ORIGINAL ARTICLE

Disease-modifying treatments for multiple sclerosis – a review of approved medications

Ø. Torkildsen[a,b], K.-M. Myhr[a,c] and L. Bø[a,b]

[a]*Department of Clinical Medicine, KG Jebsen MS Research Centre, University of Bergen, Bergen;* [b]*Department of Neurology, Norwegian Multiple Sclerosis Competence Centre, Haukeland University Hospital, Bergen; and* [c]*Department of Neurology, Norwegian Multiple Sclerosis Registry and Biobank, Haukeland University Hospital, Bergen, Norway*

Keywords:
disease-modifying, multiple sclerosis, review, treatment

Accepted 24 August 2015

European Journal of Neurology 2015, **23** (Suppl. 1): 18–27

doi:10.1111/ene.12883

Background and purpose: There is still no curative treatment for multiple sclerosis (MS), but during the last 20 years eight different disease-modifying compounds have been approved for relapsing–remitting MS (RRMS).
Methods: A literature search was conducted on published randomized controlled phase III trials indexed in PubMed on the approved medications until 21 May 2015.
Results: In this review the mode of action, documented treatment effects and side effects of the approved MS therapies are briefly discussed.
Conclusions: Based on current knowledge of risk–benefit of the approved MS medications, including factors influencing adherence, it is suggested that oral treatment with dimethyl fumarate or teriflunomide should be preferred as a starting therapy amongst the first-line preparations for *de novo* RRMS. In the case of breakthrough disease on first-line therapy, or rapidly evolving severe RRMS, second-line therapy with natalizumab, fingolimod or alemtuzumab should be chosen based on careful risk–benefit stratification.

Introduction

Multiple sclerosis (MS) is a common cause of disability in young adults. Irreversible axonal damage occurs even in the earliest phases of disease evolution [1]. Although some people with relapsing–remitting MS (RRMS) have a 'benign' disease course with minimal disease activity and impairment, most patients experience increasing disability over time and eventually convert to secondary progressive MS (SPMS). There is still no curative treatment, but during the last 20 years eight different therapies have become available including interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, natalizumab, fingolimod, alemtuzumab and mitoxantrone, and several new compounds are in development. All the approved medications have mainly anti-inflammatory effects and increasing evidence indicates that all of them are more effective in the early phases of disease development [2,3]. With the development of more effective treatments, the aim of treatment has changed dramatically in the last decades, from simply reducing relapse rates and slowing of disability progression to preventing all evidence of new disease activity [4]. In the current review, the mode of action and documented effect of the current immunomodulatory MS therapies are briefly discussed.

Correspondence: Ø. Torkildsen, Norwegian Multiple Sclerosis Competence Centre, Department of Neurology, Haukeland University Hospital, 5021 Bergen, Norway (tel.: +4755976145; fax: +4755915901; e-mail: oivind.torkildsen@gmail.com).

Methods

The article is based on English-language original clinical treatment trials and selected review articles, identified through a literature search in PubMed using the search term 'multiple sclerosis' combined with 'interferon beta', 'glatiramer acetate', 'teriflunomide', 'dimethyl fumarate', 'natalizumab', 'fingolimod', 'mitoxantrone' and 'alemtuzumab'. The search was terminated on 21 May 2015. Titles and abstracts have been reviewed, and full-text versions of articles examined in the majority of cases. Particular emphasis has been placed on randomized controlled phase III studies.

First-line medications

Interferon beta

Interferon beta is a naturally occurring polypeptide predominantly produced by fibroblasts. Its anti-inflammatory effects are largely believed to result from the inhibition of T-lymphocyte proliferation, a shift of cytokine response from an inflammatory response to an anti-inflammatory profile, and reduced migration of inflammatory cells across the blood–brain barrier [5]. Interferon beta is available for MS treatment in recombinant forms, as interferon beta-1a or interferon beta-1b. Interferon beta-1b is given as a dose of 250 μg subcutaneously every other day; interferon beta-1a is given as a dose of 30 μg intramuscularly once weekly or subcutaneously at doses of 22 or 44 μg three times a week.

