Management of relapsing–remitting multiple sclerosis in Latin America: Practical recommendations for treatment optimization

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A B S T R A C T

The Latin American MS Experts' Forum has developed practical recommendations on the initiation and optimization of disease-modifying therapies in patients with relapsing–remitting multiple sclerosis (RRMS). The recommendations reflect the unique epidemiology of MS and the clinical practice environment in Latin American countries. Treatment response may be evaluated according to changes in relapses; progression, as assessed by the Expanded Disability Status Scale and the Timed 25-foot Walk; and lesion number on magnetic resonance imaging. Follow-up assessments are recommended every six months, or annually for stable patients. Cognitive function should be evaluated in all RRMS patients at baseline and annually thereafter. These recommendations are intended to assist clinicians in Latin America in developing a rational approach to treatment selection and sequencing for their RRMS patients.

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1. Introduction

Relapsing–remitting multiple sclerosis (RRMS) is a chronic demyelinating disease of the central nervous system characterized by inflammation and neurodegeneration. First-generation disease-modifying therapies (interferon-β, glatiramer acetate) became available in the 1990s. While there have been no major safety concerns during continued therapy, these agents have overall modest efficacy, and the need to administer them by injection has limited patient adherence during long-term use.

Over the past decade, treatment options have expanded with the introduction of second-generation therapies, such as natalizumab, fingolimod, teriflunomide, dimethyl fumarate and alemtuzumab. While these agents require a more careful weighing of the benefits and risks of treatment due to safety issues, they enable clinicians to develop a longer term treatment plan to optimize outcomes in their patients with RRMS.

A number of groups have produced treatment recommendations [1–5], however, these do not fully address the current clinical practice environment in Latin America. Accordingly, the Latin American MS Experts' Forum convened in Buenos Aires, Argentina, in July 2013 to...
review the most recent data on clinical and radiological factors that indicate a suboptimal response to disease-modifying therapy, and to develop practical recommendations on the selection and modification of treatments to obtain the optimal outcomes for adult RRMS patients in Latin America.

2. Methods

The group conducted a systematic non-language-restricted literature search of the MEDLINE database for the period 1993–2012. Search terms were “multiple sclerosis” with the modifiers “relapse”, “progression”, “prognosis”, “MRI”, “cognition”, “vitamin D”, “neutralizing antibodies”, “treatment”, “interferon”, “glatiramer acetate”, “natalizumab”, “ fingolimod”, “teriflunomide”, “fumarate”, “Latin America” and “epidemiology”. Relevant clinical papers were distributed to working groups to review and summarize. The working groups addressed Relapses (JB, EA), MRI (EC), Progression (DV), Cognition (MAM, JGB), Other Factors affecting treatment response (PA, RB), and Clinical decision-making (RA, SAL, AS, JC, TC, FG). Key findings were presented for full-group discussion at the July 2013 meeting. As participating countries are highly heterogeneous with respect to the incidence and prevalence of RRMS, availability of specialist care, and access to diagnostic tools and individual disease-modifying therapies, core clinical questions were developed by the meeting chair (JC) to form the basis of the group’s recommendations. This was to ensure that recommendations could be implemented in the differing clinical practice environments across Latin America. Additional searches for recent data were performed during the drafting of the manuscript.

3. Multiple sclerosis in Latin America

The estimated annual incidence of MS in Latin America is 0.3 to 1.9 cases per 100,000 person-years, with prevalence rates ranging from 0.75 to 21.5 per 100,000 population [6]. The lowest prevalence is seen in Ecuador [7], and the highest prevalence is in Argentina and Uruguay [8–10]. The estimated number of people diagnosed with MS is 50,000 [11]. The increasing rate of MS reported in recent years has been attributed to improved diagnosis and more widespread availability of magnetic resonance imaging (MRI), although other factors may also be involved.

