Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: https://www.tandfonline.com/loi/icmo20

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To cite this article: Dirk Deleu, Beatriz Canibaño, Boulenouar Mesraoua, Gholamreza Adeli, Mohamed S Abdelmoneim, Yasir Ali, Osama Elalamy, Gayane Melikyan & Amir Boshra (2019): Management of relapsing-remitting multiple sclerosis in Qatar: an expert consensus, Current Medical Research and Opinion, DOI: 10.1080/03007995.2019.1669378

To link to this article: https://doi.org/10.1080/03007995.2019.1669378

Accepted author version posted online: 18 Sep 2019.

Management of relapsing-remitting multiple sclerosis in Qatar: an expert consensus

Dirk Deleu,[1] Beatriz Canibaño,[1] Boulenouar Mesraoua,[1] Gholamreza Adeli,[1] Mohamed S Abdelmoneim,[1] Yasir Ali,[1] Osama Elalamy,[1] Gayane Melikyan,[1] Amir Boshra.[2]

1. Department of Neurology (Neuroscience Institute), Hamad Medical Corporation, Doha, Qatar; 2. Merck Serono Middle East FZ LTD, Dubai, UAE.

Correspondence to: Dr Dirk Deleu
Department of Neurology (Neuroscience Institute),
PO Box 3050,
Hamad Medical Corporation,
Doha,
Qatar.

ddeleu@hamad.qa

Running header: RRMS management in Qatar

Abstract

Healthcare systems vary greatly between countries. International, evidence-based guidelines for the management of multiple sclerosis (MS) may need to be adapted for use in particular countries. Two years ago, the authors published a comprehensive consensus guideline for the management of MS in Qatar. Since that time, the availability of disease-modifying treatments for relapsing-remitting MS (RRMS), and our understanding of how to apply those treatments, has increased. The authors present an update to our guidance, focussing on the management of relapsing-remitting RRMS. In particular, the authors consider the optimal use of different DMTs in patients presenting with mild, medium or high disease activity.

Key words: multiple sclerosis; management; Qatar; disease-modifying therapy; immune reconstitution therapy.

Introduction

A number of new disease-modifying therapies (DMTs) for relapsing-remitting multiple sclerosis (RRMS) have been introduced in recent years, broadening and complicating the design of therapeutic interventions for an individual patient. "First-line" or "platform" DMTs (interferons, glatiramer acetate, dimethyl fumarate and teriflunomide) have been supplanted to some extent by a new generation of highly potent DMTs (alemtuzumab, Cladribine Tablets 10 mg[1], fingolimod, natalizumab, and ocrelizumab) that has changed the landscape of care for people with relapsing-remitting multiple sclerosis (RRMS).[1] Indeed, these drugs have enabled long periods (years) of disease activity-free remission for substantial proportions of patients.[2] Challenging tolerability profiles and/or paucity of information on long-term outcomes with newer agents have led to some caution on the part of regulatory authorities concerning their therapeutic use.

The debate continues as to when to prescribe a given high efficacy DMT for a given patient. Free healthcare is available for all Qatari nationals, and restrictions on prescribing a given DMT for a given type of patient are less strict than in other regions. Thus, clinical practice in Qatar is well placed to benefit from the increase in the number of efficacious DMTs. Two years ago, an expert group from Qatar published its consensus recommendations on the management of RRMS in that country.[3] This article seeks to extend and update this earlier guidance. Our primary focus here is on the optimal management of RRMS, within the context of our current understanding of how disease activity and other medical, personal and social factors impact on treatment goals and decisions.

Epidemiology and characteristics of multiple sclerosis in Qatar

Qatar is a relatively small nation, with a population estimated at about 2.7 million in December 2018.[4] All new cases of MS are assessed at a single tertiary referral centre, the Hamad General Hospital (HGH), and all treatments for MS are dispensed from there. Accordingly, the HGH provides an appropriate data source for measuring the prevalence of RRMS, and its treatment, in Qatari nationals. This was done in two publications, published in 2013.[5,6]

Identification of 154 patients with MS after exclusion of patients with neuromyelitis optica and isolated transverse myelitis yielded a crude prevalence of MS of 65/100,000 population (95% CI: 58–70).[6] Accordingly, Qatar is an area of medium-high prevalence of MS, according to the classical Kurtzke classification.[7] The female-to-male ratio was 1.33, which was broadly similar to other populations within and outside the region.[6] An analysis restricted to 142 newly-diagnosed patients at this institution demonstrated a relatively low median EDSS score of 2 (20%) and a preponderance towards sensory symptoms (63%) and visual symptoms (45%), rather than, motor (43%), cerebellar (32%), brainstem (27%), cord (14%), or bladder or bowel (10%) symptoms. The authors considered that these findings suggested a milder clinical presentation of MS, but a severe radiologic presentation, compared with nearby countries.

