STM JOURNALS

International Journal of
Brain Sciences

Volume 1, Issue 1, 2024
January–June
DOI (Journal): 10.37591/IJBS

https://journals.stmjournals.com/ijbs

Review IJBS

Multiple Sclerosis: A Brief Overview of the Disease, Its Pharmacotherapy

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Abstract

Multiple Sclerosis is an autoimmune disorder mostly affecting individuals aged between 20-40. In this disorder, the optic, vertebral, and central nervous system nerves are primarily impacted. It is a neurological condition that worsens over time and is characterized by inflammation and the breakdown of the sheath that surrounds and shields the nerve fiber. Common symptoms may include muscle weakness, numbness, tingling, fatigue, vertigo, tremor, vision complications, pain, Lhermitte sign, sexual dysfunction, muscle spasms, bladder problems, and bowel problems. Myelin around the axon composes White matter. Therefore in Multiple Sclerosis Lesions are formed around white matter. Generally, Autoreactive B-cells play an important role in Multiple Sclerosis. Many drugs are available which are used to slow or decrease the progression of but not cure the disease. Various drugs like Ocrelizumab (The MuSicalE STUDY), Bruton Tyrosine Kinase Inhibitor-Evobrutinib, Clemastine (ReBUILD STUDY), Ibudilast, and MD1003(biotin), are under trial which shows their action by acting on various target sites like B-cell, Oligodendrocytes, Toll-like receptor Macrophage migration, Acetyl Co-A carboxylase.

Keywords: Clinically isolated Syndrome, Relapse-Remitting Multiple Sclerosis, Lhermitte sign, Malonyl Co-A.

INTRODUCTION-

It is an inflammatory neurological condition that is developing that is marked by inflammation and the breakdown of the sheath that surrounds and shields the nerve fiber. Lesions in the covering that surrounds the nerves in the brain and spinal cord are caused by this disorder [1].

Types of Multiple Sclerosis [2]

- *Clinically isolated Syndrome:* The first event of neurologic symptoms may last for 24 hours.
- *Relapse-Remitting Multiple Sclerosis:* In this onset of new or worsening symptoms can be observed, which is followed by periods of remission when symptoms either completely disappear or get better.
- *Primary Progressive Multiple Sclerosis*: The symptoms worsen gradually with no sudden remissions or relapses. People may go through periods of stability during which their symptoms may get worse and then go better.
- *Secondary Progressive Multiple Sclerosis:* This condition will progressively worsen once the person has first periods of relapse and remission.

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Received Date: April 25, 2024
Accepted Date: May 18, 2024
Published Date: May 21, 2024

Citation: Aayushi Jaiswal. Multiple Sclerosis: A Brief Overview of the Disease, Its Pharmacotherapy. International Journal of Brain Sciences. 2024; 1(1): 13–25p.

SYMPTOMS

Frequent symptoms may include muscle weakness, numbness, tingling, fatigue, vertigo, tremor, vision complications, pain, Lhermitte sign, sexual dysfunction, muscle spasms, bladder problems, and bowel problems.

General causes of Multiple Sclerosis [3]

- *Age:* Shows its effects on the 20 to 40 age group.
- *Gender*: Males are less affected when compared to females.
- *Genetic factor:* Requires environmental trigger for Multiple Sclerosis to evolve in people with particular genetic factors.
- *Smoking:* A person who smokes is more prone to develop Multiple Sclerosis. Smokers have more lesions and brain shrinkage when compared to non-smokers.
- *Infection:* Exposure to a virus like Epstein Barr virus may raise the risk of Multiple Sclerosis.
- A lack of cyanocobalamin and calcium also plays a significant part in the onset of multiple sclerosis. Vitamin B has a significant role in production of myelin.

DIAGNOSIS [4]

Generally involves an MRI Scan of the brain and spinal cord to reveal the lesions.

Spinal Fluid analysis [5]: analyse antibodies IgG elevated oligoclonal Immunoglobulin bands identified in CSF of Multiple Sclerosis patients.

Evoked Potential test [4–5]: Measures electrical activity in response to stimuli.

PATHOPHYSIOLOGY

The myelin sheath is destroyed by autoreactive B cells, T cells, and macrophages that penetrate the blood-brain barrier. Cd 4+ T cell may react with components of myelin and result in the release of cytokines resulting in axonal loss and demyelination. Some autoreactive B-cell is capable of crossing BBB and mature in CNS resulting in Destruction and inflammation [6]. As myelin is provided to neurons by oligodendrocytes therefore in multiple sclerosis process of remyelination may occur up to some extent but as the disease progresses the action of oligodendrocytes may not last forever [7].Malonyl Co-A also plays an important role in the production of myelin, biotin may act as a cofactor in the generation of malonyl Co-A from acetyl Co-A carboxylase[8].

