

Clinical Evaluation of Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis: Pathophysiology, Efficacy, Safety, Patient Acceptability and Adherence

Sajida Sabsabi¹, Elio Mikhael², Georges Jalkh¹, Gabrielle Macaron^{1,3}, Mary Rensel³

¹Department of Neurology, Hotel Dieu de France Hospital, Saint Joseph University, Beirut, Lebanon; ²Department of Internal Medicine, Hotel Dieu de France Hospital, Saint Joseph University, Beirut, Lebanon; ³Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic, Cleveland, OH, USA

Correspondence: Mary Rensel, Email renselm@ccf.org

Introduction: A number of disease-modifying therapies have been approved for use in relapsing-remitting multiple sclerosis (MS) in the past two decades. However, only few treatment options are available for patients with secondary progressive multiple sclerosis (SPMS). Siponimod has recently been approved for use in patients with active forms of SPMS (who experience clinical relapses or new lesions on MRI superimposed on secondary progression independent of relapse activity).

Objective: The aim of this article is to provide a comprehensive review on the mechanism of action, efficacy, safety, cost effectiveness and patient adherence with siponimod.

Methods: We performed a PubMed search using the search terms: “siponimod”, “secondary progressive multiple sclerosis”, “sphingosine 1-phosphate modulators”. Titles and abstract were screened and selected for relevance to the key section of this article.

Findings: Siponimod is an oral sphingosine-1-phosphate receptor (S1PR) modulator with selectivity to S1PR-1 and 5. Modulation of this receptor on lymphocytes causes its internalization and degradation, preventing their egress from lymphoid tissues to the blood. In the pivotal Phase 3 randomized controlled trial EXPAND, siponimod was superior to placebo in reducing the risk of disability progression confirmed at 3 and 6 months, as well as the development of new MRI lesions and the rate of brain volume loss. Secondary analysis also showed a benefit on measures of cognitive functioning. The risk of lymphopenia and first-dose bradycardia appears to be lower with siponimod compared to non-selective S1PR modulators. Different CYP2C9 genotypes affect the metabolism of siponimod; hence, genetic testing is required to adapt the titration and final dose accordingly.

Conclusion: Long-term extension and real-world studies will allow further evaluation of efficacy and safety in this population. Future research should focus on better defining SPMS, and identifying biomarkers of progression and outcome measures of treatment response in this category of patients.

Keywords: secondary progressive multiple sclerosis, siponimod, efficacy, safety

Introduction

Multiple sclerosis (MS) is a chronic inflammatory, autoimmune disease of the central nervous system (CNS) and a common cause of non-traumatic disability in young adults.¹ The most common disease course is characterized by the development of sub-acute clinical demyelinating events (relapses) with complete or incomplete recovery, referred as relapsing remitting MS (RRMS). Inflammatory lesion formation and secondary axonal transection within the lesions is frequent in RRMS, especially early in the disease course.² Data from natural history cohorts suggest that about 85% of patients will eventually evolve into a secondary progressive course (SPMS), whereas data from recent cohorts in the treatment era have shown a much lower rate of conversion (15–30)%^{3,4} with a median time of 19 years from first MS symptom and 12 years from MS diagnosis.^{5,6} SPMS is a retrospective clinical diagnosis and there is no established criteria or biomarker to determine the exact time of conversion

from RRMS to SPMS. Active lesions are a less prominent feature of progressive MS, which is mostly driven by more diffuse pathological mechanisms such as diffuse axonal injury, microglial activation in normal appearing grey and white matter, whole brain atrophy, smoldering lesions, and subpial lesions. Patients with SPMS can develop superimposed relapses (clinical activity) or new lesion formation (radiological activity).⁷ The distinction between active and inactive progressive MS has important therapeutic implication as most approved disease-modifying therapies (DMTs) are effective on the inflammatory component causing clinical relapses and new lesion formation in the brain and spinal cord.

Recent studies suggest that the early use of high-efficacy DMTs in RRMS is associated with a lower risk of conversion to SPMS.^{8–11} However, the escalation approach (starting with lower efficacy DMTs and switching in case of breakthrough disease activity) remains widely used.⁹ In the past decade, several newer DMTs have been approved for use in MS. Injectable DMTs such as interferons β and glatiramer acetate as well as intravenous mitoxantrone were the only approved therapies in 2000 followed by natalizumab in 2006.³ Injectable DMTs, with some exceptions such as newer sub-cutaneous anti-CD-20 therapies are limited by their route of administration, lower efficacy, and poor tolerability. Mitoxantrone is limited by its toxicity and its use has been abandoned in MS. Oral DMTs are now available with a more practical route of administration, higher efficacy, and better tolerability. Sphingosine-1-phosphate receptor modulators (S1PRM) represent an important DMT category in MS therapeutics. Fingolimod (Gilenya[®], Novartis), a non-selective S1PRM, was FDA-approved as the first oral drug for RRMS in 2010. Since then, other more selective S1PRM have been developed, including siponimod (Mayzent[®], Sanofi Genzyme), which received its FDA approval in March 2019 for use in RRMS and active SPMS.

