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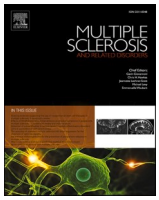

Latin American consensus recommendations on the risk of infections in people with multiple sclerosis treated with disease modifying drugs

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ABSTRACT

Introduction: The emergence of several therapeutic options in multiple sclerosis (MS), which significantly modify the immune system functioning, has led to the need for the consideration of additional factors, such as risk of infections, in the decision-making process. The aim of these consensus recommendations was to discuss and perform a practical guide to Latin American neurologists on the risk of infections at diagnosis, follow-up and prior to initiation of DMDs.

Methods: A panel of Latin American neurologists, experts in demyelinating diseases and dedicated to management and care of MS patients, gathered during 2021 and 2022 to make consensus recommendations on the risk of infections in PwMS treated with DMDs in Latin America. The RAND/UCLA methodology was developed to synthesize the scientific evidence and expert opinions on health care topics and was used for reaching a formal agreement.

Results: Recommendations were established based on relevant published evidence and expert opinion, focusing on: 1- baseline infection disease and vaccination status; 2- opportunistic infections; 3- progressive multifocal leukoencephalopathy; 4- genitourinary system infections; 5- respiratory tract infections; 6- digestive system infections, 7-others local infections and 8- COVID-19.

Conclusion: The recommendations of this consensus seek to optimize the care, management and treatment of PwMS in Latin America. The standardized evidence-based care of pwMS infections will allow better outcomes.

Abbreviations: DMD, disease modifying therapy; DMF, dimethyl fumarate; PML, progressive multifocal leukoencephalopathy; MRI, magnetic resonance imaging; DWI, Diffusion-weighted imaging sequence; GA, glatiramer acetate; JCV, JC (John Cunningham) virus; RTIs, Respiratory tract infections; TB, tuberculosis; LTBI, latent tuberculosis infection; TST, tuberculin skin test; IGRA, interferon gamma release assay; GI, gastrointestinal; EBV, Epstein Baar Virus; HHV6, herpes simplex virus type 6; HHV8, herpes simplex virus type 8; CMV, cytomegalovirus.

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1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease of the central nervous system (CNS), it being the most common cause of non-traumatic neurological disability in young adults (Reich et al., 2018). Previous studies have suggested that people with MS (PwMS) have an increased risk of more severe infections with a greater need for specialized hospital care as well as a higher mortality rate when compared with the general population (Castelo-Branco et al., 2020; Marrie et al., 2014; Montgomery et al., 2013; Persson et al., 2020; Smestad et al., 2009; Wijnands et al., 2017) Some infections such as urinary or respiratory tract have also been reported with high prevalence in PwMS, particularly those with greater scores of disability(Jick et al., 2015; Montgomery et al., 2013; Persson et al., 2020; Pirttisalo et al., 2018; Pirttisalo et al., 2020).

The rapidly expanding armamentarium of disease modifying drugs (DMDs) has modified the neurological approach to the management of PwMS (Reich et al., 2018). The emergence of several therapeutic options, which significantly modify the immune system functioning, combined with patients age and the unpredictable course of the disease have led to the need for the consideration of additional factors associated with safety, in particular risk of infections (Moiola et al., 2021; Papeix et al., 2021a; Tur et al., 2022) [10-12]. Latin America is especially vulnerable to suffer from endemic infectious diseases and those with epidemic and pandemic potential due to healthcare infrastructure that has limited capacity and is highly variable within the region (Kenneth B. Yeh, 2021). The Latin American region has extensive microbial diversity and is endemic for a wide array of infectious agents. Furthermore, this region is at particularly high risk of emerging and re-emerging infectious diseases as evidenced by the increased number of disease events of potential international public health concern (Kenneth B. Yeh, 2021). In this regard, regional endemic and prevalent infections should also be considered when selecting a therapeutic strategy in order to minimize DMD-related risk, ensuring that PwMS can receive optimal and timely therapies (Du Pasquier et al., 2014). Additionally, understanding and knowing the mechanisms of action of DMDs is also critical to make an appropriate decision (Du Pasquier et al., 2014; Moiola et al., 2021). In this line, neurologists should make a careful, detailed medical and epidemiological history-taking along with a complete physical examination to have a holistic view of PwMS. Furthermore, multidisciplinary health professionals such as neurologists, infectious disease specialists, pulmonologists, among others, must work together to minimize infection risk in this population (e.g. updating their vaccination schedule at the beginning). While serious infections related to DMDs have rarely been reported in clinical trials and real-world setting, some of these are potentially fatal (Dong-Si et al., 2015; Vermersch et al., 2011). Currently, understanding the risks related to DMDs used to treat PwMS is of paramount importance and infection risk assessment should be considered as a continuum for the management of PwMS.

