Sphingosine 1-phosphate receptor modulators in multiple sclerosis and other conditions

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The sphingosine 1-phosphate (S1P) signalling pathways have important and diverse functions. S1P receptors (S1PRs) have been proposed as a therapeutic target for various diseases due to their involvement in regulation of lymphocyte trafficking, brain and cardiac function, vascular permeability, and vascular and bronchial tone. S1PR modulators were first developed to prevent rejection by the immune system following renal transplantation, but the only currently approved indication is multiple sclerosis. The primary mechanism of action of S1PR modulators in multiple sclerosis is through binding S1PR subtype 1 on lymphocytes resulting in internalisation of the receptor and loss of responsiveness to the S1P gradient that drives lymphocyte egress from lymph nodes. The reduction in circulating lymphocytes presumably limits inflammatory cell migration into the CNS. Four S1PR modulators (fingolimod, siponimod, ozanimod, and ponesimod) have regulatory approval for multiple sclerosis. Preclinical evidence and ongoing and completed clinical trials support development of S1PR modulators for other therapeutic indications.

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Introduction

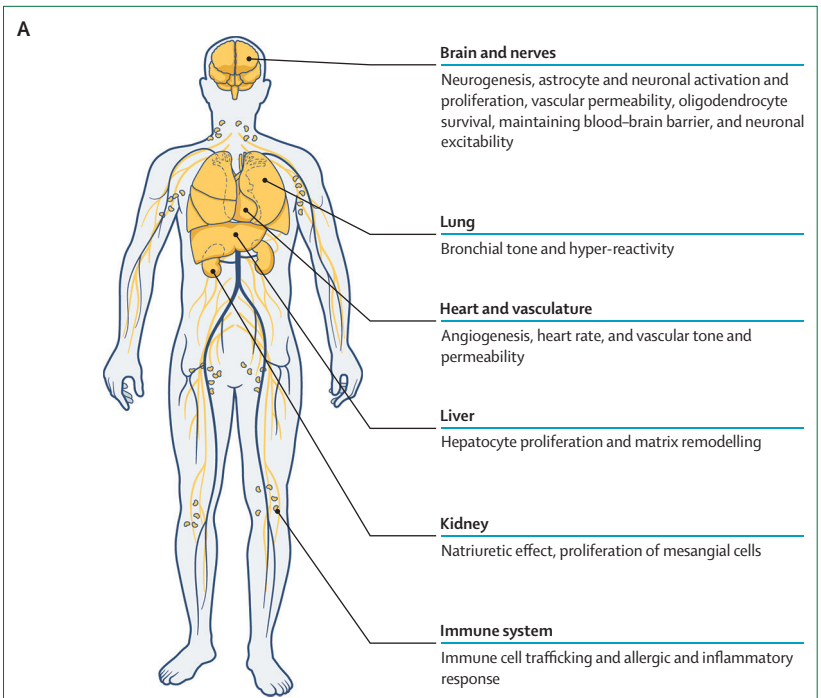
Sphingosine 1-phosphate receptors (S1PRs) are expressed throughout the body and mediate a broad range of biological functions. Sphingosine 1-phosphate (S1P) signalling pathways regulate lymphocyte trafficking, brain and cardiac development, vascular permeability, and vascular and bronchial tone (figure 1). The wide distribution and functional diversity of S1PRs make them potential therapeutic targets in a variety of diseases. S1PR modulators are a therapeutic class of small molecule medications for oral use that are structurally analogues of S1P and act as functional antagonists or agonists depending on the S1PR subtype or subtypes with which they interact and the target tissue (table 1). S1PR modulators were first investigated in renal transplantation, but subsequently were studied in a wide variety of diseases. Currently the only approved indications for S1PR modulators are relapsing remitting and active secondary progressive multiple sclerosis. This Therapeutics paper discusses the biological functions of S1PRs, providing context for the current therapeutic use of S1PR modulators in multiple sclerosis and, potentially, other diseases.

S1PRs are high affinity G protein-coupled cell surface receptors comprising five distinct subtypes (figure 1).[1] These receptors have variable cell-specific expression patterns, are linked to diverse signalling pathways, and are regulated by distinct mechanisms. S1PR subtype 1 (S1PR1) plays a key role in angiogenesis, neurogenesis, immune cell trafficking, endothelial barrier function, and vascular tone. S1PR1 mediates responsiveness to the S1P chemotactic gradient between secondary lymphoid tissues and the efferent lymphatics; when S1PR1's function is blocked, lymphocytes are sequestered in the lymph nodes and thymus. S1PR1 is also expressed on endothelium where it is involved in dendritic cell recruitment and vascular permeability. In animal models, when S1PR1 is blocked, cytokine amplification and immune cell recruitment are inhibited.[2] Inhibition of immune cell trafficking is considered the primary therapeutic target in multiple sclerosis. Additionally, expression of S1PRs on several cell populations in the CNS suggests direct CNS effects might also contribute to the therapeutic benefit. In the mouse model of multiple sclerosis, experimental autoimmune encephalomyelitis, S1PR1 blockade enhances neuron survival and inhibits gliosis and demyelination.[3] Additionally, in a mouse model of Alzheimer's disease, fingolimod decreases activation of brain microglia and astrocytes, suggesting modulation of S1PRs might have a benefit in various neurodegenerative diseases.[4]

Clinically relevant functions of the other S1PR subtypes are less well established. S1PR2 is involved in mast cell degranulation, histamine secretion, bronchial smooth muscle contraction, and hair cell survival in the inner ear.[1] In animal models, S1PR2 deletion reduces production of reactive oxygen species with resultant cytoprotection of neural cells.[5] Deletion of S1PR3 in mice substantially reduces neuronal responses and spontaneous pain behaviour.[6] Additionally, in rodents, S1PR3 is involved in heart rate regulation, although in humans both S1PR1 and S1PR3 are involved.[7] S1PR4 is expressed

Search strategy and selection criteria

We searched Ovid MEDLINE and Cochrane Trials from database inception to Sept 16, 2020. The search included both papers in English and papers not in English. We used keywords and medical subject headings related to sphingosine 1-phosphate receptor modulators. Key search terms included "sphingosine 1-phosphate receptor modulators", "sphingosine 1-phosphate receptors", "AUY 954", "ceralifimod" , "fingolimod", "NIBR 0213", "ozanimod", "ponesimod", "SEW2871", "siponimod", and "VPC23019". We identified additional articles on the basis of our knowledge of the literature and review of citations in retrieved articles. We identified a total of 4372 articles and reviewed the abstracts to select randomised clinical trials and preclinical studies on the basis of author consensus.



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	Receptor				
	S1PR1	S1PR2	S1PR3	S1PR4	S1PR5
Organ system expression	Brain, heart, spleen, liver, lung, thymus, kidney, skeletal muscle, lymphoid	Brain, heart, spleen, liver, lung, thymus, kidney, skeletal muscle	Brain, heart, spleen, liver, lung, thymus, kidney, testis, skeletal muscle	Lymphoid, lung	Brain, skin, spleen
Immune cell expression	T cells, B cells, natural killer cells, macrophages, monocytes, neutrophils, eosinophils, mast cells, dendritic cells	B cells, macrophages, monocytes, eosinophils, mast cells	B cells, macrophages, monocytes, neutrophils, eosinophils, mast cells, dendritic cells	T cells, B cells, macrophages, monocytes, neutrophils, eosinophils, mast cells, dendritic cells	Natural killer cells, eosinophils, mast cells, patrolling monocytes
Function	Immune cell migration, mast cell degranulation, angiogenesis, neurogenesis, endothelial barrier function, heart rate regulation, smooth muscle cell function, astrocyte and glia activation and proliferation, blood–brain barrier function	Immune cell migration, mast cell degranulation, endothelial barrier integrity, smooth muscle cell function, epithelial hair cell integrity and development	Immune cell migration, endothelial barrier function, heart rate regulation, smooth muscle cell function	Immune cell migration, T cell cytokine secretion, bronchial smooth muscle cell function	Natural killer cell trafficking, oligodendrocyte survival

Figure 1: **(A) S1PR locations, (B) S1PR subtypes**
S1PR=sphingosine 1-phosphate receptor. © 2021 Cleveland Clinic Center for Medical Art & Photography.

