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Review

Current and Emerging Treatment Options in Pediatric Onset Multiple Sclerosis

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Abstract: Pediatric onset multiple sclerosis (POMS), characterized by the onset of multiple sclerosis before the age of 18, is gaining increased recognition. Approximately 5 percent of MS cases manifest before the age of 18, with less than 1 percent occurring before the age of 10. Despite its rarity, pediatric MS exhibits distinct characteristics, with an association between younger age at onset and a comparatively slower disease progression. Despite this slower progression, individuals with POMS historically reach disability milestones at earlier ages than those with adult-onset multiple sclerosis. While various immunomodulatory agents demonstrate significant benefits in MS treatment, such as reduced relapse rates and slower accumulation of brain lesions on magnetic resonance imaging (MRI), the majority of disease-modifying therapies (DMTs) commonly used in adult MS lack evaluation through pediatric clinical trials. Current evidence is predominantly derived from observational studies. This comprehensive review aims to consolidate existing knowledge on the mechanisms of action, efficacy, safety profiles, and recommended dosages of available DMTs specifically in the context of pediatric MS. Furthermore, this review outlines recent advancements and explores potential medications still in developmental stages, providing a thorough overview of the current landscape and future prospects for treating POMS.

Keywords: pediatric onset multiple sclerosis (POMS); disease-modifying therapies (DMT); pediatric MS; interferons; fingolimod; siponimod; ocrelizumab; ofatumumab; rituximab; alemtuzumab; natalizumab; daclizumab; teriflunomide; dimethyl fumarate; cyclophosphamide; mitoxantrone; vitamin D; TCR vaccine; stem cell therapy; glatiramer acetate; azathioprine

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1. Introduction

Multiple sclerosis (MS) is a the most common chronic immune-mediated disorder of the central nervous system (CNS), brain, and spinal cord. MS is a highly heterogenous disorder, with a variety of clinical manifestations that result from the principal pathological mechanisms, which include inflammation, demyelination, and axonal degeneration [1,2]. Even though MS has its peak incidence in young adults aged 20 to 30 years, it is also recognized in those under the age of 18, consisting of pediatric-onset MS (POMS) [3,4]. The overall global pooled incidence of POMS was calculated in a recent systematic review and meta-analysis to be 0.87 (95% CI: 0.35–1.40) per 100,000 individuals annually [5].

Factors such as the distance from the equator and a higher socioeconomic status have a positive correlation with MS diagnosis [6–12]. The median age of onset of pediatric MS is 12 years; 17–30% are estimated to be under the age of 10 years at the time of their first attack [13,14]. Among preteen children, the prevalence of MS is similar in boys and girls. During adolescence, the prevalence starts to increase more among girls than boys, which leads to a female-to-male ratio of 2:1–2.8:1 among children aged 12 years and older [3,6].

The etiology of MS remains elusive; environmental, infectious, and genetic factors contribute to disease manifestation. The genetic predisposition hypothesis of MS is supported by the 25.4% risk of developing MS in monozygotic twins [15]. Genetic linkage studies have been performed, mostly in adults, with the human leukocyte antigen (HLA) region having the most robust association. The HLA-DR1501 allele was more prevalent in pediatric patients with MS compared to healthy controls [16,17]. More specifically, the presence of one or more HLA-DR1501 allelic variants increases independent of the hazard ratio by approximately 2.2, mainly in children with European ancestry [18,19]. Vitamin D deficiency, obesity, and smoking, active as well as passive, have been associated with an increased risk for MS [20–25]. The presence of a remote Epstein–Barr Virus (EBV) infection is strongly associated with increased susceptibility for POMS independent of age, sex, race, ethnicity, and HLA-DRB1 status [23]. This phenomenon may be attributed to "molecular mimicry", given the fact that the EBV nuclear antigen (EBNA) has a similar structure to the myelin basic protein, a major component of CNS myelin [17].

The most common clinical presentations of POMS are focal neurological deficits due to long-track involvement, episodes of transverse myelitis, ataxia and other cerebellar syndromes, optic neuritis, brainstem symptoms, and acute demyelinating encephalomyelitis (ADEM), a generally monophasic disease characterized by a sudden and widespread inflammation and demyelination of the CNS which is mostly triggered by viral infections or vaccinations [26–28]. Almost exclusively, POMS is characterized by a relapsing-remitting form; features suggesting a progressive phenotype should prompt careful evaluation for alternative diagnoses such as leukodystrophies and metabolic or mitochondrial disorders [29].

The latest POMS diagnostic criteria were published more than a decade ago, however the 2017 revised McDonald criteria for adult-onset MS (AOMS) are widely utilized in the pediatric population [30,31]. The new, revised criteria, along with the implementation of oligoclonal bands as substitutes for dissemination in time, allow a faster diagnosis of MS at the first clinical event, increasing the sensitivity and offering the possibility for a timelier initiation of treatment [32]. The sensitivity and specificity of the McDonald criteria for successfully diagnosing POMS are 71% and 95%, respectively [33].

The natural disease course of POMS, before treatment initiation, is characterized by high relapse rates, suggesting a highly active inflammatory disease process, which is also confirmed by the presence of a higher T2 lesion burden on magnetic resonance imaging (MRI) compared to AOMS patients [34–36]. Clinical recovery following a relapse in pediatric patients is largely favourable, and progression to a secondary progressive form of MS (SPMS) is typically deferred by 10–20 years compared to adults. Nevertheless, earlier onset of the disease results in reaching the SPMS landmark at a younger age and a higher burden and disability accumulation [23,26].