Analysis of hospital records showed that roughly similar numbers of patients with MS in Qatar were treated with interferon beta (44%) or were untreated (45%), due to either non-prescription of MS treatments, or non-adherence to treatment. Otherwise, patients had been treated with fingolimod

[1] [a]Refers to Cladribine Tablets 10 mg (3.5 mg/kg cumulative dose over 2 years, referred to elsewhere in this article as Cladribine Tablets).

(10%) or natalizumab (1%). However, these data reflect the availability of DMTs for MS in 2010, and a number of new DMTs for the management of MS have become available recently.

Defining the activity of RRMS

There are no consensus criteria for defining the activity of RRMS. Moreover, a recent guideline from expert European societies on the pharmacologic management of RRMS advocates treatment based on the level of disease activity, without providing objective criteria for assessing this.[8] The European Medicines Agency (EMA) recommends consideration of progression of the clinical burden of disease (number of relapses, worsening disability and increasing radiologic burden) in defining RRMS activity.[9] For our discussions, we have defined highly active disease and mild disease (moderate disease would show features of both) that follow the criteria used within the EMA's evaluation of Cladribine Tablets, fingolimod and natalizumab.[10-14] The criteria for these definitions are shown in Box 1.

These criteria provide a useful and practical guide to assessing disease activity, although individual patient or prognostic factors should be taken into account, such as older age at presentation, incomplete recovery from relapses, the presence of motor relapses at presentation, rapid progression of disability (e.g. increase of at least one EDSS point in one year), or presentation with spinal, or cerebellar or brainstem lesions. The clinical judgment of the individual neurologist will always play an important part in defining the activity of RRMS for a given patient.

Management of RRMS according to disease activity

Overview of current disease-modifying treatments for RRMS

Purpose of this section

The consensus guidance we published in 2017 included a review of individual treatments for RRMS that were available at that time: alemtuzumab, dimethyl fumarate, fingolimod, glatiramer acetate, interferons, mitoxantrone, natalizumab, ocrelizumab, and teriflunomide.[3] Accordingly, only a brief account of the properties of these medications will be given here, based on published reviews and the European labelling for these agents, with discussion focussed on new information that has appeared since our earlier consensus publication. Cladribine Tablets has become available for the management of RRMS since the previous consensus, and some of its therapeutic properties are described briefly below.

Efficacy

Interferons were the first DMT to be introduced in the management of RRMS, in the early 1990s and rapidly became the standard of care for RRMS following demonstration of reduced risk of relapses and reduced frequency of MRI lesions, and reductions in the accumulation of disability, as reviewed previously.[3] Indeed, the widespread exposure of people with RRMS to these agents may have contributed to a decline in the average severity of RRMS over time, as shown by a declining background relapse rate in randomised, controlled trials.[15]

Table 1 summarises principal results from randomised evaluations of newer, high efficacy DMTs.[16-34] Caution must always be applied when comparing results across clinical trials, due to differences in their designs and patient populations. Nevertheless, it is clear that substantial reductions in relapse rates were observed with DMTs in placebo-controlled trials, often with evidence of disability, and with significantly increased achievement of "No Evidence of Disease Activity" (NEDA) outcomes, compared with placebo. Few randomised, head-to-head Phase 3 comparisons between different DMTs are available, and all of these included a formulation of interferon as a comparator. Randomisation to alemtuzumab, ocrelizumab or fingolimod was associated with greater efficacy compared with interferon β-1a in these trials, as shown by larger reductions in relapse rates, MRI lesions, and greater achievement of NEDA over time periods up to three years (Table 1).

