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Update on multiple sclerosis treatments

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Summary

Relapsing-remitting multiple sclerosis (RRMS) management has dramatically changed over the past decade. New drugs have arrived on the market, allowing for more individualised treatment selection. However, this diversity has increased the complexity of RRMS patient follow-up. In this review, we provide summarised information about treatment efficacy, potential side-effects, follow-up recommendations, vaccinations, and pregnancy safety issues for all currently available disease modifying therapies and those awaiting approval.

Key words: *Multiple sclerosis; disease modifying therapies; recommendations; fingolimod; interferon beta; glatiramer acetate; teriflunomide; dimethyl fumarate*

Introduction

The landscape of relapsing-remitting multiple sclerosis (RRMS) treatment dramatically changed over the past decade. The release of natalizumab on the market paved the way towards stabilisation of RRMS patients, and, as the first oral drug, fingolimod significantly improved patients' quality of life. In 2013 and 2014, two additional oral drugs were released as alternate first-line treatments of RRMS: teriflunomide and dimethyl fumarate. A number of other promising new drugs will hopefully be approved soon.

As drug options increase, more individualised management of RRMS patients becomes possible. In return, follow-up of these patients is ever more challenging. This review summarises the literature on all currently available treatments of RRMS and those awaiting approval, providing information about treatment efficacy, potential side-effects, follow-up recommendations, vaccination, and pregnancy safety issues.

Oral disease-modifying therapies

Fingolimod (Gilenya®)

Fingolimod is a sphingosine-1 phosphate (S1P) receptor modulator that prevents T and B lymphocyte regress from lymph nodes [1, 2], reducing peripheral blood lymphocyte counts by 70% of baseline within 3 months of treatment initiation [3, 4]. Approved as a first-line treatment in Switzerland in 2011, fingolimod is the first oral treatment of RRMS. In the European Union, fingolimod is approved as a second-line treatment, except for patients with highly active RRMS for whom it can be prescribed as a first-line therapy.

Fingolimod 0.5 mg once daily reduced annualised relapse rate (ARR) by 54% compared to placebo in phase III trial FREEDOMS [3]. Both risk of disability progression and MRI evidence of disease activity (number of gadolinium-enhancing lesions and volume of hypointense lesions on T1–weighted scans, median volume of lesions and number of new/enlarged lesions on T2–weighted scans) were significantly reduced in fingolimod-treated patients [3]. In phase III trial TRANSFORMS [4], fingolimod was more effective in reducing ARR compared to weekly intramuscular interferon beta-1a (Avonex®), but there was no benefit of fingolimod over interferon beta-1a in terms of disability progression [4]. Over a 24 month period, brain-volume loss was reduced in fingolimod-treated patients compared to both placebo-treated patients [3] and interferon beta-1a-treated patients [5].

Three major clinical trials [3, 4, 6] and their extensions investigated the safety profile of fingolimod, including 3916 patients altogether with up to 7 years of treatment [7]. Adverse effects related to its immunosuppressive properties included a moderately increased risk of lower respiratory tract infections compared to placebo. Two cases of lethal infections occurred during TRANSFORMS in patients receiving the highest (not commercialised) dose of fingolimod (1.25 mg): a case of primary varicella infection in a previously non immunised patient who was receiving corticosteroids concomitantly and a case of herpes simplex encephalitis initially treated with intravenous corticosteroids for a suspected MS relapse [4]. No increase in risk of malignancy was observed in patients treated with fingolimod compared to placebo in these studies.

S1P receptors are expressed in many tissues including the cardiovascular system, and have roles in heart rate and blood pressure regulation [8]. Upon treatment initiation, fingolimod leads to a dose-dependent bradycardia. This effect is transient, with heart rate reaching its nadir 4–5 hours after the first dose. In most cases, bradycardia is asymptomatic and heart rate is back to baseline after a month of

continuous treatment [3, 4]. Other cardiac side-effects include 1st and 2nd degree atrio-vendricular (AV) conduction blocks, with a pooled incidence in both phase III trials of 4.7% (compared to 1.7% in the placebo group) and 0.2% (compared to 0% in the placebo group) respectively [7]. Serious cardiac side effects have been reported in the literature, including cases of asystole or cardiac arrest [9, 10].

