PHARMACOTHERAPEUTIC STRATIFICATION FOR MULTIPLE SCLEROSIS IN THE COVID-19 PANDEMIC

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Abstract: Around the globe, 2.3 million people are diagnosed with multiple sclerosis, out of this nearly 1 million peoples from the United States over the age of 18. MS is a chronic, immune-mediated, and demyelinating disorder of the central nervous system, sometimes peripheral also has no cure so far. Being the disease of neurons it's difficult to target exclusive pathologies of MS but still many drugs can provide symptomatic relief in MS. To date no one disease-modifying agent available to eradicate the root cause of this disease. The COVID-19 pandemic and the many questions about the post-pandemic period complicate the management of patients who need therapies that impact the immune system. Research is continuously going on to explore the pathology and to develop pharmacotherapeutics to target the same. We summarised all pharmacotherapeutics available to treat MS, as well as their mechanistic approaches, in a patient with COVID-19 in this study.

Keywords :- COVID-19, Multiple Sclerosis, Pharmacotherapy, Pandemic

INTRODUCTION: -

In the case of novel coronavirus (COVID 19), multiple sclerosis (MS) patients are twice as prone to be affected by infections as the normal community. [1] Patients with MS who are commonly on long-term immunotherapies are concerned about an epidemic of a severe acute respiratory syndrome caused by a COVID-19. [2] Management of disease-modifying therapies in MS during the COVID-19 pandemic is a controversial issue. COVID-19's risk and course in patients with MS are still unknown. Even though neurological dysfunction and comorbid disorders are important factors, the function of immune-based disease-modifying therapies (DMTs) in MS patients has received the most publicity. [3] MS is an autoimmune disorder represented by persistent neuroinflammatory demyelinating white and gray matter lesions along with synaptic dysfunction on the central nervous system (CNS) associated with inflammatory pain and neurodegeneration (as assessed by magnetic resonance imaging (MRI), Evoked potential, and Spinal fluid examination). [4] Clinical characterization and evaluation, however, are challenging due to disease heterogeneity. The Expanded Disability Status Scale (EDSS) is by far the most extensively adopted outcome measure in MS, providing a quick assessment of disability status, despite being widely criticized for its shortcomings. [5] Relapses and continuing focal inflammatory behaviour on MRI are linked to a worse short- to medium-term prognosis, contradicting natural history research, leading to a rise in the use of a No evident disease activity (NEDA) as a treatment target. This includes no relapses, no impairment development, and no MRI activity as disease activity indicators. [6-8] In terms of the effectiveness, or relative efficacy, of individual DMTs, this becomes less relevant in the sense of a NEDA treat-2-target strategy. Selecting a DMT with a lower efficacy rate, i.e., a lower NEDA rate, basically ensures that a higher percentage of treated patients would need to be transferred to higher efficacy therapies over time to achieve NEDA. [9] It is the world's largest cause of neurological impairment in adolescents and young adults slightly prevalent in women and affects approximately 2.3 million people worldwide. [10, 11] While MS is traditionally thought to be a CNS disorder, several findings have shown that MS have biochemical alteration associated demyelination in the peripheral nervous system (PNS) due to the overlap in myelin content like myelin basic protein (MBP) and myelin-associated glycoprotein (MAG) between the CNS and PNS. [12, 13] MS is characterized by immune cell invasion (secretion of reactive species, cytokines, chemokines, autoantibody) thereby activates microglia, astrocyte proliferation, subsequent blood-brain barrier (BBB) disruption, and axonal death, with neuronal demyelination and subsequent degeneration. The relapsing-remitting type of MS (RRMS) is identified by episodes of neurological decline interspersed with periods of normalness in an early phase, due to new remyelination by oligodendrocytes for that duration of time. [14] while progressive MS (PMS) is characterized by gradually upraising neurological impairment giving rise to primary and secondary forms over a while. [15]

Treatments: -

There are three types of MS drug therapy currently available:

1) Treatment of clinical attacks (acute relapses)

2) Disease-modifying therapies

3) Symptomatic treatments, mostly for Lower Urinary Tract dysfunctions

Treatment of clinical attacks (acute relapses): -

- **Methylprednisolone: -**

Intravenous exposure to high doses of corticosteroids, mainly methylprednisolone, is the first-line treatment for acute relapses in MS. [16] In patients with multiple sclerosis exacerbation, short-term intravenous methylprednisolone (IVMP) combined with an oral prednisone taper (OPT) regimen improved urinary tract symptoms and did not raise the risk of Urinary Tract