Tolerability and safety

The safety profile of first-line DMTs, interferon β, glatiramer acetate and dimethyl fumarate, has been reviewed elsewhere.[35-40] Briefly, the main side-effects of interferon β (flu-like symptoms and injection site reactions) rarely cause treatment discontinuation are not accompanied by more serious safety issues during long-term treatment.[35-37] Moreover, 20 years of post-trial follow-up has demonstrated a possible reduction in mortality in interferon β-treated patients, compared with patients originally randomly allocated to placebo.[37] Glatiramer acetate is associated with immediate post-injection reactions, which may include including flushing, palpitations and dyspnoea.[38,39]

Flushing and gastrointestinal side-effects are common in patients initiating dimethyl fumarate and may cause treatment discontinuation.[41] Five cases of PML in patients with RRMS receiving DMF have been reported in the literature, with an additional 14 cases observed in people receiving DMF for psoriasis; most of these cases occurred in patients who developed prolonged lymphopenia.[42] Finally, teriflunomide has been associated mainly with increased blood pressure and abnormal liver function tests.[43]

Table 2 summarises the safety profile of the high efficacy DMTs. The safety and tolerability profiles vary widely between individual DMTs. The main side-effects of alemtuzumab are infusion-associated reactions (occurring in more than 90% of patients and occasionally severe), autoimmunity (mainly involving the thyroid), and infections, principally herpes simplex and zoster in the upper respiratory tract.[44] Pretreatment with corticosteroids (and optionally, antipyretics) is given to reduce the severity of infusion-associated reactions. Immunisation against *varicella zoster* for patients previously unexposed to this virus and initiation of anti-herpes prophylaxis is recommended before initiating alemtuzumab.

Treatment with Cladribine Tablets is relatively well tolerated by people with RRMS; its main side-effects are lymphopenia/leucopenia, and opportunistic infections, mainly herpes zoster, according to published information[45,46] its European labelling and the experience of physicians. Cladribine tablets does not appear to be associated with increased risk of progressive multifocal leukoencepalopathy (PML),[46] although its European labelling contains a notes that PML has occurred in patients taking a different cladribine regimen for the treatment of leukaemia. Patients should be screened for latent tuberculosis or hepatitis to reduce the risk of later activation of these diseases. Patients with very low leucocyte counts (<500/mm^3) should be monitored actively for infections. No significant increase in the rate of malignancy was observed in patients with MS in an integrated analysis of

clinical evaluations of Cladribine Tablets, or in the PREMIERE Registry of patients with RRMS receiving this treatment,[46] consistent with data reported previously.[10.47]

The main safety concern with natalizumab is progressive multifocal leukoencepalopathy (PML), an opportunistic infection caused by JC virus.[48,49] The presence of JC virus antibodies, treatment with natalizumab for at least 2 years, and prior treatment with an immunosuppressant are all risk factors for PML during treatment with natalizumab. Consideration of these risk factors when planning to prescribe natalizumab has greatly reduced the risk of PML, and researchers are seeking biomarkers to help reduce this risk further.[50]

Infusion reactions are common with ocrelizumab, and dose adjustments, or permanent withdrawal of therapy is required where they are potentially life threatening.[51,52] The European labelling carries a warning about a possible increase in malignancy, including breast cancers.[51] The risk of PML with ocrelizumab is unknown at present, and cases of PML have not been reported in MS patients receiving this treatment.[53] Ocrelizumab is an inhibitor of CD20. PML and other opportunistic infections (including reactivation of hepatitis B) have been observed as rare events in other CD20 inhibitors in patients with rheumatoid arthritis or malignant disease who also received other antineoplastic drugs.[53-55]

Fingolimod is associated with several principal side-effects, including bradycardia, macular oedema (especially early in therapy), hepatic abnormalities and an increased risk of malignant disease.[56-58] PML has also been reported in patients taking fingolimod.[59]

Administration and treatment burden

Table 2 also summarises the administration regimens and principal requirements for initial and ongoing monitoring associated with these DMTs. Administration is oral for teriflunomide, and fingolimod, and by regular, periodic infusions or injections for natalizumab and ocrelizumab. Alemtuzumab and Cladribine Tablets are hypothesised to be members of the emerging sub-class of immune reconstitution therapies (IRT),[60,61] The rationale and mechanisms underlying IRT has been reviewed elsewhere.[62,63] Briefly, suppression of components of the immune system is followed by a gradual rebuilding of the population of T and B cells, without recovery of the clones that gave rise to inflammation and demyelination, where the treatment has been successful. The main hallmark of IRT is a period of efficacy that long outlasts both the duration of drug administration and the persistence of drug in the plasma.

