Sphingosine-1-phosphate Receptor Modulators in Multiple Sclerosis

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The introduction of oral disease modifying therapies has transformed the treatment landscape for patients with multiple sclerosis (MS). Fingolimod (Gilenya®, Novartis, Basel, Switzerland), the first oral therapy to be approved, has demonstrated clinical efficacy as a result of modulation of subtype 1 sphingosine-1-phosphate ($S1P_1$) receptors. This leads to retention of lymphocytes in the lymph nodes, preventing their entry into the central nervous system. However, fingolimod can cause adverse effects as a result of its interaction with other S1P receptor subtypes, which are expressed in numerous tissues, including cardiac myocytes. More selective S1P receptor agents are currently in phase II and III clinical development. Siponimod, ozanimod, ponesimod and amiselimod have demonstrated efficacy with improved safety profiles compared with fingolimod. While more long-term data are needed, these selective S1P receptor modulators appear to be promising options for the treatment of MS and other disorders associated with autoimmunity and inflammation.

Keywords

Multiple sclerosis, oral disease modifying therapies, sphingosine-1-phosphate receptors

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In the past decade, a number of novel therapies targeting specific molecules involved in the inflammatory or immune system activation cascades have become available, improving the management of multiple sclerosis (MS).[1] However, most new therapies are biological drugs, which need to be injected and are therefore associated with reduced convenience, compliance and injection- or infusion-related adverse effects (AEs).[2,3] Most current disease modifying therapies (DMTs) for MS primarily target the immunological inflammatory component of the disease without acting directly on the central nervous system (CNS)[4] and have been shown to be only partially effective. In addition, chronic immunosuppression is associated with mainly opportunistic infections.[5]

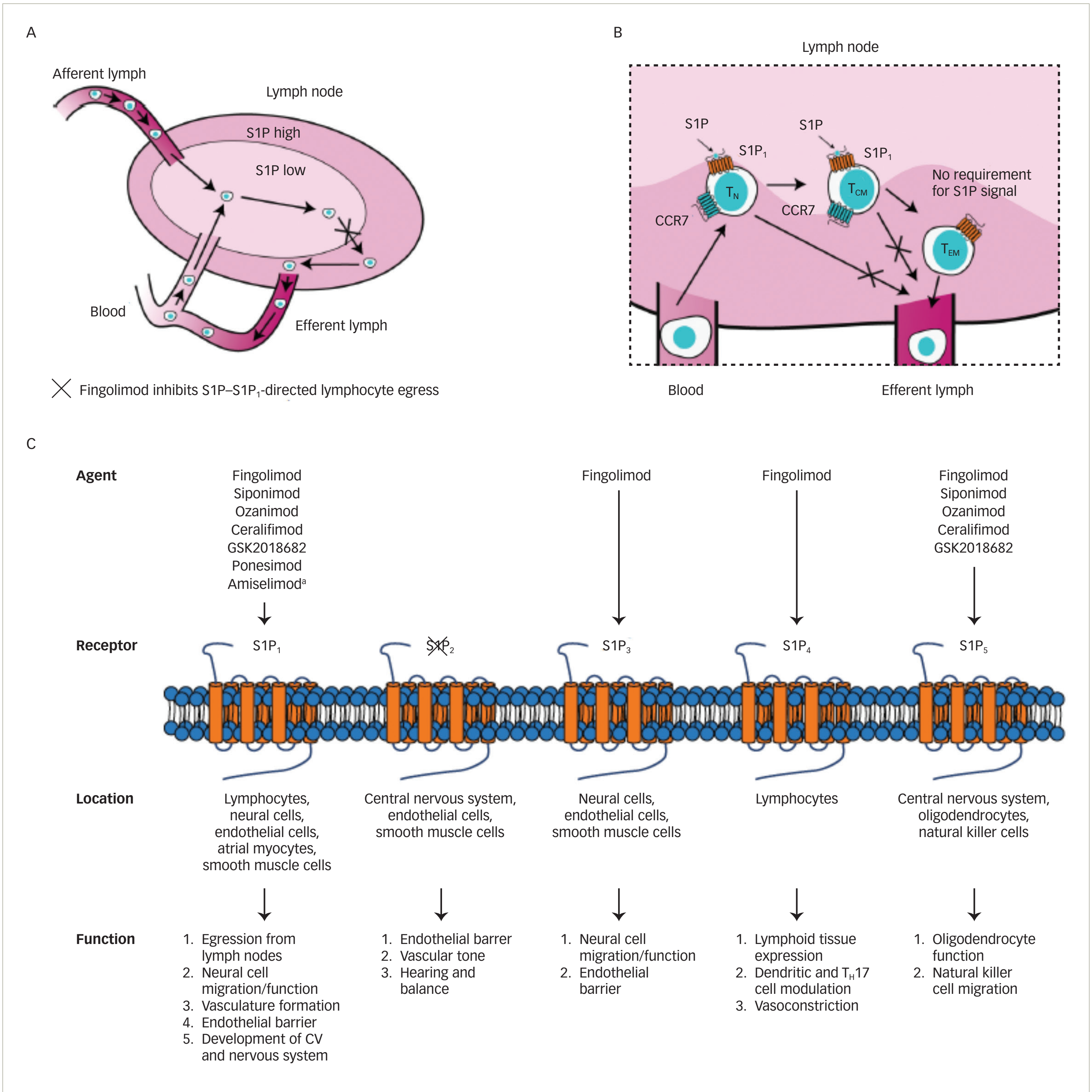
Another drawback of current DMTs is that, to date, most have shown limited efficacy against secondary progressive MS (SPMS),[6] although ocrelizumab has been approved for progressive MS after showing activity in patients with primary progressive MS.[7] A new class of oral targeted therapies for MS has the potential to overcome these limitations. This review aims to discuss the clinical development of sphingosine-1-phosphate (S1P) receptor modulators for the treatment of patients with relapsing forms of MS (RMS) or SPMS.