Although the effect on heart rate is generally benign, international guidelines from regulation authorities recommend 6–hour heart rate and blood pressure monitoring after the first dose, as well as a pre- and post-dose ECG. Absolute contraindications for fingolimod include recent (<6 months) myocardial infarction, unstable angina, stroke or transient ischemic attack, class III/IV heart failure or heart decompensation, Mobitz II second-degree or third-degree AV block, sick-sinus syndrome, prolonged QTc or treatment with class Ia or III anti-arrythmic drugs.

Lymphocyte counts must be monitored regularly to ensure levels do not fall under 0.2 G/l, below which treatment reduction or suspension should be discussed. Macular oedema is a rare side effect (0.4%) that typically arises during the first 4 months of treatment and resolves upon treatment discontinuation [3, 4]. An ophtalmological exam is therefore required before and 3 months after treatment initiation. A recent study suggests subtle sub-clinical macular oedema may occur more frequently in fingolimod-treated patients compared to placebo [11]. Optical coherence tomography (OCT) measures of total macular volume (TMV) and retinal nerve fibre layer (RNFL) thickness are used as biomarkers of disease progression. However, in light of these findings, the validity of such markers may be questioned [11, 12].

Elevation of liver enzymes 3 times above the upper limit were reported in 8% of fingolimod-treated patients compared to 1.9% in the placebo group [7]. Titres above this limit require treatment cessation.

More recently, several cases of atypical, tumefactive demyelinating lesions have been reported in fingolimod-treated MS patients, suggesting fingolimod may have a paradoxical effect in some MS patients [13, 14].

MS patients on fingolimod have similar cellular and humoral immune responses to influenza vaccination compared to healthy controls [15]. For safety reasons, live attenuated vaccines are contraindicated while on fingolimod treatment and immunisation status (including VZV) should be checked prior to treatment initiation.

Pre-clinical studies with fingolimod have demonstrated embryotoxicity and teratogenicity. Female patients are therefore advised not to become pregnant while treated with fingolimod, and a 3 month washout period with normalisation of blood tests before conception is recommended [16].

Fingolimod's efficacy is currently being investigated in the setting of primary progressive MS (INFORMS study). A similar molecule with increased specificity (Siponimod) is also under investigation in secondary progressive MS (EXPAND study).

Teriflunomide (Aubagio®)

Teriflunomide is the active metabolite of leflunomide, an anti-rheumatic drug commercialised in Switzerland since 1998 as Arava®. Teriflunomide inhibits a key enzyme (dihydro-orotate dehydrogenase, DHODH) in the *de novo* pyrimidine synthesis pathway, which is favoured over the salvage pathway in rapidly proliferating cells such as activated lymphocytes [17]. Teriflunomide's immunomodulating properties are thought to derive from the inhibition of activated lymphocyte proliferation [18]. Teriflunomide is approved as a first-line treatment of RRMS by the FDA, EMA and Swissmedic.

In first phase III study TEMSO [19], a daily dose of 14 mg reduced ARR by 31.5% compared to placebo. This efficacy was recently confirmed in a second phase III study (TOWER) [20]. In both studies, risk of sustained accumulation of disability was significantly reduced in patients taking 14 mg teriflunomide compared to placebo [19, 20]. In TEMSO, MRI evidence of disease activity (change in total lesion volume from baseline, volume of hypointense lesions on T1–weighted scans, volume of hyperintense lesions on T2–weighted scans, gadolinium-enhancing lesions on T1–weighted scans) was significantly reduced in patients taking 14 mg teriflunomide compared to placebo. Brain-volume loss did not differ significantly between teriflunomide and placebo-treated groups [19].

