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Primary Progressive Multiple Sclerosis: New Therapeutic Approaches

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ABSTRACT

Background and Purpose: Primary progressive multiple sclerosis (PPMS) is a clinically different form of MS that causes gradual and irreversible neurological impairment from symptom onset without relapses or remissions. With a mean onset age of 37–43 years, PPMS affects 10%–15% of MS patients and presents distinct diagnostic and treatment issues. Mobility issues, persistent pain, sensory disturbances, cognitive deficits, and bowel and bladder problems intensify over time. Neuroimaging shows substantial brain and spinal cord atrophy with fewer brain lesions but more spinal cord lesions.

Findings: Drugs like ocrelizumab reduce progression, whereas high-dose biotin, simvastatin, and coenzyme Q10 are being investigated. PPMS treatment is difficult, with continuing research on fingolimod, idebenone, anti-LINGO-1, neuromodulation, and plasmapheresis. Ocrelizumab has shown encouraging outcomes. Preclinical gene therapy studies on immune regulation, neuroprotection, and remyelination in MS animals show promise. Hematopoietic and non-hematopoietic stem cell therapies have also been studied for their capacity to reduce neuroinflammation, repair tissue, and boost neurotrophic support.

Conclusions: Clinical research utilizing human fetal neural precursor cells (hfNPCs) reveals neuroprotective advantages and opportunities for PPMS treatment. Early clinical trials have shown promising results, but more study is needed to prove the safety and usefulness of these new PPMS treatments.

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; EAE, experimental autoimmune encephalomyelitis; ELFs, ectopic lymphoid follicles; EVs, extracellular vesicles; FLS, follicle-like structures; hfNPCs, human fetal neural precursor cells; HSCs, hematopoietic stem cells; iPSCs, induced pluripotent stem cells; MS, multiple sclerosis; MSCs, mesenchymal stromal cells; nHSCs, non-hematopoietic stem cells; NSCs, neural stem cells; PPMS, primary progressive multiple sclerosis; ROS, reactive oxygen species; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; VEP, visual evoked potential.

1 | Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease that predominantly affects the central nervous system (CNS). While it shares characteristics with autoimmune disorders, including inflammation, demyelination, and neurodegeneration, MS is not strictly defined as an autoimmune disease due to the absence of a universally accepted autoantigen. The symptoms and their severity differ markedly among individuals, contingent upon the location and degree of the lesions in the CNS [1–3]. MS is a considerable worldwide health issue, distinguished by its diverse prevalence and incidence rates across various locations. The epidemiology of MS has been thoroughly examined, uncovering significant trends and patterns. As of 2020, over 2.8 million individuals globally are affected by MS, resulting in a prevalence rate of about 35.9 per 100000 population. This data demonstrates a rise in prevalence across all global areas since 2013, signifying an escalating public health burden for MS management and resources [4]. The highest prevalence rates are found in high-income regions such as North America (164.6 per 100000), Western Europe (127.0 per 100000), and Australasia (91.1 per 100000). Conversely, the lowest rates are observed in eastern sub-Saharan Africa (3.3 per 100000) and central sub-Saharan Africa (2.8 per 100000). This disparity highlights the influence of socio-economic factors on the epidemiology of MS [5]. Epidemiological studies consistently show that females are approximately twice as likely to be diagnosed with MS compared to males. This gender disparity is particularly pronounced in adult populations, where the ratio can reach up to 3:1 in some regions [6]. The average age of diagnosis for MS is around 32 years, although it can occur at any age, including childhood and adolescence. An estimated 30000 children under the age of 18 are diagnosed with MS globally [6, 7]. Research indicates that the global burden of MS has increased over time, with a recorded 10.4% growth in age-standardized prevalence from 1990 to 2016. The factors contributing to this increase include improved diagnostic techniques, more disease awareness, and maybe a true rise in incidence rates. Additionally, revisions to the McDonald diagnostic criteria—particularly in 2005, 2010, and 2017—have enabled earlier and more sensitive detection of MS, contributing to an increase in reported prevalence even in the absence of a proportional rise in true incidence [5]. In 2019, around 59 345 cases of MS were reported worldwide, resulting in 22 439 deaths. The worldwide burden is measured in disability-adjusted life years (DALYs), which encompass both premature mortality and years lived with disability due to MS [8].

2 | Etiology

The precise etiology of MS remains unidentified; nevertheless, the variables contributing to its pathogenesis are generally classified into three categories: immunological factors, environmental factors, and genetic linkages. Dysimmunity characterized by an autoimmune assault on the CNS is the primary proposed cause of MS. The hypothesized "outside-in" process includes CD4+ pro-inflammatory T cells among several suggested pathways. Researchers propose that an unidentified antigen stimulates and activates Th1 and Th17 cells, resulting in their adhesion to CNS endothelium, traversal of the blood–brain barrier, and ultimately inciting an immunological assault via cross-reactivity. In contrast, the "inside-out" concept posits that an inherent CNS dysfunction initiates and leads to inflammatory-mediated tissue destruction [9, 10]. Environmental influences, including latitudinal gradients in different countries, have been thoroughly examined. Vitamin D deficiency is seen as a potential cause for the observed susceptibility of individuals in higher latitudes to MS. Specific infections, such as the EBV, may potentially have a role in the disease. Complex connections between diverse environmental factors and patient genetics are evident, and current research seeks to elucidate these pathways more thoroughly [9, 11–13]. Individuals having biological relatives diagnosed with MS possess an increased susceptibility to the disease. The presence of a first-degree relative with MS correlates with a 2% to 4% risk of developing the condition, in contrast to a 0.1% risk in the general population. Concordance rates in monozygotic twins range from 20% to 30%, whereas in dizygotic twins, they are 5%. There is a 2% concordance rate between parents and children, which remains 10 to 20 times greater than the risk in the general population [14–16]. The human leukocyte antigen (HLA) DRB1*1501 allele exhibits a substantial correlation with MS and is among the most extensively researched alleles concerning its association with the disease. No discernible Mendelian pattern of genetic inheritance is seen, suggesting the involvement of several genes [17, 18].

3 | MS Subtypes

3.1 | Relapsing–Remitting MS (RRMS)

RRMS constitutes the predominant variant, representing roughly 85% of initial diagnoses. It is marked by episodes of neurological symptoms (relapses) succeeded by intervals of recovery (remissions) (Table 1). During remissions, symptoms may partially or entirely abate, whereas relapses can manifest at irregular intervals with differing intensities [19, 20].

3.2 | Primary Progressive MS (PPMS)

This subtype comprises around 10%–15% of MS cases and is characterized by a progressive deterioration of symptoms from commencement, lacking identifiable relapses or remissions. Patients undergo a gradual increase in handicap, which can be difficult to control owing to the lack of acute episodes [21–23].

3.3 | Secondary Progressive MS (SPMS)

SPMS generally ensues after an initial phase of RRMS. It is marked by a progressive deterioration in neurological function, with or without intermittent relapses. Patients may report a reduction in relapses and a more stable course of symptoms over time [3, 24].

3.4 | Progressive–Relapsing MS (PRMS)

This rare form involves a progressive course from the onset with occasional relapses. It represents about 5% of MS cases and combines features of both progressive and relapsing forms [3].

TABLE 1 | Classification of multiple sclerosis subtypes and characteristics of related signs and tips.

Multiple sclerosis subtypes	Relapsing–remitting multiple sclerosis [25–30]	Secondary progressive multiple sclerosis [31–37]	Primary progressive multiple sclerosis [21, 38–43]	Progressive–relapsing multiple sclerosis [44–48]
Prevalence	~85% of MS patients	~50% of RRMS patients will transition to SPMS	~10%–15% of MS cases	~5% of MS cases
Age of onset	Typically, 20–40 years	Typically develops 10–20 years after RRMS	Typically 40 years and older	Typically 40 years and older
Disease course	Relapses followed by periods of remission	Progressive decline with or without relapses	Steady progression from onset	Steady progression with acute relapses
Relapses	Present (acute flare-ups or exacerbations)	May still occur but become less frequent	Absent (no flare-ups)	Present (relapses with continuous progression)
Remissions	Present (complete or partial recovery)	Less frequent over time	Absent	Absent
Disability progression	Intermittent disability due to relapses	Gradual, continuous disability over time	Gradual, continuous disability from onset	Gradual, continuous disability with relapses
Gender	More common in women (2–3× higher in women)	More common in women	More common in women	More common in women
Symptoms	Fatigue, numbness, vision problems, weakness, cognitive dysfunction, dizziness, muscle spasms	Similar to RRMS, but with a more steady progression of symptoms	Fatigue, muscle weakness, gait problems, vision issues, cognitive decline	Similar to RRMS, but with continuous progression of symptoms
Common initial symptoms	Vision problems (optic neuritis), numbness, fatigue	Similar to RRMS	Difficulty walking, muscle weakness, and fatigue	Similar to RRMS
Current treatment	Disease-modifying therapies (DMTs) like interferons, glatiramer acetate, ocrelizumab, fingolimod, natalizumab	Disease-modifying therapies (for those still experiencing relapses), symptom management	Ocrelizumab (FDA-approved for PPMS), symptom management (pain, mobility aids)	Limited DMT options (Ocrelizumab for some), symptom management
Future treatment	Newer DMTs, including BTK inhibitors, stem cell therapies, remyelination therapies	Stem cell therapies, remyelination treatments, new DMTs	Stem cell and gene therapies, remyelination therapies, neuroprotective treatments	Stem cell therapies, better targeted DMTs
Prognosis	Generally favorable in early stages, though relapses can cause disability	Gradual accumulation of disability with less recovery	Continuous decline in function can lead to significant disability	Similar to PPMS, with relapses complicating the course
Life expectancy	Normal or near-normal life expectancy with treatment	May be slightly reduced with long-term progression	Slightly reduced due to disease progression	Similar to PPMS, life expectancy may be affected by severe disability