Infections (UTI) incidence. [17] The efficacy of an OPT after a corticosteroid pulse is non-superior to IVMP plus only in case, the safety and tolerability profile is comparable. [18]

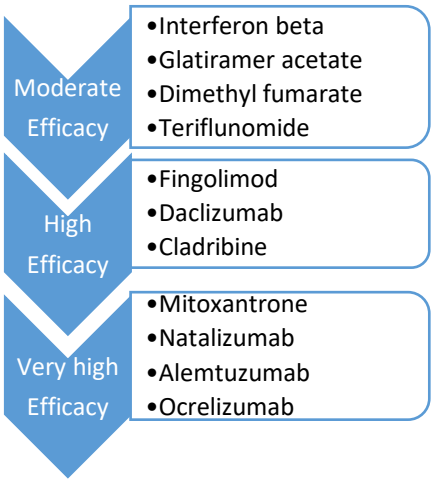
For patients who do not improve or cannot tolerate methylprednisolone, adrenocorticotropic hormone (ACTH) in a gel formulation administered intramuscularly or subcutaneously is a second-line therapeutic alternative. [19] In glucocorticosteroid (GCS)-refractory multiple sclerosis relapses, therapeutic plasma exchange (TPE) is commonly used and showed Moderate to marked benefit in 78.8% of patients. [20] Treatment with anakinra and methylprednisolone in COVID-19 patients with active MS hyper inflammation and respiratory failure could be a viable therapeutic option. [21]

DISEASE-MODIFYING THERAPIES (DMTs): -

Since a thorough discussion of each DMT is outside the reach of this review, thus we have attempted to summarise the most critical characteristics of each DMT. DMTs are drugs that are used to reduce the number, length, and severity of relapses while sustaining remission and slowing progression. These therapies will help MS patients live a better life by reducing disability and MRI lesions.

- **Classification based on effectiveness / activity: -**

Patients who choose high-efficacy treatments have a better chance of meeting NEDA with their first choice of therapy.



Interferon beta formulations: - Interferon-beta therapies, which were first introduced in 1993 (interferon beta1b) and 1996 (interferon beta1a), significantly improved the course of MS on both clinical and radiological measures in clinical trials. Type I (IFN-α and IFN –β) and Type II (IFN-γ) interferons bind to Interferon receptors (IFNGR1 and IFNGR2), activating the Janus kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) pathway, but the resulting STAT1 homodimer complex is different from the STAT1/STAT2/IRF9 complex produced by type I interferons. [22] Type I interferon induces antiviral, antiproliferative, and antitumor factors, while Type II interferon induces mild antiviral yet strong immunomodulatory factors. [23]
There are three commercially available formulations of recombinant interferon-beta:

- Interferon-beta
  1. IFN-beta-1a
     - Avonex
     - Rebif
  2. IFN-beta-1b
  3. Peg-IFNbeta-1a

1 **Interferon-beta-1a: -**

- Avonex: - (prefilled syringe, 30mg IM weekly) [Biogen Idec; Cambridge, MA]

It is a moderately effective approach involving Type 1 interferon stimulation in a Pulsatile manner. Avonex was found to be the least to cause injection site reactions (ISR) than Rebif and Betaseron. [24] In MRI studies, IFN-1a therapy decreases T2 and gadolinium-enhancing lesions, as well as grey matter atrophy, when compared to placebo. Furthermore, IFNs' antiviral properties could point to potential therapeutic applications for IFN- in the treatment of viral infections like COVID-19. [25]

- Rebif: - (prefilled syringe or cartridge, 22/ 44mg sc TIW) [EMD Serono; Rockland, MA]

It is also a moderately successful strategy that involves continuous Type 1 interferon receptor stimulation and associated downregulation. According to International Center for Neurological Restoration (ICNR) patients with relapsing-remitting MS who were treated with Rebif had a substantial reduction in the number of attacks, the disability scale ranking, and the number of lesions on MRI. [11]

2. **Interferon beta-1b: -** (Freeze-dried, 250mg s.c. alt.day)

- *Betaferon®/Betaseron®* [Bayer HealthCare Pharmaceuticals; Whippany, NJ]
- *Extavia®* [Novartis Pharmaceuticals Corporation, East Hanover, NJ].

