Repurposing multiples sclerosis disease-modifying drugs for Parkinson’s disease

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Abstract

Parkinson’s disease (PD) is an age-related neurodegenerative disease mainly affecting the elderly population. Despite recent progresses in pharmacologic therapies and surgical interventions such as deep brain stimulation, current PD therapies are limited to relieving disease symptoms rather than stopping disease progression, highlighting an urgent yet unmet need for disease-modifying interventions. Neuroinflammation has been proposed as a pivotal contributing factor that drives the initiation and progression of PD pathology. Owing to the revolution in disease-modifying drugs (DMDs) that successfully change the course of multiple sclerosis (MS), a central nervous system inflammatory autoimmune disease, it has become tempting to repurpose MS DMDs as new treatment options for PD. This review summarizes the ongoing and completed studies of MS DMDs in PD as a potential opportunity to address this unmet need. Future clinical trials are warranted to further evaluate the efficacy of DMDs in patients with PD.

Keywords: Parkinson’s disease, disease-modifying drugs, drug repurposing, neuroinflammation, multiple sclerosis

INTRODUCTION

Parkinson’s disease (PD) is a progressive neurodegenerative disease with motor and non-motor features.
Motor features of PD are characterized by resting tremor, bradykinesia, postural instability, and rigidity[4]. Non-motor symptoms can manifest in the early stage of PD, which include hyposmia, cognitive impairment, depression, sleep disorders, autonomic dysfunction, pain, fatigue, etc.[2,3]. The selective loss of dopaminergic neurons in the substantia nigra and the presence of α-synuclein (α-syn) aggregations are considered to be the hallmarks of PD neuropathology[4]. However, the exact cause of PD remains controversial. It has been proposed that a complex interaction of aging, environment and genetics participate in the development of PD[6]. Emerging studies have prompted the link between PD and immune dysregulation. Numerous investigations have revealed that neuroinflammation is a prominent factor underlying the perpetuating neurodegeneration process of PD[6]. For example, neuroinflammation caused by SARS-CoV-2 may impair brain DA homeostasis and interfere with normal α-synuclein metabolism[7].

Aging is a strong risk factor for PD[8]. A possible explanation is that the immune disturbance occurring during the aging process, known as inflamming, contributes to PD[6]. The dysregulation in the components of the innate immune system (e.g., microglia) and the adaptive immune system (e.g., T and B cells) in PD has also been reported by recent preclinical and clinical studies[10-12], suggesting that the pathological events in PD likely involve features seen in central nervous system (CNS) autoimmune diseases, where neuroinflammation drives disease development and progression[9].

The enhanced understanding of the link between PD and the immune system generates promising insights into the treatment of PD. Currently, the major therapy goal of PD is to provide symptomatic relief of the disease. Dopaminergic replacement pharmacotherapy (e.g., Levodopa) is the first-line therapy for PD patients[13]. However, these therapies cannot reverse the disease progression and they must be continuously maintained. After several years of treatment, fluctuations in response are inevitable[6]. Another side-effect of long-term dopaminergic treatment is levodopa-induced dyskinesias, which severely impairs the life quality of PD patients[14]. Considering the increasing health burden imposed by PD, it is imperative to develop disease-modifying therapies for PD patients. Ideally, the drugs with disease-modifying effects are able to address the factors contributing to disease progression to actually halt or even reverse the neurodegeneration process in PD. At present, no drugs used for PD have clinically proven disease-modifying effects[15]. However, in the field of CNS autoimmune diseases, particularly in multiple sclerosis (MS), disease-modifying drugs (DMDs) with immunomodulatory effects have achieved significant success. Apparently, immune dysregulation and pathological inflammatory responses are common events underlying the pathogenesis of PD and neurological autoimmune diseases. Therefore, it is reasonable to anticipate that the immunomodulatory mechanisms of action of DMDs, which are effective in neurological autoimmune diseases such as MS, may also be effective in PD. These drugs have been proven to be able to alleviate neuroinflammation to exert their neuroprotection effects. Along this line, a potentially feasible strategy is to repurpose those drugs that have been widely accepted in treating neurological autoimmune diseases to modulate the aberrant immune responses occurring in PD and ultimately achieve disease modification.

