ELSEVIER

Because the first oral drugs are currently being introduced in multiple sclerosis therapy, we give an update on approved and future treatment options.

Recent developments in approved and oral multiple sclerosis treatment and an update on future treatment options

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Multiple sclerosis (MS) is the most common chronic neurological disease in young adults in the western world. There was no specific treatment available for this serious disorder until the introduction of the immunomodulatory drug interferon-β in the mid-1990s. Since then, the number of agents and treatment strategies for MS has increased rapidly. Deeper knowledge on the heterogeneous nature of MS cleared the way for several more specific, more effective and more comfortable therapies. Here, because of the exciting recent developments concerning oral treatment forms for MS, we summarize the current state of approved and future therapy options. In particular, we highlight oral treatment options in MS.

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system (CNS) that predominately affects the myelin sheath of white matter but also affects the myelin sheath of grey matter. It is the most common cause of acquired disability in young adults in the western world (central Europe and the USA) with an incidence of four to eight newly diagnosed patients per 100 000 people per year, peaking at about 30 years of age [1]. In Europe, approximately 380 000 individuals are affected with MS [2].

During the past two decades, new drugs – such as interferon-β (IFN-β) preparations and glatiramer acetate (GA) – were introduced in the treatment of MS, which formerly had been an untreatable disease. These early disease-modifying drugs significantly reduced relapse rate and the formation of inflammatory lesions in the CNS, which are visualized by magnetic resonance imaging (MRI) scans [3–5]. Some patients, however, do not respond well to this therapy, and some suffer an aggressive course of MS, with little or no change prompted by these early immunomodulatory treatments. The drugs of the second generation in MS treatment yield new hope. Natalizumab, the first approved drug of the second generation, demonstrated an enormous and hitherto unknown efficacy in MS [6]. In the waiting line, there are a tremendous number of agents for MS treatment. It has been suggested that some of them will even provide better efficacy than natalizumab; however, the use of second-generation drugs is accompanied by the risk of potentially serious complications, such as progressive multifocal leukencephalopathy (PML)

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[6,7]. The risks will have to be weighed carefully against the well-known safety profile of IFN-βs and GA. Besides the potential advantages for many patients, a disadvantage of the first-generation therapeutics is that they are applied parenterally. The era of oral MS treatment will start in the next few months in Europe and will probably characterize the coming years of MS treatment. For years, extensive efforts have been undertaken to develop new and innovative drugs for MS therapy that combine therapeutic effectiveness and more comfortable application forms for this chronic disease.

Today, we are at the beginning of a new era in MS therapy as various specific individual therapeutics are on the verge of approval. Based on our former review in this journal [8], we want to give an update on approved MS drugs, new oral drugs and possible future developments.

Approved treatments, recent developments and latest news

Modern MS therapy is based on three main factors: treatment of the acute relapse to relieve relapse-related symptoms, disease-modifying therapy (DMT) to achieve a long-term delay in the course of the disease, and the symptomatic treatment of MS. Although symptomatic treatment is of great importance, it is beyond the scope of this article, in which we focus on DMT. By definition of a panel of German-speaking MS experts, the terms 'baseline therapy' and, if baseline therapy fails, 'escalating therapy' refer to recommended DMT based on best available evidence [9,10]. For a more comprehensive overview, please see our former article [8].

In 1993, the FDA approved the first DMT for relapsing remitting MS (RRMS), subcutaneous IFN-β-1b, marketed as Betaseron™ in the USA and as Betaferon™ in Europe [11]. Since then, five other parenteral medications have been approved for the treatment of MS: subcutaneous IFN-β-1a, intramuscular IFN-β-1a, GA, mitoxantrone and natalizumab [4,6,12–15] (Table 1).

Base line therapy

IFN-β

There are two different kinds of IFN-β preparations from four companies (Table 1) approved as first-line DMT in MS treatment having the support of class I evidence from several phase III trials [11,12,15].

There is evidence that early and irreversible axonal damage in the CNS of MS patients occurs before the clinical onset of the disease. Several recent studies have shown that treatment with DMT should begin early in the course of disease [16,17]. Because of the high inflammatory activity in the early stages of the disease, treatment should start even after the first clinical episode of demyelination, termed 'clinically isolated syndrome' (CIS). Intramuscular IFN-β-1a (Avonex™), IFN-β-1b (Betaferon™, Betaseron™ or Extavia™), subcutaneous IFN-β-1a 22 μg (Rebif™) and GA (Copaxone™; see below) have all been shown to be effective treatments for CIS [16,18]. An ongoing study (REFLEX) is comparing low-dose and high-dose IFN-1a (Rebif™) for CIS [19]. Two observational studies were performed to evaluate the long-term safety and efficacy of IFN-β-1b in RRMS patients [17,20]. The results of both follow-up studies (16 years and 7 years, respectively) suggested that early and continuous long-term treatment with IFN-β-1b was beneficial, owing to the excellent long-term safety profile and the fact that the progression of disability was slowed.

GA

With the support of class I evidence from phase III trials, GA (Table 1) was approved for the treatment of RRMS in 1997 [4]. As with efficacy of IFN-β for CIS, new results from a phase III study showed a significant delay in the conversion of CIS into clinically definite MS in patients treated with GA [15]. A recently presented small study suggested that a lower frequency of GA application might also be effective as the approved daily administration. In this study, 48 RRMS patients were randomized into two groups who either continued receiving GA daily or were switched to receive GA

TABLE 1

List of approved drugs for base line and escalation therapy in RRMS.

Trademark/company	Substance	Application	Dose	Indication	Therapeutic mechanism
Base line therapy					
Avonex/Biogen Idec, USA	IFN-β-1a	Weekly, i.m.	30 μg	CIS, RRMS	Immunomodulation
Betaferon/Bayer, Germany Betaseron/Bayer, USA Extavia/Novartis, CH	IFN-β-1b	Every other day, s.c.	250 μg	CIS, RRMS	Immunomodulation
Rebif/EMD Serono, CH	IFN-β-1a	Three times a week, s.c.	22 μg/44 μg	CIS (22 μg), RRMS	Immunomodulation
Copaxone/Teva Pharmaceuticals, Israel	Glatiramer acetate	Daily, s.c.		CIS, RRMS	Immunomodulation
Escalation therapy					
Tysabri/Biogen Idec, USA	Natalizumab	Monthly, i.v.	300 mg	RRMS	Blockade of immune-cell migration
Novantrone/OSI Pharmaceuticals, USA Ralenova/Wyeth Pharma, USA	Mitoxantrone	Every three months, i.v. (alternatively, every month for a maximum of six months; the protocol is not equal in all countries)	12 mg/m^2	RRMS, early SPMS	Immunosuppression

Abbreviations: μg, micrograms; CIS, clinically isolated syndrome; IFN, interferon; i.m., intramuscularly; i.v., intravenously; RRMS, relapse remitted multiple sclerosis; s.c., subcutaneously; SPMS, secondary-progressive multiple sclerosis.

twice weekly. The annualized relapse rate, mean Expanded Disability Status Scale, proportion of relapse-free patients and proportion of patients without disease progression were comparable in the two groups at month 24. Further trials investigating a larger cohort are needed.