It involves sustained Type 1 interferon receptor stimulation and associated downregulation and it is also a moderately effective approach. Evidence from patients with the most extreme types of COVID19 also shows a significant reduction in IFN-stimulated gene expression, which is further associated with AE-like lymphopenia.[26]

However, ISR, flu-like symptoms, irregular LFTs (Liver Function Tests), thyroid dysfunction, Atypical hemolytic uremic syndrome (aHUS), and leucopenia are serious side effects that may reduce a patient's adherence to Interferon beta-1a and 1b, resulting in disease progression. [24, 27, 28]

3. **Peg-IFNbeta-1a** *(Plegridy)*

It is a moderately effective Pegylated analog that involves continuous type 1 interferon receptor stimulation. (long-circulating half-life about 7 days)

PEG-IFN beta1a 125 µg subcutaneously administered every 2 or 4 weeks that prove to be safe and effective. [29, 30] Since Avonex and Rebif have a short half-life (10 hours) and are associated with a slew of side effects, PEGylation can be used to enhance IFN therapy in MS patients.

Chronic administration of PEGylated proteins induces vacuolation of the renal epithelium, often at toxic concentrations. [31]

Treatment with peginterferon beta-1a was correlated with a lower annualized relapse rate (ARRs)than treatment with either Glatiramer Acetate or Teriflunomide when comparing efficacy based on Real-world Propensity Score. [32]

- **Glatiramer Acetate** (*Copaxone*)

Glatiramer Acetate (GA) is an Immunomodulatory synthetic copolymer focused on the structure of myelin basic protein in terms of amino acid composition. It involves the induction of glatiramer-reactive regulatory cells, such as CD4+ and CD8+ T-cells, which are thought to invade the brain and produce bystander suppression, anti-inflammatory effects, and neuroprotection through cross-reactivity with myelin antigens. [33] GA is a moderately effective therapy that isn't linked to immunosuppression, autoimmune disorder, infections, or the formation of neutralizing antibodies. [34]

Interferon-1a or glatiramer acetate are often used as first-line treatments for pediatric-onset multiple sclerosis (POMS). [35] Along with ISR, lipoatrophy, and flushing reactions, the unpredictable injection site reaction, Embolia cutis medicamentosa (ECM), also known as Nicolau syndrome, has been documented with IFNs, but a very unusual necrotic ECM has been reported with GA in MS patients. [36]

The only multiple sclerosis treatment that has been given the pregnancy category B by the US Food and Drug Administration is high-dose GA (40 mg sc) given three times weekly. It is reliable, safe, and well-tolerated, with no demonstrated reproductive toxicity in treating RRMS. [37, 38] The use of the enzyme-linked immunospot (ELISPOT) technique to measure brain-reactive B-cell activity offers clinically significant predictive probabilities of individual patients' treatment response to GA or IFN, which may help with first-line treatment selection. [39]

In MS patients, GA was linked to a lower risk of COVID-19. [40] GA reduced depressive/anxiety-like behaviors and cognitive impairment in social isolation (SI) reared mice. [41]

- **Mitoxantrone** (*Novatrone*)

Mitoxantrone(MTX) is an anti-neoplastic anthracenedione derivative that inhibits topoisomerase enzyme as an intercalating agent as well as Inhibiting Autoreactive T cells, B cells, and antigen-presenting cells (macrophages in the periphery and microglia cells in the CNS) and thereby acting as an immunodepletion. [42, 43]

MTX is classified under non-selective IRT. [44] Selective immune reconstitution therapy (SIRT) is the most promising MS treatment option. This immunosuppression therapy is administered in short-term courses, resulting in long-term immune system benefits and the prevention of nerve tissue damage. [45] Cardiotoxicity, early and late-LV dysfunction, bone marrow suppression, and hematological malignancies are only a few of the possible adverse effects (AE) of MTX, which range from mild to potentially life-threatening. [46]

MTX can be considered as a valuable therapeutic choice for patients who are on the borderline of RRMS and SPMS after comparing its clinical and neuroradiological efficacy in different types of MS,[47] And With a dose of 12 mg/m2, IVI three times a month for two years to a maximum dose of 140 mg/m2 MTX prevents relapses and delays disease progression.[48] In contrast to other high-efficacy MS disease-modifying therapies, MTX is a low-cost therapy, which can be advantageous in low-resource environments. [49]

- **Natalizumab** (*Tysabri*)

Natalizumab is a second-line DMT for MS that has been approved by the FDA. And It's an Anti- integrin α4β1, selective adhesion molecule inhibitor monoclonal antibody that prevents T- and B-lymphocytes from crossing the blood-brain barrier. [50]