The management of PwMS is complex and challenging in clinical practice. Neurologists must face new challenges regarding the management of immunosuppression-related infectious complications. Therefore, different local and regional factors should be considered when recommending how PwMS should be followed and managed in order to determine the most appropriate DMD.

The goal of these consensus recommendations was to discuss and perform a practical guide to Latin American neurologists on the risk of infections (at diagnosis, follow-up and prior to initiation of DMDs), in a vulnerable region where barriers and unmet needs are highly prevalent in term of access to MS care (Carnero Contentti et al., 2020; Carnero Contentti et al., 2019).

2. Methods

An expert panel of Latin American neurologists dedicated to MS care (diagnosis, management and treatment) gathered virtually during 2021 and 2022 to conduct a consensus recommendation guideline on the risk of infections in PwMS treated with DMDs in the region. Although the precise definition for an experienced neurologist in MS is ambiguous; a Latin American panel has recommended its definition recently. Neurologists who have more than 3 years in the care of PwMS, have followed $\geq$100 or more PwMS, and have diagnosed $\geq$15 new patients per year are considered expert or experienced in MS. To achieve this consensus, the "formal consensus RAND/UCLA appropriateness method" was used (Cristiano et al., 2021; Kathryn Fitch, 2010).

The methodology to develop practice guidelines by formal consensus is both a consensus and a guideline method. As a consensus method, the goal is to establish the degree of agreement among MS expert neurologists by identifying and selecting, through iterative ratings with feedback, the statements on which experts agree and those situations on which they disagree or are undecided. The guideline method is subsequently based on agreement statements. As a practice guideline method, the goal is to establish concise and unambiguous recommendations that address the questions of interest. Thus, providing healthcare professionals and patients with assistance in deciding on the most appropriate care in different clinical scenarios. "RAND/UCLA appropriateness method" is a rigorous and explicit method based on the involvement of representatives and professionals in the field to which the guideline relates, as well as on the use of an external peer-review phase, transparency, independence of development, and conflicts of interest management.

The steering committee defined the topic of the work "infections and MS in Latin America region" and a rigorous analysis based on a systematic review of relevant articles was made. The first step in the process consisted of inclusion of a working group of MS experts in Latin America. Neurologists were identified through the Latin American Committee for Treatment and Research in MS (LACTRIMS) database, and they were selected by their experience in managing PwMS. MS experts from different regions of Latin America such as Argentina, Chile, Paraguay, Colombia, Brazil, Ecuador, Panama and México were invited to participate. The working group was then divided as follows: 1) a steering group and project manager (BS, PL, ECC, RA) 2) a rating group of neurologist who, in their daily practice, are directly involved in MS care (BS, PL, ECC, RA, JB, PCD, OG, LG, FG, FH, MAM, CN, JIR) and 3) infectious disease specialists with expertise in the MS field (JIC, SN). After the working group was conformed, the procedure consisted of the following phases:

2.1. Review and synthesis of the literature phase

A non-language restricted literature search was conducted using several online databases including MEDLINE and EMBASE for the period 1990-2021.

A detailed review of the existing peer-reviewed literature on infections, MS and DMTs was conducted using PubMed and Scopus. We identified and triaged relevant manuscripts based on the following criteria: peer- reviewed, full text and English and Spanish language manuscripts. Members of the steering group met to discuss the evidence and to develop the list of statements to be submitted to the rating group. Relevant and latest clinical papers were distributed to the working group so that they could answer the statements and recommendations of discussion.