Phase III trials of all the interferon beta preparations have shown beneficial effects in reducing the annualized relapse rate (ARR) by about 30%–34%, reducing the progression of disability in RRMS as well as magnetic resonance imaging (MRI) disease activity [6–9]. A recent study on peginterferon beta-1a, given once every 2 weeks, found comparable results, with a reduction in ARR at 36% [10]. Studies of all interferon beta preparations [11–14] have also reported a reduced risk of new disease activity amongst people with clinically isolated syndrome (CIS), as shown by a significantly prolonged time to a second relapse and reduction in new MRI lesions, in some cases also a delayed progression of disability. All the interferon beta preparations have been evaluated in the treatment of SPMS. The first interferon beta-1b study showed efficacy of the treatment as measured by both relapse rate and disability progression [15], but later studies of both interferon beta-1b and interferon beta-1a could only detect treatment effects on the relapse rate [16–18]. Thus, it seems that only SPMS patients with superimposed relapses benefit from interferon beta treatment [15–18]. Interferons have not been documented to be effective in primary progressive MS (PPMS) [19].

Most patients (50%–75%) experience flu-like symptoms, including muscle aches, fever, chills, headache and back pain, that usually appear 2–8 h after an injection and resolve within 24 h. Liver enzymes may be elevated and bone marrow function may be depressed, which warrants periodic surveillance of liver function and blood counts before starting therapy and every 6 months thereafter [11–14]. Isolated cases of severe injection-site reactions involving infection or necrosis as well as severe cases of acute liver failure and pancreatitis have been reported. Long-time exposure to interferon beta does not seem to increase the risk of cancer [20,21] or infections.

Interferon beta treatment may induce formation of specific neutralizing antibodies (NABs). NAB formation is less likely during treatment with intramuscular interferon beta-1a [22]. The NABs usually appear within 6–18 months of treatment, and evidence is accumulating that the efficacy of treatment is reduced in the presence of NABs. Accordingly, it is recommended to test all patients for the presence of NABs every 6 months during the first 2 years of therapy, and treatment should be switched in patients who are confirmed to be NAB positive [22]. In cases of clinically stable disease, switches to other non-interferon first-line treatments are recommended, but second-line treatment should be considered in cases of breakthrough disease.

Glatiramer acetate

Glatiramer acetate is a pool of synthetic peptides, resembling sequences of myelin basic protein, with an average length of 40–100 residues. The mechanisms of action have not been fully clarified but are probably largely related to anti-inflammatory effects by promoting Th2 deviation under the development of Th2 glatiramer acetate reactive CD4+ T cells. These can accumulate in the central nervous system (CNS) and promote bystander suppression by releasing anti-inflammatory cytokines [23]. Glatiramer acetate is administered as subcutaneous injections of 20 mg once a day.

Glatiramer acetate treatment trials in RRMS [24] showed a significant reduction in ARR (29%) and a reduction in gadolinium-enhanced MRI activity [25]. In a treatment trial of CIS with silent MRI lesions, glatiramer acetate treatment was found to significantly prolong time to a second relapse and to reduce the risk of new MRI lesions [26]. Glatiramer acetate has not been investigated for the treatment of SPMS and has not shown significant benefit in PPMS patients [27].

Glatiramer acetate is usually well tolerated, but most patients (65%) experience injection-site reactions (pain, erythema, swelling and pruritus). About 15% report a transient self-limited systemic reaction (immediately after injection) of facial flushing and chest tightness, accompanied at times by palpitation, anxiety and dyspnoea. Other reported side effects are lymphadenopathy, dyspnoea and lipoatrophy [24–26]. Lipoatrophy is permanent and is perhaps the most severe side effect. There have not been reports of increased cancer risk or increased risk of infections with prolonged use of glatiramer acetate.

Teriflunomide

Teriflunomide is an immunomodulatory agent that selectively and reversibly inhibits the mitochondrial

enzyme dihydroorotate dehydrogenase, required for *de novo* pyrimidine synthesis. This leads to reduced proliferation of dividing cells that need *de novo* synthesis of pyrimidine to expand. The therapeutic effect in MS is not fully understood but it is probably mediated by a reduced number of circulating lymphocytes [28]. Teriflunomide is administered as tablets, 14 mg once daily.

Two phase III trials in RRMS [29,30] showed that teriflunomide 14 mg once daily, compared to placebo, reduced the ARR by 31%–36%, the rate of disability progression by 26%–27% and MRI gadolinium-enhancing lesions by about 80%. Another phase III trial of teriflunomide 14 mg once daily, compared to interferon beta-1a 44 μg subcutaneously three times weekly, showed similar effects on the ARR (0.26 and 0.22 respectively) and on time to a new relapse or termination of treatment [31]. Teriflunomide 14 mg once daily has been tested in a randomized, double-blind, placebo-controlled trial of CIS patients with silent MRI lesions. Teriflunomide treatment was associated with significantly prolonged time to a second relapse and a reduction in new MRI lesions [32]. Teriflunomide has not been studied for the treatment of progressive MS.