Furthermore, as an off-label therapy, at a dose of 300 mg i.v. 4-weekly it has consistently reduced disease activity in POMS patients, including children with aggressive disease onset, with no significant adverse effects (AEs) identified to date. [51, 52] However, because of the possibility of progressive multifocal leukoencephalopathy, a severe central nervous system disorder, this agent's use is limited. [53]

- **Fingolimod** (*Gilenya*)

Fingolimod is the first orally administered promising prodrug agent to be approved by the FDA and the National Institute for Health and Care Excellence (NICE) for use in patients with highly active relapsing-remitting multiple sclerosis (RRMS). [54]In relapsing-remitting multiple sclerosis, fingolimod, 0.5 mg p.o, outperformed glatiramer acetate, 20 mg, in terms of clinical effectiveness and had a better benefit-risk ratio than fingolimod, 0.25 mg.[55]As fingolimod crosses the blood-brain barrier, it is phosphorylated to form fingolimod-phosphate, which modulates lymphocyte sphingosine 1-phosphate 1 (S1P1) receptor and then induces S1P1 down-regulation, preventing lymphocyte egress and reducing autoaggressive lymphocyte infiltration into the CNS. [56]

The wide range of adverse effects of fingolimod is due to the pervasive presence of the S1P receptor, which includes hypertension, heart block, bradycardia, and macular oedema. [57] However, we discovered that MS patients treated with fingolimod have a borderline substantial increased risk of invasive cancer and that it affects tumorigenicity by immunosuppressive effects. [58]

Aside from treating MS, in addition, fingolimod has been shown to enhance corneal graft survival, reduce ischemia-reperfusion injury, protect nerve cells, suppress sarcoma cell proliferation and metastasis, prevent diabetes, and treat autoimmune uveitis. [59, 60] It is also used in the management of triple-negative breast cancer, it prevents tumour growth by inducing apoptosis in tumour cells (TNBC). [61] Discontinuation of fingolimod in patients with active COVID-19 can result in a rebound of disease activity, and albeit its, continuous immunosuppressive properties, still, it is a safe approach for treating MS in COVID-19 patients. [62, 63]

- **Dimethyl Fumarate** (*Tecfidera*)

DMF has a pleiotropic response in promoting the Th1–Th2 transformation, causes moderate apoptosis in memory T and B cells, improves microglia activation, downregulation of NFKb, and provides neuroprotection by modulating the Nrf2-dependent antioxidant mechanism. [64-66] During the height of COVID cases in Lecco's province between March and May 2020, DMF developed a self-limiting COVID-19 infection as a result of these immunomodulatory

effects. [67] Since lymphopenia is not a dose-dependent AE just like other drugs, the most realistic method for restricting it is to monitor absolute lymphocyte counts regularly. [68]

- **Alemtuzumab** (*Lemtrada*)

Alemtuzumab is a humanized monoclonal antibody that reprograms the immune system rapidly by profoundly depleting B and T cells that express the CD52 (cluster of differentiation 52) receptor. [69] While it is currently used in patients with relapsing-remitting multiple sclerosis as a (nonselective) immune reconstitution therapy. [70] However, on the other hand, is linked to a high risk of secondary autoimmune disease (thyroiditis)which restricts its use. [71] COVID-19 symptoms were very mild in patients who received alemtuzumab. Treatment-induced immune reconstitution can result in positive changes in the immune system's defense against COVID-19. [72]

- **Teriflunomide** (*Aubagio*)

In COVID-19 infection, teriflunomide may have both antiviral and immunomodulatory properties. [73] They interfere with viral replication by blocking de novo pyrimidine synthesis (Dihydro-orotate dehydrogenase inhibitor) in infected cells and thus exerting an antiviral effect. Teriflunomide, on the other hand, could dampen unwanted host immune activation immune cells .by reducing cytokine production (IL-6), decreasing immune cell activation, and antiproliferative property through depletion of the intracellular pyrimidine pool. Also can be used to avoid an excessive/fulminant host immune response while retaining adequate virus protection. [2, 74]

- **Cladribine** (*Mavenclad*)

