

A Brief Review of Multiple Sclerosis Treatments

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Abstract

MS is a well-known disease and chronic inflammation in the central nervous system is one of the diseases whose etiology, despite its well-known autoimmune nature, is still debated, although according to recent studies, the role of viruses such as EBV approved. Based on the different phases that are defined for MS and the degree of progression of the disease, a specific protocol and treatment process is defined for the patient. New and safe treatments for autoimmune diseases have been a constant challenge, although side effects, albeit on a small scale and with few reports, are inevitable; In this study, we tried to classify based on how it is used on drugs used in the treatment of this disease, and at the same time the progress and achievement of new cases such as the use of monoclonal antibodies, despite all the progress made. We still do not fully meet the treatment needs of MS based on studies, in other words, in the classification system and review study, in the group of injectable drugs, we reviewed drugs such as Daclizumab, Alemtuzumab, Natalizumab, Copaxone and Mitoxantron. Oral drugs Fingolimod, Teriflunomide, and Siponimod were also discussed. In addition to discussing MS medication, we reviewed other treatments such as the use of bone marrow stem cells that were previously discussed in preventing bone marrow suppression during severe therapies such as chemotherapy in the treatment of MS.

Keywords: Multiple Sclerosis; MS Treatments

Introduction

Multiple Sclerosis (MS) is an autoimmune nerve disease that causes demyelination and axonal degeneration as inflammatory immune responses (chronic inflammation) in the Central Nervous System (CNS), including the brain and spinal cord. MS is recognized as the most common non-traumatic neurological cause worldwide. The primary course of the disease in most cases includes Relapsing-Remitting MS (RRMS) with recurrent periods followed by recovery periods. More than 50% of these patients develop secondary progressive MS (SPMS) over a period of approximately two decades. [1-6] On the other hand, about 15% of patients have undergone the phase of primary progressive MS (PPMS), which is a continuous and slow deterioration without recurrence of the disease [7,8].

Regarding the etiology of this disease There has also been a lot of discussion, and for example, viruses have always been the underlying etiology of MS. Recent research has shown that antibodies to the virus's ashtray load on glial cells in the brain, leading to disease that the event confirms the research conducted in this field. [9] Contemporary classification guidelines focus on the inflammatory picture of inflammation, which has the ability to appear at all stages of the disease and can be treated with DMTs [10]. We now have access to a number of DMTs for treatment (RRMS) that straw the level of recurrence and severity of inflammation in the CNS is their main target [11]. Over the past decades, there have been several promising advances in the treatment of MS. To date, after years of experimenting with DMTs, such as interferon beta (IFNB) and Glat-

iramer Acetate (GA) (the main treatment options), new highly effective treatments for MS have become available [12]. In 2010, Fingolimod was the first approved DMT oral drug to be an agonist of sphingosine-1-phosphate (S1P) receptors, and a number of other oral drugs have either been approved or are in Phase III testing [13,14]. Monoclonal antibodies are currently being proposed as new therapies, and good progress has been made in the treatment of MS. There is promising progress in the treatment of MS and according to the mentioned cases, the treatment of MS in different phases of this disease is under investigation; But existing drugs are not enough to fully meet future needs due to the complex nature of MS. [15,16] Therefore, in this review article, we have tried to summarize the current existing treatments for MS and review the progress of new MS treatments.

Drugs in use and approved

Injectable drugs

The three main IFNB products are available for administration as first-line DMTs for the treatment of recurrent MS. Stages of double-blind, placebo-controlled clinical trials, phase III were approved [17].

Of these three products, two are injected subcutaneously and the other intramuscularly.

Copaxone

Copaxone, which is a synthetic copolymer of four amino acids and is a synthetic analogue of myelin basic protein; After a randomized clinical trial phase III. Was confirmed and shown to be effective in the treatment of RRMS. [20-18] Copaxone and IFNB have different immunomodulatory effects but have almost the same function in reducing recurrence rates by up to 30% [21], a large observational cohort study showed that treatment with IFNB and Copaxone improved the progression of disability as assessed by the Extensive Disability Status Scale (EDSS) of 6 years of drug use [22], treatment with IFNB and Copaxone is generally considered safe and tolerable. However, both IFNB and Copaxone require periodic and long-term self-injection. [23] Side effects of IFNB include elevated liver enzymes, flu-like symptoms, and adverse reactions at the injection site. On the other hand, Copaxone side effects are adverse reactions at the injection site as well as post-injection reactions that occur in approximately 15% of patients [24,25]. Of the drugs approved for the treatment of MS, human antibodies such as Alemtuzumab, natalizumab, Daclizumab, and Mitoxantrone have been shown to have promising effects, but have side effects and should be injected under controlled conditions [26]. Medications are so common that alemtuzumab, for example, may have severe side effects and therefore require regular and accurate follow-up; Other drugs include multifocal progressive leukoencephalopathy (PML) caused by natalizumab, liver damage, skin reactions and colitis caused by daclizumab, and finally systolic dysfunction and acute leukemia caused by mitoxantrone. The last drug was not reported [30-27].