Mechanism of action of sphingosine-1-phosphate receptor modulators

Sphingosine-1-phosphate is an active phospholipid that is produced by the phosphorylation of sphingolipids, present in the cell membrane, by sphingosine kinase-1 or -2 (SphK1/2; *Figure 1*).[8] It regulates numerous biological processes including immunity, inflammation, angiogenesis, heart rate, smooth muscle tone, cell differentiation, cell migration and survival, calcium homeostasis and endothelium integrity, and is found in high concentrations in erythrocytes, brain, spleen and eyes.[8] Its effects are mediated by S1P receptors, which have seven transmembrane segments and are coupled to G-proteins. There are five known subtypes: $S1P_{1–3}$ which are broadly distributed in tissues; $S1P_4$, which is expressed mostly in lymphoid tissue and the lungs; and $S1P_5$, which is found in the spleen, skin and oligodendrocytes.[8,9] Therefore, S1P receptors are found in multiple organ systems including the immune, cardiovascular, and respiratory systems, as well as in the CNS.[9] In the CNS, expression of S1P receptors has been reported on oligodendrocytes, astrocytes, neurons and microglia in experimental conditions.[9] Both B- and T-lymphocytes express $S1P_1$ and, to a lesser extent, $S1P_3$ and $S1P_4$.[8]

Sphingosine-1-phosphate signalling plays an important role in lymphocyte trafficking, particularly egress from lymph nodes and migration into the blood and target tissues (*Figure 1*).[10,11] In patients with MS, S1P receptors reduce the release of lymphocytes from secondary lymphoid tissues, thymus and bone marrow, resulting in lymphopaenia. The binding of S1P receptor modulators to $S1P_1$ on central memory T-cells (TCM) causes these cells to internalise their own $S1P_1$, resulting in TCM that no longer respond to S1P signals. Any new S1P receptors produced inside the cell remain in an inactive state until S1P receptor modulation is removed.[11]