Cladribine is an oral artificial chlorinated deoxyadenosine (purine) analog that inhibits enzymes involved in DNA metabolism (adenosine deaminase), resulting in a targeted and long-term depletion of circulating B-cell subsets as well as T-cell migration. [75] It tends to be a semi-selective immune-reconstitution therapy (IRT) that does not necessitate the same level of control as other continuous immunosuppressive and non-selective IRTs. [76] And allowing patients to combat (COVID-19) infections and mount immune responses to both infections and vaccines. [77] After COVID-19 treatment with cladribine, the antibody response was normal. [78] Patients with multiple sclerosis (MS) that are given cladribine tablets (CTs) 10 mg (3.5 mg/kg cumulative dose for 2 years) have the lowest chance of developing malignancies and lymphopenia. [79, 80]

- **Ocrelizumab** (*Ocrevus*)

Ocrelizumab is a humanized monoclonal antibody that targets the CD20 marker in B cells, causing antibody-dependent cellular cytolysis and complement-mediated lysis. It has a high efficacy and maintenance immunosuppressive effect. [81, 82] In patients with primary progressive MS (PPMS), ocrelizumab is the first drug to show a reduction in rates of clinical and MRI-evidenced progression. [83] Two weeks after a single dose of 300 mg ocrelizumab, CD3+CD20+ T cells and CD19+CD20+ B cells were effectively depleted. [84]

T-cell lymphocytes and natural killer cells play a major role in the host immune response to viral pathogens. As a result, B-cell depletion in MS patients receiving Ocrelizumab does not significantly slow virus clearance from the body, [85, 86] and since B-cell suppression was found to be negatively proportional to disease progression in MS patients treated with Ocrelizumab, it may help to prevent severe COVID-19 infection. [87]

Infections with Babesia microti (B. microti) have been found in patients with lymphoproliferative disorders who have been treated with ocrelizumab. Hypogammaglobulinemia is also a possibility. [88] Its use after covid-19 vaccination is restricted since it decreases vaccine responses. [89]

Symptomatic treatments, mostly for Lower Urinary Tract dysfunctions: -

It is proposed that 80–90 % of MS patients will experience certainly Lower Urinary Tract Symptoms(LUTS) throughout their illness.[90]LUTS like Detrusor sphincter dyssynergia (DSD), Neurogenic Detrusor Overactivity /detrusor hyperreflexia, and Detrusor hyporeflexia are all common causes of urinary frequency, urgency, and incontinence in MS patients.[91-93]Detrusor hyperreflexia and DSD have been linked to the cervical spinal cord and subcortical white-matter lesions, while detrusor hyporeflexia has been linked to a pontine lesion.[94]LUTS were a significant topic of problems with Ms patients, and they present a challenge to the physician because of treatment outcomes.[95]

A bladder diary, urinalysis, urine culture, and urodynamics should all be included in the assessment of MS patients with LUTS. [91, 95-97] Uroflowmetry and filling cystometry are two urodynamic approaches, which can be used to assess the pressure-volume relationship during non-physiological bladder filling and voiding. [98]

- **Antimuscarinics or Beta-3 Agonist**: -

Either use of antimuscarinics or Beta 3 agonists contribute to a substantial decrease in overall detrusor pressure and a substantial improvement in patient access to care. [99]

Patients with MS who were given mirabegron (oral beta-3 agonists) or antimuscarinic treatment for LUTD show positive outcomes. Despite this, there was no

statistical disparity between the two cohorts at 3 months concerning drug efficacy in all statistically relevant parameters. [100]

Conclusion: -

Patients' treatment shifted from symptomatic to disease-modifying long-term therapy, and neurologists' functions shifted from passively monitoring and predicting patient regression to proactively managing the underlying disease in MS patients. [101]

Patients randomized to 2 years of interferon-beta-1a therapy had poor results than those who received highly active therapy from the start of recent trials of alemtuzumab, ocrelizumab, and daclizumab. Anxiety and depression, it must be concluded, have a major negative effect on medication adherence in MS patients. Patients with MS. who are more accepting of their disease, on the other hand, stick to DMT at a higher pace. [102] Since MS patients are given immunosuppressive drugs, it is thought that they are at a higher risk of developing serious COVID-19. The usage and initiation of high-efficacy drugs should be approached with caution, according to consensus statements, and lower-efficacy medications should be considered safer during the pandemic. [86] Within the treated MS population, interferons and glatiramer acetate were linked to a lower risk of COVID-19, while anti-CD20 therapies were linked to a higher risk. [40]

More definitive proof on COVID-19 in individuals with MS was reported in this article, and it is required to help the MS community find answers to questions about possible risks associated with MS and the use of DMTs during the COVID-19 disease outbreak.

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