Reasons for the low incidence of MS have not been determined but may be due to genetic and/or environmental factors. The Latin America population is very heterogeneous and comprises a multi-ethnic population of approximately 600 million people of Caucasian, Amerindian and African ancestry. In addition, numerous Latin American inhabitants are mestizos, a complex admixture of Caucasian and Amerindian (mongoloid) genes. MS is reported to be uncommon among non-mixed Amerindians across the continent [16–19]. It is possible that Latin American native Amerindians are protected against MS by their mongoloid genes, as are many Canadian aboriginal and Japanese cohorts [20–22]. Alleles associated with MS risk in Latin America include DRB1*1501 (odds ratio 2.6), DQB1*0602 (OR 2.5), DRB1*15 (OR 2.3), DQB1*06 (OR 2.2) and DRB1*1503 (OR 2.2) [23]. The presence of one or more of these risk alleles varies widely among the different peoples of Latin America. The DRB1*1501 allele [24,25] is found primarily in people of Caucasian ancestry and is more prevalent in Argentina and Uruguay. African-Brazilians with MS share some European alleles associated with MS susceptibility in Caucasians and African-Caribbeans, such as DQB1*0602, but do not share the DRB*1501 allele that is common in Brazilian whites, African-Americans and Europeans [23,25–27]. DRB1*1503 is found in people of African descent, including African-Americans [25] and African-Caribbeans [26].

Not only are the genetic backgrounds of Latin American inhabitants singular. Environmental factors, such as parasitic infections, may also influence the development or course of MS by modulating the immune response [28,29]. In accordance with this hygiene hypothesis, in some regions of Latin America, exposure to environmental pathogens may act as a protective effect by suppressing the development of MS [30]. Another environmental factor influencing MS risk, vitamin D/sun exposure, will be discussed below.

The diagnosis of MS is most commonly made using the revised McDonald criteria [31,32], according to a recent survey of Latin American neurologists [3]. The differential diagnosis of MS is complex and may be challenging in clinical practice [33,34], so referral to a specialist with expertise in demyelinating disorders is recommended if local conditions permit. In addition to the usual MS mimics, an important consideration in the differential diagnosis is infectious diseases specific to Latin American regions, such as tuberculosis, brucellosis and human T-cell lymphotropic virus type-1 [3].

The presentation and clinical course of MS differ somewhat from what is seen in North American or European populations. An estimated 65.5% of subjects present with RRMS, 21.5% with secondary-progressive MS, and 13.0% with primary-progressive or relapsing–progressive disease [35]. The prevalence of the RRMS subtype in published reports varies widely, from 50% in Ecuador [7] to 91% in Brazil [36,37]. The estimated female-to-male ratio is 1.5 to 1 [35], which is substantially different than the ratio of 2.6–3.2 to 1 reported in some regions of Europe and North America [38,39].

The main presenting symptoms are motor, optic neuritis and sensory [40]. Studies in Brazil and Argentina have reported that the age of onset is somewhat older (mean 30–34 years) [41,42], which may be attributable to disease factors or diagnostic delay.

4. Treatment of RRMS

4.1. Goals of therapy

The key recommendations of the Latin American MS Experts’ Forum are listed in Table 1 and discussed below.

The main goal of therapy for RRMS is to modify the natural history of the disease, reducing inflammatory activity in the central nervous system (CNS), and preventing or slowing the progression of neurological disability. The first-generation disease-modifying therapies (DMT) include interferon-β (IFN-β)-1a administered intramuscularly or subcutaneously, IFN-β-1b administered subcutaneously, and glatiramer acetate administered subcutaneously. All target the CNS inflammation that results in demyelination and axonal damage, and are most effective when used in the earlier phases of the disease process [43,44]. Treatment is less effective in secondary-progressive MS (SPMS) [45–47], when neurodegenerative processes become more important determinants of disability progression than inflammation. Second-generation therapies used to treat relapsing MS include natalizumab, administered by intravenous infusion, and the oral agents fingolimod and teriflunomide; none has been studied in SPMS. These treatments also act primarily on the inflammatory component of the MS disease process. Thus, there is a limited window of opportunity to influence the MS disease process and prevent the accumulation of disability [48]. Dimethyl fumarate and alemtuzumab are not available in Latin America at the time of writing.

The optimal approach to therapy is to select an agent with a favorable risk/benefit profile [3,49]. IFN-β and glatiramer acetate have been shown to be remarkably safe during continued dosing [50–52]. However, several analyses have concluded that these therapies have modest or no effect on disability progression during long-term use [53–55], even when treatment is started earlier in patients with clinically isolated syndrome (CIS) [56,57]. Prolonged exposure to IFN-β drugs may be associated with somewhat better long-term outcomes [58,59], but this may be difficult to achieve in clinical practice due to the low rates of treatment compliance [60].
more robust response to natalizumab or analyses have suggested that people of African descent may have a time between relapses [67,68], both of which may re

5. Treatment initiation

Patient’s innate CNS repair mechanisms. An incomplete recovery as

There are some data to suggest that response to IFN β–1a influenced by clinical and patient-specific factors, and guided by patient preferences that will influence adherence to treatment. Since there is a limited time window in which to act, a more aggressive approach is advised for patients presenting with more active disease at onset. As the treatment course is likely to involve more than one agent, the optimal initial treatment will be one that does not limit subsequent therapeutic options.