	S1PR1	S1PR2	S1PR3	S1PR4	S1PR5
Fingolimod	+	–	+	+	+
Siponimod	+	–	–	–	+
Ozanimod	+	–	–	–	+
Ceralifimod	+	–	–	–	+
Ponesimod	+	–	–	–	–
Cerenimod	+	–	–	–	+
Etrasimod	+	–	–	–	–
Amiselimod	+	–	–	+	+
VPC23019a	+	–	+	–	–
VPC01091	+	–	+	–	–
SEW2871	+	–	–	–	–
VPC44116	+	–	+	–	–
KRP203	+	–	–	–	+
APD334	+	–	–	–	–
MT1303	+	–	–	+	+
AKP11	+	–	–	–	–
GSK2018682	+	–	–	–	–
BMS986104	+	–	–	–	–
CS0777	+	–	–	–	–
JTE013	–	+	–	–	–
CYM5541	–	–	+	–	–
SPM242	–	–	+	–	–
CYM50138	–	–	–	+	–
CYM50358	–	–	–	+	–

The symbol + denotes that this compound has affinity for this receptor.
The symbol – denotes that this compound does not have affinity for this receptor.
S1PR=sphingosine 1-phosphate receptor.

Table 1: **Specificity of S1PR modulators**

predominantly on immune cells, but also on airway smooth muscle cells. The function of S1PR4 is less well understood than that of other S1PR subtypes, but it regulates cytokine production by T cells.[8] S1PR5 is expressed primarily in CNS white matter tracts, predominantly by oligodendrocytes, the survival of which is promoted by S1P activation.[9] S1PR5 also regulates natural killer cell trafficking.[10] Whether interaction of S1PR modulators with S1PR5 contributes to clinical effectiveness in multiple sclerosis is uncertain.

Immunological effects and systemic actions of S1PR modulators

S1PR signalling regulates various key immunological, cardiovascular, and neurological functions. The S1P signalling cascade has an integral role in immune cell trafficking and production of immune mediators, and therefore in regulation of local and systemic inflammatory processes. An S1P gradient between the lymph node and efferent lymphatics drives egress of naive T cells and central memory T cells that express the chemokine receptor CCR7 from the lymph node. When S1PR1 is internalised or blocked, cells expressing CCR7 are retained in the lymph node.[11] Effector memory T cells do not have the CCR7 receptor and do not require

S1P–S1PR1 interaction to exit lymph nodes; therefore these T cells continue to recirculate in the presence of S1PR modulators (figure 2).[12] S1PR1 also regulates B-cell egress from lymph nodes.[13] Dendritic cells, natural killer cells, mast cells, and eosinophils also express S1PRs. Mast cells and eosinophils play a role in allergic inflammation, and S1P might regulate degranulation and chemotaxis.[14] In addition to regulating egress from lymph nodes, S1P is essential in recruitment of natural killer cells and $CD8^+$ T cells to tumours.[15]

S1P signalling mediates several crucial non-immune functions, including angiogenesis, vascular permeability, vascular tone, and heart rate. When S1PR1 is absent during vascular development, adherens junctions are destabilised, and coverage of blood vessels with smooth muscle cells is incomplete.[16] Beyond development, S1PRs maintain endothelial cell barrier function and vascular tone. S1P-deficient animal models show vascular leakage, and S1PR1 blockade decreases endothelial-derived nitric oxide, leading to high blood pressure.[17] Stimulation of S1PR1 regulates heart rate through interaction with atrial potassium channels, leading to hyperpolarisation of myocardial cells and reduced action potential firing.[18] S1P signalling is also integral for nervous system development and for maintaining the blood–brain barrier. S1PR1-deficient mouse models have severe deficits in neurogenesis.[19] Additionally, S1PR1 on brain endothelial cells regulates tight junctions; S1PR1 inhibition increases small molecule penetration of the CNS.[20] These diverse biological effects are potential therapeutic targets in a variety of diseases and could also potentially cause off-target adverse effects.

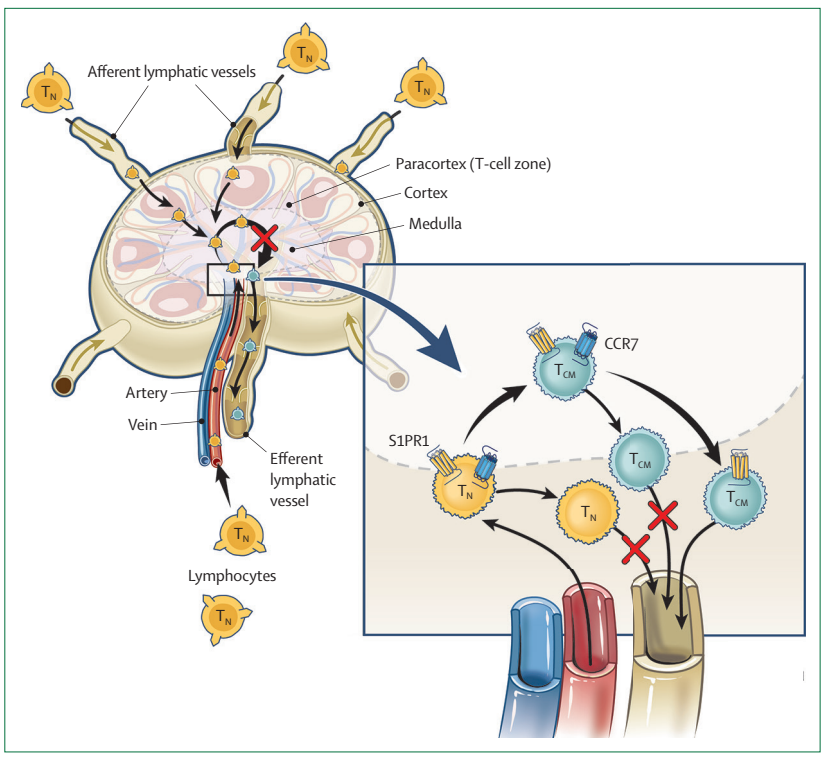

Figure 2: **Role of S1PRs in lymphocyte egress from the lymph nodes**
S1PR=sphingosine 1-phosphate receptor. T_N=naive T cells. T_{CM}=central memory T cells. © 2021 Cleveland Clinic Center for Medical Art & Photography.

S1PR modulators in multiple sclerosis

Fingolimod was the first S1PR modulator to gain regulatory approval. The proposed mechanism is through binding S1PR1 on lymphocytes resulting in receptor internalisation and loss of responsiveness to the S1P gradient that drives lymphocyte egress from lymph nodes. The reduction in circulating lymphocytes presumably limits inflammatory cell migration into the CNS. Treatment with fingolimod leads to increased proportions of regulatory T cells and naive B cells and decreased proportions of memory B cells and naive T cells, thereby inhibiting inflammatory responses.[21] In a study using $IL\text{-}17A^{Cre}$ mice, deletion of *S1pr1* from T-helper-17 cells resulted in resistance to experimental autoimmune encephalomyelitis, whereas in $Foxp3^{Cre}$ mice, deletion in regulatory T cells made the mice more susceptible to this condition.[22] Beyond systemic immunological effects, stabilisation of the blood–brain barrier might provide additional therapeutic benefits.[20] There is also evidence in experimental autoimmune encephalomyelitis that when astrocyte S1PR1 signalling is lost, there is reduced astrogliosis, axonal loss, and demyelination, along with improvement in clinical scores assessing neurological function.[23] S1PR5 is present on oligodendrocytes and its activation by S1P promotes survival of mature oligodendrocytes.[9] Thus, direct CNS effects might mediate some of the efficacy of S1PR modulators in multiple sclerosis.