In this review article, we will discuss the characteristics of SPMS, diagnostic and treatment challenges, and provide a detailed review of the efficacy, safety, patient acceptance and adherence of siponimod.

Secondary Progressive Multiple Sclerosis (SPMS)

Classifications and terminologies in progressive MS have gone through several modifications. In the latest disease course definition by Lublin et al in 2014,⁷ the importance of distinguishing active vs inactive progressive MS was highlighted (based on the presence or absence of relapses or new MRI lesions during the follow-up time), as well as the recognition of progressive disability worsening (based on the presence or absence of progression independent of relapses during the previous year).⁷ SPMS, as opposed to primary progressive MS (PPMS), requires an initial course of RRMS which progresses into SPMS. A recent study revealed that a quarter of RRMS patients progress to SPMS within the first 10 years, then half of them by 20 years, and more than 75% by 30 years.¹² The estimated prevalence of SPMS across studies and countries is variable, and this may be attributable to differences in SPMS definition, study design, and genetic differences between populations.

Nevertheless, the early detection of SPMS remains a challenge for clinicians. In fact, there are no clear clinical, biological, or imaging biomarkers for the diagnosis of SPMS.^{7,13} Consequently, the diagnosis of SPMS is frequently retrospective with an estimated diagnosis delay of 3 years.¹⁴ Irreversible axonal damage and disability accumulation in MS might not initially be present as clinically significant disabilities due to compensatory mechanisms, but can manifest later in the disease course when these mechanisms are surpassed.^{15–17} Therefore, the term “silent progression” has been recently used to describe this phase of the disease.¹⁸

Detecting the transition from RRMS to SPMS also has implications when it comes to treatment options. Focus on reducing relapse occurrence and new lesion formation is the mainstay of RRMS treatment target, whereas delaying progression of disability remains the primary goal in progressive MS.^{3,19} While the range of pharmaceutical options have been rapidly expanding in MS during the last ten years, it has more so been the case for RRMS than for progressive forms of MS. One of the reasons behind the less pronounced advances in SPMS compared to RRMS are linked to trial methodology.^{20–23} Phase 3 trials often last 2 years or less, which might not be enough to detect an effect of therapy on the slope of disability worsening in progressive MS.²⁴ Moreover, patients included in trials are not representative of all progressive MS patients, as they are often younger and have evidence of disease activity.^{20–23} Finally, efficacy outcomes in SPMS trials are not clearly defined and often reflect inflammatory processes rather than neurodegeneration.^{20–23} Efforts are significantly increasing to enhance research in progressive MS.

DMTs approved for use in SPMS include siponimod and cladribine, both approved by the FDA and EMA²⁵ (European Medicines Agency). National guidelines such as the European Committee of Treatment and Research in Multiple Sclerosis (ECTRIMS)/European Academy of Neurology (EAN) and the American Academy of Neurology (AAN) clinical practice

guidelines, both published in 2018 (prior to approval of Siponimod) are aligned on general treatment concepts.^{25,26} However, for active SPMS, theECTRIMS/EAN guidelines recommend initiation of interferons, mitoxantrone, cladribine, or ocrelizumab, whereas the AAN guidelines make no specific recommendation.²⁷ Since many decisions that arise in the real-world settings are not supported by clear practice guidelines, incorporating evidence from observational studies into recommendations will be increasingly necessary.²⁷

Sphingosine 1 phosphate Receptor Modulators

Sphingosine-1-phosphate (S1P) is a bioactive sphingolipid which binds to different G-protein-coupled receptors called (S1PR).²⁸ These receptors are present in different cells such as lymphocytes, cardiomyocytes, endothelial cells, fibroblasts, neurons, astrocytes, macular cells, microglia and oligodendrocytes.²⁹ Table 1 details S1PR distribution and relation to active S1PRM. Specifically, S1PR1-3 are ubiquitous, S1PR-4 is mostly expressed in lymphoid tissue, and S1PR-5 in the spleen and oligodendrocytes.²⁸ S1P is involved in lymphocytes egress from thymus and lymph nodes to the blood, cardiac function, inflammation, cell migration and vasogenesis among other several functions.³⁰ S1PRM indirectly antagonize the receptor's function by binding to one or several receptor subtypes (S1PR-1 to 5) causing their internalization and degradation.