Thus, early diagnosis and treatment initiation is essential for a better prognosis and lower disability outcomes. Studies have shown that treatment delay is associated with a higher annualized relapse rate (AAR) and a greater risk of reaching an Expanded Disability Status Scale (EDSS) score of 4.0 [37,38]. The EDSS is the predominant clinician-administered scale utilized for assessing disability in individuals diagnosed with MS. It serves as an efficacious instrument for quantifying functional disability levels. The EDSS employs a scoring metric that ranges from 0 to 10, delineating the severity of the patient's condition. A score of 0 indicates a normal neurological examination, whereas a score of 10 is indicative of mortality attributable to MS. Scores up to 5 signify patients who retain full ambulatory capabilities. Within the scoring framework up to this threshold, functional systems (FS) are the principal determinants of the EDSS score. Beyond a score of 5, the degree of disability is primarily driven by the patient's ambulation status [39–41].

MS in children and adolescents presents several unique considerations compared to adults, including differences in clinical presentation, diagnosis challenges, disease course, impact on development and education, psychosocial challenges, and treatment considerations. Symptoms such as cognitive impairment, fatigue, and physical disabilities may interfere with academic performance, social interactions, and overall quality of life [27]. While various immunomodulatory agents demonstrate significant benefits in MS treatment, such as reduced relapse rates and slower accumulation of brain lesions on magnetic resonance imaging (MRI), the majority of disease-modifying therapies (DMTs) commonly used in adult MS lack evaluation through pediatric clinical trials. This comprehensive review aims to encapsulate the present state of understanding and the latest developments in the treatment of Pediatric-Onset Multiple Sclerosis (POMS). It will meticulously compile and synthesize existing research findings, highlighting pivotal studies and important works in the field. By discussing these recent advancements, the review seeks to illuminate the evolving landscape of pediatric MS modifying treatment. Additionally, it will offer thoughtful insights and foresight into prospective future directions for research and clinical practice. This includes identifying emerging therapeutic strategies, where further investigation is paramount.

2. Treatment of Pediatric-Onset Multiple Sclerosis

Treatment of acute demyelinating attacks is still based on administration of glucocorticoids by reducing inflammation and hastening clinical recovery, but without altering the disease's course. Intermittent (pulse) intravenous infusion of methylprednisolone is the first-line treatment of choice with a dose of 20–30 mg/kg/day without exceeding 1 g for a total of 3 to 5 days. Gradually reducing (tapering) oral prednisone is usually recommended if resolution of symptoms is incomplete. Prednisone is commenced at a dose of 1 mg/kg/day and tapered by 5 mg every 2–3 days. Additional intravenous corticosteroids, and therapeutic plasmapheresis are commonly used in steroid-refractory disease, but without sufficient data for the pediatric population [42,43].

In addition to managing acute relapses, the primary objective continues to be the long-term modification of the disease through strategies aimed at altering its trajectory. This involves the use of disease-modifying therapies (DMTs), which are crucial for reducing the frequency of relapses, slowing the progression of the disease, and improving the overall prognosis for children and adolescents with MS.

2.1. Disease-Modifying Therapies

Disease-Modifying Therapies (DMTs) have been introduced in AOMS for many decades. In the POMS population, treatment remains largely off-label, due to the limited number of randomized controlled clinical trials (RCTs) assessing the safety and efficacy of these medications in children. The higher risk of serious adverse events and potentially unknown long-term side effects associated with these new treatments further complicates their evaluation in children. Ethical considerations, along with practical challenges such as the immunological maturity of the pediatric population, exposure to infections, neurodevelopmental factors, and age-specific toxicities, only add to the problem. Additionally, the relatively small global population of pediatric MS patients limits the feasibility of large-scale studies, affecting the ability to conduct comprehensive research [44]. The majority of the data available on those drugs are derived from adult RCTs and pediatric observational studies. A summary of the medication used in the pediatric population is depicted in Table 1.

Table 1. Summary of medication used in Pediatric Onset Multiple Sclerosis (POMS).

Medication	Proposed Mechanism of Action	Dosing in Pediatric Population	Studies
Interferon-β	reduction in cytokines inhibition of reactive T-cells induction of anti-inflammatory mediators inhibition of cell trafficking across the BBB [1]	in children > 10 years INF-β-1a: IM [8] 30 mcg once weekly INF-β-1a: sc [9] 22 mcg or 44 mcg three times weekly INF-β-1b: sc [8] 250 mcg every other day	IM INFβ-1a: Ghezzi et al. [45] sc INFβ-1a: observational studies Pohl et al., REPLAY Study Group [46,47] sc INF-β-1b: observational studies Banwell et al., BETAPAEDIC study [48,49] Peginterferonβ-1a: NCT03958877 Open-label, randomized, active controlled—currently ongoing
Glatiramer acetate	shifting Th1 cells [2] to Th2 (reg) cells [3]	in children > 10 years sc 20 mg daily or sc 40 mg three times per week	ITEMS, cohort study [50]
Fingolimod	retaining T-cells in lymph nodes reducing T-cell circulation in CNS [4]	Oral 0.25 mg daily for ≤40 kg, 0.5 mg daily for >40 kg	PARADIGMS [51], double-blind, randomized, active comparator
Teriflunomide	inhibition DHODH [5] in lymphocytes reducing T- and B-cell circulation in CNS	Oral 7 mg daily for <40 kg, 14 mg daily for ≥40 kg	TERIKIDS [52], double-blind, randomized, placebo-controlled
Azathioprine	inhibition of DNA synthesis cytotoxic immune cell depletion	Oral 2–3 mg/kg daily	
Cyclophosphamide	cytotoxic immune cell depletion	Induction regimen of 5 doses provided over 8 days followed by monthly pulse treatments or single induction course of 5 doses over 8 days or monthly without induction 600 to 1000 mg/m^2 per dose	Observational, Makhani N et al. [53]
Dimethyl fumarate	anti-inflammatory properties in microglia, astrocyte neuroprotection	Oral 120 mg BID [10] for 7 days, then 240 mg BID	FOCUS, phase II, single-arm, open-label CONNECTED, follow-up of FOCUS [54,55]
Rituximab	anti-CD20 monoclonal antibody, B-cell depletion	IV 750 mg/m^2 (500–1000 mg) every 6 months, induction with 2 doses separated by 2 weeks	Observational, Salzer J et al., Krysko KM et al. [56,57]
Daclizumab	anti-CD25 monoclonal antibody inhibition of IL-2 [6] reduction in T-cell activation	N/A	N/A
Alemtuzumab	anti-CD52 monoclonal antibody T-and B-cell depletion	First course: IV 12 mg/daily for 5 days 2nd course (one year later): 12 mg/daily for 3 days	Open-label, non-randomized—currently ongoing
Ocrelizumab	anti-CD20 monoclonal antibody, B-cell depletion	IV 600 mg every 6 months (1st dose: 2 doses of 300 mg separated by 2 weeks)	Open-label, PK/PD [11] study—currently ongoing
Natalizumab	anti-α4β1-integrin monoclonal antibody inhibition of T- and B-cell migration into CNS	IV 300 mg every 4 weeks	Open-label, PK/PD study—no results posted Retrospective observational—no results posted

