [76, 77].

Treatment Algorithms in RR-MS

A general problem in creating a treatment algorithm is that active comparator studies are scarce or lacking. There are only a few studies comparing first-line DMTs with other first- or second-line DMTs and there are none comparing second-line therapies with each other. Hence, at least parts of any such an algorithm must be based on comparing placebo-controlled studies with each other. However, that comes with many statistical pitfalls, especially when comparing the first pivotal IFN and GA trials in the 1990s with the later trials of natalizumab, the oral drugs, and alemtuzumab. The earliest trials, for example, used the Poser criteria for MS diagnosis, and later the McDonald criteria and their revised versions were applied [78–80]. Furthermore, in more recent trials patients tend to have a milder disease course with lower annualized relapse rates, to list just a few of the systematic problems of cross-study comparisons [81]. Another possibility of comparison, yet also flawed, is retrospective database analyses. Here, we present our current personal view on what such an algorithm could look like.

One particular problem in MS immunotherapy that has been with us for many years now is the risk of PML [82–85]. The rare opportunistic and potentially fatal CNS infection with JCV caught the MS community's attention, especially because of its association with natalizumab. Around one-quarter of patients die; the others experience neurological disabilities to differing extents. Correct and early PML diagnosis using MRI is important [86]. The vast majority of cases so far have been natalizumab-associated but some cases have been reported in patients on monotherapy with DMF and fingolimod. PML greatly affects treatment decisions and has stirred up a lot of uncertainty among physicians and patients. Recent developments in stratifying patients have been helpful in decision making.

The vast majority of PML cases in MS have been associated with natalizumab. Risk stratification includes previous use of immunosuppressants, the duration of natalizumab treatment, and (especially important for treatment decisions) JCV status (positive or negative for JCV-specific IgG). Recently, this has been refined by introduction of JCV index, and the JCV index is used by more and more centers [65, 87]. This—together with an intensified MRI regimen—could open up treatment options, especially for JCV-positive patients.

However, some cases have also been observed with DMF and fingolimod monotherapy. With regard to DMF, 4 cases (out of > 170,000 patients treated with DMF [88]) have been reported, and the EMA published new guidelines calling for regular lymphocyte counts, as most cases of PML presented with counts < 500/μl [89]. However, the most recent case had counts between 500/μl and 800/μl, questioning the proposed guidelines. With regard to fingolimod monotherapy, 3 cases of PML have been reported so far (out of 125,000 patients treated

with fingolimod) [54]. Here, patient stratification according to lymphocyte counts is not reasonable owing to the drug's unique mode of action, regularly associated with S1P-mediated therapeutic lymphopenia (with counts < 800/μl in the majority of patients).

Initiation of Therapy

Patients with *de novo* diagnosed RR-MS that have not been treated previously can choose between 4 first-line DMTs: the different preparations of IFN-β, GA, teriflunomide, and DMF. All of them can be considered more or less equally effective, with the exception and advantage of DMF, which in pivotal trials featured the largest reduction in relapse rates numerically (but was not statistically significantly better than the active comparator GA). If compliance is an issue, the oral drugs teriflunomide and DMF may be preferred; once-daily teriflunomide might be even more attractive than twice-daily DMF. If the patient is concerned about rare and maybe even not-yet-known adverse effects, the injectables might be a good choice because of the years of experience with these drugs. Also, women with child-bearing potential that plan to become pregnant, or at least keep open the possibility of becoming pregnant, may also opt for the injectables (in particular GA [13]). Women that are planning to become pregnant should probably not use teriflunomide. In any case, all these considerations must be discussed with patients in detail to enable them to decide individually.

Patients that are already on a first-line DMT may encounter tolerability issues and want to switch to another first-line DMT. Frequent are injection-related side effects in IFN-β and GA, influenza-like symptoms in IFN-β, and flush or bowel-related adverse effects, for example, in DMF. The everyday life of these patients can benefit from today's growing DMT arsenal. In the face of breakthrough disease, however, most clinicians do not recommend switching from 1 baseline DMT to another as a growing bulk of evidence indicates that patients benefit from an early escalation [90].