Natalizumab

Natalizumab, a recombinant human monoclonal antibody, targets the α -4 integrin. This biologic drug inhibits the migration of leukocytes from the peripheral blood to the CNS by inhibiting the binding of leukocytes by α -4 integrin to the vascular cell adhesion molecule (VCAM) located in the endothelial cell [26], interfering with blocking the binding and

subsequent diaphysis of lymphocytes. Blood-brain barrier (BBB) has a beneficial effect on CNS inflammation [31] In a placebo-controlled phase III trial that confirmed Natalizumab, intravenous injection of 300 mg monthly increased RR by 68% Reduced the progression of disability to 42% for 2 years [32] and reduced MRI activity by 92% [33]. Later, Natalizumab was re-introduced in 2006 with a description of risk management programs. [34] The risk of PML classification in patients with MS on Natalizumab underlies treatment duration is due to previous use of immunosuppressants, and the JCV antibody condition indicates JCV infection [35,36]. Studies have shown that after 3 years of using this drug, people who were positive for two factors of previous use of immunosuppressants and anti-JCV antibody were at greater risk [37].

This increases the risk classification in treatment with Natalizumab [38]. However, hypotheses have been proposed to change the dose intervals of the drug to reduce the incidence of side effects, which shows that increasing the dose interval to 8 weeks reduces the saturation of α 4-integrin receptors without affecting the clinical effectiveness while the level of safety properly created in the CNS to prevent PML; Therefore, this change has no negative effect on the effectiveness of the drug [39,40]. Natalizumab treatment may result in the production of stable neutralizing antibodies (NABs) in 4 to 6% of cases, which usually occurs within the first 12 months [41]. NABs have also been shown to be associated with increased infusion-related adverse response rates and may reduce treatment efficacy [42].

Alemtuzumab

Alemtuzumab, a human monoclonal antibody, targets CD52 expressed on natural killer cells (NK), lymphocytes, monocytes, and some other granulocytes [43,44]. Alemtuzumab, through antibody-dependent cytotoxicity (ADCC), causes rapid lymphopenia that lasts for years (average half-life is 22 days) [45]. A course of taking alemtuzumab has long-term effects on the immune system, and the prescription for taking alemtuzumab is currently two courses with an interval of 12 months [46]. Subcutaneous administration of Alemtuzumab was compared with IFNB-1 injection three times a week in two phase III RRMS trials. According to the results, Alemtuzumab increased the annual recurrence rate (ARR) to 55-49%, the rate of progression to 42% to 30%, and lesions. Gadolinium booster reduced MRI by 63-61% [47-49], risks of alemtuzumab treatment include hyper / hypo thyroidism, kidney disease, thrombocytopenia; Secondary autoimmune disease after alemtuzumab treatment also has a long latent period before onset [50]. Secondary autoimmunity after the treatment period, it is prescribed as a second-line drug [42].

Daclizumab

Daclizumab, a human monoclonal antibody, targets IL-2 (CD25) receptor subunit expressed on T cells. Although the effect of Daclizumab on the reduction of CD25⁺ T cells is short and low, but it causes the proliferation of CD56 bright NK cells, which is related to the clinical efficacy of the drug [51,52]. Double-blind randomized trials (Phase II and III trials) showed that daclizumab had a promising effect in both forms of adjunctive therapy for FNB-B1a or placebo (demonstration recorded by MRI) [55-53]. In addition, Daclizumab showed no signs of relapse after stopping treatment [56]. Unique side effects of Daclizumab include skin side effects.