Table 1 Distribution of Sphingosine 1 Phosphate Receptors by Cell Type, Effect and Corresponding S1P Modulators

Cell Type	S1PR	Fingolimod	Siponimod	Ozanimod	Ponesimod	S1P effect
Lymphocytes	S1P1	×	×	×	×	Egress from lymph nodes and thymus, dendritic cells and TH17 modulation
	S1P4	×				
Atrial myocytes	S1P1	×	×	×	×	Atrioventricular-slowng
	S1P3	×				
Neurons	S1P1	×	×	×	×	Neurogenesis, ⁸⁵ neuromigration, neurotransmission
	S1P2					
	S1P3	×				
Astrocytes	S1P1	×	×	×	×	Migration, proliferation, gap junction communication, growth factor production
	S1P2					
	S1P3	×				
	S1P5	×	×	×		
Oligodendrocytes	S1P1	×	×	×	×	Survival, differentiation, myelination
	S1P3	×				
	S1P5	×	×	×		
Microglia	S1P1	×	×	×	×	Proinflammatory cytokines production
	S1P2					
	S1P3	×				
	S1P5	×	×	×		
Endothelial cells and smooth muscles	S1P1	×	×	×	×	Permeability barrier, increase permeability in several organs ⁸⁶ but the exact role on blood brain barrier (BBB) is exactly unknown (might be a size-selective BBB opening. ⁸⁷
	S1P2					
	S1P3	×				

Abbreviations: S1P, sphingosine 1 phosphate; TH17; T cell helper 17.

Fingolimod (FTY720, Gilenya[®], Novartis Pharmaceuticals AG, Basel, Switzerland) was the first developed oral DMT and S1PRM for MS.³¹ Fingolimod undergoes phosphorylation by sphingosine kinase to become active and then binds to S1PR-1, 3, 4, and 5. S1PR-1 antagonism prevents lymphocyte egress from lymphoid tissues. S1PR-3 modulation induces atrioventricular slowing in rodent models,³² however, this adverse effect in humans is mainly secondary to S1PR-1 modulation.²⁸ In the pivotal trials, first-degree atrioventricular block occurred in 4.7%, symptomatic bradycardia in 0.5%, and second-degree atrioventricular block occurred in 0.2% of participants after the first dose, which resulted in the institution of a strict mandatory monitoring protocol for 6 hours after the first dose.³³ Other side effects as macular edema, bronchoconstriction and vasoconstriction were also noted. Fingolimod has a long half-life (>30 hours).³⁰ Despite its efficacy in RRMS, fingolimod failed to improve the course of PPMS (INFORMS trial).³⁴

In light of the unique mechanism of action and efficacy of fingolimod, newer, more selective small-molecule S1PRM with shorter half-lives and potentially less adverse effects were developed. Siponimod (BAF312, Mayzent[®], Novartis Pharmaceuticals AG, Basel, Switzerland) selectively binds to S1PR-1 and 5. It is the first FDA-approved drug for the treatment of active SPMS.³⁴ Other selective S1PR modulators demonstrated their efficacy and safety in RRMS such as ozanimod (selective for S1PR-1 and 5) and ponesimod (selective for S1PR-1).³⁵ Their similarity to siponimod regarding the selectivity pattern makes these drugs potential candidates for SPMS treatment.

Unlike fingolimod, siponimod binds directly to S1PR-1 and 5 without undergoing phosphorylation.²⁹ For a better understanding of the mechanism of action of S1PRM, it is important to know the interaction between CNS cells in the active progressive phase of MS. How and why the first immune attack to CNS occurs is unclear but inflammation and demyelination within the CNS, leads to more tissue damage and antigen release to the periphery and subsequent recruitment of more lymphocytes to invade the CNS again.³ Moreover, pro-inflammatory reactions are mediated by microglia within the CNS in response to autoimmune process. In addition, astrocytes are considered the most important regulators of immunocompetent T lymphocytes and they seem to be implicated in astrocyte-induced neurodegeneration. It is believed that immune-mediated demyelination, axonal injury, astrocytic gliosis and microglial activation play an important role in the activity and the progressive course of MS.³

Siponimod inhibits the chemotaxis of immune cells and the migration of lymphocytes to blood and CNS, but also acts directly on the CNS. This drug promotes oligodendrocytes remyelination by acting on S1PR5, limits the pro-inflammatory role of microglia and modulates astrocytic function. The latter role was confirmed in *in vitro* experiments, showing that siponimod activates glial Nrf2, inducing *in vivo* anti-oxidant, anti-inflammatory and neuroprotective responses and inhibiting astrocytic NFkB primarily involved in pro-inflammatory reactions, scar formation and neurodegeneration.³⁶ The direct effect of siponimod on CNS cells was also observed after continuous direct intracerebroventricular infusion of the molecule to the brain of mice, which reduced in autoimmune encephalomyelitis (EAE) model severity of EAE without even affecting the number of peripheral lymphocytes.³¹