Escalation of Therapy

In terms of escalation of therapy 2 questions have to be answered: 1) When do we consider an ongoing DMT ineffective or not effective enough and, 2) if we come to the conclusion that we have to switch therapies for efficacy reasons, which second-line therapy should be chosen?

Concerning the first question several approaches exist. Widely known is the so-called Rio Score, which was derived from analysis of long-term clinical data assessing the risk of substantial disability progression of patients using IFN-β by taking 3 measures into account: relapses, new MRI lesions, and Expanded Disability Scale Score progression [91]. Depending on the combination of the 3, recommendations on whether to switch or continue therapy can be based on statistics. The method was simplified later to the Modified Rio Score, relying on relapses and MRI measures only [92, 93]. For GA, DMF, and teriflunomide no such long-term data exist making it ultimately impossible for now to firmly base the decision of "not effective enough" for these drugs on evidence. However, in the absence of such data, it seems reasonable to us to extrapolate the method to the other first-line DMTs.

In recent years the concept of having a patient "free of disease activity" (i.e., no relapses, no MRI progression, no disability progression) was developed—initially in the context of the high efficacy of natalizumab [94]. Later, the term "no evidence of disease activity" was coined and is currently entering center stage in terms of evaluating efficacy data in prospective studies and also many post-hoc analyses of existing data on DMTs [95]. This paradigm also influences many clinicians and the trend goes to adopting a "zero tolerance" attitude. Clinicians recommend escalation of therapy at any hint of disease activity, also factoring in parameters such as brain atrophy rate, cognition, fatigue, depression, and quality of life. These are very interesting and much-noticed approaches, and such scores are likely to become important guidelines for treatment decisions, but most still have to prove their predictive value prospectively.

The second question, to which second-line therapy one should switch, has become increasingly complex, despite the fact that as of now, only 3 drugs are approved: natalizumab, fingolimod, and alemtuzumab. As stated before, direct comparisons are lacking, but looking at the existing data many clinicians and researchers view fingolimod as somewhat less effective while displaling a more favorable safety profile than alemtuzumab and natalizumab, monoclonal antibodies that are probably comparable in efficacy [96]. In line with this notion, a recent retrospective analysis from MSBase registry data provided evidence that a switch from injectables first-line DMTs to natalizumab provides better disease control than a switch from injectables to fingolimod [51]. Depending on the severity of breakthrough disease on first-line DMTs one might thus opt for fingolimod in less severe cases and natalizumab or alemtuzumab in more severe cases. In these severe cases natalizumab probably has a safety advantage over alemtuzumab provided no risk factors for PML are present (treatment duration, JCV antibody status, and previous immunosuppression). If JCV antibody status is positive many patients and clinicians may rather choose alemtuzumab.

Switching Between Second-line Therapies

Several issues can arise with patients on second-line DMTs that may lead to a switch from one second-line DMT to another. One reason can be the occurrence of relapses or deterioration of disability. Such breakthrough disease in fingolimod

Table 1 Overview of currently approved disease-modifying therapies (DMTs) for relapsing-remitting multiple sclerosis