(Continues)

TABLE 1 | (Continued)

Multiple sclerosis subtypes	Relapsing–remitting multiple sclerosis [25–30]	Secondary progressive multiple sclerosis [31–37]	Primary progressive multiple sclerosis [21, 38–43]	Progressive–relapsing multiple sclerosis [44–48]
Common complications	Bladder issues, muscle spasticity, vision loss, cognitive changes	Muscle spasticity, difficulty walking, cognitive decline	Severe difficulty walking, cognitive decline, pain	Difficulty walking, bladder and bowel problems, cognitive issues
Impact on quality of life	Highly variable depending on relapse severity	Disability accumulation impacts daily life	Steady decline can lead to significant challenges	Similar to PPMS, with relapses affecting quality of life

This narrative review aims to comprehensively explore the etiology, pathophysiology, current therapeutics, and emerging treatments for PPMS. Although not a systematic review, a rigorous search strategy was employed to ensure broad coverage of relevant literature. PubMed, Scopus, and Web of Science were systematically searched for English-language, full-text articles published between 2010 and 2025, focusing on diagnostic criteria, therapeutic interventions, and mechanistic insights in PPMS. Peer-reviewed original research articles with clearly defined methodologies and data were prioritized, while editorials and non-English publications were excluded. Keywords included combinations of 'primary progressive multiple sclerosis,' 'PPMS pathogenesis,' 'disease-modifying therapies,' and 'biomarkers.' The extracted data were synthesized thematically to identify trends, gaps, and consensus in the field, ensuring a balanced representation of evidence. This approach facilitated a critical appraisal of the evolving PPMS landscape while minimizing selection bias.

4 | PPMS: Characteristics, Challenges, and Diagnosis

PPMS is a specific clinical variant of MS marked by a steady increase in neurological dysfunction from the outset of symptoms, devoid of the typical relapses or remissions observed in other forms of MS. This disorder impacts roughly 10%–15% of patients diagnosed with MS, posing distinct obstacles in both diagnosis and therapy [22, 23, 49]. Unlike with RRMS, both genders are equally impacted, and the average age of onset is typically older, ranging from 37 to 43 years [50]. PPMS involves a gradual worsening of neurological function, leading to mobility difficulties, persistent pain, sensory disturbances, and cognitive impairments. Symptoms may include muscle weakness, spasticity, headaches, numbness, electric shock sensations (Lhermitte's sign), and mood changes [51, 52]. Bowel and bladder dysfunction: impairments in the regulation of these functions. In contrast to relapse types of MS, individuals with PPMS do not encounter discrete exacerbations; rather, their symptoms gradually deteriorate over time. There may be intervals of stability or slight enhancements, although the overarching pattern is one of deterioration [53]. Patients with PPMS exhibit fewer and smaller brain lesions on T2/FLAIR MR sequences, although they tend to have a greater number of lesions in the spinal cord. The inflammatory component is less pronounced in PPMS; hence, gadolinium contrast-enhanced (Gd+)-lesions (active plaques linked to significant blood–brain barrier disruption) occur with reduced frequency. Conversely, diffuse atrophy of the brain and spinal cord is widespread and progresses more rapidly than in RRMS. Advanced neuroimaging techniques elucidate specific facets of CNS injury associated with PPMS [21]. The detection of oligoclonal IgG bands (OCBs) in cerebrospinal fluid (CSF) and their absence in serum, signifying intrathecal IgG production (OCB type 2), is regarded as characteristic of MS, encompassing both relapsing–remitting and progressive forms. Oligoclonal bands (OCBs) in the CSF are observed in up to 90% of individuals with PPMS and are incorporated in the latest iteration of the McDonald diagnostic criteria for this condition [54]. Villar et al. demonstrated that in most patients with PPMS, extra oligoclonal immunoglobulin G bands (OCB) are also present in the serum (type III), in contrast to individuals with RRMS and SPMS.

Comparable results were noted in late-onset MS. This phenomenon may be attributed to an increased propensity for systemic infections and failure of the blood–CSF barrier in older individuals, thereby relating more to aging than to disease-specific mechanisms [21, 55–57].

However, this conventional view is being redefined by advanced imaging techniques. Recent studies have highlighted the importance of cortical and juxtacortical lesions in PPMS, which are frequently underdetected using standard T2/FLAIR sequences. Three-dimensional double inversion recovery (3D-DIR) and phase-sensitive inversion recovery (PSIR) MRI sequences have significantly improved the visualization of cortical demyelination, revealing that cortical lesions are not only more common than previously thought but also closely linked to clinical disability and cognitive impairment in PPMS. These imaging modalities provide higher gray–white matter contrast and suppress CSF signals, enabling the detection of lesions that are otherwise missed. Incorporating such advanced MRI techniques is increasingly critical for accurate disease characterization and may serve as a valuable biomarker for monitoring progression in PPMS patients [58].

5 | Genetic Polymorphisms in PPMS

The genetic variants enumerated in Table 2 may predispose an individual to PPMS or affect the development of the disease. Certain variants are associated with vulnerability, whereas others may influence therapy response or illness severity. A multitude of genes participate in immune system functionality, specifically with the immune system's assault on myelin and neurons in PPMS. Genetic polymorphisms in HLA-DRB1, TNF-α, and IL-7R are strongly associated with vulnerability and illness development. Additional genes such as APOE, TREM2, and Caspase-8 affect neurodegeneration, neuroinflammation, and reparative processes. These factors may hasten illness progression or affect healing. Certain genes, including IFN-β, affect the efficacy of MS therapy in patients, especially in progressive variants of the disease [9, 59].

6 | Molecular Mechanism in PPMS

PPMS is a chronic, neurodegenerative disorder marked by the persistent deterioration of neurological function. In contrast to RRMS, characterized by fluctuating symptoms, progressive MS entails a continuous deterioration, frequently resulting in considerable disability. The intricacy of this disease resides in its multifarious characteristics, wherein immunological and neurodegenerative mechanisms converge and exacerbate the damage within the CNS [95]. A primary immune-related process in MS is the clonal proliferation of B cells, a category of leukocytes. B cells are essential to the immune system, as they generate antibodies and present antigens to other immune cells. In MS, these B cells become dysregulated, resulting in heightened immunological activity within the CNS [96]. This overactivity is associated with antibody synthesis, antigen presentation, and the development of ectopic follicle-like structures (FLS) in the brain and spinal cord. These FLS establish localized areas of inflammation, exacerbating the ongoing immunological assault on brain tissues and ultimately facilitating disease progression [97]. Another immunological mechanism implicated in MS is the development of FLS itself. These structures resemble lymphoid tissues typically seen in the body's lymphatic system; nevertheless, their occurrence in the CNS is atypical. The development of FLS is linked to the release of inflammatory mediators such as IL6, TNF-α, IL10, and IL35. Furthermore, FLS secrete CXCL13, a chemokine that recruits additional B cells to the CNS, thereby sustaining the immunological response. The self-perpetuating cycle of immune cell recruitment and activation in the CNS is a primary catalyst of inflammation in PPMS [98, 99]. The EBV is associated with the pathophysiology of MS, as EBV-infected B cells worsen the disease's progression (Figure 1). These cells are believed to elicit immunological responses that harm brain tissue by activating CD8+ T lymphocytes, a category of immune cells recognized for their cytotoxic properties. CD8+ T lymphocytes secrete pro-inflammatory cytokines, including TNF-α, which can enhance neurotoxicity and result in further brain damage. This inflammatory milieu not only harms neurons but also renders them more susceptible to other neurodegenerative mechanisms [100–102].

New research shows that in PPMS patients, B-cell activity in the CNS can become self-sustaining, continuing even without ongoing EBV activity in the bloodstream. This discovery contradicts the long-standing belief that inflammation in PPMS is solely driven by EBV-activated immune responses outside the CNS. EBV-infected B cells and their interactions with CD8+ T cells help trigger the initial autoimmune attack (Figure 1). However, recent findings indicate that these same processes might also fuel long-term inflammation inside the CNS. In fact, these immune responses within the CNS seem to function independently, suggesting that EBV isn't just involved in starting the disease; it could also help keep it going and drive progression in PPMS. Because of this, treatments that target EBV-infected B cells or adjust the activity of CD8+ T cells in the CNS could be valuable, not just in early disease stages but also later on [103].

Despite the recognition of mitochondrial dysfunction, glutamate excitotoxicity, and neuronal energy failure as central drivers of progression in MS, particularly in SPMS and PPMS, therapeutic strategies directly targeting these mechanisms have faced substantial limitations. A notable phase II clinical trial (MS-SMART) evaluated three neuroprotective agents—amiloride (a sodium–calcium exchanger inhibitor), fluoxetine (a selective serotonin reuptake inhibitor with neurotrophic properties), and riluzole (a glutamate release inhibitor)—in patients with SPMS. The trial found no significant benefit of any agent in slowing brain atrophy or clinical progression compared to placebo [104]. These findings underscore the complexity of targeting neurodegeneration in progressive MS and suggest that monotherapies may be insufficient. Combination strategies or more precise targeting of molecular pathways may be required to achieve meaningful neuroprotection in future trials.

Although both SPMS and PPMS share the feature of progressive neurological decline, they differ significantly in their underlying pathology and response to treatment. SPMS often evolves from RRMS and is characterized by a transition from relapsing inflammation to neurodegeneration. In contrast, PPMS shows a predominantly degenerative course from onset, with less

TABLE 2 | The relationship between various genes, their polymorphisms, and their potential effects on primary progressive multiple sclerosis.