When initiating treatment, the optimal approach is to consider the relative efficacy of treatments with respect to reducing relapse frequency and severity, disability progression, and new MRI activity; safety and tolerability; and the convenience of dosing, which will influence the likelihood that the patient remains on therapy.

IFNβ-1a and glatiramer acetate have been commonly employed as initial treatments. However, they have modest efficacy in reducing the inflammatory component of the disease and limited impact on long-term disease progression [53–55]. On the other hand, while their long-term safety has not been systematically assessed, no major safety concerns have been observed to date. Treatment non-response has been reported to be as high as 49%, depending on the criteria used [79]. Similarly, up to 42.9% of patients in a Brazilian cohort were non-responders to IFNβ-1a and glatiramer acetate at one-year follow-up [80]. Failure to respond may be due, in part, to treatment non-adherence, which has been reported to be as high as 27% within the first six months of therapy [81]. Similarly, a study in Brazil reported that up to one-third of patients interrupt or discontinue their DMT within 6–29 months of starting therapy [82]. Treatment non-compliance is an important explanation for “pseudo suboptimal response”. Factors that improve compliance include patient education about the drug, with emphasis on anticipated side effects, risks, and potential benefits; access to medical personnel for support; and frequent follow-ups [83].

5.1. Treatment options

An oral medication may achieve greater patient acceptance than an injectable drug during chronic therapy. The decision will be influenced by patients’ circumstances, drug availability and regulatory restrictions. The current oral options in Latin America are teriflunomide and fingolimod (Fig. 1). Dimethyl fumarate (BG–12) may be another option when it is approved in the region.

5.1.1. Teriflunomide

This dihydroorotate dehydrogenase inhibitor reduces T and B cell activation and proliferation, and has been shown to reduce the annualized relapse rate (ARR) by about one-third in two phase III trials [84,85]. In the TENERE trial, teriflunomide 14 mg/day and subcutaneous IFNβ-1a had comparable effects on ARR [86], suggesting that teriflunomide is a
A reasonable alternative to an injectable DMT when starting therapy. Treatment is generally well-tolerated. Routine monitoring of liver function and white-cell counts is required due to a risk of hepatotoxicity and leucopenia. In preclinical reproductive studies, leflunomide (a prodrug of terifalunomide) was found to be embryotoxic and teratogenic. Based on these data, the U.S. Food and Drug Administration classify terifalunomide as a pregnancy category X medication (women of childbearing age must have a negative pregnancy test before starting the drug and use effective birth control during treatment). Women who are planning pregnancy or who are taking the medication and inadvertently become pregnant are advised to undergo a drug elimination procedure using cholestyramine or activated charcoal. Drug discontinuation and accelerated elimination are also recommended in males who plan to father a child since the drug is detectable in human semen.

5.1.2. Fingolimod

This oral sphingosine-1-phosphate receptor modulator prevents lymphocyte egress from lymph nodes, thereby reducing the pool of autoaggressive T cells available to invade the CNS. Two placebo-controlled phase III trials have reported a reduction in ARR of 48–54% with fingolimod 0.5 mg/day compared to placebo [87,88]. In the active-control TRANSFORMS trial, ARR was reduced 52% with fingolimod versus intramuscular IFNβ-1a [89]. While these comparative results cannot be generalized to other injectables, the phase IIIb FIRST study did report a 55% reduction in ARR when patients were switched from an IFNβ-1b to orotheracrine acetate to fingolimod [90]. The MSBase Study Group showed a 45% reduction in time to first relapse and a 78% lower discontinuation rate at one year when patients switched from an injectable DMT to fingolimod rather than to another injectable [91]. Thus, fingolimod may be a reasonable option either as an initial treatment or in patients with an inadequate treatment response or poor tolerability during prior therapy. Whether fingolimod is used as a first- or second-line agent will depend on the product label in the specific Latin American country. Treatment is well tolerated. Vaccination for varicella zoster virus (VZV) is advised prior to treatment initiation in patients with no prior exposure to VZV. A six-hour observation period (heart rate, blood pressure, 12-lead ECG) is required at first dose due to the risk of adverse cardiac events such as bradycardia or cardiac conduction abnormalities. An ophthalmic examination is required at 3–4 months due to the risk of macular edema.

