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The use of alemtuzumab in patients with relapsing-remitting multiple sclerosis: the Gulf perspective

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***Abstract*:** Over the past decade, the development of high-efficacy disease-modifying therapies (DMTs) has been responsible for more effective management of relapsing-remitting multiple sclerosis (RRMS). However, the gaps in optimal care for this complex disease remain. Alemtuzumab (Lemtrada®) is a highly efficacious DMT that shows better patient outcomes and therapeutic benefits, but its use is under-recognized in the Gulf region. Experts in the care of multiple sclerosis shared their opinions based on study data and daily clinical experience in identifying the appropriate patient profile suitable for alemtuzumab's therapeutic benefits. Age, disease activity and severity, disability status, physician experience, and economic condition are some of the key indicators for alemtuzumab use.

Keywords: alemtuzumab, disease modifying therapies, Gulf region, multiple sclerosis, patient profiles, relapsing-remitting

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Background

Multiple Sclerosis (MS) is a chronic inflammatory demyelinating and neurodegenerative disease of the central nervous system. Due to the extent of the brain damage brought by this disease, MS is considered as one of the most common disability-causing disorders among adults.[1] Although this disease generally affects young adults, the symptoms of MS may start even before the age of 16 years.[2] Of those patients with early MS, over half will require support in walking 15 years after disease onset.[3] The reasons behind the gender differences in MS risk are not fully understood; however, the prevalence in women is two to three times higher than in men, with this ratio increasing over the past decades.[4]

Critical to the management of MS is identifying its clinical forms: relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS).[5] Among these subtypes, RRMS is the most prevalent, consisting of approximately 85% of MS patients at the time of diagnosis.[6]

Over the past decades, several disease-modifying therapies (DMTs) have been approved for the management of MS. Based on numerous clinical trials, DMTs help slow down disability progression and delay the occurrence of relapse.[7,8] Several DMTs have become the standard treatment for the management of RRMS although the benefit–risk varies with each DMT, dependent on the mode of action on the immune system. Established DMTs have shown efficacy in delaying MS progression, but patient adherence may be poor due to unfavorable modes of administration or side effects, and efficacy differs greatly amongst the available treatments. New and emerging DMTs, such as alemtuzumab, are highly efficacious, and require less frequent administration, offering better treatment adherence and patient outcomes.[8]

In this article, a group of experts in MS care from five countries in the Gulf region shared their insights based on clinical data and treatment experience on the use of alemtuzumab therapy and identification of the suitable patient profile that can maximize the drug's therapeutic benefits.

Methods

This review article is based on pre-selected English-language clinical trials identified through a systematic literature search of Google Scholar, Karger, Medline, and PubMed. Search keywords used include 'multiple sclerosis', 'relapsing-remitting MS', 'alemtuzumab', 'active disease' 'disease modifying therapy', 'Middle East' and 'Gulf'. In addition, the key discussions of the esteemed members of the 2nd Lemtrada Gulf Advisory Board held in Dubai, United Arab Emirates (UAE) on 28 September 2018 were incorporated as expert opinions on the use of alemtuzumab in the region. The statements presented in this article reflect the advisors' collective analysis, evaluation, and opinion on the issues surrounding alemtuzumab use. The consensus recommendations were formed by a panel of regional MS experts and an international MS expert with experience on alemtuzumab use during the advisory board discussions and deliberations, then subsequently drafted and peer-reviewed by the authors.

RRMS treatment with high efficacy DMTs

Over the past decade, the development of DMTs has been responsible for more effective management of RRMS.[9] However, each currently available DMT has its unique mechanism of action, triggering different immune responses.[10] Based on the available efficacy data of pivotal clinical trials, the expert panel considered Alemtuzumab, Natalizumab, Ocrelizumab, Fingolimod, and Cladribine as high-efficacy DMTs, with varying efficacy and safety profiles.

The proposed mechanism of action and administration of these high efficacy DMTs are summarized in Table 1.

Treatment guidelines in the use of DMTs

International clinical practice guidelines support the use of DMTs for the management of MS.

Initiating treatment with DMTs in naïve RRMS patients

The guidelines below recommend the use of DMTs for patients with highly active RRMS, which is defined as the occurrence of two disabling relapses in the preceding year.[18]

- The 2018 National Institute for Health and Care Excellence (NICE) guidelines recommend the use of DMTs including alemtuzumab, ocrelizumab, cladribine, and natalizumab, as first- line treatments of highly active RRMS.[18]
- The American Academy of Neurology (AAN) supports the use of alemtuzumab, fingolimod, or natalizumab for patients with highly active MS. Natalizumab use in MS patients with seropositivity for John Cunningham virus (JCV) was recommended only with antibody indexes <0.9 and a reasonable chance of benefit over the serious risk of progressive multifocal leukoencephalopathy (PML).[19]
- Both the European Committee of Treatment and Research in Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) recommend cladribine, natalizumab, ocrelizumab, and alemtuzumab among those drugs for highly active disease. In terms of use in female patients of childbearing age and highly active disease, alemtuzumab can be considered after a strict 4-month interval from the last infusion date until conception.[20]
- The Middle East North Africa Committee for Treatment and Research in Multiple Sclerosis (MENACTRIMS) recommend fingolimod, cladribine, natalizumab, ocrelizumab, or alemtuzumab in patients with aggressive or highly active disease.[21]

Switching DMT: Recommendations

Before switching between DMTs, several factors require the clinician's consideration. Some of these switching considerations are patient- and disease-related, such as the age of the patient, duration and severity of the disease, disability status, compliance, and family planning.[22] Therapy-related factors such as efficacy, safety, monitoring burden, and cost are also important considerations. The AAN provided switching therapy guidelines in which clinicians are encouraged to evaluate the degree of the disease activity, patient

Table 1. List of high-efficacy DMTs.

