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REVIEW ARTICLE

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Safety concerns and risk management of multiple sclerosis therapies

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Currently, more than ten drugs have been approved for treatment of relapsing-remitting multiple sclerosis (MS). Newer treatments may be more effective, but have less favorable safety record. Interferon-β preparations and glatiramer acetate treatment require frequent subcutaneous or intramuscular injections and are only moderately effective, but have very rarely life-threatening adverse effects, whereas teriflunomide and dimethyl fumarate are administered orally and have equal or better efficacy, but have more potentially severe adverse effects. The highly effective therapies fingolimod, natalizumab, daclizumab, and alemtuzumab have more serious adverse effects, some of which may be life-threatening. The choice between drugs should be based on a benefit-risk evaluation and tailored to the individual patient's requirements in a dialogue between the patient and treating neurologist. Patients with average disease activity can choose between dimethyl fumarate and teriflunomide or the "old injectable." Patients with very active MS may choose a more effective drug as the initial treatment. In case of side effects on one drug, switch to another drug can be tried. Suboptimal effect of the first drug indicates escalation to a highly efficacious drug. A favorable benefit-risk balance can be maintained by appropriate patient selection and appropriate risk management on therapy. New treatments will within the coming 1-2 years change our current treatment algorithm for relapsing-remitting MS.

KEYWORDS
disease-modifying therapies, multiple sclerosis, relapsing-remitting multiple sclerosis, risk management, risk stratification, safety, treatment algorithm

1 | INTRODUCTION

During the last 20 years, and in particular throughout the last 5 years, we have experienced a fast evolution in treatments for relapsing-remitting (RR) multiple sclerosis (MS) (Figure 1). The availability of more effective treatments that suppress disease activity and reduce worsening of permanent symptoms may delay, and in some patients even prevent, development of the secondary progressive phase.[1] However, new drugs also carry the risk of serious or even life-threatening adverse effects. In Europe, treatments for RRMS are divided into first-line therapies that are considered more safe and second-line therapies that are considered more risky, whereas these terms are not used in the USA. Patients are usually started on a safe first-line therapy, but very active MS can be treated with a less safe, but more effective second-line treatment as the first choice.

Owing to the large number of available therapies, selection of the appropriate treatment for the individual patient has been increasingly challenging for the neurologist. It is important carefully to balance the treatment efficacy on relapses and worsening of symptoms against the burden of therapy that includes both inconvenience, requirement for monitoring, harmless, but sometime bothersome side effects and rare serious adverse effects.[2] In general, the first-line treatments with a favorable safety profile are only moderately effective and with the augmented efficacy of the second-line treatments follow increased risk of more serious adverse effects (Figure 2). When starting disease-modifying therapy, it is the task of the neurologist to assess whether

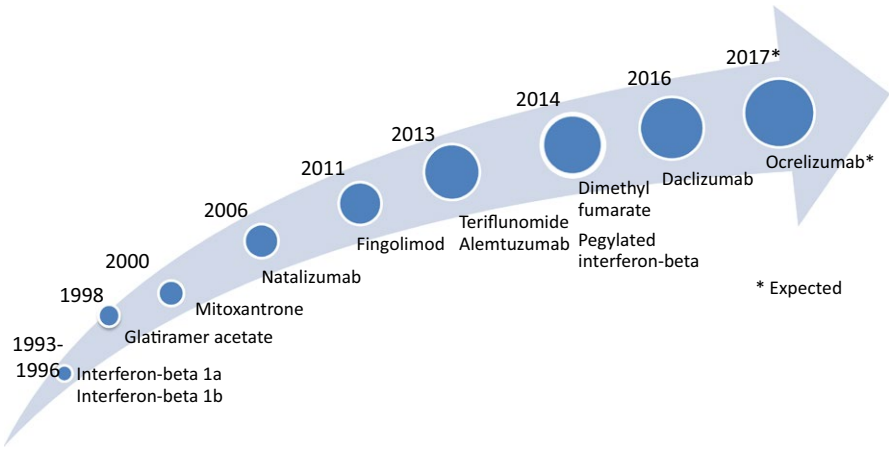


FIGURE 1 Evolution of disease-modifying drugs for treatment of relapsing-remitting multiple sclerosis with approximate year of approval in Europe and USA [Colour figure can be viewed at wileyonlinelibrary.com]

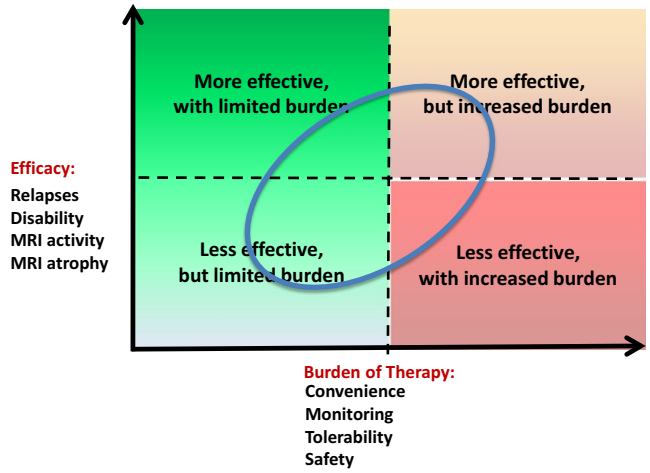


FIGURE 2 Selecting the optimal therapy in relapsing-remitting multiple sclerosis: balancing efficacy and burden of therapy. The oval circle indicates that therapies with a limited burden, for example, interferon-beta and glatiramer acetate, are less effective, and with more effective therapies, for example, natalizumab and alemtuzumab, the burden of therapy increases [Colour figure can be viewed at wileyonlinelibrary.com]

a patient can be treated satisfactorily with less effective, but safe drugs, or needs a more effective, but less safe drug from the start. Also patients initially treated with a low-risk drug may need escalation of therapy to a more effective drug with potentially serious adverse effects. However, a favorable benefit-risk profile can be maintained by appropriate treatment selection and appropriate risk management on treatment.

This article reviews the safety concerns associated with disease-modifying drugs (DMDs) and includes drugs approved for treatment of MS by the US Food and Drug Association (FDA) and/or the European Medicines Agency (EMA).

The assessment of efficacy and safety represents the opinion of the author. This article focuses on safety; efficacy data are only provided to better inform benefit-risk judgements. Currently, the decision of escalating the therapy is mainly based on a drug's efficacy on relapses and disease worsening, but including MRI activity in treatment decisions becomes increasingly recommended, and some MS neurologists advocate to aim at NEDA (no evidence of disease activity). As only very few double-blind head-to-head trials comparing two DMDs have been performed, most comparisons of preparations are based on efficacy in placebo-controlled trials, which cannot be readily compared, and on expert opinion. The safety profile of a DMD to some extent depends on the length of exposure to the therapy. DMDs that have been used for several decades, for example, glatiramer acetate, have often a long list of possible adverse effects listed in the Summary of Product Characteristics (SPC) issued by the EMA, whereas the SPC of a new DMD that only has been on the market for a limited period contains a shorter list of adverse effects, but the long-term effect of this drug may not yet be known.

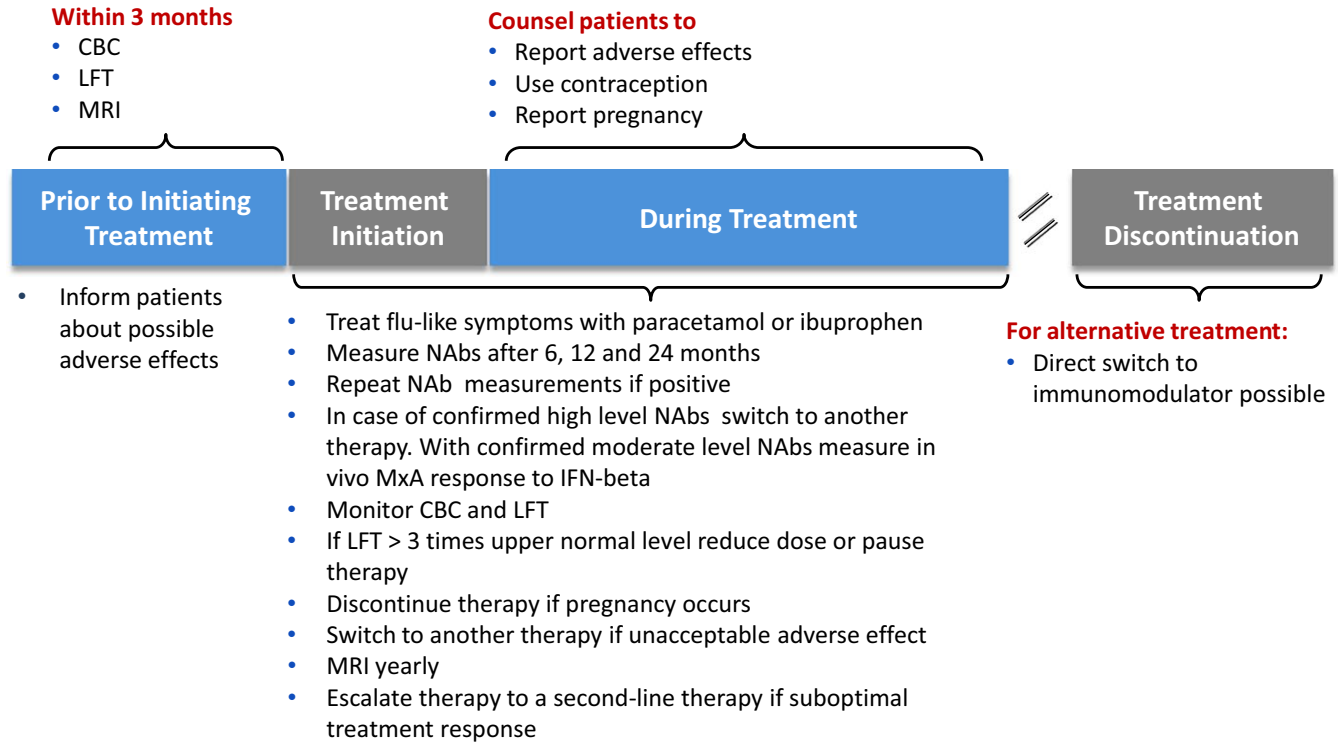
2 | THE "OLD" INJECTABLES

2.1 | Interferon-beta

Interferon (IFN)-β is a naturally occurring cytokine that binds to a cell-surface receptor on target cells, typically T cells, and induces the transcription of many genes involved in the promotion of an anti-inflammatory response within the immune system. In fact, several hundreds of genes are either upregulated or downregulated after a single injection of IFN-β, but it is still only partly known by which mechanisms the treatment exerts its anti-inflammatory action.[3] There are two genetically engineered IFN-β preparations: IFN-β 1a and IFN-β 1b that differ slightly in amino acid composition and glycosylation, but overall they have the same effect and cause similar adverse reactions.