Figure 1: Mechanism of action of sphingosine-1-phosphate receptor modulators



A: Binding of S1P receptor modulators to S1P$_1$ on central memory T-cells. B: Interaction of S1P receptor modulators with S1P receptor subtypes. C: Interaction of fingolimod and selective S1P receptor drugs with S1P receptor subtypes. [a]Amiselimod is selective, but its selectivity is unknown. CCR7 = C-C chemokine receptor type 7; CV = cardiovascular; S1P = sphingosine-1-phosphate; S1P$_{1–5}$ = sphingosine-1-phosphate receptor subtypes 1–5; T$_H$17 = T helper cell 17; T$_{CM}$ = central memory T-cell; T$_{EM}$ = effector memory T-cell; T$_N$ = naïve T-cell. Reproduced from Comi et al., 2017[11] with permission from the original sources.[54,55]

Therefore, TCM do not leave the lymph node in response to S1P signals. As a result, fewer circulating lymphocytes are available to infiltrate the CNS and mount an autoimmune reaction on the axon myelin sheath.[8,12,13] Modulators of the S1P receptor prevent these autoreactive cells from migrating into the CNS. By contrast, the levels of peripheral effector memory T-cells (TEM) are mostly unaffected by S1P receptor modulators, preserving immunosurveillance and the ability to respond to and contain locally invading pathogens.[11]

Fingolimod (Gilenya®, Novartis, Basel, Switzerland) is a lipophilic sphingosine-like agent that is phosphorylated by SphK1/2 to become fingolimod-P, an S1P analogue. Fingolimod-P binds to the S1P$_1$ receptor and is internalised in the same way as S1P, but the receptor is then degraded, preventing cell surface signalling.[8] Fingolimod is an agonist of four S1P receptor subtypes (S1P$_1$, S1P$_3$, S1P$_4$ and S1P$_5$)[14] and induces immunosuppression through inhibition of recirculation of naïve T-cells and the release of antigen-activated T-cells from the draining lymph nodes to lymph and to the blood compartment.[15] It crosses the blood-brain barrier and may have direct CNS effects, distinguishing it from immunologically targeted MS therapies, although this has not been demonstrated in humans.[13] Fingolimod has also been found to attenuate neuroinflammation in rats by regulating the activation and neuroprotective effects of microglia, mainly via S1P$_1$.[16,17] Fingolimod also has direct CNS effects via suppression of pathogenic astrocyte

Table 1: Summary of sphingosine-1-phosphate receptor modulator pharmacokinetics and pharmacodynamics

	Receptor selectivity	Pro-drug (requires phosphorylation *in vivo*)	T_{max} (h)	Time to lymphocyte count reduction (h)	Lymphocyte decrease from baseline (%)	$T_{1/2}$ (h)	Time to lymphocyte count recovery after treatment discontinuation (days)
Fingolimod[14,32]	$S1P_1$ $S1P_3$ $S1P_4$ $S1P_5$	Yes	12–16	4–6	70	144–216	30–60
Ponesimod[39,40]	$S1P_1$	No	2–4	6	50–70	30	7
Siponimod[48]	$S1P_1$ $S1P_5$	No	3.0–4.5	4–6	33–76	30	1–5
Ozanimod[42]	$S1P_1$ $S1P_5$	No	6–8	6–12	34–68	17–21	2–3
Amiselimod[46,47]	$S1P_1$ $S1P_5$	Yes	12–16	No data	60–66	380–420	49

h = hour; $S1P_{1–5}$ = sphingosine-1-phosphate receptor subtypes 1–5; $T_{1/2}$ = elimination half life; T_{max} = time to maximum plasma concentration.

activation.[18] While the therapeutic action of fingolimod is largely a result of its binding to $S1P_1$, its modulation of $S1P_3$, $S1P_4$ and $S1P_5$ has been associated with AEs.

