Drugs in R&D (2020) 20:197–207
https://doi.org/10.1007/s40268-020-00316-1

REVIEW ARTICLE

Fingolimod as a Treatment in Neurologic Disorders Beyond Multiple Sclerosis

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Published online: 22 July 2020

Abstract

Fingolimod is an approved treatment for relapsing–remitting multiple sclerosis (MS), and its properties in different pathways have raised interest in therapy research for other neurodegenerative diseases. Fingolimod is an agonist of sphingosine-1-phosphate (S1P) receptors. Its main pharmacologic effect is immunomodulation by lymphocyte homing, thereby reducing the numbers of T and B cells in circulation. Because of the ubiquitous expression of S1P receptors, other effects have also been described. Here, we review preclinical experiments evaluating the effects of treatment with fingolimod in neurodegenerative diseases other than MS, such as Alzheimer's disease or epilepsy. Fingolimod has shown neuroprotective effects in different animal models of neurodegenerative diseases, summarized here, correlating with increased brain-derived neurotrophic factor and improved disease phenotype (cognition and/or motor abilities). As expected, treatment also induced reductions in different neuroinflammatory markers because of not only inhibition of lymphocytes but also direct effects on astrocytes and microglia. Furthermore, fingolimod treatment exhibited additional effects for specific neurodegenerative disorders, such as reduction of amyloid-β production, and antiepileptogenic properties. The neuroprotective effects exerted by fingolimod in these preclinical studies are reviewed and support the translation of fingolimod into clinical trials as treatment in neurodegenerative diseases beyond neuroinflammatory conditions (MS).

Key Points

Drugs acting on several targets may be promising for the treatment of neurodegeneration.

Fingolimod had positive effects in neurodegeneration.

The reviewed data support the repurposing of fingolimod for other neurology diseases.

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1 Introduction

Fingolimod is a substrate of sphingosine kinases. It binds to sphingosine-1-phosphate (S1P) receptors in its phosphorylated state. Fingolimod is an agonist of several S1P receptor subtypes except for $S1P_2$ receptors [1]. However, in lymphocytes, fingolimod acts as a functional antagonist by inducing internalization of S1P receptors after binding [2]. The main pharmacologic effect of fingolimod is immunomodulation by lymphocyte sequestration and reducing the numbers of T and B cells in circulation [3]. In addition, other effects of fingolimod treatment can be expected because of the ubiquitous expression of S1P receptors and their participation in several pathways.

$S1P_1$ receptors are mainly expressed by immune, neural, and endothelial cells [4]. The main function of this receptor is regulation of immune cell trafficking, but it is also involved in angiogenesis and neurogenesis. The $S1P_1$ receptor is involved in T cell migration across endothelial barriers. Fingolimod induces lymphocyte retention in lymph nodes by inhibiting the function of $S1P_1$ receptors in lymphocyte egression [5]. In addition, the $S1P_1$ receptor is also involved in diverse functions in the central nervous

system (CNS) such as neurogenesis, astrocytic activation and proliferation, and communication between astrocytes and neurons and the blood–brain barrier (BBB) [4]. Furthermore, fingolimod can also bind to the $S1P_5$ receptor, which is predominantly expressed in oligodendrocytes and brain endothelial cells [4, 6, 7]. $S1P_5$ receptor activation protects adult oligodendrocytes from apoptosis and contributes to the maintenance of BBB integrity [7, 8]. In addition, fingolimod treatment regulates the biosynthesis of sphingolipids, which play important roles in neurodegenerative diseases [9].

Fingolimod can be administered orally and has high bio-availability and a half-life of 6–9 days [10]. It was first clinically tested in allograft rejection after kidney transplantation. However, its effects were not superior to those of standard therapy in these kidney-transplanted patients. On the other hand, because of its effects on inflammatory cells, fingolimod was also tested in different animal models of multiple sclerosis (MS), with promising results [11–13]. These preclinical animal studies encouraged clinical trials using fingolimod as a therapeutic agent in relapsing–remitting MS (RRMS). The 5-year FREEDOMS trial in 2010 was a placebo-controlled trial that showed a > 50% reduction in relapse rate compared with placebo treatment, together with a reduction of magnetic resonance (MR) lesions and brain volume loss [14]. Furthermore, the 6-month TRANSFORMS trial in 2010 compared the effects of fingolimod with those of the standard RRMS therapy, intramuscular interferon-β1a. Oral administration of fingolimod showed superior efficacy in terms of relapse rates and MR outcomes [15]. In 2010, the US FDA and the European Medicines Agency (EMA) approved fingolimod as a treatment for RRMS.