In this review, we aim to summarize the preclinical and clinical studies repurposing disease-modifying drugs for MS, or those targeting the immune system, in the treatment of PD and sum up their mechanisms. We also assessed the clinical potential of these drugs for future application in PD patients.

REPURPOSING MS DMDS FOR PD

MS is a neurological demyelinating disease caused by autoimmune responses. Demyelination and damage to axons and neurons caused by autoimmune inflammatory responses are key features of MS[16]. The application of disease-modifying treatment in MS has permanently changed the natural history and management approaches for MS. Disease-modifying drugs target specific pathways underpinning the
pathology of MS to halt or even reverse the progression of the disease, rather than temporarily relieve the symptoms of the disease\textsuperscript{[15]}. The prognosis of relapsing-remitting multiple sclerosis has become more favorable due to the early application of disease-modifying drugs, and there is also a trend to improve the outcome of progressive multiple sclerosis with disease-modifying therapies\textsuperscript{[17]}. At present, four kinds of disease-modifying drugs for MS have been investigated in PD models [Table 1]. Notably, these drugs also function through new, unexpected pathways beyond the immune system when used in PD.

IFN-β was the first approved DMD for relapsing multiple sclerosis (MS) in 1993 and is still a therapeutic option today. INF-β benefits MS patients by modulating T and B cell functions and regulating cytokine production\textsuperscript{[18]}. Interestingly, IFN-β signaling in neurons has been shown to be protective against PD pathology. Ifnb\textsuperscript{−/−} mice exhibit numerous characteristics of PD\textsuperscript{[19]}. The deficiency in the IFN-β-IFNAR signaling axis contributed to the impairment of dopaminergic neurons, formation of Lewy Body-like structures and the presence of parkinsonism in Ifnb\textsuperscript{−/−} mice, which could be rescued partly by the treatment of recombinant IFN-β\textsuperscript{[19]}. However, instead of immunomodulation, further studies demonstrated that IFN-β could improve autophagy functions in neurons to facilitate the clearance of α-syn through the MIR1-TBC1D15-RAB7 pathway\textsuperscript{[19,20]}. It is a typical example that the application of old drugs to new diseases leads to the discovery of new pathways\textsuperscript{[21]}. Glatiramer acetate, approved for treating relapsing-remitting MS (RRMS) in 1997, induces GA-specific T cells in the periphery\textsuperscript{[22]}. These T cells can be recruited to the central nervous system and express robust levels of regulatory cytokines IL-10 and TGF-β\textsuperscript{[23]}. Glatiramer acetate (GA, Copaxone) was hypothesized to be beneficial to PD due to its anti-inflammatory properties\textsuperscript{[24]}. Additionally, GA also facilitates the production of brain-derived neurotrophic factor (BDNF) in the brain\textsuperscript{[22,25]}. Several studies demonstrated that increasing BDNF levels in the brain was effective in inhibiting PD development and BNDF was regarded as a promising target for PD therapy\textsuperscript{[26,27]}. Studies regarding the impact of GA treatment on PD remain scarce. A recent study demonstrated that the treatment of GA alleviated microglial inflammation and upregulated BDNF levels in the MPTP mice brain, leading to improved movement performance\textsuperscript{[28]}. However, the exact mechanisms are still waiting to be elucidated.