2.2. Development of statements list

78 statements were developed by the steering group and then submitted to the rating group in the form of a questionnaire. At this stage the statements complemented or contradicted each other insofar as they considered all opinions expressed by the group members during the work sessions. Each questionnaire was then divided into sections that related to: 1- baseline infection disease and vaccination status.; 2- opportunistic infections; 3- Progressive Multifocal

Leukoencephalopathy (PML); 4- genitourinary system infections; 5- respiratory tract infections; 6- digestive system infections, 7- others local infections and 8- COVID-19. The questionnaires were written in an English version only.

2.3. Rating phase

This phase was conducted in two stages: in the first one the statements on which members of the rating group agreed were identified. For those statements on which there was no agreement or answers were inconclusive, two rounds of votes were performed with feedback sessions based on the published evidence and discussion in real-time by teleconference. After the first round and the meeting with the panel of experts, four statements did not reach consensus initially. In the second round, three of them were reworded and two reached consensus. In this round two new additional statements were formulated to clarify inconclusive answers, and both achieved consensus. The rating phase finished with the selection of the statements on which there was consensus within the rating group and statements without agreement after the final round are shown in a **supplementary material.** Consensus was defined when ≥70% of the MS experts agreed, and lack of consensus when ≥30% disagreed. The methodology for the rating and the analysis of the scores were defined initially and communicated to the rating group during the invitation phase via email and prior to start the first round of this consensus, after members of this panel accepted participating via email. At every stage of the rating phase, members of the rating group were able to comment about their response on any statement. All the comments performed were also analyzed in a qualitative way to be added if appropriate.

2.4. Drafting the initial version of the guideline phase

The steering group and the project manager wrote the first manuscript version of the consensus recommendation to be submitted to the peer review group based on the consensus statements. The latest version of the manuscript was also reviewed and validated by an external peer-review with expertise in this subject (MF).

2.5. Peer review phase

An analytical report was writing, drawing along with all scores and comments of the peer review group members and, where applicable, of the participants in the public consultation.

2.6. Finalization phase

The final version of the evidence reports, the consensus recommendations, and a summary of the guideline were drawn. The validated versions of these documents were shared. Thus, all authors provided their final approval for the manuscript.

3. RESULTS

3.1. Baseline infection disease and vaccination status

With a unanimous decision, it is considered that all patients should be assessed at the time of MS diagnosis, in order to detect conditions related to their personal and family history, previous to MS, that generates susceptibility to infections in a higher proportion than that of the general population. Additionally, this first evaluation should include serological status for HIV Ab, hepatitis B and C virus (HBsAg, HBcAb, HBsAb, HCVAb), VZV IgG, toxoplasma IgG, measles IgG, rubella IgG, syphilis (VDRL, FTAbs), and Chagas as well as PPD for TB. Based on these results and previous vaccination status, PwMS should complete immunization against influenza, pneumococcus, HPV, HAV and HBV, tetanus, measles, rubella, and mumps, COVID-19 and VZV. It is strongly recommended that this serological status should be reassessed before each DMDs change (Moiola et al., 2021).

Furthermore, in MS women, given the observed risk of cervical dysplasia and neoplastic diseases under alemtuzumab, fingolimod and natalizumab treatments gynecological control is recommended [(Rolfes et al., 2013; Triplett et al., 2019; Willis et al., 2016). In addition, it is considered important that PwMS seek for advice from an infectious disease specialist when planning a trip, depending on local regulations of destiny (Table 1).

