

Treatment Options for Relapsing-Remitting Multiple Sclerosis

Yara Mohsen Albalawi¹, Sultan Sameer Alhunbusi², Meshari Sultan Alsudayri³, Neda Ali Al-Bati⁴, Ahmad Hamza Omar Khalid², Talal Hamid Alfalaj⁵, Elham Hamid Al Fallaj⁶, Abdulrahman Zaid Alshamrani⁷, Adilah Hamoud Al Turaifi⁸, Abdulrahman Mubarak Almutairi⁹

¹ Tabuk University, ² Taif University, ³ Hail University, ⁴ Imam Abdulrahman Bin Faisal University (IAU), ⁵ Dow University of Health Sciences - Pakistan, ⁶ Almaarefa Colleges for Science & Technology (MCST), ⁷ Jeddah University, ⁸ Ibn Sina National College for Medical Studies, ⁹ Majmaah University

Corresponding Author: Yara Mohsen Albalawi, email: Yara.1993_9@live.com

ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory autoimmune demyelinating disease of the central nervous system that usually affects young adults, particularly women. The pathobiology of multiple sclerosis contains inflammatory and neurodegenerative mechanisms that affect both white and grey matter. These mechanisms cause the relapsing, and frequently progressive, course of multiple sclerosis, which is heterogeneous; confident prediction of long-term individual prognosis is not yet promising. Though, as revised MS diagnostic criteria that include neuroimaging data facilitate early diagnosis, most patients are encountered with making important long-term treatment decisions, most particularly the utilization and selection of disease modifying therapy. Presently, there are numerous approved MS disease modifying therapy with changing degrees of efficacy for decreasing relapse risk and preserving neurological function, but their long-term benefits stay imprecise. Furthermore, available disease modifying therapy vary with regard to the route and frequency of management, common adverse effects, tolerability and possibility of treatment adherence, risk of major toxicity, and pregnancy-related risks. Thorough understanding of the benefit risk profiles of these therapies is essential to establish logical and safe treatment procedures for patients with multiple sclerosis.

Keywords: Relapsing-Remitting, Multiple Sclerosis, Treatment.

INTRODUCTION

Multiple sclerosis (MS) is a putatively autoimmune, idiopathic, chronic inflammatory demyelinating disease of the central nervous system with genetic and environmental effects ^[1, 2]. The average age of clinical start of MS is nearly 29 years, and the male/female ratio in this group approaches 1:3 and might be growing ^[3]. Multiple sclerosis causes worrisome or disabling physical symptoms including vision problems, mobility problems, pain, problems with coordination, fatigue, and cognitive dysfunction.

Quality of life may be reduced by mood disorders and restrictions in employment and social functioning ^[4, 5]. Lesions of CNS white matter with loss of myelin, neuronal axons, and myelin creating oligodendrocytes portray the multifocal pathology of multiple sclerosis ^[6]. Recent research has additionally featured an overlooked association of gray matter, which might be particularly applicable to irreversible disability ^[7]. Acute inflammatory Lesions are started by actuated peripheral leukocytes that enter the central nervous system through a ruptured blood- brain boundary. The clinical correspond of this procedure is a clinical assault (equivalent words incorporate exacerbation, relapse, or flare), which comprises of subacute neurological manifestations that worsen over days to a few weeks and, primary in the disease,

frequently recover unexpectedly and completely. Current preventive disease-modifying therapies for MS principally target assaults, diminishing their recurrence and seriousness. Brain magnetic resonance imaging (MRI) can distinguish numerous new asymptomatic sores for each clinically clear attack and is utilized as a sensitive, objective, and quantifiable instrument for the estimation of multiple sclerosis movement in both clinical practice and remedial trials ^[8].

85% of the patients have relapsing-remitting multiple sclerosis (RRMS), in which a clinical attack proclaims the beginning of the disease ^[9]. If inadequate brain MRI indication is present at first clinical presentation, an impermanent diagnosis of clinically isolated syndrome might be functional, inferring high hazard for future affirmed MS, anticipating confirmation of further clinical relapses or new MRI lesions (dissemination in time and space). The lasting 15% of the patients have primary progressive multiple sclerosis (PPMS), characterized as gradually progressive and incessant loss of neurological function for more than 1 year. It typically shows as a gait disorder, is related with less proof of inflammatory action than RRMS, and possibly signifies a neurodegenerative procedure. Differentiating RRMS from PPMS is critical as all available MS disease modifying therapies have displayed adequacy for attack

diminishment in relapsing MS, however none has yet proven to influence PPMS^[10].