Currently, there are four S1PR modulators (fingolimod, siponimod, ozanimod, and ponesimod) with regulatory approval for treatment of multiple sclerosis (table 2). Fingolimod has broad receptor affinity (S1PR1, 3, 4, and 5), whereas subsequently developed S1PR modulators are more specific, with the goal of preserving effectiveness while mitigating some of the adverse effects (discussed later). Siponimod and ozanimod are selective modulators of S1PR1 and S1PR5, and ponesimod is specific for S1PR1. All S1PR modulators are thought to have a similar effect on lymphocytes. Potential direct CNS effects have been described for both fingolimod and siponimod, but are less well understood for other S1PR modulators. Additionally, the importance of the direct CNS effects mediated by S1PR5 for effectiveness in multiple sclerosis and other CNS disorders is uncertain.

Phase 3 clinical trials have been completed for fingolimod, ozanimod, and ponesimod evaluating efficacy in relapsing remitting multiple sclerosis, which is characterised by episodes of neurological disability separated by periods of clinical stability.[24–26,29–31] All studies found a significant reduction in the primary outcome of annualised relapse rate over 12–24 months, compared

	S1PR modulator	Comparator	Multiple sclerosis population	Participants (n)	Primary outcome	Results
FREEDOMS I[24]	Fingolimod	Placebo	RRMS	1272	ARR	55% RR; 0·18 (95% CI 0·15–0·22) *vs* 0·40 (0·34–0·47); p<0·001
FREEDOMS II[25]	Fingolimod	Placebo	RRMS	1083	ARR	48% RR; 0·20 (95% CI 0·17–0·25) *vs* 0·40 (0·34–0·48); p<0·001
TRANSFORMS[26]	Fingolimod	Interferon beta-1a	RRMS	1292	ARR	52% RR; 0·16 (95% CI 0·12–0·21) *vs* 0·33 (0·26–0·42); p<0·001
INFORMS[27]	Fingolimod	Placebo	PPMS	823	CDP at 3 months	5% RR; HR 0·95 (95% CI 0·80–1·12); p=0·54
EXPAND[28]	Siponimod	Placebo	SPMS	1652	CDP at 3 months	21% RR; HR 0·79 (95% CI 0·65–0·95); p=0·13
SUNBEAM[29]	Ozanimod	Interferon beta-1a	RRMS	1346	ARR	48% RR; 0·18 (95% CI 0·14–0·24) *vs* 0·35 (0·28–0·44); p<0·001
RADIANCE[30]	Ozanimod	Interferon beta-1a	RRMS	1313	ARR	38% RR; 0·17 (95% CI 0·14–0·21) *vs* 0·28 (0·23–0·32); p<0·001
OPTIMUM[31]	Ponesimod	Teriflunomide	RRMS	1133	ARR	30·5% RR; 0·20 (95% CI 0·17–0·24) *vs* 0·29 (0·25–0·33); p<0·001

ARR=annualised relapse rate. CDP=confirmed disability progression. HR=hazard ratio. PPMS=primary progressive multiple sclerosis. RR=relative reduction. RRMS=relapsing remitting multiple sclerosis. S1PR=sphingosine 1-phosphate receptor. SPMS=secondary progressive multiple sclerosis.

Table 2: **Phase 3 clinical trials of S1PR modulators in multiple sclerosis**

	S1PR subtype	Target tissue	Frequency in multiple sclerosis phase 3 trials
Bradycardia	1	Atrial myocytes	0·5–4%
Atrioventricular block	1	Atrial myocytes	1·2–3%
Hypertension	1, 3	Vascular endothelium	4–13%
Macular oedema	1, 3	Vascular endothelium	0·7–2%

These adverse effects were observed in all of the phase 3 trials listed in table 2.[24–31] S1PR=sphingosine 1-phosphate receptor.

Table 3: **Cardiac and vascular adverse effects of S1PR modulation**

with placebo, interferon beta-1a, or teriflunomide (table 2). There was also significant benefit on MRI markers of inflammatory disease activity (gadolinium enhancing lesions and new or enlarging lesions on T2-weighted images) and MRI measures of cumulative tissue damage (accrual of T2-hyperintense and T1-hypointense lesions, brain volume loss, and cortical matter and thalamic volume loss). There were variable changes in worsening of disability as measured by the Expanded Disability Status Scale and the Multiple Sclerosis Functional Composite. In the placebo-controlled FREEDOMS trial of fingolimod in relapsing remitting multiple sclerosis, benefit on disability worsening was observed, but this same effect was not seen in other trials of fingolimod, ozanimod, and ponesimod.[24] The phase 3 EXPAND trial of siponimod involved patients with secondary progressive multiple sclerosis, which is characterised by gradual worsening of disability following a previous relapsing remitting course.[28] Siponimod treatment led to significant benefit on the primary outcome, 3-month confirmed disability worsening (ie, worsening of disability on the expanded disability status scale that was confirmed 3 months later in clinic), along with reduction in clinical and MRI outcomes measuring inflammatory disease activity. A phase 3 trial of fingolimod in primary progressive multiple sclerosis, which is characterised by progressive neurological decline from disease onset, did not show benefit on disability progression.[27]

An important consideration in the use of S1PR modulators in multiple sclerosis is the slowing of heart rate and atrioventricular conduction with initiation of therapy, mainly mediated by S1PR1 expressed on atrial myocytes (table 3). S1PR3 on His-Purkinje fibres might affect QTc interval, but this receptor seems to have a less prominent role in humans compared with animal models.[32] On initiation of therapy, fingolimod acts as an agonist activating S1PR1 leading to transient bradycardia, delayed atrioventricular conduction, and prolongation of the QTc interval. With continued administration, there is downregulation of S1PR1 and resolution of the cardiac effects.[33] These known effects informed the exclusion criteria for the phase 3 trials in multiple sclerosis and subsequent contraindications in the prescribing information, which include history of several cardiovascular conditions (eg, myocardial infarction, unstable angina, decompensated heart failure, class III or IV heart failure, history of Mobitz type II second or third degree atrioventricular block, sick sinus syndrome [unless the patient has a functioning pacemaker], QTc interval more than 500 ms, or cardiac arrhythmia requiring antiarrhythmic treatment with a class Ia or class III antiarrhythmic drug). The known first dose effects lead to a requirement for first dose observation for all patients starting fingolimod, during which a patient is monitored for at least 6 h with pulse and blood pressure hourly, and has an electrocardiogram before dosing and at the end of the observational period. Uptitration of siponimod and ozanimod over the first several days of treatment attenuates the initial cardiac effects, and no second or third degree atrioventricular block was reported in the phase 3 trials, eliminating the requirement for first dose observation in the absence of a cardiac history.

Vascular effects of S1PR modulators can produce other adverse effects. Increased blood pressure, which is common and typically mild, is probably related to downregulation of S1PR1-mediated activation of nitric oxide release from endothelial cells and to activation of S1PR2-dependent and S1PR3-dependent ROCK in

vascular smooth muscle cells, leading to vasoconstriction.[33] In the early studies in patients with renal transplant, macular oedema was twice as common in the fingolimod-treated group than in the control group (4% *vs* 2%) and seven times more common in patients with diabetes than in patients without diabetes (28% *vs* 4%).[34,35] The underlying mechanism is unknown, but is hypothesised to be increased vascular permeability mediated by S1PR1 and S1PR3 on endothelial cells, which alters barrier function. Patients with diabetes are thought to be at increased risk, because of mural cell (pericyte) damage. S1PR1 activation results in CADH2-dependent cell–cell adhesion between endothelial and mural cells to mediate vascular stability; therefore existing damage could enhance the risk of macular oedema in patients with diabetes.[36] Ophthalmological examination is recommended before initiating treatment with an S1PR modulator due to the risk of macular oedema, especially for individuals who have a history of diabetes, macular oedema, or uveitis. Effects on pulmonary function are probably due to constriction of bronchial smooth muscle. In addition to S1PR subtypes 1, 2, and 3, airway smooth muscle cells also express S1PR4, which might contribute to airway constriction.[37] These known effects informed the exclusion criteria in the phase 3 multiple sclerosis trials to include pulmonary conditions (eg, pulmonary fibrosis, forced expiratory volume in 1 s or forced vital capacity less than 70% predicted), diabetes, and macular oedema, but these conditions are not absolute contraindications for prescribing S1PR modulators. There was variable reporting in the phase 3 clinical trials of reduction of baseline forced expiratory volume in 1s and diffusing capacity for carbon monoxide, but in aggregate the frequency of these adverse events and mean total reduction were modest. Infections were reported in all of the phase 3 clinical trials, primarily upper respiratory and urinary tract infections. One death occurred in a phase 3 trial of fingolimod due to disseminated varicella infection, leading to the recommendation to check varicella zoster antibodies before initiation.[25] There are also rare reports of progressive multifocal leukoencephalopathy due to reactivation of the John Cunningham virus.[38]

Many of the adverse effects observed with fingolimod were thought to be related to broader engagement of S1PRs, which led to the development of more selective S1PR modulators. However, although research using animal models suggested S1PR3 mediated the cardiac effects, subsequent studies indicated these effects are predominately mediated by S1PR1 in humans. Thus, the reductions in first dose cardiac effects with the selective S1PR modulators are probably due to the initial dose titration rather than receptor specificity.