Siponimod

Efficacy

EXPAND Trial results

The pivotal trial comparing the efficacy of siponimod to placebo in SPMS, EXPAND,³⁷ was a Phase III, double-blind, randomized controlled trial, enrolling 1651 patients with SPMS from 292 centers in 31 countries, assigned to receive oral siponimod 2 mg per day or placebo (2:1) and followed for up to 3 years. Included patients were between 18 and 60 years old, with moderate-to-advanced disability (Expanded Disability Status Scale (EDSS) score of 3.0–6.5 at screening), and no evidence of relapses in the 3 months prior to randomization. Patients with immunological, cardiac, or pulmonary conditions, ongoing macular edema, uncontrolled diabetes, CYP2C9*3/*3 genotype, and varicella zoster virus antibody negative status were excluded. The primary end-point was 3-month confirmed disability progression (CDP) defined as a 1-point increase in EDSS if the baseline score was 3.0–5.0, or a 0.5-point increase if the baseline score was 5.5–6.5. Secondary end-points included the time to 3-month confirmed worsening of the timed 25-foot walk test (T25FW) of at least 20% and baseline change in T2 lesion volume on brain MRI, 6-month CDP, annualized relapse rate (ARR), time to first relapse, proportion of relapse-free patients, and percentage change in brain volume from baseline among others.

Mean age of participants at baseline was 48 years, mean disease duration was 16.8 years, and mean time to conversion to SPMS was 3.8 years. Importantly, 64% of patients did not experience a clinical relapse in the past 2 years and 56% needed assistance for walking. In other words, this study included a typical SPMS cohort, an under-represented population in classic trials. Siponimod was superior to placebo in reducing the risk of 3-month and 6-month CDP. Siponimod was not superior to placebo on reducing worsening on the T25FW. Siponimod was also superior to placebo on other secondary outcome measures (Figure 1). Importantly, the cumulative number of gadolinium-enhancing lesions and mean number of new or enlarging T2 lesions on all post-baseline MRIs were lower with siponimod (adjusted mean (standard deviation) 0.08 (0.07–0.10) and 0.70 (0.58–0.84) respectively) compared to placebo (adjusted mean (standard deviation) 0.60 (0.47–0.76); relative risk 0.14 (0.10–0.19) and 3.60 (3.03–4.29); relative risk 0.19 (0.16–0.24), respectively, $p < 0.0001$ for both). Moreover, there was an in-between group difference in percent brain volume change from baseline of 0.15% (0.07–0.23; p -value 0.0002) in favor of siponimod.

Long-Term Efficacy

Extension studies are essential in assessing long-term efficacy of therapies and are currently not available for siponimod. The AMASIA (impact of Mayzent [siponimod] on secondary progressive multiple sclerosis patients in a long-term non-interventional study in Germany) trial, an open label study across 250 medical centers in Germany was initiated in February 2020 and is expected to terminate in 2025.³⁸

Siponimod and Cognition

Benedict et al assessed the impact of siponimod on cognitive function as a secondary analysis of the EXPAND trial. Cognitive tests were applied at baseline, every 6 months, and at the end of trial. Treatment with siponimod was associated with a lower risk of sustained clinically significant decrease in the Symbol Digit Modalities Test (SDMT, a measure of processing speed) score (hazard ratio [HR] 0.79 [0.65–0.96]; $p = 0.0157$), and even higher chances of a sustained increase in the SDMT score (HR 1.28 [1.05–1.55]; $p = 0.0131$). The effect size was larger after 12 months of siponimod use.³⁹ However, no effect on other cognitive tests was observed.

Fingolimod vs Siponimod

The efficacy of fingolimod was evaluated in patients with PPMS in a phase III, double blind, randomized, placebo-controlled trial (INFORMS), and showed that fingolimod was not superior to placebo in slowing disability progression in this cohort.⁴⁰ An indirect treatment comparison between siponimod in SPMS and fingolimod in PPMS was performed in a recent study. This comparison was feasible because trial design, patient's baseline characteristics and their inclusion/exclusion criteria and