Escalation therapy

Approval of natalizumab (Tysabri™) and mitoxantrone (Novantrone™, Ralenova™) has enabled additional strategies for treating RRMS patients who do not respond sufficiently to basic therapy with IFN-β or GA. Natalizumab (Table 1) is the first monoclonal antibody therapy for MS, approved in 2006 in Europe and in 2004 in the USA (and reapproved in 2006) [6]. This drug demonstrated enormous efficacy in RRMS with a 68% reduction in relapse rate and a 42% decrease in the rate of disability progression after one year. Post hoc analyses of data from the AFFIRM study showed that 37% of natalizumab-treated MS patients were free from clinical and radiological disease activity [21]. However, this potent drug bears a certain risk of potentially severe side-effects. The most important adverse event is the development of PML, a severe opportunistic brain infection by the JC virus [7]. Before June 2010, approximately 71 400 people, worldwide, had received at least one dose of natalizumab since marketing resumption. Between July 2006 and September 2010, 68 cases of confirmed PML were documented in MS patients during natalizumab therapy, of which 14 were fatal. The risk of PML increases with duration of exposure to natalizumab. Current estimations on the risk to develop PML range from 0.8 to 1.3 per 1000 patients who have received at least 24 infusions (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm199872.htm; http://www.biogenidec.ch/Tysabri.aspx?ID=4697). The median therapy duration to onset of PML symptoms was 25 months (range 6–80 months). There were also cases of confirmed PML in patients without any previous use of DMT for MS, but it has been suggested that previous therapy with other immunosuppressive drugs (e.g. mitoxantrone and cyclophosphamide) might increase the risk of PML [22].

The first clinical symptoms of PML present as cognition deficits, personality changes, visual disturbances, progressive hemiparesis and seizures [23]. Sometimes it can be difficult to differentiate between a relapse of MS and a slow worsening of PML symptoms. The use of MRI and the detection of the JC virus in the cerebrospinal fluid have led in all but one case to the diagnosis. Plasma exchange or immunoabsorption was used to wash out natalizumab quickly and to shorten the period in which natalizumab remains active [24]. Exacerbation of symptoms and enlargement of MRI lesions have occurred from days to a few weeks after plasma exchange, indicative of an immune reconstitution inflammatory syndrome (IRIS). IRIS is a rare condition characterized by a severe inflammatory response that can occur during immune system recovery, causing an unexpected worsening in a patient's condition after return of immune function. This treatable syndrome is known in patients with HIV-associated PML, but it seems to be more common and more severe in patients with natalizumab-associated PML [25].

It is necessary to optimize clinical vigilance for PML during natalizumab therapy. Predictive markers for patients at risk for PML would be eligible. In a study from our laboratory, we investigated the adhesion molecule profiles of mononuclear cells in blood from MS patients before natalizumab therapy and in a three-month follow-up for one year. We concluded that the determination of adhesion molecule profiles could be promising candidates for the development of a biomarker system to determine patients at risk for PML [26].

Mitoxantrone (Table 1) has shown its efficacy in RRMS and early secondary-progressive MS (SPMS) cases, in particular in cases of highly active or rapidly worsening disease, in different trials. The limiting factors for mitoxantrone are serious and life-threatening side-effects, including cardiotoxicity depending on the accumulative dose, acute myeloid leukemia and gonadal dysfunction [27]. Six new cases of acute myeloid leukemia were described in the follow-up of 230 patients with worsening relapsing MS and secondary-progressive disease treated with mitoxantrone [28]. A literature review showed 32 further cases during mitoxantrone treatment. The treatment duration to onset of acute myeloid leukemia was from 1 to 45 months. The cumulative incidence was about 2.82%. In former series, the cumulative incidence varied from 0.15% to 0.80%. Moreover, in a recent safety report, the risk of systolic dysfunction and leukemia was higher than previously reported, and adjustments to the risk are warranted [27]. A strict indication and hematological monitoring for mitoxantrone therapy are therefore necessary.

The oral treatment era

The most prominent current change in MS treatment is the implementation of the first approved oral therapies: two of them, fingolimod (FTY720) and cladribine, will presumably be available in Europe within a few months. Moreover, sustained-release fampridine (dalfampridine in the USA) has already been approved in the USA and will probably be approved in the European Community in 2011. Both oral DMTs, cladribine and fingolimod, have the potential to initiate a further revolution in future MS treatment because they will be the first two substances that have been broadly tested in modern phase III trials and will not be administered by injection. However, they also bear the – albeit rare – risk of serious side-effects, such as infections, and an increased tumor risk [29,30]. Broader application of these substances and planned extensive safety evaluation programs will indicate whether these concerns are justified.

Dalfampridine is the first MS-specific symptomatic drug. In contrast to the currently available DMTs, which are only approved for RRMS (and for SPMS with overlying relapses), dalfampridine has been shown to provide beneficial effects in all subtypes of MS (RRMS, SPMS and primary progressive MS, or PPMS) [31].

Independent of all concerns about potential risks, these three oral substances will significantly improve the therapeutic options in MS. They will, therefore, enhance the quality of MS treatment by optimizing the therapy for individual patients in this heterogeneous disease.