S1PR modulators in other conditions

S1PR modulators have been tested in a variety of conditions other than multiple sclerosis (table 4).

	S1PR modulator	Phase	Status
De novo renal transplantation			
NCT00099736	Fingolimod	3	Completed[34]
NCT00099749	Fingolimod	2/3	Completed[39]
NCT00239876	Fingolimod	3	Completed[40]
Intracerebral haemorrhage			
NCT03338998	Siponimod	2	Recruiting
NCT04088630	Fingolimod	1	Recruiting
NCT02002390	Fingolimod	2	Completed[41]
Ischaemic stroke			
NCT02956200	Fingolimod	2	Withdrawn
NCT02002390	Fingolimod	2	Completed[42]
Chronic inflammatory demyelinating polyradiculoneuropathy			
NCT01625182	Fingolimod	3	Completed[43]
Chemotherapy-induced neuropathy			
NCT03943498	Fingolimod	1	Recruiting
NCT03941743	Fingolimod	1	Recruiting
Amyotrophic lateral sclerosis			
NCT01786174	Fingolimod	2	Completed[44]
Rett syndrome			
NCT02061137	Fingolimod	1/2	Completed
High grade glioma			
NCT02490930	Fingolimod	1	Completed
Schizophrenia			
NCT01779700	Fingolimod	2	Completed[45]
Ulcerative colitis			
NCT01647516	Ozanimod	2	Completed[46]
NCT01375179	KRP203	2	Terminated[47]
NCT02447302	Etrasimod	2	Completed[48]
NCT02435992	Ozanimod	3	Completed[49]
Crohn's disease			
NCT03440372	Ozanimod	3	Recruiting
NCT02531113	Ozanimod	2	Completed[50]
NCT03440385	Ozanimod	3	Recruiting
NCT02378688	Amiselimod	2	Completed[51]
Systemic lupus erythematosus			
NCT03440385	Ozanimod	3	Recruiting
NCT02378688	Amiselimod	2	Completed[51]
Psoriasis			
NCT01208090	Ponesimod	2	Completed[52]
Asthma			
NCT02447302	Etrasimod	2	Completed[48]
COVID-19 pneumonia			
NCT04405102	Ozanimod	2	Recruiting

S1PR=sphingosine 1-phosphate receptor.

Table 4: **Completed and ongoing clinical trials of S1PR modulators in various conditions**

Acute renal transplant rejection

Fingolimod was first developed as an immunosuppressant to prevent acute renal transplant rejection. The biological rationale was that S1PR1 modulation would decrease circulating alloantigen-reactive T cells without permanently destroying these cells. Encouraging results

in preclinical and phase 2 studies led to several phase 3 trials in de novo renal transplantation. The phase 3 trials indicated that fingolimod reduced the risk of acute rejection, but did not have superior efficacy and had a higher incidence of adverse events compared with other available options, thus limiting its subsequent development for use in transplantations.[34,40]

Stroke

Use of S1PR modulators in neurological disorders seeks to leverage their immunological and vascular effects. The inflammatory response after intracerebral haemorrhage leads to increased permeability of the blood–brain barrier, cerebral oedema, and cell death, all contributing to neurological sequelae. In an animal model of intracerebral haemorrhage, administration of fingolimod led to reduced intraparenchymal blood and lymphocytic infiltration; reduced expression of ICAM1, interferon γ, and interleukin-17; reduced cerebral oedema; and improved neurological outcomes.[53] In a proof-of-concept clinical trial (n=23), participants with intracerebral haemorrhage were given either standard of care alone or combined with fingolimod for 3 consecutive days initiated within 1 h of the baseline CT scan and no later than 72 h after symptom onset.[41] Participants receiving fingolimod had less neurological impairment compared with controls (Glasgow Coma Scale score of 15 by day 7; 100% *vs* 50%, p=0·01), more improvement in National Institutes of Health Stroke Scale score (7·5 *vs* 0·5 point reduction, p<0·001), less perihaematomal oedema at day 7 (47 mL *vs* 108 mL, p=0·04) and day 14 (55 mL *vs* 124 mL, p=0·07), and less relative perihaematomal oedema at day 7 (2·5 *vs* 6·4, p<0·001) and day 14 (2·6 *vs* 7·7, p=0·003).

In ischaemic stroke, current treatments focus on promoting reperfusion, but these modalities are limited by risk of reperfusion injury and haemorrhagic transformation. In a multicentre pilot trial (n=25), participants with anterior circulation stroke were randomly assigned to receive alteplase alone or alteplase plus fingolimod for 3 consecutive days within 4·5 h of stroke onset.[42] Combination therapy with fingolimod led to smaller lesion volume (10·1 mL *vs* 34·3 mL, p=0·04), less haemorrhage (1·2 mL *vs* 4.4 mL, p=0·01), and attenuated neurological deficits on the National Institutes of Health Stroke Scale (score of 4 *vs* 2, p=0·02) at day 1. Long-term benefits included reduced lesion growth at day 7 (–2·3 mL *vs* 12·1 mL, p<0·01) and better recovery measured by scores of 0–1 at 90 days on the modified Rankin Scale (73% *vs* 32%, p<0·01). On the basis of the clinical and radiographical benefit shown in these early phase trials in intracerebral haemorrhage and ischaemic stroke, several ongoing trials will evaluate clinical efficacy (table 4).

Neuromuscular disorders

Chronic inflammatory demyelinating polyradiculoneuropathy is an inflammatory peripheral neuropathy characterised by demyelination and axonal damage. Current treatments include intravenous immunoglobulin and plasma exchange, but these options are limited by side-effects, cost, and limited effectiveness. The proposed therapeutic mechanism of S1PR modulators in this condition is similar to that for multiple sclerosis, including reduction in circulating memory T and B cells and increase in regulatory B cells.[21] In the phase 3 FORCIDP trial, participants (n=106) previously treated with intravenous immunoglobulin or corticosteroids were randomly assigned to receive fingolimod or placebo.[43] The trial was terminated due to futility after analysis of 44 confirmed worsening events indicated that fingolimod was not likely to be superior to placebo.

Peripheral neuropathy is a common dose-limiting complication of chemotherapy with no approved treatment options. Bortezomib and other chemotherapy agents have been shown to cause dysregulation of de novo sphingolipid metabolism in the spinal cord dorsal horn, leading to increased expression of S1P and S1PR1.[54] When S1PR1 was blocked with fingolimod in bortezomib-treated mice, neuropathic pain was reversed.[54] Another study reported increased serum S1P concentrations in patients treated with oxaliplatin; increased S1P concentrations are thought to disproportionately activate proinflammatory S1PR1 signalling and cause a shift from protective S1PR2 signalling.[55] Currently, there are two ongoing phase 1 trials of fingolimod in chemotherapy-induced neuropathy (table 4).