5.1.3. Natalizumab

This monoclonal antibody targets alpha4 integrin expressed on the surface of leukocytes, thereby blocking the adhesion of activated T cells to the blood–brain barrier and their subsequent migration into the CNS. ARR was reduced 68% versus placebo in the phase III AFFIRM trial [92]. Natalizumab may be employed as a first-line agent in patients with highly aggressive disease at onset, although it is generally reserved for patients with an inadequate response to one or more prior therapies. Long-term use of natalizumab is limited by the risk of progressive multifocal leukoencephalopathy (PML) caused by John Cunningham virus (JCV) reactivation [93]. The known PML risk factors are anti-JCV antibody positivity; prior immunosuppressant use; and natalizumab exposure >24 months [94]. The estimated PML risk if all three risk factors are present is 1.1% [94]. Anti-JCV antibody status using a two-step enzyme-linked immunoabsorbent assay (ELISA) [95] is strongly recommended for all natalizumab candidates prior to starting treatment. The estimated false-negative rate is at least 2.5% [95], although considerably higher rates have been reported in other small series [96]. Natalizumab may be used in patients at risk of a more severe or progressive course as long as they remain anti-JCV antibody-negative. The estimated annual seroconversion rate is 2% [95]. Recent studies in MS, however, have reported annual JCV seroconversion rates of 33–36% [97,98], but the small sample size of these investigations requires that results should be validated in further studies. While a JCV antibody index has been proposed as a way
of stratifying PML risk according to antibody titers [99], this approach needs further validation. If antibody-positive, the patient may decide to start natalizumab after being fully informed of the PML risk, or may elect to start with another agent such as fingolimod.

5.2. Evaluating treatment response

An optimal treatment response may be characterized as disease activity-free, defined as no relapses, no progression on the Expanded Disability Status Scale (EDSS), and no new/enlarging lesions on MRI [100]. This has been shown to be achievable in about one-third of patients treated with more potent agents such as fingolimod or natalizumab [101–103]. However, it remains to be determined if this combined metric will be a robust predictor of long-term outcomes. Clearly, results will vary depending on the frequency that evaluations are performed.

In the assessment of suboptimal treatment response, it is important to evaluate the individual patient’s relapses, disease progression and MRI activity (Table 3). Ideally, clinical and radiological assessments should be obtained every six months, although annual evaluations may be sufficient for patients with stable disease. However, it should be emphasized that these recommendations are not evidence-based and there is no formal consensus.

5.2.1. Relapse assessment

Despite some limitations, population-based studies have indicated that the number of relapses during the first two years of MS is predictive of long-term disability [61,62]. Given that some patients with CIS/early MS are now often treated after having a single attack, the percent reduction in relapse rate can no longer be used to judge a change over time. Therefore, other aspects of the attack may be more important, such as lesion location in the CNS, relapse severity and the degree of recovery.

An inadequate treatment response may be defined as >1 relapse in the first year of treatment, or one relapse that is severe or from which there is incomplete recovery at six months. In this context, a severe relapse would be defined as one that requires a course of steroids or hospitalization, affects >1 functional system, manifests motor/cerebellar/brainstem involvement, or has a significant impact on patient quality of life.

5.2.2. EDSS progression

The Kurtzke EDSS is the most commonly used standardized and validated measure of disease progression [104]. Transient changes in EDSS scores are largely dependent on the criteria used and may not reflect sustained disability progression [105]. A ≥2-point change in EDSS score sustained at six months is a concern in patients with EDSS ≤ 3.5.

Smaller EDSS changes are a concern in patients with greater disability; for example, an increase of 0.5 points if EDSS > 6.0 is considered to be a reliable indicator of disease progression (accuracy 87%), [106,107] and may indicate a need to change therapies. An early change on the timed 25-foot walk (T25FW) adds significant independent information and should be used in conjunction with the EDSS [108]. A >20% change on the T25FW may indicate a need to change therapies [1,108]. An alternative to the EDSS is the Multiple Sclerosis Functional Composite (MSFC) [109], which comprises quantitative functional measures of ambulation, arm and hand function, and cognition. However, the MSFC takes time to administer, requires a separate examiner, can result in some patient discomfort (related to anxiety often associated with the cognitive test) and requires a standardized reference population.

Before making treatment modifications based on disability progression alone, confirmation at 3 and 6 months is required to exclude periodic fluctuations.

