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# Progressive multiple sclerosis: latest therapeutic developments and future directions

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***Abstract*:** Multiple sclerosis (MS) is a chronic inflammatory condition of the central nervous system leading to demyelination and neurodegeneration. While the initial presentation is mostly characterized by a relapsing–remitting disease, patients often progress naturally after 10–15 years to a secondary-progressive disease course. Another 10–15% present with an initial, primary-progressive MS course. Pathogenic mechanisms possibly driving progression include continued compartmentalized inflammation by T- and B-lymphocytes and cells of innate immunity, oxidative stress, iron accumulation, and consecutive mitochondrial damage, altogether leading to neurodegeneration with accumulation of disability. Increasing knowledge about pathogenic mechanisms involved in progressive MS helps to design more specific and precise therapeutic approaches. Successful examples are the B-cell targeting monoclonal antibody ocrelizumab, effective in primary progressive MS, and the sphingosine-1-receptor modulator siponimod, effective in active forms of secondary-progressive MS. Apart from that, other medications such as the B-cell targeted antibody ofatumumab, cladribine due to T- and B-cell depletion, and other sphingosine-1-receptor modulators such as ozanimod and ponesimod are under development. Moreover, some therapeutic approaches in preclinical stages are under development. In this review, we will summarize the newest therapeutic development in the field of progressive MS of the last 3 years, and shed light on auspicious substances with similar mechanisms and new developments in the therapeutic pipeline, presumably supporting a bright future for progressive MS treatment.

***Keywords:*** neuroprotection, ocrelizumab, ozanimod, progressive multiple sclerosis, ponesimod, remyelination, siponimod

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## Introduction

Multiple Sclerosis (MS) is a chronic inflammatory condition of the central nervous system (CNS) leading to demyelination associated with axonal and neuronal degeneration,[1] eventually causing increased disability. Most of the patients (about 85%) initially present with a relapsing–remitting course of the disease, but often convert to a secondary-progressive disease course, characterized by a scarcity of new relapses with slow and steady accumulation of disability, leading to a loss of ambulation and the need to use auxiliary support such as a wheelchair.[2] While immunotherapy developed during the last decades is clearly effective in reducing relapse activity, the risk of developing secondary progression can be reduced but not eliminated.[3] Knowledge of pathogenic alterations leading to progression has increased rapidly, mostly from neuropathological studies or animal models.[4] This has led to the development of more tailored therapeutic approaches and clinical trials. Two milestone phase III clinical trials were recently completed, which showed effectiveness of ocrelizumab in primary progressive MS (PPMS) and siponimod in secondary progressive MS (SPMS). This led to the approval of both medications by the

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United States Food and Drug Administration (FDA) during the last 2 years; for siponimod, the European Medicines Agency (EMA) decision is still pending. While those successes are the 'tip of the iceberg' of the therapeutic pipeline, there are numerous medications, including new compounds and repurposed agents, being tested in preclinical and clinical settings due to diverging mechanisms of action, reviewed in detail elsewhere. In this review, we therefore focus on the latest therapeutic developments for progressive MS forms and discuss new developments, also being studied in relapsing–remitting MS (RRMS) or optic neuritis, at an advanced developmental stage, potentially leading to new therapeutics for progression due to their mechanism of action.

## Pathogenic mechanisms driving progression

While the focus of this review is on new therapeutic options, it is crucial to review key pathogenic processes leading to neurodegeneration in progressive MS. While relapsing MS is rather characterized by the influx of immune cells leading to inflammation, inflammation in progression is compartmentalized behind a relatively closed blood-brain-barrier. Inflammation by macrophages and microglia is more pronounced in progressive MS compared with RRMS and drives the spatial expansion of established lesions.[5] Another crucial driver of progression is the release of reactive oxygen and nitrogen species and inflammatory cytokines and chemokines by cells of innate immunity. This ultimately leads to mitochondrial damage. There is also impairment of the respiratory chain, as revealed in postmortem studies of progressive MS patients with reduction of complex IV, associated with axonal damage.[6] In addition, progression is characterized by the development of follicle-like structures in the meninges,[7] which lead to neuronal damage and demyelination in the underlying cortex.[8–10] Since cortical thinning is associated with disability progression, there is a good rationale to target B-cells therapeutically. As discussed above, inflammation during the progressive phase of MS is much more compartmentalized with an intact blood-brain-barrier; therefore, it is assumed that medications for progression need to readily cross the blood-brain-barrier to induce protective effects. While numerous medications have shown efficacy in preclinical stages in *in vitro* and animal models, medications with effects in clinical trials are scarce.

