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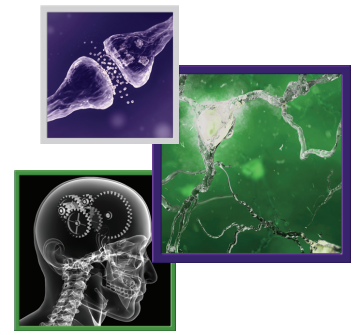

High-efficacy therapies for relapsing-remitting multiple sclerosis: implications for adherence. An expert opinion from the United Arab Emirates

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Practice points

- An increase in the number of high-efficacy disease modifying drugs (DMDs) has both improved and complicated the management of relapsing-remitting multiple sclerosis.
- Newer, high-efficacy DMDs bring the prospect of improved suppression of relapses and reduced progression of disability.
- High-efficacy DMDs may also have serious safety issues, and burdensome long-term monitoring.
- We reviewed the therapeutic profiles of currently available DMDs and concluded that cladribine tablets and alemtuzumab were the most convenient to administer in terms of route and frequency of administration.
- The monitoring burden required during treatment with alemtuzumab was the most burdensome, and ocrelizumab and cladribine tablets the least burdensome.
- Suboptimal adherence to therapy is an underestimated barrier to achieving the best outcomes for patients.

The number of disease-modifying treatments (DMDs) for relapsing-remitting multiple sclerosis has increased. DMDs differ not only in their efficacy and safety/tolerability, but also in the treatment burden of, associated with their initiation, route/frequency of administration, maintenance treatment and monitoring. High-efficacy DMDs bring the prospect of improved suppression of relapses and progression of disability, but may have serious safety issues, and burdensome long-term monitoring. Studies of patient preferences in this area have focused on side effects, efficacy and route of administration. Adherence to DMDs is often suboptimal in relapsing-remitting multiple sclerosis and there is a need to understand more about how the complex therapeutic and administration profiles of newer DMDs interact with these barriers to support optimal adherence to therapy.

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The introduction of interferons, and then glatiramer acetate, in the 1990s revolutionized the management of relapsing-remitting multiple sclerosis (RRMS) by significantly reducing the frequency of relapses, and thus modifying the course of the disease [1–4]. These drugs remained the only disease modifying treatment until the authorization of natalizumab in 2006. This was followed by a rapid increase in the number of disease-modifying drugs (DMDs) approved for the management of MS during the last decade, in a number of countries. These include 'high-efficacy

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DMDs' [5], which are generally accepted to be more effective than first-line therapies in reducing relapse rate and progression of disability. Relatively few head-to-head trials of DMDs have been conducted.

This greatly increased choice of DMDs expands the opportunities for the design of patient-centered treatment regimens for people with RRMS. Conversely, the increased number of treatments also adds complexity to these decisions. In particular, the physician must balance the efficacy, tolerability, safety and monitoring requirements of these treatments with the clinical characteristics of the patient's MS and the patient's own lifestyle needs and preferences. In this article, we aim to summarize the therapeutic profiles of current DMDs approved for the management of RRMS, with a focus on the newer, high-efficacy agents.

We discuss these therapies within the context of the authors' real-world practice in the United Arab Emirates (UAE), to highlight practical issues relevant to the delivery of effective MS care in a challenging healthcare environment.

Multiple sclerosis in the United Arab Emirates

A retrospective study from a major tertiary center in Dubai in 2007 yielded a prevalence for MS among Emirati nationals of 55 (95% CI: 47 to 63) per 100,000 population [6]. The population of the UAE is heterogeneous, however, and only about 20% of people in the UAE at that time were native Emiratis; the crude prevalence for the whole population was lower, at 19 (95% CI: 13–25) per 100,000. Another study, conducted in 2011–2014 from the four largest centers in Abu Dhabi, UAE, found that the age-standardized prevalence of RRMS among Emirati nationals was 64 (95% CI: 57–72) per 100,000 [7], in other words, among the highest in the Middle East [7,8].

The characteristics of the MS in the UAE are described briefly here from the more recent study [7]. The most common form of MS was RRMS (78%). MS was more common among women versus men (crude prevalence rates of 77 and 38/100,000, respectively), with a similar male: female ratio among Emiratis (1.7:1) and the overall population (1.8:1). The burden of disability was assessed using Expanded Disability Status Scale (EDSS) score: 85% of Emiratis and 86% of expatriates had EDSS <6 (the lowest point on the EDSS scale of 0–10 at which patients require a walking aid) [9].

Overview of high-efficacy DMDs for the management of RRMS

Efficacy & tolerability/safety

DMDs have been categorized into 'platform' or 'first-line' agents and 'high-efficacy' DMDs, with a greater effect in suppressing MS disease activity. Randomized evaluations of high-efficacy DMDs (fingolimod, natalizumab, alemtuzumab and cladribine tablets) have demonstrated numerically higher risk reductions for relapse rates (generally >50%), compared with the 'platform therapies' of interferons, glatiramer acetate or dimethyl fumarate (DMF), with reductions in relapses of about 30–50% in populations with RRMS over treatment periods of up to 1–2 years [1–4,10–22]. Within these studies, comparative, head-to-head trials have suggested greater efficacy for fingolimod, alemtuzumab, or ocrelizumab versus formulations of interferon [14,15,18–22]. *Post-hoc* subgroup analyses and a meta-analysis suggested that cladribine tablets 3.5 mg/kg, alemtuzumab, fingolimod, natalizumab and ocrelizumab exerted treatment effects in patients with higher RRMS disease activity [23–36]. A higher proportion of patients achieved 'no evidence of disease activity' (NEDA) after randomization to active treatment versus placebo for DMF [13], fingolimod [17], natalizumab [20] or cladribine tablets [28], or versus IFN-β1a for alemtuzumab [14,15], or ocrelizumab [21,22].