Cladribine

The prodrug cladribine is a synthesized purin nucleoside analogue that was developed at the Scripps Research Institute in the late 1970s [32]. The active metabolite 2-chlorodeoxyadenosine triphosphate accumulates within the cell, causes disruption of cellular metabolism, and inhibits DNA synthesis and repair, which

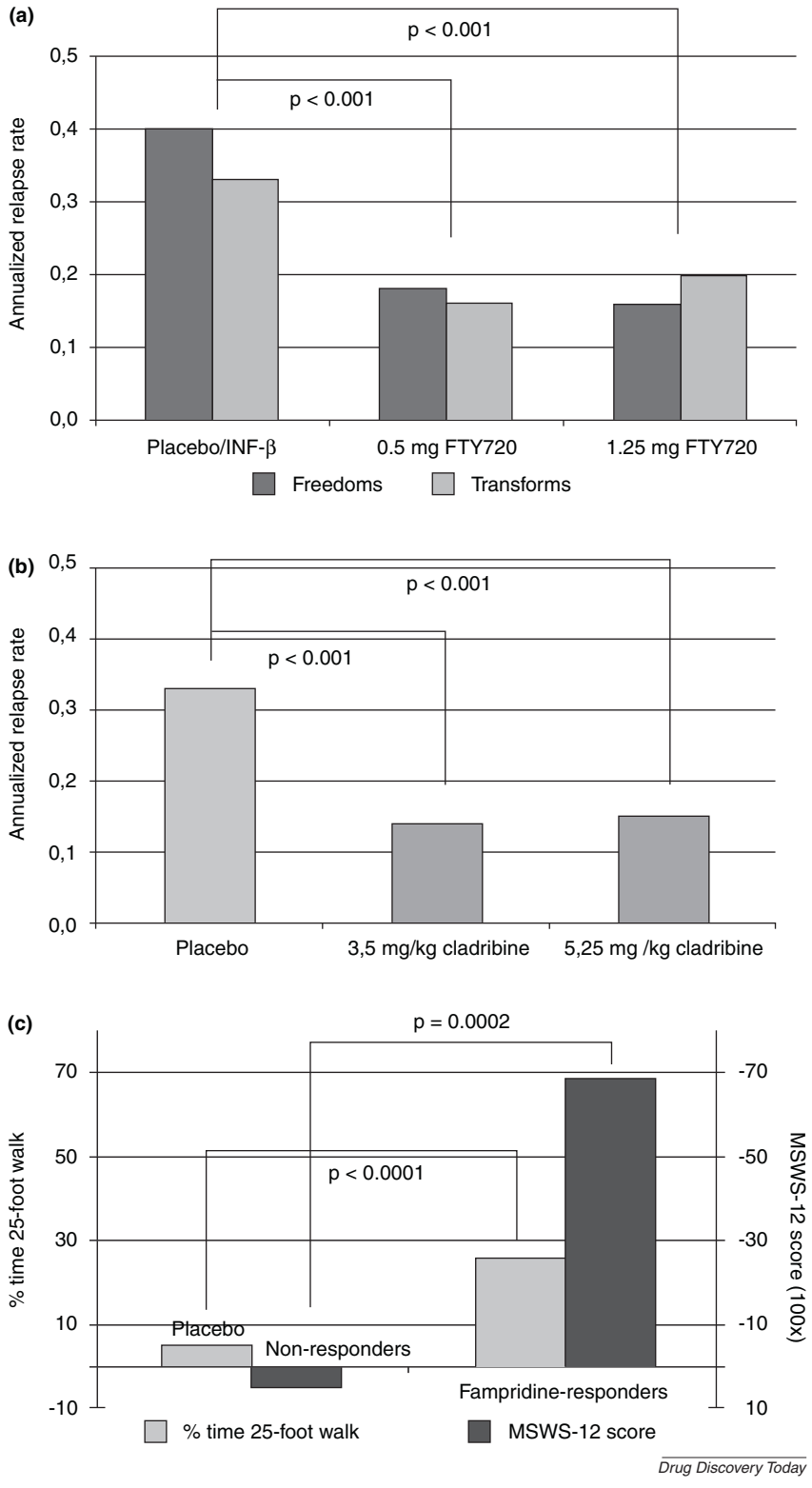

FIGURE 1

Combined results of primary outcome measures: **(a)** 0.5 mg and 1.25 mg oral fingolimod (FTY720) led to a significant decrease in the annualized relapse rate compared to placebo over 24 months (FREEDOMS) and compared to weekly interferon-beta (IFN-β)-1a i.m. over 12 months (TRANSFORMS). **(b)** 3.5 mg/kg and 5.25 mg/kg cladribine resulted in a significant decrease in annualized relapse rate compared to placebo in the 96 week CLARITY study. **(c)** Twice daily 10 mg fampridine over a 14 week treatment period significantly improved walking speed compared to placebo (measured by the time taken to walk 25 feet) and significantly improved the ambulatory disability (assessed by the 12-item MS walking scale) of fampridine responders compared to non-responders.

TABLE 2

Overview on clinical and imaging endpoints of major phase III trials evaluating oral MS treatment forms.

Clinical and imaging endpoints	Cladribine – CLARITY (Ph III)			Fingolimod – FREEDOMS (Ph III)			Fingolimod – TRANSFORMS (Ph III)		
	Placebo (*n* = 437)	**3.5 mg/kg (*n* = 433)**	**5.25 mg/kg (*n* = 456)**	**Placebo (*n* = 418)**	**0.5 mg (*n* = 425)**	**1.25 mg (*n* = 429)**	**IFN-β-1a (*n* = 431)**	**0.5 mg (*n* = 429)**	**1.25 mg (*n* = 420)**
Primary end point									
Annualized relapse rate (95% CI)	0.33 (0.29–0.38)	0.14 (0.12–0.17)	0.15 (0.12–0.17)	0.40 (0.34–0.47)	0.18 (0.15–0.22)	0.16 (0.13–0.19)	0.33 (0.26–0.42)	0.16 (0.12–0.21)	0.20 (0.16–0.26)
***p* value**		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001
Patients without relapse, *n* (%)	266 (60.9)	345 (79.7)	360 (78.9)	192 (45.6)	299 (70.4)	321 (74.7)	297 (69.3)	356 (79.0)	336 (79.8)
***p* value**		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001
Disability-related secondary end points									
Absence of disability progression (95% CI)	N/A	N/A	N/A	88.5	87.5	81.0	92.1	94.1	93.3
***p* value**		N/A	N/A		0.004	0.01		0.5	0.25
Time to 3-months sustained change in EDSS score: 10th percentile of time to event (months)	10.8	13.6	13.6	N/A	N/A	N/A	N/A	N/A	N/A
EDSS score at 24 months (mean)	N/A	N/A	N/A	0.13 ± 0.88	0.00 ± 0.88	−0.03 ± 0.88	N/A	N/A	N/A
Change from baseline in EDSS score (mean)	N/A	N/A	N/A	N/A	N/A	N/A	0.01 ± 0.78	−0.08 ± 0.79	−0.11 ± 0.90
***p* value**		0.02	0.03		0.002	0.002		0.02	0.06
MRI outcomes (lesion activity)									
Gd-enhancing T1-weighted lesions, *n* (mean)	0.91	0.12	0.11	1.1 ± 2.4	0.2 ± 0.8	0.2 ± 1.1	0.51 ± 1.86	0.23 ± 0.97	0.14 ± 0.58
***p* value**		<0.001*	<0.001*		<0.001	<0.001		<0.001	<0.001
New/enlarged/active T2-weighted lesions, *n* (mean)	1.43	0.38	0.33	2.5 ± 5.5	2.5 ± 7.2	0.51 ± 1.86	2.6 ± 5.8	1.7 ± 3.9	1.5 ± 2.7
***p* value**					<0.001	<0.001		<0.001	0.004
Combined unique lesions	1.72	0.43	0.38	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: CI, confidential interval; EDSS, Expanded Disability Status Scale; Gd, gadolinium; N/A, not available.