During the last 20 years, there have been several trials which have investigated the potential of medications approved for RRMS to also positively attenuate progressive disease. Many therapeutics, such as azathioprine, glatiramer acetate, fingolimod, or natalizumab, (reviewed here) failed.[11] However, positive trials during the last few years have led to the approval of new medications for progressive MS. In this review we will focus mostly on successful therapeutic approaches developed within the last years. Since there are also other medications with similar targets, we will also review follow up substances under development with high potential to show efficacy in future clinical trials.

## Recent therapeutic successes: B-cell targeted therapy

As summarized above, a factor contributing to progression is the development of structures with similarity to B-cell follicles, located at the meninges. Those follicle-like structures correlate with disease progression and the development of cortical neuronal degeneration.[8–10] The first B-cell targeting treatment was rituximab, which failed to reduce confirmed disability progression in the OLYMPUS trial.[12] However, there were positive effects on progression in younger patients (<51 years) with higher inflammatory disease activity, identified by gadolinium enhancing lesions. The follow-up substance ocrelizumab, which contains more humanized protein sequences, was then investigated in the ORATORIO trial in primary progressive MS,[13] which led to the approval as first treatment for primary progressive MS in active patients (successful trials summarized in Table 1). Another substance currently under development is ofatumumab. Differing from the aforementioned substances, ofatumumab is being administered subcutaneously.

### *Ocrelizumab*

Ocrelizumab is an anti-CD20 targeted B-cell depleting antibody. The pivotal ORATORIO trial comprised 732 patients with a primary progressive disease course. Ocrelizumab reduced the risk of disability progression after 12 weeks by 24% and reduced the rate of brain atrophy by 17.5%.[13] Positive effects on functional outcomes such as the timed 25-foot walk supported the positive effect on disability. After 120 weeks, there was a relative reduction of the timed 25-foot walk

**Table 1.** Approved medications and therapeutics currently under development.

| Medication | Condition | Effect | Trial | Reference | Status |
|---|---|---|---|---|---|
| Ocrelizumab | PPMS | 24% reduced risk of disability progression, reduced brain atrophy | phase III trial | Montalban[13] | **Approved for PPMS** (FDA: March 28, 2017; EMA January 11, 2018) |
| Siponimod | SPMS | 21% reduced confirmed disability progression; reduced brain atrophy of 15% | phase III trial | Kappos[14] | **Approved for SPMS** (FDA: March 27, 2019) |
| Cladribine | RRMS | Reduced risk of disability progression (HR 3.5-mg group 0.67) | phase III CLARITY trial | Giovannoni[15] | **Approved for active SPMS** (FDA March 29, 2019) |
| Opicinumab | RRMS and SPMS | Primary endpoint missed (multicomponent endpoint) | phase II SYNERGY trial | | phase III clinical trial ongoing |
| Ibudilast | PPMS, SPMS | MRI: 2.5 ml reduced loss of brain parenchymal fraction | phase II trial | Fox[16,17] | phase III clinical trial ongoing |
| Alpha lipoic acid | SPMS | MRI: Less annual percent change of brain volume | phase II trial | Spain[18] | phase II trial ongoing, NCT03161028 |

FDA, Food and Drug Administration; MRI, magnetic resonance imaging; PPMS, primary progressive multiple sclerosis; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

by 29.3% (95% CI, –1.6 to 51.5; $p = 0.04$) compared with placebo.[13] This led to the approval of ocrelizumab as first medication for PPMS in March 2017. In the ORATORIO trial, infusion related reactions occurred in 39.9% in the ocrelizumab group (compared with 25.5% in the placebo group). Adjustment of the infusion rate or stopping of the infusion had to be undertaken in 9.7% of the patients in the ocrelizumab group compared with 5.0% in the placebo group. There were no life-threatening or fatal infusion related events. Importantly, withdrawal due to infusion-related events was rare (0.4%). Regarding infections, slightly more upper respiratory tract infections were reported in the ocrelizumab group compared with placebo (10.9% *versus* 5.9%). The first infusion is split into two dosages of 300 mg, 2 weeks apart, followed by subsequent infusion of 600 mg every 6 months under antiallergic prophylaxis, which is administered 30–60 min prior ocrelizumab infusion [100 mg methylprednisolone *intravenous* (iv), antihistamine iv, paracetamol iv].