3.2. Consensus statements for opportunistic infections

It is controversial that MS per se may pose a higher risk of opportunistic infections. Increasing evidence, based on nationwide data collection, showed that PwMS are at a higher risk of infections in comparison to the general population (Ghaderi et al., 2020; Persson et al., 2020; Wijnands et al., 2017)

Regarding the use of DMTs, beta-interferons, glatiramer acetate and teriflunomide do not increase the risk on infections as demonstrated by both phase 3 trials and observational studies in each case (The IFNB Multiple Sclerosis Study Group, 1993; The IFNB Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group, 1995b; PRISMS, 1998; Calabresi et al., 2014a; Comi et al., 2012; Confavreux et al., 2014; Ford et al., 2006; Jacobs et al., 1996; Johnson et al., 1995; Johnson et al., 2000; O'Connor et al., 2011; Vermersch et al., 2014; Wijnands et al., 2017; Wijnands et al., 2018)

Additionally, many authors consider that DMF could lead to infections only if associated with treatment-related lymphopenia or neutropenia (Gold et al., 2017; Kim et al., 2021). On the other hand, only patients on fingolimod, natalizumab, alemtuzumab, ocrelizumab, rituximab, and cladribine should be considered at risk of opportunistic infections (Calabresi et al., 2014b; Cohen et al., 2010; Coles et al., 2012; Chisari et al., 2022; Giovannoni et al., 2010; Giovannoni et al., 2018; Hauser et al., 2017; Luna et al., 2020; Montalban et al., 2017; Polman et al., 2006; Wray et al., 2018).

3.2.1. Viral infections

HSV and VZV infections should be considered, particularly in patients on fingolimod, natalizumab, alemtuzumab, cladribine. The incidence of VZV infection reported in trials and in post marketing studies in PwMS on fingolimod is 11 per 1000 patients, which corresponds to a low level of risk [0.1% et 1%]. It is strongly recommended to perform a VZV immune status assessment before initiating fingolimod therapy and immunization for patients susceptible to primary VZV infection should be indicated. Routine antiviral prophylaxis is not routinely recommended, whereas clinical surveillance and patient education to identify early VZV symptoms are important to allow timely antiviral treatment (Arvin et al., 2015). HSV encephalitis and meningitis were reported in natalizumab treated patients (Kwiatkowski et al., 2012; Sharma et al., 2013). Additionally, VZV radiculitis and meningovasculitis were also reported in patients on natalizumab (Fragoso et al., 2013; Mulero et al., 2018). Of note, HSV infection is one of the most common infections

Table. 1
Baseline infection disease and vaccination status suggested by panel.

Medical history	**childhood diseases, travel history, personal, familial or labor potential sources of infection, search for possible immune deficiencies (e.g., asplenia, DBT)**
Baseline serologic evaluation	**HIV Ab, epatitis B and C virus (HBsAg, HBcAb, HBsAb, HCVAb), VZV IgG, toxoplasma IgG, measles IgG, ubella IgG, syphilis (VDRL, FTAbs), Chagas PPD for TB**
Vaccination/ immunization status	**influenza, pneumococcus, HPV, hepatitis A and B (based on previous serologic evaluation), tetanus, measles, rubella, and mumps, COVID-19 VZV (based on previous serologic evaluation).**

associated with alemtuzumab treatment. In clinical trials, this infection was increased several folds due to T-cell lymphopenia (Coles et al., 2021; Coles et al., 2012). Despite this, long-term data demonstrated that the risk of infections does not increase with subsequent new treatment courses and over time (Coles et al., 2021). All patients on alemtuzumab with grade IV lymphopenia should receive acyclovir prophylaxis 200-400 mg twice a day. Prophylaxis may be discontinued once CD4 count is 200 or higher and not earlier than 28 days after alemtuzumab treatment completion (Buonomo et al., 2018). Regarding cladribine, VZV infection are not very frequent, but more frequent than with placebo (Giovannoni et al., 2010). Therefore, performing a VZV immune status assessment before starting treatment is also recommended. Furthermore, acyclovir prophylaxis should be considered in patients with grade IV lymphopenia (Cook et al., 2019; Klotz et al., 2019). Robuster evidence for acyclovir prophylaxis in patients on fingolimod and DMF is still needed, but it can be considered in recurring cases of herpes infection. Other opportunistic infections by EBV, HHV6, HHV8 are not increased in DMD-treated PwMS. CMV infections were reported in alemtuzumab treated patients, mainly associated with lymphopenia (Aguirre et al., 2019; Clerico et al., 2017; Eichau et al., 2020).