Gene	Polymorphism	Effect on PPMS	Mechanism/function	Refs.
HLA-DRB1	C allele (risk allele)	Increased risk of developing PPMS, associated with disease susceptibility	Major histocompatibility complex, involved in antigen presentation and immune regulation	[59–61]
TNF-A	Various polymorphisms (e.g., −308 G/A)	Increased inflammation and potential influence on disease severity and progression	Regulates immune cell activity and inflammatory response; polymorphisms may enhance neuroinflammation	[62, 63]
IL-7R	A allele (risk allele)	Increased susceptibility to PPMS and faster disease progression	Modulates T-cell differentiation and survival, important in immune responses	[64, 65]
CASPASE-8	C allele (polymorphism in promoter region)	Linked to a more aggressive disease course in PPMS	Involved in apoptosis and immune regulation; dysregulation leads to inflammation and neuronal damage	[66, 67]
CD40	Various polymorphisms (e.g., −1,6 C/T)	Associated with a more severe disease course and may affect immune response to MS therapies	Key in immune cell activation and antigen presentation; polymorphisms may increase autoimmunity	[68–71]
APO E	ε4 allele	Increases risk of PPMS and correlates with faster disease progression	Involved in lipid metabolism, neural repair, and neuroprotection. The ε4 allele is associated with neurodegeneration	[72–74]
VDR	Various polymorphisms (e.g., FokI, BsmI)	Linked to susceptibility to MS and may influence PPMS onset and progression	Regulates immune function; vitamin D deficiency is implicated in autoimmune disease exacerbation	[75–77]
OMG	Various polymorphisms	Linked to myelin damage and neurodegeneration in PPMS	OMG is involved in myelin integrity. Genetic variation may affect susceptibility to myelin breakdown in MS	[78]
TREM2	Various polymorphisms	Linked to disease progression, especially in progressive forms like PPMS	Involved in microglial activation and immune response, playing a role in neuroinflammation and neurodegeneration	[79, 80]
CX3CR1	Various polymorphisms (e.g., V249I)	Associated with altered immune responses, particularly in progressive MS forms	Important for microglial and neuronal communication, influencing neuroinflammation in MS	[81, 82]
FAS/FAS (APOPTOSIS PATHWAY)	Various polymorphisms	Associated with disease severity and apoptosis regulation in PPMS	Regulates apoptosis of immune cells; polymorphisms may lead to prolonged immune activation and neuronal damage	[83–85]

(Continues)

TABLE 2 | (Continued)

Gene	Polymorphism	Effect on PPMS	Mechanism/function	Refs.
IL-10	−1082 G/A, −819 C/T	Protective in PPMS, it may reduce disease progression through anti-inflammatory effects	Anti-inflammatory cytokine; polymorphisms may influence the balance of inflammation in the CNS	[67, 86]
NOD2	R702W, G908R, 3020insC	Inflammatory role linked to susceptibility to MS and disease progression in PPMS	Involved in immune recognition of bacterial components and regulation of inflammation	[87, 88]
IL-2RA	Various polymorphisms	Linked to immune dysfunction and potential role in PPMS susceptibility	Plays a role in T-cell differentiation and immune response. Certain polymorphisms affect immune regulation in MS	[89–91]
SLC22A4	−167C/T, +1796A/G	Increased risk for MS and PPMS, especially in the presence of infections	Involved in the transport of organic cations, including drugs, and immune function regulation	[91, 92]
PRKCB	Various polymorphisms	May affect inflammation and neurodegeneration in PPMS	Regulates immune signaling pathways, which are important in autoimmune responses and CNS inflammation	[93, 94]

Abbreviations: APO E, apolipoprotein E; CX3CR1, fractalkine receptor; IL-10, interleukin-10; IL-2RA, interleukin-2 receptor alpha; IL-7R, interleukin-7 receptor; NOD2, nucleotide-binding oligomerization domain 2; OMG, oligodendrocyte myelin glycoprotein; PRKCB, protein kinase C beta; SLC22A4, solute carrier family 22; TNF-α, tumor necrosis factor-α; TREM2, triggering receptor expressed on myeloid cells 2; VDR, vitamin D receptor.

pronounced inflammation and fewer gadolinium-enhancing lesions on MRI. These differences influence therapeutic efficacy. For instance, anti-inflammatory agents such as fingolimod have shown efficacy in SPMS but have failed to meet primary endpoints in PPMS trials, suggesting lower inflammatory activity in PPMS as a limiting factor for immunomodulatory treatments [105]. Ocrelizumab remains the only FDA-approved drug for PPMS, while options such as simvastatin and high-dose biotin have been more extensively tested in SPMS with partial success [106]. Recent findings also underscore distinct mechanisms of progression, with cortical demyelination, meningeal inflammation, and smoldering microglial activity being more prominent in PPMS [107]. As a result, personalized approaches tailored to each subtype's pathophysiology are crucial, and future therapies may benefit from targeting neurodegeneration and remyelination more aggressively in PPMS compared to SPMS [108].

Microglia, the resident immune cells of the CNS, also contribute significantly to PPMS. Upon activation, microglia secrete various pro-inflammatory cytokines, such as IL1, IL6, and TNF-α, which exacerbate chronic inflammation in the CNS. Moreover, microglia generate reactive oxygen species (ROS) and nitric oxide (NO), resulting in oxidative stress and subsequent neuronal injury. The persistent activation of microglia is thought to induce continuous inflammation in the brain, leading to the progressive deterioration of neuronal structures [21, 109–111]. Astrocytes, supporting cells in the brain, represent another cell type that becomes activated in MS, hence exacerbating the condition. Activation of astrocytes results in the synthesis of inflammatory cytokines and chemokines, including CCL2, CCL5, and IP10, which promote the infiltration of more immune cells into the CNS. This disrupts the blood–brain barrier, permitting peripheral immune cells to infiltrate the brain and amplify the immunological response. The aggregation of immune cells and persistent release of pro-inflammatory substances establish an environment that is extremely detrimental to neurons [112–114]. Recent TSPO-PET imaging breakthroughs have significantly advanced our comprehension of persistent inflammation in progressive MS [115]. These sophisticated scans primarily detect activated microglia and macrophages, with astrocytic involvement playing a secondary role [116]. The technology vividly demonstrates the CNS's ongoing, low-intensity immune activation—what researchers now term “smoldering inflammation”. This chronic inflammatory signature differs markedly from RRMS's acute flare-ups [117]. In PPMS, inflammation spreads more subtly, concentrating near gradually enlarging lesions. Clinically, this insidious process appears closely tied to the disease's relentless progression and accumulating disability [118]. Beyond its diagnostic value, TSPO-PET offers two crucial benefits: it precisely locates these inflammatory hotspots and validates microglia-modulating therapies as promising strategies to protect the CNS from progressive deterioration in PPMS [119, 120].

Figure 2 illustrates the presence of ELFs in the meninges of the CNS and their correlation with demyelination and neurodegeneration in PPMS. It elucidates the anatomical layers of the CNS, the composition of extracellular fluid, and their involvement in chronic inflammation and localized immune responses that lead to neuronal injury. Besides immunological pathways, neurological processes significantly contribute to the progression of MS. Mitochondrial damage is a significant characteristic, as