The administration regimens of alemtuzumab and Cladribine Tablets require two short courses of treatment one year apart. Further treatment with alemtuzumab may be given in years three and four, if required, but there is no requirement for re-treatment with Cladribine Tablets in years three and four, based on the results of an extension to the CLARITY randomised evaluation of this agent.[64] Accordingly, these agents demonstrate some features of an IRT. Immune cells recover gradually after treatment with Cladribine Tablets, without the overshoot in B-cells seen with alemtuzumab, which may account for the difference in safety between these agents with regard to activation of autoimmunity. Cladribine Tablets also has greater effects on components of the adaptive system, with less effect on the innate immune system.[65]

Monitoring requirements during and after initiation of treatments also vary considerably between DMTs (Table 2). Of the immune reconstitution therapies, alemtuzumab has a considerably heavier monitoring burden compared with Cladribine Tablets, with a requirement for monthly monitoring of blood counts and renal function, and regular monitoring for autoimmune damage to the thyroid. Haematological monitoring requirement with Cladribine Tablets is required to ensure that lymphocyte counts have recovered sufficiently before administration of the second course of treatment in year 2 of therapy. Lymphocytes should also be measured at months 2 and 6 of each treatment year, and followed thereafter if <500/mm^3; patients with lymphocyte counts <500/mm^3 should also be monitored for signs of infection, particularly zoster. Monitoring is also required if concomitant treatments that may affect blood counts or exposure to cladribine are taken. Fingolimod and teriflunomide require monitoring for their cardiovascular and hepatic side-effects, respectively. The risk of PML increase with the duration of treatment with natalizumab, and patients should be re-counselled on this after two years of treatment.

Choosing a DMT

Table 3 summarises the authors' consensus recommendations for selection of a DMT during different clinical scenarios across the spectrum of disease severity in patients with RRMS. Specifically, we considered treatment of a patient without prior therapy with a DMT, and a patient who has demonstrated sub-optimal clinical response to one or two DMTs. Further discussion of the clinical context surrounding these decisions is given below.

Goals of treatment

The goals of management of all people with RRMS relate to the disease (reducing relapse rates, preserving-long-term functional status), the treatment (avoiding side-effects as far as possible, minimising the burden of treatment and its associated monitoring), and the patient's lifestyle (maintaining quality of life, supporting good adherence with therapy, delivering treatment in a way that fits well with the individual patient's lifestyle, and accommodating the patient's need to plan a family).[66-68] Disease activity may alter priorities to some extent. Where disease activity is low or moderate, convenience and family planning may take a relatively high priority, and the relatively benign and the first-line DMTs often used in these patients have well understood safety and tolerability profiles. For the patient with high disease activity and a likely adverse long-term prognosis, preventing further relapses, radiologic progression and associated progression of disability is paramount. The more effective suppression of disease activity with high efficacy DMTs may come at a price of more, and potentially serious, side-effects and more monitoring, although this varies between individual drugs as described above. Family planning presents an especially difficult challenge in this setting. The following sections address the impact of disease activity at presentation on the choice of a DMT.

Disease activity and selection of treatment

In Qatar, it is a usual practice to prescribe a "first-line" or "platform" DMTs where disease activity is low: RRMS in these patients can often be controlled adequately by interferon (preferably at the higher dose) or glatiramer acetate, without need for agents with more challenging safety and tolerability profiles.[8] High efficacy DMTs are preferred where interferons are considered unlikely to

provide sufficient protection from relapses for patients with highly active disease, or patients who have already experienced breakthrough disease while receiving a first-line DMT.[8] For patients with moderate disease, the choice between a first-line or high efficacy DMT is likely to depend on the outcome of discussions with the patient regarding their personal circumstances and preferences (see below).

Most DMTs induce suppression of immune function, either temporarily (IRT-like DMTs) or continuously (immunosuppressant drugs given regularly throughout their use). Switching between DMTs is problematic where either drugs persist on the body (e.g. teriflunomide) or have long-lasting effects on white cell counts.[69] If the chosen DMT cannot be administered immediately, for example because of leucopenia persisting from earlier treatment, a period without treatment, or bridging therapy with a corticosteroid, interferon or glatiramer acetate are options for filling this treatment gap.[70] These strategies are not without risk however; for example, switching between natalizumab and fingolimod, for example, has been shown to result in increased relapse rates, especially in patients with more pronounced disability.[71]

Switching between DMTs

Alemtuzumab and Cladribine Tablets both require two administrations one year apart before the full dose has been given. It is unclear whether the occurrence of a relapse subsequent to this time, should prompt a treatment switch or retreatment with the original treatment; the debate continues as to how many relapses constitute failure of a DMT with characteristics of an IRT in a patient who probably received this therapy due to high disease activity.[72]