Amyotrophic lateral sclerosis (ALS) is a degenerative disorder that affects motor neurons and results in progressive muscle weakness. There is currently only one regulatory approved treatment, riluzole, which only modestly prolongs survival. In mouse models of ALS, there is evidence of microglial activation and decreased numbers of regulatory T cells, which correlate with disease progression.[56,57] The number of regulatory T lymphocytes correlates with disease progression rates in patients with ALS, suggesting regulatory T cells might contribute to neuroprotection through interactions with microglia.[57] In a phase 2 trial in ALS (n=28), fingolimod treatment significantly decreased circulating lymphocytes and had similar adverse events to placebo.[44] In a murine model of ALS, there was significant downregulation of *FOXP3*, a measure of regulatory T-cell function shown to influence disease progression rates, along with seven other immune-related genes implicated in disease progression.[57] The trial was not powered to test clinical efficacy, and no significant effect was seen on the study outcomes (slow vital capacity, forced expiratory volume in 1 s, and score on the ALS Functional Rating Scale–Revised).

Rett syndrome

Rett syndrome is an X-linked neurodevelopmental disorder caused by mutations in *MECP2*, which results in severe intellectual disability. Currently, there are no approved treatments. In a mouse model with *MECP2*

gene deletion, fingolimod treatment increased concentrations of brain-derived neurotrophic factor and improved clinical signs.[58] In another study, metabolic profiling in 14 women with *MECP2* mutations found alterations in sphingolipid metabolism.[59] An open label trial of fingolimod in Rett syndrome was completed, but no results have been published (table 4).

Brain tumour

Fingolimod penetrates the blood–brain barrier and inhibits cancer cell growth. In a study of human glioblastoma tissue, fingolimod treatment inactivated ERK MAPK and synergised with temozolomide to induce tumour stem-cell apoptosis, slow the growth of intracranial tumour xenografts, and prolong survival.[60] In another study of mice that had undergone cranial irradiation, fingolimod mitigated radiation-induced learning deficits.[61] A phase 1 trial evaluating the safety of fingolimod combined with temozolomide and radiation therapy in high grade glioma was completed in 2017, but no results have been published as yet (table 4). Although there is animal model evidence to suggest therapeutic benefit for glioblastoma treatment, there have also been case reports of glioblastoma occurring in patients with multiple sclerosis treated with fingolimod.[62] These case reports do not prove causality, but future studies are needed to evaluate the possibility that lymphocyte sequestration and reduced immune surveillance might lead to cancer development.

Schizophrenia

Schizophrenia is a lifelong illness involving psychiatric and cognitive impairment. Microstructural white matter damage has been reported in patients with schizophrenia, with evidence that inflammatory mechanisms might contribute.[63] In an 8-week double-blind pilot trial (n=40), participants with schizophrenia or schizoaffective disorder were randomly assigned to receive fingolimod or placebo.[64] Fingolimod treatment resulted in an expected reduction in circulating lymphocytes and no serious adverse events, but no significant benefit on cognitive or psychiatric symptom measures. Additionally, there was no significant effect on fractional anisotropy measured by diffusion tensor imaging, an indicator of white matter integrity.

Inflammatory bowel disease

Ulcerative colitis and Crohn's disease are inflammatory gastrointestinal diseases often requiring lifelong treatment. Corticosteroids are a mainstay for initial control, but steroid-sparing agents are needed to avoid the many adverse effects of long-term steroid use. There currently are several biologics available for treatment of these conditions including TNFα inhibitors, α4 integrin blockers, and anti-interleukin-12 and anti-interleukin-23 monoclonal antibodies. However, in some patients these therapies produce an inadequate response or have a loss of effectiveness over time. Therefore, additional therapeutic options are needed.

In addition to expression of S1PRs by immune cells, there is increased expression of S1PR1 in the colonic vasculature of patients with ulcerative colitis, which can contribute to vascular permeability and bleeding.[65] S1PR modulators reduce clinical and histopathological severity of experimental colitis in animal models of human ulcerative colitis and Crohn's disease.[66,67] These observations suggest S1PR modulators might be effective in inflammatory bowel disease. In the phase 2 TOUCHSTONE trial (n=197), ozanimod treatment led to a higher rate of clinical remission than did placebo (16% *vs* 6%, p=0·048).[68] In the 32-week, double-blind, placebo-controlled phase 3 TRUE NORTH trial (n=457) in moderate-to-severe ulcerative colitis, ozanimod induction followed by maintenance treatment produced a higher rate of clinical remission compared with placebo (18·6% difference, 95% CI 10·8–26·4, p<0·0001).[49] A phase 2 proof-of-concept trial of etrasimod in moderate-to-severe ulcerative colitis over 12 weeks showed that treatment with etrasimod 2 mg led to significantly greater improvement compared with placebo in clinical scores (least squares mean improvement in modified Mayo Clinic score difference 0·99, 90% CI 0·30–1·68, p=0·009) and endoscopic findings (improvement in modified Mayo Clinic endoscopic subscore in 42% *vs* 18% of patients, p=0·003).[48] A phase 2 trial of KRP203 was terminated early (30 [42%] of 72 patients enrolled) after a preplanned interim analysis showed KRP203 failed to meet the minimum clinically relevant threshold of 20% remission (KRP203 14% *vs* placebo 0%).[47]

STEPSTONE was a 12-week phase 2 trial of ozanimod in Crohn's disease; this trial showed a significant improvement in the primary outcome, Simple Endoscopic Score for Crohn's Disease (mean change in Simple Endoscopic Score for Crohn's Disease –2·2 [SD 6·0]); 16 patients (23%, 95% CI 14–35) experienced endoscopic response.[50] There are two ongoing phase 3 trials of ozanimod in Crohn's disease (table 4). A phase 2 trial (n=78) of amiselimod did not show a clinical or biochemical (serum C-reactive protein, faecal calprotectin) benefit at 12 weeks in treatment-refractory Crohn's disease.[51]

In summary, phase 2 and phase 3 trials of several of the S1PR modulators have shown clinical and endoscopic benefit in inflammatory bowel diseases. There are ongoing trials to further evaluate safety and efficacy.

Systemic lupus erythematosus

S1PR modulators have been considered for several rheumatological conditions, including systemic lupus erythematosus (SLE). The hypothesised therapeutic mechanism is similar to other conditions—ie, modulation of immune cell trafficking and function. In animal models of SLE, fingolimod inhibited production of antibodies against double-stranded DNA, reduced

the glomerular deposition of immunoglobulin, and prolonged survival compared with control animals.[69,70] In a two-part, multicentre, double-blind placebo-controlled trial, cenerimod caused a significant estimated treatment effect on change in the SLE Disease Activity Index 2000 of –2·420 (p=0·0306) compared with placebo.[71] A phase 2 trial of KRP203 in subacute cutaneous lupus erythematosus (NCT01294774) was completed, but no results have been reported as yet.

Psoriasis

In addition to immunological effects, fingolimod reduced epidermal hyperproliferation in a mouse model of psoriasis.[72] A phase 2 trial of oral ponesimod (n=326) showed efficacy measured by the Psoriasis Area and Severity Index. The primary outcome (reduction in score on the index of at least 75% from baseline at week 16) was attained by 46·0% of patients taking 20 mg ponesimod, 48·1% of patients taking 40 mg ponesimod, and 13·4% of patients taking placebo; p<0·0001 for both ponesimod doses.[52]

Pulmonary conditions

Several lines of evidence suggest S1PR modulators might be helpful in the treatment of asthma. S1PR2 is implicated in mast cell degranulation.[14] In an ovalbumin-induced animal asthma model, deletion or blockade of S1PR2 with a selective antagonist inhibited eosinophil accumulation and reduced T-helper-2 cytokine concentrations in lung tissue.[73] S1P also has been implicated in regulation of bronchial tone and hyper-reactivity.[74] A phase 2 trial of fingolimod in patients with moderate asthma (n=36) found no significant differences between placebo and 0·5 mg fingolimod on pulmonary function outcomes.[75] Participants receiving a higher dose of fingolimod (1·25 mg or 2·5 mg) had a mild reduction in pulmonary function and a six-times increase in rescue bronchodilator use compared with placebo.