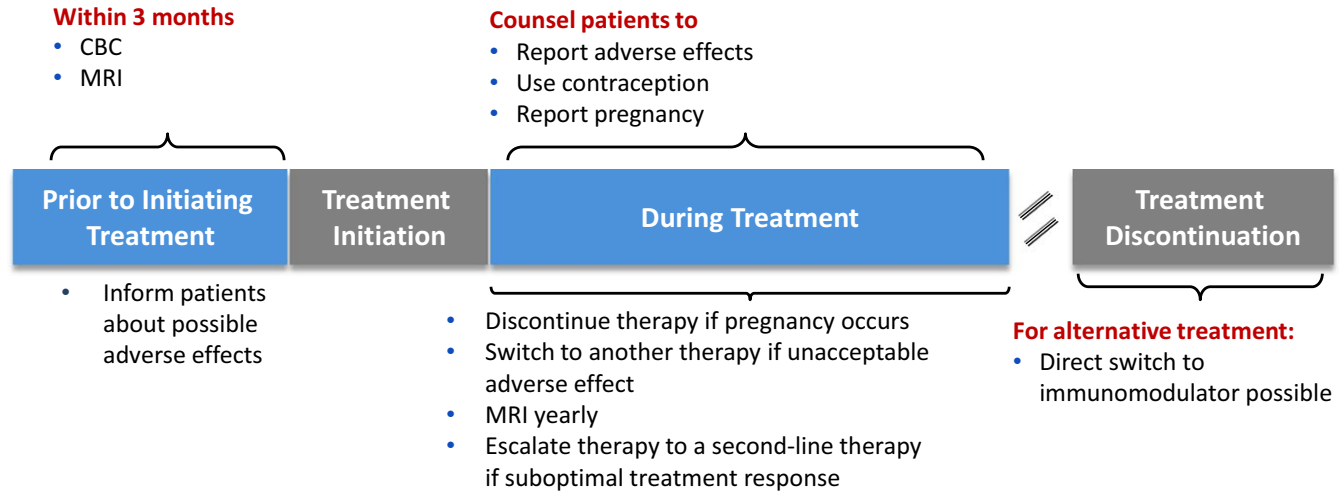
IFN-β preparations are administered either intramuscularly or subcutaneously at intervals of between 2 days and 1 week, although the recently approved pegylated IFN-β 1a needs only biweekly subcutaneous administration.[4] The interferons are first-line therapies approved for treatment of RRMS and clinically isolated syndromes (CIS), and they are considered safe. IFN-β is contraindicated in patients with current severe depression and/or suicidal ideation.

In clinical trials, the efficacy on relapses was a reduction of approximately 30% compared with placebo, the effect on confirmed worsening of symptoms was a little less, and the effect on disease activity on MRI somewhat larger.[5-8] Most adverse effects are directly associated



CBC: complete blood count; LFT: liver function tests; MRI: magnetic resonance imaging; Nabs: neutralizing antibodies.

FIGURE 3 Recommendations for maximizing safety of interferon-beta [Colour figure can be viewed at wileyonlinelibrary.com]



CBC: complete blood count; MRI: magnetic resonance imaging.

FIGURE 4 Recommendations for maximizing safety of glatiramer acetate [Colour figure can be viewed at wileyonlinelibrary.com]

to the injection of the drug: flu-like symptoms and reactions at the injection site, which, although they may be distressing for the patients, are relatively harmless (Table 1). The flu-like symptoms can be treated with paracetamol or NSAID drugs. Serious or life-threatening safety reactions occur very rarely with IFN-β treatment. A proportion of patients treated with IFN-β develop neutralizing antibodies that in high concentrations weaken or abolish the therapeutic effect.[9,10] Increased liver enzymes are frequently seen, although rarely above five times upper normal limit. However, while rare serious hepatic events can occur, only 0.4% of patients overall discontinued interferon-beta-1a treatment because of hepatic adverse effects.[11] Recommendations to maximize safety related to treatment with interferon-β are shown in Figure 3.

The drug has been used for treatment of MS for more than 20 years, and hence, it can be concluded that side effects that are causing serious permanent symptoms or are life-threatening are rare and there are there are no long-term safety issues and, hence, that the physician can feel comfortable about prescribing IFN-β.

TABLE 1 Adverse effect of disease-modifying drugs based on European Medicines Agency (EMA) Summary of Product Characteristics (SPC). Adverse effects in the SPC originate from placebo-controlled, randomized studies (more frequently reported in active- vs placebo-treated patients) and post-marketing reports

	Common adverse effects (≥1/100)	Uncommon adverse effects (≥1/1000 to <1/100)	Rare adverse effects (<1/1000)
Interferon-beta	Neutropenia, lymphopenia, leukopenia, thrombocytopenia, anemia, hepatic enzyme increased, depression, insomnia, headache, diarrhea, vomiting, nausea, pruritus, rash, alopecia, myalgia, arthralgia, Injection site inflammation, injection site reaction, influenza-like symptoms, fatigue, rigors, fever, anti-interferon beta antibodies.	Thyroid dysfunction, hepatitis with or without icterus, seizures, retinal vascular disorders, thromboembolic events, dyspnea, urticaria, injection site necrosis, injection site mass, injection site abscess, increased sweating.	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura, pancytopenia, anaphylactic reactions, hepatic failure, autoimmune hepatitis, suicide attempt, Quincke's edema, erythema multiforme, Stevens Johnson syndrome, drug-induced lupus erythematosus, nephrotic syndrome, glomerulosclerosis, injection site cellulitis.
Glatiramer acetate	Upper respiratory tract infection, gastroenteritis, herpes simplex, otitis media, rhinitis, tooth abscess, vaginal candidiasis, benign neoplasm of skin, neoplasm, hypersensitivity, anorexia, weight increase, anxiety, depression, headache, dysgeusia, hypertonia, migraine, speech disorder, syncope, tremor, ear disorder, palpitations, tachycardia, vasodilatation, dyspnea, cough, rhinitis seasonal, nausea, anorectal disorder, constipation, dental caries, dyspepsia, dysphagia, fecal incontinence, vomiting, liver function test abnormal, rash, ecchymosis, hyperhidrosis, pruritus, skin disorder, urticaria, arthralgia, back pain, neck pain, micturition urgency, pollakiuria, urinary retention, asthenia, chest pain, injection site reactions, pain, chills, face edema, injection site atrophy, local reaction, edema peripheral, pyrexia.	Abscess, cellulitis, furuncle, herpes zoster, pyelonephritis, skin cancer, leukocytosis, leukopenia, splenomegaly, thrombocytopenia, goitre, hyperthyroidism, alcohol intolerance, gout, hyperlipidemia, blood sodium increased, serum ferritin decreased, abnormal dreams, confusional state, euphoric mood, hallucination, hostility, mania, personality disorder, suicide attempt, carpal tunnel syndrome, cognitive disorder, convulsion, dystonia, myoclonus, neuritis, neuromuscular blockade, peroneal nerve palsy, stupor, visual field defect, cataract, corneal lesion, dry eye, eye hemorrhage, eyelid ptosis, mydriasis, optic atrophy, extrasystoles, sinus bradycardia, tachycardia paroxysmal, varicose vein, apnea, epistaxis, hyperventilation, laryngospasm, lung disorder, enterocolitis, esophageal ulcer, periodontitis, rectal hemorrhage, salivary gland enlargement, cholelithiasis, hepatomegaly, angioedema, dermatitis contact, erythema nodosum, skin nodule, arthritis, bursitis, flank pain, muscle atrophy, osteoarthritis, hematuria, nephrolithiasis, urinary tract disorder, abortion, breast engorgement, erectile dysfunction, priapism, prostatic disorder, smear cervix abnormal, testicular disorder, vaginal hemorrhage, vulvovaginal disorder, hangover, hypothermia, immediate post-injection reaction, inflammation, injection site necrosis, mucous membrane disorder, post vaccination syndrome.	Hypersensitivity reactions.
Teriflunomide	Influenza, upper respiratory tract infection, urinary tract infection, bronchitis, sinusitis, pharyngitis, cystitis, gastroenteritis viral, oral herpes, tooth infection, laryngitis, tinea pedis, neutropenia, anaemia, mild allergic reactions, anxiety, headache, paraesthesia, sciatica, carpal tunnel syndrome, palpitations, hypertension, abdominal pain, nausea, vomiting, toothache, rash, acne, hair thinning, musculoskeletal pain, myalgia, arthralgia, pollakiuria, menorrhagia, pain, hepatic enzyme increased, weight decrease, neutropenia, leukopenia, lymphopenia, creatine-phosphokinase increased	Thrombocytopenia, hyperesthesia, neuralgia, peripheral neuropathy, posttraumatic pain.	Interstitial lung disease, pancreatitis, stomatitis, severe skin reactions.

(continues)

TABLE 1 (continued)

	Common adverse effects (≥1/100)	Uncommon adverse effects (≥1/1000 to <1/100)	Rare adverse effects (<1/1000)
Dimethyl fumarate	Gastroenteritis, lymphopenia, leucopenia, flushing, hot flush, diarrhea, nausea, abdominal pain, vomiting, dyspepsia, gastritis, gastrointestinal disorder, pruritus, rash, erythema, proteinuria, feeling hot, ketones in urine, albumin urine present, hepatic enzyme increased, white blood cell count decreased.	Hypersensitivity.	Progressive multifocal leukoencephalopathy (PML).
Fingolimod	Influenza, sinusitis, herpes viral, infections, bronchitis, tinea versicolor, basal cell carcinoma, lymphopenia, leucopenia, depression, headache, dizziness, migraine, vision blurred, bradycardia, atrioventricular block, hypertension, cough, dyspnea, diarrhea, eczema, alopecia, pruritus, back pain, asthenia, hepatic enzyme increased, blood triglycerides increased, neutrophil count decreased.	Pneumonia, macular edema, nausea.	Progressive multifocal leukoencephalopathy (PML), cryptococcal infections, lymphoma, peripheral edema, hypersensitivity, reactions, including rash, urticaria and angioedema upon treatment initiation, posterior reversible encephalopathy, syndrome (PRES), T-wave inversion.
Natalizumab	Urinary tract infection, nasopharyngitis, urticaria, headache, dizziness, vomiting, nausea, arthralgia, rigors, pyrexia, fatigue, anti-natalizumab antibodies.	Hypersensitivity, progressive multifocal leukoencephalopathy (PML).	
Alemtuzumab	Upper respiratory tract infection, urinary tract infection, lower respiratory tract infections, herpes zoster, gastroenteritis, oral herpes, oral candidiasis, vulvovaginal candidiasis, influenza, ear infection, lymphopenia, leukopenia. cytokine release syndrome, Basedow's disease, hyperthyroidism, autoimmune thyroiditis, hypothyroidism, goitre, anti-thyroid antibody positive, insomnia, anxiety, dizziness, paresthesia, tremor, dysgeusia, vision blurred, vertigo, tachycardia, bradycardia, palpitations, flushing, hypotension, hypertension, dyspnea, cough, epistaxis, oropharyngeal pain, nausea, urticaria, rash, pruritus, ecchymosis, alopecia, hyperhidrosis, acne, myalgia, muscle weakness, arthralgia, back pain, pain in extremity, muscle spasms, neck pain, proteinuria, hematuria, menorrhagia, irregular menstruation, pyrexia, fatigue, chest discomfort, chills, pain, edema peripheral, asthenia, influenza-like illness, malaise, infusion site pain.	Lymphadenopathy, tooth infection, genital herpes, onychomycosis, immune thrombocytopenic purpura, thrombocytopenia, hemoglobin decreased, hematocrit decreased, depression, sensory disturbance, hyperesthesia, conjunctivitis, throat tightness, hiccups, throat irritation, abdominal pain, vomiting, diarrhea, dyspepsia, stomatitis, constipation, gastroesophageal reflux, disease, gingival bleeding, dysphagia, hepatic enzyme increased, blister, night sweats, weight decreased.	Immune-mediated nephropathy
Daclizumab	Nasopharyngitis, pneumonia, respiratory tract infection, bronchitis, viral infection, influenza, laryngitis, tonsillitis, pharyngitis, folliculitis, rhinitis, lymphadenopathy, lymphadenitis, anaemia, depression, oropharyngeal pain, diarrhea, stomach pain, anorexia, icterus, dark coloured urine, dermatitis, dermatitis allergic, eczema, psoriasis, seborrhoeic dermatitis, skin exfoliation, rash, rash maculopapular, acne, erythema, pruritus, dry skin, pyrexia, ALT increased, AST increased, liver function test abnormal, hepatic enzyme increased, lymphocyte count decreased	Exfoliative rash, toxic skin eruption, eczema nummular, depression	