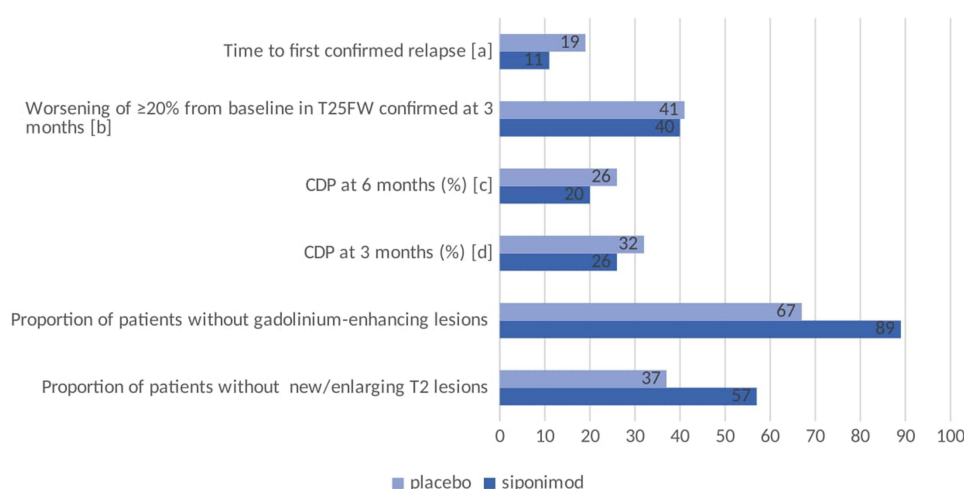


Figure 1 Efficacy of siponimod vs placebo on different outcome measures in the EXPAND trial³⁷ add all outcome measures. [a] Hazard ratio [HR] 0.54, 95% CI 0.41–0.70; risk reduction 46%; $p < 0.0001$. [b] HR 0.94, 95% CI 0.80–1.10; risk reduction 6%; $p = 0.44$. [c] HR 0.74, 95% CI 0.60–0.92; $p = 0.0058$. [d] HR 0.79, 95% CI 0.65–0.95; risk reduction 21%; $p = 0.013$. Data from Kappos et al.³⁷

Abbreviations: T25FW, timed 25-foot walk; CDP, confirmed disability progression.

outcome definitions were similar between the two trials. For 3 and 6-months CDP, siponimod and fingolimod were not significantly different (HR 0.80, 95% CI 0.52–1.22; $p = 0.3$, and HR 0.76, 95% CI 0.48–1.20; $p = 0.24$ respectively).^{40,41}

Safety of Siponimod

Safety in EXPAND

The safety of selective S1PRM was the key feature as compared to fingolimod. Atrio-ventricular slowing was thought to be secondary to S1PR-3 modulation, as demonstrated in mice model. However, cardiac side effects also occur in S1PR-3-sparing agents. Studies concluded that in humans, cardiac AEs were also attributable to S1PR-1 modulation, via activation of G protein-inwardly rectifying potassium channels (GIRK) expressed on atrial myocytes. The finding outlined species-specific differences in S1PR specificity.^{42,43}

In EXPAND, AEs occurred in 89% in the siponimod vs 82% in the placebo group. Eight percent in the siponimod arm discontinued treatment because of AEs vs placebo (Figure 2).

On day 7 post treatment with siponimod, the mean decrease of HR was 3.1 beats per minute. Telemetry for up to 6 days after the first siponimod dose did not register any second degree AV block (Mobitz II) or third degree AV block.³⁷ While treatment with fingolimod was associated with an increased risk of basal cell carcinoma and malignant melanoma, this risk did not differ between siponimod and placebo patients.³⁷ Long-term data are however needed to confirm this finding. Infectious AEs were similar between placebo and siponimod group except for the risk of varicella zoster reactivation and herpes infection which was higher with siponimod. The risk of developing cardiac AEs is mitigated by a dose titration protocol (Table 2).⁴⁴

Lymphopenia is a potential risk expected with all S1PR modulators. Grade IV lymphopenia (absolute lymphocyte count $<200/\text{mm}^3$) was seen in 1% of patients on siponimod whereas it is observed in up to 18% of patients on fingolimod.^{45,46} Moreover, after discontinuation of siponimod, lymphocyte count return to normal levels within 10 days in 90% of patients, while it typically takes 14–21 days and can reach 2 months in fingolimod after treatment discontinuation.⁴⁷

The pre-treatment work-up includes a baseline ECG, ophthalmologic examination, CBC and liver function tests (within 6 months before starting therapy), a pregnancy test, counseling on the use of effective contraception in females of reproductive, and VZV serology or confirmation of prior exposure, along with the CYP2C9 genetic test.⁴⁸ Respiratory function tests are recommended for patients with pulmonary symptoms because siponimod may cause a decline in respiratory function.⁴⁹ First-dose cardiac observation is only mandatory in high-risk patients (those with sinus