* *p* value for all comparisons with placebo for imaging measurements.

TABLE 3

Summarized severe adverse events of oral cladribine observed during the CLARITY study.

	CLARITY study (n%)		
Cladribine	**3.5 mg/kg**	**5.25 mg/kg**	**Placebo**
Total severe adverse events	8.4	9.0	6.4
Death	0.5	0.4	0.5
Neoplasms	1.4	0.9	0
• **benign**	0.7	0.4	0
• **malignant**	0.7	0.4	0
Serious infections	2.3	2.9	1.6

subsequently results in apoptosis of the cell [33]. Interestingly, this cladribine metabolite accumulates predominately within lymphocyte subsets (CD4+ T cells, CD8+ T cells and CD19+ B cells), resulting in a rapid and sustained reduction of the respective lymphocyte subsets [29].

Parenteral cladribine has been approved for leukemia subtypes, in particular hairy cell leukemia and chronic lymphatic B cell leukemia, for several years [34]. Driven by the fact that cladribine leads to a depletion of lymphocyte subsets that have been shown to exert an important pathogenic role in MS, the effect of parenteral cladribine on disease activity in MS patients was investigated in the late 1990s in three (two phase II and one phase III) randomized, double-blind placebo-controlled (DBPC) studies [35–37]. These three studies showed significant reductions in T1 gadolinium-enhancing MRI lesions as a measure for disease activity and an improvement in clinical disability scores. The results from these trials were difficult to interpret, however, because patients with different disease stages (RRMS, SPMS and PPMS) were included.

Encouraging efficacy and safety data both from parenteral MS trials and from studies and clinical experience with leukemia patients led to the development of an oral formulation of cladribine. The cladribine tablets for treating MS orally (CLARITY) study is a randomized, DBPC trial investigating the efficacy of two doses of cladribine (cumulative doses 3.5 mg/kg and 5.25 mg/kg) in 1326 RRMS patients over 96 weeks [29]. Oral cladribine resulted in a significant reduction of the annual relapse rate compared with placebo (Fig. 1). Both doses had a comparable efficacy (Table 2), with a slightly favorable side-effect profile in the low-dose group (Table 3). The application regime of only the first four to five days of the first two months within a year is extraordinarily comfortable for patients. This application regime is responsible for the major concerns regarding the substance, however, because the drug stays within the body, effectively suppressing key players of the cellular immune surveillance, for more than ten months. As cladribine leads to a lymphopenia of unknown duration, further concerns to be clarified in future are a potentially increased susceptibility for infections (in particular herpes virus), the potential for a slightly increased risk of malignant diseases and up-to-date potential long-term side-effects. Keeping in mind that MS is a disease of young adults, there is also an open question of adverse effects on unborn children in pregnancies and on fertility.

Because of its promising efficacy and safety data (and after the approval of Movectro™ by the Russian Health Ministry in July 2010), it was anticipated that cladribine would be the first oral MS treatment available in the European Community. On 23 September 2010, however, the Committee for Medicinal Products for Human Use (the expert panel of the European Medicines Agency) adopted a negative opinion, recommending the refusal of the marketing authorization for Movectro™. It is, therefore, not clear when and for what indication cladribine will be available. The trademark name of oral cladribine in North America will presumably be Encadix™. It is also not yet clear for which indications (highly presumable for RRMS) it will be approved, whether it will be approved as a first-line or a second-line treatment and what the contraindications will be.

Fingolimod

Although fingolimod – like cladribine – leads to a reduction of pathogenic lymphocytes, it has a different and novel mode of action. Fingolimod (2-amino-2[2-(4-octylphenyl)ethy]-1,3-propanediol, or FTY720) is a structural analogue of myriocin (also known as sphingosine 1-phosphate, or S1P), a metabolite of the ascomycete *Isaria sinclairii* [38]. Interestingly, this fungus has already been applied in Chinese traditional herbal medicine. Once phosphorylated, fingolimod becomes a high-affinity agonist of

TABLE 4

Summarized severe adverse events of oral fingolimod observed during the FREEDOMS and the TRANSFORMS trials.

	FREEDOMS study (n%)			TRANSFORMS study (n%)		
Fingolimod (FTY720)	**0.5 mg**	**1.25 mg**	**Placebo**	**0.5 mg**	**1.25 mg**	**IFN-β-1a**
Total severe adverse events	10.1	11.9	13.4	7.0	10.7	5.8
Death	0	0.2	0.5	0	0.5	0
Cardiovascular disorders	0.9	0.7	0.7	0.9	3.6	0
Localized skin cancers	0.9	0.4	0.9	1.4	0.5	0.2
Breast cancer	0	0.2	0.7	0.5	0.5	0
Dyspnea	N/A	N/A	N/A	0	0.5	0
Eye disorders	0	0.7	0	N/A	N/A	N/A
Serious infections	N/A	N/A	N/A	0.2	1.7	1.4
Appendicitis	N/A	N/A	N/A	0	0.5	0.5
Herpes viral infections	N/A	N/A	N/A	0.2	0.7	0.2

Abbreviations: N/A, not available.

the G-protein-coupled S1P receptor-1 on lymphocytes. The most relevant mechanism of FTY720 is entrapment of disease-relevant autoreactive lymphocytes within lymph nodes, which leads to a reduced infiltration of potentially autoaggressive immune cells into the CNS [39]. Additional therapeutic effects beyond this immune-cell based mechanism are very likely: the lipophilic structure of FTY720 enables the compound to readily cross the blood–brain barrier [40] and related G-protein-coupled S1P receptors are expressed in the immune system, cardiovascular system and CNS [41]. In particular, the fact that S1P receptor-1 was detected on neural cells was the rationale for conducting animal experiments, with promising data suggesting that fingolimod might promote neuroprotective and reparative processes [42].