2.2 | Glatiramer acetate

Glatiramer acetate is a complex mixture of polypeptides composed of four amino acids with variable lengths of between 10 and 100 amino acids. The drug induces proliferation of anti-inflammatory Th2 cells in the periphery, which on exposure to glatiramer acetate are activated and can enter the CNS and exert an anti-inflammatory effect by bystander suppression of inflammation locally.[12] These cells also release the neurotrophic factor BDNF, which may have consequences for neuroprotection or myelin repair.[13] Glatiramer acetate is a first-line therapy approved for treatment of RRMS and CIS. Until recently, treatment with glatiramer acetate has required subcutaneous injections 20 mg once daily, but lately 40 mg administered three times weekly was approved. The efficacy on relapse reduction and confirmed worsening of symptoms is quite similar to that of IFN-β as shown in several head-to-head studies.[14-16] The only frequently occurring side effects are injection site reactions after 2-24 hours and eventually subcutaneous infiltrations making daily injections very difficult. Acute systemic post-injection reactions with palpitations, chest tightness, sweating and anxiety occur in 15% of the patients, but usually only at one or few occasions. The episodes are self-limiting lasting for a few up to 30 minutes. Recent studies have not been able to show any negative effects on pregnancy and fetal outcomes. Although the list of adverse effects reported in patients treated with glatiramer acetate appears long in the SPC (Table 1), it is probably the safest DMD for treatment of MS and has very rarely been associated with serious, life-threatening, adverse effects, and there are no long-term safety issues.[14-16]

Recommendations to maximize safety related to treatment with glatiramer acetate are shown in Figure 4.

3 | IMMUNOSUPPRESSANTS

Both azathioprine and cyclophosphamide have been used for treatment of MS, but mitoxantrone is the only immunosuppressant has been approved by the US FDA and in many European countries.

3.1 | Mitoxantrone

Mitoxantrone is a synthetic anthracenedione derivate, originally developed as a cytotoxic treatment for acute myeloid leukemia. Mitoxantrone interacts with the enzyme topoisomerase and causes single- and double-strand breakage by intercalating the DNA. The immunosuppressive effect is in particular targeting proliferating B and T lymphocytes by induction of cell lysis or initiation of programmed cell death.[17]

Mitoxantrone is an effective drug with significant reduction in relapse rate and worsening of permanent symptoms and was approved in 2000 for treatment of worsening RRMS, progressive-relapsing MS and secondary progressive (SP) MS in the USA, and later in several European countries.[18] Mitoxantrone is administered intravenously 12 mg/m^2, usually at 3-month intervals.

Chemotherapy-induced reversible bone marrow suppression and nausea are common side effects associated with mitoxantrone infusions. Amenorrhea was reported in more than 20% of mitoxantrone-treated women.[19] Cardiotoxicity increases with the cumulative dose of mitoxantrone, and therefore, the maximum cumulative dose is restricted to 100-140 mg/m^2. Typically, the left ventricular ejection fraction is reduced and in some patients potentially fatal congestive heart failure occurs. Hence, the left ventricle ejection fraction should be measured prior to the initial treatment and at each subsequent dose of mitoxantrone using multigated radionuclide angiography, echocardiography or MRI. Unfortunately, cardiotoxicity may occur several months or even years after discontinuation of mitoxantrone, and measurement of left ventricular ejection fraction should be performed annually, at least 5 years after discontinuation of mitoxantrone.[19,20] The most serious adverse effect is therapy-related acute promyelocytic leukemia that in an Italian study occurred in up to 1% of patients treated with mitoxantrone[21] and may be higher with long-term follow-up. The leukemia has a mortality of about 40%. The occurrence of leukemia may increase at higher cumulative doses, but has been observed after a single dose, and the onset may be several years after discontinuation of therapy.[22]

Owing to the unfavorable safety profile, patients with RRMS should not be treated with mitoxantrone and the drug should be restricted to selected patients with SPMS or PRMS for whom other effective therapies are not available.

4 | ORAL THERAPIES

The oral therapies comprise the two first-line therapies, teriflunomide and dimethyl fumarate, and the second-line therapy fingolimod.

4.1 | Teriflunomide

Teriflunomide is the active metabolite of leflunomide that has been used for treatment of rheumatoid arthritis. It inhibits dihydro-orotate dehydrogenase, which is the rate limiting enzyme in the de novo synthesis of pyrimidine, leading to an inhibition of proliferation of autoreactive B and T cells. Replication of hematopoietic and memory cells is preserved through the salvage pathway based on the existing pyrimidine pool. In addition, teriflunomide has immunomodulatory properties with induction of a shift to an anti-inflammatory cytokine profile, a class switching of immunoglobulins, and a reduction of interleukin (IL)-2 production and IL-2 receptor expression.[23]

Teriflunomide is approved by the US FDA and European Medicines Agency (EMA) and is marketed as 14 mg tablets in Europe and 7 and 14 mg tablets in USA taken once daily for treatment of RRMS and CIS. The efficacy and safety have been assessed in a large program of controlled trials.

In two placebo-controlled clinical phase III trials, teriflunomide 14 mg daily reduced the annualized relapse rate by 32% and 36%, respectively, and had a similar effect on confirmed worsening of symptoms in both trials.[24,25] In a short head-to-head trial against IFN-β 1a subcutaneously, teriflunomide 14 mg daily showed similar reduction of the relapse rate.[26]

Teriflunomide is generally well tolerated, and common adverse effects include gastrointestinal symptoms, hair thinning, skin rashes, weight loss, infections, and increased liver function tests (Table 1). In clinical trials, most adverse effects were mild and self-limiting.[24,26] Adverse events based on a pooled analysis of data from 1002 patients treated with teriflunomide 14 mg daily in controlled studies included headache (16%), increased ALT (15%), diarrhea (14%), hair thinning (13%), nausea (11%); peripheral neuropathy confirmed by nerve conduction studies occurred in 1.9%.[27] Mild-to-moderate reduction in neutrophil and lymphocyte counts and increased liver enzymes were noted in the first 3 months of therapy.[24] During therapy with teriflunomide, lymphocyte count and in Europe liver function tests should be performed every 2 weeks in the first 6 months, while in USA once per month for the first 6 months.

Long-term follow-up (8.5 years) in 147 patients revealed no opportunistic infections and no increased occurrence of malignancies.[28]

As leflunomide has shown teratogenetic properties, a concern with teriflunomide is a potential for teratogenicity.[29] After discontinuation of teriflunomide, patients should not attempt to get pregnant until plasma level has dropped to <0.02 mg/L, which may take 2 years. However, washout treatment with cholestyramine or activated charcoal administered for 11 days decreases teriflunomide blood concentrations to a level associated with minimal teratogenetic risks.[27] Washout treatment should also be performed in a woman who becomes pregnant when treated with teriflunomide, if the patient decides to go through with the pregnancy.

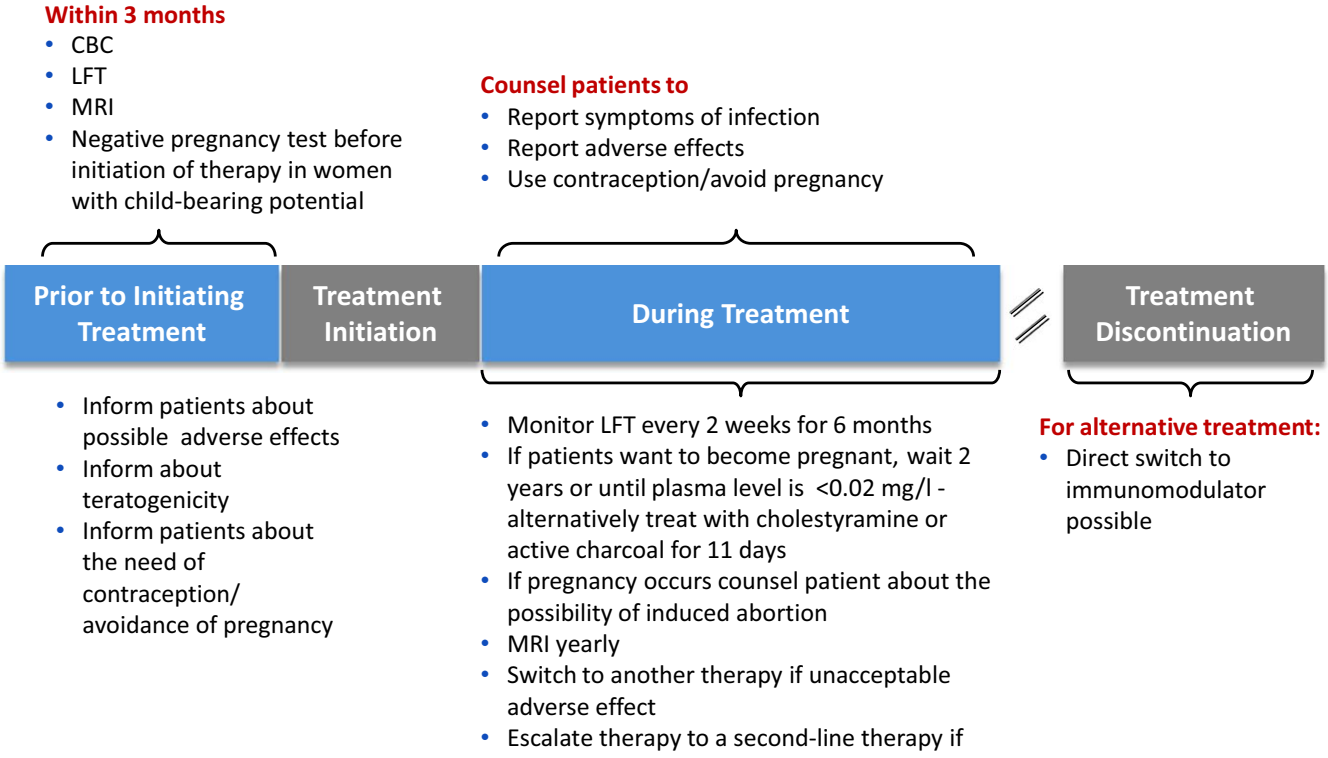
Recommendations issued to maximize safety related to treatment with teriflunomide are shown in Figure 5.