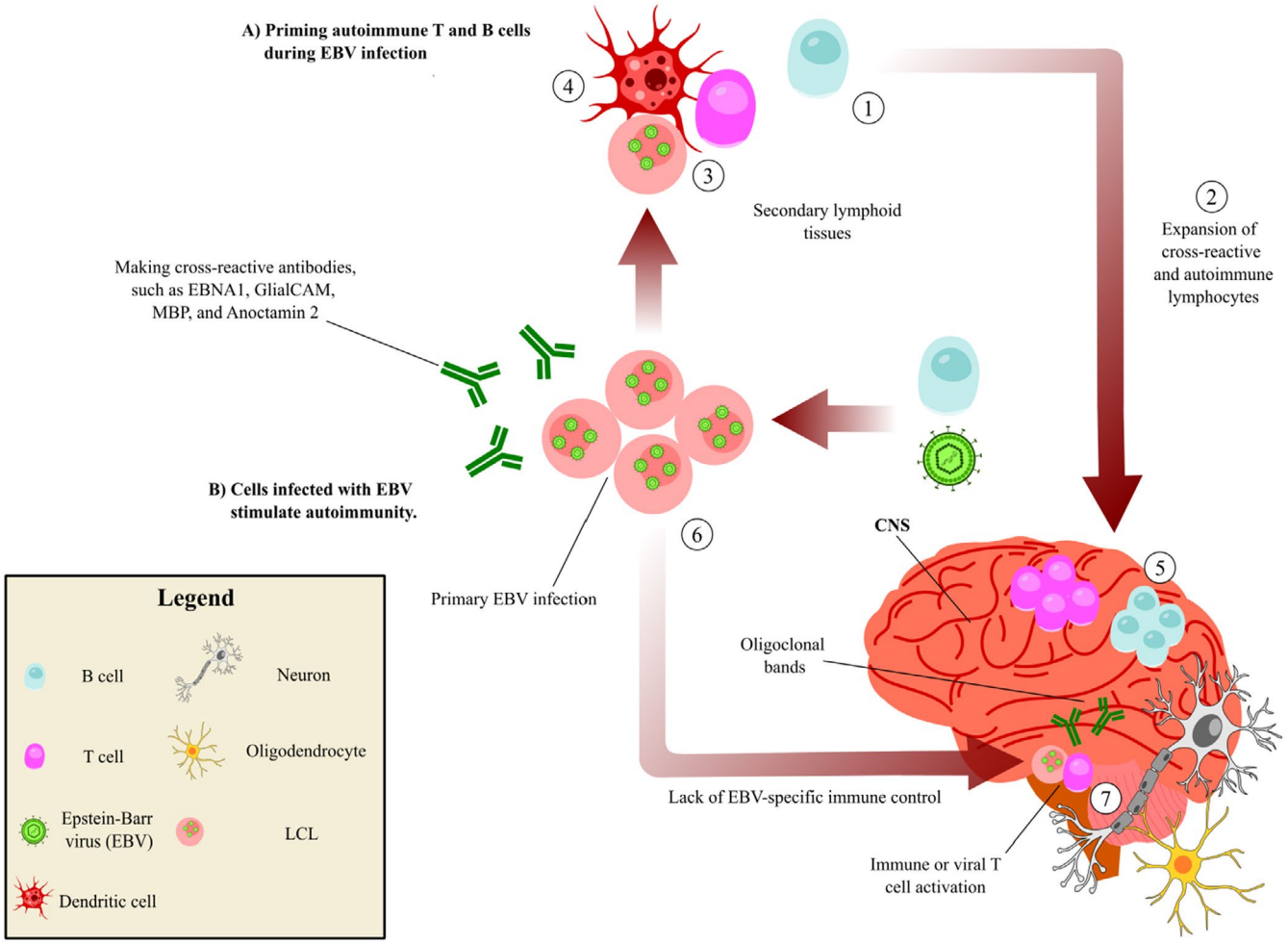

FIGURE 1 | Proposed method via which EBV infection facilitates the onset of PPMS. This diagram emphasizes two key pathways: Autoimmune T-cell and B-cell priming during EBV infection: EBV infects B cells and dendritic cells in secondary lymphoid organs (step 1), resulting in the proliferation of autoreactive and cross-reactive lymphocytes (step 2). These cells translocate to the CNS, where they initiate additional immune activation (step 3). Stimulation of autoimmunity by EBV-infected cells: EBV-infected cells generate antigens, including EBNA1, that exhibit cross-reactivity with neural proteins (e.g., GlialCAM, MBP, or anoctamin 2), leading to the production of antibodies that target the CNS (step 4). This autoimmune response leads to the loss of immunological regulation over EBV and the persistence of infected B cells in the CNS (step 5). Within the CNS, the sequence progresses with the generation of oligoclonal antibody bands and T-cell activation, resulting in direct harm to neurons and oligodendrocytes (step 6). Chronic inflammation and persistent inflammatory reactions ultimately result in axonal injury, demyelination, and neurodegeneration, which are characteristic features of PPMS pathology (step 7). The figure elucidates the involvement of EBV in the onset and maintenance of CNS-specific autoimmunity, offering insights into its possible contribution to the progression of PPMS.

mitochondria are essential for generating the energy required for neuronal function. Mitochondrial function is compromised in MS, resulting in the dysfunction of critical cellular functions such as the sodium-potassium ATPase pump. This disruption results in an imbalance of sodium and calcium ions, further disrupting neurons and contributing to their demise. The energy deficit caused by mitochondrial impairment makes neurons increasingly vulnerable to harm [121–124]. Another neurodegenerative mechanism involves the release of iron from damaged oligodendrocytes, the cells responsible for insulating neurons with myelin. Iron, when unbound, can promote the production of detrimental free radicals, exacerbating oxidative stress in the CNS. This oxidative stress causes additional damage to neural structures, worsening neurodegeneration. The release of iron in this manner underscores the intricate interplay between cellular damage and inflammation in the advancement of MS [121, 125–127]. Abnormal distribution of ion channels is another factor leading to neurodegeneration associated with MS. The reallocation of sodium channels in neurons elevates the energy requirements necessary for sustaining cellular homeostasis. Nonetheless, mitochondrial malfunction restricts energy production, preventing neurons from fulfilling this requirement, which results in additional injury and impairment. This imbalance intensifies neuronal susceptibility to injury, ultimately affecting neural signaling and facilitating disease development [128–130]. Glutamate excitotoxicity is a neurotoxic mechanism that exacerbates neuronal injury in PPMS. Glutamate is an excitatory neurotransmitter that, in surplus, can excessively activate neurons and result in cellular apoptosis. In MS, elevated glutamate concentrations result in calcium influx into neurons, initiating a series of deleterious cellular mechanisms. Excitotoxicity is especially detrimental in the context of MS, where neurons are already compromised by inflammation and energy deficiencies, resulting in expedited neurodegeneration [131–133].

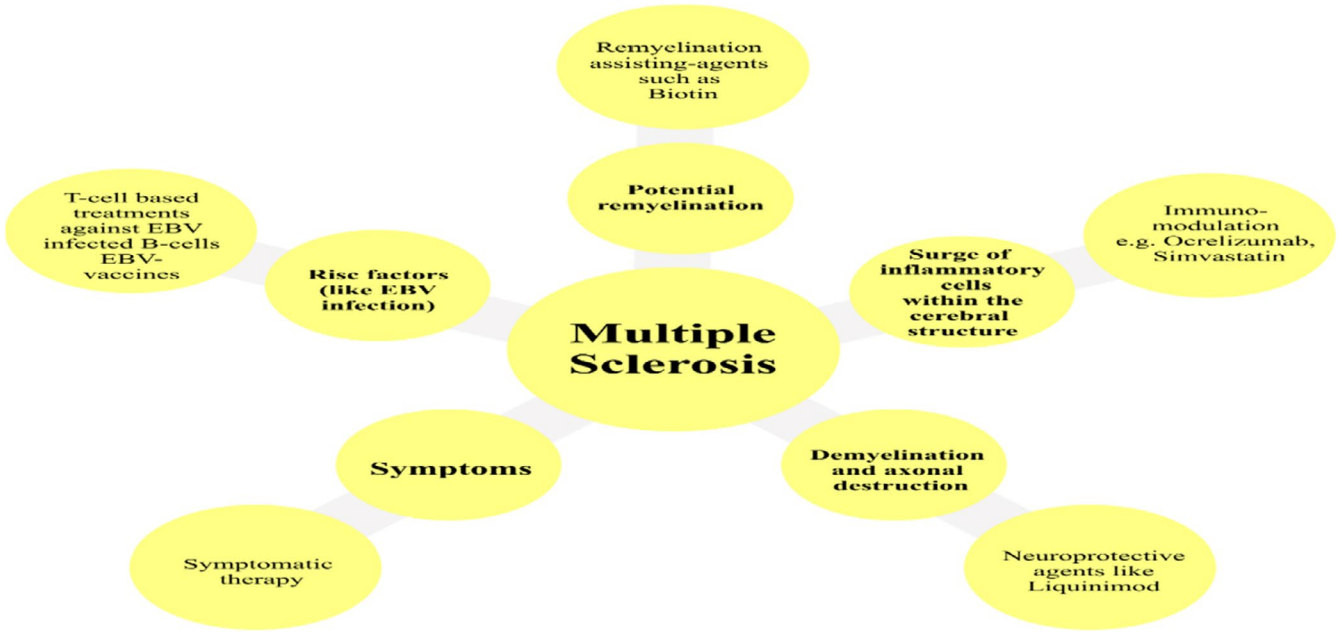

FIGURE 2 | Overview of the disease progression and therapeutic strategies in PPMS. The upper row outlines the key stages in disease development, including risk factors such as EBV infection, the influx of inflammatory cells into the brain, demyelination and axonal damage, the onset of clinical symptoms, and the possibility of remyelination. The lower row highlights corresponding therapeutic approaches targeting each stage: T-cell-based treatments against EBV-infected B cells and potential EBV vaccines; immunomodulation therapies, such as ocrelizumab and simvastatin, to reduce inflammation; neuroprotective agents, such as laquinimod, to minimize axonal damage; symptomatic treatment to manage clinical manifestations of the disease; and remyelination-supporting agents, such as biotin, to promote repair of damaged myelin. This figure emphasizes the need for a multifaceted therapeutic approach addressing both the underlying pathology and symptomatic burden of PPMS [42]. EBV, Epstein–Barr virus; PPMS, primary progressive multiple sclerosis.

The advancement of MS entails a confluence of immunological effector mechanisms and neurodegenerative processes that collectively lead to a gradual deterioration in neurological function. B cells, CD8+ T cells, microglia, and astrocytes instigate inflammation, whereas mitochondrial damage, iron release, and glutamate excitotoxicity result in direct neuronal injury. Comprehending these systems offers insights into possible treatment targets that may mitigate the course of MS by diminishing inflammation and safeguarding neurons from harm [134–137].