In two recently published phase III trials, orally administered FTY720 was shown to significantly improve MRI and clinical disease activity in patients with RRMS [30,43] (Table 2). Interestingly, investigated daily doses of both 0.5 mg and 1.25 mg were similarly effective in the Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis over 12 months (TRANSFORMS) and in the placebo-controlled FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis over 24 months (FREEDOMS) study (Fig. 1). In the TRANSFORMS study, however, serious adverse events (Table 4) – such as an increased infection rate, including two fatal herpes virus infections and cardiovascular and ocular events (in particular bradycardia and macular edema) – were predominately seen in the high-dose group. Furthermore, a slightly increased risk of neoplasm, in particular skin tumors, was suggested. By contrast, the FREEDOMS study reported more neoplastic diseases in the placebo group than in the treatment group (Table 4). Broader use of fingolimod after approval and the ongoing extension phases of the two clinical phase III trials will further clarify long-term safety, particularly regarding (herpes) infection rates and adverse cardiovascular and ocular side-effects.

According to its impressive therapeutic efficacy and promising safety data in an extensive number of patients investigated in the two phase III trials, low-dose (0.5 mg) fingolimod (traded as Gilenia™) has recently been approved as the first available disease-modifying oral MS therapy on the US market and in Russia for RRMS patients. For fingolimod, however, it can only be speculated what its exact indications and contraindications will be after its approval by the European Medicines Agency.

Fampridine

Unlike cladribine and fingolimod, which are disease-modifying drugs, the sustained-release (SR) formulation of fampridine (fampridine-SR or dalfampridine) is a new attempt at the symptomatic treatment of walking disturbances in MS. Since 1980s, the potassium-channel blocker fampridine has been investigated in various neurological conditions, in particular to improve nerve conduction and muscular weakness [44], and 14 studies assessing the benefit of fampridine on MS symptoms have been published [44,45]. Data on the efficacy of fampridine were inconsistent, however, presumably because of fluctuating plasma levels [44,46,47]. Moreover, evidence was gathered for the occurrence of epileptic seizures and impaired consciousness during phases with elevated plasma levels [48,49]. An SR formulation of fampridine, therefore, was developed.

In a recently published randomized, multicentre, DBPC phase III trial involving 301 patients with any type of MS, the efficacy of fampridine-SR treatment (10 mg twice daily) on walking parameters was assessed over 14 weeks [31]. Because it is a symptomatic treatment approach, patients with different MS subtypes (RRMS, SPMS and PPMS) were included. Thirty-five per cent of the fampridine-SR treated MS patients were determined as treatment responders, showing a maintained improvement in the applied walking tests as compared to patients receiving placebo (Fig. 1).

Positive efficacy data in combination with an excellent safety profile have led to the approval of dalfampridine (Ampyra™, Elan/Accorda Therapeutics) by the FDA in January 2010. Moreover, data from the open-label extension phase indicate that the drug continues to improve walking speed in some patients over a longer period without any safety concerns [50]. The approval of fampridine-SR by the European Medicines Agency is expected for 2011.

Although a responder rate of 35% seems low, an improvement in walking is of major importance for patients with impaired ambulation because this highly influences individual independency. Another important achievement of the approval of fampridine-SR is new hope for individuals with PPMS and SPMS because MS-specific treatment options for patients suffering from the chronic progressive disease courses are strongly limited.

Trends in MS treatment

In spite of recent extraordinary developments, the current therapeutic options for MS are still limited for some individual patients. In some patients, there is a long way to go to achieve the eligible aim of immune therapy: fewer relapses, less disability, fewer neurological deficits, fewer T2 lesions and gadolinium-enhancing lesions, and less axonal loss and brain atrophy, in combination with more safety in long-term treatment. Here, we show trends in MS therapy for alternative treatment regimes to achieve these aims. Because this is a fast-growing field with numerous studies, we listed the most important developments in our view in Table 5, but the list is not exhaustive. Below, we introduce the highlights of treatment regimes and new drugs for MS therapy in more detail.

Combination therapy in MS

There are numerous combination therapies in medical treatment, and the rationale for combination therapy in MS seems to be strong. Larger trials of combination therapy have shown conflicting results, but there are some factors supporting the use of combination therapy. Drug combinations could target different aspects of immunopathogenesis, and severe side-effects could be prevented by the use of lower doses of individual medications than are necessary for monotherapy, improving tolerability and compliance. In Table 6, recent studies of combination therapies in MS are listed.

Induction versus escalation therapy

Recently, there has been a rethinking of the current therapeutic concept in RRMS. The traditional concept of a baseline therapy followed by an escalation in patients with insufficient response has been challenged by the concept of induction therapy [51]. An initial treatment of MS patients with more potent immunosuppressive therapies – such as cytotoxic drugs – with a subsequent

TABLE 5

Overview on new drugs under evaluation.[a]