Table 1. *Cont.*

Medication	Proposed Mechanism of Action	Dosing in Pediatric Population	Studies
Mitoxantrone	inhibition of DNA and RNA synthesis inhibition B-, T-cell and macrophage proliferation decrease in TNFa [7] and IL-2	IV 12–14 mg/m^2 every 3 months	Off label
Ofatumumab	anti-CD20 monoclonal antibody, B-cell depletion	N/A	NEOS, 3-arm double-blind, non-inferiority, randomized—currently ongoing
Siponimod	retaining T-cells in lymph nodes reducing T-cell circulation in CNS	N/A	NEOS, 3-arm double-blind, non-inferiority, randomized—currently ongoing

[1] BBB: blood brain barrier, [2] Th1: T-helper 1 cells, [3] Th2 (reg) cells: T-helper-2 regulatory cells, [4] CNS: central nervous system, [5] DHODH: dihydro-orotate dehydrogenase, [6] IL-2: interleukin-2, [7] TNFa: tumor necrosis factor alpha, [8] IM: intramuscular, [9] sc: subcutaneous, [10] BID: twice a day, [11] PK/PD: pharmacokinetic/pharmacodynamic.

2.2. Interferons

Interferons (INFs) are cytokines produced mostly by different types of cells of the immune system. They have immunomodulatory effects as well as antiviral and antitumor properties. In MS treatment, the interferons of the type I family are used. Those are IFNβ-1b, IFNβ-1a and peginterferon beta-1a [58].

The precise mechanism of action of INFs in MS is not fully understood. INF functions by generating the interferon-stimulated gene factor 3 (ISGF3) transcription complex through the activation of janus kinases (JAK1) and tyrosine kinases (TYK2), thereby exerting its immunomodulatory effects [59]. This complex is essential for the regulation of multiple genes known as INF-stimulated genes. These produce a variety of effects, which range from reduction of lymphocyte cytokines, inhibition of autoreactive T-cells, to induction of anti-inflammatory mediators and inhibition of immune cell trafficking across the brain blood barrier (BBB) [60].

Subcutaneous (sc) INFβ-1a has been evaluated in two major pediatric observational studies by Pohl et al. and by the REPLAY Study Group, including 46 and 307 pediatric patients, respectively [46,47]. In both studies there was a significant decrease in AAR from a mean pre-treatment value of 1.9 and 1.79 to 0.8 and 0.77, respectively. Treatment was initiated with 22 μg three times a week in the first study, but due to ongoing disease activity, 47,8% of the patients switched to the adult dose of 44 μg. In the REPLAY Study Group at treatment initiation, doses were 44 μg three times weekly in half of the patients, including children under the age of 12. Discontinuation of treatment was observed in both studies, mainly due to clinical relapse or adverse effects.

Sc INFβ-1b efficacy was analysed in two observational studies by Banwell et al. and Gartner et al. on behalf of the BETAPAEDIC study, including 39 and 67 POMS cases, respectively [48,49]. Treatment was initiated in the majority of patients at a dose of 250 μg every alternate day. Dose titration was primarily advised for patients younger than 10 years old. A 50% reduction in ARR was observed after a mean treatment duration of 2 years [48]. Similar results were obtained from the BETAPAEDIC study with an AAR reduction from a 2.4 pre-treatment value to a 1.0. Furthermore, for 76,9% of the patients, no EDSS progression was recorded up to their last follow-up [49].

Intramuscular (IM) INFβ-1a with a dose of 30 mg once a week was studied by Ghezzi et al. [45]. A total of 52 pediatric patients were included and were followed up for a mean of 3.5 years. Mean AAR decreased from 1.9 to 0.4 following treatment initiation. Additionally, EDSS score showed a minor reduction (from 1.5 to 1.3), although this change was not statistically significant.

Currently, there is an ongoing open-label, randomized, ctive-controlled, parallel-group study that aims to evaluate the safety, tolerability, and efficacy of Peginterferonβ-1a in POMS (ClinicalTrials.gov identifier: NCT03958877).

Adverse effects of INFs are common but rarely serious. The majority of the patients report injection site reactions, headache, fatigue, and flu-like symptoms. The latter can be alleviated with paracetamol/acetaminophen or ibuprofen intake 1 h prior to the injection. Gastrointestinal symptoms are also reported. Blood count abnormalities (leukopenia), liver enzyme derangement, and thyroid function abnormalities (mainly hypothyroidism) can occur at the initiation of therapy but mostly those are transient and do not cause permanent impairment [45–49].