The efficacy of teriflunomide in terms of ARR reduction is comparable to that of the first line injectable treatments interferon-beta 1a (Rebif®), but "Treatment Satisfaction Questionnaire for Medication (TSQM)" scores were higher for teriflunomide, underscoring the benefit of an oral formulation on patient's quality of life [21]. A phase II study showed no benefit of teriflunomide as an add-on therapy in patients receiving interferon beta-1a [22].

In Phase III [19, 20], Phase II [23] and long-term follow-up of Phase II [24] trials (up to 8.5 years follow up), no serious adverse events were demonstrated. Side effects included nausea, diarrhoea, and reversible hair thinning [19, 20, 23–24]. Tuberculosis (TB) reactivation having been reported in patients treated with leflunomide, a TB test and treatment (if positive) prior to teriflunomide initiation are mandatory. A slight increase in blood pressure as well as elevated transaminase levels were reported and should be monitored regularly [19, 20, 23, 24]. Teriflunomide activates cytochrome P450 and interaction with other drugs including warfarine, antibiotics and anti-epileptics may occur.

Live attenuated vaccines are contraindicated in patients treated with teriflunomide, and immune status should be verified prior to treatment initiation. Patients treated with teriflunomide were shown to have a normal response to influenza vaccine [25].

Preclinical studies with teriflunomide in rats, rabbits and mice have demonstrated embryotoxicity and teratogenicity [16], and female patients are advised not to become pregnant while treated with teriflunomide. Due to the long drug half-life, the recommended washout period is 8 months. Cholestyramine and activated charcoal may be used to accelerate elimination of teriflunomide [16].

Dimethyl Fumarate (Tecfidera®)

Dimethyl fumarate, a fumaric acid ester, is thought to have both immunomodulatory and neuroprotective effects, but the exact mechanisms of action remain to be elucidated [26]. The molecule is approved for RRMS treatment. Though new in the landscape of RRMS treatment, fumaric acid esters have been used for several decades in Germany for psoriasis treatment under the brand name Fumaderm® [27].

In phase III study DEFINE, oral dimethyl fumarate 240 mg twice daily reduced ARR by 53% compared to placebo [28]. Risk of disability progression was reduced by 38% compared to placebo in the DEFINE study [28], but did not reach significance in a second phase III trial CONFIRM [29]. MRI signs of disease activity (number of gadolinium-enhancing lesions on T1–weighted scans, number of new/enlarged lesions on T2–weighted scans [28, 29] and number of new hypointense lesions on T1–weighted scans [29]) were reduced in both phase III trials. Brain-volume loss was not assessed in either phase III trials.

No serious side effects were reported in Phase II [30] and III trials [28, 29]. Most frequent side effects included flushing (31%), diarrhoea (13%), nausea (11%) and abdominal pain (10%) [29]. Two cases of PML in patients treated with dimethyl fumarate for psoriasis were recently published [31, 32]. However, both patients had sustained lymphopenia with titres below 500 per cubic millimetre, titres significantly lower than the 3000 per cubic millimetre threshold under which the drug should be terminated according to Fumaderm® guidelines [33].

Patients enrolled in phase III trials were allowed to be vaccinated. However, available data are insufficient to assess safety or efficacy of vaccines in combination with dimethyl fumarate.

Animal studies showed embryolethality and teratogenicity in various animals, and female patients taking dimethyl fumarate are advised not to become pregnant [16].

Laquinimod (Nerventra®)

Laquinimod is a quinolone-3–carboxamide small molecule awaiting FDA and Swissmedic approval for RRMS treatment. In January 2014, it received a negative evaluation from the EMA, due to potential risks observed in animal studies.

Laquinimod is a central nervous system (CNS) and peripheral immunomodulator with both anti-inflammatory [34] and neuroprotective properties [35, 36]. Interestingly, unlike currently approved RRMS drugs which mainly target the peripheral immune system, laquinimod seems to modulate CNS immunity independently of effects on the peripheral immune system [34, 37]. The exact mechanisms of action of laquinimod remain to be clarified.