The common history of MS is famously factor and to a great extent flighty on an individual level. In RRMS, lingering impacts of clinical relapses can result in aggregating neurological impairment, commonly enumerated in practice and clinical trials with the Expanded Disability Status Scale (EDSS), an ordinal scale extending from 0 (ordinary) to 10 (death from MS)^[11]. Nonetheless, the most critical indicator of future inability for individuals with RRMS is the advancement of secondary progressive multiple sclerosis. Transformation to secondary progressive multiple sclerosis happens in around 60% to 70% of those with RRMS, frequently 1 to 3 decades after illness start, and when EDSS scores go from 2 to 5, reflecting gentle to moderate incapacity in an ambulatory patient^[12]. Secondary progressive MS acts much like PPMS, generally showing as a gradually worsening gait disorder and causing ambulatory dysfunction demanding mobility assistance with cane (EDSS score 6), walker (6.5), or wheelchair (8). Surprisingly, up to 15% of the individuals with RRMS may at last demonstrate to have benign MS, getting away from both significant attack related incapacity and change to SPMS. Unfortunately, there is restricted capacity to foresee which result is likely for an individual patient with early stage malady^[13].

Numerous people with recently diagnosed or early stage multiple sclerosis are overwhelmed by the combination of uncertain prognosis, the frequently disturbing prospect of embarking on preventive immunotherapy with no clear time frame, and the lengthy roster of available disease modifying therapies with diverse benefit-risk profiles. Here, we review currently available and emerging disease modifying therapies, concentrating on recent improvements, and several strategies to include them into contemporary patient and physician shared decision models.

Signs and symptoms

- Optic neuritis
- Trigeminal neuralgia - bilateral facial weakness or trigeminal neuralgia
- Facial myokymia (irregular twitching of the facial muscles) - may also be a presenting symptom
- Eye symptoms - including diplopia on lateral gaze; these occur in 33% of patients
- Heat intolerance
- Sensory loss (ie, paresthesias) - usually an early complaint

- Spinal cord symptoms (motor) - muscle cramping secondary to spasticity
- Spinal cord symptoms (autonomic) - bladder, bowel, and sexual dysfunction
- Cerebellar symptoms - Charcot triad of dysarthria, ataxia, and tremor
- Constitutional symptoms - fatigue
- Pain - occurs in 30-50% of patients at some point in their illness
- Subjective cognitive difficulties - with regard to attention span, concentration, memory, and judgment
- Depression – a common symptom
- Euphoria - less common than depression
- Bipolar disorder or frank dementia - may appear late in the disease course but is sometimes found at the time of initial diagnosis.
- Symptoms associated with partial acute transverse myelitis

Treatment options for relapsing-remitting multiple Sclerosis

Treatment of multiple sclerosis has two aspects: immunomodulatory therapy for the underlying immune disorder and therapies to relieve or change symptoms. Immunomodulatory therapy is concentrating on decreasing the occurrence of relapses and slowing progression. At present, most disease-modifying agents have been approved for use only in relapsing forms of MS. Mitoxantrone is similarly approved for the treatment of secondary progressive and progressive relapsing MS.

Approved disease modifying therapies

Disease-modifying therapies have shown useful effects in patients with relapsing MS, containing reduced incidence and severity of clinical attacks. These agents perform to slow the progression of disability and the decrease accumulation of lesions within the brain and spinal cord. The disease-modifying agents for MS (DMAMS) at this time approved for use by the US Food and Drug Administration (FDA) include the following:

- Interferon beta-1a (Avonex, Rebif)
- Interferon beta-1b (Betaseron, Extavia)
- Peginterferon beta-1a (Plegridy)
- Glatiramer acetate (Copaxone)
- Natalizumab (Tysabri)
- Mitoxantrone
- Fingolimod (Gilenya)
- Teriflunomide (Aubagio)
- Dimethyl fumarate (Tecfidera)
- Alemtuzumab (Lemtrada)
- Daclizumab (Zinbryta)

- **Ocrelizumab**

Fingolimod, teriflunomide, and dimethyl fumarate are managed orally; natalizumab and mitoxantrone are managed by intravenous infusion; interferon beta-1a (Avonex) is managed intramuscularly; and interferon beta-1a (Rebif), interferon beta-1b, and glatiramer acetate are managed by subcutaneous injection.