2.3. Glatiramer Acetate

Glatiramer acetate is an acetate salt made from a mixture of synthetic polypeptides containing L-alanine, L-glutamic acid, L-lysine, and L-tyrosine, analogous to those of the myelin basic protein [61]. Glatiramer acetate suppresses the inflammatory response by shifting the population of T-cells from proinflammatory T-helper (Th)-1-cells to regulatory Th2-cells, through its interaction with the trimolecular complex (MHC II/Proteolipid peptide/T-cell receptor) [62]. There have been limited studies examining glatiramer acetate's efficacy in the pediatric population. In the ITEMS study, 14 patients with POMS were treated with daily glatiramer acetate sc injection of 20 mg and followed up for a period of 5.3 years [50]. In five cases (36%), treatment was shifted either to INFβ or to other DMTs during the follow-up period. In the remaining nine patients that continued treatment with glatiramer acetate, the ARR decreased from a mean value of 3.1 in the pre-treatment period to 0.2. At the end of the follow-up period, EDSS score was compared to the pretreatment period [50]]. The observational study by Kornek et al. [63] followed up with seven patients with POMS that received glatiramer acetate at the same dose, for 2 years. Two patients remained relapse-free during the observational period and EDSS scores remained stable in three patients [63]. Treatment was well tolerated with mild side effects, mostly attributed to injection site reactions. There is one case study that reports Glatiramer acetate-induced hepatocellular injury due to mitochondrial damage, which resolved after treatment discontinuation [64].

Moreover, the Italian MS registry, which included 97 patients that received either INFs or glatiramer acetate, concluded that during the 12-year follow-up, the majority (84.5%) underwent at least one switch of treatment option mostly due to lack of efficacy. The first switch was mainly to other INFs, followed by natalizumab or fingolimod. Subsequent switches were mainly to second-line therapies [65].

2.4. Fingolimod

Fingolimod (FTY720) is the first of a novel class sphingosine 1-phosphate (S1P) receptor modulator, currently known as DMT, of both AOMS and POMS. Fingolimod was first synthesized in 1992 by chemical modification of an immunosuppressive natural product, ISP-I (myriocin). It is a functional antagonist of the G-protein-coupled sphingosine 1-phosphate (S1P) receptors S1P1, S1P2, S1P3, S1P4 and S1P%. In the treatment of relapsing forms of multiple sclerosis (RMS), fingolimod acts by reversibly retaining central memory T-cells and naive T-cells in lymph nodes, thereby reducing the recirculation of autoreactive lymphocytes to the CNS. Fingolimod was approved as the first oral DMT for relapsing forms of AOMS by the US Food and Drug Administration (FDA) in 2010, and subsequently by the European Medicines Agency (EMA) in 2011, and based on the PARADIGMS trial was subsequently approved for pediatric population in 2018 by both organizations [66]. S1P receptors are widely distributed within the CNS, and S1P-mediated signaling has been reported in astrocytes, neurons, oligodendrocytes, and microglia [67]. In summary, these effects are the following: in astrocytes, fingolimod inhibits proinflammatory cytokine production, stimulates cell migration, and inhibits astrogliosis. Furthermore, it reduces dendritic spinal loss, restores neuronal function, and protects from excitotoxic death. It promotes oligodendrocyte progenitor cell (OPC) survival, it effects migration, differentiation and process dynamics, and enhances remyelination. Finally, fingolimod modulates microglial activation [68]. Clinical studies suggest that the benefits of fingolimod may be in part due to a direct action on the CNS. Fingolimod has an early and sustained impact on brain atrophy, suggesting an effect on diffuse as well as focal damage [69–73]. A Placebo-Controlled Trial of Oral Fingolimod in relapsing MS in 2006 showed fingolimod at either a dose of 0.40 mg or 1.25 mg resulted in a significantly reduced risk of disability progression over a 2-year period compared to the placebo. Serious adverse effects were dose dependent, as bradycardia and atrioventricular block were mostly reported in the group that received 1.25 mg [74]. Since then, 11 RCTs enrolling 7184 patients were pooled for analyses of efficacy and safety outcomes [75]. Although 1.25 mg/day is more than twice the dose of 0.5 mg/day, the effect size was almost similar between them. Doses of 5 mg/day obtained an unsatisfactory efficacy while showing a greater risk of adverse events than the other three doses (RR 1.17, 95% CI 1.05–1.30, p-value: 0.003). Additionally, fingolimod 0.25 mg/day not only showed a better performance in delaying the radiological disease progression (MRI), but also achieved a certain degree of patient treatment satisfaction [75]. The proposed oral dosage for fingolimod is 0.5 mg once a day in adults and children 10 years of age and older weighing more than 40 kg, and 0.25 mg once a day in children 10 years of age and older weighing 40 kg or less, while in pediatric patients younger than 10 years of age the safety and efficacy have not yet established [76]. While there were no serious adverse events reported in observational studies, there were a few cases of seizures and leukopenia among others in the PARADIGMS trial. In terms of mild adverse events, lymphopenia and mild infectious complications were most commonly reported. It is believed that leukopenia and lymphopenia, as a result of fingolimod's mechanism of action, increase infection risks [51]. Looking at the literature data of both POMS and AOMS treatment groups of fingolimod, several adverse effects are reported only in adults, such as melanoma, breast cancer, and macular edema [77].