In the preclinical and clinical studies performed to date in MS, fingolimod has been proven to exert different protective effects, including inhibition of lymphocyte egress, inhibition of microglial and astroglial activation, reduction of neuronal death, restoration of lost synapsis, and reduction of dendritic spine loss, among others [14, 16–19]. In addition, preclinical and clinical data have shown that fingolimod promotes remyelination in optic neuritis [20, 21] and Krabbe disease [22]. The effects seen in MS include several potential targets shared by many neurodegenerative diseases, such as neuronal loss and neuroinflammation. The multiple pathways targeted by fingolimod suggest that this drug may be a promising therapy for neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). Here, we summarize the reported effects of fingolimod treatment in animal models of neurodegenerative diseases that support the positive expectations of fingolimod repurposing for several conditions with neurodegeneration.

2 Search Strategy

All literature searches were conducted using the PubMed database. The search terms used were "neurodegenerative disease," "Alzheimer's disease," "Parkinson's disease," "epilepsy," "Huntington's disease," "Rett syndrome" OR "neuronal ceroid lipofuscinoses," AND "fingolimod" or "FTY720." Only publications written in English were considered. Additionally, other studies were identified from citations in review articles and reference lists from the search results. All references were screened to ensure relevant studies were included.

3 Neurodegenerative Diseases

3.1 Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is an incurable disease characterized by progressive degeneration of motor neurons in the spinal cord and the motor cortex, resulting in global muscle weakness, paralysis, and ultimately death due to respiratory dysfunction [23, 24]. Currently, the only FDA-approved treatments for this neurodegenerative disease (riluzole and edaravone) have limited effects [25]. Therefore, new therapeutic approaches to halt or slow down this pathology are needed. Patients with ALS and animal models both present an increased number of macrophages and T cells in the spinal cord as well as activated microglia [26–28]. Because of the effects of fingolimod on inflammatory cell infiltration and the inhibition of pro-inflammatory cytokines, it has been proposed as a potential therapy and has been tested both in an animal model and in patients with ALS [29, 30].

Potenza et al. [29] described the disease-modifying effects of fingolimod treatment in an animal model of ALS. They reported a modulation of neuroinflammation in treated SOD mice, along with improvements in phenotype and survival rate [29]. In addition, Berry et al. [30] tested the safety of fingolimod in patients with ALS in a phase IIa trial in 2017 to rule out potential side effects in this population, which differ from those described in patients with MS. The authors reported no serious adverse effects from the treatment and concluded that fingolimod administration in patients with ALS was safe and well-tolerated [30]. However, this study did not evaluate long-term safety.

3.2 Alzheimer's Disease

AD is currently the most common cause of dementia and affects more than 30 million people worldwide [31]. AD is

characterized by the accumulation of neurotoxic proteins (amyloid-β [Aβ] plaques and tau tangles), leading to neurodegeneration and irreversible cognitive decline [32, 33]. The precise mechanisms responsible for the accumulation of Aβ in the brain remain unknown, impeding the development of successful therapeutic strategies. Several molecular mechanisms have been identified as involved in AD pathogenesis, including Aβ overproduction and impaired Aβ clearance, dysregulated tau protein phosphorylation, altered glutamatergic neurotransmission, and astrocyte and microglia activation, starting before the first clinical signs appear [34–36]. Recently, it has been shown that ceramide-enriched exosomes are increased in the serum and brain tissue in mouse models of AD and that this may drive Aβ neurotoxicity [37, 38]. Fingolimod treatment downregulates the expression of ceramide metabolism genes [38]. Thus, targeting these mechanisms during the preclinical stage may reduce AD prevalence and/or delay its onset [39].