### *Ofatumumab*

The substance ofatumumab is currently under development in MS, and may be a new paradigm in B-cell targeted therapy: it does not aim at eliminating but only reducing B cell levels. Ofatumumab is an immunoglobulin 1κ (IgG1κ) lytic monoclonal antibody that binds to CD20. Unlike ocrelizumab, ofatumumab is administered subcutaneously. Ofatumumab was investigated in the MIRROR-study in 232 patients with RMS who showed a reduction of the cumulative number of new lesions by 65% and >90% lesion reduction compared with placebo.[19] While this study was performed in RRMS, this may also have potential impact for progressive MS. Currently, ofatumumab is being investigated in another study in RRMS (NCT03249714). This large phase III clinical trial (estimated enrollment $n = 2010$ patients) investigates long-term effects of monthly 20 mg subcutaneous injections of ofatumumab regarding safety, relapse rate, and confirmed disability progression of up to 5 years. While this long-term study might also inform

about the risk of disability progression, we are not aware of any studies being performed currently in a progressive MS cohort.

## Targeting the sphingosine-1-phosphate receptor

The sphingosine-1-phosphate (S1P) receptor has been described early as potential therapeutic target for MS therapy. While the substance fingolimod showed high efficacy in RRMS due to its mechanism of action with inhibition of lymph node lymphocyte egress, fingolimod failed to attenuate progression in primary progressive MS (INFORMS-trial).[20] The newest developments in the field are much more specific, targeting not all isoforms of S1P and thereby reducing side effects of the medication. Important side effects of fingolimod consist of cardiac events with bradycardia, an atrioventricular conduction block and ocular side effects with the development of macular oedema. More specific S1P receptor modulators targeting specific subunits of S1P thus promise to reduce off-target side effects. Siponimod is the latest development by Novartis, which received market authorization in the United States in March 2019 and is expected to receive market authorization in Europe soon. Apart from that, ozanimod and ponesimod are most advanced in the developmental pipeline.

### *Siponimod*

(E)-1-(4-[1-([(4-cyclohexyl-3-[trifluoromethyl]benzyl)oxy]imino)ethyl]-2-ethylbenzyl)azetidine-3-carboxylic acid (32, BAF312, siponimod) is a selective oral S1P receptor 1,5 modulator. Siponimod targets specifically the S1P receptor subunit 5. Siponimod has a mean half-life of 56.6 h in plasma (human) and is excreted in feces mostly as oxidative metabolites after hepatic biotransformation, largely mediated by cytochrome P450 2C9 (CYP2C9).[21]

Siponimod has pleiotropic effects on immune and CNS cells. The medication has lipophilic properties and therefore crosses the blood brain barrier and can impact CNS cells directly.[22] First studies about the mechanism of action in experimental autoimmune encephalomyelitis (EAE) showed that siponimod antagonizes S1P 1 and 5 receptor leading to an inhibition of the lymphocyte egress from the thymus and secondary lymphoid organs.[23] Siponimod does not influence the $S1P_3$ such as fingolimod, which is mainly responsible for adverse cardiac effects such as bradycardia.[24] In a model of demyelination in *Xenopus* tadpoles, treatment with siponimod leads to strong remyelination,[25] suggesting that the medication might be effective in progressive forms of MS. Siponimod reduces the release of IL-6 in TNFα/IL17 activated microglia *in vitro* and has protective effects on demyelination in LPC-mediated demyelination in organotypic slice cultures.[26] Siponimod has positive effects on the clinical course of EAE in C57BL6 mice, in accordance with reduced astrogliosis and microgliosis.[27] Moreover, it rescues the loss of parvalbumin-positive (PV+) GABAergic interneurons *in vivo* and reduces the release of RANTES and IL-6 in microglia *in vitro*,[27] suggesting potential neuroprotective effects of the medication. Positive effects on cognition in the SDMT testing underline neuroprotective properties of siponimod (AAN 2019).