7 | Current Treatments (Table 3)

7.1 | Ocrelizumab

Ocrelizumab is a humanized monoclonal antibody that specifically targets CD20-expressing B cells and is authorized for the treatment of both relapsing forms and PPMS. The efficacy of this treatment in PPMS has been validated by multiple clinical trials, notably the ORATORIO experiment, which showed substantial advantages in postponing disease progression relative to placebo. The ORATORIO trial included 732 individuals with PPMS, who were randomized to receive either ocrelizumab or a placebo. Results demonstrated that ocrelizumab diminished the likelihood of verified disability advancement by roughly 24% at 12 weeks and 25% at 24 weeks in comparison to placebo [138–140]. In a prolonged follow-up, ocrelizumab consistently showed advantages, evidenced by diminished rates of progression to wheelchair dependence and maintained impairment over extended durations [139, 141]. Retrospective research examined data from individuals administered ocrelizumab who did not meet the ORATORIO eligibility criteria. It was determined that patients under the age of 65 also derived advantages from treatment, indicating that ocrelizumab may be efficacious in middle-aged populations with extended disease durations [140]. Ocrelizumab therapy has demonstrated a substantial reduction in MRI-detected disease activity in individuals with MS. A phase II trial showed that ocrelizumab considerably decreased the incidence of new T1 gadolinium-enhancing lesions by week 4 compared to placebo ($p = 0.042$) and also markedly reduced the number of new or expanding T2 lesions by week 8 (both $p < 0.001$). This indicates a fast attenuation of MRI activity subsequent to the commencement of treatment [142]. A systematic analysis indicated that ocrelizumab likely leads to a significant decrease in the number of participants with new or expanding T2-hyperintense lesions on MRI compared to interferon beta-1a, demonstrating its efficacy in alleviating overall disease burden [143]. Research indicated that ocrelizumab medication resulted in an 89% decrease in gadolinium-enhancing lesions relative to placebo at week 24 ($p < 0.0001$), demonstrating substantial efficacy in diminishing MRI-detected disease activity [144]. Another analysis highlighted that ocrelizumab significantly decreased new MRI lesion counts to almost imperceptible levels and consistently lowered annualized relapse rates (ARR) across many exposure groups, hence validating its efficacy in alleviating disease development. These trials collectively demonstrate that ocrelizumab is linked to substantial decreases in MRI-detected disease activity, including a reduction

TABLE 3 | Current drug treatments for primary progressive multiple sclerosis.

Drug	Class	FDA approval	Mechanism of action	Effectiveness	Administration	Side effects	Notes	Refs.
Ocrelizumab (Ocrevus)	Monoclonal antibody	Yes (2017)	Targets CD20+ B cells, modulating immune activity and reducing inflammation	Reduces disease progression, improves walking, and decreases relapses	Intravenous (IV) every 6 months	Infusion reactions, respiratory infections, headache, nausea	First and only FDA-approved drug for PPMS Highly effective in slowing progression and improving motor function	[138, 166–169]
Methotrexate	Immunosuppressant	No	Inhibits folate metabolism, suppresses immune system activity	Mixed results; less effective for PPMS, not a first-line treatment	Oral or subcutaneous (weekly)	Nausea, liver toxicity, fatigue, mouth sores	Used off-label for progressive forms of MS	[170–172]
Mitoxantrone	Immunosuppressant	No	Inhibits DNA synthesis and suppresses immune system activity	Limited benefit in PPMS, can reduce relapse rates but has long-term toxicity	Intravenous (IV) (every 3 months)	Cardiotoxicity, nausea, fatigue, hair loss	Limited use due to serious side effects	[173–176]
Corticosteroids (e.g., prednisone)	Anti-inflammatory	No (used off-label)	Suppresses inflammation and modulates immune response	Used for acute flare-ups, not effective for long-term disease progression	Oral or intravenous (IV)	Weight gain, mood swings, hypertension, infection risk	Typically used for short-term symptom management during flare-ups	[176]
Symptom-specific medications	—	No	Varies depending on symptom (e.g., spasticity, pain, fatigue)	Helps manage specific symptoms (e.g., pain, fatigue, spasticity)	Oral, IV, or topical (varies)	Varies (e.g., drowsiness, dizziness, gastrointestinal issues)	Includes medications like baclofen, modafinil, and gabapentin for symptom relief	[177–179]
Cladribine (Mavenclad)	Purine nucleoside analog	No (approved for RRMS)	Inhibits DNA synthesis and reduces B and T-cell activity	No significant benefit in PPMS; approved for RRMS, mixed results for PPMS	Oral (two courses per year)	Decreased white blood cells, headache, nausea	Typically used for RRMS, but may be considered off-label for PPMS	[180–183]

in new lesions and total disease burden relative to placebo [145]. Ocrelizumab, the first disease-modifying therapy specifically approved for PPMS, received FDA approval in 2017 and signifies a substantial progression in its treatment. It effectively reduces disability progression and MRI activity while maintaining a tolerable safety profile. Given its demonstrated efficacy across various patient demographics, including those outside traditional clinical trial criteria, ocrelizumab may offer substantial benefits for many individuals suffering from PPMS [139, 140].

7.2 | Biotin

High-dose biotin, also known as MD1003, has been investigated as a potential treatment for PPMS. This vitamin is involved in myelin repair and brain energy metabolism, both of which are essential for mitigating neurodegeneration linked to progressive types of MS. Preliminary pilot trials indicated that high-dose biotin may enhance functionality in individuals with progressing MS. A noteworthy trial indicated that 12.6% of individuals administered MD1003 experienced substantial disability reversal, but none in the placebo cohort did [146]. The phase III SP12 experiment sought to validate these preliminary results with an expanded cohort of 642 people. Nevertheless, the results demonstrated that MD1003 failed to achieve its primary goals concerning the reversal of functional disability, as assessed by the expanded disability status scale (EDSS) or walking speed during a 12-month period [146]. High-dose biotin was predominantly well tolerated, with side events occurring at comparable rates in both treatment and placebo groups. However, certain patients had worse symptoms while using biotin, prompting doubts over its overall effectiveness [147, 148]. Biotin is thought to stimulate essential enzymes that facilitate myelin synthesis and cellular energy production. Enhancing these processes, high-dose biotin may theoretically facilitate myelin repair and enhance neuronal function, potentially decelerating disease progression. Notwithstanding the initial promise demonstrated in smaller studies, the bigger phase III trials have failed to validate the efficacy of high-dose biotin for the treatment of PPMS. The absence of substantial enhancement in clinical outcomes, along with accounts of symptom aggravation in certain individuals, has resulted in a prudent approach to its application in clinical practice [147, 149].

7.3 | Simvastatin

Simvastatin, generally recognized as a cholesterol-lowering agent, has been investigated for its possible advantages in the treatment of PPMS. Although the majority of clinical research has concentrated on SPMS, the ramifications for PPMS are significant due to the drug's neuroprotective and anti-inflammatory characteristics [150, 151]. Simvastatin is believed to operate by multiple mechanisms, including the lowering of cholesterol levels, which may contribute to the stabilization of cell membranes and the attenuation of inflammation. Furthermore, it exhibits anti-inflammatory properties by obstructing the activation and migration of T cells into the CNS, a mechanism vital to the pathophysiology of MS. Moreover, simvastatin may confer neuroprotection, potentially decelerating neurodegeneration in progressive forms of MS by safeguarding neurons from injury [150, 152–154]. The MS-STAT trial was a Phase II study primarily targeting SPMS, although it offers information pertinent to PPMS. This trial involved 140 patients who were administered either 80 mg of simvastatin daily or a placebo during a two-year period. Results demonstrated a 43% decrease in brain atrophy relative to the placebo group. Enhancements in disability scores, as assessed by the EDSS, and quality of life indicators were observed, although cognitive assessments revealed no significant disparities between groups [155, 156]. Simvastatin has demonstrated potential in diminishing brain atrophy and enhancing quality of life metrics in PPMS. Nonetheless, its efficacy in modifying illness development remains unsubstantiated according to recent extensive investigations concentrating on SPMS. Additional research is required to investigate its potential advantages specifically for patients with PPMS [150, 155, 157].

7.4 | Fingolimod

Fingolimod, an oral sphingosine 1-phosphate receptor modulator, has been studied for its possible application in the treatment of PPMS. The INFORMS study was a multicenter, double-blind, placebo-controlled experiment assessing the efficacy and safety of fingolimod in individuals with PPMS. Notwithstanding its recognized advantages in RRMS, the trial revealed that fingolimod did not markedly impede disease progression in PPMS patients relative to placebo. The principal outcome, evaluating confirmed disability progression over a three-month period, revealed no significant difference between the fingolimod and placebo cohorts (hazard ratio 0.95; $p = 0.544$). Fingolimod exhibited certain anti-inflammatory effects; however, it did not substantially influence brain volume loss (BVL) in individuals with PPMS. This indicates that the pathophysiological mechanisms underlying BVL in PPMS may differ from those in RRMS, where fingolimod has demonstrated more pronounced effects [157]. The safety profile of fingolimod in the INFORMS study aligned with prior trials in relapse MS. Adverse events comprised lymphopenia and bradycardia; nevertheless, the overall infection rates were comparable between the fingolimod and placebo cohorts. The results of the INFORMS study demonstrate that although fingolimod is efficacious for RRMS, its effectiveness in PPMS is constrained. The study determined that various therapeutic approaches may be required for the management of PPMS as opposed to relapse-onset MS, owing to the unique pathophysiological features of these disease variants [158, 159].

7.5 | Coenzyme Q10 (CoQ10)

Coenzyme Q10 (CoQ10) has attracted interest as a prospective therapy for PPMS owing to its antioxidant properties and capacity to diminish oxidative stress, a factor involved in the pathogenesis of MS. Although the majority of research has concentrated on RRMS, growing data indicate that CoQ10 may also be advantageous for people with PPMS [160–162]. CoQ10 is recognized for its vital role in mitochondrial activity and energy production, in addition to serving as a powerful antioxidant. Research indicates that oxidative stress plays a substantial role in the pathogenesis of MS by harming neuronal cells. CoQ10 administration can improve the scavenging efficacy against reactive oxygen species and mitigate oxidative damage

in individuals with MS [160]. Besides its antioxidant capabilities, CoQ10 has been linked to a transition toward a more anti-inflammatory condition in the body. This includes decreases in pro-inflammatory cytokines, including TNF-α and interleukin-6 (IL-6), which are frequently increased in MS patients. CoQ10 may improve certain symptoms associated with PPMS by reducing inflammation [163, 164]. Although direct research on CoQ10 for PPMS is limited, numerous trials involving MS patients offer insights into its possible advantages. A randomized controlled experiment showed that CoQ10 supplementation at 500 mg/day effectively alleviated fatigue and depressed symptoms in patients with MS. This is especially pertinent for people with PPMS, who frequently endure these incapacitating symptoms [164, 165]. A further study indicated that CoQ10 supplementation resulted in substantial reductions in inflammatory markers such as TNF-α and IL-6 in patients with MS. These data indicate that CoQ10 may assist in managing the inflammatory aspect of PPMS [162, 163]. Studies indicate that CoQ10 can reduce oxidative stress markers and enhance overall clinical severity in MS patients receiving traditional treatments such as interferon beta. While this research predominantly focused on RRMS, the fundamental mechanisms are probably relevant to PPMS [160].