2.5. Teriflunomide

Teriflunomide was first used in rheumatoid arthritis and is known to possess both anti-proliferative and anti-inflammatory actions [78]. Teriflunomide exerts its selective anti-inflammatory action by reversibly inhibiting the mitochondrial enzyme dihydro-orotate dehydrogenase (DHODH) which is highly expressed in rapidly proliferating lymphocytes, thus preventing infiltration and possible CNS damage by activated T and B-cells [79]. Its efficacy in POMS was recently assessed in the TERIKIDS trial, a phase 3 double-blind RCT, in which patients between 10 and 17 years with at least one relapse in the preceding year were randomised to either teriflunomide or placebo [52]. The dose used was equivalent to the adult dose of 14 mg once daily. The study showed no change in the time period to clinical relapse, but this may have been due to loss of statistical power given the high level of switching to open label extension because of unacceptably high rates of new radiological lesions. It did, however, show a reduction in new or enlarged MRI lesions by 55% compared to placebo. While teriflunomide has a generally acceptable safety profile, some possible adverse effects associated with its use include pancreatitis and hepatotoxicity [52,80]. In 2021, EMA approved teriflunomide for treatment of POMS patients aged 10–17 years old, while the FDA rejected its application in pediatric patients due to insufficient data [81,82].

2.6. Azathioprine

Azathioprine (AZA) is a purine analogue [83]. It is a classical cytotoxic drug that acts as a prodrug for mercaptopurine, inhibiting an enzyme that is required for DNA synthesis. Thus, it strongly affects proliferating cells, such as the T-cells and B-cells of the immune system [84]. It has been used for the treatment of patients with relapsing forms of MS that frequently require steroids. Favourable results have been reported by placebo-controlled RCTs and it is an alternative to INF-β. Also, compared to other DMTs it is less expensive [83,85]. Treatment with azathioprine may have a moderate effect in decreasing the relapse rate, but the evidence of efficacy measured in clinical and radiological endpoints is very uncertain [86]. No superiority of AZA has been established versus other DMTs in ARR ratios, the time until the first relapse or MRI findings [87]. Additionally, one RCT that compared the efficacy of AZA and IFNβ-1a in terms of mean number of relapses and mean EDSS scores showed the superiority of AZA [86]. AZA's efficacy has been evaluated in pediatric patients with neuromyelitis optica spectrum disorders (NMOSD) in a retrospective study by Costanzi et al. that included six patients with a 12-month follow-up. AAR was significantly reduced from a median pre-treatment value of 4.2 to 1.0 [88]. There is one case report that exhibits AZA's possible efficacy in POMS, where AZA was administrated in a 10-year-old patient with POMS that first presented as ADEM, which was seropositive for MOG-IgG. The patient showed clinical and MRI stability for at least 3 years after treatment initiation [89]. The dose in pediatric patients is 2–3 mg/kg/day. Cumulative doses of 600 g should not be exceeded in relation to a possible increased risk of malignancy [83,85]. Neutropenia is a common mild side effect. There is a reported risk of malignancy development.

2.7. Cyclophosphamide

Cyclophosphamide (CYC) is a nitrogen mustard that exerts its anti-neoplastic effects through alkylation [90]. As CYC exerts immunosuppressive properties in addition to its anti-neoplastic effects, it is indicated in the management of other immune conditions such as severe MS and nephrotic syndrome [90–92]. CYC has been used for relapsing-remitting MS (RRMS) especially in regions with limited access to high-efficiency therapies [91]. The same applies to children with aggressive MS refractory to first-line therapies [53]. In the retrospective study of Makhani et al. that examined CYC's efficacy in 17 pediatric patients showed that one year after treatment completion AAR was reduced to a mean value of 1.6, whereas the pre-treatment value was 3.8. EDSS was stabilized or improved in 83% of the cases, with a mean reduction of 1.3 points. CYC had no significant effect in haltering the development of new MRI lesions [53]. CYC therapy was associated with several adverse events in the cohort of Talar-Williams et al., the most significant being the development of bladder carcinoma. Risk of bladder carcinoma has been linked to cumulative CYC dosage of 100 g or higher [93]. The risk of secondary lymphoma, leukemia, and other malignancies are also a concern for children exposed to CYC, and these risks may be partially dependent on the total cumulative dose [94]. The risk of infertility is an important consideration and must be carefully balanced with the potential benefits of treatment. A study in childhood cancer survivors found that CYC exposure between the ages of 13 and 20 years was an independent risk factor for acute ovarian failure [95].

2.8. Dimethyl Fumarate

Dimethyl fumarate (DMF) and its primary metabolite monomethyl fumarate (MMF), have an immunomodulatory as well as neuroprotective effect, by involving both nuclear factor erythroid 2-related factor 2 (Nrf2)-dependent and independent molecular pathways. DMF affects immune cell composition and infiltration and skews the immune response towards an anti-inflammatory phenotype [96]. DMF preserves myelin, axons, and neurons as well as is thought to protect the oligodendrocytes, which are depleted in MS lesions, from oxidant stress while reducing inflammatory activation in astrocytes. DMF exerts its neuroprotective action also by switching the phenotype of activated microglia from pro- to anti-inflammatory [96]. The efficacy of DMF in POMS is shown in two studies: the FOCUS study, an open-label, multiple-dose study that included 22 patients for a 24-week treatment period and its extension, the CONNECTED study that evaluated the long-term effects of the drug for a total period of 120 weeks [54,55]. The end results of the FOCUS study showed an approximately threefold reduction in new or newly T2 hyperintense lesion formation [54]. During the full 120-week treatment period encompassed by FOCUS and CONNECTED, ARR was 0.2 from a pre-treatment value of 1.5, representing an 84.5% relative reduction in relapses [54,87]. The dosage of DMF was 240 mg twice a day, which was reduced by 50% during the first week of treatment initiation. DMF was well tolerated and 40% of the participants reported side effects that were attributed to the drug and none of them were serious [54,87]. Currently, there is an ongoing phase III, open-label, randomized, active-controlled, parallel-group study evaluating the efficacy and safety of DMF in comparison with INFβ-1a (ClinicalTrials.gov identifier: NCT02283853).