More recently, S1PR modulation has been proposed as a way to mitigate the aberrant immune response in COVID-19, a condition that can lead to acute respiratory distress syndrome. In an animal model of H1N1 2009 influenza virus infection, an S1PR1 agonist reduced pulmonary injury and improved clinical symptoms.[76] There is an ongoing phase 2 trial to evaluate the effect of ozanimod on clinical outcomes in patients with COVID-19 pneumonia (table 4).

Future directions

S1PR modulators have been studied in a wide range of conditions with variable efficacy. In renal transplantation and chronic inflammatory demyelinating polyradiculoneuropathy, the negative phase 3 clinical trial results make further clinical development unlikely. Similarly, smaller clinical trials in schizophrenia and asthma did not indicate clinical benefit. Preliminary trials of other disorders, including stroke, chemotherapy-induced neuropathy, psoriasis, and SLE, yielded promising results that warrant further investigation. The most promising data to date outside of multiple sclerosis are for inflammatory bowel disease. Phase 2 trials and a phase 3 trial showed both clinical and histological benefits.

The widespread tissue expression of S1PRs leads to their involvement in a diverse array of important biological functions. S1PR modulators are already approved for treatment in multiple sclerosis and have ongoing or completed clinical trials in a variety of neurological, gastrointestinal, rheumatological, and pulmonary conditions. The first approved S1P modulator, fingolimod, acted through multiple receptors; subsequently developed modulators have more selective action on primarily S1PR1 and S1PR5. Future efforts should continue to fine tune receptor selectivity to more precisely target the pathway of therapeutic interest. S1PR1 modulation has been used to treat several diseases; other receptor subtypes have been less well explored. For example, to date, no selective S1PR2 modulators have been tested in human trials, but there is evidence S1PR2 has an important role in permeability of the blood–brain barrier, cytoprotection of neural cells, and degranulation of mast cells, which might be of therapeutic benefit.[73,77,78] S1PR modulators also might have novel effects beyond the well known systemic actions. Fingolimod has been shown to reduce detectable latent HIV infection through disruption of the HIV lifecycle.[79] Additionally, beyond targeting the S1PRs, other components of the S1P signalling cascade have therapeutic potential. A novel monoclonal antibody against S1P (sonepcizumab) neutralises S1P and inhibits extracellular signalling, resulting in suppressed tumour growth and metastasis.[80] Sphingosine kinase 1 and 2 are crucial for regulating the synthesis of S1P and inhibitors of these enzymes have been proposed as a therapy in several cancers.[81] As a better understanding of the complex functions of the S1P system are obtained, more therapeutic targets can be identified. Currently, there is preclinical evidence supporting the potential use of S1PR modulators in Parkinson's disease,[82] myasthenia gravis,[83] Alzheimer's disease,[84] Huntington's disease,[85] spinal cord injury,[86] gastric cancer,[87] type 1 diabetes,[88] autoimmune myocarditis and dilated cardiomyopathy,[89] hypertrophic cardiomyopathy,[90] corneal allografts,[91] and sepsis.[92] The successful use of S1PR modulators in multiple sclerosis along with the extensive preclinical evidence in other diseases support efforts to further investigate refined targets and therapeutic options.

Contributors

MPM drafted all sections of the manuscript and provided modifications to the text. JAC provided modifications to all sections and final editing before submission.

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References

1 Rosen H, Gonzalez-Cabrera PJ, Sanna MG, Brown S. Sphingosine 1-phosphate receptor signaling. *Annu Rev Biochem* 2009; **78:** 743–68.

2 Teijaro JR, Walsh KB, Cahalan S, et al. Endothelial cells are central orchestrators of cytokine amplification during influenza virus infection. *Cell* 2011; **146:** 980–91.

3 Gonzalez-Cabrera PJ, Cahalan SM, Nguyen N, et al. S1P(1) receptor modulation with cyclical recovery from lymphopenia ameliorates mouse model of multiple sclerosis. *Mol Pharmacol* 2012; **81:** 166–74.

4 Carreras I, Aytan N, Choi JK, et al. Dual dose-dependent effects of fingolimod in a mouse model of Alzheimer's disease. *Sci Rep* 2019; **9:** 10972.

5 Herr DR, Reolo MJY, Peh YX, et al. Sphingosine 1-phosphate receptor 2 (S1P2) attenuates reactive oxygen species formation and inhibits cell death: implications for otoprotective therapy. *Sci Rep* 2016; **6:** 24541.

6 Camprubí-Robles M, Mair N, Andratsch M, et al. Sphingosine-1-phosphate-induced nociceptor excitation and ongoing pain behavior in mice and humans is largely mediated by S1P3 receptor. *J Neurosci* 2013; **33:** 2582–92.

7 Sanna MG, Liao J, Jo E, et al. Sphingosine 1-phosphate (S1P) receptor subtypes S1P1 and S1P3, respectively, regulate lymphocyte recirculation and heart rate. *J Biol Chem* 2004; **279:** 13839–48.

8 Wang W, Graeler MH, Goetzl EJ. Type 4 sphingosine 1-phosphate G protein-coupled receptor (S1P4) transduces S1P effects on T cell proliferation and cytokine secretion without signaling migration. *FASEB J* 2005; **19:** 1731–33.

9 Jaillard C, Harrison S, Stankoff B, et al. Edg8/S1P5: an oligodendroglial receptor with dual function on process retraction and cell survival. *J Neurosci* 2005; **25:** 1459–69.

10 Jenne CN, Enders A, Rivera R, et al. T-bet-dependent S1P5 expression in NK cells promotes egress from lymph nodes and bone marrow. *J Exp Med* 2009; **206:** 2469–81.

11 Matloubian M, Lo CG, Cinamon G, et al. Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. *Nature* 2004; **427:** 355–60.

12 Hofmann M, Brinkmann V, Zerwes HG. FTY720 preferentially depletes naive T cells from peripheral and lymphoid organs. *Int Immunopharmacol* 2006; **6:** 1902–10.

13 Kabashima K, Haynes NM, Xu Y, et al. Plasma cell S1P1 expression determines secondary lymphoid organ retention versus bone marrow tropism. *J Exp Med* 2006; **203:** 2683–90.

14 Jolly PS, Bektas M, Olivera A, et al. Transactivation of sphingosine-1-phosphate receptors by FcepsilonRI triggering is required for normal mast cell degranulation and chemotaxis. *J Exp Med* 2004; **199:** 959–70.

15 van der Weyden L, Arends MJ, Campbell AD, et al. Genome-wide in vivo screen identifies novel host regulators of metastatic colonization. *Nature* 2017; **541:** 233–36.

16 Jung B, Obinata H, Galvani S, et al. Flow-regulated endothelial S1P receptor-1 signaling sustains vascular development. *Dev Cell* 2012; **23:** 600–10.

17 Cantalupo A, Gargiulo A, Dautaj E, et al. S1PR1 (sphingosine-1-phosphate receptor 1) signaling regulates blood flow and pressure. *Hypertension* 2017; **70:** 426–34.

18 Ochi R, Momose Y, Oyama K, Giles WR. Sphingosine-1-phosphate effects on guinea pig atrial myocytes: alterations in action potentials and K+ currents. *Cardiovasc Res* 2006; **70:** 88–96.

19 Mizugishi K, Yamashita T, Olivera A, Miller GF, Spiegel S, Proia RL. Essential role for sphingosine kinases in neural and vascular development. *Mol Cell Biol* 2005; **25:** 11113–21.

20 Yanagida K, Liu CH, Faraco G, et al. Size-selective opening of the blood-brain barrier by targeting endothelial sphingosine 1-phosphate receptor 1. *Proc Natl Acad Sci USA* 2017; **114:** 4531–36.

21 Claes N, Dhaeze T, Fraussen J, et al. Compositional changes of B and T cell subtypes during fingolimod treatment in multiple sclerosis patients: a 12-month follow-up study. *PLoS One* 2014; **9:** e111115.