In phase III study ALLEGRO, 0.6 mg laquinimod once daily reduced ARR by 23% compared to placebo [38]. MRI markers of disease activity (number of gadolinium- enhancing lesions on T1–weighted scans and number of new/enlarged lesions on T2–weighted scans) were reduced compared to placebo [38]. The risk of confirmed disability progression was reduced by 36% and 48% at 3 and 6 months respectively, compared to placebo [38]. Brain-volume loss over a 24 month period was reduced in laquinimod-treated patients compared to patients receiving placebo [38].

In phase III trial BRAVO, 0.6 mg laquinimod once daily was compared to both placebo and interferon-beta 1a (Avonex®) once-weekly [39]. Compared to placebo, there was no significant reduction in ARR in patients receiving laquinimod, thereby failing to reproduce the results of ALLEGRO [39]. However, similarly to what was observed in ALLEGRO [39], brain-volume loss over a 24 month period was reduced in laquinimod-treated patients compared to patients receiving placebo.

No serious adverse events were reported in phase II and III trials [4, 38–40]. Side effects included a moderate increase in the risk of urinary tract infection (RR 1.6), abdominal pain (RR 2), back pain (RR 1.8) and elevated liver transaminase (RR 2.6), compared to placebo [4, 38, 40].

Injectable disease-modifying therapies

First generation disease-modifying therapies

Interferon-beta 1b (Betaferon®/Betaseron®) [41, 42], **interferon-beta 1a** (Rebif®, Avonex®) [43, 44], and **glatiramer acetate** (Copaxone®) [45], now prescribed for more than fifteen years, marked a turning point in MS therapy. With an approximately 30% reduction in ARR compared to placebo, beta-interferons (IFNs) and glatiramer acetate (GA) set a benchmark for treatment efficacy to which new drugs are compared. In 2014, the FDA approved the three-times-a-week subcutaneous injection of GA 40 mg/mL.

The most striking advantage of first generation treatments is there long term safety, as observed in the million patient-years treated for more than 20 years [46, 47]. Flu-like side effects, more frequent with IFNs than with GA, as well as the method of administration (intra-muscular or subcutaneous self-injections) limit their use.

In a prospective study of 88 MS patients treated with interferon-beta 1a and 77 untreated MS patients, similar proportions of each group developed protective immune responses after receiving a seasonal influenza vaccine [48]. A recent study found a reduced response to influenza vaccine in MS patients receiving GA compared to non-treated patients [49]. Live-attenuated vaccines are permitted in IFN and GA-treated patients, taking into account specific recommendations for MS patients.

No significant increase in rates of birth defects or spontaneous abortion were observed in interferon-beta 1a and GA treated patients compared to untreated MS patients and healthy controls [50, 51].

Natalizumab (Tysabri®)

Natalizumab is a humanised monoclonal antibody targeting the lymphocyte adhesion molecule alpha4–beta1 integrin, disrupting its interaction with vascular adhesion molecule VCAM-1, thereby reducing lymphocyte migration from blood vessels into the CNS [52].

Natalizumab, one of the most effective RRMS treatment currently available, was approved by the FDA in 2004, before completion of phase III trials SENTINEL [53] and

AFFIRM [54]. Less than a year later, it was withdrawn from the American market after 2 cases of progressive multifocal leucoencephalopathy (PML) were diagnosed in natalizumab-treated patients participating in one of the trials [55, 56]. Both phase III trials confirmed high efficacy of natalizumab, with a monthly infusion of 300 mg reducing ARR by 68% compared to placebo [54]. Natalizumab was also very effective in reducing the accumulation of new/enlarging T2 lesions and gadolinium-enhancing lesions [57] and the risk of sustained disability progression [54, 29]. Brain-volume loss was not assessed in either phase III trials.

Besides the risk of PML, serious adverse events included a higher risk of hypersensitivity reactions in the natalizumab group compared to placebo. Additional research allowed the risks and benefits of natalizumab treatment to be determined. Its remarkable efficacy led to its re-commercialisation in more than 65 countries.