Substance (application form)	Mechanism of action	Results	Ongoing studies/perspectives	Reference
Unspecific immunomodulation and immunosuppression				
Atorvastatin (oral)	Cholesterol synthetase inhibitor, anti-inflammatory and immunomodulatory	Ph II (monotherapy or as comedication with IFN-β): active MRI lesions reduced. Well tolerated.	Ph IIb (SWABIMS): comedication with IFN-beta.	[80,81]
Cladribine (oral)	Lymphocytotoxic effects	Ph II: active MRI lesions reduced. Ph III (CLARITY): significant reduction in relapse rate.	Ph III (CLARITY extension phase). Approval for treatment of RRMS expected in 2012.	[29]
Cyclophosphamide (i.v.) high-dose	Immunoablative, anti-inflammatory	Ph I/II (monotherapy): effective in patients with very active RRMS. Not effective in SPMS and PPMS.	Ongoing and planned trials: as induction/escalation therapy and in connex to stem cell therapy.	[82–84]
Fumaric acid (oral)	Shift to TH-2 cytokines, putative neuroprotective	Ph IIb: active MRI lesions reduced. Well tolerated.	Ph III (CONFIRM).	[85]
Laquinimod (oral)	Shift from TH-1 to TH-2, release of neurotrophic factors, putative neuroprotective	Ph II: active MRI lesions reduced. Well tolerated.	Ph III (ALLEGRO and BRAVO).	[86,87]
Minocyclin (oral)	Anti-inflammatory, putative neuroprotective	Ph II (add on to GA, RRMS): safe and well tolerated.	Further trials warranted.	[88]
Mycophenolate (oral)	Immunosuppressive	Ph II (comedication with Avonex, RRMS): safe and well tolerated, promising clinical and MRI data.	Further trials warranted.	[89]
Simvastatin (oral)	Cholesterin synthetase inhibitor, anti-inflammatory	Ph III (comedication with Avonex): reduction in relapse rate.	Ph IV (comedication with Avonex, CIS); Ph II (SPMS); Ph III (comedication with Copaxone).	[90]
Stem cells	Hematopoietic stem cell therapy (inf.): reestablishment of new immune system	12-year observational study (EBMT): sustained remission for more than five years.	Ph III (ASTIM).	[58]
	Mesenchymal stem cell therapy (inf.): axonal protection, remyelination	Ph I/II: relative safety.	Consensus for future trials recently established.	[57]
Teriflunomide (oral)	Reduced B- and T-cell proliferation, anti-inflammatory	Ph II (monotherapy; comedication with IFN-β or GA): active MRI lesions reduced. Improvement of clinical endpoints. Well tolerated.	Ph III (monotherapy).	[91,92]
Treosulfan (i.v.)	Cytotoxic alkylating agent	Open-label study in patients with active SPMS: active MRI lesions reduced. Well tolerated.	Larger trials required.	[93]
Specific immunomodulation: antibodies				
Alemtuzumab (i.v.)	Lymphocyte depletion (anti-CD52)	Ph II (CAMMS-223): active MRI lesions reduced. Reduced relapse rate and disability progression.	Ph III (two studies). Ph II (CAMMS-223) extension study for long-term effects.	[94,95]
Daclizumab (i.v.)	Reduced T-cell activation and stimulation of natural killer cells (anti-CD25)	Ph II: active MRI lesions and relapse rate reduced in patients non responsive to IFN-β. Ph II (CHOICE): active MRI lesions reduced upon add-on administration to IFN-β.	Ph III (DECIDE).	[96,97]
Ocrelizumab (i.v.)	Depletion of B cells (anti-CD20)	Humanized form of rituximab.	Ph II ongoing; Ph III (RRMS and PPMS) planned.	[98]
Rituximab (i.v.)	Depletion of B cells (anti-CD20)	Ph II (RRMS): active MRI lesions reduced. Reduced relapse rate. Ph II/III trial (OLYMPUS, PPMS): failed primary endpoints.	Trials on long-term safety warranted.	[99,100]
Specific immunomodulation: small molecules and others				
BAF-312 (oral)	Blocks lymphocyte egress from secondary lymphatic organs (S1P receptor modulator)	Reduction of absolute lymphocyte numbers in healthy volunteers.	Ph II.	[101]

TABLE 5 (*Continued*)

Substance (application form)	Mechanism of action	Results	Ongoing studies/perspectives	Reference
CDP323 (oral)	Blocks lymphocyte transmigration (binds to alpha-4 integrin subunit)	Ph II safety and tolerability study: discontinued – lacking efficacy!	–	[102]
CS-0777 (oral)	Blocks lymphocyte egress from secondary lymphatic organs (S1P receptor modulator)	Ph I: transient, dose-dependent decrease in circulating lymphocytes.	Further trials warranted.	[103]
Fingolimod (oral)	Blocks lymphocyte egress from secondary lymphatic organs (S1P receptor modulator)	Ph III (FREEDOMS, TRANSFORMS): efficacy in relapse rates and MRI outcomes.	Ph III (FREEDOMS, TRANSFORMS) extension studies. Approval by EMA expected in 2011.	[30,43]
T-cell vaccination (inf.)	Autologous attenuated T-cell vaccine of myelin-reactive T cells	Ph I/II: dose-finding for development of the T-cell vaccine Tovaxin.	Ph I and II.	[56]
Neuroprotective agents				
Lamotrigine (oral)	Putative sodium-channel blocker	Ph II (SPMS): failed primary endpoints.	Ph II (comedication with Avonex, RRMS).	[69,104]
Lipoic Acid (oral)	Antioxidant	Pilot study: well tolerated.	Further trials are planned.	[75]
Riluzole (oral)	Glutamate receptor antagonist	Pilot study (PPMS): cervical cord atrophy and development of T1 hypointense lesions reduced.	Ph II (comedication with Avonex, CIS).	[71]
Symptomatic treatment: highlights				
Fampridine – SR (oral)	Potassium-channel blocker	Ph III: improved walking ability.	Ph III (extension study). Approval by EMA expected in 2011.	[31]
Donepezil (oral)	Cholinesterase-inhibitor	Ph II/III: significant improvement in memory performance.	Results from a larger multicenter trial are awaited.	[105,106]

Abbreviations: CIS, clinically isolated syndrome; EBMT, European Group for Blood and Marrow Transplantation; EMA, European Medical Agency; i.v., intravenous; inf., infusion; MRI, magnetic resonance imaging; MS, multiple sclerosis; Ph, phase of trial; PPMS, primary progressive MS; RRMS, relapse remitting MS; S1P, sphingosine 1-phosphate; SPSS, secondary-progressive MS; TH, T-helper cell.

[a] Mechanism of action and results from completed trials and future perspectives are summarized. Information on ongoing studies have been collected from www.clincialtrials.gov.

switch to weaker immunomodulatory agents might yield a greater effect on the course of the disease. A study investigating induction therapy with mitoxantrone followed by IFN-β-1b has been performed [52]. The induction group received monthly mitoxantrone for six months, followed after three months by IFN-β-1b every other day for the remainder of the three-year trial. The other group received IFN-β-1b combined with monthly intravenous methylprednisolone 1000 mg for the first six months, then IFN-β-1b alone for the remainder of the three-year trial. All endpoints, including time to progression of disability, annual relapse rate and proportion of participants who remained relapse-free were significantly better in the induction group.

Alemtuzumab

This humanized monoclonal antibody targets the CD52 antigen, a glycosyl-phosphatidylinositol-anchored protein on lymphocytes and monocytes. Alemtuzumab binding induces complement-mediated lysis, antibody-dependent cell toxicity and apoptosis and, therefore, depletion of leukocytes [53]. In MS trials, it is applied once a year over a cluster of several days, which is comfortable for patients. In a recent phase II trial, alemtuzumab was compared to IFN-β-1a in patients with RRMS. In comparison to high-dose IFN-β-1a (44 μg s.c. three times a week), alemtuzumab significantly reduced the rate of sustained disability and the annualized relapse rate and demonstrated superiority in reducing MRI lesions [54]. These impressive and promising results were accompanied by serious side-effects, such as immune-mediated thrombocytopenic purpura (six patients, one death caused by brain hemorrhage) and thyroid complications in 22.7% of the patients. Although these risks seem to limit a broader use of the drug at the moment, the profound effect of this drug on the disease course might make it an important treatment option in particular aggressive disease courses in MS. Moreover, strategies have already been developed and are necessary in future to discover serious side-effects earlier, to prevent and to treat them.