Common adverse events include upper respiratory tract infection, urinary tract infection, paraesthesia, diarrhoea, nausea, hair thinning, alanine aminotransferase increase, reduction in blood leucocytes and increase in blood pressure [29,30]. Relatively frequent (every second week) alanine aminotransferase screening during the first 6 months of treatment is recommended and thereafter every second month [29,30]. Teriflunomide treatment should be stopped if liver transaminase levels increase three times above upper normal levels. Regular measurements of blood pressure, white blood cells and platelet counts are also recommended. Teriflunomide has a long half-life. Elimination with cholestyramine or activated charcoal for 11 days can accelerate teriflunomide elimination, leading to more than 98% decrease in teriflunomide plasma concentrations. Liver function needs to be carefully monitored during teriflunomide treatment, and discontinuation of therapy should be considered if a serum transaminase increase more than three times the upper normal level is confirmed. Rare cases of pancytopenia have been reported with the use of leflunomide; this should also lead to treatment termination.

Dimethyl fumarate

Dimethyl fumarate is an immunomodulatory agent with anti-inflammatory properties, but the mechanism of action in MS is only partially understood. Pre-clinical studies indicate that dimethyl fumarate responses are primarily mediated through activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway. Dimethyl fumarate has also been shown to upregulate Nrf2-dependent antioxidant genes in patients [33]. Dimethyl fumarate is administered as a 240 mg capsule twice daily.

Two phase III trials of RRMS [34,35] showed that dimethyl fumarate 240 mg twice daily, compared to placebo, reduced the ARR by 44%–53%, the rate of disability progression by 22%–32% and MRI gadolinium-enhancing lesions by about 75%–94%. Compared to glatiramer acetate as an active comparator in one of the trials [35], dimethyl fumarate 240 mg twice daily reduced the ARR by 24% and the rate of disability progression by 17%. These differences were not significant and the study was not powered to detect statistically significant differences in treatment effect. The number of new and enlarging MRI T2 lesions was significantly reduced by about 36%. Dimethyl fumarate has not been studied for the treatment of CIS or progressive MS.

Common adverse events include flushing, nausea, diarrhoea and abdominal pain [34,35]. The treatment may also reduce white blood cell counts and give elevations of hepatic transaminases; regular blood tests are therefore recommended [34,35]. Dimethyl fumarate should be stopped if liver transaminase levels increase three times above upper normal levels. Recently, a case of John Cunningham virus (JCV) induced progressive multifocal leucoencephalopathy (PML) was reported in a patient who had received dimethyl fumarate [36]. An additional four PML cases have been previously reported in psoriasis patients who had received fumaderm [37]. Prolonged severe lymphopaenia (<500 cells per cubic millimetre) that persists for more than 6 months has been suggested as a risk factor for PML. In the case of persistent lymphopaenia, dimethyl fumarate should be terminated in JCV-positive patients.

Second-line medications

Fingolimod

Fingolimod is an oral sphingosine 1-phosphate receptor (S1PR) modulator that subsequent to its phosphorylation binds with high affinity to S1PR, which in turn leads to an internalization and degradation of the receptor in different tissues and cell types, including lymphocytes. As a consequence, fingolimod inhibits the ability of autoreactive lymphocytes to egress from the lymph nodes towards the CNS. Fingolimod 0.5 mg capsules are given orally once daily [38].

Two phase III trials in RRMS [38,39] showed that fingolimod 0.5 mg once daily, compared to placebo,

reduced the ARR by 48%–55%, the rate of disability progression by 25%–30% and MRI gadolinium-enhancing lesions by more than 80%. Another study comparing fingolimod 0.5 mg once daily to interferon beta-1a 30 μg intramuscularly once weekly showed a reduced ARR by 52%, a reduced rate of disability progression by 25% and a reduced number of MRI gadolinium-enhancing lesions by more than 50% amongst those who received fingolimod [40]. Fingolimod is currently not documented to be effective against CIS, SPMS or PPMS.