Up to now, more than 370 cases of PML have been diagnosed worldwide among the 700'000 natalizumab-treated patients, making it an overall rare complication of treatment. Treatment duration, positive JCV serological status (anti-JCV+) and prior immunosuppressant use are well characterised risk factors for PML in natalizumab-treated patients. Further risk stratification of PML in anti-JCV+ patients has been evaluated through anti-JCV antibody titres. Patients with high anti-JCV titres (index >1.5) seem to be at particularly high risk of PML (0.8% after 24 doses), whereas patients with low anti-JCV titres (<0.9) have a low PML risk (0.03 % after 24 doses) [58].

Other adverse events in phase III trials included the presence of anti-natalizumab antibodies [54]. The incidence of anti-natalizumab antibodies was measured in 9% of natalizumab-treated patients, one third of which (3%) were transiently positive and had no clinical significance, and two thirds of which (6%) were persistently positive and were associated with loss of clinical efficacy of natalizumab [59]. Unlike anti-interferon antibodies which are rarely neutralising [60], persistently positive anti-natalizumab antibodies, defined as antibodies detectable on at least two occasions (more than 6 weeks apart), are always neutralising and treatment should be terminated.

Natalizumab has been reported inefficient in terms of relapse prevention in anti-aquaporine-4 positive neuromyelitis optica (NMO) patients [61]. Cases of catastrophic exacerbation of NMO patients after natalizumab treatment have been reported [62, 63], underscoring the importance of careful NMO exclusion before natalizumab initiation.

Vaccination against influenza in patients treated with natalizumab was shown to yield a humoral immune response comparable to that achieved in healthy individuals [64]. Live-attenuated vaccines are permitted in natalizumab-treated patients, taking into account specific recommendations for MS patients.

Based on animal studies showing teratogenicity of natalizumab, female patients on natalizumab are advised not to become pregnant [65]. Ideally, natalizumab should be discontinued 3 months before conception.

Alemtuzumab (Lemtrada®)

Alemtuzumab is a humanised monoclonal antibody targeting CD52, depleting T and B lymphocytes shortly after treatment infusion [66]. Within weeks post-treatment, a distinct pattern of T and B cell repopulation begins, with B cells repopulating to baseline within 3–6 months. T-cell counts slowly rise towards normal within 12 months, without returning to baseline [67], leading to long lasting changes in adaptive immunity. In 2013, alemtuzumab was approved by the EMA for RRMS but was rejected by the FDA. The file is currently under revision by Swissmedic.

Two phase III studies, CARE-MS I and CARE-MS II, evaluated the efficacy of alemtuzumab compared to interferon beta-1a three-times a week (Rebif®). In CARE-MS I and its extension CAMMS223, which included patients naïve of MS treatment, alemtuzumab reduced ARR by 54.9% at 2 years [67] and 66% at 5 years [68] compared to Rebif®. In CARE-MS II, which included MS patients who relapsed on prior interferon or glatiramer acetate therapy, alemtuzumab reduced ARR by 49.4% compared to Rebif® [69]. A significant reduction in sustained disability progression was observed in alemtuzumab-treated patients compared to interferon-treated patients in CARE-MS II [69] but not in CARE-MS I [67]. A significant reduction in new/enlarging T2 lesions and Gadolinium enhancing lesions in alemtuzumab-treated patients compared to Rebif® was observed in both trials [67, 69]. Brain-volume loss was reduced in alemtuzumab-treated patients compared to placebo and interferon beta-1a-treated patients [67, 69].

Six clinical trials and there extensions investigated the safety profile of alemtuzumab [67, 69–72]. A total of 90% of patients reported infusion-associated reactions including headache, skin rash and pyrexia [67]. An increased risk of autoimmune conditions was observed in patients receiving alemtuzumab compared to those receiving interferon, including autoimmune thyroid disease [67, 69, 70], immune thrombocytic purpura [67, 69] and less frequently a range of haematologic, renal and dermatologic autoimmune diseases [71]. Cumulative risk of autoimmune disease in MS patients following alemtuzumab treatment was estimated at 22.2% and culminated 12–18 months after the 1st dose [71]. This effect is thought to result from a change in the balance of the immune system from a Th1 mediated response towards a Th2 mediated response [71].