Most skin problems are patches of eczema that usually do not require medication, although mild to severe rashes require discontinuation in 19% of cases. Skin lesions show non-specific features of Athos eczema dermatitis. Infiltration of CD56 + lymphocytes, which were not associated with clinical manifestations [57,58]. Because Daclizumab is approved by the FDA for the treatment of RRMS, it should be prescribed to patients who have an inadequate response to two or more conventional treatments for MS, and due to side effects, evaluate patients' liver function before starting treatment with Daclizumab is required for patients as well as monthly before each dose, and thereafter, up to 6 months after the last dose [59].

Mitoxantron

Mitoxantron by inhibiting topoisomerase type II and disrupts DNA synthesis. Mitoxantron is transported through a disrupted blood-brain barrier (BBB) and may induce microglial death [60,61], as approved by the FDA for rapid recovery of SPMS and RRMS after a number of clinical trials [62,63] Mitoxantron is administered as a monthly infusion at a dose of 12 mg / m², although its cumulative dose is limited due to blood and cardiac side effects [64], Mitoxantron is administered due to severe complications such as acute leukemia and also due to the appearance More effective and less toxic alternative drugs decreased rapidly, which we mentioned at the beginning of the discussion [65].

Oral Medications

Teriflunomide

Teriflunomide has been approved for the treatment of mild to moderate rheumatoid arthritis (RA) [66]. The mechanism of action of this drug is that it interrupts the mitochondrial enzyme involved in the new synthesis of pyrimidine dihydrothymine dehydrogenase (DHODH) [67] Studies in two phase III trials in RRMS showed that Teriflunomide ARR. The placebo reduced the level of progression of disability by 31-36% to 26.27% and showed gadolinium-enhancing lesions by 80% MRI. Studies have shown that Teriflunomide has the same effects on ARR and discontinuation of treatment as IFNB-1a subcutaneously, and that both antiproliferative and anti-inflammatory activities are performed [68,69]. Teriflunomide has been evaluated in a double-blind, randomized, placebo-controlled trial of patients with clinically isolated syndrome (CIS) with silent MRI lesions, leading to recurrence progression and improvement in recent MRI lesions [70].

Including the side effects of Teriflunomide. Increased alanine aminotransferase (ALT), diarrhea, headache, nausea and thinning hair [71,72]. More precisely, according to studies, in at least 10% of the teriflunomide group included inflammation of the nasopharyngeal duct, injection site reactions, alopecia areata, upper respiratory tract infection, headache, diarrhea, serious destructive events in 7.9%. The teriflunomide-treated group was observed [73], the most common reason for stopping teriflunomide treatment being increased ALT. Therefore, periodic evaluation of ALT in the first 6 months of treatment and every second thereafter is recommended [71].

The recently approved oral DMT for the treatment of RRMS is delayed dimethyl fumarate (DMF) administered in a 240 mg capsule twice daily. Although its mechanism of action has not yet been fully elucidated, according to preclinical studies, DMF has immunomodulatory and antioxidant properties similar to other DMTs such as IFNBs, and it has been suggested that DMF activates nuclear factor (2 erythroid deriva-

tives) such as 2 (Nrf2) [74, 75]. DMF was evaluated in two phase III trials in RRMS, which showed a reduction in ARR of up to 53-44%, a progression of disability of up to 32-32%, and an MRI of gadolinium-enhancing MRI of up to about 94-75% [76, 77]. In addition, phase III trials showed that DMF treatment reduced clinical disease and MRI activity [78]. Common side effects of DMF include nausea, diarrhea, hot flashes, and abdominal pain. [77] In addition, DMF may cause leukopenia and elevated hepatic transaminases [79].

Fingolimod

was approved by the FDA in 2010 and was the first oral treatment line for recurrent forms of MS. It is administered as a 0.5 mg capsule once daily. Fingolimod is a sphingosine-1-phosphate (S1P) receptor antagonist and acts selectively on lymphocytes by degrading the S1P1 receptor [80,81]. It absorbs T lymphocytes into secondary lymphoid tissues, which is to counteract the invasion of native tissue and thus improves inflammation in MS. [82,83] Fingolimod in two phase III trials in RRMS was evaluated and showed a reduction in ARR of 55-48%, a rate of progression of disability of up to 25-30%, and gadolinium-enhancing MRI lesions of more than 80%. [84] Compared to IFNB-1a, intramuscular injection of Fingolimod once a week reduces ARR by 52%, progression of disability by up to 25%, and MRI of gadolinium-enhancing lesions by more than 50% [85]. A phase Fingolimod III trial in patients with PPMS resulted in no delay in progression of disability [86]. The most common side effects of fingolimod are cough, diarrhea, headache, back pain and upper respiratory tract infection [87]. Due to the possibility of bradycardia and atrial block at the first administration, it is recommended that electrocardiogram monitoring be performed for 6 hours after the first dose of fingolimod. Then in cases treated with fingolimod, examination of varicella zoster infection is recommended [88,89]