Agent	Mechanism of action	Administration form and recommended dose
Natalizumab	A humanized monoclonal antibody directed against VLA4-integrin, decreasing the migration of immune cells across the blood-brain barrier into the central nervous system.[11]	IV infusion: 300 mg/15 ml (20 mg/ml) solution in a single-dose vial for dilution prior to infusion every 4 weeks.[11]
Fingolimod	Metabolized to activate sphingosine 1-phosphate receptor modulator that binds to sphingosine 1-phosphate receptors 1,3,4 and 5 regulating lymphocyte egress from lymphoid tissues into the circulation.[12,13]	Oral administration: 0.5 mg once daily taken with or without food, indicated in adults and children 10 years of age and older. First dose monitoring required for at least 6 h with hourly pulse and blood pressure measurement to manage bradycardia.[12]
Alemtuzumab	A humanized monoclonal antibody that targets the CD52 surface protein on all B and T-cells.[14]	IV infusion over 2 treatment courses (12 mg/day on 5 consecutive days, 12 mg/day on 3 consecutive days,12 months later).[14]
Ocrelizumab	A humanized immunoglobulin G1 anti-CD20 antibody targeting mature B lymphocytes.[15]	IV infusion: 600 mg/10 ml (30 mg/ml) as a divided initial dose separated by 2 weeks, followed by 600 mg every 6 months.[15]
Cladribine	Synthetic deoxyadenosine analog prodrug, that acts in T and B lymphocytes by interacting with cell division resulting in discontinuous depletion of T and B cells.[16,17]	Oral route: the cumulative dose is 3.5 mg/kg body weight over 2 years or 1.75 mg/kg per year. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight.[16]

DMT, disease-modifying therapy; IV, intravenous.

adherence, adverse events, and mechanism of action of DMTs whenever switching between therapies.[19] Another factor that necessitates treatment consideration is the risk of progressive multifocal leukoencephalopathy, which is estimated higher at >4 per 1000 with overall natalizumab use.[23] Rare cases of PML were reported with the use of fingolimod.[24] B-cell depleting therapies and alemtuzumab are considered potential options. Although several safety reports on the use of rituximab in MS patients indicated no significant risk of PML,[25–27] there are other studies that reported PML cases in patients with lymphoma, rheumatic arthritis (RA), or concurrent chemotherapeutic agents, all of which are known risk factors for this opportunistic infection.[28,29]

Based on the accumulative data of rituximab use in MS and other immunological/hematological disorders, ocrelizumab may have a similar potentials risk, although more long-term data is needed.[16] One case of *de novo* PML was reported with the use of ocrelizumab in MS patients.[30] However, the contributing factors (confounders) reported by the physician were the patient's age (78) with potential immunosenescence, and low absolute lymphocyte count (ALC) prior to treatment with ocrelizumab.[30] Thus, it is too early to comment on any potentials increase in PML risk at this stage.[31]

Given the PML risk and JCV seropositivity, AAN guidelines recommend alternative DMTs with lower PML risk.[19] Moreover, MENACTRIMS recommendation for JCV seropositive patients (index >1.5) on natalizumab for more than 2 years, is to consider the change of therapy to other DMTs, which may include fingolimod, alemtuzumab, rituximab, or ocrelizumab.[21]

Gaps in MS treatment

Global outlook

Even with the wide variety of current DMTs, gaps in management abound in the MS therapeutic landscape. These gaps arise from the unmet needs of patients and their caregivers: emotional support, need for information, symptomatic treatment, assessment, and recognition of invisible MS symptoms (cognitive deficits, fatigue, etc.) and addressing quality of life issues.

The psychological impact due to MS results in long-term emotional stress for patients, who generally do not communicate this problem to their doctors. Similarly, caregivers of patients also experience psychological stress brought about by the demands of the long-term care of MS patients.[32]

Effective communication between the physician and the patients, with the caregivers, about the complexities of MS is therefore crucial in improving disease awareness and access to available treatment.[33]

To date, current therapies have been able to halt or delay the disease progression of MS, but curative treatment is still unavailable. Studies to understand neuroprotection or inhibition of the neurogenerative effects of the disease, which may prolong remission and prevent disability, have not been fully implemented.[32]

Finally, most routine clinical assessments of MS patients do not capture the status of a patient's quality of life, which greatly impacts treatment adherence and outcomes. Therefore, there is a need for health care providers to address this aspect of the disease through promotion of emotional support, self-efficacy, and skills development.[34]

Barriers to optimal care: the Gulf experience

The global problem in MS care is trickling down to the regional level, which is reflected by the issues faced by patients and health care professionals in various regions. Health care systems, increasing disease prevalence, cultural factors, and others are some of the barriers to optimal care specific to the Gulf region.