Common adverse events include upper respiratory tract infection, headache, cough, diarrhoea and back pain [38,39]. Fingolimod may also cause a transient bradycardia and atrioventricular block. It is therefore recommended to monitor patients continuously with an electrocardiogram for 6 h after the first dose, and to extend the monitoring of patients who develop specific clinically relevant signs of heart arrhythmia (http://www.fda.gov/Drugs/DrugSafety/ucm303192.htm). Generally, fingolimod should not be used by patients with known cardiac arrhythmias or patients using other medications known to induce bradycardia. Rare adverse events of elevated liver enzymes and macular oedema may occur, and regular blood sampling and a routine eye examination after 3 months of treatment are therefore recommended. One death due to a fulminant primary varicella zoster infection was reported in one of the phase III trials [40]. Therefore a blood sample for screening of previous varicella zoster infection is advised, and in the case of a negative screening test vaccination is recommended prior to treatment initiation.

Natalizumab

Natalizumab is a monoclonal antibody against α4-integrin, blocking the interaction with its ligands. The mechanism of action is largely through preventing adherence of activated leucocytes to inflamed endothelium, thus inhibiting the migration of inflammatory cells into the CNS. Natalizumab is administered as a 300 mg intravenous infusion every 4 weeks [41].

The pivotal phase III trial of RRMS showed that natalizumab monotherapy reduced the ARR by 68%, the rate of disability progression by 54% and MRI gadolinium-enhancing lesions by more than 90% compared to placebo [41]. Another study [42] found that treatment with natalizumab added to interferon beta-1a was significantly more effective than interferon beta-1a alone in reducing ARR, new T2 lesions and disability progression. Natalizumab is currently not documented to be effective against CIS, SPMS or PPMS.

Although natalizumab is generally well tolerated, the treatment is associated with an increased risk of developing PML [43]. This is a potentially life-threatening CNS infection of oligodendrocytes by the JCV. Therefore all patients receiving natalizumab should be screened for previous JCV infection. The risk for PML in JCV-negative patients is low (<0.09/1000) and is probably associated with recent seroconversion (estimated as 2%–3% each year) or a false negative test. Amongst the JCV-positive patients the risk of developing PML is influenced by treatment duration and previous immunosuppressive treatment. The risk is relatively low during the first 2 years of treatment and increases thereafter. The highest risk is found amongst JCV-positive patients who previously have also received immunosuppressive treatment after 2 years of treatment (~1/60) [44]. Anti-JCV antibody levels seem also to differentiate PML risk in anti-JCV antibody positive patients with no prior immunosuppressant use [45]. As a general rule, it is recommended that JCV-positive patients who have been treated with natalizumab for more than 2 years should be switched to another second-line therapy. Based on current knowledge, a washout time of 8 weeks seems to reduce the risk of rebound effect compared to longer washout periods. In the case of a low JCV index (<1.5), natalizumab treatment may in some cases be continued after thorough information is given to the patient and under careful evaluation for new symptoms that may represent PML [44]. Three-monthly JCV index evaluation and MR examination is then recommended. It is recommended to retest JCV-negative patients every 6 months and JCV-positive patients should be carefully informed about the risk for PML at treatment initiation and after 2 years of treatment.

Natalizumab treatment may induce an immune response, with the formation of persistent NABs (~4%–6%) against the preparation. NABs usually appear within the first 12 months of treatment, reduce the efficacy of the treatment and are associated with higher rates of infusion-related adverse events. Accordingly, patients should be tested for NABs at 6 and 12 months of therapy and later for infusion-related adverse events or treatment failure. NABs can occur transiently and positive findings should therefore be confirmed within 3 months before deciding to switch therapy. Testing can be discontinued in patients who remain NAB negative during the first year of therapy.

Alemtuzumab

Alemtuzumab is a recombinant, humanized monoclonal antibody directed against CD52, a cell surface antigen present at high levels on especially T and B lymphocytes. Alemtuzumab acts through antibody-dependent cellular cytolysis and complement-mediated

lysis following cell surface binding. The mechanism by which alemtuzumab exerts its therapeutic effects in MS is suggested to be by a depletion and repopulation of lymphocytes that reduces the potential for relapses and thereby delays disease progression [46]. Alemtuzumab is administered by intravenous infusion for two treatment courses. The initial treatment course is 12 mg/day for five consecutive days (60 mg total dose), and the second treatment course is 12 mg/day for three consecutive days (36 mg total dose) administered 12 months after the initial treatment course. Additional courses may be given 12 months after the latest treatment course if necessary. Based on the European Medicines Agency (EMA) licence alemtuzumab has indication as a first-line medication in active RRMS. Because the treatment increases the risk of secondary autoimmunity, most European neurologists would use this drug as a second-line preparation, however.