7.6 | MitoQ

MitoQ is a modified variant of CoQ10 engineered for enhanced mitochondrial targeting [184]. This targeting is accomplished via a lipophilic triphenylphosphonium cation that improves its absorption into mitochondria, enabling it to efficiently mitigate oxidative stress and safeguard against mitochondrial damage. Considering that oxidative stress is a pivotal element in the neurodegeneration linked to PPMS, MitoQ's mechanism indicates it may contribute to alleviating these consequences [185–187]. Studies demonstrate that patients with PPMS display elevated ROS and diminished antioxidant levels, which contribute to neurodegeneration [122, 188]. MitoQ may mitigate one of the fundamental difficulties in PPMS by potentially diminishing oxidative stress via its antioxidant qualities. Research indicates that mitochondrial dysfunction is associated with elevated ROS production in MS patients, implying that therapy aimed at enhancing mitochondrial health may be advantageous [122, 189].

7.7 | Idebenone

Idebenone, a synthetic analogue of CoQ10, has been explored as a mitochondrial-targeting antioxidant with potential benefit in neurodegenerative conditions. However, no major clinical trials have been conducted specifically for PPMS to date. Most available data derive from studies in other neurological disorders or in RRMS populations. While its favorable safety profile supports further exploration, current evidence does not establish any proven clinical benefit of idebenone in PPMS patients. Therefore, idebenone remains an experimental option for PPMS, requiring targeted research to clarify its role, if any, in this progressive MS subtype.

Idebenone, a synthetic derivative of CoQ10, has been investigated for its possible application in the treatment of PPMS. Idebenone is recognized for its antioxidant effects and its capacity to improve mitochondrial activity. It is believed to potentially enhance energy metabolism in neurons, which may be advantageous in neurodegenerative disorders such as MS. Nonetheless, despite these theoretical advantages, practical evidence substantiating its efficacy specifically for PPMS is still scarce. Currently, research is underway to examine idebenone's involvement in numerous neurological illnesses; however, specialized large-scale trials targeting PPMS are necessary to definitively prove its efficacy. The current research indicates that although idebenone may be safe for this population, it does not substantially impact disease progression. Its advantageous safety profile renders it a possibility for further exploration; nevertheless, more rigorous clinical trials are needed to ascertain its potential therapeutic efficacy in this patient population [190, 191].

7.8 | Plasmapheresis

Plasmapheresis, or plasma exchange, has been studied for its possible efficacy in treating PPMS. Plasmapheresis entails the extraction of plasma from the bloodstream, which encompasses several proteins, including antibodies that may play a role in autoimmune mechanisms. The plasma is subsequently substituted with a replacement, such as albumin or fresh frozen plasma. This procedure seeks to diminish the concentrations of deleterious chemicals in circulation that may be aggravating neurological injury [192–194]. The use of plasmapheresis for PPMS is experimental. Evidence indicates that the elimination of autoantibodies and pro-inflammatory cytokines may impede advancement in PPMS; nevertheless, the advantages remain contentious and inadequately substantiated by extensive research. The concept posits that plasmapheresis may mitigate the autoimmune activity implicated in MS pathophysiology by eliminating plasma components such as IgG antibodies, complement proteins, or other inflammatory agents. The direct involvement of these immune components in the neurodegenerative process of PPMS remains contentious, as PPMS is believed to be mostly neurodegenerative rather than primarily inflammatory in nature. Nonetheless, there is inadequate evidence from extensive, randomized, controlled trials to endorse plasmapheresis as a conventional treatment for PPMS [195, 196].

7.9 | Anti-LINGO-1

Anti-LINGO-1 (opicinumab) is a monoclonal antibody studied for its potential to facilitate remyelination and safeguard axons in individuals with PPMS. This method focuses on LINGO-1, a protein that obstructs the development of myelin, the protective layer around nerve fibers that is compromised in MS. LINGO-1 is known to play a significant role in inhibiting oligodendrocyte differentiation and myelination. By blocking LINGO-1, anti-LINGO-1 aims to facilitate the repair of myelin and improve neurological function [197–199]. The phase 2 RENEW trial and its two-year follow-up (RENEWED) assessed the efficacy of opicinumab (anti-LINGO-1) in patients with first-episode acute optic neuritis. While no statistically significant differences were observed in full-field visual evoked potential (VEP) latency between treatment and placebo groups in either intention-to-treat or per-protocol populations, exploratory analysis using

multifocal VEP indicated a nominally significant improvement with opicinumab. Overall, opicinumab showed modest signs of remyelination activity, but results should be interpreted cautiously due to small sample size and study design limitations [200].

7.10 | Ibudilast

Ibudilast is an emerging treatment for PPMS, presently undergoing clinical studies. The drug's mechanism of action encompasses the suppression of leukotriene activity, phosphodiesterases, and nitric oxide synthase [25]. Ibudilast functions by obstructing multiple cellular signaling pathways linked to inflammation and neurodegeneration. It inhibits pro-inflammatory cytokines, including IL-1β, TNF-α, and IL-6, while perhaps augmenting anti-inflammatory responses [201]. The SPRINT-MS trial was a crucial Phase II randomized, placebo-controlled study involving patients with both PPMS and SPMS. The trial included 255 patients, consisting of 134 with PPMS and 121 with SPMS, and extended over a duration of 96 weeks. Key findings demonstrated that ibudilast therapy resulted in a 48% decrease in brain atrophy relative to placebo. The therapy impact was notably significant in patients with PPMS, with statistical analysis indicating a substantial difference in brain shrinkage rates ($p < 0.01$). The impact on SPMS patients was not statistically significant ($p = 0.97$) [201, 202]. Adverse symptoms commonly reported in the trials encompassed gastrointestinal disturbances, including nausea, diarrhea, and abdominal pain, and psychological manifestations such as melancholy and exhaustion [201]. Ibudilast demonstrates potential as a therapeutic intervention for PPMS, especially in decelerating cerebral atrophy and maybe enhancing neuroprotection. Nonetheless, additional research, encompassing larger Phase III trials, is essential to validate its efficacy and safety profile in this patient demographic [203].

8 | Neuromodulation Therapies

Neuromodulation therapies operate through multiple pathways, such as the increase of neuroplasticity, modulation of pain, and management of mood. These therapies can facilitate alterations in brain structure and function, aiding the nervous system in adapting to damage induced by MS. Neuromodulation aids in the management of chronic pain frequently seen by MS patients by modifying pain pathways. Moreover, numerous approaches exhibit antidepressant effects, which are especially significant considering the elevated incidence of depression in MS populations [204, 205]. Neuromodulation therapies such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), cranial nerve non-invasive neuromodulation (CN-NINM), and electroconvulsive therapy (ECT) can be effective [203, 206, 207].

9 | Gene Therapy

Gene therapy has shown significant promise in preclinical studies using animal models to investigate potential treatments for MS. The most extensively used animal model for studying MS is experimental autoimmune encephalomyelitis (EAE), which mimics key pathological features of MS, including demyelination, inflammation, and axonal damage. Induced in rodents such as mice and rats, EAE enables researchers to evaluate the effectiveness of gene therapy in mitigating immune-mediated myelin degradation and facilitating brain healing. Research indicates that the administration of genes producing anti-inflammatory cytokines, such as interleukin-4 (IL-4) or IL-10, might mitigate illness severity in EAE models, offering substantial support for immune modulation tactics [208–210]. IL-21 is pivotal in the immunopathogenesis of MS. IL-21 and its receptor are expressed on CD4 T cells in the CNS lesions of MS patients, underscoring their role in the disease process. Increased IL-21 mRNA expression is noted during inflammatory relapses, suggesting a correlation between this cytokine and disease exacerbations. Moreover, elevated levels of IL-21-producing CD4 T cells are present in the cerebral fluid of individuals with PPMS, indicating that IL-21 may significantly contribute to disease development [211, 212]. A treatment strategy including gene therapy with a soluble IL-21 receptor (sIL21R) administered through adeno-associated vectors (AAV) has been investigated to inhibit IL-21 signaling. The prophylactic treatment of AAV8.sIL21R in animal models of EAE, a murine model of MS, exhibited protective effects. The findings encompassed a decrease in disease frequency, enhanced histopathology results, and an alteration of the immunological profile, suggesting that inhibiting IL-21 signaling may represent a viable approach for modifying the immune response and averting disease progression in MS [211]. Besides direct gene transfer, the genetic modification of immune cells is a promising strategy for the treatment of MS. Researchers have modified regulatory T cells (Tregs) to overexpress particular genes that augment their capacity to inhibit pro-inflammatory responses. Gene-modified Tregs that express IL-35 or TGF-β have demonstrated the ability to diminish inflammation and enhance immunological tolerance in EAE mice. This method not only mitigates the autoimmune reaction but also reorients the immune system toward a state of balance, potentially averting relapses and improving long-term disease management [209, 213, 214]. Gene therapy shows potential for safeguarding neurons and maintaining axonal integrity, both essential for sustained functionality in MS. In animal models, neuroprotective medicines have utilized the administration of genes that encode anti-apoptotic factors, such as B-cell lymphoma 2 (Bcl-2), or antioxidant enzymes like superoxide dismutase (SOD). These medicines have demonstrated efficacy in decreasing neuronal mortality and oxidative stress, hence alleviating neurological impairments. The efficacy of these therapies in EAE models highlights the promise of gene therapy in tackling both the immune-mediated and neurodegenerative components of MS [215–218]. Facilitating remyelination is an essential objective of gene therapy in the treatment of MS. Initiatives to induce oligodendrocyte precursor cells (OPCs) to develop into myelin-producing cells have demonstrated potential in animal models. Genes such as platelet-derived growth factor-alpha (PDGF-α) and fibroblast growth factor-2 (FGF-2) have been utilized to enhance oligodendrocyte precursor cell proliferation and differentiation in experimental autoimmune encephalomyelitis models [215, 219]. Furthermore, the administration