	Trade name	DMT	Route	Dose	FDA/EMA approval	Mechanisms of action	AE/SAEs
First-line	Betaferon/Betaseron/Extavia	IFN-β1b	s.c.	3 × weekly, 250 μg	1993/1995	Modulates multitude of cell-based functions including modulation of, e.g., IL-10, IL-4, IFN-γ, IL-17, TNF-α, osteopontin and others; stabilizes BBB, modulates cell trafficking across the BBB	Mainly injection site side effects, influenza-like symptoms; SAEs rare
	Avonex	IFN-β1a	i.m.	1 × weekly, 30 μg	1996/1996		
	Rebif	IFN-β1a	s.c.	3 × weekly, usually 44 μg	2002/1998		
	Plegridy	PegIFN-β1a	s.c.	125 μg, 2 × weekly	2014/2014		
	Copaxone	GA	s.c.	20 mg daily or 40 mg 3 × weekly	1996/2001	Shifts from Th1- to Th2-driven immune response and others	Mainly injection site side effects; SAEs rare
	Tecfidera	DMF	p.o	240 mg twice daily	2013/2014	Modulates Nrf-2 and others	Bowel disorder, flushing, very rarely PML
	Aubagio	Teriflunomide	p.o.	14 mg daily	2012/2013	Inhibits proliferating lymphocytes by blocking DHODH	Nausea, hair thinning, liver enyme elevation, possibly teratogenic
Second-line	Gilenya	Fingolimod	p.o.	0.5 mg daily	2010/2011	Inhibits lymphocyte egress from lymph nodes by modulation of S1P receptors	Opportunistic infections, cardiac side effects (bradycardia, AV-node block), very rarely PML
	Tysabri	Natalizumab	i.v.	300 mg, 4-weekly	2003 (and reapproved 2006)/2006	Prevents lymphocytes from crossing BBB by blocking adhesion molecule α1β4-integrin	PML, infusion reactions
	Lemtrada	Alemtuzumab	i.v.	5 consecutive daily infusions of 12 mg; after 1 year, 3 more infusions	2014/2013	Long-term depletion of CD52-positive cells (mainly lymphocytes)	Very commonly infusion reactions, autoimmune phenomena (thyroid, kidney), opportunistic infections

FDA = Food and Drug Administration; EMA = European Medicines Agency; AE = adverse event; SAE = serious adverse event; IFN = interferon; pegIFN = pegylated interferon; GA = glatiramer acetate; IL = interleukin; TNF = tumor necrosis factor; BBB = blood–brain barrier; Th1 = T helper 1 cell; Th2 = T helper 2 cell; Nrf2 = nuclear factor E2-related factor; DHODH = dihydroorotate-dehydrogenase; S1P = sphingosine-1-phosphate; PML = progressive multifocal leukencephalopathy; AV = atrioventricular

treatment would prompt consideration of an escalation to natalizumab or alemtuzumab, as delineated above. Breakthrough disease on either natalizumab or alemtuzumab could lead to switching to the other. One would probably not opt for fingolimod in that situation if the expected disease activity is very high despite very effective therapy. A few centers offer autologous stem cell transplantation in such a situation [97], but this approach is still in development and safety and efficacy still have to be assessed in larger cohorts. Breakthrough disease is, however, not the only reason for a need to switch therapies. Testing for JCV antibodies has greatly aided in stratification of PML risk in natalizumab treatment but has also generated the difficult question of what to do with a patient that is stable on natalizumab with no signs of PML but who has a positive JCV antibody test. Depending on treatment duration and previous immunosuppression, the risk may still be very low, but many patients want to change therapy in such a situation. The obvious candidate in this situation appears to be fingolimod which was recently shown to be advantageous over injectables after cessation of natalizumab [98], but is probably clinically less potent than natalizumab. Furthermore, some recent data strongly suggest that a switch from natalizumab to fingolimod may be associated with an increased risk of developing new disease activity [99, 100]. A recent report came to the conclusion that too-long washout phases between natalizumab discontinuation and fingolimod initiation may elevate that risk and recommends waiting 4–8 weeks between treatments [101]. There is still very limited experience of switching from natalizumab to alemtuzumab, and PML risk in JCV antibody-positive patients on alemtuzumab treatment after natalizumab is currently impossible to predict.

Treating Aggressive MS

According to their label, all 3 second-line drugs—fingolimod, natalizumab, and alemtuzumab—can also serve as treatment options in *de novo* patients if the disease course is considered highly active. Therefore, the classification as first line and second line is being questioned more and more, and some recommend a classification for mild/moderate and active/highly active disease courses. There is no universal definition of "highly active" MS, though, but taking into account the labeling of the substances, it is generally defined by the occurrence of 2 relapses in the past year with disability progression and a significant increase of T2 lesions at critical locations (e.g., brainstem, cerebellum) on MRI [102]. In this setting, special attention must be paid to assessing the therapeutic risk in light of the expected efficacy of a drug [103]. Of course, all these considerations must be discussed with the patient extensively and joint decision-making should be entered, taking into account the patient's preferences.