2.9. Rituximab

Rituximab is an anti-CD20 monoclonal antibody which is thought to act in POMS by depletion of B-cells, as well as populations of CD3+ T-cells which express CD20 and have a pro-inflammatory phenotype. While rituximab has not been approved for use in POMS, a recent study demonstrated that it is the third most commonly off-label DMT commenced in pediatric patients [97]. The most prominent study of rituximab in the pediatric population is a Swedish retrospective case series in which 14 POMS patients were identified, who had received rituximab at doses between 500 and 1000 mg intravenously every 6–12 months, for a median duration of 23.6 months [56]. Thirteen of fourteen patients had no progression of EDSS, all were clinically relapse-free for the duration of treatment, and only one demonstrated radiographic progression during the study period [56]. A larger study by Krysko et al. demonstrated a 62% reduction in relapse rate among a cohort of 56 patients (mean age 16), the majority of whom were treated with 1000 mg for 6 months [57]. Adverse effect rates in the above studies tend to be similar to the rates seen in adults treated with anti-B-cell therapies, with Krysko et al. reporting 16.8 side effects per 100 person years, including hepatotoxicity, rash, and injection-site reactions [57,98].

2.10. Daclizumab

Daclizumab is an antibody-targeting CD25 which inhibits IL-2 binding to its receptor, reducing activation of T-cells. Despite inciting high hopes with its novel mechanism of action, daclizumab was withdrawn from the market after its approval for adult-onset RRMS after numerous cases of fatal encephalitis developed with this therapy [99]. It had been historically trialed in pediatric population, in two small case series, where it was used as a second-line therapy [100].

2.11. Alemtuzumab

Alemtuzumab is a humanized IgG1 monoclonal antibody targeting CD-52, which is expressed primarily on B and T-cells. It does also have some expression on other immune cells including monocytes and macrophages. While it is considered an immune reconstitution therapy (IRT), due to its deep T and B-cell depletion, its exact mechanism of action in MS remains to be elucidated [101]. While a Phase III RCT is currently ongoing to assess the efficacy and safety of alemtuzumab in a POMS population, thus far only two small observational studies have been completed [102,103]. In one Canadian case series, patients were treated with 60 mg over 5 days initially, followed by a course of 3 days of 36 mg daily one year later. On 36 and 20-month follow-ups, both patients had an EDSS reduction of one point, and no radiological progression, although one patient may have had a clinical relapse, experiencing a one-week episode of ataxia. No serious adverse effects were noted [102]. Another, slightly larger study assessed alemtuzumab as a follow-on therapy after 2 years of natalizumab and conversion to John Cunningham virus (JCV) positivity in five POMS patients. All patients retained their No Evidence of Disease Activity (NEDA)—3 status over a median of 1.9 years after switching to alemtuzumab, and only mild infusion reactions (pyrexia and rash) were noted [103].

2.12. Ocrelizumab

Ocrelizumab is a humanised monoclonal antibody against CD20, which works in a similar manner to rituximab [104]. It is used less often than its chimeric counterpart in the pediatric population currently, but two large RCTs are ongoing to assess its safety and efficacy in this group. A phase II trial assessing safety and tolerability of ocrelizumab in

POMS is currently ongoing, with an estimated completion date in 2029 (ClinicalTrials.gov Identifier: NCT04075266). In addition, Operetta 2 is a phase III double-blind, double-dummy study comparing ocrelizumab at a dose of 600 mg (given in halves over 2 weeks, then 6 monthly) and fingolimod in POMS patients. It is still recruiting and aims to be completed in 2025 (ClinicalTrials.gov Identifier NCT05123703). Observational studies have already shown promising results, with a Turkish study in 2023 demonstrating mean ARR reduction of 2.01 to 0 over a 28-month follow-up period in 10 POMS patients receiving Ocrelizumab, with only one severe adverse effect (anaphylaxis) [105].

2.13. Natalizumab

Natalizumab is a monoclonal antibody against the α4-integrin component of α4β1 and α4β7 cell adhesion molecules, which are involved in migration of leucocytes across the blood–brain barrier. According to a 2018 cohort study conducted by the US Network of Pediatric MS Centers, natalizumab is the second most commonly used DMT in POMS. Dosing in studies so far has varied, but generally adheres to the adult dose of 300 mg/dose. Numerous observational studies over the last decade have demonstrated efficacy and tolerability of natalizumab in this cohort [106]. One of the most recent, and largest, studies was a retrospective case series of 20 patients, conducted by Margoni et al., which demonstrated a mean reduction in EDSS of 1.1, with no adverse effects noted [103]. Adverse effects noted in other observational studies include injection site reactions, deranged liver function tests, and headache. No reports of progressive multifocal leukoencephalopathy (PML) in the pediatric population have yet been documented [106].

2.14. Mitoxantrone

Mitoxantrone (MX) is an anthracenedione-derived antineoplastic agent widely used for treatment of breast cancer and leukemia [107]. MX exerts its cytotoxic action by intercalating into DNA through hydrogen bonding and causing crosslinks and strand breaks by interfering with RNA and by inhibiting topoisomerase II, an enzyme responsible for uncoiling and repairing damaged DNA, thus blocking both DNA and RNA synthesis [107,108]. MX also presents immunomodulatory effects by inducing macrophage-mediated suppression of B-cell, T-helper, and T-cytotoxic lymphocyte functions [107,108]. MX has been evaluated in a 2-year study in secondary progressive AOMS (MIMS study) [109]. Treatment with MX 12 mg/m^2 resulted in less EDSS deterioration as well as clinical or radiological relapses [109]. Etemadifar M. et al. assessed MX's use in relapsing remitting and secondary progressive forms of POMS [110]. A total of 19 pediatric patients received MX either as induction therapy (73.7%) or as escalation therapy from INFβ (26.3%). MX was administered intravenously, 20 mg monthly in children older than 12 years, whereas patients under the age of 12 received half the standard dose. In both groups, ARR decreased from a median pre-treatment value of 2 to 0. Median EDSS reduction was 0.5 and 1.2 in the induction and escalation groups, respectively. In the group of patients who had not previously received disease-modifying therapy (DMT), the median number of gadolinium-enhanced lesions before treatment was 2.5, which decreased to zero lesions in subsequent MRI scans after treatment [110]. Cardiac toxicity was observed in five cases, of which two cases had treatment discontinued due to cardiomyopathy. Other reported adverse effects were nausea and vomiting, fatigue, alopecia, blue discoloration of nails, sclera or urine, anorexia, vertigo, injection site reactions, headache, cough, and constipation [110].