Health care system in the Gulf region. Over the last decade, the number of neurologists in the Gulf countries has increased, with an average of 1.2 per 100,000 population. However, there is a significant demand for neurologists with MS expertise along with multi-disciplinary MS clinics since only a few of these dedicated clinics are operating in the Gulf countries. In terms of accessibility, patients in all Gulf countries have access to DMTs as most countries adopt either the United States (US) Food and Drug Administration (FDA) or European Medicines Agency (EMA) guidelines to hasten the approval of local authorities in getting newly approved DMTs to clinics. Although healthcare infrastructure has improved in the region, patients do not immediately consult medical help during the early stages of the disease. Delay in magnetic resonance imaging (MRI) appointments may take months in some government hospitals due to the increased number of cases and low numbers of MRI machines available.[35]

The burden of increasing prevalence of MS cases. Throughout the years, the incidence of MS cases has increased in the Gulf countries. UAE, Qatar, and Kuwait are considered countries with a high frequency of MS cases, while Saudi and Oman have the lowest frequency. In UAE, the prevalence of MS in 2007 was 54.77/100,000 [95% confidence interval (95% CI) = 46.99–62.55], the mean age of onset was 26.66 ± 6.6 years with 76.9% diagnosed with RRMS.[36] The prevalence in the Kingdom of Saudi Arabia (KSA) was 7.70/100,000 population in 2015, with a median age of 32.[37] Qatar's prevalence is 64.57/100,000 (95% CI = 58.31–70.37),[38] with 58% of cases diagnosed with RRMS.[39] In Kuwait, MS prevalence has increased 1.6 times from 85.05/100,000 (95% CI = 82.80–87.04) in 2013 to 104.88 per 100,000 persons (95% CI: 89.5–121.9) in 2015.[40,41] In the Omani population, the prevalence of MS was much lower, at 4/100,000 between 1990 and 2000, mean age at disease onset was 27, and 23 out of 30 patients with RRMS.[42,43]

Cultural factors such as contiguous marriage and isolated cultures could be contributors to the increased incidence and prevalence of MS in the Gulf.

Economic burden. According to a study conducted at Mafraq Hospital (UAE), the average insurance cost covered by the Abu Dhabi Healthcare Services (SEHA) for an MS patient is Dh110,000 (US$ 29,947) per year.[44] In a recently published study in Kuwait using the national registry, the average annual cost per MS patient has increased from US $10,271 in 2011 to US $17,296 in 2015. The use of disease-modifying therapies was the main driver of costs reaching 89.9% in 2015.[45] Even with standard health insurance, the economic burden of MS may be challenging for a number of patients. The financial burden transcends beyond the direct cost of treatment, inclusive of production costs due to sick days at work and the hours of care spent by caregivers and family members.[46]

Insurance reimbursement. Aside from treatment costs, the issue of adequate reimbursement for new MS treatments may be problematic for some patients. Educating the government and agencies responsible for providing access to care is crucial to provide wider reimbursement for treatments.[47]

Patient education and communication with health care professionals. Active involvement between patients and health care professionals (HCPs) is essential to support treatment adherence. Often, physicians may undervalue the repercussions of poor patient adherence to current therapies, and may not have fully understood this type of patient behavior. Therefore, sufficient information and emotional support from physicians and other stakeholders are immediate needs to support optimal management of this complex disease.[47]

More therapeutic options. Current DMTs have shown clear benefits to reduce disability progression and the rate of MS relapses. However, these therapies fall short in achieving relapse-free lives. There remains the unmet need for treatments that balance high efficacy with lower risks while supporting compliance through favorable routes of drug administration.[47]

Alemtuzumab: T and B cell depleting therapy for RRMS

Alemtuzumab is a humanized monoclonal antibody against the cell surface protein CD52, which causes depletion of T and B lymphocytes *via* antibody-dependent cytolysis and complement-dependent cytolysis. Repopulation of lymphocytes subsequently follows depletion with B lymphocyte counts returning to baseline by 6 months and T cells in 12 months post treatment. The therapeutic effect of alemtuzumab is derived from this unique mechanism of action, which results in protection from further MS-type autoimmunity by allowing lymphocyte repopulation in a new environment; for example, the presence of a relative increase in regulatory T cells. Originally developed as a leukemia therapy, alemtuzumab was licensed by the EMA in 2013 as a therapy for RRMS. It was approved by the FDA in 2014 for use in patients with RRMS who have demonstrated inadequate response to two or more MS drug therapies.[48]

The efficacy and safety of alemtuzumab in patients with RRMS were investigated in two phase III core studies: The Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis (CARE-MS) I and II studies. The first trial (CARE-1) included treatment naïve patients whereas the second study enrolled patients with inadequate response to prior MS treatment. A 5-year follow-up analysis of these trials was also conducted – the TOPAZ study – which strengthened the clinical evidence on the efficacy and safety of this high efficacy drug.

Efficacy outcomes

The CARE MS I trial is a 2-year randomized controlled study that demonstrated alemtuzumab's efficacy with a 54.9% risk reduction and annualized *relapse rates* (ARR) of 0.16 on clinical relapse *versus* IFN β 1a in patients with active disease.[49] Further investigation with the randomized trial CARE MS II confirmed higher efficacy with a risk reduction on relapse rate of 49.4% and ARR of 0.28.[50] This study also showed a significant reduction in disability progression, which was later confirmed in the follow-up study, the TOPAZ trial. Here, stability and disability improvement in more than 70% of patients for over 7 years was shown[51] Moreover, the MRI-data showed alemtuzumab's distinctiveness in slowing brain volume loss over 7 years to the level of healthy controls, while re-treatment rates with a third course of alemtuzumab were low (52% for CARE MS I, 47% for CARE MS II), which translate to disability and economic benefits for the patients.[51]

Safety profile

As with every MS drug, alemtuzumab demonstrates unique side effects that would require active risk management.