Autologous T-cell vaccination

Increased frequency of encephalitogenic myelin antigen-specific T cells in patients with MS support the theory of the involvement of myelin basic protein, proteolipid protein and myelin oligodendrocyte glycoprotein in the pathogenesis of MS [55]. The rationale behind T-cell vaccination is to trigger protective immunity through the use of an attenuated form of the disease-causing antigen in autoimmune disease. The strategy is the selection and expansion of autologous myelin-reactive T cells from MS patients, which are reintroduced after irradiation. In animal studies, T-cell vaccination seemed a promising approach, and a panel of clinical phase I and II studies including patients with RRMS and chronic progressive MS is underway. In addition, one was successfully completed recently. The phase I/II trial was a dose-escalation study to identify the optimal dose for the further development of the T-cell vaccine Tovaxin [56].

Stem cells

At present, two different kinds of stem cells are being investigated as therapeutic options for severe diseases: bone-marrow-derived hematopoietic stem cells and adult mesenchymal stem cells (MSCs). MSCs are heterogeneous populations of stromal cells

TABLE 6

Overview on trials of combination therapy

Combination therapy with corticosteroids

	ACT	ASA [21]	NORMIMS [107]	MECOMBIN [108]
Platform therapy	IFN-β-1a (i.m.)	IFN-β-1a (i.m.)	IFN-β-1a (s.c.)	IFN-β-1a (i.m.)
Combination therapy	Oral methotrexate 20 mg weekly (i.v.) methylprednisolone for three days every two months	Oral azathioprine 50 mg per day, oral prednisone 10 mg every other day	Oral methylprednisolone 200 mg for 5 consecutive days every month	Oral methylprednisolone 500 mg for three days every month
Design	Multicentered, randomized, controlled, 12-month follow-up period	Randomized, DBPC study	Multicentre, randomized, DBPC study	Multicentered, DBPC study
Primary endpoint	New or enlarging T2 lesions	Annualized relapse rate	Mean annualized relapse rate	Time to sustained EDSS progression
Result	Negative	Negative	Positive	Negative

Combination therapy with natalizumab

	SENTINEL [109]	GLANCE [110]
Platform therapy	IFN-β-1a (i.m.)	Glatiramer acetate (s.c.)
Combination therapy	Monthly natalizumab 300 mg (i.v.)	Monthly natalizumab 300 mg (i.v.)
Design	Multicentered, randomized, DBPC	DBPC
Primary endpoint	Relapse rate at one year, cumulative probability of sustained EDSS progression at two years	Development of new active MRI lesions
Result	Positive (trial stopped one month early because of two cases of PML)	Negative

Combination therapy with cytotoxic drugs

	French-Italian Mitoxantrone-Interferon-beta Trial [52]	Cyclophosphamide Trial [111]
Platform therapy	IFN-β-1b (s.c.)	IFN-β (s.c.)
Combination therapy	Mitoxantrone	Cyclophosphamide
Design	Three years, randomized, controlled. Mitoxantrone induction followed by IFN-β-1b maintenance	Randomized, DBPC
Primary endpoint	Time to progression of disability, annualized relapse rate	Not yet applicable
Result	Positive	Not yet applicable

Abbreviations: ACT, Avonex Combination Trial; ASA, Avonex-Steroids-Azathioprine trial; DBPC, double-blind placebo-controlled; EDSS, Expanded Disability Status Scale; GLANCE, GA and Natalizumab Combination Evaluation; IFN, interferon; i.m., intramuscularly; i.v., intravenously; MECOMBIN, Methylprednisolone in Combination with IFN-β-1a trial; NORMIMS, Nordic Trial of Oral Methylprednisolone as Add-On Therapy to IFN-β-1a for the Treatment of RRMS; PML, progressive multifocal leukencephalopathy; s.c., subcutaneously.

derived from connective tissue, adipose tissue or bone marrow. While in their physiological environment, MSCs regulate hematopoietic stem cell activity in the bone marrow and are able to differentiate into cells of the mesenchymal lineage; in addition, they are immunosuppressive, provide neuroprotection and influence endogenous neural progenitors in their activity [57].

By contrast, the key idea of hematopoietic stem cell transplantation (HSCT) is to remove the pool of disease-causing differentiated immune cells executing the autoimmune response by immunoablative chemotherapeutics and to re-establish a 'new' immune system by transplanting autologous hematopoietic stem cells. Autologous HSCT has been used since 1996 in selected patients with very severe courses of autoimmune disease who are unresponsive to conventional therapy, justifying the increased risk of transplant-related mortality. Recent results from the largest observational cohort study worldwide, which combined HSCT data reported to the European Group for Blood and Marrow Transplantation between 1996 and 2007, showed that autologous HSCT induced sustained remissions for more than five years [58]. About one-third of the 900 patients reported to the study were MS patients. The encouraging result is supportive for an ongoing phase III trial (ASTIM) comparing HSCT with standard therapy in cases of severe and treatment-refractory MS [58].

A different approach is treatment with a pulse of high-dose cyclophosphamide over four days, followed by treatment with granulocyte colony-stimulating factor. As cyclophosphamide should spare subsequent HSCT, a 'new' immune system is allowed to reconstitute more naturally. A small study with nine patients showed promising results with fewer adverse effects than HSCT, encouraging further trials with more patients [59,60].

Transplantation of autologous MSCs is a novel therapeutic approach for MS. In contrast to HSCT and other MS treatment forms that reduce inflammation but have little or no effect on CNS injury, MSC transplantation (MSCT) is expected to launch regeneration, repair through axonal protection or remyelination and be immunomodulatory [57]. The rationale of this approach is based on promising results from preclinical studies and experimental autoimmune encephalomyelitis (EAE) models showing MSCs to be protective for axons, to improve neuronal survival, and to induce endogenous neurogenesis and oligodendrogenesis [61–64]. To date, only a few patients with MS have received MSCs but, importantly, preliminary results from a phase I/II study indicate relative safety – hence, a newly formed international MSCT study group has prepared a consensus on the rationale for MSCT, which comprises methodology for generating MSCs and treatment protocols [57].

Neuroprotective and neurorestorative agents for MS

Besides the novel aspect of MSCT, various other neuroprotective and neurorestorative therapeutic approaches aim to prevent and counteract progression of CNS injury and axonal degeneration.