Family planning

Planning a pregnancy provides a dilemma for patients with RRMS and their physicians, in which the risks of active treatment must be balanced with the risks of relapse if treatment is withdrawn.[73] Cultural issues around pregnancy may be particularly problematic in Middle-Eastern countries such as Qatar, as there is a widespread preference for achieving pregnancy early in marriage, followed by raising large families, so that some Qatari women may spend substantial period of their childbearing years in pregnancy.[74]

Most DMTs are is contraindicated during pregnancy.[75] Most physicians recommend stopping DMT treatment in the event of pregnancy.[76] Relapse rates reduce during pregnancy for most women, especially in the third trimester. However, women with high relapse rates before pregnancy that required treatment with a high-efficacy DMT, especially where disability is present, may be at risk of a catastrophic relapse in early pregnancy.[77] A recent expert consensus guideline from the UK recommends that women with RRMS should not delay initiation of DMTs for family planning.[73] While the reduction in relapse rates that occurs during pregnancy may allow some women to discontinue their DMT when they become pregnant, this expert consensus supports the continuation of DMTs during pregnancy for women with highly active disease.[73]

More research is needed to confirm the role of IRT-like DMTs for women who wish to plan a pregnancy. European labelling requires the avoidance of pregnancy for 6 months after the last dose of Cladribine Tablets and for 4 months after administration of alemtuzumab. As described above, a

prolonged period of freedom from relapses has been observed with Cladribine Tablets and alemtuzumab in non-pregnant patients that outlasts the period of treatment and persistence of the drug in the body. However, more data are required to demonstrate whether this long-term efficacy is maintained in the setting of pregnancy, and that there are no adverse effects of treatment on maternal of foetal outcomes, before definitive guidance can be proposed regarding the place of IRT-like DMTs in the management of patients planning a family.

The postpartum period is associated with increased risk of relapses, and the need for restarting DMT (if this has been stopped prior to or during pregnancy) needs to be balanced against providing the opportunity for the mother to breastfeed.[77] New guidance from the UK stresses women should be encouraged to breastfeed, alongside other treatment considerations, taking the mother's needs and preferences into account.[78] US and European labelling for some DMTs does not contraindicate their use during breastfeeding, according to individualised risk:benefit considerations. At the time of writing, both US and European labelling support cautious use of beta interferons and glatiramer acetate during breastfeeding. US labelling does not rule out use of natalizumab and ocrelizumab during breastfeeding, but European labelling does not support this use.

Patient preferences

Patients with RRMS often deal with their devastating diagnosis by seeking information on the internet and from support groups and other people with RRMS via social media.[80,81] Accordingly, patients are increasingly knowledgeable, motivated and determined to participate actively in their care when they arrive for their consultation. Healthcare professionals tend to focus on adverse aspects of treatments for RRMS (safety issues), while patients may also focus on positive aspects (e.g. beneficial impact on treatment outcomes).[81] RRMS is a disease primarily of onset in young adulthood, and some patients may accept the risks of adverse events with a high-activity DMT or IRT-like DMT in return for the prospect of a longer period of freedom from relapses and a good long-term functional outcome.[82] Preference for oral vs. injectable treatment, frequency of administration, or ability to accommodate monitoring requirements into a patient's lifestyle may also be important.[81,83] Treatment preferences themselves are modified by patients' current mode of treatment and disability status.[84]

Managing relapses

A systematic review of clinical trials in relapsing patients with MS concluded that i.v. or oral methylprednisolone is effective for the management of acute relapses in patients with RRMS, including where acute optic neuritis is present, with use of doses of at least 500 mg/day for 3–5 days, depending on presentation.[85] The European labelling for powdered formulations of methylpredisolone includes an indication for "acute exacerbations of multiple sclerosis superimposed on a relapsing-remitting background". An infusion of 1 g methylprednisolone daily, infused over 30 minutes is recommended for management of acute MS relapses using these preparations. Current guidance for the management of MS supports the use of corticosteroid treatment to reduce the duration and severity of relapses, with appropriate counselling on possible adverse effects of high-dose steroids, such as temporary psychological disturbances, or deterioration of glycemic control in people with diabetes.[86] Steroid treatment for MS relapses does not preclude

breastfeeding.[78] Plasmapheresis is effective in patients with acute relapses refractory to steroids, and this treatment is supported by US guidelines.[87]

Declaration of funding

The consensus meeting that gave rise to this article was funded by Merck Serono Middle East FZ-LTD]. This company did not influence the treatment recommendations made here, which are the views of the authors.