3.2.2. Fungal infections

Mucocutaneous candidiasis has also been observed in patients on fingolimod, natalizumab, rituximab, ocrelizumab and alemtuzumab. Its manifestations should be monitored to establish timely therapy (Boulton et al., 2012; Coles et al., 2012; Epstein et al., 2018; Gutwinski et al., 2010; Winkelmann et al., 2016).

Cryptococcal infection should be considered especially in patients older than 50 years of age and/or treated with fingolimod for longer than 2 years (Chong et al., 2019; Grebenciucova et al., 2016; Wienemann et al., 2020).

3.2.3. Bacterial infections

Listeria monocytogenes infections were reported in patients under alemtuzumab treatment (Buonomo et al., 2018; Mazzitelli et al., 2020; Rau et al., 2015). Consumption of foods potentially contaminated by Listeria monocytogenes (i.e., unpasteurized dairy products, cream cheeses, Brussels sprouts and celery; raw meat and fish; cured meats, especially if stuffed/ground) should be avoided at least 1 month before and for 1 month after the course of alemtuzumab and antimicrobial chemoprophylaxis should be considered (Holmoy et al., 2017; Mazzitelli et al., 2020). In case of a life-threatening opportunistic infection, the discontinuation of the DMD treatment must be rapidly considered.

3.3. Progressive multifocal leukoencephalopathy (PML)

PML is a rare, debilitating and often fatal disease of the CNS caused by JC virus (JCV). JCV establishes asymptomatic, lifelong persistent or latent infection in immune competent hosts, but impairment of cellular immunity can lead to reactivation of JCV and PML. PML most commonly occurs in patients with HIV infection or lymphoproliferative disease (i.e., immunosuppressed patients). On the other hand, many immunosuppressive drugs represent a risk factor for its development. MS does not pose a higher risk per se, while DMDs account for less than 5% of all PML cases; the relative risk attributable to each individual treatment is highly variable (Cortese et al., 2021; Tur et al., 2022). PwMS treated with beta interferons or GA are not at risk of developing PML. Patients on alemtuzumab, teriflunomide, cladribine, rituximab and ocrelizumab have virtually no risk of PML, as no or isolated cases have been reported in PwMS on theses DMDs (Berger et al., 2013; Gerevini et al., 2019; Kim et al., 2021; Major et al., 2018; Patel et al., 2021; Tur et al., 2022; Winkelmann et al., 2016). The PML risk in PwMS treated with fingolimod or DMF is low, and other factors such as older age and persistent lymphopenia might play a relevant additional role (Berger et al., 2018; Jordan et al., 2022). In this line, PwMS on DMF and moderate-severe prolonged lymphopenia for longer than 6 months should be considered at increased risk of developing PML (Kim et al., 2021).

The current DMD with the highest intrinsic PML risk is natalizumab, with an overall incidence of about 4 cases per 1000 treated patients. Duration of natalizumab treatment, particularly longer than 2 years, anti-JCV antibody-positive status and index score, and prior classic immunosuppressive therapy are all well-known risk factors for the development of PML (Major et al., 2018; Schwab et al., 2017; Toboso et al., 2020). Consequently, multiple strategies have been developed and implemented over the years in order to mitigate PML risk. Unlike patients on fingolimod or DMF, those treated with natalizumab must have a baseline risk assessment with JCV antibody testing and index estimation. Patients with negative JCV antibody tests or with an index < 1.5 should be reassessed every 6 months (Epstein et al., 2018; McGuigan et al., 2016).

As MRI is the most effective surveillance method for the detection of asymptomatic PML, patients at higher risk should undergo an MRI scan that includes DWI, FLAIR, T2, T1 and T1 after gadolinium sequences every 4 to 6 months (Ho et al., 2017; Major et al., 2018).