of remyelination-enhancing agents, such as insulin-like growth factor-1 (IGF-1), has been shown to expedite myelin restoration and enhance motor function in the subjects receiving treatment. These findings underscore the potential of gene therapy to regenerate destroyed myelin in MS and enhance neurological outcomes [215, 220]. The emergence of gene-editing technologies, such as CRISPR-Cas9, has expanded the horizons of gene therapy research in MS. In animal models, CRISPR has been employed to inhibit pro-inflammatory genes or to introduce protective genes into targeted cell populations. CRISPR-mediated modification of immune cells to diminish the expression of harmful cytokines such as interferon-gamma (IFN-γ) has resulted in decreased disease activity in EAE models. The accuracy of gene editing facilitates tailored interventions, reducing off-target effects and enhancing the safety profile of gene therapies for MS [219, 221–223]. One of the major challenges in gene therapy is the effective delivery of therapeutic genes to the CNS, especially due to the existence of the blood–brain barrier (BBB). Animal models have been essential for investigating innovative gene delivery techniques. Intrathecal and intracerebral injections have been evaluated in EAE models to circumvent the blood–brain barrier and enhance gene expression in the CNS. Moreover, researchers are exploring nonviral delivery technologies, including nanocarriers and lipid nanoparticles, to augment gene transfer efficiency, diminish immunogenicity, and enhance overall safety. The improvements in gene delivery methods are crucial for transitioning gene therapy from animal models to human applications [224–226]. The efficacy of gene therapy can be enhanced when integrated with additional treatment modalities, such as stem cell therapy or established pharmacological interventions. Research involving animals has investigated the interaction between gene therapy and mesenchymal stem/stromal cell (MSC) transplantation, revealing that gene therapy augments the reparative capabilities of MSCs. Likewise, the integration of gene therapy with disease-modifying therapies (DMTs) such as natalizumab or ocrelizumab has demonstrated synergistic effects in diminishing disease activity in EAE models. These combination therapies may facilitate future multimodal treatment strategies for MS [227–231]. A critical question in gene therapy research pertains to its long-term safety and efficacy. Longitudinal studies in animal models have assessed the durability of therapeutic gene expression and possible adverse effects. Numerous studies have indicated enduring advantages without considerable toxicity or immune responses; however, further investigation is required to assess the longevity of these effects and to detect any possible late-onset complications. These findings are essential for evaluating the feasibility of gene therapy in clinical applications [209, 210]. Although animal models provide a valuable platform for preclinical testing, the translation of these results to humans poses distinct challenges. The intricacy of MS in humans, encompassing genetic and environmental influences, may not be entirely mirrored in animal models. Nonetheless, findings from animal studies inform the design of clinical trials by pinpointing promising therapeutic targets and delivery mechanisms. Successful gene therapies in EAE models have informed current clinical trials targeting immune modulation and remyelination in MS patients [232, 233]. In conclusion, gene therapy has exhibited remarkable potential in animal models of MS, targeting both the autoimmune and neurodegenerative aspects of the condition. Researchers are advancing toward the clinical application of these therapies by utilizing sophisticated delivery systems, cutting-edge gene-editing technologies, and combinatorial approaches. Despite existing challenges, advancements in animal studies underscore the transformative potential of gene therapy, providing optimism for a future in which MS can be effectively halted or potentially reversed. Gene therapy has shown significant promise in animal models of MS, targeting both the autoimmune and neurodegenerative aspects of the condition. Researchers are advancing toward the clinical application of these therapies by utilizing sophisticated delivery systems, cutting-edge gene-editing technologies, and combinatorial approaches. Despite existing challenges, advancements in animal studies underscore the potential of gene therapy to transform MS treatment, providing optimism for a future where the disease may be effectively halted or even reversed.

10 | Stem Cell Therapy

Stem cells are being investigated for the treatment of numerous diseases, such as hepatitis, diabetes mellitus, epidermolysis bullosa, Parkinson's disease, Covid-19, and spinal cord injury, owing to their capacity to differentiate into specific cell types and facilitate tissue repair [234–240]. Stem cell therapy for PPMS has emerged as a promising treatment approach, aiming to address the complex pathology of the disease, including neuroinflammation, demyelination, and axonal degeneration [241, 242]. Stem cells operate via various mechanisms, including immunomodulation, which diminishes CNS inflammation by modifying the activity of T cells, B cells, macrophages, and microglia through the release of anti-inflammatory cytokines and direct cellular interactions. They additionally offer neurotrophic support through the secretion of growth factors, including brain-derived neurotrophic factor (BDNF), which facilitates neuronal survival, axonal growth, and remyelination. Furthermore, stem cells facilitate cell replacement by differentiating into oligodendrocytes and neurons to restore damaged cells, although this occurs as a secondary effect in most therapeutic applications. Finally, they participate in metabolic reprogramming, altering the metabolic milieu in the CNS by diminishing inflammatory metabolites such as succinate and enhancing energy production in impaired neurons [243–247]. Two primary classifications of stem cells have been investigated: hematopoietic stem cells (HSCs) and non-hematopoietic stem cells (nHSCs).

10.1 | HSCs

HSCT was among the initial utilizations of stem cell therapy in MS. HSCs are predominantly utilized to rejuvenate the immune system via immunoablation, succeeded by reconstitution with stem cells. This method effectively diminishes the autoreactive immune responses typical of RRMS and active PPMS. HSCT "reboots" the immune system by eradicating pathogenic lymphocytes that cause CNS inflammation. However, HSCs are incapable of directly regenerating CNS tissue, as they cannot differentiate into neurons, oligodendrocytes, or

astrocytes. Consequently, their efficacy is constrained in quiescent PMS or when degenerative processes surpass inflammatory activity [248–250].

10.2 | nHSCs

nHSCs, originating from neural or mesenchymal sources, have shown enhanced potential in addressing the degenerative characteristics of PMS. nHSCs comprise MSCs, neural stem cells (NSCs), and induced pluripotent stem cells (iPSCs). These cells can affect the CNS via mechanisms such as neuroprotection, neurotrophic support, and cellular replacement [242, 251–254].

10.2.1 | MSCs

MSCs, sourced from bone marrow, adipose tissue, or umbilical cord, exhibit multipotency and possess the ability to modulate immune responses. They release anti-inflammatory cytokines, growth factors, and extracellular vesicles (EVs), which mitigate neuroinflammation and facilitate repair. Although MSCs exhibit restricted potential for in vivo differentiation into CNS cell types, their paracrine effects—facilitated by secreted factors—play a crucial role in diminishing inflammation and promoting axonal survival [244, 247, 255–258].

10.2.2 | NSCs

NSCs exhibit a higher degree of specialization than MSCs and are intrinsically dedicated to neural lineages. They possess the ability to differentiate into neurons, oligodendrocytes, and astrocytes, providing potential for direct tissue repair. NSCs also regulate the immune response by releasing neuroprotective factors and engaging with local immune cells. These cells have demonstrated the ability to enhance remyelination by augmenting oligodendrocyte progenitor cell activity and diminishing astrogliosis. Nonetheless, challenges such as sourcing (e.g., from fetal tissue) and scalability must be resolved [242, 254].