Declaration of financial/other relationships

AB is an employee of Merck Serono Middle East FZ-LTD. DD has served on Served on Advisory Boards of Merck, Novartis, Biologix, Roche and Sanofi and is a member of MENACTRIMS. BC has received travel, speaker and consultant honoraria from Merck, Novartis, Biologix, Roche and Sanofi. ORE has received an Honorarium from Merck. YA has participated in Advisory Boards for Merck. MSA, GA, BM and GM report no duality of interest additional to participation in the consensus meeting funded by Merck Serono Middle East FZ-LTD, described above. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgements

A medical writer (funded by Merck Serono Middle East FZ-LTD) provided editorial assistance.

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Box 1. Criteria for defining highly active relapsing-remitting multiple sclerosis (RRMS).

Highly active RRMS

Treatment-naive patients:

≥2 relapses in one year

And ≥1 Gadolinium-enhancing lesions on brain MRI

Or a significant increase in T2 lesion load as compared to a previous recent MRI

Patients treated with at least one disease modifying therapy[a]:

≥1 relapse in the previous year while on therapy

And ≥9 T2 hyperintense lesions in cranial Magnetic Resonance Image (MRI)

Or ≥1 Gadolinium-enhancing lesion

Mild RRMS

Treatment-naive patients:

≤1 disabling relapse in 1 year

Or no Gadolinium-enhancing lesions, and no significant increase in T2 lesion load compared with a recent MRI

Patients treated with at least one disease modifying therapy[a]:

Decreased relapse rate and no ongoing severe relapses

No relapses in the past year

Or no Gd+ lesions ***and*** no more than 8 T2 lesions

[a]Treatment usually for at least one year.

Table 1. Overview of principal randomised Phase 3 evaluations of disease-modifying therapies (DMTs) for multiple sclerosis

DMT/TRIAL	Overview of efficacy outcomes		
	Relapses	**Disability**	**NEDA**
Interferons (IFN)			
PRISMS (sc IFNβ1a vs. placebo)[19]	Risk reductions for relapses vs. placebo of 27%(14 to 39) and for IFN 22 mg tid 33% (21 to 44) for INF 44 mg tid	Reduced accumulation of long-term disability for INF vs. placebo	See studies below that employed IFNβ1a as a comparator
MSCRG (im IFNβ1a vs. placebo)[18]	Over 2 y, annual exacerbation rate was 0.90 on placebo and 0.61 on INF	EDSS score progressed ≥1 point in 34.9% on placebo and 21.9% on IFN (p=0.02)	–
MSSG (sc IFNβ1b vs. placebo)[16]	Annual "exacerbation rate" at 2 y was 1.27 for placebo, 1.17 for 1.6 million IU dose (p=0.01) and IFNB, and 0.848 million IU (p=0.0001) after 2 y	No differences between groups for effects on EDSS scores	See studies below that employed IFNβ1a as a comparator
ADVANCE (pegylated INFβ1a vs. placebo)[17]	Rate ratios 0·644 (0.500 to 0.831, p=0·0007) for 2-weekly treatment, 0·725 (0.565 to 0.930, p=0·0114) for monthly treatment	–	–
Glatiramer acetate (GA)			
CMSSG (vs. placebo)[20]	34.0% reduction in risk of relapses for GA vs. placebo (p<0.0001)	–	–