22 Eken A, Duhen R, Singh AK, et al. $S1P_1$ deletion differentially affects TH17 and regulatory T cells. *Sci Rep* 2017; **7:** 12905.

23 Choi JW, Gardell SE, Herr DR, et al. FTY720 (fingolimod) efficacy in an animal model of multiple sclerosis requires astrocyte sphingosine 1-phosphate receptor 1 (S1P1) modulation. *Proc Natl Acad Sci USA* 2011; **108:** 751–56.

24 Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010; **362:** 387–401.

25 Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010; **362:** 402–15.

26 Khatri B, Barkhof F, Comi G, et al. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomised extension of the TRANSFORMS study. *Lancet Neurol* 2011; **10:** 520–29.

27 Lublin F, Miller DH, Freedman MS, et al. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2016; **387:** 1075–84.

28 Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet* 2018; **391:** 1263–73.

29 Comi G, Kappos L, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial. *Lancet Neurol* 2019; **18:** 1009–20.

30 Cohen JA, Comi G, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial. *Lancet Neurol* 2019; **18:** 1021–33.

31 Kappos L, Fox RJ, Burcklen M, et al. Ponesimod compared with teriflunomide in patients with relapsing multiple sclerosis in the active-comparator phase 3 OPTIMUM study: a randomized clinical trial. *JAMA Neurol* 2021; **78:** 558–67.

32 Tran JQ, Hartung JP, Olson AD, et al. Cardiac safety of ozanimod, a novel sphingosine-1-phosphate receptor modulator: results of a thorough QT/QTc study. *Clin Pharmacol Drug Dev* 2018; **7:** 263–76.

33 Camm J, Hla T, Bakshi R, Brinkmann V. Cardiac and vascular effects of fingolimod: mechanistic basis and clinical implications. *Am Heart J* 2014; **168:** 632–44.

34 Tedesco-Silva H, Pescovitz MD, Cibrik D, et al. Randomized controlled trial of FTY720 versus MMF in de novo renal transplantation. *Transplantation* 2006; **82:** 1689–97.

35 Salvadori M, Budde K, Charpentier B, et al. FTY720 versus MMF with cyclosporine in de novo renal transplantation: a 1-year, randomized controlled trial in Europe and Australasia. *Am J Transplant* 2006; **6:** 2912–21.

36 Paik JH, Skoura A, Chae SS, et al. Sphingosine 1-phosphate receptor regulation of N-cadherin mediates vascular stabilization. *Genes Dev* 2004; **18:** 2392–403.

37 Brinkmann V. Sphingosine 1-phosphate receptors in health and disease: mechanistic insights from gene deletion studies and reverse pharmacology. *Pharmacol Ther* 2007; **115:** 84–105.

38 Berger JR, Cree BA, Greenberg B, et al. Progressive multifocal leukoencephalopathy after fingolimod treatment. *Neurology* 2018; **90:** e1815–21.

39 Tedesco-Silva H, Szakaly P, Shoker A, et al. FTY720 versus mycophenolate mofetil in de novo renal transplantation: six-month results of a double-blind study. *Transplantation* 2007; **84:** 885–89

40 Hoitsma AJ, Woodle ES, Abramowicz D, Proot P, Vanrenterghem Y. FTY720 combined with tacrolimus in de novo renal transplantation: 1-year, multicenter, open-label randomized study. *Nephrol Dial Transplant* 2011; **26:** 3802–05.

41 Fu Y, Hao J, Zhang N, et al. Fingolimod for the treatment of intracerebral hemorrhage: a 2-arm proof-of-concept study. *JAMA Neurol* 2014; **71:** 1092–101.

42 Zhu Z, Fu Y, Tian D, et al. Combination of the immune modulator fingolimod with alteplase in acute ischemic stroke: a pilot trial. *Circulation* 2015; **132:** 1104–12.

43 Hughes R, Dalakas MC, Merkies I, et al. Oral fingolimod for chronic inflammatory demyelinating polyradiculoneuropathy (FORCIDP Trial): a double-blind, multicentre, randomised controlled trial. *Lancet Neurol* 2018; **17:** 689–98.

44 Berry JD, Paganoni S, Atassi N, et al. Phase IIa trial of fingolimod for amyotrophic lateral sclerosis demonstrates acceptable acute safety and tolerability. *Muscle Nerve* 2017; **56:** 1077–84.

45 Francis M, Liffick E, Hummer T, et al. Effects of the potent anti-inflammatory agent fingolimod in schizophrenia. *Neuropsychopharmacology* 2017; **43:** S218.

46 Sandborn WJ, Feagan BG, Wolf DC, et al. Ozanimod induction and maintenance treatment for ulcerative colitis. *N Engl J Med* 2016; **374:** 1754–62.

47 Radeke HH, Stein J, Van Assche G, et al. A multicentre, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of the S1P receptor agonist KRP203 in patients with moderately active refractory ulcerative colitis. *Inflamm Intest Dis* 2020; **5:** 180–90.

48 Sandborn WJ, Peyrin-Biroulet L, Zhang J, et al. Efficacy and safety of etrasimod in a phase 2 randomized trial of patients with ulcerative colitis. *Gastroenterology* 2020; **158:** 550–61.

49 Silvio D, Brian F, Stephen H, et al. P030 Ozanimod efficacy, safety, and histology in patients with moderate-to-severe ulcerative colitis during maintenance in the phase 3 True North study. *Am J Gastroenterol* 2020; **115** (suppl 1)**:** S8.

50 Feagan BG, Sandborn WJ, Danese S, et al. Ozanimod induction therapy for patients with moderate to severe Crohn's disease: a single-arm, phase 2, prospective observer-blinded endpoint study. *Lancet Gastroenterol Hepatol* 2020; **5:** 819–28.

51 D'Haens G, Danese S, Davies M, Watanabe M, Hibi T. Amiselimod, a selective S1P receptor modulator in Crohn's disease patients: a proof-of-concept study. *J Crohn's Colitis* 2019; **13** (suppl 1)**:** S055–56.

52 Vaclavkova A, Chimenti S, Arenberger P, et al. Oral ponesimod in patients with chronic plaque psoriasis: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet* 2014; **384:** 2036–45.

53 Rolland WB, Lekic T, Krafft PR, et al. Fingolimod reduces cerebral lymphocyte infiltration in experimental models of rodent intracerebral hemorrhage. *Exp Neurol* 2013; **241:** 45–55.

54 Stockstill K, Doyle TM, Yan X, et al. Dysregulation of sphingolipid metabolism contributes to bortezomib-induced neuropathic pain. *J Exp Med* 2018; **215:** 1301–13.

55 Wang W, Xiang P, Chew WS, et al. Activation of sphingosine 1-phosphate receptor 2 attenuates chemotherapy-induced neuropathy. *J Biol Chem* 2020; **295:** 1143–52.

56 Beers DR, Henkel JS, Zhao W, et al. Endogenous regulatory T lymphocytes ameliorate amyotrophic lateral sclerosis in mice and correlate with disease progression in patients with amyotrophic lateral sclerosis. *Brain* 2011; **134:** 1293–314.

57 Henkel JS, Beers DR, Wen S, et al. Regulatory T-lymphocytes mediate amyotrophic lateral sclerosis progression and survival. *EMBO Mol Med* 2013; **5:** 64–79.

58 Deogracias R, Yazdani M, Dekkers MP, et al. Fingolimod, a sphingosine-1 phosphate receptor modulator, increases BDNF levels and improves symptoms of a mouse model of Rett syndrome. *Proc Natl Acad Sci USA* 2012; **109:** 14230–35.

59 Cappuccio G, Donti T, Pinelli M, et al. Sphingolipid metabolism perturbations in Rett syndrome. *Metabolites* 2019; **9:** 9.

60 Estrada-Bernal A, Palanichamy K, Ray Chaudhury A, Van Brocklyn JR. Induction of brain tumor stem cell apoptosis by FTY720: a potential therapeutic agent for glioblastoma. *Neuro-oncol* 2012; **14:** 405–15.