Adverse events. In the clinical studies, several adverse events (AEs) were described: infusion-associated reactions, infections, autoimmune AEs such as idiopathic thrombocytopenic purpura (ITP), thyroid disorders, and nephropathies.[49] The most common AEs in alemtuzumab trials were infusion-associated reactions (IARs), such as headache, rash, nausea, and pyrexia, which range from mild to moderate.[52] The incidence of IARs showed a decrease with succeeding courses of alemtuzumab: 85%, 69%, 65%, 63%, and 46%, respectively in the CARE MS studies.[52] The incidence of infections, evidently highest in the

first treatment, decreased subsequently from 56.1% in the first year to 35.5% in the sixth year for CARE MSI.[52] At year 2, thyroid disorders occurred with a cumulative incidence of 16%, all of which were managed conventionally, except for two patients who underwent for either thyroidectomy or radioiodine treatment.[50] In the follow-up study, the reported incidence of infections declined from 63.32% at year 1 to 43.4% in the sixth year.[52] The predictability of these adverse events from happening with alemtuzumab use enables appropriate monitoring of the risks as well as proper and timely clinical management of these conditions.[50] The availability of long-term safety data demonstrate consistent safety and tolerability profile, with a monitoring program that allows for early detection and management of secondary autoimmune events.

Cardiovascular effects. On 16 January 2020, the EMA updated the recommendation on the use of alemtuzumab to patients with highly active RRMS who had a suboptimal response to at least one DMT treatment or when the disease is rapidly evolving.[53] This recommendation is based on reported rare but serious side effects on alemtuzumab use, such as vascular (cardiac and cerebral) disorders that can occur within few days of alemtuzumab infusion (myocardial ischaemia, myocardial infarction, cerebral haemorrhage, cervicocephalic arterial dissection, pulmonary alveolar haemorrhage). These vascular events are now listed as contraindications to the use of alemtuzumab.

To reduce the risk, EMA recommended that baseline electrocardiogram (ECG) should be performed prior to the infusion. Patients with clinical symptoms suggesting the development of a serious AE temporarily associated with the infusion should be closely monitored until complete resolution of the symptoms.[53]

Recent studies also reported cardiovascular risks in the use of alemtuzumab. One such complication is intracranial hemorrhage in patients with RRMS.[54] Other complications include ischaemic or hemorrhagic stroke and cervical arterial dissection, regarding which the FDA issued a warning in 2018 after 13 cases emerged with alemtuzumab use.[55] This finding was also supported by a study from 2016 to 2017, with five cases of spontaneous intracranial haemorrhage identified in patients from four MS clinics in the US. Researchers hypothesized that hypertension may be the causative factor for this condition. Patients with 20% or more increase in systolic blood pressure may be at risk of intracranial bleeding; therefore, intensive screening is crucial before undergoing infusion with alemtuzumab.[54]

Infections. With the use of alemtuzumab, infections caused by herpes simplex virus, herpes zoster, and mycetes, are common and frequent occurrences. In the CAMMS223 trial, 66% of patients on alemtuzumab 12 mg had infections *versus* 47% of patients on IFN β 1a.[56] CARE MS I and II studies showed 67% *versus* 45%, and 77% *versus* 66%, respectively.[49,50] Although infections are slightly higher with alemtuzumab groups, these cases range from mild to moderate in severity, with a subsequent decrease seen after the first year of treatment.[57] Increased incidence of herpes virus infections in clinical trials with alemtuzumab warrants prophylactic treatment with an oral anti-herpes agent and testing for anti-VZV antibodies as part of infection risk management.[14] Administration of live vaccines is not recommended since effects are yet to be further investigated.[14] In MS, listeria meningitis was also reported in several cases with alemtuzumab 24 mg,[57–59] such as single cases of cerebral nocardiosis,[60] and *Nocardia beijingesis*.[58] In two pivotal studies, one case was reported in the CAMMS223 study,[56] and two cases in another study.[59] Dietary restriction of food such as unpasteurized milk and raw milk, a month before treatment with alemtuzumab was recommended to reduce the infection risk among patients.[14]

Autoimmunity. Increased risk of developing autoimmune diseases, specifically thyroid disease (hyperthyroidism, Graves' disease, and thyroiditis) was seen at 6–60 months from the end of infusion cycle in clinical studies.[49,50] There were 29.6% of patients with thyroid disorders in phase III clinical studies,[49,50] and, in CAMM223, 39% and 29% were reported with alemtuzumab 12 mg and in 24 mg, respectively.[56] Due to the frequency of thyroid disorders, there is a recommendation that thyroid function tests be conducted before treatment, and every 3 months during treatment.[14] Clinical trials also reported a 2% overall incidence of ITP.[49,50] Six patients were reported to have ITP in the CAMMS223 trial, with one death caused by intracranial hemorrhage.[56] Thus, a complete blood count is required during treatment, and up to 48 months after the last infusion.[14]

Malignancy. Malignancies were reported with alemtuzumab, but the incidence is not high. The onset of malignancies (breast, lymphoma, and cervical cancer) were observed in the CAMMS223 trial, within 22–64 months after a year of infusion.[56] In clinical studies, 0.5% and 0.6% malignancies were seen in alemtuzumab 12 mg patients compared with 0% and 1.5% in the IFN β 1a group.[49,50]

Disseminated necrotizing leukoencephalopathy. One reported case of disseminated necrotizing leukoencephalopathy (DNL) was seen with alemtuzumab use in a patient of 14 years with active RRMS. DNL was confirmed after brain autopsy, suggesting the development of the condition together with autoimmune hemolytic anemia and sepsis.[61]

Risk management plan. Reduction of risks in alemtuzumab use requires periodic monitoring. Laboratory tests, such as complete blood count with differential serum transaminases and serum creatinine levels, urinalysis and test of thyroid function, as well as clinical examination until at least after 48 months following the last treatment course, are needed to identify autoimmune disease at an early stage. At pre-infusion, patient education is crucial to encourage self-monitoring of autoimmune symptoms, to inform them of possible side effects such as IARs and infusion reactions, and, most importantly, to ensure commitment to monitoring until after 48 months. During infusion, continuous and frequent monitoring of heart rate, blood pressure, and overall clinical status of the patients should be conducted to detect and manage the cardiovascular risk associated with infusion. A minimum of 2 h of observation of infusion reaction is required at the post-infusion stage, and platelet count should be obtained immediately after infusion on days 3 and 5 of the first infusion course, as well as immediately after infusion on Day 3 of any subsequent course. Referral to a hematologist is also recommended for proper management of AEs such as thrombocytopenia.[14] Strict monitoring is therefore advised to enable early detection of risks as well as patient compliance to monitoring and risk management plan.[49]

Overcoming the challenges of alemtuzumab use in the Gulf region

Although alemtuzumab is highly efficacious, there are challenges in its use specific to the Middle Eastern primary health care setting. The group of experts acknowledged gaps in the use of this therapy, and provided their insights on how to surpass these challenges.