2.15. Ofatumumab

Ofatumumab is a fully human monoclonal antibody that targets a distinct small loop epitope on the CD20 molecule, a different epitope from rituximab's target, and is a more potent activator of complement-dependent cytotoxicity in vitro [111]. The ASCLEPIOS I and II trials assessed the efficacy of ofatumumab versus teriflunomide in adult patients with relapsing forms of MS, in which the AAR was significantly lower in those treated with ofatumumab [112]. Ofatumumab has also been shown to be superior to teriflunomide in suppressing lesion activity in MRI. Long-term safety was assessed in the ALITHIOS study that included patients that completed the previous studies [113]. Adverse events were reported in 83.8% of the participants; 9.7% of the patients treated with ofatumumab reported serious adverse effects. PML or other opportunistic infections were not identified and risk of malignancy remained low (0.6%). The majority of the adverse events reported were injection site related. In the pediatric population, ofatumumab is being currently investigated together with siponimod in a phase II, three-arm, randomized, double-blind, active-controlled (fingolimod) trial (ClinicalTrials.gov identifier: NCT04926818).

2.16. Siponimod

Siponimod selectively modulates sphingosine-1-phosphate (S1P) receptors $S1P_1$ and $S1P_5$, thus reducing the egress of lymphocytes from lymphoid tissues and preventing lymphocytes' migration into the CNS [114]. Furthermore, preclinical studies suggest that siponimod might prevent synaptic neurodegeneration and promote remyelination in the CNS [115]. In a phase II dose-finding study (BOLD trial) including 1032 adult patients with relapsing-remitting form of MS, siponimod reduced active brain lesion counts and the ARR was decreased by 44% with a 2 mg dose [92,116]. Additionally, siponimod reduced the risk of disability progression by 34% compared to placebo. During the 6 months of treatment, adverse events were observed in 98% with siponimod dose of 2 mg (four serious), and 80% of controls (none serious). As previously mentioned, siponimod alongside ofatumumab is being investigated versus fingolimod for POMS (ClinicalTrials.gov identifier: NCT04926818).

2.17. Vitamin D

Vitamin D is obtained primarily via sun exposure (UVB, wavelengths ~295–315 nm) and/or by taking vitamin D supplements, with limited intake from food in most populations. Higher MS prevalence and earlier onset are associated with geographical locations of increasing latitude and/or with reduced annual sunlight exposure [6,117,118]. Both the circulating and biologically active forms of vitamin D (25(OH)D3 and 1,25(OH)2D3, respectively) cross the BBB into the CNS, where they can act on various neuronal and glial cells [119,120]. Neurons, microglia, and astrocytes express 1α-hydroxylase (CYP27B1), the enzyme responsible for converting 25(OH)D3 into 1,25(OH)2D3. Along with oligodendrocytes, these cells also all express the vitamin D receptor (VDR) [121–126]. The neuroprotective mechanism of vitamin D is attributed to the enhancement of oligodendrocyte lineage differentiation, neurotrophins expression, attenuating aberrant microglial, and reactive astrocyte activation stabilizing the BBB and reducing oxidative stress [127–130]. A longitudinal cohort study that included 110 patients with POMS assessed the effect of vitamin D on the relapse rate of the disease [131]. For every 10 ng/mL increase in the adjusted serum 25-hydroxyvitamin D3 level, there was an estimated 34% decrease in the rate of subsequent attacks, which was independent of HLA-DRB1*1501/1503 status [131]. This study demonstrates a preventive rather than a therapeutic effect of vitamin D in POMS. There are conflicting results based on the therapeutic role of vitamin D in MS. Some studies revealed improvement in the relapse rate and MRI findings on an increased dose of vitamin D (14,000 IU/day) [132]. The American Academy of Pediatrics recommends a daily dose of 400 IU in the pediatric and adolescent population for maintaining innate immunity and preventing the occurrence of diseases such as MS [133].

2.18. T-Cell Receptor (TCR) Vaccine

Multiple attempts have explored the possible efficacy of MS vaccines due to the immunogenic nature of the disease. Potentially encephalitogenic T-cells specific for myelin antigens, particularly myelin basic protein (MBP), proteolipid protein (PLP), and myelin oligodendrocyte glycoprotein (MOG), are thought to contribute to disease progression during the inflammatory phase of MS. The emergence of pathogenic T-cells in MS appears to be permitted as a result of reduced suppression mediated by interleukin (IL)-10-secreting

T regulatory (Tr) 1 cells, natural CD4+ CD25 Tregs, and possibly CD8+ T suppressor cells. Thus, development of an immune-based vaccine strategy that can restore deficient suppressive mechanisms remains an important therapeutic goal [134,135]. The first trial utilized vaccinations with peptides specific towards Vβ5.2 expressing T-cells [136]. In the TCR-peptide responders, no clinical progression of MS was noted, but due to the small sample size, statistical correlation could not be determined. A second trial used the TCR CDR2 peptides (BV5S2, BV6S5 and BV13S1), which induced vigorous T-cell responses, but no clinical or radiological differences were found between the responders and the non-responders [137]. There is an ongoing phase I study examining a novel TCR peptide vaccine for POMS with an estimated enrolment of 12 participants (ClinicalTrials.gov identifier: NCT02200718).