Self-Injectable Therapies (First-Generation)

- **Interferon beta-1a therapy (Avonex or Rebif)**

In a study of 301 patients with relapsing-remitting ailment were given a weekly intramuscular injections (30 µg) of interferon beta-1a (Avonex), the yearly exacerbation rate reduced 29%. For 2 years, disease progression arisen in 21.9% of patients in the interferon beta-1a group and 34.9% of those in the placebo group. Furthermore, MRI information presented a drop in the mean lesion volume and number of improving lesions in the interferon beta-1a group^[14].

In 2002, the FDA approved interferon beta-1a (Rebif) in 22 µg and 44 µg formulations given 3 times per week. The average number of active unique MRI lesions per scan per patient was lower in the Rebif than in the Avonex group (0.17 vs 0.33). Patients on Rebif experienced fewer flulike symptoms, on the other hand more injection site reactions, white blood cell disorders, and hepatic function disorders. Rebif-treated individuals had a greater frequency of neutralizing antibodies (Nabs). A reduced MRI result was distinguished for Nab-positive patients on Rebif associated with Nab-negative patients on Rebif. Nonetheless, Nab-positive Rebif individuals had better clinical and similar MRI outcomes to Avonex patients^[15]. In individuals with uncontrolled depression, interferons ought to be utilized with risk avoidance. Glatiramer might be a suitable choice in such cases.

- **Interferon beta-1b therapy**

The first medication approved by the FDA for multiple sclerosis, in 1993, was interferon beta-1b (Betaseron, Extavia). It is specified for the treatment of relapsing procedures of MS to decrease the occurrence of clinical exacerbations. It has demonstrated viability in patients who have encountered a first clinical scene of multiple sclerosis and has MRI features predictable with multiple sclerosis. Interferon beta-1b is managed each other day subcutaneously by self-injection. The most regularly stated adverse responses incorporate depression, asthenia, hypertonia, flu-like symptoms, myasthenia, leukopenia, infusion

site responses, and expanded liver enzymes. Interferon beta-1b can be administered with antipyretics or analgesics to support with the occurrence of flu-like symptoms^[16].

- **Glatiramer acetate**

Glatiramer acetate (Copaxone) is a synthetic polypeptide affirmed for the lessening of the recurrence of relapses in patients with relapsing-remitting MS, containing patients who have encountered a first clinical period and have MRI features dependable with MS. Glatiramer acetate's mechanism of action is unidentified, however this agent can hypothetically adjust a portion of the immune processes thought to be engaged in the pathogenesis of MS^[17]. In 2014, a higher dose and lower rate dosage regimen of glatiramer was permitted. The 20-mg/mL SC injection is precise for the original once-daily treatment, while the new 40-mg/mL SC injection is precise for the 3 times per week dosage course of therapy. Approval for the new regimen was based on the phase 3 Glatiramer Acetate Low-Frequency Administration (GALA) study. The GALA trial included 1,404 patients and showed that treatment with 40 mg SC 3 times/wk reduced mean annualized relapse rates by 34% compared with placebo at 12 months^[18].

- **Peginterferon beta-1a**

Peginterferon beta-1a (Plegridy) was approved by the FDA in August 2014 for treatment of relapsing forms of multiple sclerosis. It is the first pegylated interferon approved for multiple sclerosis and could be self-administered by SC injection every 2 weeks. Approval was based on outcomes from the ADVANCE trial of >1,500 patients with MS over a 2-year period. In the first year of the sample, peginterferon beta-1a medicated each 2 weeks considerably decreased annualized relapse rate (ARR) at 1 year by 36% compared with placebo (P= 0.0007). Hazard of 12-week confirmed incapacity progression, as measured by the Expanded Disability Status Scale, was furthermore compact with peginterferon beta-1a by 38% (P= 0.0383) compared with placebo. Peginterferon beta-1a likewise considerably reduced the number of new gadolinium-enhanced [Gd+] lesions by 86% (P<0.0001) and reduced newly increasing T2-hyperintense lesions by 67% (P<0.0001) compared with placebo^[19].