HCPs perception of alemtuzumab's use

There is a need to change the perception of alemtuzumab as a last treatment option and instead position it as a drug of choice in a select group of patients with RRMS and highlight its advantage in optimizing patient outcomes and benefits of early use (see paragraph on choosing the right patient profile). This perception of alemtuzumab's high efficacy was supported by an expert consensus study in the Gulf in which alemtuzumab was ranked highest for reducing overall disease activity in comparison to other DMDs (natalizumab, fingolimod, cladribine tablets, and ocrelizumab).[62] Leveraging on its efficacy, long-term use, and cost-effectiveness are additional key benefits that can drive the use of alemtuzumab among physicians.

Misconceptions on safety

Neurologists in the Gulf region are apprehensive about the side effects of alemtuzumab owing to a lack of experience with the drug. It is crucial that they are informed in order that they understand what they can expect from the reported side effects, and how these can be well managed. Highlighting alemtuzumab's long-term safety data, and risk/benefit profile can ease the concerns of treatment-related risks. Although most general neurologists in the region treat MS patients, it is advised that patients requiring the use of alemtuzumab are referred to specialized MS clinics in order to discuss the updated serious adverse events, address patients' concerns, and facilitate the vigorous monitoring aspects.

Monitoring burden

Blood and urine samples can be administered anywhere, but patients still face the burden of the monthly monitoring required for alemtuzumab for up to 4 years after the last infusion. To address this burden, setting up patient and HCP supporting programs to facilitate the monitoring are advised. Educating and informing patients and HCPs about the relevance and importance of this monitoring can improve effective diagnosis and early treatment of any secondary autoimmunity. It can also avoid possible concerns that may arise about the drug, since frequent monitoring may imply a negative perception of alemtuzumab's safety profile.

Cost-effectiveness

Alemtuzumab is a highly active DMT that may change the course of RRMS over a long time. Favorable effects are seen on disability progression, improvement on brain volume loss (BVL) rate to the level of healthy controls, and relapse prevention. Its efficacy, in addition to low retreatment and switch rates, contributes to the cost-effectiveness of alemtuzumab in comparison with other DMTs. Cost analyses data from the Institute for Clinical and Economic Review (ICER) and NICE supports alemtuzumab's value for money.

- ICER reported that alemtuzumab "Dominates," or is an option that is more effective and less costly compared with other therapies.[63]
- NICE evaluated the total cost and incremental cost of alemtuzumab at about half the cost and eight-fold lower as compared with other DMTs.[63]

Analysis of the annual acquisition cost of alemtuzumab concerning the dosage recommendations and net prices also strengthened its value proposition. In a span of 5 years, the cost of treatment with alemtuzumab is lowest at US$ 72,900, as compared with other DMTs, with a total cost ranging from US$ 115,550 to US$ 170,174.[63]

Selection of candidate patients for alemtuzumab

Although alemtuzumab demonstrated efficacy in RRMS, it may not be beneficial for every patient with MS due to safety concerns. Therefore, careful consideration of suitable patient profiles is critical. Following the most recent recommendation on alemtuzumab by the EMA, the panel of experts further explored the patient profile appropriate for its use.[53] Weighing the importance of clinical experience, the experts defined specific patient profiles eligible for alemtuzumab (Table 2).

Age at onset

Immune reconstitution therapy (IRT) is preferable to use for young patients, about 18–35 years of age. The baseline age of patients in the core clinical studies is 32–50 years. Beyond this time duration, treatment efficacy will not be the same compared with the results of the studies.[64,65] Most physicians tend not to use IRTs in older patients given the associated long-term safety. On the other hand, young patients tend to be prescribed IRTs either when naïve or after 1–2 prior DMTs.

Severity of disease

Understanding the severity of RRMS depends on the disease activity [presence or absence of relapses/magnetic resonance imagining (MRI) changes such as new T2 lesion/Gad-enhancing lesions] and the disease progression [3–6 months confirmed an increase in Expanded Disability Status Scale (EDSS) scores].[6] For alemtuzumab, the panel of MS experts suggests that patients exhibiting early active disease with at least two relapses within 1 year can achieve the best results.

Pregnancy

There is reluctance amongst physicians to prescribe this medication to women of childbearing age due to possible teratogenic effects.[66] Based on the expert's insight, natalizumab may be a good option in highly active patients who are considering pregnancy, given its potential use in active cases during pregnancy until the end of the second trimester with minimal teratogenic effects. Similarly, alemtuzumab or cladribine may serve as potentials DMTs in highly active MS patients, who may consider postponing pregnancy until 4 months after the second course of alemtuzumab or 6 months after the second course of cladribine. According to the ocrelizumab label, it is recommended to wait for at least 1 year after the last infusion before planning a pregnancy. This may not be a practical option as there will be the chance of disease reactivation.