In conclusion, teriflunomide appears to have similar efficacy as the injectable first-line DMDs and the oral administration is an advantage. Although no major safety signals were observed in the clinical trials, post-marketing long-term safety should be explored.

4.2 | Dimethyl fumarate

Dimethyl fumarate reduces the production and release of inflammatory molecules and has antioxidant properties. By activating the transcription factor nuclear factor E2-related factor 2 (Nrf2), fumarates induce expression of endogenous antioxidative factors in vitro, which may protect the CNS from the detrimental effect of reactive oxygen radicals. Fumarates also inhibit the transcription factor nuclear factor κB, which is important for the expression of several inflammatory cytokines.[30] Dimethyl fumarate is administered orally as a 240 mg tablet twice daily.

In placebo-controlled clinical trials, the relapse rate was reduced about 50% and disability progression by 38% in one trial but not significantly in another.[31,32] The effect on gadolinium-enhancing lesions or new or enlarging T2 lesions in MRI was between 80% and 90%. Dimethyl fumarate was generally well tolerated. The most frequently occurring adverse effects in patients taking dimethyl fumarate 240 mg tablet twice daily were flushing and gastrointestinal symptoms that occurred in 38% and 36%, respectively, and that each caused premature discontinuation of the drug in approximately 10% of the



CBC: complete blood count; LFT: liver function tests; MRI: magnetic resonance imaging.

FIGURE 5 Recommendations for maximizing safety of teriflunomide

patients.[32] A Cochrane analysis including 2667 patients from the two placebo-controlled phase III trials[31,32] reported the frequency of flushing (28.2%), gastrointestinal symptoms (pain, nausea, and diarrhea) (35.9%), and lymphopenia <0.5 × 10^9/L (0.4%).[33]

Post-marketing, a small number of progressive multifocal leukoencephalopathy (PML) cases have been reported, in particular in patients with a low lymphocyte count, but in one patient with a lymphocyte count >0.5 × 10^9/L. EMA has issued a warning and requested that lymphocyte count should be performed every 3 months in patient treated with dimethyl fumarate. If the lymphocyte count is maintained below 0.5 × 10^9/L during a 6-month period, the benefit-risk of continued treatment with dimethyl fumarate should be re-considered in the context of other therapeutic options available (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/11/WC500196421.pdf.)

Recommendations suggested to maximize safety related to treatment with dimethyl fumarate are shown in Figure 6.

In conclusion, dimethyl fumarate treatment results in a considerable reduction of the annual relapse rate with less evidence of effect on confirmed worsening of symptoms. It is generally well tolerated, but a few cases of PML make monitoring of the lymphocyte count mandatory.

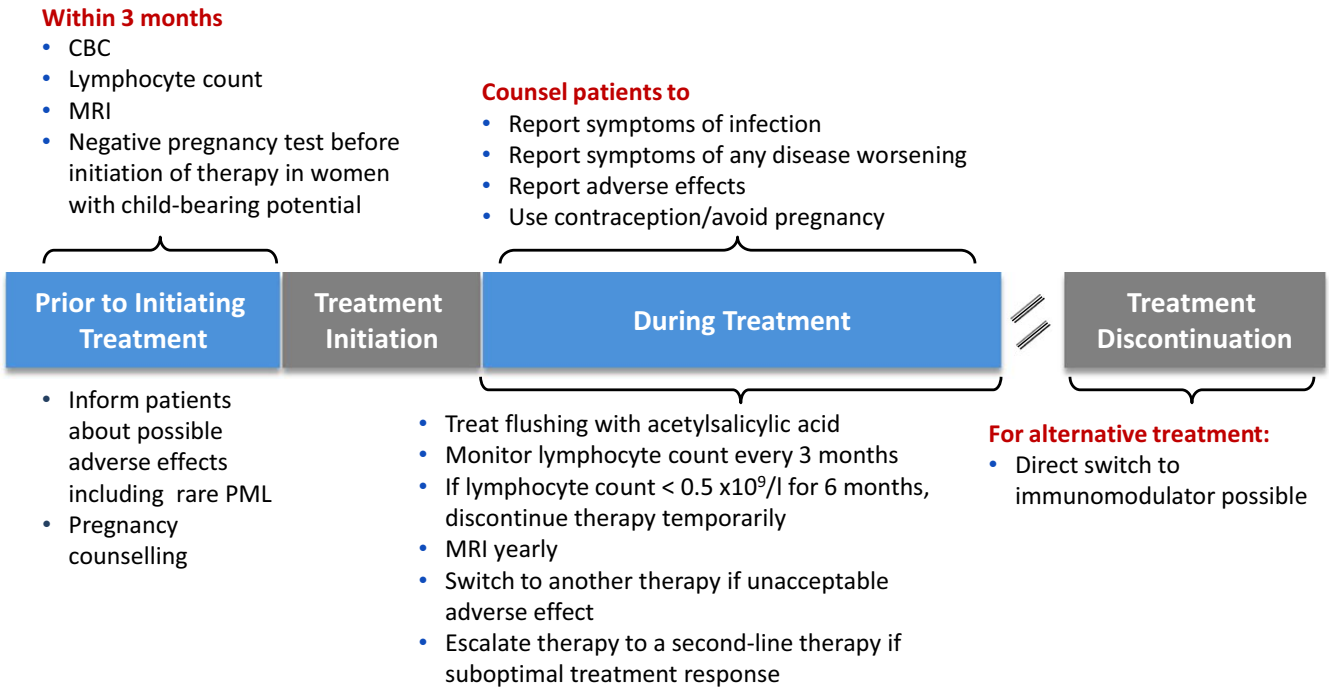
4.3 | Fingolimod

Fingolimod is a sphingosine-1-phosphate (S1P) analogue that acts as a functional antagonist of S1P receptors.[34] Fingolimod was the first oral drug to be approved by the FDA and EMA for treatment of RRMS. EMA has rated fingolimod as a second-line therapy. It is administered as a 0.5 mg capsule taken once daily.

After administration, fingolimod is immediately phosphorylated and when phosphorylated fingolimod is bound to the S1P receptor; the receptor is stimulated and subsequently internalized and degraded resulting in a functional antagonism of the receptor. Presence of S1P receptors on the surface is a prerequisite for lymphocyte to egress from the secondary lymphoid tissue, and without S1P receptors, the lymphocytes are trapped, resulting in a decrease in circulating lymphocyte count in the peripheral blood. Effector memory T cells are, however, not sequestered, and theoretically, the immune surveillance is preserved.[34,35] The reduction in $CD4^+$ T cells and B cells in the peripheral blood is responsible for the decreased T-cell-mediated CNS inflammation. Fingolimod is lipophilic, crosses the blood-brain barrier, and binds to neurons, oligodendrocytes, astrocytes, and microglia that all have S1P receptors,[36,37] but the significance of this is mainly unknown.

In placebo-controlled clinical trials in RRMS, fingolimod reduced the annualized relapse rate by 48%-55% and confirmed worsening of symptoms by 28% in one study, but was without significant effect in another.[38,39] In a head-to-head comparison with IFN-β 1a intramuscular 30 μg weekly, fingolimod reduced the annualized relapse rate by 52%.[40]

The presence of S1P receptors in many body tissues explains a number of unwanted effects of fingolimod treatment including effects on the heart, macula, lungs, and liver[34] (Table 1). In clinical trials, fingolimod tablets were generally well tolerated. After administration of the first dose of fingolimod, the effect on the heart may cause bradycardia



CBC: complete blood count; MRI: magnetic resonance imaging.

FIGURE 6 Recommendations for maximizing safety of dimethyl fumarate [Colour figure can be viewed at wileyonlinelibrary.com]

and grade 2 atrioventricular conduction block that occurred in <2% of patients.[41] Adverse effects that were seen during therapy with fingolimod included macula edema, elevated liver function tests, increased risk of respiratory tract infections, urinary tract infections, regional herpes virus infections, and hypertension.[42] Two patients treated with 1.25 mg fingolimod daily encountered fatal herpes virus infections: One patient died of disseminated primary varicella-zoster infections with liver failure and the other died from herpes simplex encephalitis.[40] Post-marketing one patients treated with fingolimod 0.5 mg daily suffered a fatal reactivation of varicella-zoster infection with liver failure. Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported at a 5.0 mg dose in clinical trials and 0.5 mg post-marketing.[43] Occurrence of PML has been reported in a small number of patients compared to the extensive use of the drug, in particular, but not exclusively, in patients who had been treated with natalizumab prior to fingolimod.[44]

EMA recommends that before administration of first dose, a baseline ECG should be performed and pulse and blood pressure measured, and in the 6 hours following the first dose, continuous monitoring of ECG should be performed and pulse and blood pressure monitored. If the patient becomes symptomatic, observation should be continued until the symptoms have resolved [http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/12/WC500199040.pdf].

Fingolimod should not be taken together with certain antiarrhythmics and only with careful monitoring together with beta blockers and calcium channel blockers, preferably after advice from a cardiologist, and patients with a history of ischemic cardiac disease or congestive heart failure should not be treated with fingolimod. In patients without a history of chickenpox, varicella-zoster serology should be performed, and if the patient is antibody-negative, varicella-zoster virus vaccination is recommended. Before treatment a recent ECG should be available.

During treatment with fingolimod, regular blood cell counts are recommended and ophthalmologic examination should be performed 3-4 months after starting fingolimod.[45] Ophthalmologic examination is recommended before treatment in patients with diabetes mellitus and a history of uveitis, and in these patients, regular follow-up is recommended during treatment with fingolimod. As fingolimod can cause respiratory symptoms, assessment of lung function may be indicated.[38,40] Liver enzymes should be monitored at regular intervals. During treatment with fingolimod, patients should avoid live attenuated vaccines and women of child-bearing potential should use effective contraception. If treatment is interrupted for: 1 day or more during the first 2 weeks; more than 7 days during weeks 3 and 4; or more than 2 weeks after 1 month of treatment monitoring after first dose as for treatment initiation should be performed. After discontinuation of fingolimod, a period of 6 weeks should be introduced before start of new DMD to allow the lymphocyte count to recover.

Fingolimod may have teratogenetic properties,[46] and women should be advised to use adequate contraception during treatment with fingolimod.

Recommendations issued to maximize safety related to treatment with fingolimod are shown in Figure 7.

In conclusion, fingolimod is a treatment for RRMS with proven efficacy, and apart from the inconvenience and potential for cardiac arrhythmias associated with administration of the first dose, the treatment is easy to manage. Its future use will mainly be determined by evolution of the safety profile and will also depend on whether EMA will approve the use of fingolimod as a first-line therapy for RRMS.

5 | THERAPEUTIC MONOCLONAL ANTIBODIES

The currently approved therapeutic monoclonal antibodies comprise natalizumab, alemtuzumab, and daclizumab, and in addition, the monoclonal antibody ocrelizumab is expected to be approved and marketed in 2017 and is thus included in this review.