61 Stessin AM, Banu MA, Clausi MG, Berry N, Boockvar JA, Ryu S. FTY720/fingolimod, an oral S1PR modulator, mitigates radiation induced cognitive deficits. *Neurosci Lett* 2017; **658:** 1–5.

62 London F, Cambron B, Jacobs S, Delrée P, Gustin T. Glioblastoma in a fingolimod-treated multiple sclerosis patient: causal or coincidental association? *Mult Scler Relat Disord* 2020; **41:** 102012.

63 Hummer TA, Francis MM, Vohs JL, Liffick E, Mehdiyoun NF, Breier A. Characterization of white matter abnormalities in early-stage schizophrenia. *Early Interv Psychiatry* 2018; **12:** 660–68.

64 Francis MM, Hummer TA, Liffick E, et al. Effects of fingolimod, a sphingosine-1-phosphate (S1P) receptor agonist, on white matter microstructure, cognition and symptoms in schizophrenia. *Brain Imaging Behav* 2020; published online Sept 7. https://doi.org/10.1007/s11682-020-00375-7.

65 Montrose DC, Scherl EJ, Bosworth BP, et al. $S1P_1$ localizes to the colonic vasculature in ulcerative colitis and maintains blood vessel integrity. *J Lipid Res* 2013; **54:** 843–51.

66 Daniel C, Sartory NA, Zahn N, et al. FTY720 ameliorates oxazolone colitis in mice by directly affecting T helper type 2 functions. *Mol Immunol* 2007; **44:** 3305–16.

67 Dong J, Wang H, Zhao J, et al. SEW2871 protects from experimental colitis through reduced epithelial cell apoptosis and improved barrier function in interleukin-10 gene-deficient mice. *Immunol Res* 2015; **61:** 303–11.

68 Sandborn WJ, Feagan BG, Wolf DC, et al. Ozanimod induction and maintenance treatment for ulcerative colitis. *N Engl J Med* 2016; **374:** 1754–62.

69 Okazaki H, Hirata D, Kamimura T, et al. Effects of FTY720 in MRL-lpr/lpr mice: therapeutic potential in systemic lupus erythematosus. *J Rheumatol* 2002; **29:** 707–16.

70 Ando S, Amano H, Amano E, et al. FTY720 exerts a survival advantage through the prevention of end-stage glomerular inflammation in lupus-prone BXSB mice. *Biochem Biophys Res Commun* 2010; **394:** 804–10.

71 Hermann V, Batalov A, Smakotina S, Juif P-E, Cornelisse P. First use of cenerimod, a selective $S1P_1$ receptor modulator, for the treatment of SLE: a double-blind, randomised, placebo-controlled, proof-of-concept study. *Lupus Sci Med* 2019; **6:** e000354.

72 Schaper K, Dickhaut J, Japtok L, et al. Sphingosine-1-phosphate exhibits anti-proliferative and anti-inflammatory effects in mouse models of psoriasis. *J Dermatol Sci* 2013; **71:** 29–36.

73 Park SJ, Im DS. Blockage of sphingosine-1-phosphate receptor 2 attenuates allergic asthma in mice. *Br J Pharmacol* 2019; **176:** 938–49.

74 Roviezzo F, Di Lorenzo A, Bucci M, et al. Sphingosine-1-phosphate/sphingosine kinase pathway is involved in mouse airway hyperresponsiveness. *Am J Respir Cell Mol Biol* 2007; **36:** 757–62.

75 Boulton C, David OJ, Meiser K, Schmouder R. Tolerability and pulmonary pharmacodynamic effects during treatment initiation of once-daily oral fingolimod in subjects with moderate asthma. *Clin Pharmacol Drug Dev* 2013; **2:** 2–10.

76 Teijaro JR, Walsh KB, Long JP, et al. Protection of ferrets from pulmonary injury due to H1N1 2009 influenza virus infection: immunopathology tractable by sphingosine-1-phosphate 1 receptor agonist therapy. *Virology* 2014; **452–453:** 152–57.

77 Cruz-Orengo L, Daniels BP, Dorsey D, et al. Enhanced sphingosine-1-phosphate receptor 2 expression underlies female CNS autoimmunity susceptibility. *J Clin Invest* 2014; **124:** 2571–84.

78 MacLennan AJ, Carney PR, Zhu WJ, et al. An essential role for the H218/AGR16/Edg-5/LP(B2) sphingosine 1-phosphate receptor in neuronal excitability. *Eur J Neurosci* 2001; **14:** 203–09.

79 Resop RS, Fromentin R, Newman D, et al. Fingolimod inhibits multiple stages of the HIV-1 life cycle. *PLoS Pathog* 2020; **16:** e1008679.

80 Ponnusamy S, Selvam SP, Mehrotra S, et al. Communication between host organism and cancer cells is transduced by systemic sphingosine kinase 1/sphingosine 1-phosphate signalling to regulate tumour metastasis. *EMBO Mol Med* 2012; **4:** 761–75.

81 Pitman MR, Costabile M, Pitson SM. Recent advances in the development of sphingosine kinase inhibitors. *Cell Signal* 2016; **28:** 1349–63.

82 Pépin É, Jalinier T, Lemieux GL, Massicotte G, Cyr M. Sphingosine-1-phosphate receptors modulators decrease signs of neuroinflammation and prevent Parkinson's disease symptoms in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model. *Front Pharmacol* 2020; **11:** 77.

83 Kohno T, Tsuji T, Hirayama K, et al. A novel immunomodulator, FTY720, prevents development of experimental autoimmune myasthenia gravis in C57BL/6 mice. *Biol Pharm Bull* 2005; **28:** 736–39.

84 Asle-Rousta M, Oryan S, Ahmadiani A, Rahnema M. Activation of sphingosine 1-phosphate receptor-1 by SEW2871 improves cognitive function in Alzheimer's disease model rats. *EXCLI J* 2013; **12:** 449–61.

85 Di Pardo A, Amico E, Favellato M, et al. FTY720 (fingolimod) is a neuroprotective and disease-modifying agent in cellular and mouse models of Huntington disease. *Hum Mol Genet* 2014; **23:** 2251–65.

86 Zhang J, Zhang A, Sun Y, Cao X, Zhang N. Treatment with immunosuppressants FTY720 and tacrolimus promotes functional recovery after spinal cord injury in rats. *Tohoku J Exp Med* 2009; **219:** 295–302.

87 Zheng T, Meng X, Wang J, et al. PTEN- and p53-mediated apoptosis and cell cycle arrest by FTY720 in gastric cancer cells and nude mice. *J Cell Biochem* 2010; **111:** 218–28.

88 Tsuji T, Yoshida Y, Fujita T, Kohno T. Oral therapy for type 1 diabetes mellitus using a novel immunomodulator, FTY720 (fingolimod), in combination with sitagliptin, a dipeptidyl peptidase-4 inhibitor, examined in non-obese diabetic mice. *J Diabetes Investig* 2012; **3:** 441–48.

89 Boldizsar F, Tarjanyi O, Olasz K, et al. FTY720 (Gilenya) treatment prevents spontaneous autoimmune myocarditis and dilated cardiomyopathy in transgenic HLA-DQ8-BALB/c mice. *Cardiovasc Pathol* 2016; **25:** 353–61.

90 Ryba DM, Warren CM, Karam CN, et al. Sphingosine-1-phosphate receptor modulator, FTY720, improves diastolic dysfunction and partially reverses atrial remodeling in a TM-E180g mouse model linked to hypertrophic cardiomyopathy. *Circ Heart Fail* 2019; **12:** e005835.

91 Jia L, Liu Y, Wang L, Zhu J, Huang Y. Effects of topical sphingosine-1-phosphate 1 receptor agonist on corneal allograft in mice. *Cornea* 2014; **33:** 398–404.

92 Hemdan NY, Weigel C, Reimann CM, Gräler MH. Modulating sphingosine 1-phosphate signaling with DOP or FTY720 alleviates vascular and immune defects in mouse sepsis. *Eur J Immunol* 2016; **46:** 2767–77.