ECGASG (vs. placebo)[21]	29% reduction in relapse rate for GA vs. placebo (p=0.007)	More on GA vs. placebo improved EDSS score and more on placebo vs. GA worsened (p=0.037 for the difference)	–
Dimethyl fumarate (DMF)			
DEFINE (vs. placebo)[22]	Relative risk reductions vs. placebo of 53% (bid dosing) and 48% (tid dosing), p<0.001 for each	Relative risk reductions vs. placebo for 1-step EDSS progression of 38% (bid, p=0.005) and 34% (tid, p=0.01)	More NEDA on DMF (39% vs. 27%), p<0.05
CONFIRM (vs. glatiramer acetate)[34]	Risk reductions vs. placebo: bid DMF 44%, p<0.001; tid DMF 51%, p<0.001; GA 29%, p=0.01	No significant changes in EDSS progression between groups	–
Alemtuzumab			
CARE-MS I (vs. IFNβ-1a)[25]	54.9% reduction in relapses[a] (p<0.0001) 78% relapse free at 2 y, vs. 59% on IFN (p<0.0001)	Similar sustained disability accumulation[a] (HR 0·70 [0·40-1·23]); p=0·22	More NEDA on alemtuzumab (39% vs. 27%), p<0.05
CARE-MS II (vs. IFNβ-1a)[26]	49.4% reduction in relapses[a] (p<0.0001) 65% relapse free at 2 y, vs. 47% on IFN (p<0.001)	42% improvement[a] in sustained disability (p=0.008)	More NEDA on alemtuzumab (32% vs. 14%), p<0.0001
Cladribine Tablets			
CLARITY (vs. placebo)[23,24]	57.6% reduction in relapse rates[b] (p<0.001) Higher proportion relapse free[b] (OR 2.53 [1.87 to 3.43]) (p<0.001)	More with no change in 3-month EDSS[b] (OR 1.55 [1.09 to 2.22]) (p=0.02)	More with NEDA at 96 weeks (47% vs. 17% on placebo)

Fingolimod			
FREEDOMS (vs. placebo)[27,28]	Annualised relapse rate 0.16–0.18 over 2 y vs. 0.40% on placebo (p<0.001) 52–62% increase in relapse free over 2 y[b] for 2 fingolimod regimens (p<0.001)	No disability progression in 82–83% vs. 75% on placebo (p=0.01–0.03)	More NEDA on fingolimod[b] (33% vs. 13%), p<0.001
TRANSFORMS[27] (vs. intramuscular interferon)	Annualised relapse rates 0.20 for fingolimod 1.25 mg and 0.16 for fingolimod 0.5 mg vs. 0.33 for interferon (p<0.001 for each)	No difference between groups for progression of disability	–
Natalizumab			
AFFIRM (vs. IFNβ-1a)[30,31]	68% reduction in relapses over 1 y[b]	42% reduction in sustained disability progression over 2 y (p<0.001)[a]	More NEDA on natalizumab[a] (37% vs. 7%), p<0.0001
Ocrelizumab			
OPERA I (vs. IFNβ-1a)[32,33]	46% reduction in annualised relapses over 1 y[b]	40% reduction in risk of 24 week disability progression (p<0.001; prespecified pooled analysis for OPERA I and II)	More NEDA on ocrelizumab[a] (48% vs. 29%), p<0.0001
OPERA II (vs. IFNβ-1a)[32,33]	47% reduction in annualised relapses over 1 y[b]		More NEDA on ocrelizumab[a] (48% vs. 25%), p<0.0001

[a]Compared with interferonβ-1a (IFN); [b]compared with placebo. IFN was given subcutaneously as per label, except for the DECIDE trial where IFN was given via the intramuscular route (30 □g once weekly). A Cladribine Tablets 5.25 mg/kg arm was included in the CLARITY trial, but this dosage strength is not used clinically and so is not included here. Other abbreviations not defined in the table: bid twice-daily administration, tid: three times daily administration.

Table 2. Most common side-effects and monitoring burden associated with DMTs, according to their European Summaries of Product Characteristics.

DMT	Administration	Principal side-effects	Monitoring requirements
Alemtuzumab	Five daily infusions followed by a course of 3 daily infusions one year later (all infusions contain 12 mg of alemtuzumab) One or two additional treatment courses can be given if required (each involving infusions on three consecutive days)	• Infusion-associated reactions (>90% of patients) • Autoimmune conditions, mainly thyroid disorders and also thrombocytopenic purpura, nephropathies, and cytopenias • Infections (mainly herpes simplex and zoster)	Before initiation and thereafter: • Monthly complete differential blood count • Monthly serum creatinine measurement • Thyroid testing
Dimethyl fumarate (DMF)	Twice-daily oral administration	• Flushing • Gastrointestinal effects • Possibility of severe, prolonged lymphopenia (one case of PML has been reported in a patient taking DMF who had prolonged lymphopenia)	• Complete blood counts, including lymphocytes, every three months (consider withdrawal if lymphocytes <500/mm^3 for 6 months) • Check renal status at 3 and 6 months, every 6–12 months during long term treatment (more often if indicated clinically)