As described, fingolimod targets several mechanisms that have been proposed to play a key role in AD pathogenesis, such as neuroinflammation and neuronal loss. In addition, fingolimod has shown promising inhibitory effects on Aβ toxicity and synthesis in vitro. Fingolimod ameliorated Aβ neurotoxicity in neuronal cultures, reducing neuronal death, probably by increasing concentrations of brain-derived neurotrophic factor (BDNF) [40, 41]. Moreover, Takasugi et al. [42] reported that fingolimod decreased Aβ production in neuronal cells. Thus, in recent years, various groups have tested fingolimod in preclinical models of AD.

Fingolimod exerted neuroprotective effects in intracerebral Aβ injection models, reducing neuronal loss in parallel with a reduction in the activation of the Caspase-3 pathway and Aβ concentration. This neuroprotection was accompanied by attenuation of memory and learning deficits [43–46]. In the 5xFAD transgenic mouse model of AD, fingolimod also showed a reduction of Aβ load and attenuation of neuroinflammatory signs (astrocyte and microglia activation) and cognitive improvement [47, 48]. In addition, McManus et al. [49] reported attenuation of the effects of infection on Aβ accumulation and astrocyte activation after fingolimod treatment in APPswe/PS1dE9 mice.

In combination, the results of these in vitro and in vivo studies indicate that fingolimod reduced neuronal loss by inhibiting the Caspase-3 pathway, increasing the concentration of BDNF and enhancing pro-survival signaling. In addition, fingolimod decreased microglial and astroglial activation, reducing leukocyte infiltration and pro-inflammatory cytokine production. Furthermore, fingolimod treatment also reduced Aβ load in mice by inhibiting beta-secretase (BACE) and ceramide and, possibly, by modulating the transport of Aβ through the BBB [49, 50]. In summary, fingolimod treatment in these animal models suggests a potential benefit of this treatment in patients with mild cognitive impairment and patients with AD.

3.3 Parkinson's Disease

PD is a neurological disease characterized by the loss of dopaminergic neurons in the substantia nigra and dysregulation of the extrapyramidal network caused by aggregation of misfolded toxic α-synuclein [51]. In addition, neuroinflammation occurs in areas with neurodegeneration in patients with PD, although it remains unclear whether activated astrocytes and microglia have beneficial or deleterious effects on the progress of PD [52]. Patients with PD experience tremor, postural instability, cognitive impairment, fatigue, and psychiatric symptoms, among other alterations [52]. Current therapies for PD effectively treat symptoms but do not exert disease-modifying effects that stop or delay disease progression. Potential pharmacological targets for disease modification in PD include neuroinflammation, mitochondrial dysfunction, calcium channel activity, LRRK2 kinase activity, and α-synuclein aggregation, as well as regeneration of lost dopamine neurons [52, 53]. Thus, targeting several mechanisms is thought to be more effective than targeting single targets. A successful disease-modifying treatment could transform PD into a chronic disease with modest nondisabling symptoms.

The anti-inflammatory and neuroprotective properties of fingolimod may be advantageous in the treatment of PD. Effects of fingolimod treatment has been studied in different animal models of PD. In the 6-hydroxydompamine (6-OHDA) intracerebral injection mouse model, animals receiving fingolimod showed attenuated neuroinflammation and motor deficits and reduced neuronal loss compared with vehicle-treated mice [54, 55]. Similarly, fingolimod administration was reported to attenuate motor dysfunction in the MPTP mouse model [56, 57]. In addition, mice receiving fingolimod showed increased dopamine release compared with vehicle-treated PD mice [55, 56]. Finally, genetic models of PD (A53T Tg and GM2 ± mice) showed an attenuated phenotype and increased BDNF expression when receiving fingolimod [58, 59]. However, Komnig et al. [60] reported no beneficial effects of fingolimod pretreatment in the MPTP mouse model.

Some animal studies suggest that fingolimod may improve PD therapy by targeting neuroinflammation. In addition, fingolimod treatment has shown effects on BDNF expression, which may recover lost dopaminergic neurons in early phases of the disease. However, the positive effects of this treatment in PD are unclear, as some animal studies have shown no improvement [60].