5.1 | Natalizumab

Natalizumab is a humanized monoclonal antibody directed against α4-integrin, a component of the very late antigen (VLA)-4 present on lymphocytes.[47] It was the first drug designed for treatment of MS and the first monoclonal antibody to be approved for treatment of RRMS. Natalizumab is administered intravenously 300 mg at 4-week intervals. When natalizumab binds to VLA-4, it blocks the interaction between VLA-4 and the ligand VCAM (vascular cell adhesion molecule) on the surface of endothelial cells, and thereby inhibits the migration of autoaggressive lymphocyte through the blood-brain barrier into the CNS.[47]

In a placebo-controlled phase III clinical trial, natalizumab was very effective. The annualized relapse rate was reduced by 68%, the risk of confirmed worsening of symptoms by 42%, and the effect on MRI activity was even more pronounced[48] (Table 1).

In the clinical trials, natalizumab showed a favorable safety profile. Infusion reactions were reported in a small proportion of patients. Serious hypersensitivity reactions occurred in 1.3% of the patients and were often associated with the presence of neutralizing antibodies.[48] Neutralizing antibodies occurred in 9% of the patients, of whom 3% developed transient and 6% permanent antibodies. Permanent neutralizing antibodies were associated with abolition of the therapeutic efficacy.[49] Other adverse effects were mild lymphocytosis and increased liver enzymes.[48]

However, in the extension of one of the phase III trials, two patients developed PML, which turned out to be the major safety issue with natalizumab therapy.[50] Post-marketing (August 2015), 588 patients have encountered this serious opportunistic infection out of more than 140.000 patients treated with natalizumab [https://medinfo.biogenidec.com/medinfo]. PML is caused by John Cunningham (JC) virus that is ubiquitous throughout the world and presents as an asymptomatic infection in 50%-60% of the MS population.[51] PML is a rare event, likely resulting from convergence of multiple factors including virus mutation, host factors, and effects of drugs that reduce CNS immune surveillance.[52] Today, three independent risk factors for natalizumab-associated PML are known and can be used for risk stratification in patients treated with

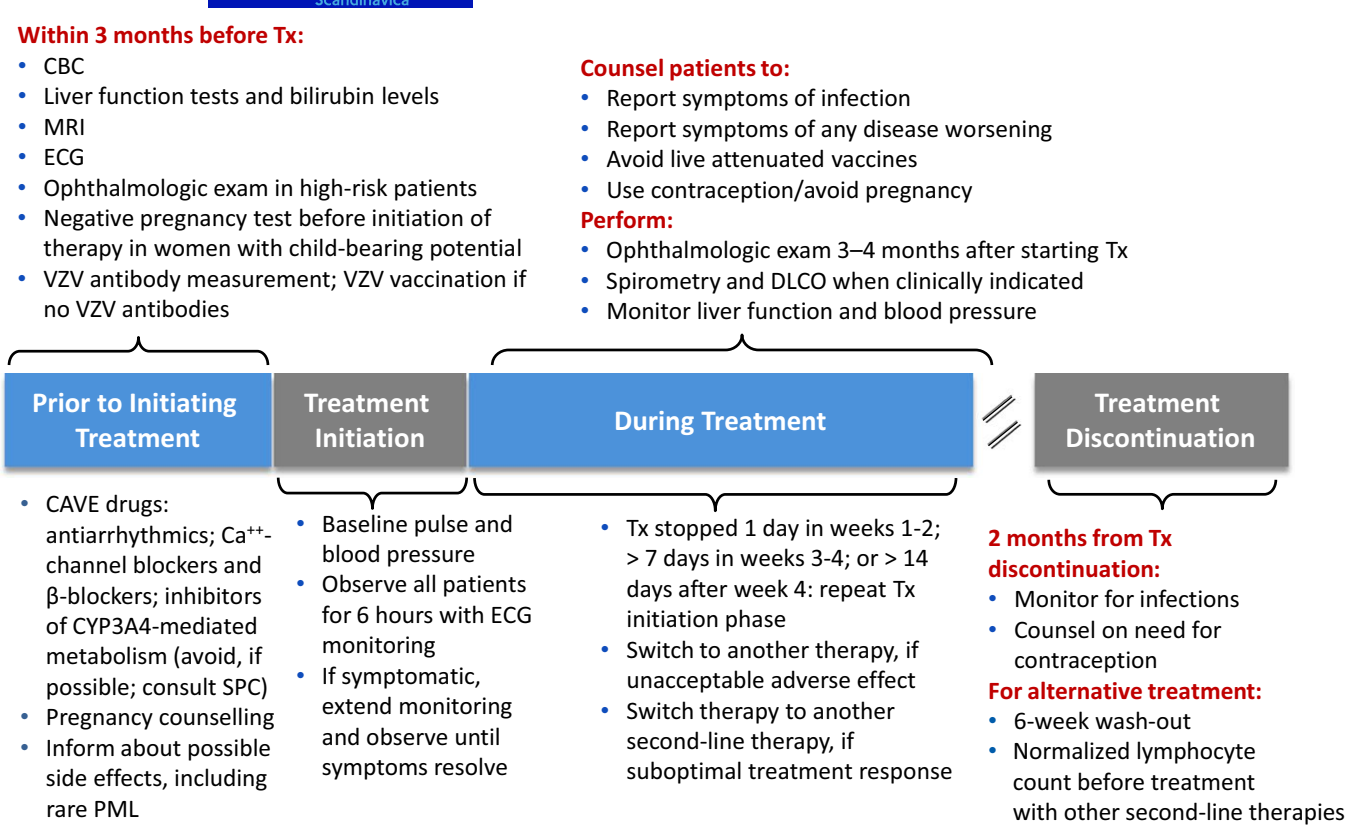
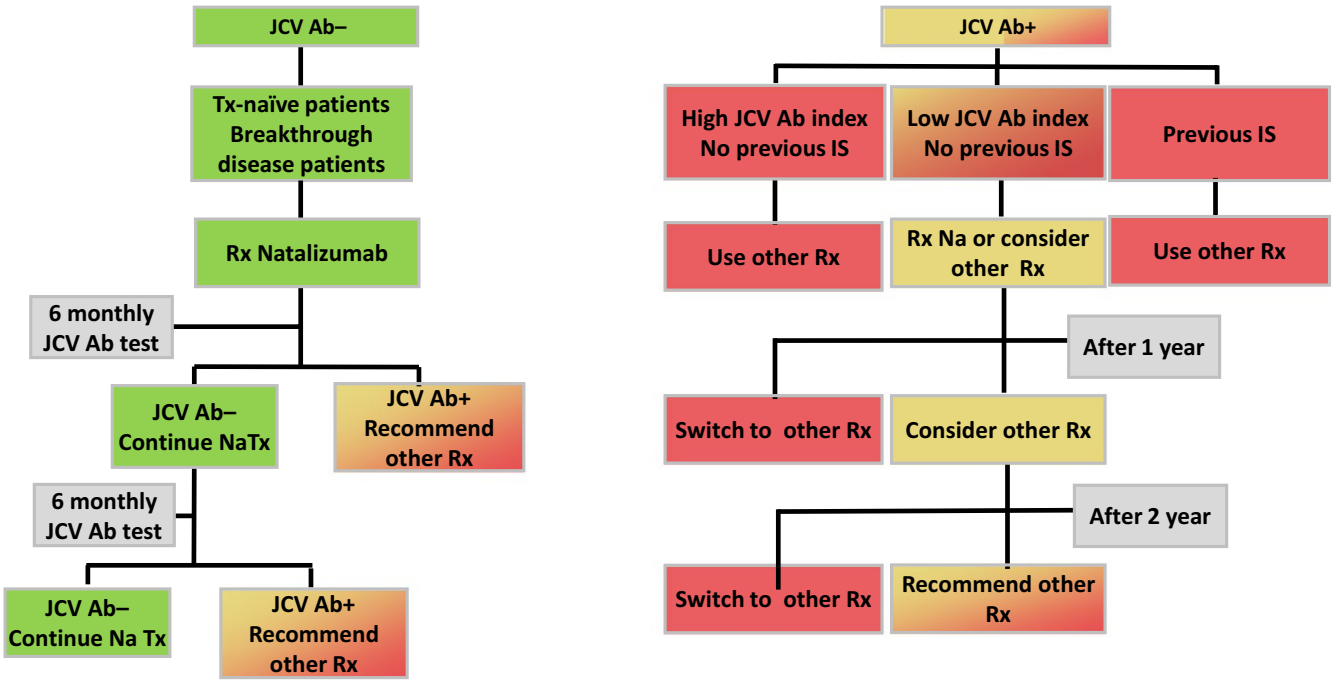


FIGURE 7 Recommendations for maximizing safety of fingolimod [Colour figure can be viewed at wileyonlinelibrary.com]

natalizumab[53]: (i) The presence of JC virus is a prerequisite for development of PML and can be determined by measurement of anti-JC virus antibodies in the blood using ELISA technique,[52] which is a robust test with <2% false-negative results. Nowadays, the concentration of JC virus antibodies is expressed as an index.[54] (ii) The duration of natalizumab therapy is a risk factor. During the first 12 months of therapy, the risk of PML is very low, and it rises significantly beyond 2 years. (iii) Prior use of immunosuppressants increases the risk of PML by a factor 4. A few percent of JC virus antibody-negative patients become antibody-positive per year, and hence, it is recommended to perform 6-monthly JC virus antibody tests in during treatment with natalizumab in JC virus antibody-negative patients. The theoretical risk of PML in JC virus antibody-negative patients has been estimated to 1 in 10.000 treated patients. In JC virus antibody-positive patients, who have been treated with prior immunosuppressants, PML risk after 2 years is more than 1 in 100 patients, and thus, I do not favor treatment with natalizumab in patients who are JC virus antibody-positive and previously have been treated with immunosuppressants.[53] In JC virus antibody-positive patients without prior use of immunosuppressants, the risk of PML is low in the first 12 months and it increases to approximately 1 in 2.000 treated patients during the next 12 months. After 24 months of therapy, the annual risk has been estimated to approximately 2 in 1000 treated patients (0.5%), and the estimated risk of PML during 72 months of natalizumab therapy is 0.9% [https://medinfo.biogenidec.com/medinfo].[53] However, the risk is determined by JC virus antibody index: In patients with a low JC virus antibody index (<0.9), the risk of PML during 72 months of natalizumab therapy can be assessed to 0.8 per 1.000 patients, whereas in patients with an index >1.5, the risk is 17.6 per 1.000 patients.[54] Consequently, natalizumab should not be used as the first choice of a second-line therapy in patients with a high index.[53] In patients with an index <0.9, continuous treatment with natalizumab in JC virus antibody-positive patients should be reconsidered after 12 and 24 months of therapy taking into consideration the efficacy of natalizumab therapy, assessment of the risk of PML with continued natalizumab therapy vs the perceived efficacy and risk of an alternative therapy.[53] Administration of natalizumab every 6-8 weeks may be a possible way to reduce the risk of PML. Recently, the presence of a decreased percentage of l-selectin-expressing $CD4^+$ T cells has been suggested as a risk factor for PML in natalizumab-treated MS patients.[55]

A flowchart of the use of PML risk stratification is shown in Figure 8.

Symptoms indicating PML or new symptoms atypical of a MS relapse in patients treated with natalizumab should prompt acute MRI to exclude PML and CSF examination for JC virus DNA with a sensitive rt-real-time polymerase chain reaction (PCR) assay, as many patients only have few copies present in the CSF.[56] Patients with PML should be treated with plasma exchange to remove circulating natalizumab.[57] Following removal of natalizumab from the circulation and reconstitution of the immune surveillance in the brain, patients develop immune reconstitution inflammatory syndrome (IRIS) that transiently worsens symptoms of PML.[58]



JCV Ab: John Cunningham virus antibodies; Ab– = antibody negative; Ab+ = antibody positive; IS: Immunosuppressant therapy; Tx = treatment; Rx = prescription; Na = natalizumab.