Cladribine Tablets	Two treatment weeks at the beginning of year 1 and year 2 of treatment, to a total dose of 3.5 mg/kg Each treatment week consists of 4 or 5 days in which patients receive 1 or 2 cladribine 10 mg tablets, depending on body weight	• Lymphopenia/leukopenia • Opportunistic infections (mainly herpes zoster)	• Ensure lymphocyte counts are "normal" before initiation, and at least 800/mm^3 before the second course in year 2. • Measure lymphocyte count at months 2 and 6 of each treatment year; monitor for signs of infection where lymphocyte count is <500/mm^3 and follow lymphocyte count until it is increased. • Monitor patients taking treatments that may affect blood counts or exposure to cladribine.
Fingolimod	Single oral dose of 0.5 mg daily	• Bradycardia and transient atrioventricular conduction delays • Opportunistic infections • Macular oedema • Raised liver function tests • Possible increased risk of malignancy, especially of the skin	• ECG and blood pressure before and 6 hours after the first dose • Complete blood count 3 months after initiation and at least annually thereafter
Natalizumab	300 mg by intravenous infusion every 4 weeks	• Progressive multifocal leukoencephalopathy (PML) and other, potentially serious opportunistic infections • Hepatic disturbance • Immune Reconstitution Inflammatory Syndrome (on withdrawal)	• JC virus test and MRI scan to check for PML before initiation • Re-counsel patients receiving natalizumab for more than 2 years on risk of PML

Ocrelizumab	Two 300 mg infusions, 2 weeks apart, followed by single 600 mg infusions every 6 months Corticosteroid and antihistamine treatment (and optionally, an antipyretic) is required before infusion to limit the potential for infusion reactions	• Infusion reactions, which may be severe or even life-threatening • Risk of PML or other serious infections cannot be ruled out, based on observations with other treatments with a similar mechanism	• Screen for hepatitis B, as per local guidelines
Teriflunomide	14 mg orally once daily	• Alopecia, nausea, increased liver enzymes • Increased blood pressure	• Measure complete blood count, blood pressure, liver enzymes, before treatment • Monitor liver enzymes every 2 weeks during the first 6 months and every 8 weeks thereafter • Conduct complete blood count when prompted by symptoms on treatment, e.g. infection

Information in this table is from European Summaries of Product Characteristics as of 11 March 2019, available for each therapy at www.medicines.org.uk. Descriptions of side-effects are abbreviated, always consult full labelling.

Table 3. Consensus recommendations on the pharmacologic management of RRMS according to disease activity.

First-line treatment	Following sub-optimal response	Following further sub-optimal response
Mild RRMS disease activity[a]		
Glatiramer acetate (A) High-dose interferonβ (A) Low-dose interferonβ (C) Teriflunomide (C)	Dimethyl fumarate (A) Fingolimod (A) Cladribine Tablets (A) Natalizumab (B) High-dose interferonβ (C) Ocrelizumab (C)	Alemtuzumab (A)[b] Cladribine Tablets (A) Natalizumab (A) Ocrelizumab (A)
Moderate RRMS disease activity[a]		
Cladribine Tablets (A) Dimethyl fumarate (A) Fingolimod (A) High-dose interferonβ (A) Natalizumab (C)	Alemtuzumab (A)[b] Cladribine Tablets (A) Natalizumab (A) Ocrelizumab (A)	Alemtuzumab (A)[b] Cladribine Tablets (A) Natalizumab (A) Ocrelizumab (A)
High RRMS disease activity[a]		
Alemtuzumab (A)[b] Cladribine Tablets (A) Natalizumab (A) Ocrelizumab (A) Fingolimod (C)	Alemtuzumab (A)[b] Cladribine Tablets (A) Natalizumab (A) Ocrelizumab (A)	Alemtuzumab (A)[b] Cladribine Tablets (A) Natalizumab (A) Ocrelizumab (A)

Letters in parentheses show the level of expert consensus, defined according to the number of votes of independent clinical experts (representatives of the company that sponsored this meeting did not take part in this exercise): A=supported by at least 5/8 consensus panel members, B=3–4/8, C=1–2/8. Treatments are listed alphabetically within each level of consensus and order of listing does not imply preference over other drugs supported by the same level of consensus. [a]See text for definitions of RRMS disease activity. [b]The consensus meeting was held before the European medicines Agency applied new restrictions to the use of alemtuzumab as follows: "Lemtrada should only be started in adults with relapsing-remitting multiple sclerosis that is highly active despite treatment with at least two disease-modifying therapies…or where other disease-modifying therapies cannot be used".