Analysis of pregnancy outcomes from three follow-up trials in 193 alemtuzumab-treated female patients with RRMS showed no evidence of teratogenicity. Of the completed pregnancies, no congenital anomalies or birth defects were observed. There were 22% spontaneous abortions and 1% stillbirths.[67] Further studies on the safety and potential risks of alemtuzumab in pregnancy are also recommended.[66]

Treatment experience

Patients with inadequate response to previous treatments have demonstrated potential therapeutic benefit from alemtuzumab. CARE-MS II

Table 2. Characteristics of patients suitable for alemtuzumab use.

Indicators	Characteristic
Age	Young (age 18–35 years)
Severity of the disease	Highly active, early pickup of severe MS
Child-bearing potential	4 months after treatment with alemtuzumab
Treatment experience	Treatment naïve with a highly active or rapidly evolving disease, early escalation from any other DMT
Disease duration	Shorter, early onset
EDSS score	0–4
Cost	Not for self-paid patients
Monitoring burden	Compliant and adherent

EDSS, expanded disability status scale; DMT, disease modifying therapy; MS, multiple sclerosis.

is the only phase III trial to date, which examined patients who had breakthrough disease prior to the randomization of therapy.

Disease duration

Patients with short-disease duration may be more suitable for treatment as repair in the CNS is still effective and they have less likelihood of accumulating disability. CARE-MS I study included patients with disease duration of 5 years or less and showed significant efficacy in reducing disease activity.

EDSS score

During treatment, alemtuzumab demonstrated a higher improvement in disability scores with patients presenting an EDSS score of ⩽3 to ⩽5 at baseline. Although the beneficial effect may extend to patients who are in the transitional phase, the likelihood of significant improvement in patients with a confirmed progressive course is low. Therefore, the experts suggest that patients with disability scores of 0–4 are appropriate for alemtuzumab therapy.

Cost

In the long run, alemtuzumab is more cost-effective compared with other DMTs when efficacy and duration of treatment are considered. However, the cost of the therapy upfront may be challenging for self-paying patients.

Monitoring burden

Monthly monitoring of blood and urine is mandatory up to 4 years after the last infusion, to pick-up and treat possible secondary autoimmune diseases early. Due to the regularity of alemtuzumab's monitoring program, treatment adherence and compliance should be high in patients who are prescribed this DMT.

JCV seropositivity

In cases where there is a need to switch therapies (such as natalizumab) due to the presence of JCV and consequent PML risk, several DMTs may serve as potentials options including alemtuzumab, with B-cell depleting therapies such as rituximab.[68,69] Accordingly, it is crucial to check for any carryover of PML in JCV-positive patients by performing MRI of the brain and meticulous evaluation for early signs of PML prior to starting alemtuzumab.[70]

Real-world evidence on the use of alemtuzumab also supports the identification of characteristics suitable patients who would benefit most from this treatment. In a Kuwait study, young patients, with shorter duration of disease, mean EDSS score of 3.9, and highly active disease, showed greater improvement with the use of alemtuzumab.[71]

Conclusion

Despite its high efficacy and well-known risk/benefit profile, alemtuzumab is yet to be fully

utilized in the Middle East for patients with RRMS. A patient profile identified carefully by experts in MS care provided key indicators that can help physicians develop an informed treatment decision. The experts suggest that patients who are of a younger age, treatment naïve, with highly active disease and short disease duration, of child-bearing potential, and at high risk of developing disability can achieve better outcomes with alemtuzumab.

Conflict of interest statement

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References

1. Hersch C and Fox R. *Multiple sclerosis*. Cleveland Clinic Center for Continuing Education, 2018.
2. Ozakbas S, Idiman E, Baklan B, *et al*. Childhood and juvenile onset multiple sclerosis: clinical and paraclinical features. *Brain Dev* 2003; 25: 233–236.
3. Noseworthy J, Lucchinetti C, Rodriguez M, *et al*. Multiple sclerosis. *N Engl J Med* 2000; 343: 938–952.
4. Voskhul R and Gold S. Sex-related factors in multiple sclerosis: genetic, hormonal and environmental contributions. *Nat Rev Neurol* 2012; 8: 255–263.
5. Lublin F. New multiple sclerosis phenotypic classification *Eur Neurol* 2014; 72: 1–5.
6. McKay K, Kwan V, Duggan T, *et al*. Risk factors associated with the onset of relapsing-remitting and primary progressive multiple sclerosis: a systematic review. *BioMed Res Int* 2015; 2015: 1–11.
7. Hamidi V, Cuoto E, Ringerike T, *et al*. A multiple treatment comparison of eleven

disease-modifying drugs used for multiple sclerosis. *J Clin Med Res* 2018; 10: 88–105.