FIGURE 8 Risk stratification for progressive multifocal leukoencephalopathy (PML) in daily clinical practice in patients treated with natalizumab (modified from Sorensen et al.[53]) [Colour figure can be viewed at wileyonlinelibrary.com]

Prophylactic treatment with high-dose corticosteroids before plasma exchange may diminish the symptoms of IRIS. Overall, natalizumab-associated PML has a mortality of >20% and the majority of the surviving patients have severe sequelae following PML and IRIS.[58]

A number of studies have reported intense flare-up of disease activity after cessation of natalizumab,[59-61] whereas others reported a return of disease activity in a pattern that was consistent with known pharmacokinetic and pharmacodynamic properties of natalizumab.[62,63] Severe relapses have been observed in patients treated with fingolimod 3-4 months after cessation of natalizumab.[64] In a Danish study of 375 patients who had discontinued natalizumab after at least 24 weeks on therapy, the annualized relapse rate before start of natalizumab therapy was 0.94 (95% confidence interval (CI) 0.88-1.00), 0.47 (95% CI 0.43-0.52) during natalizumab therapy, 0.63 (95% CI 0.51-0.76) months 1-6 after natalizumab, and 0.55 (95% CI 0.42-0.70) months 7-12 after natalizumab. However, 83 (22%) of the patients could be classified as showing rebound of relapses defined as a higher individual relapse rate after cessation of natalizumab than before natalizumab.[65]

When switching to another DMD after cessation of natalizumab, a MRI scan should be performed to examine for the presence of asymptomatic PML, and before switching to a high-risk therapy, for example, alemtuzumab, a lumbar puncture with CSF examination for JC virus DNA using a sensitive rt-PCR assay is recommended.

EMA has recommended yearly MRI as a part of PML risk management. Although no teratogenic effect of natalizumab has been observed so far, patients should ensure contraception under natalizumab therapy.

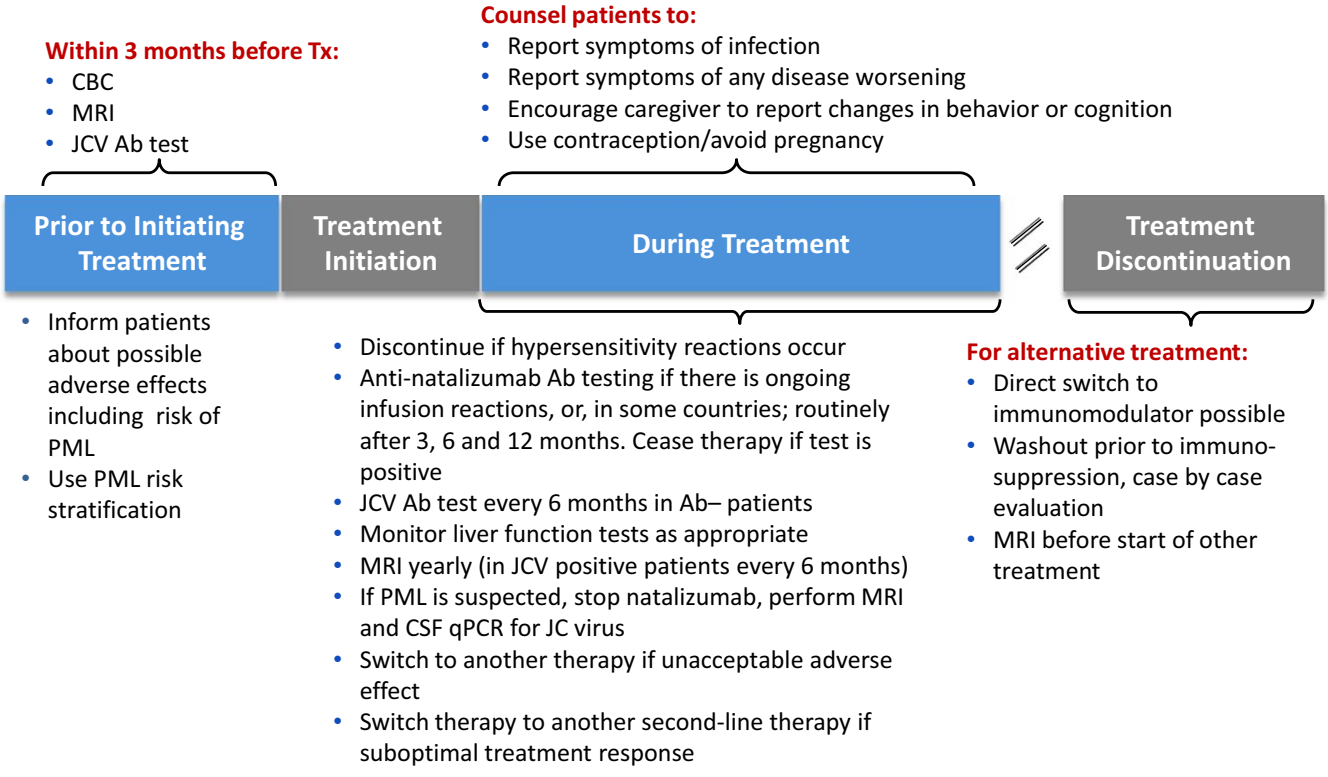
Recommendations issued to maximize safety related to treatment with natalizumab are shown in Figure 9.

In conclusion, natalizumab is a very effective treatment for RRMS yielding a profound reduction of the annual relapse rate and of worsening of permanent symptoms. The risk of PML is the limiting factor in the use of natalizumab, but risk stratification is possible and should be utilized. Natalizumab is a good choice in JC virus antibody-negative patients, but should probably not be the first choice among second-line therapies in JC virus high-index (>1,5) antibody-positive patients.

5.2 | Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody against CD52 that causes a long-lasting depletion of lymphocytes and monocytes. After depletion, B cells recover to the lower limit of normal within 7 months, whereas $CD8^+$ T cells are recovered only after 20 months and $CD4^+$ T cells after 35 months. After alemtuzumab treatment, the B-cell compartment is composed of naive cells that have emerged from the bone marrow, whereas T cells are largely memory T cells and dominated for 6 months by regulatory T cells.[66,67] Alemtuzumab is administered intravenously, 12 mg daily for 5 consecutive days and after 12 months 12 mg daily for 3 consecutive days.

Alemtuzumab is approved in EU for treatment of active MS, while in the US FDA has advised: "Because of its safety profile, the use of Lemtrada should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS."



CBC: complete blood count; MRI: Magnetic resonance imaging; JCV Ab: John Cunningham virus antibodies; PML: Progressive multifocal leukoencephalitis; Ab: Antibodies; CSF: Cerebrospinal fluid; PCR: polymerase chain reaction; qPCR: quantitative real-time PCR.

FIGURE 9 Recommendations for maximizing safety of natalizumab [Colour figure can be viewed at wileyonlinelibrary.com]

Alemtuzumab was compared with subcutaneous IFN-β 1a 44 μg three times weekly in two large randomized trials, one in de novo-treated patients and one in patients who previously had been treated with a first-line therapy. Compared to IFN-β 1a, the relapse rates were reduced by 55% and 48%, respectively, and the effect on confirmed worsening on EDSS was 42% reduction in the trial with patients previously treated with a first-line therapy, whereas the difference did not reach statistical significance in the trial with de novo-treated patients.

Recently, encouraging results after 5 years of therapy have been reported.[68] Alemtuzumab lowered the risk of sustained accumulation of disability by 72% and the rate of relapse by 69% compared with IFN-β 1a, and only 35% of the alemtuzumab patients received retreatment with alemtuzumab after the initial two treatment courses. Long-term observations suggest that early treatment with alemtuzumab in the relapsing-remitting may delay disease worsening for many years and reduce the proportion of patients entering the secondary progressive phase of the disease.[69]

Infusion reaction occurred in the majority of patients of whom 3% experienced serious reactions,[70,71] and in the first clinical trials, patients experienced transient increase in MS symptoms associated with cytokine release,[72] which can be avoided by pretreatment with corticosteroids and antihistamines. Other adverse effects are increased number of infections, including herpetic and fungal infections (Table 1). Oral antiherpes medication is recommended for at least 1 month after alemtuzumab administration. One fatal infection was reported in a patient with pancytopenia suffering sepsis. No serious opportunistic infections were reported.[70,71]

The most important adverse effect in patients treated with alemtuzumab is secondary autoimmunity with a delayed onset,[70,71] which occurred in 47.7% over a median 7-year follow-up (range 33-144 months)[73] (Table 2). Autoimmunity may be predicted by a pretreatment high concentration of IL-21 in the blood.[74]

Thyroid disorders, both hypo- and hyperthyroidism, occur in 30% of patients during a 4-year observation period with onset 12-48 months after start of alemtuzumab, peak onset 24-36 months.[68] Thyroid function tests should be performed every 3 months during alemtuzumab therapy and 48 months after the last dose.

Immune thrombocytopenia (ITP) was observed in 2.3% of patients.[68] In the clinical trials, one case was associated with a fatal intracranial hemorrhage. The thrombocytopenia typically develops rather abruptly, and the time of onset is 14-36 months after start of alemtuzumab, but it may occur several years after the last dose and patients need to have performed a complete blood count monthly during treatment and 48 months after the last alemtuzumab dose. Patients need counseling to report signs of bruising, bleedings, or petechiae. The thrombocytopenia usually responds to standard medical therapy that induces durable remission.

Three patients have encountered immune-mediated nephropathies; two cases of Goodpasture's syndrome (anti-GMB) and one cases of membranous nephropathy, two of which needed a renal

transplant.[68] The onset was 9-40 months after start of alemtuzumab. Early detection is crucial for prognosis, and therefore, patients need to undergo monthly urinalysis and Se-creatinine measurements until 48 months after the last administration of alemtuzumab. Female patients need to practice effective contraception and avoid pregnancy until 4 months after treatment with alemtuzumab.

Recommendations issued to maximize safety related to treatment with alemtuzumab are shown in Figure 10.

In conclusion, alemtuzumab is a very effective MS therapy that not only reduces the annual relapse rate, but also seem be able to stabilize or improve disability for several years after two courses. Adverse events occur frequently, in particular secondary autoimmune disorders, some of which are serious, but treatable.