Infections were more frequent in alemtuzumab-treated patients and most commonly included upper respiratory tract, urinary tract, herpes (predominantly cutaneous), and localised fungal infections [67, 69].

Alemtuzumab-treated MS patients were shown to retain the ability to mount a humoral response against influenza and other viruses [73]. Women of child bearing potential should use effective contraceptives when receiving alemtuzumab and for 4 months after treatment infusion.

The benefit-risk ratio of alemtuzumab will have to be assessed carefully for each patient in light of its relatively high rate of side effects and complex administration requiring herpes simplex prophylaxis, methylprednisolone premedication and antipyretic and anti-histaminic co-administration.

Ocrelizumab

Ocrelizumab is an anti-CD20 monoclonal antibody that leads to depletion of $CD20^+$ B cells. Unlike rituximab, which is of murine origin, ocrelizumab is a humanised antibody, reducing risks of infusion-related reactions.

A phase II randomised controlled study including 220 RRMS patients studied the efficacy and safety of two ocrelizumab regimens: low dose (600 mg) and high dose (2000 mg) ocrelizumab, which were infused in two doses on day 1 and 15. Over a 24 week period, ARR was reduced by 80% and 73% in the 600 mg and 2000 mg group respectively, compared to placebo. Both ocrelizumab regimens were better in reducing gadolinium-enhancing lesions on T1–weighted scans and new/enlarged lesions on T2–weighted scans over a 24 week period, compared to interferon beta-1a (Avonex®). Brain-volume loss was not assessed. Serious adverse events were reported in 4% of patients in the placebo group, 2% in the 600 mg ocrelizumab group, 5% in the 2000 mg ocrelizumab group and 4% in the Avonex® group [74]. Efficacy and safety issues are currently being further assessed in phase III trials.

Daclizumab

Daclizumab is a humanised monoclonal antibody that blocks the alpha sub-unit (CD25) of interleukin-2 receptor, limiting activated T cell expansion.

In phase II study SELECT [75], monthly subcutaneous injections of 150 mg or 300 mg daclizumab reduced ARR by 54% and 50% respectively, compared to placebo, over 52 weeks. At 1 year, more patients were relapse free in the 150 mg (81%) and 300 mg (80%) daclizumab groups compared to the placebo group (64%). Over a 24 week period, brain-volume loss was no different in daclizumab- treated patients versus placebo-treated patients [75].

Serious adverse events were reported in 6% of patients in the placebo group, 7% in the 150 mg group, and 9% in the 300 mg group, excluding MS relapse [75]. One patient in the 150 mg daclizumab group died of a local complication of a psoas abscess. Efficacy and safety issues are currently being further assessed in phase III trials.

Concluding remarks

Since the approval of interferon-beta 1a in 1993, options to treat MS have increased significantly. While long term safety of first generation injectable DMTs is well established, potential side-effects of chronic treatment with second and third generation drugs are unknown. Given their immunosuppressive properties, careful long term monitoring of potential infectious and/or tumoural side-effects is critical. Yet-to-be published extensions of phase III clinical trials with patient follow-up beyond 2 years will be informative.

Twenty years ago, DMTs were evaluated on their ability to reduce neuroinflammation, measured by their effectiveness to reduce ARR and MRI markers of inflammation. While these endpoints remain central in all phase III clinical trials, potential neuroprotective proprieties of new drugs have become an area of great interest. Neurodegenerative processes in MS and their contribution to accumulation of irreversible disability are now better characterised, and the need for drugs that promote regeneration or limit neuronal damage is explicit. Laquinimod, which has marked effects on clinical disease progression and MRI markers of brain tissue damage but only mild effects on ARR and MRI markers of inflammation, may have such properties. Clinical trials evaluating the effect of potential neuroprotective drugs on primary progressive or secondary progressive MS will be very informative.

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