3.4 Epilepsy

Epilepsies are a group of neurological diseases characterized by the occurrence of unprovoked seizures [61]. Idiopathic epilepsy, i.e., unknown cause, represents about 40% of cases globally [62]. Currently, only symptomatic treatments are available. Furthermore, 30–40% of patients with epilepsy are partially or fully resistant to the therapy [63]. In recent years, research has focused on understanding the processes leading to epilepsy, i.e., epileptogenesis, to better understand the pathophysiology of this disorder and has identified neuroinflammation, neurotransmitter dysregulation, and neuronal loss, among others, as potential key actors in epilepsy pathogenesis [64–68].

Fingolimod has previously shown effects in neuroinflammation, neuronal loss, impaired neurogenesis, and BBB integrity. All these mechanisms have been described as altered during epileptogenesis and/or in patients with chronic epilepsy. Thus, fingolimod could exert anti-epileptogenic effects or, at least, slow the progression of epileptogenesis by altering key mechanisms in the epileptogenic process. Various groups have tested the potential of this drug in animal models of epileptogenesis. Gao et al. [69] showed that fingolimod treatment after status epilepticus reduced neuroinflammation, neuronal loss, and mossy fiber sprouting in the early phase of epileptogenesis in the rat lithium-pilocarpine model. More importantly, fingolimod also had an anti-epileptogenic effect, shown by a reduction of spontaneous convulsions in treated rats [69]. The same group reported an attenuation of the ABCB1 overexpression described in this model, which is thought to be partially responsible for the high rate of drug-resistant epilepsy [70]. Similarly, fingolimod showed antiepileptic effects during the chronic epileptic phase of the mouse kainate model. Pitsch et al. [71] reported decreased seizure frequency in animals receiving fingolimod compared with the vehicle group. In addition, treated animals showed reduced neuroinflammation and attenuated neuronal loss. Fingolimod also exerted beneficial effects in the pentylenetetrazol mouse-kindling model. Treated animals showed reduced epileptic activity when applied before pentylenetetrazol and in kindled animals, suggesting anticonvulsant effects from fingolimod. In addition, treatment reduced neuroinflammation signs and neuronal loss [72]. Finally, fingolimod exerted positive effects in WAG/Rij rats, an animal model of genetic epilepsy. Rats treated with fingolimod showed a transitory reduction of the frequency of absence seizures and long-lasting reductions in depression-like behavior [73].

In line with other animal models of neurodegenerative diseases, fingolimod showed neuroprotective and anti-inflammatory effects in animal models of epileptogenesis. Neuroinflammation and neurodegeneration are hypothesized to be key players in the development of epilepsy. The ameliorating effects of fingolimod shown in these studies support the further evaluation of this drug as anti-epileptogenic treatment, whether alone or in combination with other drugs, in patients at risk of developing epilepsy (e.g., status epilepticus, stroke, etc.). In addition, fingolimod showed anticonvulsant properties, which were not explored in other animal or clinical studies. This effect warrants the investigation of fingolimod treatment during chronic epilepsy.

3.5 Huntington's Disease

Huntington's disease (HD) is a genetic neurodegenerative disease that causes involuntary movements, cognitive impairment, and severe neuropsychological alterations. It is caused by a CAG repeat expansion in the huntingtin protein, leading to neuronal death and synaptic maladjustments, among other alterations [74, 75]. Patients with HD show neuronal loss, most prominently in the striatum and cerebral cortex, loss of neurotransmitters and glutamate, γ-amino-hydroxy-butyric acid (GABA) and dopamine receptors, reactive gliosis, metabolic alterations, and huntingtin aggregates [76]. Despite the identification of the genetic cause of the disease in 1993 [75], only symptomatic treatment of HD is available, and not all symptoms respond to the available treatments. Currently, no treatment can stop or reverse the disease [77].