Strategies include protection of oligodendrocytes from oxidative injury, protection of demyelinated axons from further injury, promotion of remyelination and restoration of neuronal functions [65]. Phase II trials have been designed or are being planned to investigate the anti-inflammatory and neuroprotective properties of a panel of substances, including the sodium-channel blocker

BOX 1

What is MS?

Pathogenesis

Multiple sclerosis (MS) is a chronic, progressive, inflammatory disease of the central nervous system (CNS) that predominately affects the white matter in brain and spinal cord. Despite decades of research on the pathogenesis of MS, the etiology of the disease is still unknown. According to a broadly accepted hypothesis, MS is a complex T-cell-mediated autoimmune disease with a genetic predisposition that is triggered by a combination of unknown environmental factors, presumably viral infections [1].
Inflammation and formation of acute lesions are initiated by activated T lymphocytes migrating across the blood–brain barrier. In the CNS, T cells are activated and release effector cytokines. This acute inflammatory component is followed by a more degenerative process resulting in increased axonal loss [112].

Clinical symptoms

Patients suffering MS experience a variety of symptoms. Early clinical symptoms resulting from inflammatory CNS lesions are often visual disturbances, sensibility deficits and limb weakness [1]. Disease progression and increased motor weakness can result in loss of gait control and confinement into a wheelchair.
Further symptoms involve changes of sensation, locomotion, coordination, cognition, and loss of bladder and bowel control. The Kurtzke Expanded Disability Status Scale (EDSS) ranks the degree of disability according to severity of clinical symptoms and number of functional systems involved and is the gold standard for rating disease disability in clinical routine. The EDSS is often used in combination with the more comprehensive Multiple Sclerosis Functional Composite, a multidimensional clinical outcome measure, in clinical trials.

Disease course

Three distinct clinical disease patterns have been outlined in MS: relapsing remitting (RRMS), secondary-progressive (SPMS) and primary progressive (PPMS) [113]. Initially, most patients (about 85%) are suffering RRMS. In this type, symptom-free periods are interrupted by sudden advances of the disease with complete or incomplete remission. Patients develop new neurological deficits within 24–48 hours during such a relapse, and symptoms usually resolve after several weeks. The first occurrence of clinical MS symptoms is known as clinically isolated syndrome (CIS). The initial stages of RRMS are dominated by inflammation and the formation of new lesions in the brain, which can be assessed by gadolinium-enhancing MRI scans.
Owing to the accumulation of clinical and subclinical damage of axons, further relapses cause permanent disability, and the disease often aggravates to secondary-progressive MS [114]. This stage of the disease is dominated by the progression of disability, and 50% of untreated patients will require help with walking approximately 15 years after their diagnosis [1].

Economic burden

MS is the most common cause of acquired neurological disability in young adults and middle-aged individuals in the western world [1]. In a recent study, it was estimated that in 28 European countries with a population of 466 million people, approximately 380 000 individuals suffer from MS with annual treatment costs of €12.5 billion [2]. Even if the new drugs – which are more effective in preventing disability and could provide a better quality of life – are expensive, the clinical benefit experienced by the patients has been demonstrated to justify the costs. It has also been shown that over a long period of time, the reduction of disability progress leads to a decrease in disease costs, which could exceed the costs of the new drugs [2].

lamotrigine, the glutamate receptor antagonist riluzole and the antioxidant lipoic acid.

A major pathogenic factor for axonal injury is abnormal activity with sustained sodium influx of voltage-gated sodium channels (VGSCs). Furthermore, VGSCs have been shown to be involved in the activation and phagocytic function of microglia in mouse models of EAE and MS [66]. Accordingly, the sodium-channel blockers phenytoin, carbamazepin and lamotrigine were shown to significantly improve the course of the disease in EAE [67,68]. Moreover, withdrawal of phenytoin and carbamazepin led to acute worsening of EAE symptoms, inflammatory infiltrates and death of mice [68]. According to these results, one of the ongoing trials has been stopped earlier. It demonstrated that sodium-channel blockers have multiple, complex actions. Disappointingly, a phase II trial with lamotrigine recently failed primary endpoints in patients with SPMS [69]. Although initially promising for neuroprotection, it is not yet clear whether sodium-channel blockers provide a safe and effective treatment option in MS [70].

Extracellular accumulation of glutamate is another potential cause for excitotoxic neuronal injury, and the oral N-methyl-D-aspartate receptor antagonist riluzole is being investigated for beneficial effects in MS [71]. Riluzole was initially developed as an antiepileptic drug but has since been approved for use in amyotrophic lateral sclerosis. Interestingly, besides its known effect as glutamate receptor blocker, riluzole was also characterized as a classic VGSC [72]. It is currently being evaluated in conjunction with IFN-β-1a in a phase II trial for early MS.

Lipoic acid is an antioxidant with immunomodulatory properties that is capable of crossing the blood–brain barrier. It has been proposed that the known neuroprotective effects of lipoic acid result from its powerful metabolic antioxidant activities as a recycler and scavenger of reactive oxygen and nitrogen species [73]. Accordingly, daily oral administration of lipoic acid significantly delayed disease progression and decreased demyelination in EAE [74]. In a pilot study with 37 MS patients, lipoic acid proved to be well tolerated [75]. Further trials are either ongoing or being planned.

Strategies to promote endogenous remyelination involve the long-term survival of oligodendrocyte precursor cells (OPCs) and their proliferation and differentiation to remyelinating oligodendrocytes [76]. Ciliary neurotrophic factor and leukemia inhibitory factor have been described as protective for axons and oligodendrocytes [77]. Brain-derived neurotrophic factor and insulin-like growth factor-1 have been shown to stimulate differentiation of OPCs [78]. By contrast, leucin-rich repeat and Ig domain containing 1 (LINGO-1) is known to inhibit OPC differentiation, and LINGO-1 antagonism has been shown to promote OPC differentiation and myelination in adult rodents [79]. Thus, anti-LINGO-1 agents might evolve to be a future therapeutic option (Box 1).

Concluding remarks

In this review, we have shown the fast-growing field of MS therapy and the immense increase of interest in it, not only from scientists but also from pharmaceutical companies. In the past 20 years, we have seen the development of effective medications that modulate disease progression in MS, and an increased understanding of MS has led to the development of more specific and more effective agents. Moreover, within the next few years, further efforts will be undertaken to reach the stage where complete disease control could become reality. New treatment options that very effectively control MS, however, imply unknown and potentially severe safety risks. Thus, risks and benefits will have to be weighed carefully against the efficacy and proven safety of the IFN-βs and GA.

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