Table 1. First-Generation Self-Injectable Multiple Sclerosis Disease-Modifying Therapies

Characteristic	Disease-modifying therapy					Peginterferon beta-1a
	Interferon beta-1b		Interferon beta-1a		Glatiramer acetate	
Brand name	Betaseron	Extavia	Avonex	Rebif	Copaxone	Plegridy
Year approved	1993	2009	1996	2002	1997	2014
Dose	250 µg	250 µg	30 µg	22 or 44 µg	20 µg	125 µg
Route	SC	SC	IM	SC	SC	SC
Frequency	Every other day	Every other day	Weekly	Twice weekly	Daily	Once every 2 weeks

General immunosuppression

- **Mitoxantrone**

Mitoxantrone is a general immunosuppressive medicine approved for quickly deteriorating relapsing MS and is the only agent approved to treat SPMS. At normal doses, its usage is restricted to 2 years due to accumulative dose related cardiomyopathy. After initial extensive utilization, it became obvious that mitoxantrone was related with higher than predictable rates of cardiomyopathy and postponed treatment-related acute leukemia, prominently decreasing its use^[20].

- **Natalizumab**

Natalizumab (Tysabri) is a refined monoclonal neutralizer that ties to the grip particle alpha-4 integrin, hindering its adherence to its receptors. Natalizumab is shown as monotherapy for the treatment of patients with backsliding types of MS, to postpone the gathering of physical handicap and lessen the recurrence of clinical intensifications. It is for the most part utilized as a part of patients who have not reacted to a first-line sickness adjusting treatment or who have extremely dynamic malady. In a placebo controlled clinical trial, the utilization of natalizumab diminished relapse rate (68%) and movement of inability (42%) over a time of 2 years^[21].

Natalizumab is given as a 300 mg IV implantation more than 1 hour at regular intervals. A review audit of 906 patients from 5 clinical trials by Cadavid et al found that after treatment with natalizumab, handicapped patients with backsliding transmitting MS will probably total a coordinated 25-foot walk fundamentally quicker; responders took a normal of 24– 44% less time to walk 25 ft than nonresponders. Natalizumab additionally seemed to have some adequacy in impaired patients with SPMS^[22].

Oral disease modifying therapies

Three oral DMTs are approved for relapsing MS: fingolimod, teriflunomide, and dimethyl fumarate/BG-12.

- **Fingolimod**

Fingolimod (Gilenya) is the primary oral malady changing treatment for relapsing types of MS affirmed by the FDA. Like other sickness changing operators for MS, fingolimod can diminish the recurrence of clinical intensifications and defer the amassing of physical incapacity. The suggested measurement for fingolimod is 0.5 mg once every day^[23]. The mechanism of action of fingolimod is partly understood but seems to be primarily different from other MS medications. Fingolimod-phosphate blocks the capacity of lymphocytes to departure from lymph nodes, decreasing the quantity of lymphocytes in peripheral blood. Fingolimod advances sequestration of lymphocytes inside the lymph nodes, which can diminish lymphocyte migration into the central nervous system^[24].

Fingolimod may be related with macular edema, pulmonary dysfunction, and cardiac adverse effects. In 2012, the FDA established that new name changes are required for fingolimod. Within an hour of managing fingolimod, heart rate diminishes are noted. The nadir in heart rate regularly happens at 6 hours; however it can be seen up to 24 hours after the principal dosage in a few patients. As a result of its heart antagonistic impacts, the principal dosage of fingolimod ought to be regulated in a setting in which assets are accessible to suitably oversee symptomatic bradycardia. In this manner, all patients began on fingolimod must be observed for no less than 6 hours following the primary measurement. Furthermore, an ECG ought to be performed preceding dosing fingolimod, circulatory strain and heartbeat ought to be checked hourly, and an ECG

ought to be performed toward the finish of the perception time frame. Extra perception past 6 hours ought to be initiated if bradycardia happens and until the point when the finding has settled in the accompanying circumstances: the heart rate 6 hours post measurements is under 45 thumps for every moment, the heart rate 6 hours post dosage is the most reduced esteem watched post measurements, or the ECG 6 hours post measurement indicates new-beginning second-degree or higher (atrioventricular) AV block.