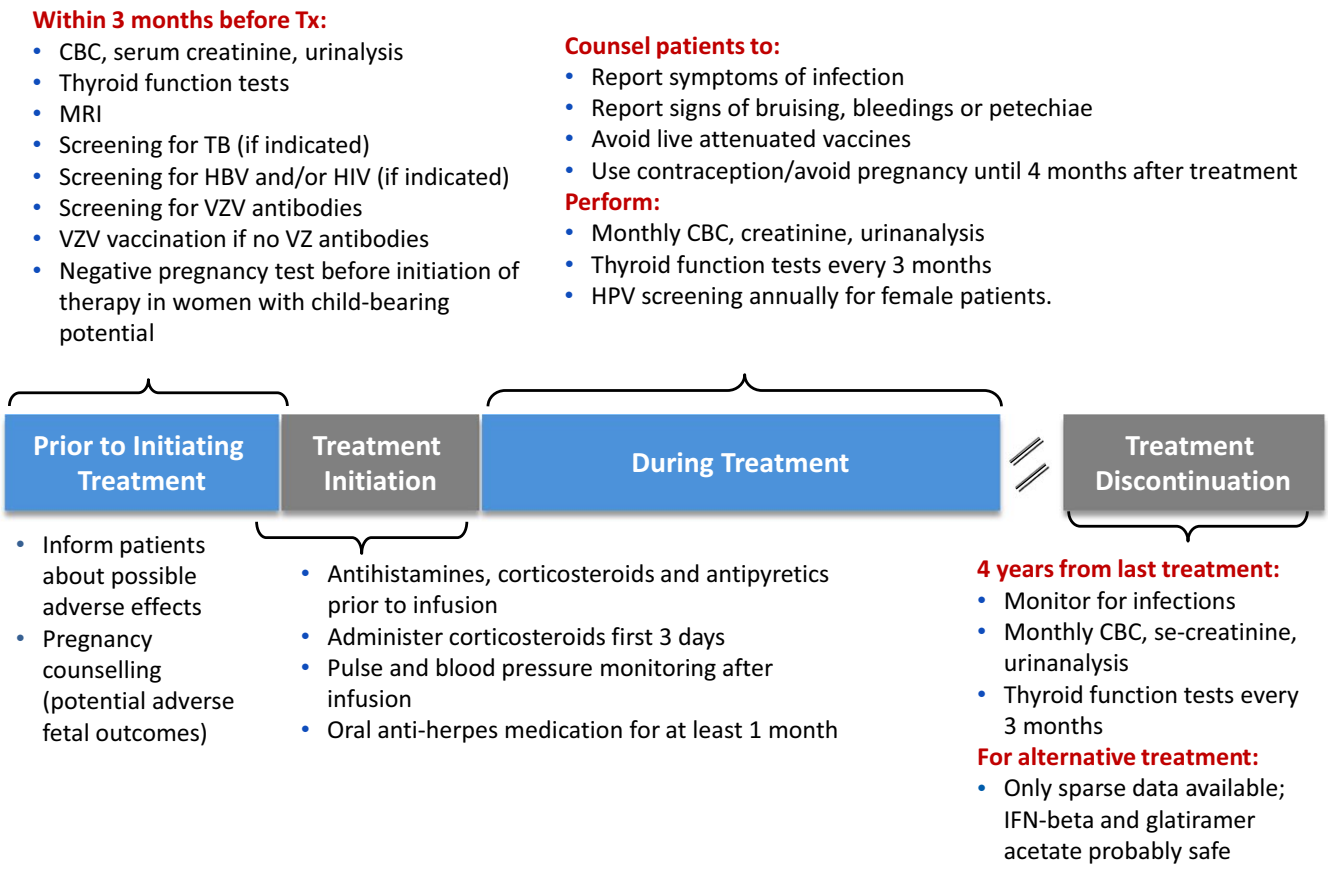
TABLE 2 Secondary autoimmunity after treatment with alemtuzumab

Thyroid disorder
Cumulative incidence of 36% of patients on alemtuzumab (4-year follow-up). Not all with clinical symptoms
Onset 12-48 months after alemtuzumab
Peak incidence years 2 and 3
Immune thrombocytopenia (ITP)
Cumulative incidence of 1.1% in phase 2 and phase 3 trials (alemtuzumab 12 mg)
Onset 14-36 months after alemtuzumab (may occur several years after)
Responsiveness to standard medical therapy
Nephropathies
Two types of glomerular disease observed in clinical trials: anti-GBM (two cases) and membranous nephropathy (one case)
Onset 9-40 months after alemtuzumab
Early detection is crucial for prognosis

5.3 | Daclizumab

Daclizumab is a recently approved humanized monoclonal antibody targeting CD25, the α subunit of the human high-affinity IL-2 receptor. Daclizumab decreases IL-2 signaling at the high-affinity IL-2 receptor, but increases signaling on cells that express the intermediate-affinity receptor. Targeting CD25 causes several immunological effects including expansion of immunoregulatory CD56^{bright} natural killer cells, inhibition of T-cell activation by dendritic cells, and a reduction in lymphoid tissue inducer cells.[75]

In a randomized placebo-controlled study subcutaneous injections of daclizumab 150 or 300 mg every 4 weeks for 52 weeks, the annualized relapse rate (ARR) was 54% (95% CI 33%-68%; *P*<.0001) lower



Tx: Treatment; CBC: complete blood count; MRI: Magnetic resonance imaging; TB: Tuberculosis; HBV: Hepatitis B virus; HIV: Human; VZV:varicella-zoster virus; HPV: Human papillomavirus; Tx:treatment.

FIGURE 10 Recommendations for maximizing safety of alemtuzumab [Colour figure can be viewed at wileyonlinelibrary.com]

for patients given daclizumab 150 mg (ARR: 0.21) and 50% lower (95% CI 28%-65%; *P*=.00015) for patients given daclizumab 300 mg (ARR: 0.23) compared with placebo (ARR: 0.46).[76] Serious infections were more common in daclizumab-treated patients and so were cutaneous adverse event that in a few percent were serious including rash, atopic dermatitis, allergic dermatitis, exfoliative dermatitis, and erythema nodosum. One patient given daclizumab, who was recovering from a serious rash, died because of complications of a psoas muscle abscess.[76] A phase III study compared daclizumab 150 mg subcutaneously every 4 weeks and IFN-β 1a 30 μg intramuscularly once weekly for up to 144 weeks. The annualized relapse rate was 45% lower with daclizumab (ARR: 0.22) than with IFN-β 1a (ARR: 0.39) (*P*<.001), whereas worsening of disease on EDSS did not show statistically significant difference. Cutaneous events and elevated liver enzymes >5 times upper limit occurred more frequently with daclizumab.[77]

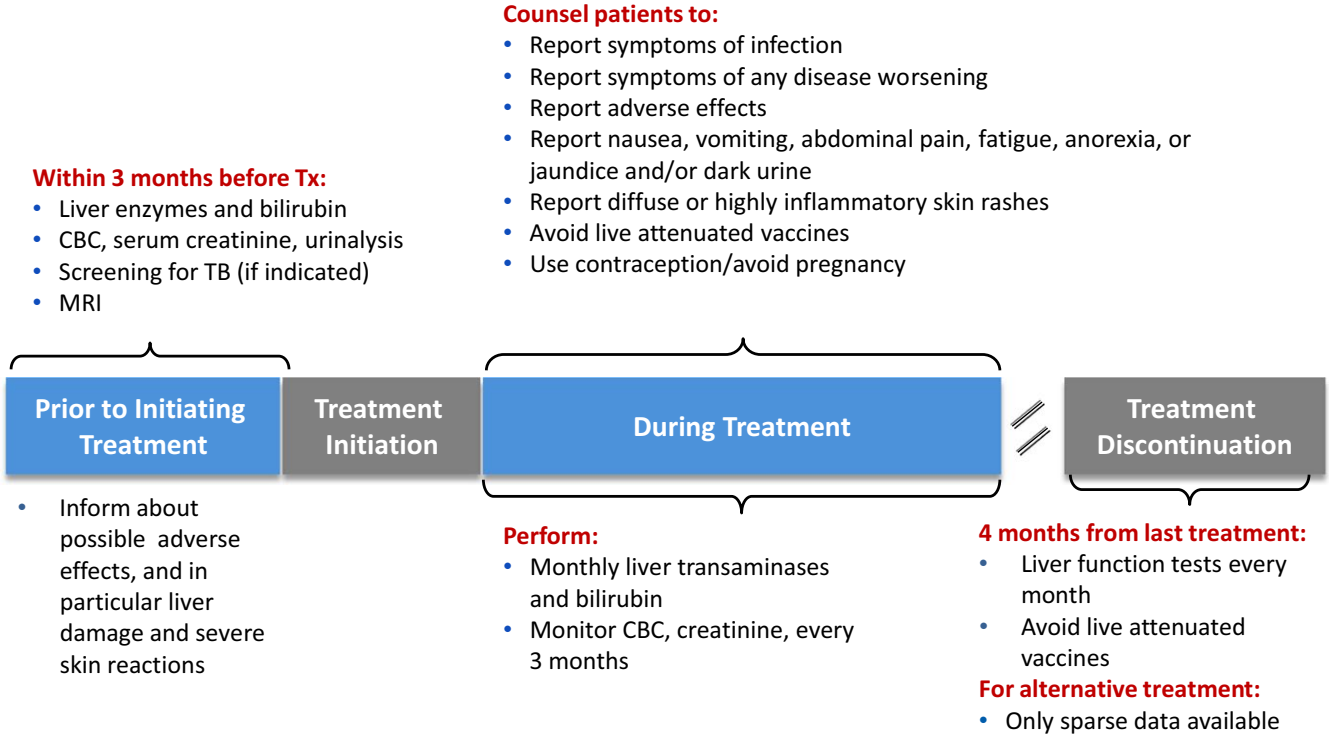
Recommendations issued to maximize safety related to treatment with alemtuzumab are shown in Figure 11.

5.4 | Ocrelizumab

Ocrelizumab is a recombinant humanized second-generation anti-CD20 monoclonal antibody with a humanized IgG1 tail designed to selectively target cells that express the B lymphocyte antigen CD20 on their surface. The CD20 molecule is an activated glycosylated phosphoprotein expressed on a broad range of cells of the human B-cell lineage, with increasing concentrations from pre-B cell through naïve and memory B cell, whereas CD20 is not expressed on stem cells, pro-B cells, or differentiated plasma cells. Although the exact mechanism of action is unknown, three different mechanisms of action have been suggested: complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and apoptosis.[78,79]

In a placebo-controlled phase II study including an active reference arm with IFN-β 1a 30 μg intramuscularly once weekly, intravenous ocrelizumab 300 or 1000 mg administered twice with 2-week interval, the number of gadolinium-enhancing lesions was reduced by 89% (95% CI 68%-97%; *P*<.0001) in the ocrelizumab 600 mg group and by 96% (95% CI 89%-99%; *P*<.0001) in the 2000 mg group, and both ocrelizumab groups were better than IFN-β 1a.[80] The annualized relapse rate was significantly reduced in both ocrelizumab groups (0.13 with ocrelizumab 600 mg and 0.17 with ocrelizumab 2000 mg) compared with 0.64 in the placebo group.[80] The results of two recently completed randomized, double-blind phase III studies have been reported, but not yet published. They confirmed efficacy of ocrelizumab 300 mg in comparison with IFN-β 1a subcutaneously in RRMS patients.[81] Ocrelizumab seemed well tolerated both in the phase II and phase III trials. Compared with IFN-β, infusion-related side effects and upper respiratory tract infections were the only adverse effects reported more frequently with ocrelizumab, and the frequency of serious adverse events was similar, and no opportunistic infections were reported.[80,81]

In the open-label follow-up of the phase II study, there was, however, one death in the high-dose ocrelizumab group, due to acute-onset thrombotic microangiopathy, where a possible relation to the study treatment could not be excluded.[82] There is only limited experience with repeated ocrelizumab therapy over long time, both regarding



CBC: complete blood count; MRI: Magnetic resonance imaging; TB: Tuberculosis.

