

# Disease-modifying therapies in multiple sclerosis in Latin America

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## Abstract

The treatment of multiple sclerosis (MS) has become increasingly complex during the last 10 years, mainly because of the advent of new and more potent disease-modifying therapies (DMTs). In Latin America, the therapeutic repertoire available for MS treatment is similar to the one in the rest of the world, but the high costs of these drugs, in conjunction with the limited resources of the social security health systems, makes the treatment of MS more difficult. For neurologists in Latin America, providing personalized MS treatment has become a challenge. We present a review of the status of the DMT in Central and South America, benefits as well as limitations for providing full access to these medications in Latin America.

**Keywords:** Disease-modifying therapies, second-line treatment, treatment response

Date received: 19 April 2017; accepted: 29 June 2017

## Introduction

The increasing number of disease-modifying therapies (DMTs) over the past decade has dramatically improved the way we treat multiple sclerosis (MS). The therapeutic armamentarium has increased from only four available treatments before the year 2000, to more than 10 options nowadays. The emergence of generic drugs has also contributed to an increased exposure of patients to these molecules.

Treatments for MS may have similar indications in patient selection and disease forms, but differ considerably in efficacy and safety profiles. For this reason, an individualized therapeutic approach is preferred; being able to select a drug from all the medical alternatives is the best standard of care in MS. Part of that optimal standard of care in MS includes the concept of no evidence of disease activity (NEDA). Being strict in accomplishing NEDA criteria, patients should be free of clinical and radiological activity, and the only way to achieve this objective is to have a full repertoire of DMTs and adequate surveillance of treatment effect.

Latin America (LATAM) comprises the territory that extends from the southern border of the United States (US), to the Argentinean and Chilean Patagonia in South America. Treatment algorithms

for MS in LATAM do not differ greatly from international recommendations. However, global access to DMTs is a limiting factor in many cases. Interferons (IFNs) and glatiramer acetate (GA), as part of the first era of DMTs, are used in the treatment of relapsing–remitting multiple sclerosis (RRMS) as first-line agents and clinically isolated syndrome (CIS); oral therapies such as fingolimod, dimethyl fumarate and teriflunomide are approved also for RRMS, and can be used as first-line or second-line therapies or in patients with intolerance to injectables. The intravenous agents natalizumab and alemtuzumab were approved for use in RRMS in patients who fail other DMTs, as well as in aggressive forms of RRMS as first-line in selected patients. Mitoxantrone is infrequently used for treatment in secondary progressive multiple sclerosis (SPMS) or as an induction therapy in RRMS. Ocrelizumab, not available yet in LATAM, was recently approved in the US for RRMS and progressive forms of MS. Daclizumab has been approved in Europe and the US for the treatment of active MS; however, it is not yet available in LATAM.

The full therapeutic repertoire available for MS treatment is usually present and first approved in the US and in Europe; as a general rule, there is a delay in appearance in LATAM. A noticeable exception to

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this rule was the early introduction of alemtuzumab in some LATAM countries, even before it was approved by the Food and Drug Administration (FDA) in the US. Another regional limitation is the scarce representation of LATAM countries in clinical trials. In the past, less than 2% of patients recruited in multinational randomized clinical trials for novel therapies in MS belonged to LATAM countries. This issue can sometimes delay the introduction of novel DMTs in the region. On many occasions, drug approval in the LATAM market can take several months to years once approved for use in other parts of the world. Once available in each specific country, DMTs are not globally accessible because of their high costs and/or lack of global health care. In most cases, the public health system is essential in offering these drugs to MS patients, but the lack of presence of all the medical armamentarium in the public health system could delay the access to treatment a few more years.