Table 1 summarizes the tolerability and safety profiles of the high-efficacy DMDs described here, derived from their European Summaries of Product Characteristics (SmPC, available from the EMA website). This section can provide only an overview and will focus on more common side effects and key safety issues. Some high-efficacy DMDs demonstrate a range of potentially troublesome side effects. Increased risk of infections is seen with several DMDs, although the risk of viral infections such as varicella zoster, or reactivation of latent infections such as tuberculosis, can be mitigated by appropriate immunization and screening before treatment [29]. Natalizumab has been associated with increased risk of progressive multifocal leukoencephalopathy (PML), as has rituximab, which shares ocrelizumab's anti-CD20 mechanism of action [30]. The risk of PML is minimized by screening for JC virus before, and careful monitoring during, treatment, as described in the products' labeling. While natalizumab-associated PML is now uncommon in our routine clinical practice, careful selection of patients and assiduous attention to the monitoring requirements for this DMD is crucial when prescribing natalizumab.

Infusion-related reactions may be severe with alemtuzumab, natalizumab or ocrelizumab. European labeling includes mentions of increased risk of malignancy with fingolimod, and a 'higher incidence' of malignancy with

Table 1. Overview of tolerability and safety findings of high-efficacy disease-modifying treatments for the management of relapsing-remitting multiple sclerosis.

DMD	Common tolerability and key safety findings
Alemtuzumab	Infusion-related reactions (most patients). Increased risk of infections, including serious infections, has been associated with alemtuzumab vs placebo, including herpes zoster, cervical human papilloma virus, cytomegalovirus, activation of tuberculosis, listeriosis, fungal infections, and pneumonitis, among others. Increased risk of autoimmunity, especially ITP and thyroid disorders, and more rarely in the kidney and liver
Cladribine tablets	Infections, mainly varicella zoster, associated with lymphopenia arising via the drug's mechanism of action (see text). The risk of activation of latent infections, including tuberculosis and hepatitis may be increased. PML has not been reported in patients receiving cladribine tablets 3.5 mg/kg for RRMS, although PML has been observed in patients receiving a different (parenteral) dose regimen of cladribine for the treatment of leukaemia. The SmPC notes a higher incidence of malignancies for cladribine tablets vs placebo in clinical trials
Fingolimod	Reduced heart rate and sometimes intracardiac conduction disorders (especially early in treatment), increased blood pressure, immunosuppression and opportunistic infections (including PML and cryptococcal meningitis after 2–3 years of treatment), an increased risk of malignancy (especially in the skin), macular oedema (sometimes with blurred vision), and increased circulating transaminases
Natalizumab	Dizziness, nausea, urticaria and rigors associated with drug infusions. Increased risk of PML, especially where the patient has a positive titre for anti-JC virus antibodies, has received prior immunosuppression, and has received natalizumab for at least 2 years. Other opportunistic infections associated with herpes simplex and varicella zoster viruses, including zoster-related encephalitis or meningitis, and acute retinal necrosis
Ocrelizumab	Infusion-related reactions (pruritus, rash, urticaria, erythema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal oedema, nausea, tachycardia), neutropenia and opportunistic infections. PML has not been observed specifically in patients receiving ocrelizumab but has been observed with other agents expressing the same cellular mechanism (CD20 inhibition). Reactivation of hepatitis B, and an increased rate of malignancies (though within the rate expected from background population) have been observed

Compiled from European Summaries of Product Characteristics, available from the European Medicines Agency website.
DMD: disease-modifying drug; GI: Gastrointestinal; ITP: Immune thrombocytopenic purpura; JC virus: John Cunningham virus; PML: Progressive multifocal leukoencephalopathy; RRMS: relapsing-remitting multiole sclerosis.

Table 2. Current European indications for high-efficacy disease modifying drugs for relapsing-remitting multiple sclerosis.

DMD	Indication(s) relating to RRMS
Alemtuzumab	Highly active disease despite a full and adequate course of treatment with at least one DMD or rapidly evolving severe RRMS (≥2 disabling relapses in 1 year, and with ≥1 Gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a recent MRI
Cladribine tablets	Highly active RRMS
Fingolimod	Highly active MS despite a full and adequate course of treatment with ≥1 DMD Rapidly evolving severe RRMS defined by ≥2 disabling relapses in 1 year, and with ≥1 Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared with a previous recent MRI
Natalizumab	Highly active MS despite a full and adequate course of treatment with ≥1 DMD Rapidly evolving severe RRMS defined by ≥2 disabling relapses in 1 year, and with ≥1 Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared with a previous recent MRI
Ocrelizumab	MS with active disease

Indications relating to conditions other than RRMS are not included here.
DMD: Disease-modifying drug; RRMS: Relapsing-remitting multiple sclerosis.

cladribine tablets and ocrelizumab. Recent research suggests that the risk of malignancy may not be higher with cladribine tablets compared with other DMDs, however [31,32]. Reductions of lymphocyte counts are expected from the mechanism of action of cladribine tablets: Grade 3 lymphopenia occurred in 25% of patients, and Grade 4 lymphopenia occurred in <1% of patients who received cladribine tablets 3.5 mg/kg in the randomized CLARITY trial [32]. Finally the EMA has recently restricted the use of alemtuzumab, due to concerns over autoimmunity, thrombocytopenia, neutropenia and adverse effects on the heart and blood vessels ("problems . . . occurring within 1–3 days of receiving the medicine, including bleeding in the lungs, heart attack, stroke, cervicocephalic arterial dissection") [33]. Alemtuzumab is now indicated in Europe for patients with highly active or rapidly evolving MS (Table 2) [33].