Expanded Disability Status Scale [9]: The scale ranges from 0-10. Based on its measurements impairment to the functional system can be assessed.

PHARMACOTHERAPY

FDA approved drugs currently being used in treatment of Multiple Sclerosis.

Teriflunomide (Aubagio) [10]

Dosag: Oral-7 mg or 14 mg once daily [11].

Mechanism of Action: Prevents immune cells from multiplying which results in a decreased number of B-cell and T-cell.

Indication: Relapsing-Remitting Multiple Sclerosis.

Adverse Effect: Difficulty in breathing, abnormal liver function tests, loose stools, headache.

Interferon Beta 1a (Rebif) [12]

Dosage: Subcutaneous injection 22 mcg or 44 mcg, 3 times/week

Mechanism of Action: It shows its action by decreasing inflammation and immune response that attacks its body's myelin.

Indication: Relapsing-Remitting Multiple Sclerosis, Secondary Progressive Multiple Sclerosis.

Adverse Effect: Joint and muscle pains, fatigue, vomitings, depression, chills and fever.

Glatiramer Acetate (Copaxone) [13]

Dosage: 40 mg/ml injected 3 times/week.

Mechanism of Action: It acts by blocking myelin damaging T-cells.

Indication: Multiple sclerosis with relapse remitting, secondary progressive, and clinically isolated syndromes.

Adverse Effect – Irregular heart rythms, difficulty in breathing, chest pain, rashes.

Cladribine (Maveclan) [14]

Dosage: 3.5 mg/kg orally.

Mechanism of Action: Targets certain types of leukocytes which are responsible for an immune attack in Multiple Sclerosis. Temporary reduce both T and B lymphocytes without suppression of the Immune system.

Indication: Relapse Multiple Sclerosis, Secondary Multiple Sclerosis.

Adverse Effects: Melena, blood in urine, fever,difficulty in passing urine, rashes and cough.

Promising Novel Drugs Under Clinical Trials for the Treatment of Multiple Sclerosis

Section A

Ocrelizumab

Trial Phase: FDA approved Retrospective analysis under study

Dosage: Ocrelizumab 600 mg, Placebo 300 mg in two doses

Indication: Relapse -Remitting and secondary progressive Multiple Sclerosis

Target site: B-cell

Mechanism of Action: Depletes circulating immature and mature CD-20 expressing B-cell.

Bruton Tyrosine Kinase Inhibitor-Evobrutinib

Trial Phase: Phase 2 trial

Dosage: Drug dose divides into five groups

25 mg once daily

75 mg once daily

75 mg twice daily

Placebo: 240 mg twice daily

120 mg twice daily

Indication: Relapse-Remitting and secondary progressive Multiple Sclerosis

Target Site: B-cell

Mechanism of Action: Receptors in B cell and myeloid cell plays a important role by helping BTK to transmit signals . Evobrutinib may inhibit the role of BTK by blocking B-cell activation and cytokine release.

Clemastine

Trial Phase: Phase 2 trial

Dosage: 5-36 mg twice daily, Placebo-5-36 mg

Indication: Optic neuritis in Multiple Sclerosis, Relapsing-Remitting

*Target Site: O*ligodendrocytes

Mechanism of Action: Oligodendrocytes can form myelin. Clemastine fumarate may cross BBB and stimulate differentiation of oligodendrocyte precursor cells to myelinate cell

Ibudilast

Trial Phase: Phase 2 Trial

Dosage: Less than 100 mg per day

*Placebo pills:*2-3 divided doses

Indication: Primary and secondary Multiple Sclerosis.

Target site: Toll-like receptor Macrophage migration.

Mechanism of Action: Inhibit toll-like receptor and macrophage inhibition**.**

MD1003 (biotin)

Trial Phase: Phase 3 trial

*Dosage:*100 mg thrice a day

Placebo 100 mg thrice a day

Indication: Progressive Multiple Sclerosis and optic neuritis.

Mechanism of Action: Acetyl Co-A carboxylase Activate Acetyl Co-A carboxylase to promote Myelin repair.