5.2.3. MRI

It is clear that MRI is not always well correlated with either relapses or disease progression. However, new MRI lesions that develop while a patient is on therapy indicate a poor response to treatment and are predictive of a worse outcome. An inadequate treatment response may also be defined as the presence of ≥2 new Gd-enhancing lesions, or the accumulation of ≥2 new T2 lesions per year. As some drugs may take up to six months to become effective, it is recommended that an MRI that will be used as a reference be obtained at least six months after initiating therapy, and annually thereafter. Prospective studies have found that the presence of ≥2 active lesions during treatment significantly increases the risk of progression [110,111]. Although the presence of spinal cord lesions has a worse prognosis in MS patients, spinal cord lesions have the same value as brain lesions when assessing treatment response. However, routine spinal cord imaging requires specialized expertise for adequate image acquisition and interpretation, which is not widely available in Latin America, and therefore it may be difficult to apply in practice. Likewise, although there is evidence that some drugs slow brain atrophy [87], and that atrophy is a predictor of clinical disease progression [112], at present brain atrophy measures alone do not have a role in the assessment of a suboptimal treatment response that warrants a change in therapy. This is because the rate of atrophy varies from year to year; in addition, technical challenges limit the use of quantitative atrophy measures in monitoring treatment responses in individual patients with RRMS [113].

The combined results of these three assessments – relapses, MRI and EDSS – will provide an adequate picture of an individual patient’s response to therapy and is consistent with published models for predicting disease progression in DMT-treated RRMS patients [114,115]. As there is a limited time window for effective therapeutic intervention, clinicians need to optimize treatment promptly (see below). A more aggressive approach to treatment may be warranted in patients with additional risk factors for progression (e.g. male gender, African ancestry).

5.3. Cognitive assessment

Patients with all MS subtypes (including patients with CIS and radiologically isolated syndrome [RIS]) exhibit cognitive impairment [116–118]. An estimated 40–60% of MS patients have cognitive changes, according to Latin American studies [119,120]; processing speed, sustained attention/vigilance and verbal memory are the principal domains affected. Cognitive dysfunction has a significant impact on patients’ quality of life, social functioning and employment [121,122]. Thus, it is recommended that neuropsychological assessments be performed by a qualified psychologist in all RRMS patients at baseline and every 12 months. More frequent testing is recommended if cognitive worsening is suspected by the physician, the patient or the family. Assessment should be performed with the Brief Repeatable Battery of

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Table 3

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<thead>
<tr>
<th>Criteria for treatment optimization in RRMS patients after 1 year on therapy. Treatment modification may be considered if at least one criterion is met.</th>
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<tbody>
<tr>
<td><strong>Relapse</strong></td>
</tr>
<tr>
<td>&gt;1 relapse OR 1 severe relapse*</td>
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<tr>
<td>*Criteria for relapse severity</td>
</tr>
<tr>
<td>• Incomplete recovery at 6 months</td>
</tr>
<tr>
<td>• Steroids/hospitalization required</td>
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<tr>
<td>• &gt;1 functional system affected</td>
</tr>
<tr>
<td>• Severe motor/cerebellar/brainstem involvement</td>
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<tr>
<td>• Significant impact on patient QOL</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
</tr>
<tr>
<td>≥2 new Gd-enhancing lesions; or</td>
</tr>
<tr>
<td>≥2 new T2 lesions/year; or</td>
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<tr>
<td>≥2 spinal cord lesions</td>
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<tr>
<td><strong>EDSS</strong></td>
</tr>
<tr>
<td>≥2-point change in EDSS score sustained at six months</td>
</tr>
<tr>
<td>(0.5 points if EDSS ≥6.0); and/or</td>
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<tr>
<td>≥20% increase on the T25FW confirmed at 6 months</td>
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Neuropsychological Tests (BRBNT) [123] or the Minimal Assessment of Cognitive Function in MS (MACFIMS) [124], which have been shown to have comparable sensitivity in MS patients [125]. Versions of the BRBNT are available in Spanish and Portuguese [126,127]. Additionally, the Symbol Digit Modalities Test (SDMT) [128], which evaluates processing speed and working memory, can be administered.

As the higher rate of brain atrophy seen in MS is significantly associated with ongoing cognitive impairment [129], consideration should be given to annual MRI assessment of brain volume changes, where available.

Since the clinical assessment of cognitive impairment may be confounded by coexisting fatigue and depression [130,131], these should be separately evaluated as part of the routine management of MS patients. Depression may be assessed with the Beck Depression Inventory-Fast Screen (BDI-FS) [132], and fatigue can be evaluated using the Modified Fatigue Impact Scale (MFIS) [133]. Worsening of depression and/or fatigue do not necessarily indicate suboptimal treatment response.