Conclusions

Treatment options in RR-MS have increased considerably in recent years, with currently a dozen different preparations of

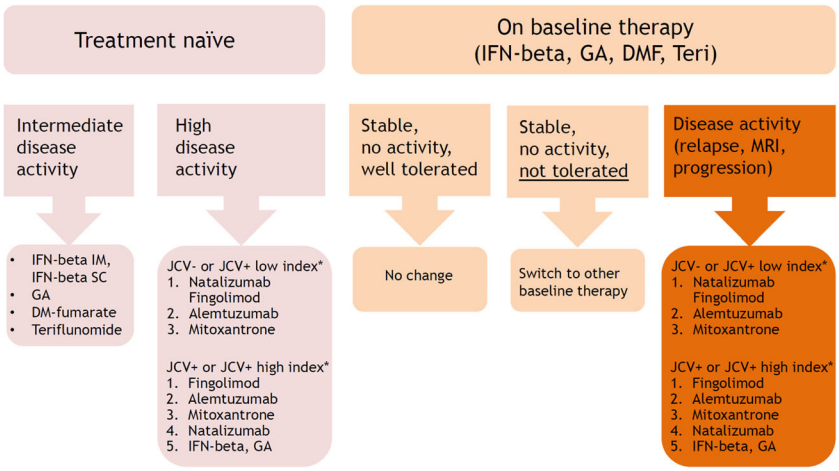

Fig. 1 Suggested treatment algorithm in relapsing-remitting multiple sclerosis (RR-MS). Patients with low or intermediate disease activity should use one of the baseline disease-modifying therapies (DMTs) of interferon (IFN)-β, glatiramer acetate (GA), dimethyl fumarate (DMF), or teriflunomide (Teri). The decision for one of them is based on a number of considerations (side effects, convenience, wish for children, etc.). Patient with aggressive MS (high disease activity) can start with one of the escalation DMTs, stratified by JC virus (JCV) status. JCV antibody-negative patients should preferably start with natalizumab or fingolimod, JCV antibody-positive patients preferably with fingolimod or alemtuzumab. Patients that are already on baseline therapy can switch to another baseline DMT when encountering tolerability issues. At breakthrough disease, patients should be treated as patients with high disease activity (i.e., stratified by JCV antibody status). Modified according to [107]. *According to Plavina et al. antibody indices may accurately predict PML risk in natalizumab [65]. The index is increasingly used for stratification, but should be used with caution until validated in independent samples. IM = intramuscular; SC = subcutaneous; DM = dimethyl; MRI = magnetic resonance imaging

DMTs available that exhibit differing efficacy, safety profiles, mechanisms of action, and modes of treatment, resulting in a quite complex landscape of individualized therapy in RR-MS (Table 1). Herein, we have described current knowledge and experience with the existing therapies and suggest a treatment algorithm for most of the situations commonly encountered in clinical management (see Fig. 1). Further treatment options are being evaluated [2], and more knowledge about the safety profile of the existing DMTs is to be expected. In addition to ongoing developments regarding B- and T-cell-targeted approaches combination therapies have been proposed in the past but remain an unresolved issue. Apart from economic considerations (the already high cost of all DMTs could be increased by combination preparations), only a few systematic approaches have been undertaken and have rather tamed enthusiasm: some were unsuccessful (e.g., CombiRx, comparing a combination of intramuscular IFN-1βa plus GA with either 1 of the 2 [104]), or raised safety issues when combining 2 immunomodulatory agents (e.g., PML cases in SENTINEL comparing natalizumab plus intramuscular IFN-1βa with IFN-β alone). An interesting approach, however, may be the combination of immunomodulatory agents with neuroprotective ones like LINGO-1 [105, 106]. The field of stratification of patients to the optimal DMT is also developing with so far only some rough approximations (e.g., JCV status, planned pregnancy). Further research is required for profiling patients, for example to T- or B cell-targeted approaches or to susceptibility for specific infectious side effects. The landscape is therefore going to evolve and new information has to be incorporated constantly into the management decisions that we make.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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