Fingolimod effects such as neuroprotection and inhibition of neuroinflammation may be of interest for the therapy of HD [78]. In addition, research has shown promising effects of fingolimod treatment in animal models of HD. Di Pardo et al. [79] found that low-dose fingolimod (0.1 mg/kg) improved motor function, reduced brain atrophy, and extended survival of R6/2 mice, a mouse model of HD expressing a portion of the human HD gene [79]. In addition, fingolimod induced phosphorylation of huntingtin in vitro and reduction of huntingtin aggregates in vivo [79]. Miguez et al. [80] also showed beneficial effects on R6/1 mice after fingolimod treatment. Treated animals showed ameliorated memory deficits and neuroinflammation. Fingolimod also prevented the loss of dendritic spines and increased BDNF, which might lead to the cognitive improvement observed in these animals [80].

Preclinical research has shown that fingolimod treatment has effects on huntingtin aggregation, neuroinflammation, and neurogenesis. Based on the effects on HD pathology shown in in vitro and animal research, fingolimod may be an interesting option to be tested in patients with HD in combination with current therapies.

3.6 Rett Syndrome

Rett syndrome is a severe neurological disorder that affects mainly females. Patients with Rett syndrome experience

compromised brain function, mental retardation, language and learning disabilities, and development regression [81]. The most prevalent cause is a mutation in the X-linked methyl-CpG binding protein 2 (*Mecp2*) gene [82]. *Mecp2* controls the expression of a large set of genes, including BDNF. Dysfunctional *Mecp2* decreases BDNF levels in patients and in animal models. Increasing BDNF levels, one of the described effects of fingolimod, may be an important approach to generate new therapies in Rett syndrome [83].

Deogracias et al. [84] showed beneficial effects with fingolimod treatment in *Mecp2*-deficient mice, an animal model of Rett syndrome. After showing increased BDNF secretion, together with reduced *N*-methyl-D-aspartate (NMDA)-induced neuronal loss and an increased network activity in vitro induced by fingolimod, the authors treated *Mecp2*-deficient mice with fingolimod and showed higher BDNF levels in the cortex and recovery of striatal weight in parallel with improvements in motor deficits [84]. A clinical trial is currently assessing the safety and efficacy of oral fingolimod (FTY720) in children aged > 6 years with Rett syndrome (FINGORETT; NCT02061137).

3.7 Neuronal Ceroid Lipofuscinoses

Neuronal ceroid lipofuscinoses (NCL) are rare genetic lysosomal storage diseases characterized by progressive axonal degeneration and neurodegeneration. Patients with NCL present diverse neurological manifestations, including seizures, intellectual and motor deterioration, sleep problems, visual loss, anxiety, and psychosis [85–87]. NCLs are grouped together because of the common presence of neuronal and extraneural autofluorescent pigment accumulations, although they have diverse genetic etiologies. NCLs were traditionally classified according to the age at onset: infantile, late infantile, juvenile, and adult NCL. However, NCLs are now classified according to the affected gene combined with the age at onset. To date, 14 genetically distinct NCLs have been identified (represented by the genes CLN1–14), with CLN3 being the most prevalent form [86, 88].

Groh et al. [89] showed beneficial effects from fingolimod treatment in an animal model of NCL. The authors described a reduction in neuroinflammatory signs, brain atrophy, and frequency of myoclonic jerks in CLN3 animals treated with fingolimod compared with the untreated group [89], which suggests that fingolimod treatment could alleviate or postpone some of the symptoms of these rare genetic diseases in patients.

4 Discussion

Fingolimod has shown promising effects in the treatment of RRMS in several clinical trials, showing better results than placebo and the traditional therapy, interferon-β1a [14, 15]. However, fingolimod has not shown such effects on primary progressive MS, in which neurodegenerative processes might have more importance than inflammatory infiltrates in the CNS [90]. Nevertheless, the diverse anti-inflammatory and neuroprotective effects exerted by fingolimod in different animal models suggest that this drug may also be an interesting medication for neurodegenerative/neuroinflammatory conditions other than RRMS. Besides the anti-inflammatory effects of fingolimod shown in RRMS, its regulation of sphingolipid biosynthesis may be of interest in the treatment of neurodegenerative diseases [9]. In recent years, preclinical research has focused on the therapeutic effects of fingolimod in other diseases in addition to MS. The studies summarized here have reported common neuroprotective and anti-inflammatory properties of fingolimod treatment in different preclinical models of neurological diseases (Table 1). In addition to the effects already described in MS models and patients with MS, these authors have shown additional mechanisms of fingolimod that may increase the therapeutic potential of this drug in specific diseases such as AD or epilepsy. Fingolimod has been shown to inhibit BACE and Aβ production and to have anticonvulsant properties, which are of interest in the treatment of these neurodegenerative disorders, respectively. In addition, fingolimod has modulatory effects on diverse pathways that are not targeted by current conventional therapies in the neurodegenerative diseases described (Fig. 1).