Therapeutic indications

Table 2 summarizes the current European indications for high-efficacy DMDs in the management of RRMS. Higher efficacy agents (fingolimod, natalizumab, alemtuzumab, cladribine tablets and ocrelizumab) tend to have

Table 3. Administration and principal monitoring requirements for high efficacy disease-modifying drugs for the management of relapsing-remitting multiple sclerosis.

DMD	Mode of administration and recommended maintenance dose[†]	Precautions required during administration	Monitoring requirements
Alemtuzumab	Infusion over ~4 h[‡]: – 12 mg iv. QD for 5 consecutive days – 12 mg iv. QD for 3 consecutive days 12 months after the 1st course – Second course may be repeated for years 3 and 4	Pretreat with corticosteroids for 1st 3 days of any treatment course; consider use of antihistamines and/or antipyretics. Oral prophylaxis for herpes virus on first day of any treatment course continuing for 1 month following treatment	Follow for 48 months after most recent infusion. Monitor liver function and vital signs before and during treatment. At initiation and then to 48 mo after last infusion: • CBC + differential monthly (immediately if signs of ITP) • SCr and urinalysis with microscopy monthly • Thyroid tests 3 monthly
Cladribine tablets	Oral (3.5 mg/kg over 2 years) See footnote for details of administration regimen[§]	Ensure lymphocyte counts are 'normal' before initiation. Check for pregnancy for women of childbearing age, and counsel men and women on need to avoid pregnancy. Screen for latent infections, esp. TB and hepatitis B and C	Ensure lymphocytes >800/mm^3 before second course (2nd year treatment can be delayed for ≤6 mo to allow recovery). Monitor lymphocytes 2 and 6 months after start of treatment in each treatment year; consider herpes prophylaxis of lymphocytes fall to <200/mm^3. Monitor lymphocyte counts actively and monitor for infections (esp. zoster) if lymphocytes <500/mm^3
Fingolimod	Oral: 0.5 mg QD	Electrocardiogram and BP before and hourly for 6 h after the 1st dose (repeat after treatment interruptions); monitor overnight after 1st and 2nd doses if pharmacological intervention needed for bradycardia after the 1st dose. Check varicella antibody status	CBC at initiation and 3 months, and then at least annually. Monitor patients at risk of infections, e.g., due to prior immunosuppressive therapy. Monitor LFTs frequently during year 1 of treatment and periodically thereafter. Check for cutaneous neoplasms every 6–12 months
Natalizumab	Infusion: 300 mg Q4W[¶]	Infuse over 1 h, monitor for injection-related reactions for a further 1 h	Test for JCV before initiation if JCV status unknown. Test for JCV every 6 months (JCV-negative patients and JCV-positive patients at low antibody titer). Obtain MRI before treatment and annually thereafter (more frequently for higher risk of PML). Reconsider use if no clinical benefit beyond 6 months
Ocrelizumab	Infusion (iv.)[#]: – 1st treatment: 2 × 300 mg infusions 2 weeks apart over ~2.5 h – Maintenance treatment: 600 mg infusion every 6 months over ~3.5 h	Pretreat with corticosteroid and antihistamine; consider use of antipyretic. Verify immune status and check for hepatitis B infection before treatment. Monitor during and for at least 1 h after infusions	Physicians should be vigilant for early signs and symptoms of PML, and for reactivation of hepatitis B in carriers of this virus

Information compiled from European Summaries of Product Characteristics.
[†]For adults with RRMS; see label for pediatric indications (where present) and details of titration toward the recommended maintenance dose.
[‡]Initiated by specialist with expertise in MS; specialists experienced in diagnosis and management of most frequent reactions should be available, including hypersensitivity and/or anaphylactic reactions.
[§] "Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year. Each treatment week consists of 4 or 5 days on which a patient receives 10 or 20 mg (one or two tablets) as a single daily dose, depending on bodyweight."
[¶]Initiated and monitored continuously by physician with expertise in diagnosis and management of neurological conditions; timely access to MRI is also required.
[#]Should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of neurological conditions and who have access to appropriate medical support to manage severe reactions such as serious infusion-related reactions.
BP: Blood pressure; CBC: Complete blood count; CKD: Chronic kidney disease; DMD: Disease-modifying drug; ITP: Immune thrombocytopenic purpura; JCV: John Cunningham virus; LFT: Liver function test; PML: Progressive multifocal leukoencephalopathy; QD: Once daily; SCr: Serum creatinine; TB: Tuberculosis.

restricted indications referring to different definitions of active or highly active disease. This reflects either the more severe side effects associated with these agents (see above) and/or the shorter period of clinical experience, compared with interferons, for example.