Dimethyl fumarate (DMF), a nuclear factor-like (Nrf2) pathway activator, received its approval for the treatment of relapsing MS in 2013\textsuperscript{[29]}. This drug modulates the immune responses in MS mainly by altering the immune cell composition and preventing immune cell infiltration into CNS\textsuperscript{[29]}. The mechanisms of action of DMF in MS have been reviewed in detail\textsuperscript{[30,31]}. However, the role of Nrf2 pathway in PD remains controversial. The enhanced systemic activation of Nrf2 was observed in blood leukocytes of PD patients recently, revealing a potential pathological role of the Nrf2-pathway in PD\textsuperscript{[32]}. However, the neuroprotective functions of Nrf2 pathway in PD have also been reported\textsuperscript{[33]}. In addition, a growing body of evidence suggests that DMF is a promising candidate for PD therapy, supporting the protective role of Nrf2 axis\textsuperscript{[34,35]}. Multiple mechanisms of action for this drug have been identified in different types of PD animal models. An in vitro and in vivo study demonstrated that treatment of DMF resulted in an upregulated anti-oxidant gene expression in SH-SY5Y cells and reduced oxidative stress damage in 6-OHDA mice\textsuperscript{[36]}. In mice injected with rAAV6-α-SYN, DMF treatment dampened microgliosis and astrogliosis\textsuperscript{[34]}. The anti-inflammatory and anti-oxidant functions of DMF were further proved by a study on the MPTP mice model, which highlighted that DMF not only exerted its anti-oxidant functions via Nrf2-mediated pathway but also displayed anti-inflammatory properties through downregulating NF-κB pathway to reduce the production of inflammatory cytokines in the brain\textsuperscript{[37]}. Additionally, DMF was shown to be able to regulate energy metabolism. A study demonstrated that DMF enhanced glycolysis to reduce oxidative stress damage,
Table 1. Multiple sclerosis disease-modifying drugs investigated in PD models

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Models</th>
<th>Mechanisms</th>
<th>Effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPTP mice</td>
<td>Nrf2 pathway↑</td>
<td>Reducing behavior impairment and DA tract degeneration</td>
<td>[37]</td>
<td></td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>6-OHDA mice</td>
<td>Nrf2 pathway↑</td>
<td>Improvement of motor functions</td>
<td>[36]</td>
</tr>
<tr>
<td>Mice receiving rAAV6-α-SYN</td>
<td>Nrf2 pathway↑</td>
<td>Better motor performance</td>
<td>[34]</td>
<td></td>
</tr>
<tr>
<td>DJ-1β mutant flies</td>
<td>Glycolysis↑</td>
<td>Improvement of motor functions of 5-day-old DJ-1β mutant flies</td>
<td>[38]</td>
<td></td>
</tr>
<tr>
<td>Transgenic A53TSyn mice</td>
<td>Nrf2 pathway↑</td>
<td>Improvement of neuronal arborization</td>
<td>[35]</td>
<td></td>
</tr>
<tr>
<td>Mice receiving rAAV6-α-SYN</td>
<td>CD4+ T cell responses↓</td>
<td>Amelioration of α-syn-induced neurodegeneration</td>
<td>[10]</td>
<td></td>
</tr>
<tr>
<td>MPTP mice</td>
<td>SIP receptor(s)-dependent Akt kinase pathway↑</td>
<td>Improvement of the locomotor functions</td>
<td>[41]</td>
<td></td>
</tr>
<tr>
<td>Fingolimod</td>
<td>6-OHDA mice</td>
<td>AKT and ERK1/2 pro-survival pathway↑</td>
<td>Amelioration of motor deficits</td>
<td>[42]</td>
</tr>
<tr>
<td>GM2+/- mice</td>
<td>BDNF↑</td>
<td>Improvement of motor and bladder functions</td>
<td>[43]</td>
<td></td>
</tr>
<tr>
<td>transgenic A53TSyn mice</td>
<td>BDNF↑</td>
<td>Improvement of gut motility</td>
<td>[44]</td>
<td></td>
</tr>
<tr>
<td>MPTP mice</td>
<td>NLRP3 inflammasome activation↑</td>
<td>Enhanced motor functions</td>
<td>[45]</td>
<td></td>
</tr>
<tr>
<td>IFN-β mice</td>
<td>Autophagy↑</td>
<td>Improvement of α-synuclein clearance</td>
<td>[19]</td>
<td></td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>MPTP mice</td>
<td>BDNF↑</td>
<td>Improvement of motor functions</td>
<td>[28]</td>
</tr>
</tbody>
</table>

BDNF: brain-derived neurotrophic factor; Nrf2: nuclear factor-like.

leading to the improvement of PD symptoms in DJ-1β mutant flies[38]. DMF can also exert neuroprotective effects by improving mitochondrial functions in neurons of transgenic A53TSyn mice[35]. Taken together, DMF is a highly pleiotropic agent and participates in the regulation of neuroinflammation, ameliorating oxidative stress and modulation of energy metabolism.