The current therapeutic armamentarium is not completely available in most LATAM countries; and it is well known that MS care in LATAM, as well as in many other regions of the world, poses great challenges for health systems because of noticeable socioeconomic impact and costs involved in diagnosis acquisition, medications, and long-term care of the disease.<sup>1</sup> There is another caveat: Coverage for medications and medical services varies markedly among countries, and among country regions; discrepancies in treatments depend not only on the presence or absence of a product in a specific region, but also on the capability of the health professionals to prescribe each treatment. Rivera et al.<sup>1</sup> reported that in 2014 in the Caja Costarricense del Seguro Social (Costa Rica's social security), which benefits 4.7 million people by national law, despite this degree of coverage, only two DMTs, both IFN products, were available. In El Salvador, the only therapeutic option was IFN beta-1b. In Mexico (2014) the social security system provided treatment with all the IFNs, and GA; at present the Mexican repertoire of medications has increased, but is still incomplete.

There are increasing number of papers regarding epidemiological and demographic information of MS in LATAM, but scarce information about treatment availability and health care coverage. In a study by Gracia and Armien in 2012,<sup>2</sup> the authors concluded that the availability of drugs for treating acute MS crisis (methylprednisolone and intravenous immunoglobulin) was covered in 100% of the countries, but the coverage of immunomodulators was below 35% in half of the countries studied. IFNs were present in

all the countries studied, but GA in only 35% (7/20); newer medications like natalizumab and fingolimod were covered in only 55% and 20% of the countries, respectively, and old medications like azathioprine and cyclophosphamide had a coverage of 100%, mitoxantrone was available in 90% of the countries studied, and these last medications were still a part of the standard of treatment of MS in many cases. The countries included in this study (in alphabetical order) were Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Puerto Rico, Uruguay and Venezuela. Even though the study was made by applying a voluntary survey using a structured questionnaire to participating neurologists involved in MS and LACTRIMS delegates, it showed a picture of the panorama occurring in 2012 in LATAM regarding DMTs for MS.

In a systematic review of health economic data of MS in LATAM<sup>3–8</sup> from January 1990 to September 2011, the estimated yearly costs of treatment in RRMS in Argentina 2004 was in US dollars (USD):<sup>5</sup> GA \$35,280, IFN beta-1a 44 mcg \$43,080 and IFN beta-1a 30 mcg, \$29,256. The source of pharmacy data was taken from the market and it possibly overestimated the cost of DMTs. In Brazil the total MS expenditure in DMTs was USD 14 million for 2006 compared with USD 123 million for 2009. DMTs accounted for 12.9% of high-cost medications supplied by the public sector in Brazil;<sup>7</sup> the annual cost per patient treated was (in USD) \$27,824 for GA, \$42,151 for IFN beta-a (subcutaneous (SC)/intra-muscular (IM)) and \$34,038 for IFN beta-1b. The total treatment cost estimated for 2007 was 92 million USD. In Colombia<sup>6</sup> the cost of DMTs represented 91.5% of the mean total annual cost in patients with MS with an Expanded Disability Status Scale (EDSS) between 1 and 7.5; 58% of the population was treated with DMTs. In a study by Sharac et al.,<sup>9</sup> the cost of MS in developing countries ranged from \$6511 to \$77,938 USD per patient per year;<sup>9</sup> however, this information could not be extrapolated to other regions where costs clearly have variations.

A well-known situation in LATAM and growing experience around the world is the presence of generic DMTs. These generic products have been integrated in private practice as well as the social security institutes, offering lower costs than the original brands, but many of them lack studies of bioequivalence, safety and tolerability. Generic products in LATAM lack of studies on bioequivalence, and

there are no clinical trials proving the same effect as the original brand. In spite of this, most regulatory agencies have allowed commercialization of these products with no substantial reduction in health costs. The generic drugs are available in different markets in LATAM, such as Mexico, Argentina, and Uruguay, among others.

### Availability of DMTs in LATAM

#### *Injectable therapies in LATAM*

Injectable therapies are the best-known DMTs on the market with more than 20 years of experience. Injectable therapies include IFNs, GA and the newly approved daclizumab. A humanized monoclonal antibody of immunoglobulin (Ig)G1 subtype that binds to the Tac epitope on the interleukin-2 (IL-2)

receptor  $\alpha$ -chain (CD25), blocking the formation of the high-affinity interleukin (IL)-2 receptor and selectively inhibiting T-cell activation, daclizumab is still not available in LATAM, but it could be available on the market by 2018 (Table 1).