Siponimod

is a new selective S1P₁ / S1P₂ agonist and a cost-effective treatment for RRMS and SPMS. Wenckebach shows that they are well tolerated. [90,91] Peak plasma levels of oral Siponimod max (10 mg) and total radioisotope components at 4 and 6 hours after ingestion and time of maximum radioactivity (T_{max}) for single-dose Siponimod 3 to 6 hours and for multi-dose 2: Up to 8 hours after consumption. Unchanged Siponimod accounts for 57% of total plasma radioactivity, indicating significant exposure to metabolites. The main metabolite of Siponimod is circulating plasma M3 and is the most important systemic metabolite in M17 mice. During 9 days after consumption, the mean total recovery of radioactivity in urine was 0.4 + 3.6% with the predominance of M3 metabolite and in feces 43.5% with 84.1 with the dominance of M5 metabolite and on the 13th day the radioactivity recovery is nearing completion (2.7 + 90.4%). The predominant factor in the biotransformation is the CYP 2C9 (P450 2C9) and the small contribution of CYP 3A4 and other cytochrome P450 enzymes. [92,93] To evaluate the safety and efficacy of Siponimod, it was designed in an experimental study in which those who received Siponimod continued to receive the initial dose of Siponimod and those who received placebo received one of 5 doses of 10.2, They received 1.25,0.5,0.25 randomly and the initial treatment was titrated within 10 days. In people receiving Siponimod 1.25, 2, 10 0.5, the estimated mean number of T1 lesions decreased and with increasing dose, the number of T1 enhancing lesions decreased. In patients who switched from placebo to Siponimod,

the number of Gd-enhancing T1 lesions was lower than the baseline extension. Doses of 10,2,1.25 Siponimod showed less recurrence and doses 2 and 1.25 showed less Tz lesion enlargement than other groups; lymphopenia was also highest in the 10 mg group. [94,95] Cardiovascular findings after titration, slight reductions in HR and secondary ventricular atrial blocks shortly after ingestion (days 1 and 7) and AVB and Mobitz type 1 in the long term (12 months) after showed of consumption. Reduction of lymphocyte count to less than 200 during dose blinded extension phase at 10mg Siponimod in 54.5% of patients, at 2mg dose at 87.2% of patients, at 1.25mg dose at 9.3% patients and none of patients at 0.5mg and 0.25mg doses Occurred. Sip onium at 2 mg and 10 mg doses had stable effects on MRI and clinical procedures, low disease activity and low ARR. In general, higher doses reduced overall recurrences [94,96]

Compared with Siponimod and placebo, 26% of patients receiving Siponimod and 32% of patients receiving placebo experience CDP for three months. Point-to-quarter estimates of time to CDP based on recurrence activity, disease progression and disease severity, exploratory analyses with recurrence or contrast enhancement up to 3mCDP, and post-hoc analyses up to 6-month CDP all demonstrate the superiority of Siponimod to placebo. ARR, increased Tz lesion and enhancing gadolinium lesions, and the rate of decrease in brain volume with Siponimod were lower than placebo. In contrast, the rate of serious adverse event, seizures, hypertension and cardiovascular lesions are more reported in the use of Siponimod than placebo. [97,98] Adverse event in this drug includes headache, nasopharyngitis, urinary tract infection and fall and serious adverse event includes increased liver transaminases, basal multiple gait disturbance suicide attempts urinary tract infection depression concussion. Cell carcinoma sclerosis relapse and paraparesis [97,99]. Death from Siponimod due to metastatic gastro-intestinal melanoma septic shock in terminal colon cancer or suicide can occur infrequently. [97] The effect

of Siponimod on preventing the development of disability is independent of its effect on disease recurrence. The spot effect of Siponimod shows a 14% to 20% reduction in quarterly CDP and a 29% to 33% reduction in 6-month CDP. While considering the recurrences during the study, patients fall into 3 categories: non-recurrent (83% 75%), definitely recurrent (11% -15%) and profitable (6% -6%) and reducing the risk of CDP in the 2017 quarter. % And 6-month CDP is estimated at 29.320% compared to the placebo exposure period. The approximate correspondence of these statistics indicates the effect of Siponimod on disability independent of the effect on recurrence. [100,101] Siponimod can also be very cost-effective as an alternative to various treatments for RRMS and SPMS. Siponimod treatment strategy reduces overall treatment costs by decreasing the mean incremental costs of drug acquisition, the mean means incremental overall strategy costs, the mean incremental QALYS, and the incremental mean Lys [90].