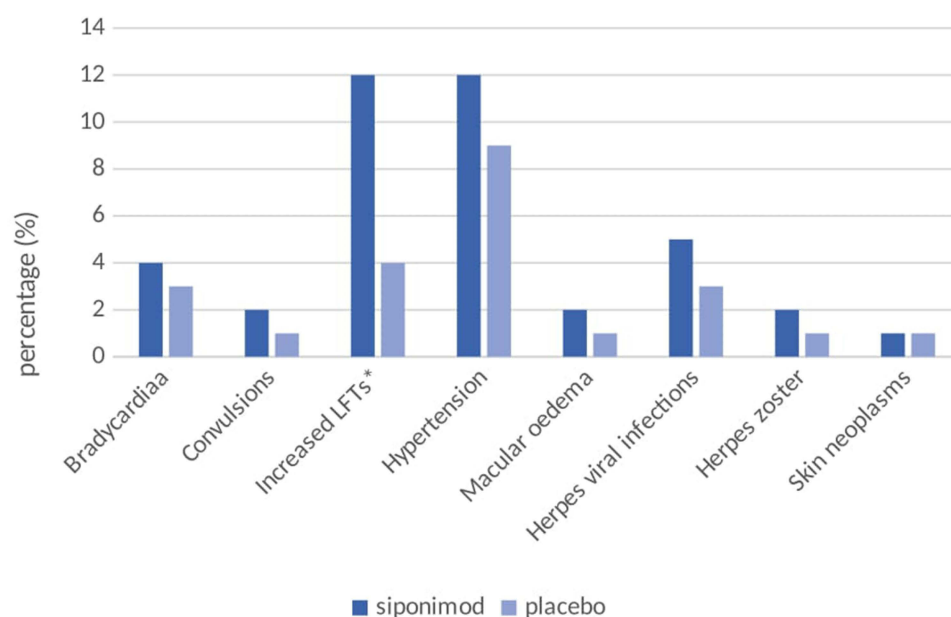


Figure 2 Frequency of side effects in the siponimod arm compared to the placebo arm in the EXPAND trial. Data from Kappos et al.³⁷
Abbreviation: *LFT, liver function tests.

Table 2 Siponimod Titration protocol⁴⁸ *

Titration for a Maintenance Dose of 1 mg/day (CYP2C9 *1/*3, *2/*3)	Titration for a Maintenance Dose of 1mg/day (CYP2C9 *1/*1, *1/*2, *2/*2)
Day 1: 0.25 mg/day	Day 1: 0.25 mg/day
Day 2: 0.25 mg/day	Day 2: 0.25 mg/day
Day 3: 0.5 mg/day	Day 3: 0.5 mg/day
Day 4: 0.75 mg/day	Day 4: 0.75 mg/day
Day 5 and thereafter: 1 mg/day	Day 5: 1.25 mg/day
	Day 6 and thereafter: 2 mg/day

Notes: *If a dose is missed during the initiation protocol, the dosage titration should be restarted. However, in the maintenance period, repeat dosage titration is not needed for drug discontinuation of <4 consecutive days.^{38,48}

bradycardia, first- or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure). In general, routine vaccination is recommended prior to treatment start, specifically the VZV vaccine in patients with a negative VZV serology and older individuals.⁵⁰

CYP2C9 Status

Siponimod is metabolized in the liver via the Cytochrome P450 (CYP) 2C9 enzyme, which contributes to 79.3% of the metabolism, and to a lesser extent via the CYP3A4 enzyme. Siponimod is excreted in the feces. The pharmacokinetics, more specifically the elimination rates of siponimod, differs according to CYP2C9 genotypes. Serum concentration of siponimod increases by twofold with CYP2C9*2/*3 and fourfold with CYP2C9*3/*3 genotype compared to CYP2C9*1/*1 (counts for up to 65% of genotypes of white population). The elimination half-life was also prolonged with CYP2C9*2/*3 and CYP2C9*3/*3 genotypes (reaching 126 hours for the latter compared with 28 hours for CYP2C9 *1/*1)⁵¹ Gene testing for CYP2C9 is hence required prior to initiation siponimod to adjust both titration and maintenance dosages (Table 2).

Siponimod is contraindicated in CYP2C9 *3/*3 genotype,⁴⁸ CYP2C9 *3/*3 is present only in 0.3–0.4% of white individuals.⁵¹ CYP2C9/3A4 inhibitors like fluconazole interact with siponimod elimination,^{51,52} and are not recommended to use concomitantly with siponimod.⁴⁸ On the other hand, CYP2C9/3A4 inducers can decrease serum drug concentration. For instance, the dual strong CYP3A4/moderate CYP2C9 inducers reduce siponimod exposure by up to 78%, and are to be avoided for all CYP2C9 genotypes. Moderate/strong CYP3A4 inducers are not recommended for patients with CYP2C9*1/*3 and *2/*3 genotypes.⁵²

Extension Studies and Latest Case Reports and Case Series

Long-term data regarding safety and efficacy of siponimod is lacking to date, since this medication was only recently approved and used. The AMASIA study as discussed above will be helpful to inform us on real-world safety in the next few years.³⁸ To date, one case of breakthrough disease after switching from fingolimod to siponimod without a washout period was reported in a 49-year-old female patient.⁵³

Safety Monitoring

To mitigate the risk of adverse events, a series of follow-up tests should be performed as seen in Table 3.