If any radiological or clinical evidence of PML is detected, ultrasensitive JCV-DNA PCR testing in cerebrospinal fluid (CSF) is recommended. Should this test result negative, a brain biopsy must be considered (Berger et al., 2013; Major et al., 2018). DMDs should be immediately discontinued if manifestations of PML are detected.

3.4. Genitourinary system

MS does not increase risk of HPV infection and progression to preinvasive or invasive disease. However, several cases of cervical dysplasia have been described in PwMS on DMDs, especially alemtuzumab (Buonomo et al., 2018; Willis et al., 2016). A few cases have been reported in patients on natalizumab and fingolimod (Durrieu et al., 2019; Rolfes et al., 2013; Triplett et al., 2019). Because of this, all women with MS on DMD should be referred to a gynecologist for cervical screening, and adherence to HPV vaccination schemes should be recommended (Buonomo et al., 2018).

Due to bladder dysfunction, PwMS have an increased risk of UTIs. Regarding DMDs, only alemtuzumab showed a higher risk of UTIs compared to beta - interferon in clinical trials (Investigators et al., 2008; Wray et al., 2018).

3.5. Respiratory tract infections (RTIs)

There is great variability in the incidence of RTIs reported in PwMS on different DMDs. While RTIs in patients on interferons, glatiramer acetate, DMF or teriflunomide have shown in clinical trials to be less frequent than those in patients who received placebo or a comparator agent, patients on fingolimod, cladribine, natalizumab, alemtuzumab or ocrelizumab have had a higher incidence of RTIs when compared to those on placebo or other DMDs (Calabresi et al., 2014b; Cohen et al., 2012; Coles et al., 2012; Goodman et al., 2009; Hauser et al., 2017; Investigators et al., 2008; Kappos et al., 2011; Montalban et al., 2017; Riva et al., 2021; Tzelepis and McCool, 2015). Ocrelizumab showed a particularly higher associated incidence of RTIs when compared with placebo in patients with (primary progressive MS (PPMS) (Montalban et al., 2017), whereas this difference in incidence was not as marked when compared with that of ocrelizumab vs. interferon in patients with RMS (Hauser et al., 2017). Patients with progressive phenotypes and higher EDSS scores are at higher risk of RTIs and respiratory complications (Tzelepis and McCool, 2015).

The reported incidence of TB in PwMS on DMDs is low. There have been only a few cases of TB in PwMS patients on teriflunomide, alemtuzumab or cladribine in the context of RCTs. However, patients starting treatment with theses DMDs should be screened for latent TB infection, especially in Latin American patients where prevalence is higher than other areas (WHO, 2015) The information on the risk of TB in patients on ocrelizumab is scares, and other DMDs, such as beta interferons, GA,

DMF, fingolimod, natalizumab and rituximab do not seem to pose a significant higher risk of TB infection. Nevertheless, it would be appropriate to screen all patients about to start any DMD as the future need for a switch for riskier drugs cannot be fully estimated at treatment initiation and delays on the effective immunosuppressant treatments should be avoided (Epstein et al., 2018; Klotz et al., 2019; Suh et al., 2014; Winkelmann et al., 2016).

The diagnostic method of choice for latent TB infection detection in the region, due to costs and availability, is tuberculine skint test (TST), also known as purified protein derivative (PPD) test. Test results should be interpreted with caution in patients already on DMDs, those who are immunosuppressed, immunocompromised or have a history of TB vaccination, due to low sensitivity and/or specificity of the method in these subgroups. Interferon-γ release assay (IGRA) is a reasonable option in these situations (WHO, 2015; Lewinsohn et al., 2017), but its availability is low in Latin American countries.

Patients with positive screening test results should be referred to infectious disease specialists and/or pulmonologists in order to undergo further investigations and either confirm a latent TB infection or diagnose a TB active infection (WHO, 2015; Lewinsohn et al., 2017). Patients on DMDs should stop their treatment until the final diagnosis is reached and the course of action decided. If latent TB infection is confirmed, preventive therapy should be considered and prescribed by a specialist before starting, resuming, or switching DMD treatment. In cases of active TB, patients should receive the full and appropriate TB treatment scheme (WHO, 2015).