Clinical efficacy and safety of fingolimod

Fingolimod has demonstrated efficacy and safety in three large phase III studies. In the FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis (FREEDOMS) study (n=1,033), over 24 months, fingolimod decreased annualised relapse rate (ARR) by over 50%, as well as reducing the risk of disability progression compared with placebo in patients with RMS.[19] These findings were confirmed in the FREEDOMS II study[20] and the TRial Assessing injectable interferoN vS FTY720 Oral in RRMS (TRANSFORMS) trial (n=1,153), in which fingolimod demonstrated superior efficacy to intramuscular interferon beta-1a (IFN β-1a) in patients with RMS, although there was no difference between fingolimod and IFN β-1a in terms of disability progression.[21] In 2010, the US Food and Drug Administration (FDA) approved fingolimod as the first oral DMT to treat RMS.[22]

Compliance with fingolimod has been shown to be superior to injected and infused DMTs.[23,24] In recently presented data from the phase III Safety and Efficacy of Fingolimod in Pediatric Patients With Multiple Sclerosis (PARADIGMS) study (n=190), fingolimod resulted in a clinically meaningful, statistically significant reduction in the ARR of paediatric RMS patients compared with IFN β-1a injections.[25,26] Another recently published study, Fingolimod on cognitive symptoms and brain atrophy (GOLDEN), found positive effects of fingolimod in cognitive, magnetic resonance imaging (MRI), and clinical outcomes in 157 patients with RMS over 18 months.[27] However, fingolimod is not effective in all forms of MS; in the phase III Oral fingolimod in primary progressive multiple sclerosis (INFORMS) study (n=970) it did not slow disease progression.[28]

Despite a growing body of clinical evidence supporting the efficacy of fingolimod,[11] its clinical use has been limited by safety concerns with respect to cardiac effects, infections and macular oedema.[29] However, cardiac symptoms, including bradycardia and atrioventricular conduction block on drug initiation, are transient.[21] A number of factors should be considered before initiation of fingolimod or require monitoring while on treatment, including first-dose monitoring, pregnancy, diabetes mellitus, posterior reversible encephalopathy syndrome, basal cell carcinoma, infections such as varicella, opportunistic cryptococcal infections and progressive multifocal leukoencephalopathy (PML).[11] These cardiac effects are due to activation of $S1P_1$ on cardiac myocytes, which subsequently disappears by downregulation of $S1P_1$.[30] Cases of PML have been reported,[31,32] but the estimated risk is considered low, based on experience to date with fingolimod.[33] There is also a need for regular dermatological follow-up because of the slightly increased risk of basal cell carcinomas.[32] Studies assessing the long-term safety and efficacy of fingolimod are currently ongoing; to date, no new safety signals have been observed.[34]

The use of selective S1P modulators may overcome these safety concerns. Unlike fingolimod, which suppresses lymphocyte recirculation for 4–6 weeks after withdrawal,[35] $S1P_1$-selective agonists induce reversible lymphopaenia while persisting in the CNS and are therefore less likely to activate latent infections.[36]

Selective sphingosine-1-phosphate receptor modulators

Following the approval of fingolimod, a number of selective $S1P_1$ modulators entered clinical development (*Table 1*) and several are currently being evaluated in phase III clinical studies (*Table 2*). These agents differ in their selectivity and activation potency (EC_{50}).[30,37,38] The therapeutic effects of these compounds are caused by rapid internalisation, degradation and functional antagonism of $S1P_1$, leading to lymphocyte sequestration in the lymph nodes.[11] Since they do not affect $S1P_{3–4}$ receptors, they are expected to be associated with fewer AEs, including those occurring after the first dose. In contrast to the long half-life and slow elimination of fingolimod, all of the selective $S1P_1$ modulators in clinical development (apart from amiselimod) have a shorter half-life and show a reduced time to lymphocyte recovery after treatment discontinuation compared with fingolimod, which is an important consideration for patients who need to interrupt medication.[11]

Ponesimod

Ponesimod (Actelion, Basel, Switzerland) is an orally active selective $S1P_1$ and $S1P_5$ modulator that is eliminated within 1 week after discontinuation and its pharmacological effects are rapidly reversible.[39] Ponesimod activates $S1P_1$- and $S1P_5$-mediated signal transduction with high potency and selectivity.[37] The quicker elimination of ponesimod may be an advantage in managing serious or opportunistic infections and may also help to prevent complications in case of AEs such as macular oedema, pulmonary function changes and liver enzyme elevations.