Two phase III trials of RRMS have shown that alemtuzumab 12, compared to interferon beta-1a 44 μg administered subcutaneously three times weekly, reduced the ARR by 49%–55%, the rate of disability progression by 30%–42% and MRI gadolinium-enhancing lesions by 61%–63% [47,48]. Alemtuzumab has currently not been studied in patients with CIS or PPMS and has not been demonstrated to be effective in SPMS [49,50].

Patients commonly experience infusion-associated reactions including flushing, nausea, headache, tachycardia, urticaria, rash, pruritus, pyrexia and fatigue [47–50]. Oral antiviral prophylaxis with aciclovir 200 mg twice daily (or equivalent) should be administered and continued for a minimum of 1 month after the last dose. Alemtuzumab treatment is associated with increased risk of upper respiratory tract infection and urinary tract infection. Alemtuzumab treatment may also result in the formation of autoantibodies and increased risk of autoimmune-mediated conditions (occurring a median of 32 months after the first treatment), including thyroid disorders (41%), immune thrombocytopenic purpura (3.5%) or, rarely, nephropathies (e.g. anti-glomerular basement membrane disease) (<1%) [51]. Based on the risk of autoimmune-mediated conditions, monthly blood and urine analyses are recommended for 4 years after the last dosing of alemtuzumab.

Mitoxantrone

Mitoxantrone is a synthetic anthracenedione derivative and is mostly used in treating various malignancies. It interacts with nuclear DNA and is a potent immunosuppressive agent targeting proliferating immune cells, inhibiting proliferation and inducing apoptosis of T lymphocytes, B lymphocytes, macrophages and other antigen-presenting cells.

Limited efficacy data are available, but controlled studies of highly active RRMS have shown significant efficacy of the treatment, as shown by a 60%–70% reduction in the relapse rate (compared with placebo or intravenous methylprednisolone) as well as reduced disability progression and MRI disease activity [52,53]. The largest phase III investigator-blinded study randomized patients with worsening RRMS and SPMS for 5 or 12 mg of mitoxantrone per square metre of body surface or placebo every 3 months for 2 years [54]. The treatment showed a 66% reduction in the ARR in the high-dose arm compared with placebo, and reduced disability progression and MRI disease activity. Mitoxantrone has not been included in treatment trials of patients with CIS or PPMS.

Side effects such as transient nausea, fatigue, mild hair loss (for days to a week) and menstrual disturbances are frequent (60%–70%) [54]. Additional side effects are urinary tract infection (about 30%) as well as elevated liver enzymes and leucopenia (about 15%–20%). Mitoxantrone-induced amenorrhoea and acute promyelocytic leukaemia have also been reported. The treatment induces transient leucopenia, with a nadir after about 10 days, and thus follow-up blood control is needed. Although not in the phase III trial, lethal congestive heart failure and therapy-related leukaemia have been reported, even years after treatment ends [55,56]. Due to the potential cardiotoxicity, the maximum cumulative dose is restricted to 120–140 mg/m^2 of body surface, and echocardiograms should be done before, during and after treatment. Mitoxantrone is teratogenic and is absolutely contraindicated in pregnancy. The use of mitoxantrone has rapidly decreased due to the risk of severe complications and the increasing number of alternative highly effective and less toxic treatment options.

Suggested treatment strategies

Individualized therapy is advocated; the ideal treatment option would be the safest treatment that eliminates clinical and radiological evidence of disease activity [3]. Most patients would start on a first-line therapy but then be changed quickly to a second-line medication in the case of breakthrough disease activity (Fig. 1). Evidence of clinical disease activity (relapses and/or accumulating disability) with or without new MRI lesions is in general accepted as an indication for switching to more potent second-line therapies. In this context, models like the Rio or modified Rio score [57] have been increasingly accepted as a tool to monitor the treatment effect. The score is