Siponimod was first investigated in the phase II BOLD study in patients with RRMS (NCT00879658). In this dose-response study, the medication led to a dose-dependent reduction of combined unique active lesions at 3 months compared with placebo, with an effect of 82% (70–90) for siponimod 10 mg.[28] Moreover, the medication was investigated in a phase III clinical trial in 1651 patients with secondary-progressive MS (EXPAND, NCT01665144). The primary end-point consisted of 3-month confirmed disability progression. Siponimod treatment led to a 21% relative risk reduction compared with placebo ($p = 0.013$). The medication also delayed the risk of 6-month confirmed disability progression (26% *versus* placebo; $p = 0.0058$). The annualized relapse rate was also reduced by 55%.[14]

Those studies were the basis for the application at both FDA and EMA. Since 27 March 2019, the medication has been approved by the FDA as first therapy in patients with active secondary progressive MS for 15 years, in RRMS and in clinically isolated syndrome (CIS). This approval is an important step, since until now therapeutic options for secondary progression remain limited. Although the positivity of the trial is great news for MS patients and clinicians, it should not be overlooked that the effect size of reduced disability progression was limited, with a relative risk reduction of 21%. Hence, it is clear that much effort remains to develop therapeutics with better efficacy. Apart from siponimod, two other S1P receptor modulators are currently under development: ozanimod and ponesimod. Both medications have until now been tested only in RRMS. Since those medications target the same

receptor as siponimod, effective in SPMS, we will review data for ozanimod and ponesimod here, since it might be worthwhile to develop those substances as therapeutics for SPMS.

### *Ozanimod*

Ozanimod is a selective S1P receptor 1 and 5 modulator that has been investigated in two phase III clinical trials, SUNBEAM and RADIANCE. The active metabolite of ozanimod is RP-101075.

First, ozanimod was evaluated in the combined phase II/III randomized placebo-controlled RADIANCE trial in relapsing MS.[29] The intention-to-treat population consisted of 258 patients, with 88 in the placebo-group, 87 in ozanimod 0.5 mg, and 83 in the ozanimod 1 mg group. Ozanimod showed efficacy in reducing the number of gadolinium-enhancing lesions (compared with placebo: 0.5 mg group: OR ratio 0.16, 95% CI 0.08–0.30; $p < 0.0001$ and 1 mg group: OR 0.11, 95% CI 0.06–0.21; $p < 0.0001$). The secondary endpoint consisted of reduction in annualized relapse rate (ARR). Compared with placebo there was a trend, but no significant improvement [0.5 mg group: 0.69 (0.36–1.34); $p = 0.2714$ and 1 mg group: 0.47 (0.22–1.01); $p = 0.0531$]. The medication was well tolerated. There were three serious adverse events consisting of optic neuritis, somatoform autonomic dysfunction, and cervical squamous metaplasia (HPV-related). The medication did not induce any cardiac side effects or macular edema. Only 2% of the patients in the treatment-arm discontinued therapy; this was not related to side effects. The duration of the study was short (24 weeks), which is probably the reason why the study was not able to detect significant effects on the ARR, as discussed by the authors. The 2-year dose-blinded extension of the study, however, confirmed both efficacy on gadolinium-enhancing lesions and showed efficacy on ARR.[30]

### *Ponesimod*

Ponesimod (d [(Z,Z)-5-[3-chloro-4-([2R]-2,3-dihydroxypropoxy)-benzylidene]-2-propylimino-3-o-tolylthiazolidin-4-one]) is an orally available $S1P_1$ receptor modulator. Ponesimod has been investigated in a double-blind, placebo-controlled, dose-finding phase IIb study comprising 464 patients on ponesimod 10, 20 or 40 mg or placebo.[31] The study was conducted over a duration of 24 weeks. The mean number of gadolinium-enhancing lesions was lower with all concentrations of ponesimod compared with placebo [10 mg: rate ratio (RR) 0.57; $p = 0.0318$; 20 mg RR 0.17; $p < 0.0001$; 40 mg RR 0.23; $p < 0.0001$]. This was corroborated in a reduction of mean ARR of 52% (40 mg group: 0.25 *versus* 0.53; $p = 0.0363$). The medication was well tolerated. Side effects consisted of anxiety, dizziness, dyspnea, increased alanine aminotransferase, influenza, insomnia, and peripheral edema. Currently, ponesimod is being investigated in the phase III OPTIMUM-trial in patients with RRMS (NCT02425644) with teriflunomide as active comparator. A second phase III trial is being conducted in RRMS patients treated with dimethyl fumarate (POINT-trial). While there have not been any trials in progressive patients, both ozanimod and ponesimod are auspicious medications for progression since they target the same receptors as siponimod, effective in SPMS.