Table 2: Summary of clinical studies of sphingosine-1-phosphate receptor modulators

Drug	Clinical trial details	Efficacy findings	Safety findings
Ponesimod	Phase IIb, n=464, 24 weeks, RMS[40]	Mean cumulative number of new T1 Gd+ lesions at weeks 12–24 was lower in ponesimod 10 mg (3.5; RR 0.57; p=0.0318), 20 mg (1.1; RR 0.17; p<0.0001) and 40 mg (1.4; RR 0.23; p<0.0001) compared with placebo (6.2). Mean ARR was 53% lower with 40 mg ponesimod versus placebo, (0.25 versus 0.53; p=0.0363). Time to first confirmed relapse increased with ponesimod compared with placebo.	Proportions of patients who had ≥1 AE during the treatment period were similar across all ponesimod groups (73.9–77.2%) and placebo (74.4%). Frequent TEAEs with a higher incidence in ponesimod groups were anxiety, dizziness, dyspnoea, increased ALT, influenza, insomnia and peripheral oedema. Some cardiac and respiratory TEAEs, but all resolved on treatment discontinuation.
Ozanimod	Phase III, n=1,313, 24 weeks, RMS[44]	Significant reduction in ARR for ozanimod 1 mg (0.17, p<0.0001) and 0.5 mg (0.22, p=0.0168) compared with IFN β-1a (0.28). Significant reduction in new or enlarging T2 lesions for ozanimod 1 mg (42%, p<0.0001) and 0.5 mg (35%, p=0.0001) compared with IFN β-1a, as well as a significant reduction in Gd+ MRI lesions for ozanimod 1 mg (53%, p=0.0006) and ozanimod 0.5 mg (47%, p=0.0030). Reduction in BV loss of 27% with 1 mg ozanimod (p<0.0001) and 25% in 0.5 mg group (p<0.0001).	Three serious TEAEs were reported in patients assigned ozanimod 0.5 mg: optic neuritis, somatoform autonomic dysfunction and cervical squamous metaplasia (HPV-related). No serious infectious or cardiac AEs were reported, and no cases of macular oedema. The most common TEAEs in the ozanimod 0.5 mg and 1 mg groups compared with placebo were nasopharyngitis (11 and 5 versus 12), headache (5 and 5 versus 8), and urinary-tract infections (6 and 2 versus 2). No clinically relevant cases of bradycardia, AVB or sinus pause with ozanimod.
Ozanimod	Phase III (SUNBEAM) n=1,346, mean 13.6 months, RMS[45]	Both ozanimod 0.5 and 1 mg treatment groups had statistically significant reductions in ARR compared with IFN β-1a. Significant reduction in number of new or enlarging T2 lesions and the adjusted mean number of Gd+ at month 12 for both ozanimod groups compared with IFN β-1a.	Rate of discontinuation due to AEs was also low and similar across treatment groups. No first dose, clinically relevant cases of bradycardia and no AVB of second degree or higher were reported.
Amiselimod	Phase II, n=415, 24 weeks, RMS[46]	Median total number of Gd+ T1-weighted lesions from weeks 8 to 24 did not differ between the amiselimod 0.1 mg and placebo groups (median 2.0 in 0.1 mg group versus 1.6 lesions in the placebo group) but was significantly lower in the two higher amiselimod dose groups than in the placebo group (0.0 lesions in the 0.2 mg group [median difference versus placebo -1.0, 95% CI -1.0, 0.0; p=0.0021] and 0.0 [range 0–30] in the 0.4 mg group [-1.0, 95% CI -1.2, 0.0; p=0.0003]). The estimated incident rate ratio compared with placebo was dose-dependently decreased with amiselimod (0.1 mg 0.53 [95% CI 0.33, 0.85; p=0.0079], 0.2 mg 0.39 [95% CI 0.24, 0.63; p=0.0001], and 0.4 mg 0.23 [95% CI 0.14, 0.38; p<0.0001]).	Incidence of TEAEs including infections and cardiac disorders, were similar in the amiselimod treatment groups (56%) in the 0.1 mg group of 105 patients, 67% in the 0.2 mg group of 103 patients, and 56% of 104 patients in the 0.4 mg group compared with the incidence in the placebo group (64% of 103 patients); the most common TEAEs were headache (10%, 10%, 10% versus 4%) and nasopharyngitis (9%, 7%, 10% versus 8%). No serious TEAEs reported for more than one patient in any group and no clinically significant heart rate reduction at any amiselimod dose.
Siponimod	Phase III, n=1,651, 3 months, SPMS[49]	Siponimod reduced the risk of 3-month CDP by 21% versus placebo (p=0.013). RR for T25FW observed for siponimod was 6.2% and not statistically significant (p=0.440). Siponimod reduced the risk of 6-month CDP by 26% (p=0.006), ARR by 55.5% (p<0.0001), T1 Gd+ lesion number by 86.6% (p<0.0001), and new T2 lesion number by 81% (p<0.0001).	At least one TEAE in 88.7% of siponimod group and 81.5% of placebo group. More heart rate and conduction AEs, hypertension, macular oedema, and convulsions in the treatment than in the placebo group. Incidence of infections was similar between groups, except for an increased herpes zoster incidence in the treatment group. No cases of opportunistic infections, including PML, and no increased incidence of malignancies.