Several treatments that worked in animal models of neurodegenerative diseases have failed in their translation to human patients. Thus, it is important to test the effects described in preclinical models in clinical studies to confirm that the action of fingolimod is similar in human patients. The pathways targeted by fingolimod in the animal models used in these studies need to be confirmed as affected in human neuropathology and that fingolimod can induce similar changes in patients as seen in the animal models. In this regard, a significant advantage of fingolimod is that it is already approved by the FDA and the EMA as a treatment for MS. Thus, translation of the results from animal models to clinical assays potentially requires less time than would newly developed drugs, which need years before the first test in humans.

However, fingolimod has also shown side effects in human patients, such as bradycardia after the first dose, lymphopenia, increased liver transaminases, herpes virus infections, or hypertension [91]. Nevertheless, the

Table 1 Summary of fingolimod treatment in different preclinical studies of neurodegenerative diseases

Disease	Study	Model	Doses	Clinical effects	Neuropathology effects
AD	Asle-Rousta et al. [45]	Microinjection Aβ, rats	1 mg/kg	Attenuated learning and memory impairment	Reduced neuronal loss, reduced Cas-3
	Doi et al. [40]	Neuronal cultures	1–100 pM	–	Increased neuronal survival, increased BDNF
	Hemmati et al. [44]	Intracerebral Aβ, rats	0.5 mg/kg	Reduced memory deficits	Attenuated neuronal loss, altered gene expression toward neuroprotection
	Takasugi et al. [42]	A7 tg mice	0.5 mg/kg	–	Decreased soluble Aβ40, increased Aβ42
	Asle-Rousta et al. [43]	Microinjection Aβ, rats	1 mg/kg	Attenuated learning and memory impairment	Reduction inflammatory markers (Cox-II and TNFα)
	Ruiz et al. [41]	Neuronal cultures	200 nM	–	Reduced Aβ oligomer toxicity
	Fukumoto et al. [46]	Aβ icv, mice	1 mg/kg	Ameliorated memory and learning impairment	Restored BDNF to normal levels
	Aytan et al. [47]	5xFAD mice	1 and 5 mg/kg	–	Decreased soluble and insoluble Aβ, decreased neuroinflammation
	McManus et al. [49]	APP/PS1 mice	0.3 mg/kg	–	Attenuated infection-enhanced Aβ accumulation, reduced BBB permeability
	Carreras et al. [48]	5xFAD mice	0.03–1 mg/kg	Reduced memory deficits	Decreased Aβ levels, reduced neuroinflammation and lymphocyte count
PD	Vidal-Martinez et al. [59]	A53T tg mice	0.5 mg/kg	Reduced constipation, enhanced gut motility	Reduced αSyn aggregation, increased BDNF
	Ren et al. [54]	6-OHDA mice	0.5 mg/kg	Decreased motor deficits	Decreased neurotoxicity, reduced neuroinflammation, increased BDNF
	Zhao et al. [55]	6-OHDA and rotenone mice	0.5 and 1 mg/kg	Attenuated motor dysfunction	Reduced TH + neuronal loss in substantia nigra, attenuated decrease of dopamine
	Komnig et al. [60]	MPTP mouse model	0.1 and 1 mg/kg	–	No beneficial effects
	Motyl et al. [57]	MPTP mouse model	1 mg/kg	Improved motor activity	Attenuated TH + neuronal loss, increased BAD protein phosphorylation
	Vidal-Martinez et al. [58]	GM2 ± mice	0.5 mg/kg	Movement improvements	Reduced αSyn, increased BDNF
	Yao et al. [56]	MPTP mouse model	2 mg/kg	Attenuated motor dysfunction	Reduced loss dopaminergic neurons, increased dopamine, reduced neuroinflammation