## Immune restoring approaches: cladribine

Cladribine is a purine nucleoside that is phosphorylated in cells with high amount of deoxycytidine kinase, thereby leading to nuclear accumulation and death of the target cell.[32] After a halted approval process in 2011 due to safety signals related to suspected increase of malignancies, development of the medication was pursued further and, in August 2017, cladribine received market authorization in Europe (summarized in Faissner and Gold).[33]

Cladribine was investigated in the phase III CLARITY study and in the phase II ONWARD study in CIS. The pivotal CLARITY study, conducted in patients with RRMS, showed an improvement of the relapse rate (3.5-mg/kg group 0.14/year; 5.25-mg/kg 0.15/year; 0.33 in the placebo group and a reduced risk of 3-month confirmed disability progression {hazard ratio 3.5-mg group 0.67 [95% confidence interval (CI), 0.48–0.93; $p = 0.02$]; hazard ratio 5.25-mg group 0.69 (95% CI, 0.49–0.96; $p = 0.03$)}.[15]

More interesting for progression was the ONWARD study, which included patients with relapsing MS but also progressive MS in case the disease was still active. In the ONWARD study, $n = 172$ patients were included and randomized in a 2:1 ratio to receive either IFN-β with cladribine 3.5 mg/kg tablets or with placebo. The phase II study was conducted over a period of 96 weeks. Patients on cladribine were 63% less likely to have a relapse (relative risk 0.37, 95% CI 0.22, 0.63; $p < 0.001$).[34]

**Table 2.** Therapeutics in preclinical stages with promising effects in culture and in animal models or small clinical trials.

| Medication | Effect | Model |
|---|---|---|
| Clemastine | Promoting remyelination[35] | Cell culture, cuprizone model |
| Clomipramine | Targeting iron mediated neurotoxicity[36] | Cell culture, chronic EAE |
| Hydroxychloroquine | Normalizing microglial activity[37,38] | Cell culture, EAE |
| DMF | Cytoprotective, modification of the KEAP-1/nuclear factor (erythroid derived 2)-like 2 complex leading to reduced oxidative stress[39] | Cell culture, EAE, positive effects in a small observational study in progressive MS[40] |
| Riluzole | Reduces demyelination and axonal degeneration in EAE.[41]<br>Reduced rate of cervical cord atrophy in small study in PPMS[42,43]<br>Currently investigated in MS-SMART trial (interim analysis: negative) | EAE[41]<br>Small study in PPMS[42,43] |
| Amiloride | Decreased brain atrophy in small PPMS-study[44]<br>Currently investigated in MS-SMART trial (interim analysis: negative) | PPMS[44] |

EAE, experimental autoimmune encephalomyelitis; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis.

As well, there was a positive effect on magnetic resonance imaging (MRI) activity. Cladribine treated patients had 90% less new T1 Gd+ lesions. In the US, Cladribine is approved for patients with RRMS and active SPMS (FDA label) while in Europe cladribine is available for highly active RRMS. Whether cladribine therapy might have positive long-term effects on progression remains to be investigated in further trials.

Apart from those medications with proven efficacy in progression, there are several therapeutic approaches with potential, targeting remyelination, chronic inflammation by cells of innate immunity and neuroprotection (Table 2).

## Remyelination promoting approaches

One postulated approach to improve neuroprotection is to enhance remyelination and install remyelinating therapies (reviewed by Plemel and colleagues).[45] Remyelination occurs spontaneously but is less pronounced in the aging brain. Myelin is crucial for fast axonal conduction and important for axonal support. Axons use lactate as energetic source, which is supplied *via* oligodendrocyte monocarboxylate transporter 1 (MCT1), and MCT1 disruption leads to axonal degeneration.[46] Another contributing factor for the inhibition of remyelination is the inflammatory environment within lesions. Chondroitin sulfate proteoglycans (CSPGs) impair the process of remyelination, and, as evidenced with huge screening approaches, it is difficult to find therapies that might overcome the inhibitory environments.[47] There are several interesting candidates that target remyelination, some of which have already been tested in clinical trials in differing settings with contradictory results.