Administration & monitoring requirements

The initiation and maintenance regimens of high-efficacy DMDs vary considerably in their complexity (Table 3). Among the high-efficacy agents, only cladribine tablets and fingolimod are given orally, others are given by iv. infusion (natalizumab, and alemtuzumab, ocrelizumab). Fingolimod requires lengthy attendance at the clinic for the monitoring required during initiation of treatment for potential cardiovascular reactions, with the potential two sessions of for overnight monitoring in the case of persistent bradycardia. Ocrelizumab and alemtuzumab require lengthy infusions (2.5 or 3.5 h, and about 4 h, respectively), with an additional requirements for post-infusion monitoring. Natalizumab requires a 1-h infusion followed by a 1-h monitoring period. Initiation and further administration of interferons or glatiramer acetate is less complex.

Cladribine tablets are given as two short courses over 2 years, comprising a total of up to 16–20 days of oral treatment, depending on bodyweight, to reach the total recommended dose of 3.5 mg/kg given over a 2-year period. There is no requirement to continue treatment with cladribine tablets during years 3 and 4, as an extension to the CLARITY study demonstrated continued clinical efficacy in reducing relapse rates (about three-quarters remained relapse-free without further active treatment following the randomized phase of the trial) and MRI activity over this period, following an initial 2-year treatment course [34,35]. This is consistent with its hypothesized action as a pharmacologic immune reconstitution therapy (IRT), whereby the clinical efficacy of a treatment outlasts both the period of drug administration and its effects on lymphocyte counts [36–38]. Monitoring requirements for cladribine tablets consist mainly of ensuring lymphocyte counts are sufficiently high before administration, with active monitoring of lymphocytes for patients with counts $<500/mm^3$ (Table 3).

Alemtuzumab is also hypothesized to act as a pharmacologic IRT, although optional re-treatments in years 3 and 4 may be given in addition to the initial 2-year course of treatment mandated by its label. Ocrelizumab is a monoclonal antibody directed against the lymphocyte CD20 antigen [39]. A similar immune reconstitution-like effect has been observed after administration of another anti-CD20 antibody, rituximab, within the management of conditions other than MS [40,41]. However, the current indication for ocrelizumab requires ongoing administration, albeit with intervals of 6 months between doses (Table 3), so it is not possible at this time to categorize ocrelizumab unambiguously as an immune reconstitution therapy. Indeed, experts in MS management have suggested that ocrelizumab "might be either called a chronic immunosuppressive or pulsed immune reconstitution therapy" [37]. Further clinical evaluation of ocrelizumab will be needed to clarify the nature of its action in MS, to determine whether the duration of its efficacy outlasts the period of administration and/or its effects on lymphocyte counts [37]. Further research will be needed to verify the extent to which all aspects of the immune system function recover after the application of pharmacologic immune reconstitution therapy.

Monitoring requirements also vary considerably (Table 3). Fingolimod requires monitoring of blood counts regularly throughout treatment, as these agents can provoke severe and/or prolonged lymphopenia [42,43]. Monitoring for specific side effects is needed for patients receiving alemtuzumab (vital signs, blood counts and liver, kidney and thyroid function), and a rebound in white cell counts following treatment with alemtuzumab has been associated with a clinically significant risk of developing autoimmune conditions [33,44–46]. Natalizumab requires continued surveillance for JCV virus to manage the risk of progressive multifocal leukoencephalopathy (PML) [47].

Adherence to disease-modifying therapy in MS

Maintaining good adherence to therapy is essential to optimize long-term treatment outcomes, in RRMS, as in other diseases. Adherence to, or persistence with, DMDs within populations of patients with RRMS is often sub-optimal, and the perceived efficacy [48], route of administration of a DMD [49–51], disability [52] and side effects [53–56] have emerged as key drivers of suboptimal adherence.

Relatively few data are available on rates of adherence to individual high-efficacy DMDs. Early discontinuation from treatment (lack of persistence with therapy) is one important aspect of nonadherence. Discontinuation from fingolimod was uncommon during the first year of treatment (3.9%) in a study in Spain [57]. Only 2/496 patients treated with fingolimod for ≥3 months discontinued in a study in Denmark [58], while 11.3% of 240 patients in the Czech Republic discontinued fingolimod in the first year [49]. Twenty-two percent of patients in the Tysabri® (natalizumab) Observational Program discontinued before 2 years of treatment, among whom 5% discontinued for lack of efficacy and the rest for other (unreported) reasons [59]. A prospective observational study in Germany reported a lower discontinuation rate of 13% for natalizumab over an average of about 9 months of treatment [60]. Natalizumab initiators were more likely to remain on treatment compared with platform therapy initiators according to real-world data from the USA [61].

Information on adherence to/persistence with newer DMDs is lacking. In particular, the IRT concept is challenging in this regard. A patient who responds to a 2-year course of cladribine tablets or alemtuzumab may not need further DMD therapy for at least 2 years, rendering the concept of adherence (as defined by the accuracy of treatment intakes over a period of time) redundant beyond the initial short administration periods.