Fingolimod is presently contraindicated in patients with late myocardial localized necrosis, shaky angina, transient ischemic assault (TIA), decompensated heart disappointment requiring hospitalization, or class III/IV heart disappointment; history or nearness of Mobitz sort II second-or third-degree AV piece or wiped out sinus disorder, unless the patient has a working pacemaker; benchmark QTc interim more noteworthy than or equivalent to 500 ms; or treatment with class Ia or class III antiarrhythmic drugs. The diminishment of peripheral lymphocyte tally by fingolimod can prompt an expanded danger of contamination. Reversible, asymptomatic rises of liver proteins may likewise happen. Other antagonistic responses that have been regularly revealed incorporate diarrhea, headache, ALT/AST elevations and back agony. In the event that a MS tolerant is being changed from natalizumab to fingolimod oral treatment, a washout time of two months or less is prudent. In an observational accomplice think about including 350 such patients, those with a washout time longer than 2 months had a higher danger of backslide; in a moment consider including 142 patients, shorter washout times of 8 or 12 weeks were related with less dynamic injuries and less illness repeat than was a washout time of four months ^[25].

• **Teriflunomide**

Teriflunomide (Aubagio) was affirmed by the FDA in September 2012 for the treatment of patients with backsliding types of MS (endorsed tablet

frames are 7 mg and 14 mg). The endorsing data contains a discovery cautioning for the dangers of hepatotoxicity and teratogenicity (pregnancy classification X) . It is an oral pyrimidine union inhibitor for treatment of backsliding types of MS. Endorsement depended on a randomized trial (TEMSO) of 1088 patients with at least 1 backslide in the earlier year or 2 backslides over the most recent 2 years. Teriflunomide was appeared to fundamentally diminish annualized backslide rates (31% relative hazard decrease contrasted and fake treatment P<0.001). It was additionally appeared in the TEMSO trial to lessen handicap movement at measurements of 14 mg/day ^[26]. However, the FDA has not endorsed the utilization of teriflunomide to moderate incapacity movement. Stage III of the TEMSO contemplate found that teriflunomide fundamentally impeded mind volume misfortune contrasted and fake treatment more than 2 years in patients with backsliding MS. Information got from MRI were utilized to evaluate patients treated with 14 mg or 7 mg of the medication, or fake treatment. By month 12, middle percent lessening from the benchmark in cerebrum volume was 0.39, 0.40, and 0.61 for teriflunomide 14 mg, 7 mg, and fake treatment, separately ^[27]. The most common adverse reactions of teriflunomide are headache, alopecia, diarrhea, nausea, increased ALT, influenza, and paresthesias.

Dimethyl fumarate

Dimethyl fumarate (DMF) is an oral Nrf2 pathway activator specified for relapsing forms of MS. The active metabolite, monomethyl fumarate (MMF), initiates the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway, a transcription factor encoded by the NFE2L2 gene. FDA approval for DMF in adults with relapsing forms of multiple sclerosis was built on data from 2 phase 3 studies, the DEFINE ^[28] and CONFIRM ^[29] studies, that included more than 2600 patients. An on-going addition study (ENDORSE) includes some patients that have been followed for longer than 4 years.

Table 2: Developed Multiple Sclerosis Disease-Modifying Therapies

Characteristic	Disease-modifying therapy				
	Natalizumab	Fingolimod	Teriflunomide	Dimethyl fumarate	Alemtuzumab
Brand name	Tysabri	Gilenya	Aubagio	Tecfidera	Lemtrada
Year approved	2004, 2006	2010	2012	2013	2014
Dose	300 mg	0.5 mg	7 or 14 mg	240 mg	12 mg
Route	IV	Oral	Oral	Oral	IV
Frequency	Every 4 wk	Daily	Daily	BID	Annual course