Fingolimod (FTY720) was approved for treating relapsing-remitting multiple sclerosis due to its effective immunosuppressive functions[39,40]. Fingolimod is phosphorylated by Sphingosine kinase in vivo to generate fingolimod-P, which competes with S1P and induces internalization and degradation of S1P receptors, resulting in functional antagonism of S1P[39]. The downregulation of S1P on T cells impairs its ability to egress out of secondary lymphoid organs, preventing pathogenic T cells from entering the CNS[39,40]. Similarly, suppression of T cell responses by fingolimod also confers protection against PD pathology[9]. In addition to immunomodulation functions, the neuroprotective functions of fingolimod can mainly be attributed to the stimulation of S1P receptor pathways and/or inducing the production of BDNF in the CNS[41-44]. Another study employing the MPTP mice model revealed that NLRP3 inflammasome activation, which is associated with PD development, could be inhibited by fingolimod[45]. However, there are existing controversies regarding the protective effects of fingolimod in PD models[46]. Notably, except for locomotor abilities, treatment of fingolimod also improves other PD-related symptoms, including urinary functions and gut motility[43,44]. Considering urinary dysfunctions and constipation precede the development of motor symptoms of PD, the use of fingolimod has the potential to halt PD progression in the early stage.
REPURPOSING OTHER DRUGS WITH IMMUNOMODULATORY EFFECTS FOR PD

Although the studies of disease-modifying drugs for MS are still in the preclinical stage, several clinical studies have aimed to validate the feasibility and evaluate the benefits of repositioning other types of drugs targeting the immune system for PD patients [Table 2].

Sargramostim, a recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF), has been approved for use in the recovery of myeloid function and anti-cancer therapies, such as melanoma, due to its abilities to promote bone marrow regeneration and modulate the immune system[47]. In a randomized, double-blind phase 1 clinical trial, patients receiving 6 μg/kg/day sargramostim for six weeks showed modest improvement in motor functions measured by MDS-UPDRS-III score, which was associated with the concomitant improvement of Treg numbers and function[48]. A further study proposed 3 μg/kg/day as a more optimal dose with higher tolerability and fewer adverse events[49]. The absence of a reliable biomarker to monitor disease progression and therapeutic efficacy has been a persistent issue waiting to address in the treatment of PD. This issue has impeded the development of effective treatments and made it difficult for clinicians to accurately evaluate the effectiveness of current therapies. A recent study analyzed transcriptomic and proteomic data from monocytes of Parkinson’s disease patients undergoing sargramostim treatment. The findings indicated that the monocyte profile could serve as a potential biomarker for assessing the therapeutic response to sargramostim of PD patients[50]. These results provide important insights into the mechanisms of action of sargramostim and could lead to improved treatment strategies for Parkinson’s disease.

Simvastatin belongs to the class of statin drugs, which reduce blood cholesterol levels by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase[51]. In addition, simvastatin is able to penetrate the blood-brain barrier effectively[51]. In PD models, simvastatin displayed several neuroprotective mechanisms of action that can improve the disease outcome[52]. There is evidence to suggest that individuals who take simvastatin have a significantly lower incidence of PD[53]. However, a recent randomized clinical trial demonstrated that simvastatin displayed no significant effect on stopping disease progression in PD patients with moderate severity, which discouraged a further phase 3 trial[54]. A possible reason for the discrepancy in results is that it may be more effective in preventing the initial development of the PD, rather than slowing its progression once it has advanced to a certain extent. This may explain why the drug did not show significant therapeutic benefit in the recent clinical trial, as the patients had already reached a moderate stage of PD.