Patient preferences for treatments for MS

Patient preferences are another important factor in the prescribing decision, and may change at different stages of MS progression, or be influenced by treatments already received [62]. The side effects of treatment may be more important that the prospect of delayed disease progression in patients with MS [63–66], especially in patients with

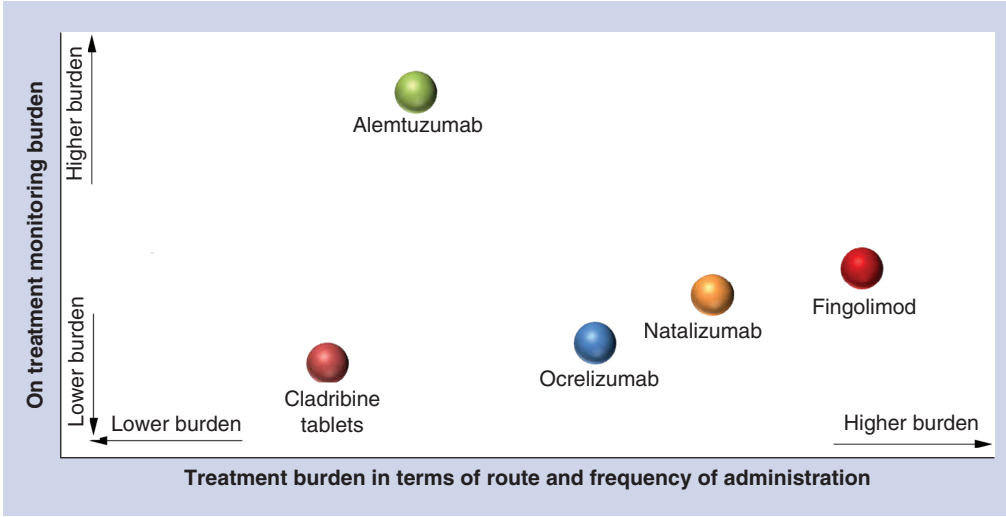

Figure 1. Consensus on monitoring burden of high-efficacy disease-modifying treatments for relapsing-remitting multiple sclerosis by a group of expert neurologists from the United Arab Emirates.

MS of longer duration (>5 years in one study [64]), although patients would trade off some increase in side effects for a greater delay in disability progression [64]. Alternatively, patients who already have some disability progression may place greatest emphasis on preservation of functional status, compared with side effects [67]. A further study found efficacy to be the most important driver of preference between DMDs, though avoidance of discomfort with injections and convenience of administration were valued highly by patients [68].

There is some evidence that patients prefer oral therapy to injectables, particularly those without experience of injectable therapy (see also above) [48,63–67,69]. Frequency of administration also emerged as a driver of preference [63,66,69,70], with comparable importance given to efficacy and safety in one study [70]. Finally, a study from the USA showed that out-of-pocket costs of therapy was the main driver of preference among DMDs for MS [71], illustrating the need to consider patients' treatment preferences within the context of the healthcare provision that they receive.

Comparing the treatment profile & monitoring burden profile of high-efficacy DMDs

The expert group of physicians who co-authored this article compared properties of individual DMDs based on their clinical experience. Each property of a DMD was assigned scores between 1 ('worst') and 10 ['best'), via a real-time, online voting application/web-based audience response system that physicians accessed from their smartphones. Voting was followed by a discussion between experts to reach a consensus view. Figure 1 shows the consensus position relating to the treatment profile (route and frequency of administration) and monitoring burden of high-efficacy DMDs. Cladribine tablets and alemtuzumab were considered the most convenient in terms of route and frequency of administration (x-axis in Figure 1). The monitoring burden (Y-axis) required during treatment with alemtuzumab was the most burdensome, and ocrelizumab and cladribine tablets the least burdensome.

Future perspective

The higher efficacy of the newer DMDs will undoubtedly be an important factor in a prescribing decision when faced with a patient with high disease activity, or rapidly evolving RRMS. This is only one dimension of the prescribing decision, however. The reality of MS care is that each patient is essentially unique, affected differently by MS, and potentially responding differently to the positive and negative consequences of specific interventions [72]. Each patient requires a unique treatment plan to maximize the benefits "de-risk" the process of treatment [72]. For example, the administration and monitoring of some DMDs for MS are potentially burdensome. We know, from the data summarized above, and our own clinical experience, that adherence/persistence to DMD therapy in MS is frequently sub-optimal. The current literature on patients' preferences for DMDs has focused largely on attributes of treatment such as efficacy, side effects and route of administration. Further research is needed to assess the effects

of the monitoring regimens of newer agents to assess their impact on patient preferences, particularly for younger patients with busy lifestyles.

The prescription of DMDs for patients who are, or are planning to be, pregnant, is a complex issue that is beyond the scope of our concise review. Interferonβ is indicated for use during pregnancy, subject to clinical need, and may be administered when a woman is breastfeeding, according to its European labeling. Fingolimod, siponimod, teriflunomide, and cladribine tablets are contraindicated during use in pregnancy in Europe, while other DMDs have warnings and precautions associated with their use in this setting. In addition to these agents, DMF, alemtuzumab, natalizumab and ocrelizumab are contraindicated in the USA for pregnant women. Additional guidance for the use of DMDs in this challenging population is required [73,74].

Multiple barriers to achieving truly patient-centered care exist in our region: important gaps in our understanding of MS exist at the levels of epidemiology, society, the healthcare system, individual healthcare practitioners, and patients, as illustrated by our own day-to-day experience. We believe that education of physicians, patients and the public will be needed to improve the diagnosis and management of MS, to gain the commitment of patients to their regimen, and to remove the stigma of MS (and other conditions) within our societies. Such considerations will be especially important in areas of relatively high MS prevalence, such as the UAE.

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References

Papers of special note have been highlighted as: •• of considerable interest

1. IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing–remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 43, 655–661 (1993).