DISCUSSION

Ocrelizumab [15]

It's Humanized Anti-CD20 monoclonal antibody that depletes CD-20 expressing B -Cells mainly in Primary Progressive Multiple Sclerosis and Relapsing form.The pathogenesis of multiple sclerosis involves B cells which is responsible for cytokine, antigen and antibody production.

Mechanism of Action: Ocrelizumab selectively depletes CD-20 expressing circulating immature and mature B cells while preserving the capacity for B cell reestablishment and pre-existing humoral activity [15].

Eligibility Criteria [16]

Age: 18 to 55

EDSS*:* 3.0 to 6.5

An elevated IgG oligoclonal band in Cerebrospinal fluid

Trial design

600 mg ocrelizumab as two infusions of 300 mg Or placebo every 24 weeks was randomized in ratio of 2:1.

End Result

The percentage of the patients within 12 weeks confirmed disability progression was 32.9% with ocrelizumab versus 39.3 with placebo. Within 24 weeks confirmed disability progression of 29.6% with ocrelizumab versus 35.7% with placebo was seen in patients.

Adverse Effects [17]: In case of Relapsing Multiple Sclerosis adverse reactions with Ocrelizumab are Back ache, Upper and Lower Respiratory tract infections, Joint pains, Depression, Infections associated with Herpes Virus, Anaphylactic reaction to infusion.

CONCLUSION-

Compared to placebo, ocrelizumab demonstrated reduced rates of clinical and MRI progression in patients with primary progressive multiple sclerosis. Ocrelizumab's safety and efficacy in the real world are currently being evaluated as part of The MuSicalE STUDY [18].

Bruton Tyrosine Kinase Inhibitor-Evobrutinib

Evobrutinib, a selective oral bruton tyrosine inhibitor, suppresses the release of cytokines and B-cell activation. It also prevents proinflammatory M1 macrophage activation, differentiation, and polarization, as well as cytokine release.

Eligibility Criteria of Patients for Trial [19]

Age: 18-65

EDSS: Not more than 6 to 10

Method [19]

Phase 2 trial was conducted at 54 centres in Europe and Russia. After 4 weeks of screening, patients were randomly assigned to Five groups in a ratio 1:1:1:1:1 ratio. This was a Placebo-controlled randomized trial.

They also used Dimethyl Fumarate as a reference by comparing it with Evobrutinib and placebo.The doses of drug, placebo and DMF were divided as follows-

Oral Evobrutinib-25 mg once daily

75 mg once daily or twice daily

Placebo o– 120 mg twice daily for the first week and 240 mg twice daily.

Patients in the placebo group were randomized to receive 25 mg of Evobrutinib once daily for an additional 24 weeks while patients receiving DMF or Evobrutinib continued to receive the same medication. A 4-week safety follow-up phase was also conducted following the trial's completion.

End points [19]

The total number of Gadolinium-enhancing lesions found on MRI at weeks 12, 16, 20, and 24 was the primary outcome.

Results [19]

267 participants in all were allocated to a trial group. Patients with relapsed multiple sclerosis who received 75 mg of evobrutinib once daily had significantly fewer enhancing lesions throughout weeks 12 through 24 as compared to those who received a placebo. During the trial, no recorded deaths occurred. At 52 weeks, greater Evobrutinib doses were linked to a higher rate of increase in Lipase, ALT, or AST levels compared to other study groups. The trial has some limitations as it lead to hepatobilary disorders along with alterations in aminotransferase levels.

Adverse Effects [20]: Diarrhoea, nasopharyngitis, urinary tract infections, rise in alanine aminotransferases were most commonly observed**.**

Goals of treatment: Decrease the rate of relapses and slowing disability progression was the primary goal of the treatment

Clemastine Fumarate

The patients with myelin injury shows impaired conduction of action potentials which results in development of neurological dysfunction in the affected pathway. Oligodendrocytes is responsible for enabling saltatory conduction of action potentials and ensheathing of axon. If differentiad terminally it results in formation of myelin along with enwrapping axons in central nervous system. Finally causing demyelinating damage to the anterior visual pathway.

Oligodendrocyte Differentiation takes place as follows [21]

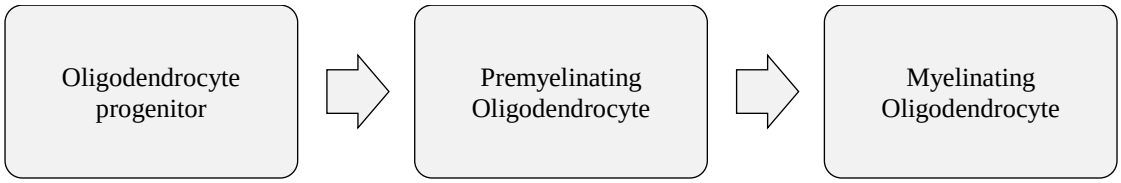

Figure 1: Oligodendrocyte Differentiation

About the Drug-

Clemastine Fumarate is a first-generation antihistamine efficient in inducing oligodendrocyte differentiation and off-target antimuscarinic effects.