Azathioprine, which interferes with nucleic acid metabolism to inhibit immune cell proliferation, is a widely used immunosuppressant drug in autoimmune diseases[55]. Specifically, azathioprine is still used as the first-line treatment in the long-term immunosuppression therapy of neuromyelitis optica spectrum disorder (NMOSD)[56-58]. Therefore, it is reasonable to consider the possibility of applying azathioprine to the treatment of PD. An ongoing phase 2 trial was conducted to explore the efficacy of the use of azathioprine in PD patients. The primary outcome was the motor function of patients measured by MDS-UPDRS III score. The study also included immune-related markers in blood and cerebral spinal fluid, as well as the results of PK-11195 positron emission tomography imaging, which measures microglia activation, into observation[59].

In summary, ongoing clinical trials are testing the potential of the aforementioned drugs with immune modulatory effects in patients with PD. The new results in the coming years may provide evidence to extend the original pharmaceutical scope of these old drugs for clinical use in PD.
Table 2. Repurposing other drugs with immune modulatory effects for PD

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Original use</th>
<th>Mechanisms of action</th>
<th>NCT number</th>
<th>Phase</th>
<th>Status</th>
<th>Start date</th>
<th>Publications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sargramostim</td>
<td>Growth factor for leukocytes therapy</td>
<td>Treg cells</td>
<td>NCT01882010</td>
<td>1</td>
<td>Completed</td>
<td>2013</td>
<td>[48]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT03790670</td>
<td>1</td>
<td>Active, not recruiting</td>
<td>2019</td>
<td>[49]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT05677633</td>
<td>1</td>
<td>Not yet recruiting</td>
<td>2023</td>
<td>-</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Cholesterol control</td>
<td>Anti-inflammation</td>
<td>NCT02787590/ISRCTN16108482</td>
<td>2</td>
<td>Completed</td>
<td>2016</td>
<td>[54,65]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suppression of the peripheral immunity</td>
<td>ISRCTN14616801/EudraCT-2018-003089-14</td>
<td>2</td>
<td>Active, not recruiting</td>
<td>2018</td>
<td>[59]</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Immunosuppression</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

CONCLUSION AND FUTURE PERSPECTIVES

Owing to the aging demographic structure of the global population, the prevalence of PD has grown exponentially in the past decades. In the absence of effective disease-modifying therapy, the subsequent increasing health burden imposed by PD is becoming an issue that cannot be ignored. Treatment options for MS have been tremendously improved over the past 20 years. The success of these newly developed oral DMDs and monoclonal antibodies in MS and their various mechanisms of action have led to active investigations to test their efficacy in PD and other age-related neurological disorders.

Mounting evidence has indicated neuroinflammation as a pivotal contributor that drives the initiation and progression of PD pathology. Ongoing clinical trials are being carried out to explore whether repurposing drugs with immunomodulatory effects could be a viable approach to benefit patients with PD, although current clinical studies are still limited to the early phase. Considering the success of DMDs in MS to control CNS inflammation and their favorable features of pharmacokinetics and tissue distribution, it is reasonable to postulate their efficacy in modulating the inflammatory responses in the brain, which might benefit patients with PD. Furthermore, repurposing approved drugs is a more time and cost-efficient approach compared to the de novo development of a new agent.

Multiple mechanisms of MS DMDs have been identified in PD animal models. Among MS DMDs, DMF and fingolimod have been demonstrated to generate positive outcomes in a wide array of PD models via various mechanisms, suggesting that they are promising candidates to be tested in future clinical trials. Additionally, we should keep in mind that the newly developed DMDs such as Bruton tyrosine kinase inhibitors might also be promising candidates for future experimental studies in PD. Future investigations regarding these drugs may lead to the identification of promising new therapies for PD and other neurodegenerative disorders that represent a significant unmet clinical need.
Figure 1. Mechanisms of MS drugs repurposing for PD. BDNF: Brain-derived neurotrophic factor; Nrf: nuclear factor.

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Wrote the manuscript: Cao T

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