8. Weinstock-Guttman B. An update on new and emerging therapies for relapsing-remitting multiple sclerosis. *Am J Manag Care* 2013; 19: S34–S54.
9. Freedman M, Hughes B, Mikol D, *et al.* Efficacy of disease-modifying therapies in relapsing remitting multiple sclerosis: a systematic comparison. *Eur Neurol* 2008; 60: 1–11.
10. Pardo G and Jones D. The sequence of disease-modifying therapies in relapsing multiple sclerosis: safety and immunologic considerations. *J Neurol* 2017; 264: 2351–2374.
11. Tysabri Prescribing Information. (2018) Cambridge, MA: Biogen Inc.
12. Fingolimod Product Monograph. (2019) East Hanover, NJ: Novartis.
13. Chun J and Hartung H. Mechanism of action of oral fingolimod (FTY720) in multiple sclerosis. *Clin Neuropharmacol* 2010; 33: 91–101.
14. Alemtuzumab (Lemtrada®). *Summary of product characteristics.* (2020) Cambridge, MA: Sanofi Genzyme.
15. Ocrevus Prescribing Information. (2018) South San Francisco, CA: Genetech Roche.
16. Giovannoni G, Comi G, 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 J* 2018; 24: 1594–1604.
17. EMC. Merck Serono. Summary of product characteristics; *Mavenclad 10mg*, https://www.medicines.org.uk/emc/product/8435#gref (2018, accessed 14 April 2019).
18. National Institute for Health and Care Excellence Pathways. *Disease-modifying therapies for multiple sclerosis*. UK: NICE, 2019, p. 13.
19. Rae-Grant A, Day GS, Marrie RA, *et al.* Practice guideline: disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Presented at: 2018 American Academy of Neurology Annual Meeting, 21–27 April 2018, Los Angeles, CA.
20. Montalban X, Gold R, Thompson A, *et al.* ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler J* 2018; 24: 96–120.
21. Yamout B, Alroughani R, Sahraian, *et al.* Consensus recommendations for the diagnosis and treatment of multiple sclerosis: 2019 revisions to the MENACTRIMS guidelines. *Mult Scler Relat Disord* 2020; 37: 101459.
22. Grand'Maison F, Yeung M, Morrow S, *et al.* Sequencing of high-efficacy disease-modifying therapies in multiple sclerosis: perspectives and approaches. *Neural Regen Res* 2018; 13: 1871–1874.
23. US Food and Drug Administration. FDA drug safety communication: new risk factor for progressive multifocal leukoencephalopathy (PML) associated with Tysabri (natalizumab), https://www.fda.gov/drugs/drugsafety/ucm288186.htm (2012, accessed 28 February 2020).
24. US Food and Drug Administration. FDA drug safety communication: FDA warns about cases of rare brain infection with MS drug Gilenya (fingolimod) in two patients with no prior exposure to immunosuppressant drugs, https://www.fda.gov/Drugs/DrugSafety/ucm456919.htm (2015, accessed 28 February 2020).
25. Salzer J, Svenningsson R, Alping P, *et al.* Rituximab in multiple sclerosis. *Neurology* 2016; 87: 2074–2081
26. Barra M, Soni D, Vo K, *et al.* Experience with long-term rituximab use in a multiple sclerosis clinic. *Mult Scler J Exp Transl Clin* 2016; 2: 1–8.
27. Alldredge B, Jordan A, Imitola J, *et al.* Safety and efficacy of rituximab: experience of a single multiple sclerosis center. *Clin Neuropharmacol* 2018; 41: 56–59.
28. Clifford D, Ances B, Costello C, *et al.* Rituximab-associated progressive multifocal leukoencephalopathy in rheumatoid arthritis. *Arch Neurol* 2011; 68: 1156–1164.
29. Sikkema T, Schuiling W and Hoogendoorn M. Progressive multifocal leukoencephalopathy during treatment with rituximab and CHOP chemotherapy in a patient with a diffuse large B-cell lymphoma. *BMJ Case Rep* 2013; 2013: bcr2012008142.
30. Ocrelizumab & PML. https://www.ocrelizumabinfo.com/content/dam/gene/ocrelizumabinfo/pdfs/progressive-multifocal-leukoencephalopathy.pdf (accessed 14 June 2020).
31. De novo PML on Ocrelizumab. https://multiple-sclerosis-research.org/2019/10/de-novo-pml-on-ocrelizumab/ (accessed 4 June 2020).
32. Mehr S and Zimmerman M. Reviewing the unmet needs of patients with multiple sclerosis. *Am Health Drug Benefits* 2015; 8: 426–431.

33. Rieckmann P, Centonze D, Elovaara I, *et al*. Unmet needs, burden of treatment, and patient engagement in multiple sclerosis: a combined perspective from the MS in the 21st century steering group. *Mult Scler Rel Dis* 2018; 19: 153–160.

34. Zwibel H and Smrtka J. Improving quality of life in multiple sclerosis: an unmet need. *Am J Manag Care* 2011; 17: S139–S145.

35. Mohammed E. Multiple sclerosis is prominent in the Gulf states: review. *Pathogenesis* 2016; 3: 19–38.

36. Inshasi J and Thakre M. Prevalence of multiple sclerosis in Dubai, United Arab Emirates. *Int J Neurosci* 2011; 121: 393–398.

37. AlJumah M, Bunyan R, Al Otaibi H, *et al*. Rising prevalence of multiple sclerosis in Saudi Arabia, a descriptive study. *BMC Neurol* 2020; 20: 49.

38. Deleu D, Mir D, Al Tabouki A, *et al*. Prevalence, demographics, and clinical characteristics of multiple sclerosis in Qatar. *Mult Scler* 2013; 19: 816–819.

39. Heydarpour P, Khoshkish S, Abtahi S, *et al*. Multiple sclerosis epidemiology in Middle East and North Africa: a systematic review and meta-analysis. *Neuroepidemiology* 2015; 44: 232–244

40. Alroughani R, Ahmed S, Behbahani R, *et al*. Increasing prevalence and incidence rates of multiple sclerosis in Kuwait. *Mult Scler* 2014a; 20: 543–547.

41. Alroughani R, Hamdan F, Shuaibi F, *et al*. The prevalence of multiple sclerosis continues to increase in Kuwait. *Mult Scler Relat Dis* 2019; 32: 74–76.

42. Al-Hashel J, Besterman AD and Wolfson C. The prevalence of multiple sclerosis in the Middle East. *Neuroepidemiology* 2008; 31: 129–137.

43. Tharakan JJ, Chand RP and Jacob PC. Multiple sclerosis in Oman. *Neurosciences* 2005; 10: 223–225.

44. Al Nowais S. Breakthrough multiple sclerosis drug brings hope to UAE's high population of MS patients. *The National*, February 25, 2018.