•• **This important trial marked the start of the era of disease-modifying drugs (DMDs) for multiple sclerosis (MS).**

2. Calabresi PA, Kieseier BC, Arnold DL *et al.* Pegylated interferon β-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, Phase III, double-blind study. *Lancet Neurol.* 13, 657–665 (2014).

3. Jacobs LD, Cookfair DL, Rudick RA *et al.* Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Ann. Neurol.* 39, 285–294 (1996).

4. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *Lancet* 352, 1498–1504 (1998).

5. Grand'Maison F, Yeung M, Morrow SA *et al.* Sequencing of high-efficacy disease-modifying therapies in multiple sclerosis, perspectives and approaches. *Neural. Regen. Res.* 13, 1871–1874 (2018).

6. Inshasi JI, Thakre M. Prevalence of multiple sclerosis in Dubai, United Arab Emirates. *Int. J. Neurosci.* 121, 393–398 (2011).

•• **Important background on MS in the UAE.**

7. Schiess N, Huether K, Fatafta T *et al.* How global MS prevalence is changing. A retrospective chart review in the United Arab Emirates. *Mult. Scler. Relat. Disord.* 9, 73–79 (2016).

•• **Important background on MS in the UAE.**

8. Kurtzke JF. A reassessment of the distribution of multiple sclerosis – part 1. *Acta Neurol. Scand.* 51, 110–136 (1975).

9. Multiple Sclerosis Trust. Expanded Disability Status Scale (EDSS). www.mstrust.org.uk/a-z/expanded-disability-status-scale-edss

10. Johnson KP, Brooks BR, Cohen JA *et al.* Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis, results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. *Neurology* 45, 1268–1276 (1995).
11. Fox RJ, Miller DH, Phillips JT *et al.* Placebo-controlled Phase III study of oral BG-12 or glatiramer in multiple sclerosis. *N. Engl. J. Med.* 367, 1087–1097 (2012).
12. Khan O, Rieckmann P, Boyko A *et al.* Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. *Ann. Neurol.* 73, 705–713 (2013).
13. Giovannoni G, Gold R, Kappos L *et al.* BG-12 Increases the proportion of patients free of clinical and radiologic disease activity in relapsing-remitting multiple sclerosis, findings from the DEFINE Study. *Neurology* 78(Suppl. 1), PD5.005 (2012).
14. Cohen JA, Coles AJ, Arnold DL *et al.* Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis, a randomised controlled Phase III trial. *Lancet* 380, 1819–1828 (2012).

•• **Initial efficacy data on one of two currently available DMDs believed to act as immune reconstitution therapies.**

15. Coles AJ, Twyman CL, Arnold DL *et al.* Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy, a randomised controlled Phase III trial. *Lancet* 380, 1829–1839 (2012).
16. Giovannoni G, Comi G, Cook S *et al.* A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N. Engl. J. Med.* 362, 416–426 (2010).

•• **Initial study of the second DMD believed to act as an immune reconstitution therapy in RRMS.**

17. Kappos L, Radue EW, O'Connor P *et al.* A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N. Engl. J. Med.* 362, 387–401 (2010).
18. Cohen JA, Barkhof F, Comi G *et al.* Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N. Engl. J. Med.* 362, 402–415 (2010).
19. Polman CH, O'Connor PW, Havrdova E *et al.* A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N. Engl. J. Med.* 354, 899–910 (2006).
20. Havrdova E, Galetta S, Hutchinson M *et al.* Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis, a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study. *Lancet Neurol.* 8, 254–260 (2009).
21. Hauser SL, Bar-Or A, Comi G *et al.* Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N. Engl. J. Med.* 376, 221–234 (2017).
22. Traboulsee A, Arnold D, Bar-Or A *et al.* Ocrelizumab No Evidence of Disease Activity (NEDA) status at 96 weeks in patients with relapsing multiple sclerosis. analysis of the Phase III double-blind, double-dummy, interferon beta-1a-controlled OPERA I and OPERA II Studies (PL02.004). *Neurology* 86(Suppl. 1), Abstract PL02, 004 (2016).
23. Fernández Ó. Is there a change of paradigm towards more effective treatment early in the course of apparent high-risk MS? *Mult. Scler. Relat. Disord.* 17, 75–83 (2017).

•• **Important review charting the recent move toward earlier intervention in people with RRMS.**

24. Giovannoni G, Soelberg Sorensen P, Cook S *et al.* Efficacy of cladribine tablets in high disease activity subgroups of patients with relapsing multiple sclerosis, a *post hoc* analysis of the CLARITY study. *Mult. Scler.* 25, 819–827 (2019).

•• **Demonstration of greater efficacy of immune reconstitution therapy in patients with higher RRMS disease activity.**

25. Devonshire V, Havrdova E, Radue EW *et al.* Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod, subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. *Lancet Neurol.* 11, 420–428 (2012).
26. Turner B, Cree BAC, Kappos L *et al.* Ocrelizumab efficacy in subgroups of patients with relapsing multiple sclerosis. *J. Neurol.* 266, 1182–1193 (2019).
27. Huisman E, Papadimitropoulou K, Jarrett J *et al.* Systematic literature review and network meta-analysis in highly active relapsing-remitting multiple sclerosis and rapidly evolving severe multiple sclerosis. *BMJ Open* 7, e013430 (2017).
28. Giovannoni G, Cook S, Rammohan K *et al.* Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the CLARITY study, a post-hoc and subgroup analysis. *Lancet Neurol.* 10, 329–337 (2011).
29. Epstein DJ, Dunn J, Deresinski S. Infectious complications of multiple sclerosis therapies, implications for screening, prophylaxis, and management. *Open Forum Infect. Dis.* 5, ofy174 (2018).
30. Clavel G, Moulignier A, Semerano L. Progressive multifocal leukoencephalopathy and rheumatoid arthritis treatments. *Joint Bone Spine* 846, 671–675 (2017).
31. Pakpoor J, Disanto G, Altmann DR *et al.* No evidence for higher risk of cancer in patients with multiple sclerosis taking cladribine. *Neurol. Neuroimmunol. Neuroinflamm.* 2, e158 (2015).
32. Cook S, Leist T, Comi G *et al.* Safety of cladribine tablets in the treatment of patients with multiple sclerosis, an integrated analysis. *Mult. Scler. Relat. Disord.* 29, 157–167 (2019).