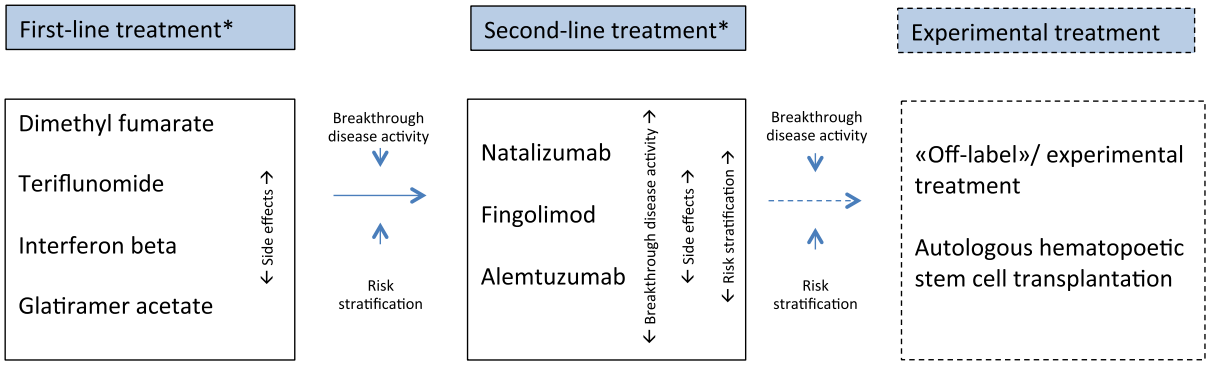

Figure 1 Treatment algorithm for treatment-naïve patients with RRMS. *Patients with rapidly evolving severe RRMS should start directly on a second-line therapy. Breakthrough disease activity is defined as one new clinical relapse with significant influence on disability and/or new signs of radiological disease activity (≥3 active MRI lesions) during the last year whilst on first-line medication.

based on evaluation of treatment response by the combination of clinical (relapse and disability progression) and MRI disease activity (Rio score) or relapse and MRI disease activity only (modified Rio score) during the first year of interferon treatment. Increasing evidence indicates that patients experiencing a new clinical relapse with significant influence on disability and/or new signs of radiological disease activity (≥3 active MRI lesions) during the last year, whilst on first-line medications, should be considered for switching to more potent medications [58,59].

Another possible treatment strategy is induction treatment, which consists of early use of immunosuppressive medications followed by long-term maintenance therapy [60]. This treatment regime has been used with success for patients with aggressive RRMS, using mitoxantrone [61]. The use of mitoxantrone is declining because of its long-term safety profile. Alemtuzumab is approved as a first-line therapy, and could also be considered an induction treatment because of its long-term effects on the immune system. This could be an attractive treatment option for patients with a highly active disease course, as 70.1% of the alemtuzumab-treated patients in the CARE-MS study remained free of new lesions and MRI activity in year 4, despite most receiving their last treatment course 3 years prior [62].

Choosing amongst the first-line medications

The main findings from the pivotal and phase III studies performed are given in Tables 1 and 2. Although the placebo-controlled trials indicate numerically higher efficacy on ARR from dimethyl fumarate (about 44%–53%) compared to the other first-line preparations (about 30%–35%), data on direct comparisons of the agents are limited. Head-to-head comparison between dimethyl fumarate and glatiramer acetate indicated numerically (although not statistically significant) better effect from dimethyl fumarate [35]. Head-to-head comparison between teriflunomide and high-frequency interferon beta-1a showed comparable effects on the ARR [29]. Head-to-head comparisons between intramuscular low-dose and low-frequency interferon beta-1a and subcutaneous high-dose and high-frequency interferon beta-1a and interferon beta-1b have shown that high-dose and high-frequency interferon beta regimens have short-term benefits on the relapse rate and MRI activity [63,64]. Limitations in the design of these studies have been widely discussed, however, and the long-term differences in efficacy may be reduced by a significantly lower frequency of NAB formation with low-dose and low-frequency interferon beta-1a. Head-to-head comparisons of glatiramer acetate and subcutaneous high-dose and high-frequency interferon beta-1a and interferon beta-1b have shown similar clinical benefit from the treatments, with some MRI parameters in favour of the interferon beta preparations [65,66].