The development of new or worsening cognitive impairment during treatment is clinically worrisome, however, it has not been established that it indicates disease progression or an inadequate treatment response. Moreover, there are no compelling data to suggest that switching treatment will improve or stabilize cognitive deterioration [134]. Thus, a change in therapy is generally not indicated in patients with worsening cognitive function in the absence of other clinical or radiological signs of suboptimal treatment response.

5.4. Other factors affecting treatment response

5.4.1. Neutralizing antibodies

The most recent estimated prevalence of neutralizing antibodies (NAbs) to IFNβ is 19% [135]. However, the frequency of NAbs will vary depending on the drug formulation and frequency of administration. NAbs generally develop 6–24 months after the patient starts IFNβ, and patients who are negative for NAbs after 24 months of therapy are unlikely to develop NAbs later on. Persistent high titers of NAbs reduce the efficacy of IFNβ on relapses and MRI lesions [136,137]; the effect of NAbs on EDSS progression is less consistent. However, NAbs effects are often transient, with median NAb titers typically declining with follow-up testing [138], and about one-third of NAb-positive individuals become NAb-negative spontaneously over the treatment course [139]. Thus, the long-term clinical significance of NAbs has not been fully determined, and there is no clear consensus on NAb testing in practice. Moreover, determination of NAbs is not routinely available in Latin America.

About 6% of natalizumab-treated patients will develop persistent NAbs, which have been associated with reduced efficacy and an increase in allergic infusion reactions [140]. Accordingly, an alternative treatment is advised in patients who develop persistent NAbs to natalizumab. Unlike antibodies that developed in response to IFNβ, treatment antibodies to natalizumab appear earlier, at between 3 and 6 months.

5.4.2. Vitamin D

Vitamin D has significant immunomodulatory effects and may help to regulate T cell homeostasis [141]. Observational studies have suggested that the risk of developing MS is higher in subjects with low serum 25-hydroxyvitamin D levels (25[OH]D) [142,143]. Increased sun exposure may be a factor in the low prevalence of MS in Latin American countries lying near the equator, such as Ecuador [67]. Better outcomes have been observed in MS patients with higher sun exposure and/or higher serum 25(OH)D levels [144–147]. One study reported a declining rate of subsequent disability with increasing serum 25(OH)D levels, although relapse rates were not significantly affected [148]. Prospective studies have failed to show a clinical benefit of vitamin D supplementation in RRMS patients [149,150]; modest benefits have been reported when vitamin D is used as an add-on therapy to IFNβ or fingolimod [151,152].

Although there is a lack of evidence for vitamin D in improving clinical outcomes, vitamin D supplementation may be used adjunctively in DMT-treated patients. The recommended dose is 800–4000 IU/day [1,153], with different dosing advised according to country. Prospective studies are needed in Latin America, notably in regions with more constant sun exposure throughout the year, high luminosity and varying elevations. Routine monitoring of serum 25(OH)D levels is not cost-effective but assays may be obtained in selected patients as part of the normal blood work. It has been suggested that UV exposure has beneficial immunomodulatory effects that act independently of vitamin D production [154], but this requires further study.

6. Treatment optimization in RRMS

The goal of treatment optimization is to modify a therapeutic regimen to achieve better control of the disease process and/or improve treatment tolerability and acceptance. The availability of several DMTs offers the possibility of tailoring treatment to individual patients with RRMS, and altering treatment in patients with suboptimal responses. However, it should be noted that there is no Class I evidence to guide alternative therapy in patients with suboptimal responses. Appropriate monitoring includes regular follow-up visits, discussion and management of adverse events, and assessment of relapses, disability and MRI measures.

There are two main strategies for treatment optimization in RRMS (Fig. 1). A lateral switch from one drug to another of comparable effectiveness (e.g. IFNβ or glatiramer acetate to teriflunomide) may be appropriate for patients who have an adequate treatment response but who have poor tolerability to a particular medication. Similarly, use of a more potent agent may not be required in patients who have had no relapses, no progression and/or no significant changes on MRI before developing a single mild relapse. These patients should be re-evaluated within three months and a change in treatment may be considered if there is evidence of further inflammatory disease activity.

The second strategy is treatment escalation to fingolimod or natalizumab, which would be the preferred approach for patients with an inadequate response to an initial therapy. Observational studies and retrospective analyses have reported substantial reductions in disease activity when patients with an inadequate response to IFNβ or glatiramer acetate were switched either to natalizumab [155,156] or fingolimod [90,91,157].