In cases of latent TB infection, treatment with DMDs may be started or resumed simultaneously with preventive therapy. Disease activity, immunosuppression degree of the DMD and risk of hepatotoxicity of combined treatment must be all taken into consideration. Patients with highly disease activity might initiate both therapies simultaneously, choosing preferably a DMD with a low risk of hepatotoxicity. If DMD initiation can postponed, it may be starter after one or two month of preventive TB therapy. In patients with active TB, DMDs might be started after at least two months of anti-TB treatment, based on evidence in patients with rheumatoid arthritis and immunosuppressive treatment (Grebenciucova and Pruitt, 2017; Ozguler et al., 2016; Suh et al., 2014).

Pneumocystis jirovecii pneumonia can cause life-threatening pneumonia in immunocompromised patients. This entity has been described in PwMS on alemtuzumab and in patients receiving corticosteroids in high doses or for prolonged periods. Prophylaxis should be considered in patients under treatment with both drugs simultaneously (Candel et al., 2020; Catherinot et al., 2010; Lau et al., 2020).

3.6. Digestive system

PwMS on beta-interferons, GA, teriflunomide, natalizumab, cladribine or ocrelizumab do not have an increased risk of gastroenteritis. However, PwMS on DMF or alemtuzumab may have an increased risk of severe gastroenteritis (Coles et al., 2012; Gold et al., 2012; Investigators et al., 2008). Additionally, PwMS on all DMDs should be counseled by an infectious disease specialist on their eating and travelling habits to prevent foodborne infections.

Infections with HBV and HCV should also be considered. PwMS naïve for treatment or on DMDs do not have an increased risk of infections with HBV or HCV. Since reports of HBV/HVC reactivation have been published in patients on corticosteroids, rituximab and ocrelizumab, infectious evaluation prior to initiation of treatment with these drugs is strongly recommended (Ciardi et al., 2019; Epstein et al., 2018; Shouval and Shibolet, 2013). Screening should include HBsAg, HBcAb, HBsAb and HCVAb. All patients positive for any of these markers should be referred to a specialist, except for HBV vaccinated patients with isolated HBsAb reactivity. PwMS with acute or chronic HBV or HCV infections should be managed according to international guidelines by an infectious disease specialist and/or a hepatologist to decide about DMD (European Association for the Study of the Liver. Electronic address and European Association for the Study of the, 2017, 2018; Moiola et al., 2021; Tur et al., 2022)

3.7. Other regional infections

Insufficient data are available to consider PwMS with or without DMD on a higher risk of having tropical emergent infections, such as leishmaniasis, Chagas disease, malaria, arbovirosis, yellow fever, leprosy, paracoccidioidomycosis, disseminated strongyloidiasis, and ectoparasitosis (Alonso and Galleguillos, 2021; Fragoso et al., 2016; Guerra et al., 2021; Ringer et al., 2021; Shu Kurizky et al., 2020). Furthermore, there are no association between worse prognosis of dengue fever and DMD treatment in patients on fingolimod, natalizumab and ocrelizumab (Alonso and Galleguillos, 2021; Fragoso et al., 2016; Guerra et al., 2021).

In spite of this, we recommend (see 3.1) to perform serological status to Chagas, taking into account the case reports of Chagas reactivation in immunosuppressed patients (Bartalesi et al., 2017; Pinazo et al., 2013).

On the other hand, disseminated strongyloidiasis is related to corticosteroids use. Accordingly, stool studies to search for strongyloidiasis, prior to the start of DMD and corticosteroids treatment, should be considered (Shu Kurizky et al., 2020).