Disease-modifying treatment for MS is a long-lasting therapy for most patients. Adherence to treatment is thus crucial, and many patients may therefore prefer oral treatment. Consequently starting with an oral first-line drug is suggested. In the case of intolerability or unacceptable side effects, switching between the oral preparations or with one of the injectable preparations should be considered. The injectable medications have been used for a longer period than the oral medications, and more long-term safety data are therefore available [20,21]. Similarly, there are more long-term safety data on pregnancies occurring during treatments with both glatiramer acetate and interferons, pointing to a relative safety of use [67]. These could be good reasons for still choosing an injectable medication as first-line treatment. It is important to

Table 1 Randomized placebo-controlled phase III clinical trials of the approved relapsing–remitting multiple sclerosis medications

Medication	*N*	Trial name (reference)	ARR		Disability progression	
			Relative reduction	ARR	Relative reduction	EDSS progression
First-line						
Interferon beta-1b	124 vs. 123	MSSG [6]	34%	0.84 vs. 1.27	29% (N.S.)	0.20 vs. 0.28
Interferon beta-1a i.m.	158 vs. 143	MSCRG [7]	18%	0.67 vs. 0.82	37%	0.22[a] vs. 0.35[a]
Interferon beta-1a s.c.	184 vs. 187	PRISMS [8]	32%	1.73 vs. 2.56	32%	0.26 vs. 0.38
Peginterferon-1a	500 vs. 512	ADVANCE [10]	36%	0.26 vs. 0.40	36%	0.07 vs. 0.11
Glatiramer acetate	125 vs. 126	CMSSG [24]	29%	1.19 vs. 1.68	12% (N.S.)	0.22 vs. 0.25
Teriflunomide	358 vs. 363	TEMSO [29]	31%	0.37 vs. 0.54	26%	0.20 vs. 0.27
Teriflunomide	370 vs. 388	TOWER [30]	36%	0.32 vs. 0.50	24%	0.16 vs. 0.21
Dimethyl fumarate	410 vs. 408	DEFINE [34]	53%	0.17 vs. 0.36	41%	0.16 vs. 0.27
Dimethyl fumarate	359 vs. 363	CONFIRM [35]	44%	0.22 vs. 0.40	24% (N.S.)	0.13 vs. 0.17
Second-line						
Fingolimod	425 vs. 418	FREEDOMS [38]	55%	0.18 vs. 0.40	28%	0.18 vs. 0.25
Fingolimod	358 vs. 355	FREEDOMS-2 [39]	48%	0.21 vs. 0.40	14% (N.S.)	0.25 vs. 0.29
Natalizumab	627 vs. 315	AFFIRM [41]	68%	0.23 vs. 0.73	42%	0.17 vs. 0.29
Mitoxantrone[b]	60 vs. 64	MIMS [54]	66%	0.35 vs. 1.02	64%	0.08 vs. 0.22

N, number of patients included in each treatment arm – note that the number only includes treatment arms with US Food and Drug Administration/European Medicines Agency approved dosages; ARR, annualized relapse rate, active medication versus placebo; EDSS, Expanded Disability Status Scale; N.S., not significant; i.m., intramuscular; s.c., subcutaneous. Disability progression is the proportion of patients with 3 months confirmed progression in EDSS score, active medication versus placebo. [a]6 months confirmed progression in EDSS score; [b]not approved in all European countries.

Table 2 Randomized controlled phase III clinical trials of the approved relapsing–remitting multiple sclerosis medications, where the medications have been compared head-to-head with another active multiple sclerosis medication

Medication	Compared to	*N*	Trial name (reference)	ARR		Disability progression	
				Relative reduction	ARR	Relative reduction	EDSS progression
First-line							
Interferon beta-1b	Interferon beta-1a i.m.	92 vs. 96	INCOMIN [63]	24%	0.5 vs. 0.7	44%	0.13 vs. 0.30
Interferon-beta-1a s.c.	Interferon-beta-1a i.m.	339 vs. 338	EVIDENCE [64]	16%[a]	0.54 vs. 0.64	13% (N.S.)	0.13 vs. 0.15
Interferon beta-1a s.c.	Glatiramer acetate	386 vs. 378	REGARD [65]	3% (N.S)	0.30 vs. 0.29	25% (N.S.)	0.12 vs. 0.09
Interferon-beta-1b	Glatiramer acetate	899 vs. 448	BEYOND [66]	3% (N.S)	0.33 vs. 0.34	5% (N.S.)	0.22 vs. 0.20
Teriflunomide	Interferon-beta 1a s.c.	111 vs. 104	TENERE [31]	4% (N.S)	0.26 vs. 0.22	-	-
Dimethyl fumarate	Glatiramer acetate	359 vs. 350	CONFIRM [35]	24% (N.S)	0.22 vs. 0.29	17% (N.S.)	0.13 vs. 0.16
Second-line							
Fingolimod	Interferon beta-1a i.m.	431 vs. 435	TRANSFORMS [40]	52%[a]	0.16 vs. 0.33	25% (N.S.)	0.06 vs. 0.08
Alemtuzumab	Interferon beta-1a s.c.	376 vs. 202	CARE MS-1 [47]	55%	0.18 vs. 0.39	30% (N.S.)	0.08[b] vs. 0.11[b]
Alemtuzumab	Interferon beta-1a s.c.	426 vs. 202	CARE MS-2 [48]	49%	0.26 vs. 0.52	42%	0.13[b] vs. 0.21[b]