Mechanism of Action

Clemastine fumarate crosses the Blood Brain Barrier and stimulates the differentiation of oligodendrocyte precursor cells (progenitor cells) leading to the formation of Myelin in this way it acts as a remyelinating agent.

Eligibility Criteria of patients for Trial-

EDSS: 2.2 minimal disability in two functional system

The average age of patient-40 years

The patient must be suffering from MS for less than 15 years

The patient must have a demyelinating injury in the visual pathway having VEP100 latency in at least one eye of 118 ms.

Method [22]

Medication was administered as unmarked blue capsules of 5-36 mg Clemastine Fumarate or placebo.

They divided patients into two groups.

Group 1: 25 patients

Active treatment: 90 days, 5-36 mg orally twice daily

Placebo: 60 days

Group 2-25 patients

Active treatment -60 days

Placebo-90 days

VEP is visual evoked potential induced by visual stimuli such as alternating checkboard patterns on a computer screen.

Results [23-24]

No Relapses occurred during the Trial. VEP latency was reduced by 1.7 milliseconds/eye during treatment. In each visit adverse events were documented. Laboratory parameters like transaminases, triglycerides, creatinine, and thyroid stimulating hormone concentrations were documented. The effect of Clemastine Fumarate was continuous throughout the timeframe of the study.

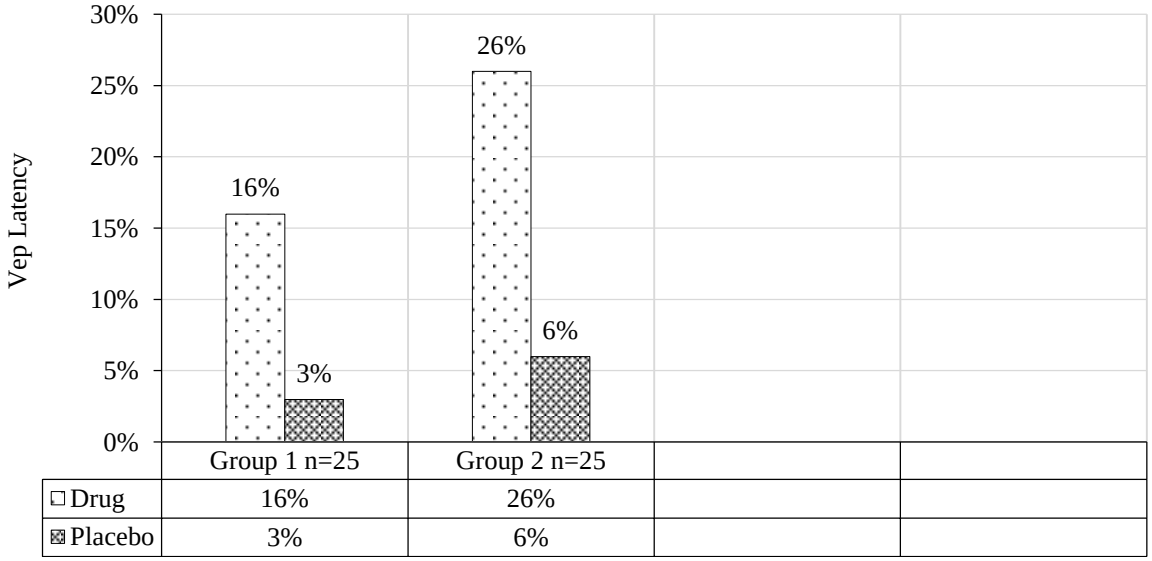

Figure 2. Graph representing VEP latency of Drug vs Placebo.

Graph representing the percentage of improvement after administering clemastine fumarate and placebo to the Multiple Sclerosis patients resulting in reduced VEP latency by 1.7 millisecond/eye during treatment.

Latency improvement of more than 6 ms was observed in group 1 and group 2 with 16% and 2% while on treatment compared with placebo with 3% of group 1 and 6% of group 2 .