### *Opicinumab*

The oligodendrocyte differentiation inhibitor LINGO-1 is an interesting candidate to improve remyelination by inhibition. Targeting LINGO-1 showed efficacy in EAE regarding clinical signs and remyelination.[48] Therefore, the anti-LINGO-1 targeted antibody opicinumab was investigated in several studies with the goal to improve remyelination. After a successful phase I trial, which showed safety and tolerance of opicinumab,[49] the medication was investigated in a phase II double-blind, dose-ranging proof-of-concept SYNERGY trial in RRMS or SPMS (3, 10, 30, or 100 mg/kg). Patients also received IM IFN beta-1a 30 mg once weekly. The primary endpoint was the percentage of participants with $\geq$3 month confirmed improvement of neurophysical or cognitive function over 72 weeks (multicomponent endpoint consisting of EDSS, Timed 25-Foot Walk, 9-Hole Peg Test, and 3-Second Paced Auditory Serial Addition Test). A total of 418 patients were enrolled; the primary endpoint, however, was missed ($p = 0.8931$).

Interestingly, the intermediate dosage showed more responders [65.6% for 10 mg/kg (OR 1.79; 95% CI 0.97–3.31), 68.8% for 30 mg/kg (OR 2.06; 95% CI 1.11–3.84)] than placebo (51.6%) (https://n.neurology.org/content/88/16_Supplement/S33.004). Another study investigated the medication in optic neuritis. The rationale that this approach might be more successful is that nerve fibers in the optic nerve have a high percentage of myelinated fibers. The primary endpoint, which consisted of improvement of latency of visual evoked potentials, was missed at study completion.[50] Since the duration of the study might have been too short (32 weeks), a trial extension is running for another 2 years (RENEWed [NCT02657915]).

### *Biotin*

Biotin is a medication that is a cofactor of four carboxylases, and is thought to improve remyelination.[51] Biotin has been investigated in a phase III clinical trial in 154 patients with progressive MS. The primary endpoint was ambitious, being improvement of the EDSS within 12 months of therapy.[51] The primary end-point was met in 12.6% ($n = 13$ patients) in the treated group compared with 0% in the placebo group. To evaluate and confirm those effects in a larger trial, high-dose biotin is now investigated in a follow-up study in patients with SPMS and PPMS (primary endpoint EDSS, T25FW; NCT02936037).

### *Clemastine*

The first-generation antihistamine clemastine, found to be effective regarding remyelination in a large *in vitro* screening of more than 1000 medications and *in vivo* in the toxic demyelination cuprizone model,[35] was investigated in patients with MS and chronic demyelinating optic neuropathy. The phase II ReBUILD trials showed improvement of the latencies of visual evoked potentials by 1.7 ms ($p = 0.0048$).[52] The ReCOVER study currently evaluates clemastine in acute optic neuritis [NCT02521311; Assessment of Clemastine Fumarate as a Remyelinating Agent in Acute Optic Neuritis (ReCOVER)] and is expected to be terminated in 2021. Although both studies did not investigate clemastine in progressive MS, clemastine is an interesting potential candidate as therapy for progressive MS, maybe as add-on therapy to medications with another mechanism of action.

## Targeting myeloid cells

Ibudilast is a small molecule that is approved in Japan for the treatment of asthma and for the improvement of dizziness following cerebral infarction. Ibudilast inhibits phosphodiesterases and modifies the invasion of macrophages into the CNS. Ibudilast was investigated in a study in 255 patients with PPMS and SPMS with the primary end-point rate of change in the brain parenchymal fraction (NCT01982942).[16,17] Ibudilast reduced the rate of parenchymal loss by 2.5 ml over a period of 96 weeks.[17] While this effect on MRI-measures was robust, it still remains to be proven whether this is also clinically relevant regarding prevention of disability progression or cognitive decline.

Dimethylfumarate, approved as therapy for RRMS,[33,53] has cytoprotective effects by modulation of the KEAP-1/nuclear factor (erythroid derived 2)-like 2 complex leading to reduced oxidative stress.[39] We showed stability or amelioration in 75% of treated patients in a small study in PPMS ($n = 26$), treated with Fumaderm or DMF.[40] Currently, dimethyl fumarate is being investigated in a phase II clinical trial (FUMAPMS); data are expected for the end of 2019.