There are no comparative data to guide the selection of natalizumab or fingolimod as the preferred option. A network meta-analysis recently estimated that both of these agents are more effective than injectable DMTs or teriflunomide [158]. An observational cohort study found a high proportion of patients were relapse-free and progression-free in the one year following a switch to either natalizumab (62.03%), or fingolimod (71.05%) [159]. Therefore, the choice of agent may be determined by considerations other than efficacy, such as patient preference and the balance of benefits versus risks.

As noted previously, anti-JCV antibody status should be determined prior to starting therapy with natalizumab as part of the PML risk assessment. Natalizumab is generally not recommended in antibody-positive patients who have received prior immunosuppressants (e.g. mitoxantrone, cyclophosphamide) [160]. These recommendations may be revisited as more information becomes available about the utility of the JCV antibody index and other possible PML risk biomarkers, such as L-selectin [161]. If antibody-positive with no prior immunosuppressant exposure, the patient may decide to start natalizumab after being informed of the PML risks, or may elect to start with another agent such as fingolimod. Another approach is to start natalizumab for a period shorter than 24 months to reduce PML risk, and then either to de-escalate to a first-line drug or switch to fingolimod. There are no controlled trials...
on de-escalation after discontinuation of natalizumab. Observational studies have indicated that in patients who switch from natalizumab to current platform therapies, there is a loss of clinical benefit and a return to pre-treatment disease activity [162,163]. Large, prospective studies are warranted.

Patients who are anti-JCV antibody-negative may be considered as candidates for natalizumab, notably if they have highly aggressive inflammatory disease. The concerns in the clinical practice setting are the rates of false-negative results with antibody testing and of JCV seroconversion during treatment. Thus, JCV antibody testing is recommended every 6 months. A further caveat if natalizumab needs to be discontinued is the risk of substantial disease reactivation that has been reported in some [164,165] but not all [166] case series. In the largest cohort studied, RRMS patients with highly active disease often return to pre-treatment levels of disease activity in the 4–7 months after stopping natalizumab, regardless of overall natalizumab exposure and use of subsequent treatments [162]. Clinicians should also closely monitor patients for early signs of immune reconstitution inflammatory syndrome (IRIS), most notably in patients with significant baseline disease activity who interrupt natalizumab for a prolonged period [167].

Since the anti-JCV antibody status may limit the duration of treatment with natalizumab, a more rational treatment plan may be to initiate fingolimod first in suitable candidates, keeping natalizumab in reserve for those patients who have an inadequate response or poor tolerability with fingolimod. It should be noted, however, that it is not known if PML risk is increased during natalizumab therapy if patients have received prior fingolimod. Fingolimod should not be used in patients with pre-existing ischemic heart disease (angina pectoris, congestive heart failure, cerebrovascular disease, history of myocardial infarction), cardiac conduction abnormalities (atrioventricular or sino-atrial block, sick-sinus syndrome, history of syncope or symptomatic bradycardia), uncontrolled hypertension or severe sleep apnea. Fingolimod is contraindicated in patients with known immunodeficiency syndrome, severe liver impairment or severe active infections (e.g. hepatitis, tuberculosis). Fingolimod should also be avoided in patients on concomitant beta-blockers, calcium channel blockers that lower heart rate, or Class la (quinidine, disopyramide) or Class III (amiodarone, sotalol) anti-arrhythmic drugs. Ophthalmic evaluation and closer monitoring are advised in patients with diabetes or a history of uveitis due to a risk of macular edema.

Patients starting on fingolimod or natalizumab should be clinically evaluated every 3–4 months. An ophthalmic examination is required with fingolimod at months 3–4.

6.1. Washout period

The data are inadequate regarding the optimal washout period when switching from one drug to another. A washout period may not be required when switching from one injectable to another, or from an injectable DMT to teriflunomide, fingolimod or natalizumab. There are no data on washout periods when switching from teriflunomide to fingolimod or natalizumab. An accelerated elimination protocol may be advisable when switching from teriflunomide to an agent with hematological effects due to the long half-life of teriflunomide [168]. There are no data on switching from fingolimod to natalizumab; a minimum 4-week washout period may be advised.

When switching from natalizumab to fingolimod, a longer washout period (>3–4 months) is associated with an increased risk of disease reactivation [169,170]. Recent observational studies have suggested an optimal washout period of 1–2 months to reduce the risk of worsening symptoms [171–173].