Ibudilast

Toll-like receptors which are expressed on macrophage and the dendritic cell gets activated by Pathogen associated molecules that are different for different pathogen and result in the production of cytokines which may finally lead to inflammation.

Mechanism of Action

Ibudilast is responsible for inhibition of nucleic phosphodiesterases, macrophage migration inhibitory factor, toll-like receptor 4 by crossing blood brain barrier and having effects on the Central nervous system. In Multiple Sclerosis toll-like receptors 4 and macrophage inhibitor factor increased in Cerebral spinal fluid patients with primary Multiple Sclerosis

The goal of Treatment [25]

To slow the Progression of neurologic impairment which may arise from permanent tissue injury which is the degree of brain atrophy.

Eligibility Criteria [26]

Age: 21 to 65

EDSS: 3.0-6.5 and clinical evidence in medical record progression of disability in preceding two years at least by o.5 points

Diagnostic Criteria [27]

Primary or Secondary Multiple Sclerosis with typical lesions on two or more following regions-

- Proventricular
- Juxtacortical
- Spinal cord
- Infratentorial (brain stem and cerebellum)

Method [26]

Ibudilast was randomly assigned in a 1:1 ratio.

Dose: >100 mg per day

Placebo: 2 to 3 divided doses for 96 weeks

For first two weeks 60 mg of ibudilast or a matching placebo per day, later the dose was increased to 100mg of Ibudilast or an equivalent number of placebo capsules per day.

The dosage modifications are done based on side effects including vomiting, diarrhoea and vertigo to 60 mg, 80 mg, or 100 mg of Ibudilast or placebo. Safety visits was conducted for every 4 weeks

Clinical disability, according to the EDSS score was observed for every 24 weeks. The brain parenchymal fraction, which measures the pace of brain degeneration, ultimately decided the outcome. The brain parenchymal factor is the amount of brain tissue present within a contour that covers the entire brain, including the Cerebrospinal Fluid. As atrophy increases the CSF replaces brain tissue and brain parenchyma reduces.

Results [26]

With Ibudilast, the change in brain parenchymal fraction was -0.0010 per year, compared to -0.0019 per year with a placebo. This indicates that Ibudilast causes around 2.5 milliliters less brain tissue loss over the course of 96 weeks.

The adverse effects included– Gastrointestinal symptoms, headache and depression.

Ibudilast was responsible for the slower progression of brain atrophy which may finally lead to slower progression of Multiple Sclerosis.

Adverse Effects [28]: Depression, gastrointestinal disturbances and headache.