33. European Medicines Agency. Press release 12/04/2019. Lemtrada. Overview. Measures to minimise risk of serious side effects of multiple sclerosis medicine Lemtrada. www.ema.europa.eu/en/medicines/human/referrals/lemtrada

34. Giovannoni G, Soelberg Sorensen P, Cook S *et al.* Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis, Results from the randomized extension trial of the CLARITY study. *Mult. Scler.* 24, 1594–1604 (2018).

35. Comi G, Cook S, Rammohan K *et al.* Long-term effects of cladribine tablets on MRI activity outcomes in patients with relapsing-remitting multiple sclerosis, the CLARITY Extension study. *Ther. Adv. Neurol. Disord.* 11, 1756285617753365 (2018).

36. Boyko AN, Boyko OV. Cladribine tablets' potential role as a key example of selective immune reconstitution therapy in multiple sclerosis. *Degener. Neurol. Neuromuscul. Dis.* 8, 35–44 (2018).

37. Sorensen PS, Sellebjerg F. Pulsed immune reconstitution therapy in multiple sclerosis. *Ther. Adv. Neurol. Disord.* 12, 1756286419836913 (2019).

•• **Authoritative review on immune reconstitution therapy from a leader in the field.**

38. Karussis D, Petrou P. Immune reconstitution therapy (IRT) in multiple sclerosis, the rationale. *Immunol. Res.* 66, 642–648 (2018).

39. Frampton JE. Ocrelizumab, first global approval. *Drugs* 77, 1035–1041 (2017).

40. Saadoun D, Rosenzwajg M, Landau D, Piette JC, Klatzmann D, Cacoub P. Restoration of peripheral immune homeostasis after rituximab in mixed cryoglobulinemia vasculitis. *Blood* 111, 5334–5341 (2008).

41. López J, Merino L, Piris L *et al.* Rituximab induces a lasting, non-cumulative remodelling of the B-cell compartment. *Clin. Exp. Rheumatol.* 37, 615–622 (2019).

42. Sainz de la Maza S, Medina S, Villarrubia N. Factors associated with dimethyl fumarate-induced lymphopenia. *J. Neurol. Sci.* 398, 4–8 (2019).

43. Nakhaei-Nejad M, Barilla D, Lee CH, Blevins G, Giuliani F. Characterization of lymphopenia in patients with MS treated with dimethyl fumarate and fingolimod. *Neurol. Neuroimmunol. Neuroinflamm.* 5, e432 (2017).

44. Phelps R, Winston JA, Wynn D *et al.* Incidence, management, and outcomes of autoimmune nephropathies following alemtuzumab treatment in patients with multiple sclerosis. *Mult. Scler.* 25, 1273–1288 (2019).

45. Alamo A, Condorelli RA, La Vignera S, Calogero AE. Autoimmune thyroid disease following treatment with alemtuzumab for multiple sclerosis. *Int. J. Immunopathol. Pharmacol.* 33, 2058738419843690 (2019).

46. Richter S, Wagner B, Celius EG. Two cases of diabetes mellitus type 1 after alemtuzumab treatment for multiple sclerosis, another probable secondary autoimmune disease. *J. Neurol.* 266, 1270–1271 (2019).

47. Ho PR, Koendgen H, Campbell N *et al.* Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis, a retrospective analysis of data from four clinical studies. *Lancet Neurol.* 16, 925–933 (2017).

48. Wicks P, Rasouliyan L, Katic B, Nafees B, Flood E, Sasané R. The real-world patient experience of fingolimod and dimethyl fumarate for multiple sclerosis. *BMC Res. Notes.* 9, 434 (2016).

49. Tichá V, Kodým R, Počíková Z, Kadlecová P. Real-world outcomes in fingolimod-treated patients with multiple sclerosis in the Czech Republic, Results from the 12-month GOLEMS Study. *Clin. Drug Investig.* 37, 175–186 (2017).

50. Fernández-Fournier M, Tallón-Barranco A, Chamorro B, Martínez-Sánchez P, Puertas I. Differential glatiramer acetate treatment persistence in treatment-naive patients compared to patients previously treated with interferon. *BMC Neurol.* 15, 141 (2015).

51. Warrender-Sparkes M, Spelman T, Izquierdo G *et al.* The effect of oral immunomodulatory therapy on treatment uptake and persistence in multiple sclerosis. *Mult. Scler.* 22, 520–532 (2016).

52. Degli Esposti L, Piccinni C, Sangiorgi D *et al.* Changes in first-line injectable disease-modifying therapy for multiple sclerosis, predictors of non-adherence, switching, discontinuation, and interruption of drugs. *Neurol. Sci.* 38, 589–594 (2017).

