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Multiple Sclerosis: A Review of Pathophysiology, Current Treatments, and Potential Therapeutic Agents

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KANSAS HEALTH SCIENCE CENTER EST. 2018
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Abstract

Multiple sclerosis is an autoimmune disease that affects the central nervous system. The precise etiology of MS is unknown, however, several factors like EBV, vitamin D deficiency, a dysfunctional glymphatic system, along with transglutaminase-2 dysregulation have all been implicated as components in the pathophysiology of MS. The fact that there are several subtypes of MS underscores the complexity of its pathophysiology and complicates its treatment .

Over the past several years, the use of disease modifying therapies to target the pathophysiology of MS has greatly improved. There are now over twenty DMTs that are available for MS patients. These include interferons, glatiramer acetate, sphingosine-1-phosphate receptor modulators, fumarates, etc.

The existing DMTs are well tailored to treat the neuroinflammation in MS, however, there aren't many option for the treatment of progressive multiple sclerosis (PMS). The lack of treatment for PMS is an area within the field of neurology with significantly unmet needs. Likewise, many of the currently available DMT's have many risk factors that impact the efficacy of these drugs also with the use for patients.

Key Findings

- The current DMT's available most effective in the relapsing remitting form of MS.
- There is a gap in treatments available for the progressive form of MS.
- Studies are being done to try and meet this need by targeting the pathophysiology of progressive disease. One example is the use of BTK inhibitors.
- At the moment, the only approved DMT for PMS is ocrelizumab.

Summary_of_Drugs_for_Multiple_Sclerosis

Drug	Mechanism of Action	Pivotal Clinical Trials	Adverse Effects
Interferon beta (IFN-B)	Induces IL-10, decreases Th1, increases Th2, suppresses T cell activity	PRISM	Injection site reactions, flu-like symptoms
Glatiramer acetate (GA)	Reduces autoreactivity, promotes Th2 phenotype	GA 20 mg and 40 mg studies	Injection reactions, panic attacks
Fingolimod	Lymphocyte sequestration via S1P receptor modulation	FREEDOMS, TRANSFORMS	Bradycardia, macular edema
Siponimod	Selective binding to S1P1 and S1P5 receptors	EXPAND	Bradycardia, macular edema, neuroprotection
Ozanimod	High affinity for S1P1 and S1P5 receptors	RADIANCE, SUNBEAM	Bradycardia, hepatotoxicity, lower risk than fingolimod
Ponesimod	Selective S1P1 receptor modulation	OPTIMUM	Bradycardia, macular edema, GI effects
Teriflunomide	Inhibits de novo pyrimidine synthesis	TENERE	Hepatotoxicity, hair thinning, teratogenic
Dimethyl fumarate (DMF)	Activates NRF2 for redox homeostasis	DEFINE, CONFIRM	GI symptoms, flushing, lymphopenia
Diroximel fumarate	Similar to DMF, less GI effects	EVOLVE-MS-1	GI symptoms, better tolerability
Monomethyl fumarate	Similar to DMF, increased tolerability	N/A	GI symptoms, similar to DMF
Natalizumab	Blocks VLA-1, prevents CNS inflammation	AFFIRM	Infusion reactions, PML risk
Ocrelizumab	Anti-CD20 monoclonal antibody, depletes B cells	OPERA I, OPERA II	Infusion reactions, mild infections
Alemtuzumab	Depletes CD52+ B and T lymphocytes	CARE-MS I, CARE-MS II	Secondary autoimmune disorders, infusion-related toxicity
Cladribine	DNA disruption, depletes B and T cells	CLARITY, ORACLE MS	Lymphopenia, herpes zoster reactivation
Mitoxantrone	Cytotoxicity via DNA crosslinking	MIMS	Cardiotoxicity, leukemia
Evobrutinib	BTK inhibitor, reduces B lymphocyte and microglia activity	N/A	N/A

Figure 1. Summary of Drugs for Multiple Sclerosis.
This table summarizes key therapeutic agents used in the treatment of multiple sclerosis, detailing each drug's mechanism of action, pivotal clinical trials, and notable adverse effects.

Treatment	Mechanism	Preclinical Evidence	Potential Application
Small-molecule targeting AMPA-mediated excitotoxicity	Targets an allosteric binding site on the AMPA receptor (GluA2 subunit) to reduce excitotoxicity without affecting basal neurotransmission	Demonstrated therapeutic effects in mouse models for MS (EAE and cuprizone) with improvements in neurological function and myelination	An alternative to current immune-modulating drugs, with potential use in progressive MS and as a complementary treatment to existing therapies
ZCAN262 (lead candidate)	Binds to GluA2 allosteric site and blocks AMPA-mediated excitotoxicity	Restored neurological function and myelination, reduced immune response and demyelination in cuprizone mouse model	Potential for treating progressive MS, particularly neurodegenerative aspects

Figure 2 . Preclinical Evidence and Potential Application of Small Molecules Targeting AMPA-Mediated Excitotoxicity in Multiple Sclerosis
This table summarizes the mechanism of action, preclinical evidence, and potential therapeutic applications of two treatment approaches targeting AMPA-mediated excitotoxicity.

Other Key Findings

- There is ongoing research dedicated to developing remyelination and neuroprotective agents.
- Potential agents include siponimod, a-lipoic acid, ibudilast, etc.
- As of 2023, three new molecules have been identified to bind to GluA2, with effects that could potentially restore neurologic function and myelination.

Conclusions

Over the past several years, the use of disease modifying therapies to target the pathophysiology of MS has greatly improved. There are now over twenty DMTs that are available for MS patients. Likewise, research for new avenues of treatment are continuing to evolve. The use of autologous hematopoietic stem cell transplantation has provided patients with severe disease and those who are refractory to typical treatment an alternative option for therapy.

While the advancement in treatment options for MS has progressed, there is an area of unmet needs in treatment for progressive MS. This has led to increased research to identify neuroprotective and remyelinating agents.

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