Alpha lipoic acid is an antioxidant, and was investigated in a study in 51 patients with SPMS over 2 years. The primary outcome of the trial was annual percent change of brain volume (PCBV). After 2 years, patients treated with alpha lipoic acid 1200 mg had significant less PCBV compared with placebo (–0.21 *versus* –0.65; $p = 0.002$).[18] The timed 25-foot walk just missed significance in the alpha lipoic acid group (−0.535 *versus* 0.137, 95% CI −1.37 to 0.03, $p = 0.06$). The medication was overall well tolerated. Side effects consisted of significantly more gastrointestinal side effects. Since 2017, alpha lipoic acid has been investigated in a phase II trial in progressive MS with T25FT as primary outcome (estimated enrollment 118 patients; NCT03161028).

## Neuroprotective and experimental approaches

Apart from the above-mentioned therapeutics, there is a plethora of substances and treatment strategies that might potentially be effective due to positive effects in culture or animal models,

reviewed elsewhere by the authors.[54] A large screening of potentially remyelinating therapies showed that antimuscarinergic medications, especially clemastine, might be effective in promoting remyelination.[35] Since iron-mediated neurotoxicity is another feature driving progression, we performed a screening to find protective generic medications. Tricyclic antidepressants and antipsychotics showed especially strong efficacy.[36] Clomipramine was also effective in acute and chronic EAE.[36] The medications riluzole, amiloride, and fluoxetine are being tested in a phase IIB clinical trial in SPMS (MS-SMART; NCT01910259). The primary outcome in this trial consists of MRI-derived PCBV. Interim results of the 96-week analysis, presented at ECTRIMS 2018, however, showed no effect; final results are pending.

## Summary

Knowledge about pathogenic processes involved in progression has increased tremendously during the last years and led to more specific therapeutic approaches that finally showed efficacy with two different therapeutic strategies, targeting B-cells by ocrelizumab and the S1P receptor using siponimod. Follow-up substances with similar targets such as ofatumumab as well as ozanimod and ponesimod will presumably have similar, but not higher, efficacy as the 'mother' substances. Moreover, the constraint that all the current data regarding these treatments have been assessed through investigation in RRMS cohorts, has to be kept in mind. Since active RRMS and progressive MS differ in pathological processes, as summarized above, successful treatment of RRMS in current trials does not necessarily guarantee success in halting the accumulation of disability in progressive MS, as evidenced by several negative trials using RRMS drugs in the past.

Until now, other strategies such as remyelination-promoting approaches using the anti-LINGO-1 directed antibody, or several medications with neuroprotective properties, have not been successful in clinical trials. In the future it is, however, imaginable that those medications might be effective, for example, in an early stage of progression, and therefore be applicable to a certain subgroup of progressive MS patients. Secondary analyses from negative trials such as OLYMPUS, which investigated rituximab and showed that patients younger than 51 years with higher inflammatory activity profited from the medication,[12] guide the trial design of upcoming studies, but might also inform which subgroups of patients might be more suitable for a particular therapeutic approach.

Repurposing old medications developed for other conditions is interesting, both from a medical point of view since there is knowledge about side effects and safety, and from an economical perspective, since those medications are usually cheap and also available for patients in areas with poor health care coverage. This, however, is challenging, due to the emerging 'translational gap', since those medications might not be tested in phase II/III clinical trials because costs for public funding agencies for large trials needed in this population are too high, and pharmaceutical entities are not interested due to missing patents. Therefore, it is of increasing importance to develop new trial regimes, or to test several compounds in one trial with only one placebo group, such as performed in the MS-SMART-trial.

Another important aspect is to define better markers of therapy response, guided by knowledge obtained from completed trials. Outcome parameters used in RRMS cohorts are easy to define with relapse activity, disability accumulation, and inflammatory MRI activity. During progression, other domains, such as cognitive deficits, or upper extremity function often get more important; hence, there is a mismatch between outcomes of successful treatment in RRMS and progressive MS.

It is obvious that future therapeutic approaches need to target several mechanisms of progression, combining anti-inflammatory strategies, remyelination promoting therapies, and neuroprotective medications. The combination of those approaches might eventually lead to personalized progressive MS therapy, a hopeful scenario for patients and treating neurologists.

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