When to Discontinue Siponimod?

For all DMTs, it remains unclear when to discontinue DMTs. In the current practice, experts recommend discontinuing DMTs in patients with progressive disease without evidence of clinical or radiological activity who continue to worsen despite treatment. For example, The Canadian agency for drugs and technologies in health (CADTH) recommends the discontinuation of siponimod if the EDSS score reaches 7 (equivalent to being wheelchair-bound), or if there is a worsening of the T25W test of $\geq 20\%$ while on siponimod.⁵⁴

Table 3 Monitoring of Patients on Siponimod per FDA Recommendations.^{48–50,88}

Potential Adverse Event	Monitoring Test
Lymphopenia	Complete blood count at 3–6 months after initiation then every 6–12 months thereafter
Hypertension	Monitor BP regularly during treatment
Macular Edema	Ophthalmologic evaluation if visual symptoms occur or after 3–4 months for patients with diabetes and uveitis.
Dyspnea	Pulmonary function test (spirometry) if respiratory symptoms occur
Liver Injury	Liver enzymes testing after 3–6 months after initiation then every 6–12 months thereafter
Fetal Risk	Evaluation of use of effective contraception during treatment with siponimod and up to 10 days after discontinuation

It is important to mention that no cases of rebound inflammatory activity after siponimod discontinuation are reported to date. However, a potential risk exists since it has been described with fingolimod. Thus, close monitoring after siponimod discontinuation is warranted.

COVID-19 and Siponimod

In the Coronavirus disease-19 (COVID-19) era, the vulnerability to the SARS-CoV-2 viral infection itself and the COVID-19 vaccine response with different DMTs is in the spotlight. Recent data suggest that the risk of serious COVID-19 infection is not increased in patients on S1PRM (particularly fingolimod), however the vaccine response is significantly blunted.^{45,55} An observational study of 54 SPMS patients (mean age of 54 years) treated with siponimod with confirmed SARS-CoV-2 infection, showed that 85.7% of those patients were asymptomatic, or had mild-to-moderate infection, 17% were hospitalized (compared to 14% in overall population), and 6% died (mortality of 5% in the general population). The slight increase in hospitalization and death may be due to older age and disability in the siponimod population, making this group of patient more prone to severe infection independently of treatment.^{56,57}

The benefit of COVID-19 vaccination for patients on DMTs often outweigh the risk of not taking the vaccine and the risk of stopping DMTs abruptly to receive the vaccine; however, this decision should be done in a case-by-case approach. A recent study reported significantly lower post-vaccination reactive IgG rates in patients receiving anti-CD20 therapies and S1PRM.⁴⁵ Even though S1PRM can reduce vaccine efficacy, vaccination is nevertheless encouraged in all patients.^{56,57,58}

A Phase 4, multicentric, prospective trial evaluating the development of functional anti-SARS-CoV-2 antibodies and T-cell titers following SARS-CoV-2 mRNA vaccines is ongoing, and siponimod-treated SPMS patients will be included. The study started in March 2021, and should be extended over 14 months (NCT04792567).

Cost-Effectiveness

In the USA (according to the Institute for Clinical and Economic Review) and Canada (according to the National Institute for Health and Care Excellence), siponimod was considered a non-cost-effective agent.⁵⁹ In Canada, a reduction of 63% of its price was suggested for this drug to be cost-effective as compared to best supportive care with a threshold of \$50,000 per quality-adjusted life-year (QALY).⁵⁴ In the UK, the National Institute for Health and Care Excellence (NICE) considered siponimod a non-cost effective in June 2020 but after price reduction by the campaigners, this decision had been cancelled. In Switzerland, siponimod, compared to beta interferon drugs in treatment of active SPMS, was labeled as cost effective in April 2021.⁶⁰

Patient Adherence and Expectations

Patient adherence to DMT is crucial for optimal response to treatment. It has previously been reported that a level of adherence above 80% in terms of proportion of days covered (PDC) contributes to the reduction of costs in MS

management (including risk of hospitalization and outpatient visits).⁶¹ In the only study reporting adherence to siponimod in MS,⁶² a PDC above 80% was observed in 81.1% of patients with a follow-up duration of more than 6 months, and in 82.4% of patients with a follow-up duration of more than 12 months.⁶² Similarly, a meta-analysis reported PDC above 80% in 75.6% of patients on oral DMT (not including siponimod) during a follow-up of one year.⁶³ Some demographic characteristics increase the risk of non-adherence, such as age and disease duration. In fact, non-adherence is higher in patients with pediatric-onset MS and adolescents with MS and increases with disease duration.⁶⁴ Of note, siponimod is not approved for use in this population. Numerous psychosocial factors also drive non-adherence, including cognitive impairment and psychiatric comorbidities, poor socio-economic status, lack of peer support, and higher level of physical disability.^{64–66}