N, number of patients included in each treatment arm – note that the number only includes treatment arms with US Food and Drug Administration/European Medicines Agency approved dosages; ARR, annualized relapse rate during 2 years of follow-up, medication in column 1 versus medication in column 2; EDSS, Expanded Disability Status Scale; i.m., intramuscular; s.c., subcutaneous; N.S., not significant. Disability progression is the proportion of patients with 3 months confirmed progression in EDSS score, medication in column 1 versus medication in column 2. [a]1 year follow-up.; [b]6 months confirmed progression in EDSS score.

continuously evaluate the treatment regimen, aiming for optimal adherence, considering both the administration form and side-effect profiles.

Choosing amongst the second-line medications

In the case of breakthrough disease activity despite a full and adequate course of a first-line preparation, switching to natalizumab, fingolimod or alemtuzumab should be considered. Although alemtuzumab is licensed as a first-line medication in active RRMS, many European neurologists would use this drug as a second-line preparation, due to potential side effects. Second-line therapy should also be considered in the case of patients with rapidly evolving severe RRMS

defined by two or more disabling relapses in 1 year, and with gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared to a previous recent MRI. Careful risk stratification for potential adverse effects is important, and most neurologists would prefer fingolimod or alemtuzumab for patients who are JCV positive. Similarly, in the case of contraindications for fingolimod or alemtuzumab, one of the other second-line treatment options should be considered. The use of mitoxantrone has become less frequent due to the relatively high risk of serious side effects, and may only be used in some cases of SPMS. Stratification for differences in clinical effect is difficult due to the lack of treatment studies with head-to-head comparisons of second-line therapies. Some neurologists would prefer natalizumab for JCV-negative patients due to the numerically higher reduction of ARR in pivotal trials, although treatment effect cannot be directly compared between different study populations.

For a small group of patients who do not respond to the approved second-line treatments, off-label treatments like rituximab [68] or ofatumumab [69] or experimental therapy with autologous haematopoietic stem cell transplantation [70] may be considered. These treatment options have currently not been tested in large phase III trials, but phase II trials or case series reports have shown promising results. These treatment options also seem to be effective against RRMS and not the progressive forms of the disease [71].

Conclusions and future challenges

Although the last decade has shown a revolution in treatment options for patients with MS, this has mainly benefited newly diagnosed patients with an RRMS disease course. None of the approved medications or experimental therapies has shown convincing evidence of slowing down or preventing disease progression in patients with SPMS or PPMS. Thus there is an urgent need to also improve the treatment options for patients who have entered a progressive phase.

Disclosure of conflicts of interest

Ø. Torkildsen has participated on a scientific advisory board for Biogen Idec, Merck-Serono and Genzyme and received speaker honoraria and travel grants from Genzyme, Merck-Serono, Novartis and Biogen Idec. K.-M. Myhr has participated on scientific advisory boards for Novartis Norway, Biogen Idec and Genzyme; received funding for travel from Bayer, Novartis, Merck-Serono and Biogen Idec; received speaker honoraria from Bayer, Genzyme, Sanofi-Aventis, Novartis, Merck-Serono and Biogen Idec; and received unrestricted research support from Bayer, Sanofi-Aventis, Novartis, Merck-Serono, Biogen Idec, Pronova Biocare and the Norwegian MS Society. L. Bø has participated on scientific advisory boards for Novartis Norway; received funding for travel from Sanofi-Aventis, Novartis, Merck-Serono and Biogen Idec; received speaker honoraria from Bayer, Genzyme, Sanofi-Aventis, Novartis, Merck-Serono and Biogen Idec; and received unrestricted research support from Bayer, Sanofi-Aventis, Novartis, Merck-Serono and Biogen Idec.

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