Table 1 (continued)

Disease	Study	Model	Doses	Clinical effects	Neuropathology effects
Epilepsy	Gao et al. [69]	Rat lithium-pilocarpine model	1 mg/kg	Reduced spontaneous seizures	Reduced neuroinflammation, attenuated neuronal loss, reduced mossy fiber sprouting
	Gol et al. [72]	Mouse PTZ kindling	0.3 and 1 mg/kg	Anticonvulsant effect	Reduced neuroinflammation, reduced neuronal loss, attenuated demyelination
	Leo et al. [73]	WAG/Rij rats	1 and 3 mg/kg	Transitory reduction absence seizures and depression-like behavior	–
	Gao et al. [70]	Rat lithium-pilocarpine model	1 mg/kg	–	Attenuated overexpression ABCB1, reduced TNFα and Cox-II
	Pitsch et al. [71]	Mouse intracerebral kainic acid, mouse pilocarpine model	2 and 6 mg/kg	Reduced seizures, antiepileptogenic effects	Reduced neuroinflammation and neuronal loss
HD	Di Pardo et al. [79]	R6/2 mice	0.1 mg/kg	Improved motor function, prolonged survival	Attenuated brain atrophy, increased BDNF
	Miguez et al. [80]	R6/1 mice	0.3 mg/kg	Ameliorated memory deficits	Prevented dendritic spine loss, reduced astrogliosis, increased BDNF
ALS	Potenza et al. [29]	SOD mice	0.1 and 1 mg/kg	Extended survival, reduced neurological scores	Modulated neuroinflammation (M2 > M1)
	Berry et al. [30]	Patients	0.5 mg/kg	No serious adverse events	Decreased circulating lymphocytes
Rett Syndrome	Deogracias et al. [84]	Mecp2-deficient mice	0.1 mg/kg	Improved motor deficits, extended lifespan	Increased BDNF, reduced striatum atrophy
CLN	Groh et al. [89]	CLN1, CLN3 mice	0.5 mg/kg	Reduced myoclonic jerks	Attenuated neuroinflammation, reduced brain atrophy

6-OHDA 6-hydroxydopamine, *ABCB1* ATP binding cassette subfamily B member 1, *Aβ* amyloid-beta, *BAD* BCL2-associated death, *BDNF* brain-derived neurotrophic factor, *Cas-3* caspase-3, *Cox-2* cyclooxygenase-2, *MPTP* 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, *PTZ* pentylenetetrazol, *TH* + tyrosine hydroxylase positive, *TNF-α* tumor necrosis factor alpha, *α-syn* alpha-synuclein

symptoms derived from the different neurological diseases reviewed here are severe and, in most cases, incapacitating and potentially lethal. Therefore, the benefits described in these models are expected to outweigh the potential risks of the use of fingolimod in patients with neurodegeneration. In addition, fingolimod has already been shown to be safe in MS [91, 92] and ALS [30]. However, the target populations of some of the diseases included here differ significantly from those used in these studies as some include children or the elderly. Although no further side effects are expected in other neurodegenerative diseases, some of the side effects previously described may be of importance in specific patient populations. New S1P modulators such as ozanimod have shown higher receptor specificity and fewer side effects than fingolimod [93]. These new drugs might provide new opportunities in treatment of neurodegenerative diseases that focus on neuroprotective mechanisms instead of anti-inflammatory effects.

The positive effects offered by fingolimod in the treatment of patients with RRMS and the numerous pathways in which S1P receptors are involved have made this drug an attractive option for treating other neurodegenerative diseases. The animal experiments reviewed here showed positive effects on different neurological diseases together with additional alterations in pathways not identified in MS research. These promising results support the implementation of new clinical trials repurposing fingolimod to treat other neurodegenerative diseases in addition to MS.