45. Alowayesh M, Ahmed S, Al-Hashel J, *et al*. Economic burden of multiple sclerosis on Kuwait health care system. *PLoS One* 2019; 14: e0216646.

46. Ernstsson O, Gyllensten H, Alexanderson K, *et al*. Cost of illness of multiple sclerosis - a systematic review. *PLoS One* 2016; 11: e0159129.

47. Aljumah M, Alroughani R, Alsharoqi I, *et al*. Future of management of multiple sclerosis in the middle east: a consensus view from specialists in ten countries. *Mult Scler Int* 2013; 2103.

48. Havrdova E, Horakova D and Kovarova I. Alemtuzumab in the treatment of multiple sclerosis: key clinical trial results and considerations for use. *Ther Adv Neurol Disord* 2015; 8: 31–45.

49. Cohen J, Coles A, Arnold D, *et al*. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing–remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012; 380: 1819–1828.

50. Coles A, Twyman C, Arnold D, *et al*. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet* 2012; 380: 1829–1839.

51. Singer B, Alroughani R, Brassat D, *et al*. Durable improvements in relapse and disability outcomes over 7 years with alemtuzumab in CARE-MS II patients: results from the TOPAZ study. ACTRIMS/ECTRIMS. 2017. *Presented at the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum*, 1–3 February 2018, San Diego, CA, USA.

52. Ziemssen T and Thomas K. Alemtuzumab in the long-term treatment of relapsing-remitting multiple sclerosis: and update on the clinical trial evidence and data from the real world. *Ther Adv Neurol Disord* 2017; 10: 343–359.

53. European Medicines Agency. *Measures to minimise risk of serious side effects of multiple sclerosis medicine Lemtrada*, https://www.ema.europa.eu/en/medicines/human/referrals/lemtrada (2020, accessed 2 March 2020).

54. Azevedo C, Kutz C, Dix A, *et al*. Intracerebral haemorrhage during alemtuzumab administration. *Lancet* 2019; 18: P329–P331.

55. Food and Drug Administration. *FDA warns about rare but serious risks of stroke and blood vessel wall tears with multiple sclerosis drug Lemtrada (alemtuzumab)*, https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-serious-risks-stroke-and-blood-vessel-wall-tears-multiple-sclerosis-drug (2018, accessed 17 May 2020).

56. CAMMS223 Trial Investigators, Coles AJ, Compston DA, *et al*. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *N Engl J Med* 2008; 359: 1786–1801.

57. Wray S, Havrdova E, Snydman D, *et al*. Infection risk with alemtuzumab decreases over

time: pooled analysis of 6-year data from the CAMMS223, CARE-MS I, and CARE-MS II studies and the CAMMS03409 extension study. *Mult Scler J* 2019; 25: 1605–1617.

58. Sheikh-Taha M and Corman LC. Pulmonary Nocardia beijingensis infection associated with the use of alemtuzumab in a patient with multiple sclerosis. *Mult Scler* 2017; 23: 872–874.
59. Rau D, Lang M, Harth A, *et al*. Listeria meningitis complicating alemtuzumab treatment in multiple sclerosis—report of two cases. *Int J Mol Sci* 2015; 16: 14669–14676.
60. Penkert H, Delbridge C, Wantia N, *et al*. Fulminant central nervous system nocardiosis in a patient treated with alemtuzumab for relapsing-remitting multiple sclerosis. *JAMA Neurol* 2016; 73: 757–759.
61. Metz I, Rieckmann P, Kallmann BA, *et al*. Disseminated necrotizing leukoencephalopathy eight months after alemtuzumab treatment for multiple sclerosis. *Acta Neuropathol Commun* 2016; 4: 81.
62. Alroughani R, Inshasi J, Deleu D, *et al*. An overview of high-efficacy drugs for multiple sclerosis: Gulf region expert opinion. *Neurol Ther* 2019; 8: 13–23.
63. Sanofi Genzyme. Lemtrada *Alemtuzumab 12 mg* Value Proposition. (2019) UAE-MOHAP.
64. Charles P, Reynolds R, Seilhean D, *et al*. Re-expression of PSA-NCAM by demyelinated axons: an inhibitor of remyelination in multiple sclerosis? *Brain* 2002; 125: 1972–1979.
65. Kuhlmann T, Miron V, Cui Q, *et al*. Differentiation block of oligodendroglial progenitor cells as a cause for remyelination failure in chronic multiple sclerosis. *Brain* 2008; 131: 1749–1758.
66. Alroughani R, Altintas A, Al Jumah M, *et al*. Pregnancy and the use of disease-modifying therapies in patients with multiple sclerosis: benefits versus risks. *Mult Scler Inter.* 2016;2016:1034912.
67. Rog D, Chambers C, McCombre P, *et al*. Pregnancy outcomes in alemtuzumab-treated patients with RRMS. *J Neurol Neurosur PS* 2016; 87: 63-e1.
68. Malucchi S, Capobianco M, Lo Re M, *et al*. High-risk PML patients switching from natalizumab to alemtuzumab: an observational study. *Neurol Ther* 2017; 6: 145–152.
69. Alping P, Frisell T, Novakova L, *et al*. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. *Ann Neurol* 2016; 79: 950–958.
70. Berger T, Elovaara I, Fredrikson S, *et al*. Alemtuzumab use in clinical practice: recommendations from European multiple sclerosis experts. *CNS Drugs*. Epub ahead of print 23 November 2016. DOI: 10.1007/s40263-016-0394-8.
71. Alroughani R, Behbehani R, Ahmed S, *et al*. The use of alemtuzumab in multiple sclerosis patients in a clinical setting, Kuwait experience. *J Neurol Sci* 2017; 381: 235.