53. Sejbaek T, Nybo M, Petersen T, Illes Z. Real-life persistence and tolerability with dimethyl fumarate. *Mult. Scler. Relat. Disord.* 24, 42–46 (2018).

54. Smoot K, Spinelli KJ, Stuchiner T *et al.* Three-year clinical outcomes of relapsing multiple sclerosis patients treated with dimethyl fumarate in a United States community health center. *Mult. Scler.* 24, 942–950 (2018).

55. Schwab N, Schneider-Hohendorf T, Melzer N, Cutter G, Wiendl H. Natalizumab-associated PML, Challenges with incidence, resulting risk, and risk stratification. *Neurology* 88, 1197–1205 (2017).

56. Miclea A, Leussink VI, Hartung HP, Gold R, Hoepner R. Safety and efficacy of dimethyl fumarate in multiple sclerosis, a multi-center observational study. *J. Neurol.* 263, 1626–1632 (2016).

57. Mallada-Frechin J, Meca-Lallana V, Barrero F *et al.* Efficacy and safety of fingolimod in routine clinical practice in patients with relapsing-remitting multiple sclerosis in Spain, an intermediate analysis of the MS NEXT study. *Rev. Neurol.* 67, 157–167 (2018).

58. Voldsgaard A, Koch-Henriksen N, Magyari M, Sellebjerg F, Sørensen PS, Oturai AB. Early safety and efficacy of fingolimod treatment in Denmark. *Acta Neurol. Scand.* 135, 129–133 (2017).

59. Trojano M, Butzkueven H, Kappos L *et al.* Natalizumab treatment shows low cumulative probabilities of confirmed disability worsening to EDSS milestones in the long-term setting. *Mult. Scler. Relat. Disord.* 24, 11–19 (2018).

60. Krämer J, Tenberge JG, Kleiter I *et al.* Is the risk of progressive multifocal leukoencephalopathy the real reason for natalizumab discontinuation in patients with multiple sclerosis? *PLoS ONE* 12, e0174858 (2017).
61. Bonafede MM, Johnson BH, Wenten M, Watson C. Treatment patterns in disease-modifying therapy for patients with multiple sclerosis in the United States. *Clin. Ther.* 35, 1501–1512 (2013).
62. Lynd LD, Traboulsee A, Marra CA *et al.* Quantitative analysis of multiple sclerosis patients' preferences for drug treatment, a best-worst scaling study. *Ther. Adv. Neurol. Disord.* 9, 287–296 (2016).
63. Arroyo R, Sempere AP, Ruiz-Beato E *et al.* Conjoint analysis to understand preferences of patients with multiple sclerosis for disease-modifying therapy attributes in Spain, a cross-sectional observational study. *BMJ Open* 7, e014433 (2017).
64. Garcia-Dominguez JM, Muñoz D, Comellas M, Gonzalbo I, Lizán L, Polanco Sánchez C. Patient preferences for treatment of multiple sclerosis with disease-modifying therapies, a discrete choice experiment. *Patient Prefer. Adhere.* 10, 1945–1956 (2016).
65. Wilson LS, Loucks A, Gipson G *et al.* Patient preferences for attributes of multiple sclerosis disease-modifying therapies, development and results of a ratings-based conjoint analysis. *Int. J. MS Care.* 17, 74–82 (2015).
66. Poulos C, Kinter E, van Beek J, Christensen K, Posner J. Preferences of patients with multiple sclerosis for attributes of injectable multiple sclerosis treatments in the United Kingdom and France. *Int. J. Technol. Assess Health Care* 34, 425–433 (2018).
67. Mansfield C, Thomas N, Gebben D, Lucas M, Hauber AB. Preferences for multiple sclerosis treatments, using a discrete-choice experiment to examine differences across subgroups of US patients. *Int. J. MS Care.* 19, 172–183 (2017).
68. Shingler SL, Swinburn P, Ali S, Perard R, Lloyd AJ. A discrete choice experiment to determine patient preferences for injection devices in multiple sclerosis. *J. Med. Econ.* 16, 1036–1042 (2013).
69. Bergmann A, Lang M, Bischoff CL. Patient preferences in the choice of disease modifying drugs for multiple sclerosis. *Neurology* 82(Suppl. 10), P3.137 (2014).
70. Poulos C, Kinter E, Yang JC *et al.* A discrete-choice experiment to determine patient preferences for injectable multiple sclerosis treatments in Germany. *Ther. Adv. Neurol. Disord.* 9, 95–104 (2016).
71. Hincapie AL, Penm J, Burns CF. Factors associated with patient preferences for disease-modifying therapies in multiple sclerosis. *J. Manag. Care Spec. Pharm.* 23, 822–830 (2017).
72. Giovannoni G. Risks, risk management and the choice of treatments for MS x. *ECTRIMS Online Library* 134, 231883 (2018).
73. Dobson R, Dassan P, Roberts M, Giovannoni G, Nelson-Piercy C, Brex PA. UK consensus on pregnancy in multiple sclerosis: 'Association of British Neurologists' guidelines. *Pract. Neurol.* 19, 106–114 (2019).

•• **Important early example of guidance for the use of DMDs suring pregnancy.**

74. Canibaño B, Deleu D, Mesraoua B, Melikyan G, Ibrahim F, Hanssens Y. Pregnancy-related issues in women with multiple sclerosis: an evidence-based review with practical recommendations. *J. Drug Assess.* 9, 20–36 (2020).