Hematopoietic Stem Cells Transplantation

Mesenchymal and hematopoietic stem cell transplants were initially used to save patients from long-term bone marrow aplasia undergoing severe chemotherapy, but with advances in the method of this treatment, a relatively new approach to combat autoimmune disorders [102] MS, however, in Autologous Hematopoietic Stem Cell (AHSC) transplantation in RRMS patients, a 89% reduction in disease recurrence and a 76.9% sustained improvement in disability were observed 24 months after transplantation. At 24 months after transplantation, there is little effect on information processing speed and visual memory and a significant effect on verbal learning. The most common side effect of this procedure is febrile neutropenia or FN (79). The second complication is reactivation of the nBarr Epstei virus (/ VA). Patients are positive for anti-EBV igG [105-103]. Acute respiratory distress syndrome (ARDS), idiopathic thrombocytopenic purpura (ITP), and haemorrhagic cystitis are rare. Given that most of these cases are treated with

Reference / study	Type of stem cell	Experimental groups	Tissue tested	Duration and method of testing	Results
[103]	AHSC	24 RRMS patients	Bone marrow	6-month follow-up in all patients and 24-month follow-up in 13 patients	89 Reduction of ARR reduction (annual recurrence) at least 0.5 points Improvement in EDSS score and sustained improvement of disability without T2 lesion in MRI Safe and effective treatment
[107]	MSC	3 SPMS patients and 1 RRMS patients	Bone marrow	2 patients had 1 intrathecal injection and the other patient (SPMS) had 2 injections 1 year apart	Stopping the progression of SPMS Motor Exacerbation after 12 months in RRMS patient Increasing ARR from 0.4 to 0.5 -0.5 changes. 1 -... 0.5+ score in patients' EDSS in 24 months Multiple injections are more effective
[109]	ASC	3 SPMS patients and 1 RRMS patients	Bone marrow	Receiving part of the cells intrathecally in 3- and 6-months care	No change in EDSS score during 12 months Recurrence of 2 patients with Gd + lesions on MRI during 18 months Recurrence of 3 RRMS patients and improvement of 35% of patients in terms of MSFC training and effective measures to stop myelin loss

appropriate treatments, it can be said that this treatment is safe and effective; The effectiveness of this treatment method in the early stages of autoimmune disease has had better and more favourable results [103,106]. Intrathecal injection of mesenchymal stem cells (MSCs) in RRMS and SPMS patients in the first few hours shows mild fever and mild headache, but then stops the progression of the disease and improves recovery from disability, and as a conclusion on the topic Side effects of this method of treatment include fever, sepsis, and immunosuppression, which are also the most common [107,108]. This treatment provides a better response in SPMS patients and stops the progression of the disease in all of them. Be. In this link, the annual recurrence rate (ARR) increases from 0.4 to 0.5 and the EDSS changes. Multiple injections of MSC at one-year intervals are more effective than single injections and are a safe and uncomplicated treatment. Fat-derived stem cells (ASCs), which are a type of MSC, are isolated from adipose tissue by enzymatic digestion [107]. Intrathecal injection of ASC in patients with RRMS and SPMS who did not respond to first-, second-, and third-line therapies did not alter the level of disability (EDSS). This anti-inflammatory treatment is safe and slows the recurrence and progression of the disease. During the 18 months after treatment, recurrence was seen in only 15% of patients, and 35% of patients showed significant improvement in exploratory efficacy measures. No side effects are observed until 24 months after transplantation [109].

PGLA

In recent years, the use of PGLA nanoparticles has been proposed as a better carrier for the treatment of autoimmune diseases such as MS, although PGLA itself is FDA approved and also due to its biodegradability. Biocompatibility is an attractive carrier in this area, but nano-based therapies have not entered the clinical phase; On the other hand, the use of PGLA nanoparticles has a good effect on autoimmune encephalomyelitis in laboratory mice and the prevention and treatment of MS has also been successful [110-112].

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