AEs = adverse events; ALT = alanine aminotransferase; ARR = annualised relapse rate; AVB = atrioventricular blocks; BV = brain volume; CDP = confirmed disability progression; CI = confidence interval; Gd+ = gadolinium; HPV = human papillomavirus; IFN β-1a = interferon beta 1a; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy; RMS = relapsing multiple sclerosis; RR = risk ratio; SPMS = secondary progressive multiple sclerosis; TEAE = treatment-emergent adverse event; T25FW = timed 25-foot walk.

In a double-blind, placebo-controlled, dose-finding phase IIb study (n=464), once-daily treatment with ponesimod 10, 20 or 40 mg significantly reduced the number of new T1 gadolinium enhancing (Gd+) lesions and ARR, as well as increasing the time to first confirmed relapse compared with placebo in patients with RMS.[40] In all ponesimod groups, the majority of AEs were mild or moderate in intensity and the proportions of patients who had one or more AE during the treatment period were similar across all ponesimod and placebo groups. Frequently reported treatment emergent AEs (TEAEs) with a higher incidence in the ponesimod groups compared with placebo were anxiety, dizziness, dyspnoea, increased alanine aminotransferase (ALT), influenza, insomnia and peripheral oedema. Incidences of dyspnoea and peripheral oedema appeared to be dose related, with substantially more cases reported in the ponesimod 40 mg group compared with the ponesimod 10 and 20 mg groups. During the treatment period, a total of 27 serious AEs (excluding hospitalisations for MS relapse) were reported. These included two malignancies: one in the ponesimod 10 mg group and one in the placebo group. Cardiac AEs associated with ponesimod treatment initiation included first-degree and second-degree atrioventricular block (AVB) and bradycardia. All AEs relating to heart rate and rhythm occurred on day 1; there was no need for intervention and no recurrence of these AEs later during treatment. Among patients receiving ponesimod who discontinued due to cardiac AEs, 2.6% required treatment compared with none in the placebo group. The proportion of patients with one or more infection-associated AE was similar across the four groups. There were no treatment discontinuations due to lymphopaenia. The proportion of patients with one or more respiratory AE was higher in the ponesimod than in the placebo group (ponesimod 10 mg, 9.3%; ponesimod 20 mg, 16.7%; ponesimod 40 mg, 31.9%; placebo, 6.6%), leading to premature discontinuation of ponesimod in seven patients. The onset of dyspnoea usually occurred within the first month of treatment; all cases resolved. A dose-dependent decrease in forced expiratory volume in 1 second (FEV1) was also observed with ponesimod treatment.[40]