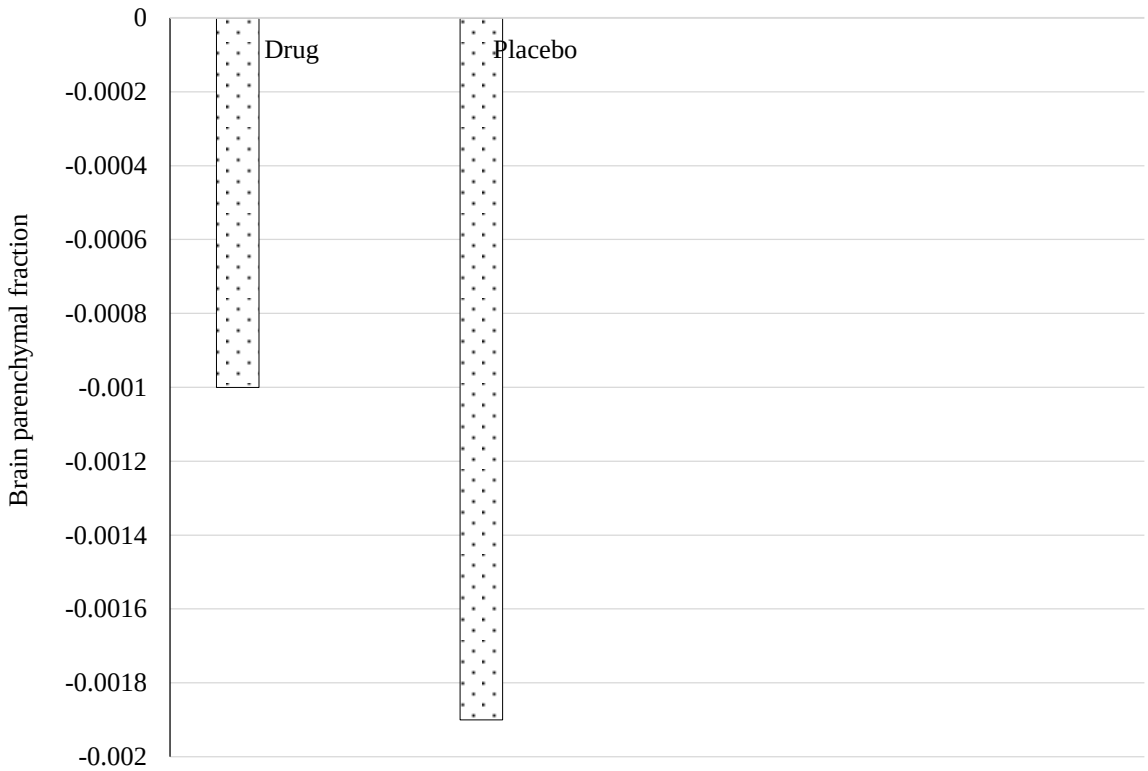

Figure 3. Graph showing brain parenchymal loss Drug vs Placebo.

This is a graph that illustrates the rate of change in brain parenchymal fraction for patients with multiple sclerosis while taking Ibudilast and a placebo. The rate of illness progression decreases with increasing brain tissue loss.

MD1003 (High dose Biotin) [29]

As in Multiple Sclerosis, Myelin degeneration takes place Malonyl Co-A plays an important role in the production of myelin. Synthesis of malonyl Co-A requires biotin as cofactor. Chronic demyelination and mitochondrial dysfunction lead to virtual hypoxia.

Myelin covers the optic nerve therefore inflammation or demyelination may lead to acute optic neuritis.

Mode of Action

MD1003 is an oral composition of high-dose pharmaceutical-grade biotin.

Biotin (cofactor)

Acetyl carboxylase Malonyl Co-A

Malonyl Co-A is an essential component of the myelin sheath. In absence of biotin, fatty acid synthesis is decreased. To increase the supply of precursors for fatty acid synthesis and Myelin synthesis high-dose pharmaceutical grade biotin is administered.

Biotin is also an important co-factor Pyruvate carboxylase,3-methylcrotonyl C0-A carboxylase and propionyl Co-A carboxylase (expressed in neurons) produce intermediates for the tricarboxylic acid cycle.

MD1003 may activate carboxylases against hypoxia-driven axonal degeneration.

Eligibility Criteria

Age: 18-75 years

EDSS: 4.5-7 with proof of disease progression over 2 years.

Method [29]

The study was 12 months randomized double-blind placebo-controlled trial followed by an open-label 12-month extension phase where all patients received MD1003. Patient was randomised in a 2:1 ratio to receiveMD1003-100 mg thrice a day (orally), placebo-100 mg thrice a day.MD1003 was followed thrice daily for further 12 months.

Neurological assessments were conducted by neurologists every 12 weeks in a placebo-controlled phase.

Results [29]

This trials output showed reversal in MS-related disability in 12.6% of the patient while none of the placebo patients.

Multiple Sclerosis was higher in patients with placebo which is by 50% when compared to a patient with MD1003 which was 31%.

No deaths were recorded at the time of the study. Adverse effects ranged from mild to moderate. Adverse effects with MD1003 include Back Pain, Retina artery occlusion and with placebo includes fatigue.Many studies have confirmed the good safety and tolerability of MD1003. It has also been observed that MS relapse was also decreased. Further results from the ongoing clinical trial may help us to know the safety and efficacy of a drug.

The below table represents brief information about the drugs which are under trial which were discussed above and which may result in massive development in the treatment of Multiple Sclerosis.

SECTION B

Drugs Undergoing Clinical Trials from year 2021[30-32]

1. *Drug:* Orelabrutinib**,** Placebo

   Trial: Randomized Double blind Placebo Controlled

   Phase: 2

   Start Year: 2021

   End Year: 2024

2. Drug -IMU-838 (Vidofludimus calcium)
   Trial: Placebo Multicenter Randomized Double blind Placebo Controlled

   Phase: 2

   Start Year: 2021

   End Year: 2024

3. *Drug*: Remibrutinib, Teriflunomide

Trial: Randomized Double blind Double dummyParallel group study

Phase: 3

Start Year: 2021

End Year: 2029

CONCLUSION-

There are various types of Multiple Sclerosis like Clinically isolated Syndrome, Relapse - Remitting Multiple Sclerosis, Primary Progressive Multiple Sclerosis, and Secondary Progressive Multiple on which several novel drugs have shown promising results in clinical trial.

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