FIGURE 11 Recommendations for maximizing safety of daclizumab [Colour figure can be viewed at wileyonlinelibrary.com]

efficacy and adverse effects. Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with anti-CD 20 monoclonal antibodies for other indications and post-marketing long-term follow-up data are warranted.[83]

6 | CONCLUSIONS

More than 10 DMDs are available for treatment of RRMS. With several highly effective drugs, the burden of therapy and in particular the safety will become a more important determinant for the choice of therapy. Based on the available efficacy and safety information, a suggested treatment algorithm for the use of disease-modifying therapies in patients with RRMS is shown in Figure 12. Patients with average disease activity can choose between dimethyl fumarate and teriflunomide or use an IFN-β preparation or glatiramer acetate. Women with child-bearing potential, who plan pregnancy within the next 1-2 years, should probably not choose teriflunomide. With more than average disease activity, dimethyl fumarate may be tried first. If patients develop unacceptable adverse effects, switching to another first-line drug can be tried.

Patients with very active disease may start with a second-line drug as first choice, and this practice should probably be employed more extensively in the future, because it is important to find the appropriate DMD as soon as possible in the individual patient to achieve optimal long-term results.

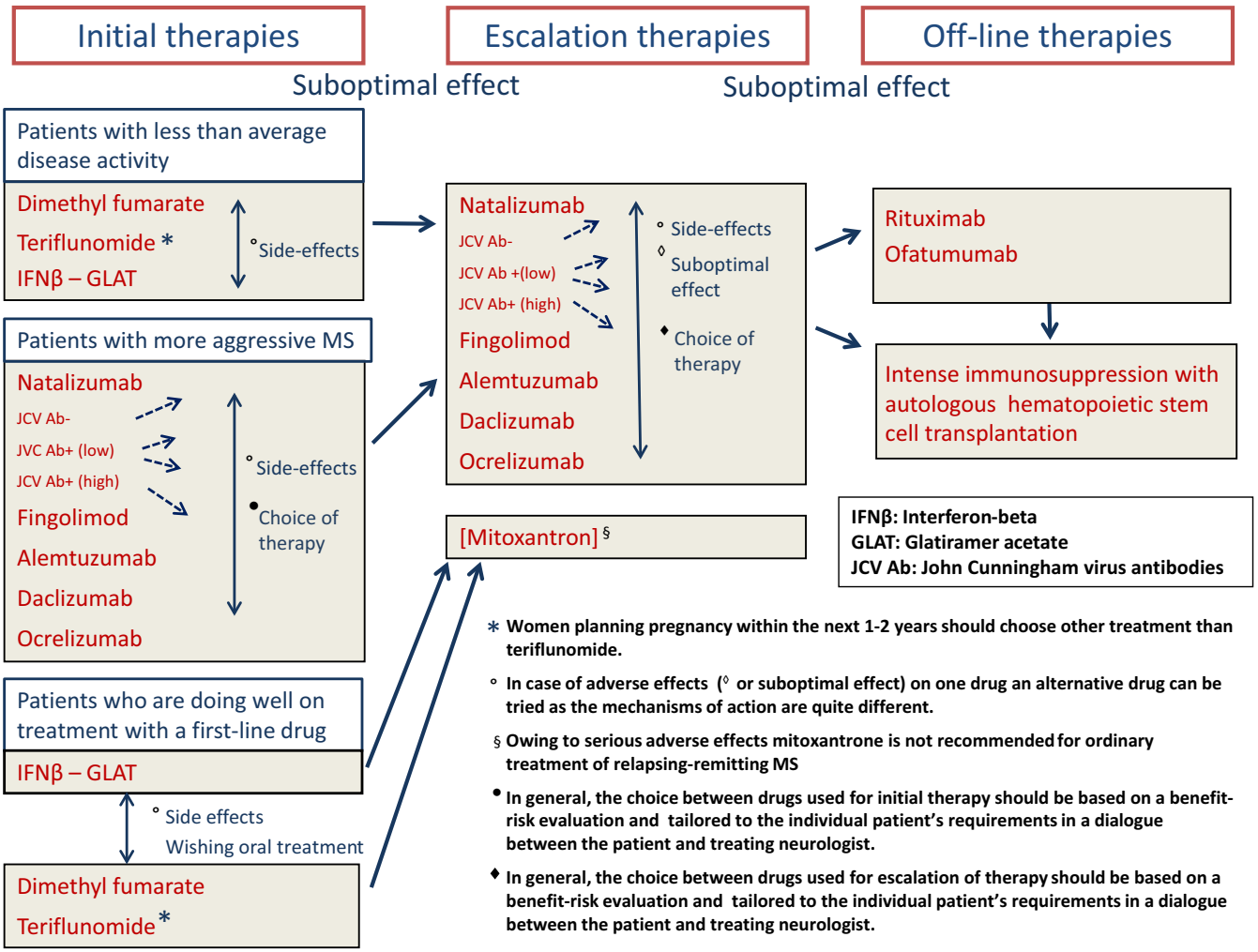


FIGURE 12 Suggested treatment algorithm for relapsing-remitting multiple sclerosis (RRMS) as of November 2016. In general, the choice between drugs used for initial therapy should be based on a benefit-risk evaluation and tailored to the individual patient's requirements in a dialogue between the patient and treating neurologist. Patients with average disease activity can choose between dimethyl fumarate and teriflunomide or the "old injectable." In patients with disease activity above average dimethyl fumarate should be tried first. Women with child-bearing potential, who plan pregnancy within the next 1-2 years, should probably not choose teriflunomide. Patients with more active MS may choose a more effective drug as the initial treatment. In case of side-effects on one drug, switch to another drug can be tried. Suboptimal effect of the first drug indicates escalation to a highly efficacious drug, and the choice between drugs used for escalation of therapy should be based on a benefit-risk evaluation and tailored to the individual patient's requirements in a dialogue between the patient and treating neurologist. Today, mitoxantrone is not recommended for routine use in patients with RRMS, owing to the safety profiles. JCV: John Cunningham virus (modified from Sorensen[1]). [Colour figure can be viewed at wileyonlinelibrary.com]

In case of suboptimal effect on a first-line drug, it is recommended that treatment is escalated to a second-line therapy. However, if a patient is reluctant to start treatment with a more risky second-line drug, switch to another first-line drug could be tried, because of different mechanisms of action.

In general, natalizumab or fingolimod alemtuzumab should be chosen before owing to the safety profiles. Mitoxantrone is not recommended for routine use in patients with RRMS. As more treatments for RRMS are launched, use of natalizumab might primarily be reserved for patients who are JC virus antibody-negative. Refined risk stratification or development of new assays for detecting presence of infectious mutated JC virus could increase the use of natalizumab. Although no comparative trials have been performed between natalizumab and other DMDs, natalizumab is by the majority of MS neurologists considered as one of the most effective therapies currently available for treatment of RRMS.

In addition to approved therapies a number of drugs are used off-label for treatment of MS (rituximab,[84] ofatumumab[85,86]), and these therapies, together with others not appearing in the treatment algorithm, are used in many countries with widely differing frequencies. However, these treatments should be reserved for patient who cannot effectively be treated with approved drugs. Intense immunosuppression followed by autologous hematopoietic stem cell transplantation can be used in patients not responding to treatment with one or more highly effective DMD.

Overall, a favorable benefit-risk profile can be maintained by appropriate patient selection and appropriate risk management on treatment.

7 | FUTURE USE OF DMDS

Within the next 5 years, I foresee that the use of the "old injectables" will decrease substantially. Although a proportion of patients today are treated with IFN-β or glatiramer acetate with acceptable efficacy, the use of these drugs in Europe and North America will slowly fade away for several reasons: (i) If the patients can choose freely between all DMDs, very few patients starting a disease-modifying therapy for the first time will choose an injectable drug (of approximately 500 patients, who in Denmark started de novo therapy of RRMS last year, <20 chose an injectable drug, personal communication); (ii) some patients who currently are treated with "old injectables" will develop disease activity and the threshold for escalating therapy is gradually lowered as the concept of NEDA (no evident disease activity) gains ground; and (iii) some patients who have been treated with IFN-β or glatiramer acetate will progress to a disease stage at which continued treatment with DMDs no longer is meaningful.

However, approval of cheaper generic glatiramer acetate may prolong the use of glatiramer acetate, and similarly price reduction may prolong the use of IFN-β.

"Real-world experience" over the next few years will help to determine the appropriate use of the new oral agents and monoclonal antibodies.

The approval of ocrelizumab will probably dramatically change the current treatment algorithm. If ocrelizumab is approved as a first-line therapy, and there is nothing to suggest otherwise, the use of other very effective second-line monoclonal antibodies like natalizumab and alemtuzumab may decrease owing to the apparently favorable safety record of ocrelizumab.

We shall probably have new S1P antagonists that may be more selective than fingolimod,[87] an alternative formulation of dimethyl fumarate, and other B-cell-depleting monoclonal antibodies, that is, ofatumumab that can be administered subcutaneously at 4-week intervals.[85]

Possibly, cladribine (2-chloro-2′deoxy-β-D-adenosine), a synthetic deoxy-adenosine analogue that causes sustained reduction in lymphocytes and monocytes, resulting in long-lasting depletion of $CD4^+$ and $CD8^+$ T cells, could be introduced. Cladribine administered orally 3.5 or 5.25 mg/kg over 96 weeks, given in two or four short courses yearly, was very effective with reduction of the annualized relapse rate by 58% and 55%, respectively ($P<.001$).[88] However, the drug was not approved, mainly because only one clinical trial was completed when filed for approval. Cladribine may be approved after an extension study and a study in CIS have been completed[89] and might be a useful drug as induction therapy in patients with very active RRMS.

Hence, treatment of patients with RRMS will become increasingly complex, and only treatment by neurologists with expertise in the management of MS can secure an optimal therapy for the individual patient.

8 | KEY ISSUES

- The development of new drugs has made more effective treatment of relapsing-remitting MS possible, but the new drugs also carry the risk of serious or even life-threatening adverse effects.
- Interferon-β, glatiramer acetate, teriflunomide, and dimethyl fumarate are in Europe classified as first-line therapies that are considered safer than the drugs classified as second-line therapies: fingolimod, natalizumab and alemtuzumab.
- Among the first-line therapies, the new oral drugs teriflunomide and dimethyl fumarate are more convenient than the older injectable drugs IFN-β and glatiramer acetate that, however, may have better safety records.
- For some drugs, risk stratification can be performed, for example, risk stratification for progressive multifocal leukoencephalopathy (PML) associated with natalizumab therapy based on the concentration of JC virus antibodies in the blood and the treatment duration.
- Risk management programs have been developed for several of the new MS therapies.
- The suggested treatment algorithm for relapsing-remitting MS is based on therapeutic efficacy, safety, and tolerability of disease-modifying drugs.

- A favorable benefit-risk profile can be maintained by appropriate patient selection and appropriate risk management during treatment with disease-modifying drugs.
- The appearance of new drugs within the coming 1-2 years will substantially change the current treatment algorithm for relapsing-remitting MS.

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None.

CONFLICT OF INTEREST

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