2.19. Stem Cell Therapy

Stem cell therapy has been used in MS treatment for almost 30 years [138]. There are various stem cell sources that have been investigated over the past years; mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), and neural stem cells (NSCs) [139]. The rationale behind stem cell therapy is the self-renewal properties and differentiation capacity of those cells that could regenerate demyelinated areas (immune reconstitution treatment). A recent systematic review and meta-analysis that included 4831 patients with MS calculated the efficacy and safety of autologous hematopoietic stem-cell transplantation (AHSCT). EDSS scores and ARR after treatment were significantly reduced (SMD: −0.48 and −1.58, respectively). A total of 81% of the patients remained relapse-free and 68% retained their NEDA. Four percent died due to transplant-related adverse events [140]. AHSCT for POMS was retrospectively investigated by Burman et al. in 21 pediatric patients that had previously been treated with at least one DMT [141]. The procedure included mobilization of the peripheral hematopoietic stem cells with cyclophosphamide and filgrastim and after conditioning protocols all patients received at least 2×10^6/kg CD34+ hematopoietic stem cells. No patient experienced an EDSS increase post-AHSCT above baseline; in fact, 16 patients reported improvement in EDSS. The ARR after AHSCT was 0.022. Two patients relapsed 2 years after the procedure, and both were classified as secondary progressive MS (SPMS) patients. No deaths were noted in this study, although one patient required intensive care due to *Pseudomonas aeruginosa* sepsis, two patients had culture-verified bacteraemia, and another two had a CMV reactivation that was successfully treated with ganciclovir or foscarnet. No malignancies were reported [141].

3. Discussion

The International Pediatric Multiple Sclerosis Study Group (IPMSSG) in 2012 released a consensus statement that dictated a treatment approach in relapsing-remitting POMS [142]. As a first-line treatment all pediatric patients should receive either INFβ or glatiramer acetate (injectable DMTs). Inadequate response was defined as two or more confirmed clinical or MRI relapses within one year and/or an increase or no reduction in relapse rate, with full treatment compliance and with at least 6 months of full-dose therapy. In such cases they proposed switching between first-line therapies (horizontal switching) or switching to a second-line drug [142]. A recent retrospective multicentre cohort study, that included 741 pediatric patients with MS demonstrated superiority of the new DMTS as first treatment over the injectable forms [97]. More specifically, 43% of the INFβ or glatiramer acetate treated groups reported a relapse versus 19% in the newer DMT groups. Additionally, 42% of the patients on newer DMTs compared to 74% on injectable DMTs showed at least one new or enlarged T2 lesion. Safety issues play a key role in deciding treatment approach. INFβ and glatiramer acetate have favourable safety profiles in the pediatric population, as no malignancies or life-threatening events were reported [45–49,63]. On the other hand, newer DMTs have a reported risk for malignancies and serious adverse effects, such as hepatotoxicity or life-threatening PML [51,77,83,85,94,95,106,143–145]. The daily need for subcutaneous drug administration for INFβ and glatiramer acetate is particularly distressing in both the pediatric and adolescent population and could lead to poor treatment compliance. Other treatment options look more enticing. Oral DMTs or infusion protocols could offer a better adherence in the adolescent population [146]. Clinicians treating pediatric patients with MS must consider whether they should start with a safer but less efficacious first-line injectable treatment and escalate if inadequate response is reported, or whether a more effective treatment but with a less favourable safety profile should be initiated, thus treatment strategy should be personalized. Rapid diagnosis of POMS and early initiation of treatment are mandatory due to the high inflammatory burden of the disease. Close monitoring to identify possible complications or treatment failure is necessary for optimal outcomes in children with MS.

The discrepancy in the therapeutic approach for pediatric patients with MS compared to adults is evident and is demonstrated by the few RCT studies concerning this population, despite the available data that suggest a comparable safety profile. There are limitations in conducting RCTs in POMS; the administration of placebo or active comparator drug is unethical when a similar RCT in the adult population shows the superiority of the drug under study. Furthermore, due to the lower prevalence of POMS compared with AOMS, those trials have a longer recruitment time, a smaller sample size, and a limited study duration. As a result, the data resulting from these studies are underpowered. Therefore, well-designed, large observational studies are necessary in documenting the safety and efficacy of DMTs in POMS. Real-world evidence could also provide insights into the effectiveness and safety of DMTs outside the strict clinical trial settings, offering a better understanding of different treatment approaches in diverse patient populations and over longer periods.

A recent opinion paper called for regulatory agencies to reassess the evaluation and approval process of new medications based on pediatric-onset multiple sclerosis. Given the essentially similar immunopathophysiologic mechanisms observed in pediatric and adult MS, and the accumulating evidence over recent years indicating a comparable safety profile of DMTs in children and adolescents with MS to that in adults, studies should predominantly prioritize pharmacokinetic/pharmacodynamic (PK/PD) evaluations [147].

4. Conclusions

POMS is still a challenging therapeutic issue. Even in the absence of large, optimal clinical studies, the efficacy of the DMTs currently used is evident and those drugs have significantly changed the long-term treatment approach in pediatric patients. However, individuals with POMS, despite a slower progression of the disease, historically attain disability milestones at younger ages compared to those with AOMS, likely due to the earlier onset of symptoms. Enhancing the quality of life for pediatric and adolescent patients remains fundamental, thus addressing daily symptoms, such as fatigue, depression, and cognitive impairment is mandatory. Early diagnosis and treatment initiation reduce disease progression. The use of newer DMTs have shown to be beneficial in the pediatric population. While the majority of the drugs currently used in POMS are still off-label, recently more drugs are being investigated by clinical trials, hoping it will stimulate further research and approval by the regulatory bodies responsible for evaluating and approving medication for the pediatric population.

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