10.2.3 | iPSCs

iPSCs are generated through the reprogramming of somatic cells, including fibroblasts, into a pluripotent state. These cells can differentiate into NSCs or oligodendrocyte progenitor cells, offering a potentially inexhaustible supply of patient-specific therapeutic cells. iPSCs mitigate ethical dilemmas linked to embryonic stem cells and diminish the likelihood of immune rejection owing to their autologous source. Nonetheless, guaranteeing the safety of iPSCs in preventing tumorigenesis continues to be a primary research emphasis [242, 259–261]. Stem cell therapies are categorized into HSCs and nHSCs. HSC transplantation, primarily employed to recalibrate the immune system, has demonstrated effectiveness in inflammatory variants of MS but has had restricted success in mitigating neurodegeneration in PMS. In contrast, nHSCs, originating from sources such as MSCs or NSCs, provide regenerative capabilities through cell replacement, neurotrophic support, and immunomodulation. These cells function via paracrine signaling, the secretion of neurotrophic factors, and interactions with immune cells to regulate the inflammatory microenvironment and promote tissue repair [262–265]. Preclinical studies offer substantial evidence for the effectiveness of stem cell therapies in animal models of MS. MSCs and NSCs exhibit capabilities to diminish inflammation, safeguard neurons, and facilitate remyelination via mechanisms such as the secretion of anti-inflammatory cytokines and metabolic reprogramming. Novel strategies, including EV-based therapies, demonstrate the potential to leverage the therapeutic advantages of stem cells while reducing risks linked to cell transplantation, such as tumorigenicity or immune rejection [266–269]. The clinical application of stem cell therapies for PMS is promising yet encounters obstacles, such as optimizing cell delivery techniques, timing of intervention, and addressing patient-specific variables like disease stage and progression. Subsequent research should concentrate on optimizing therapeutic protocols, enhancing cell engraftment efficiency, and performing long-term studies to ascertain safety and efficacy. Notwithstanding these challenges, stem cell therapies present a revolutionary prospect for tackling the intricate pathology of PMS, providing optimism for enhanced patient outcomes [241, 270, 271]. The investigation of intrathecally transplanted human fetal neural precursor cells (hfNPCs) for PPMS was conducted in a phase 1 clinical trial (STEMS). The research focused on the unfulfilled requirement for therapies that integrate neuroprotection, immunomodulation, and regeneration to mitigate disability progression in PMS. The findings indicated the safety, tolerability, and possible neuroprotective advantages of hfNPC therapy in 12 subjects. Significant findings revealed no severe adverse reactions during a two-year follow-up and a tendency for diminished loss of brain and gray matter (GM) volume in patients administered higher hfNPC dosages. Mechanistic investigations indicated that hfNPCs may facilitate neuroprotection via the secretion of trophic and immunomodulatory factors; however, the findings are preliminary due to the limited sample size and lack of controlled design. The trial entailed increasing doses of hfNPCs (ranging from 0.7×10^6 to 5.7×10^6 cells per kilogram) delivered through lumbar puncture. Participants underwent neurological evaluations, MRI imaging, CSF analysis, and biomarker assessments. The safety protocol encompassed immunosuppressive therapy to avert transplant rejection and reduce adverse events. Significant alterations in CSF biomarkers were observed, including elevated levels of neuroprotective and immune-related molecules, such as GDNF and IL-10. The study indicated a correlation between increased hfNPC doses and diminished GM atrophy, implying a possible dose-dependent therapeutic effect. Adverse events were predominantly mild or moderate, with one severe relapse of MS not associated with the treatment. The results advocate for additional trials involving larger cohorts and extended follow-ups to confirm these findings and investigate the capacity of hfNPCs to affect the clinical trajectory of PMS. The trial represents a crucial advancement in the development of regenerative therapies for PMS, demonstrating the viability and potential of hfNPC transplantation while emphasizing the necessity for further research to validate its effectiveness and long-term advantages [272].

In the STEMS Phase I clinical trial, intrathecal transplantation of hfNPCs was evaluated in 12 patients with progressive

TABLE 4 | Future treatments for PPMS.

Treatment	Class	Expected mechanism of action	Current status	Expected benefits	Administration	Potential side effects	Other notes	Refs.
Remyelination therapies	Regenerative medicine	Stimulates repair of damaged myelin, possibly via enhancing oligodendrocyte function or remyelination	Early clinical trials	May promote remyelination and restore nerve function, improving mobility and cognition	Oral/Injectable (varies by drug)	Mild headaches, nausea, fatigue, injection site reactions	Still experimental, requires more clinical validation	[276–278]
Opicinumab (Anti-lingo-1)	Monoclonal antibody	Inhibits LINGO-1, a protein that suppresses remyelination, allowing for regeneration of myelin	Phase 2 completed, not yet FDA-approved	Potential for improved myelin repair and recovery of function	Intravenous infusion	Immune reactions, fatigue, headache, rash	Specifically targets remyelination without immune suppression	[197, 279–282]
BTK inhibitors	Small molecule inhibitors	Inhibit Bruton's Tyrosine Kinase (BTK), reducing B-cell activation and inflammation in the CNS.	Phase 3 trials ongoing	Reduces neuroinflammation, potentially slows disease progression.	Oral	Diarrhea, upper respiratory infections, headache, nausea.	Promising for inflammatory MS and PPMS	[283–288]
Evobrutinib	BTK Inhibitor	Blocks BTK activity, preventing activation of B cells and microglia, which contribute to MS pathology	Phase 2 completed, Phase 3 trials ongoing	Reduces inflammation and damage to neurons. May slow disease progression	Oral	Infections, liver enzyme elevations, headache, diarrhea	Less immunosuppressive compared to other agents	[289–292]
Neuroprotective drugs	Pharmacological agents	Protects neurons from oxidative stress and excitotoxicity; may reduce CNS degeneration	Phase 2/3 trials	Protects nerve cells, potentially preventing further disability	Oral/Intravenous	Headache, nausea, fatigue, dizziness	Still being investigated, with variable results	[293–296]

(Continues)

TABLE 4 | (Continued)

Treatment	Class	Expected mechanism of action	Current status	Expected benefits	Administration	Potential side effects	Other notes	Refs.
Immunocell therapy (CAR T-cell)	Cellular therapy	Genetically modifies T cells to target and eliminate autoreactive immune cells contributing to MS	Early Phase 1/2 trials	Potential for resetting the immune system, halting disease progression	Infusion (after collection, gene modification)	Cytokine release syndrome, infections, fatigue, headache	Highly experimental, tailored for each patient	[297–300]
Gene therapy	Genetic medicine	Delivers genes encoding neurotrophic factors or anti-inflammatory proteins directly to the CNS	Preclinical/Phase 1	Promotes neuronal survival, remyelination, and reduces inflammation	Direct CNS injection/ viral vectors	Immune responses to viral vectors, injection site reactions	Experimental, with focus on viral vector safety	[301–304]
AAV-Mediated gene delivery	Viral-based therapy	Uses adeno-associated virus (AAV) to deliver genes that promote repair and protect against neurodegeneration	Preclinical	Potential to treat multiple aspects of MS by delivering neuroprotective genes	Intracerebral/ Intrathecal injection	Immune responses to AAV, headache, infection, inflammation	Limited clinical data, safety concerns with viral vectors	[305–307]
Hematopoietic stem cell transplantation (HSCT)	Stem cell therapy	Transplants hematopoietic (blood-forming) stem cells to reset the immune system, reducing inflammation	FDA-approved for certain MS cases (HSCT)	Potentially halts disease progression and reduces disability	IV infusion (after conditioning regimen)	Infections, blood clots, organ damage, fatigue	Used in severe, treatment-resistant cases of MS	[308–310]
Mesenchymal stem cells (MSC)	Stem cell therapy	Promotes tissue repair, modulates inflammation, and may help in remyelination and neuroprotection	Phase 1/2 trials ongoing	Improves neurological function, reduces inflammation, and protects neurons	Intrathecal/ intravenous	Mild fever, headache, infection, fatigue	Less invasive compared to HSCT, but still experimental	[311–313]

multiple sclerosis (PMS), including PPMS. The primary goal was to assess safety and tolerability, which were confirmed over a two-year follow-up, with no severe treatment-related adverse events reported. Patients who received higher hfNPC doses (up to 5.7 million cells/kg) showed reduced GM volume loss, suggesting dose-dependent neuroprotective effects. Biomarker analysis of CSF revealed increased levels of GDNF, IL-10, and other neuroprotective/immunomodulatory factors. Ethical considerations played a significant role in the trial design due to the fetal origin of the stem cells. Full ethical approval was obtained, and strict donor consent protocols were followed. Despite promising results, the limited cohort size and lack of a control arm highlight the need for larger randomized trials to confirm efficacy. These findings offer a foundation for the further development of hfNPC-based regenerative strategies in progressive MS [273].

11 | Challenges and Future Directions

Although the preclinical and initial clinical evidence for stem cell therapy is encouraging, numerous obstacles persist. Primary challenges encompass optimizing delivery mechanisms, identifying the optimal timing for intervention, and guaranteeing long-term safety and efficacy. Intravenous delivery is less invasive but may exhibit reduced CNS targeting efficiency, whereas intrathecal or intracerebroventricular methods are more precise yet invasive. Furthermore, issues regarding tumorigenicity, immune rejection, and the scalability of stem cell production must be resolved. Future research is investigating cell-free therapies utilizing stem cell-derived EVs or secretomes, which preserve the therapeutic attributes of stem cells while mitigating the risks associated with cell transplantation. Progress in bioengineering and personalized medicine, including the genetic modification of stem cells to augment their therapeutic efficacy, is facilitating the development of more effective treatments [274, 275]. In Table 4, we briefly discuss drugs that could be the target of future studies and clinical trials in the treatment of PPMS.

12 | Conclusions

Managing PPMS poses a considerable challenge in neurology, requiring innovative therapeutic approaches to tackle the intricate interactions of neuroinflammation, demyelination, and neurodegeneration characteristic of this disorder. Present therapies, such as ocrelizumab, have demonstrated efficacy in decelerating disability progression and diminishing MRI-detected disease activity, providing optimism in the treatment landscape. Although high-dose biotin and simvastatin exhibit potential, their clinical efficacy is still ambiguous, highlighting the necessity for additional research. Innovative therapies, including stem cell treatments—especially those utilizing non-HSCs—present promising opportunities for tackling the neurodegenerative characteristics of PPMS. Recent Phase 1 clinical trials employing hfNPCs have demonstrated potential neuroprotective advantages and the safety of these interventions. Nonetheless, issues including optimal delivery methods, therapy timing, and long-term efficacy and safety must be resolved through comprehensive clinical studies. Future research should concentrate on enhancing stem cell therapies, investigating gene therapy, and creating cell-free therapies to utilize regenerative potential while mitigating associated risks. Progress in bioengineering and personalized medicine may augment treatment methodologies, resulting in enhanced patient outcomes. The complex characteristics of PPMS require a unified research initiative to convert these encouraging discoveries into practical clinical applications, facilitating innovative treatment strategies that could profoundly change the trajectory of this debilitating condition.

Author Contributions

M.R., S.S.: writing – review and editing. M.R., G.A., N.T., M.K.: data collection. S.A.: data curation, draw table. R.R., E.S.: investigation. R.R., E.S.: project administration. R.R.: manuscript review. H.A.: draw figures. E.S.: supervision, manuscript editing.

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Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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