In a small study (n=16) in healthy subjects, ponesimod treatment led to a marked reduction in overall T- and B-cells, with a dramatic reduction in the number of CD4+ cells, whereas CD8+ and natural killer (NK) cells were less affected.[41] A phase III study is currently ongoing to investigate the efficacy and safety of ponesimod in 1,100 patients with RMS (NCT02425644). The primary objective of the trial is to assess whether ponesimod is superior to teriflunomide in reducing the ARR over 108 weeks. This study will be the first to compare the efficacy and safety of two oral treatments in RMS patients. Another ongoing phase III study, the Clinical Study to Compare the Efficacy and Safety of Ponesimod to Placebo in Subjects With Active Relapsing Multiple Sclerosis Who Are Treated With Dimethyl Fumarate (Tecfidera®) (POINT) is evaluating ponesimod as add-on therapy with dimethylfumarate (DMF) in patients in patients who have received DMF for at least 6 months prior to commencing the study (NCT02907177).

Ozanimod

Ozanimod (formally RPC1063, Celgene) is an orally active selective $S1P_1$ and $S1P_5$ modulator that induces lymphopaenia and regulates immune response.[38,42] It was evaluated in a phase II/III randomised, multicentre trial (n=258), Efficacy and Safety Study of RPC1063 in Relapsing Multiple Sclerosis Patients (RADIANCE). The number of Gd+ enhancing lesions were significantly lower with ozanimod compared with placebo.[43]

Two recent phase III studies have evaluated two doses of oral ozanimod compared with IFN β-1a in people with relapsing-remitting MS (RRMS). The RADIANCE Part B study compared two doses (1.0 mg and 0.5 mg) of oral ozanimod with IFN β-1a in 1,313 patients with RMS. Two-year findings showed significant reduction in ARR for ozanimod 1.0 mg (ARR=0.17, p<0.0001) and 0.5 mg (ARR=0.22, p=0.0168) compared with IFN β-1a (ARR=0.28).[44] There was also a significant reduction in new or enlarging T2 lesions for ozanimod 1.0 mg (42%, p<0.0001) and 0.5 mg (35%, p=0.0001) compared with IFN β-1a, as well as a significant reduction in Gd+ MRI lesions for ozanimod 1.0 mg (53%, p=0.0006) and ozanimod 0.5 mg (47%, p=0.0030) compared with IFN β-1a. A total of 75% of patients taking ozanimod 1.0 mg, 74% taking ozanimod 0.5 mg and 83% taking IFN β-1a reported TEAEs. The majority were mild; the most common AEs across all treatment groups were nasopharyngitis, headache, increased ALT, influenza-like illness, hypertension, increased gamma-glutamyl transferase, pharyngitis and urinary tract infection. Incidences of ALT increase were low, transient and generally resolved without study drug discontinuation. The overall incidence of serious AEs was low and similar across treatment arms. Discontinuation of study drug due to AEs occurred in 3.0% of the ozanimod 1.0 mg group, 3.2 % for ozanimod 0.5 mg and 4.1 % for IFN β-1a. No second degree or higher AVBs were observed. Serious cardiac AEs occurred in 0.0% for ozanimod 1.0 mg, 0.7% for ozanimod 0.5 mg and 0.5% for IFN β-1a groups. Infection rates were similar across treatment arms; serious infection rates were low and similar across treatment arms, with no serious opportunistic infections.

Recently, positive results were announced from the phase III Study of RPC1063 in Relapsing MS (SUNBEAM, n=1,346).[45] Both ozanimod 0.5 and 1.0 mg treatment groups demonstrated statistically significant reductions compared with IFN β-1a in ARR. The number of new or enlarging T2 lesions and the adjusted mean number of Gd+ at month 12 demonstrated a significant reduction for both ozanimod groups compared with IFN β-1a. The rate of discontinuation due to AEs was also low and similar across treatment groups. No first dose, clinically relevant cases of bradycardia and no AVB of second degree or higher were reported.