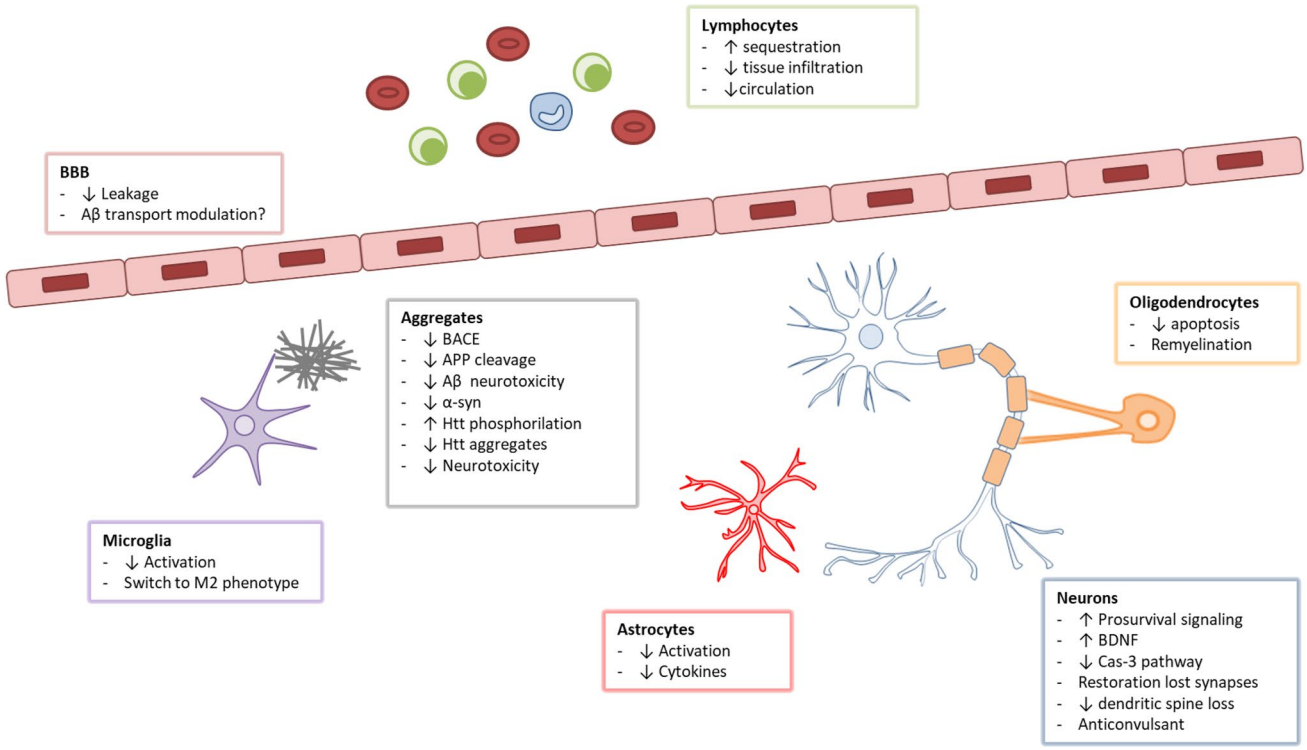

Fig. 1 Summary of reported effects of fingolimod relevant to neurological disorders. Effects are specifically shown in different cell types, blood–brain barrier and brain deposits. These effects include different pathways involved in neuroinflammation and neurodegeneration as well as disease-specific effects. *APP* amyloid precursor protein, *Aβ* amyloid-beta, *BACE* beta-secretase, *BBB* blood–brain barrier, *BDNF* brain-derived neurotrophic factor, *Cas-3* caspase-3, *Htt* huntingtin, *α-syn* alpha-synuclein

Acknowledgements The work of JP was supported by the following grants: Deutsche Forschungsgemeinschaft, Germany (DFG PA930/12); Ministerium für Wirtschaft und Wissenschaft Sachen-Anhalt, Germany (ZS/2016/05/78617); Leibniz Gemeinschaft, Germany (SAW-2015-IPB-2); Latvian Council of Science, Latvia (lzp-2018/1-0275); Nasjonalforeningen (16154), HelseSØ, Norway (2016062, 2019054, 2019055); Norges forskningsrådet, Norway (251290, 260786); and the European Commission (643417).

Compliance with Ethical Standards

Conflict of Interest Pablo Bascuñana, Luisa Möhle, Mirjam Brackhan, and Jens Pahnke have no conflicts of interest that are directly relevant to the content of this review/study.

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