6.2. Combination therapy

Although using multiple therapies with different mechanisms of action is an effective strategy in other diseases, evidence supporting a similar approach in RRMS is limited. Further studies are needed to evaluate the effectiveness and safety of this approach. Several small published studies cannot provide significant data on efficacy, and results could be misleading. Patients who do not adequately respond to the treatment strategies listed above may be considered for treatment with novel agents (e.g. alemtuzumab) or for entry in clinical trials of experimental treatments (e.g. mitoxantrone induction, high-dose cyclophosphamide, ocrelizumab or bone marrow transplantation) (Fig. 1).

6.3. Stopping treatment

RRMS patients receiving immunomodulatory treatment may elect to discontinue therapy. These patients should be periodically monitored both clinically and with MRI. If disease worsening is detected, the decision to stop treatment should be revisited with the patient. IFNβ and glatiramer acetate are not advised for the treatment of MS patients who have progressed to SPMS, although there are some data suggesting that post-progression relapses accelerate disability [174] and that IFNβ may provide modest benefit in SPMS with superimposed relapses [175]. There are no data on teriflunomide, fingolimod or natalizumab in SPMS; the use of these agents must await the results of ongoing trials. The decision to stop therapy must be made on a case-by-case basis. For SPMS patients with a two-year history of no relapses, no Gd-enhancing lesions and significant progression (EDSS > 6), treatment should be discontinued after consultation with the patient and a further two-year observation period. A six-month drug holiday with subsequent clinical and MRI evaluations may be appropriate to aid in this decision.

7. Summary

The availability of new treatment options for RRMS has made patient management more complex, but provides an opportunity for improving long-term clinical outcomes. This proposed treatment optimization plan is an attempt to provide clinical neurologists in Latin America with an approach to therapy and practical recommendations to assist them in their management of RRMS patients. At a minimum, a DMT should reduce the inflammatory disease activity that results in relapses and MRI activity and contributes to disability progression. If treatment response is inadequate, it is essential that clinicians act promptly to achieve better disease control since the window of opportunity for modifying the disease course is very limited.

Additional research is needed about genetic and environmental factors that affect the incidence, presentation and clinical course of MS in Latin American populations. Research on patient-specific factors that influence response to individual therapies will also help to inform our decision-making and refine the selection of the best available therapy for Latin Americans with MS. This is important since extrapolating pharmacogenomic data from defined ethnic groups to admixed populations may be misleading [176]. It is hoped that current and emerging therapies will help to meet the unmet need of effective treatment for patients in the progressive phases of the disease.

Conflict of interest statements

JC is a board member of Merck-Serono Argentina, Merck-Serono LATAM, and Novartis Argentina; and has received reimbursement for developing educational presentations for Merck Serono Argentina, Merck Serono LATAM, Biogen Idec Argentina, TEVA-Tuteur Argentina, and Novartis LATAM, as well as professional travel/accommodations stipends. PA has received reimbursement for developing continuous educational programs and presentations for Merck-Serono and Novartis. RA has nothing to disclose. SAI is an advisory board member for Novartis, Genzyme and Biogen Idec; and has received reimbursement for developing educational presentations for Novartis and Biogen Idec. EA has received reimbursement for developing educational presentations for Bayer Venezuela, Merck Serono, Novartis and Stendhal. JB has received
reimbursement for developing educational presentations and has participated in advisory boards and consulting for Biogen Idec, Bayer Schering, Merck Serono, Lundbeck, Novartis, Sanofi-Aventis and Teva Pharmaceuticals. RB has received reimbursement for developing educational presentations for Novartis, Biogen Idec and Boehringer Ingelheim. TC has nothing to disclose. EC has received reimbursement for developing educational presentations, educational and research grants, consultations fees and travel stipends from Biogen, Genzyme, Merck, Novartis and Roche. FG has received reimbursement for developing educational presentations for Merck Serono and Genzyme-Sanoﬁ. JGB has received reimbursement for developing educational presentations for Biogen Idec and Merck Serono. DV is an advisor for Teva; and has received research grants and reimbursement for developing educational presentations from Novartis. MSF has received research or educational grants from Bayer Healthcare and Genzyme; honoraria or consultation fees from Bayer Healthcare, Biogen Idec, EMD Canada, Genzyme, Novartis, Sanofi-Aventis, Teva Canada Innovation; is a board member of the speaker’s bureau for Genzyme; and an advisory board member for Bayer Healthcare, Biogen Idec, Hoffmann La-Roche, Merck Serono, Novartis, Operaex and Sanofi-Aventis.

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