Amiselimod

Amiselimod (formerly MT-1303, Mitsubishi Tanabe Pharma, Japan) is a potent $S1P_1$ modulator that also shows high selectivity for $S1P_5$ receptors. In a phase II trial of patients (n=415) with active RRMS, amiselimod 0.2 mg and 0.4 mg significantly reduced the total number of Gd+ T1-weighted lesions after 24 weeks of treatment (patients treated with 0.1 mg amiselimod had a similar number of these lesions compared with the placebo group). ARRs were lower with amiselimod 0.2 and 0.4 mg than with placebo, although the difference was significant only in the 0.4 mg group (n=104). Brain volume loss was similar in the amiselimod and placebo groups, although reductions in grey matter volume were significantly smaller with all amiselimod doses than with placebo (n=103).[46] The incidence of TEAEs, including infections and cardiac disorders, were similar in the amiselimod treatment groups (56% of the 0.1 mg group, 67% of the 0.2 mg group, and 56% of the 0.4 mg group) to the incidence in the placebo group (64%); the most common TEAEs were headache and nasopharyngitis. No serious TEAE was reported for more than one patient in any group and no clinically significant heart rate reduction was observed at any amiselimod dose.[46] A recent study found that amiselimod showed high potency with minimal cardiac effects at the anticipated clinical dose and is unlikely to require dose titration.[47]

Siponimod

Siponimod (Novartis, Basel, Switzerland) is a novel alkoxyimino derivative that binds to both $S1P_1$ and $S1P_5$. Its half-life is relatively short, allowing for fast immune reconstitution.[48] Its efficacy and safety was investigated versus placebo in the phase III Exploring the Efficacy and Safety of Siponimod in Patients With Secondary Progressive Multiple Sclerosis (EXPAND) study in 1,651 patients with SPMS, a condition for which treatment options are limited. Siponimod reduced the risk of 3-month confirmed disability progression (CDP) by 21% versus placebo (hazard ratio [HR]: 0.79; p=0.013). Siponimod also reduced the risk of 6-month CDP by 26% (p=0.006), ARR by 55.5% (p<0.0001), T1 Gd+ lesion number by 86.6% (p<0.0001) and new T2 lesion number by 81% (p<0.0001).[49] At least one TEAE was reported in 88.7% in the siponimod group and 81.5% in the placebo group. The incidence of heart rate and conduction AEs, hypertension, macular oedema and convulsions was higher in the treatment than in the placebo group. The incidence of infections was similar between groups, except for a higher incidence of herpes zoster in the treatment group. There were no cases of opportunistic infections, including PML, and no increased incidence of malignancies, including skin cancers.[49]

Discontinued sphingosine-1-phosphate 1 agents

Although successful in phase II clinical trials, clinical development of the $S1P_1$ modulator ceralifimod (Merck KGaA, Darmstadt, Germany)[50] was halted after the premature discontinuation of a phase III study. Clinical development of CS-0777[51] and GSK2018682 for MS reached phase I stage but appears to have been discontinued since.[52] Possible reasons are competition from emerging therapies.

Summary and concluding remarks

The discovery of the ability of S1P receptors and their modulators to block immune cell trafficking led to the regulatory approval of fingolimod, the first orally active drug treating RMS. This has stimulated research into more selective S1P receptors, which have improved pharmacodynamics and are less likely to cause off-target AEs than fingolimod. These include selective $S1P_1$ modulator (ponesimod) and dual agonists on $S1P_1$ and $S1P_5$ (siponimod, ozanimod, amiselimod). Selective S1P receptor agonists offer a convenient alternative to other MS drugs that are associated with broad immune suppression, as well as the potential for benefit in a number of autoimmune and inflammatory conditions such as psoriasis, Crohn's disease, ulcerative colitis, polymyositis, dermatomyositis, liver failure, renal failure, acute stroke and transplant rejection.[53] While long-term safety data of selective S1P receptor agonists are needed, the growing body of such data on the efficacy and safety of fingolimod is reassuring. It is likely that, in the near future, more S1P receptor modulators will be approved for the treatment of MS and other disorders associated with autoimmunity and inflammation. ❑

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