Regarding yellow fever, vaccination against it is currently recommended for people older than 9 months who live in or plan to visit to many different regions within several LATAM countries (Chen and Wilson, 2020). Moreover, some studies show a re-emergence of yellow fever in the neotropics and suggest approaches to better predict and control future emergence events (Sacchetto et al., 2020). Even though preliminary data suggested that PwMS who were vaccinated against yellow fever might present an increase in their MS relapse rate (Farez and Correale, 2011), newer evidence indicates that yellow fever vaccination does not worsen the course of RRMS (Huttner et al., 2020; Papeix et al., 2021b). On the other hand, many PwMS receive immunosuppressant drugs as DMDs, and as a consequence, live-attenuated vaccines are contraindicated. In those cases, people living in or planning to move to areas at risk for yellow fever virus should be vaccinated before starting a DMD. As to travelers, depending on specific patient travel plans, potential local epidemics, and length of stay, the final decision on whether to administer the vaccine should result from a careful assessment of the DMD mechanism of action, the necessity of traveling and the likelihood of exposure to the yellow fever virus (de Jong et al., 2019).

3.8. COVID-19

MS is not a risk factor *per se* for severe COVID-19. The evidence suggests that having MS does not increase the risk of SARS-CoV-2 infection or worsen clinical outcomes compared to those without MS (Evangelou et al., 2020; Parrotta et al., 2020). Most studies about COVID-19 outcomes in PwMS showed that the risk factors for severe COVID-19 infection identified in the general population (older age, obesity, male sex, cardiovascular diseases) were also valid for PwMS (Louapre et al., 2020a; Louapre et al., 2020b; Sormani and Italian Study Group on, 2020). However, a higher MS disability status was identified as a predictive negative factor influencing the neurological outcome and PwMS with progressive forms are at higher risk of a worse COVID-19 outcome (Arrambide et al., 2021; Michelena et al., 2022).

Regarding DMD role, data showed that interferons, GA, teriflunomide, DMF, fingolimod, natalizumab, cladribine and alemtuzumab do not pose an increased risk of poor COVID-19 evolution. On the other hand, rituximab and ocrelizumab treatments could be associated with higher COVID-19 severity and an increased frequency of Intensive Care Unit admission, although there was not association with a higher mortality (Alonso et al., 2021; Sormani et al., 2021). On the other hand, during COVID-19 symptomatic infection, suspension or postponement of cladribine, natalizumab, ocrelizumab and alemtuzumab treatments are recommended (Giovannoni et al., 2020).

Currently, all PwMS, on any DMD treatments, must be vaccinated with a complete COVID-19 vaccine schedule (Cabreira et al., 2021; Tur et al., 2022).

4. Conclusion

Due to the increase in the number of DMDs, management of PwMS has become more complex and challenging in clinical practice. Local and regional factors should be considered when recommending how PwMS should be managed and treated. The recommendations of this consensus seek to optimize the care, management and treatment of PwMS in Latin America.

Author statement

BAS, PAL, ECC and RA developed the idea and participated in the LACTRIMS grant application. BAS and PL developed the statements, browsed the references, and wrote/revised the manuscript. ECC and RA developed the statistics and methodology and reviewed the statements and manuscript. All authors voted on the statements and reviewed the manuscript

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Declaration of Competing Interest

BAS has received personal compensation for consulting, congresses, serving on a scientific advisory board, speaking, or other research activities with Biogen-Idec, Genzyme, Merck-Serono, Novartis, Teva, Roche, Bristol Myers Squibb, LACTRIMS, International Society For Neurochemistry, International Brain and Research Organization. ECC has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Biogen-Idec, Genzyme, Merck-Serono, Novartis, Teva, Roche, LACTRIMS and the Guthy-Jackson Charitable Foundation. RA has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Biogen-Idec, Genzyme, Merck-Serono, Novartis, Bristol Myers Squibb, Janssen, Roche and LACTRIMS. PAL has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Biogen-Idec, Genzyme, Merck-Serono, Novartis, Bristol Myers Squibb, Raffo, Roche, Teva, and LACTRIMS. MFF has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Biogen-Idec, Merck-Serono, Novartis, Teva. MFF is CEO and co-founder of Entelai LLC. OG has received personal compensation for consulting, congresses, serving on a scientific advisory board, speaking, or other research activities with Biogen-Idec, Merck-Serono, Novartis, Roche, Bristol Myers Squibb, LACTRIMS, Synthon Bago, Raffo. Rest of the authors had nothing to disclose.

Supplementary materials

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