Recent Therapies

- **Alemtuzumab**
Alemtuzumab (Lemtrada) was affirmed by the FDA in November 2014 for relapsing types of multiple sclerosis. As a result of the hazard for extreme immune system antagonistic impacts, it is saved for use in patients who have a deficient reaction to at least 2 different medications for MS. Alemtuzumab is a recombinant monoclonal neutralizer against CD52 (lymphocyte antigen). This activity advances antibody-dependent cell lysis. Approval depended on 2 randomized Phase III open-mark rater-blinded investigations contrasting treatment with alemtuzumab with high-measurement subcutaneous interferon beta-1a (Rebif) in patients with backsliding dispatching MS who were either new to treatment (CARE-MS I) or who had backslid while on earlier treatment (CARE-MS II). In CARE-MS I, alemtuzumab was essentially more powerful than interferon beta-1a at diminishing annualized backslide rates; the distinction saw in moderating incapacity movement did not achieve factual hugeness. In CARE-MS II, alemtuzumab was altogether more successful than interferon beta-1a at lessening annualized backslide rates, and collection of disability was additionally essentially moderated^[30]. The clinical improvement program for alemtuzumab use in MS included about 1,500 patients with more than 6,400 patient-years of wellbeing development^[31]. In a single-arm, open-label study in 45 patients with MS that was refractory to treatment with interferon, alemtuzumab efficiently decreased relapse rates and enhanced clinical scores^[32].
- **Daclizumab**
Daclizumab (Zinbryta) was approved by the FDA in May 2016 for relapsing types of MS. It is an adapted monoclonal counter acting agent that ties to the high-affinity interleukin-2 (IL-2) receptor subunit (CD25). These subunits are communicated at abnormal states on T-cells that turn out to be anomalous enacted in different sclerosis. Endorsement depended on comes about because of 2 trials, DECIDE and SELECT, in which daclizumab 150 mg was directed SC each 4 wk in individuals with relapsing dispatching MS. In the DECIDE trial, daclizumab was contrasted and interferon beta-1a (30 mcg/wk IM). The annualized backslide rate was bring down with daclizumab than with interferon beta-1a (0.22 versus 0.39; 45% lower rate with daclizumab; P<0.001). The SELECT trial demonstrated that the annualized backslide rate was brought down for patients given daclizumab contrasted and fake treatment (54% lessening, 95% CI 33-68%; p<0.0001)^[33].

- **Ocrelizumab**

Ocrelizumab (Ocrevus) was approved in March 2017 for adults with relapsing or primary progressive forms of multiple sclerosis. Approval for RRMS was built on the OPERA 1 and 2 phase 3 trials that involved around 800 patients with RMS who received intravenous ocrelizumab or subcutaneous interferon-beta1a. Outcomes indicated the annualized relapse rate was lesser with ocrelizumab than with interferon beta-1a in trial 1 (0.16 vs. 0.29; 46% lower rate with ocrelizumab; P<0.001) and in trial 2 (0.16 vs. 0.29; 47% lower rate; P<0.001). The percentage of patients with disability progression confirmed at 12 weeks was significantly lower with ocrelizumab than with interferon beta-1a (9.1% vs. 13.6%; P<0.001), as was the percentage of patients with disability progression confirmed at 24 weeks (6.9% vs. 10.5%; P=0.003). The average number of gadolinium-enhancing lesions per T1-weighted MRI was 0.02 with ocrelizumab versus 0.29 with interferon beta-1a in trial 1 (94% lower number of lesions with ocrelizumab, P<0.001) and 0.02 versus 0.42 in trial 2 (95% lower number of lesions, P<0.001)^[34].

CONCLUSION

The past decades have observed remarkable developments in treatment options for multiple sclerosis. New medications have been developed on the basis of the awareness of the pathobiology of multiple sclerosis; consecutively, we have made discoveries about multiple sclerosis from the therapies. The current therapies have persuasively altered the short and intermediate-term natural history of the disease, and many more are composed to do so. It is possible that the current sequential monotherapy or treatment failure representation will ultimately give way to personalized methods, guided by valid predictive biomarkers and pharmacogenomics. Available disease-modifying therapies provide both immediate options and optimism for people suffering from multiple sclerosis.

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