Factoring patient preferences in treatment choices is a key element in optimizing adherence,⁶⁷ as recommended in the AAN and the EAN guidelines for MS management.^{25,26} While data on patient expectations regarding siponimod in SPMS is lacking, patient expectations from other DMTs have been the subject of recent studies.^{68–73} Among the patient concerns, the method of administration, safety profiles, and efficacy of therapy are the 3 main themes of interest.^{68–73} Concerning the preferred route of administration, prior studies suggest that oral DMT is favored by patients,^{68,69,72,73} whereas in a newer study, infusions seem to be gaining popularity, particularly when less than three injections per year are required.⁷⁰ Regarding safety, liver toxicity, severe adverse events, and common side effects were the most important for the patients.⁷⁴ A few studies evaluated whether patients prioritize safety or efficacy. The results mainly differed between treatment-naïve patients with shorter disease duration and patients who have been exposed to DMTs with a longer time since diagnosis. Patients within five years of the diagnosis were more concerned about adverse events than treatment efficacy, whereas patients who were diagnosed for >5 years had opposite preferences.⁶⁹ These results were later confirmed by Bauer et al with a cut-off of ten years since diagnosis.⁷⁰

When comparing the patient and the provider goals and concerns of treatment, patients seem to focus on specific symptoms (ability to walk, vision loss, cognitive dysfunction, body strength), whereas physicians were more concerned about the overall progression of the disease.⁷¹ Among reported physician goals in MS treatment, preventing disability ranked first, followed by efficient DMT choice, and quality of life improvement.⁷¹ Previous studies have suggested that demographic factors such as sex and age, the level of disability and prior use of DMT can predict adherence to treatment.^{75,76} Physician can rely on several factors that can predict patient adherence namely treatment goals, past treatments, disease course and demographics.

Future Directions

Several challenges in the care and treatment of patients with SPMS are to be mentioned. First, there is no clear consensus on the definition of SPMS and biomarkers of transition from RRMS to a SPMS are lacking. In phase 3 SPMS trials, a definition of SPMS is used in the inclusion criteria, yet medications such as siponimod and cladribine are only approved for active SPMS. Some studies have worked on finding an objective and accurate definitions of SPMS, both active and inactive, to enable comparability of studies and guide clinical decisions.¹³

The lack of consensus on the definition of SPMS in clinical trials is also shared in clinical practice. Clinical progression independent of relapse activity can be very difficult to capture in clinical practice, which makes the diagnosis of SPMS retrospective and delayed by about 3 years after a period of clinical uncertainty.¹⁴ Most definitions take into account worsening on the EDSS; however, this instrument is not consistently used in clinical practice and lacks sensitivity to evaluate functional systems other than ambulation such as upper extremity and cognitive functions and could fail to capture “progression” in other important quality of life indicators for MS patients.⁷⁷ To mitigate this limitation, modern trials have used a variety of outcome measures to assess treatment efficacy. The AMASIA trial is an example, and will evaluate the EDSS coupled to the SDMT for cognitive functioning.^{78,79} The latter composite outcome has been validated for use in MS.⁸⁰ Other outcome measures focused on longitudinally and objectively capturing progression independent of relapses are needed. Technology-enabled tools to capture such data and analyse them at the individual level can be incorporated in clinical practice and have emerged in the past few years. Standardized definition and technology-enabled tests will hopefully fill the needed gap to better identify the onset of clinical progression.⁸¹

Recent research efforts to better understand the heterogeneity of SPMS and of therapeutic responses are increasing. For example, data from the AMSIA trial will be integrated to the MSD-3D⁸² virtual platform designed to store and compare patients' data from various clinical studies, and could help the MS community to compare data from different studies. Possible examples include the PANGAEA 2.0 EVOLUTION study, comparable to AMASIA in its methodology, and designed to assess patients with SPMS or high-risk RRMS treated according to the standard of care before the approval of siponimod in SPMS.⁸³

Conclusion

The extensive therapeutic options favor a patient-centered approach in MS management. That said, therapeutic success is not solely measured via objective tools such as clinical and radiological response to treatments but by equally important criteria such as patient adherence to treatment, satisfaction with therapeutic regimen and effect on quality of life. This holistic aspect of patient care is underrepresented in treatment efficacy evaluation. An important benchmark of clinical meaningfulness for patients would be employment. Ocrelizumab was found to positively impact employment in MS and this outcome should be evaluated in other trials.⁸⁴ Patient-centred outcomes in SPMS trials will help to shape future care of this population. Future studies may include a consensus-driven definition of active SPMS and also focus on patient's goals and expectations to enhance long-term quality of life of those living with MS.

Disclosure

Sajida Sabsabi, Georges Jalkh, and Elio Mikhael have nothing to disclose.

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