IFNs were reported as effective in 1993 and quickly became the mainstay of treatment or RRMS globally for their immunomodulatory properties. Beta-interferons (IFNBs) have a diverse array of immunomodulatory properties, enhancing the production of natural anti-inflammatory cytokines, such as IL-10 and IL-4 and inhibiting the production of tumor necrosis factor, T-cell activation and oxygen free radicals by phagocytes.<sup>10</sup> Their efficacy regarding reduction of annualized relapse rate (ARR) and disability progression is low to moderate

**Table 1.** Different brands of disease-modifying treatments available in Latin America.

Drug	Commercial name	Generic drug
<i>Interferon beta-1b SC</i>	Betaferon <sup>®</sup>	Uribeta <sup>®</sup> (MEX) Extavia <sup>®</sup> (MEX)
<i>Interferon beta-1a SC</i>	Rebif <sup>®</sup>	Emaxem <sup>®</sup> (MEX) Xerfelan <sup>®</sup> (MEX) Neuraxa <sup>®</sup> (MEX) Blastoferon <sup>®</sup> (ARG) Immunomas <sup>®</sup> (ARG) Beta IFN Clausen <sup>®</sup> (URU)
<i>Interferon beta-1a IM</i>	Avonex <sup>®</sup>	Jumtab <sup>®</sup> (MEX)
<i>Glatiramer acetate</i>	Copaxone <sup>®</sup>	Probioglat <sup>®</sup> (MEX) Doxelev <sup>®</sup> (MEX) Polimunol <sup>®</sup> (ARG)
<i>Fingolimod</i>	Gilenya <sup>®</sup>	Lebrina <sup>®</sup> (ARG) Fibroneurina <sup>®</sup> (ARG) Mogibe <sup>®</sup> (ARG)
<i>Teriflunomide</i>	Aubagio <sup>®</sup>	Terflimida <sup>®</sup> (ARG)
<i>Dimethyl fumarate</i>	Tecfidera <sup>®</sup>	Catira <sup>®</sup> (ARG) Dimeful <sup>®</sup> (ARG)
<i>Alemtuzumab</i>	Lemtrada <sup>®</sup>	Not available
<i>Natalizumab</i>	Tysabri <sup>®</sup>	Not available
<i>Mitoxantrone</i>	Novantrone <sup>®</sup>	Bresnix <sup>®</sup> (MEX) Formyxan <sup>®</sup> (MEX) Mitoxgen <sup>®</sup> (ARG) Mitoxantrona Filaxis <sup>®</sup> (ARG) Mitoxantrona Varifarma <sup>®</sup> (ARG)
<i>Rituximab</i>	MabThera <sup>®</sup>	Kikuzubam <sup>®</sup> (MEX)
Disease-modifying treatments not available in Latin America		
<i>Peginterferon beta-1a IM</i>	Plegridy <sup>®</sup>	Not available
<i>Daclizumab</i>	Zinbryta <sup>®</sup>	Not available
<i>Ocrelizumab</i>	Ocrevus <sup>®</sup>	Not available

MEX: Mexico; ARG: Argentina; URU: Uruguay; SC: subcutaneous; IM: intra-muscular.

(approximately 30% reduction in ARR). Currently, IFNBs are widely used as platform therapies both in RRMS and CIS. Since their commercial availability in 1995, IFNBs have been the most widely available DMTs for MS in LATAM. In the previously mentioned survey conducted in 2011 among MS experts in 20 LATAM countries, 100% stated that IFNBs were used in their countries as standard of care for MS. However, on average, access to DMTs in the different health care systems was low (35%).<sup>11</sup> Particularly in LATAM, the introduction of biosimilars of IFNBs has been a controversial issue. Since 2004, the first formulation of generic IFNB-1b was introduced.<sup>11</sup> In the previously mentioned survey the use of biosimilars was reported in 35% of these countries. Current use of biosimilars is expected to be greater.

In a survey organized in Brazil in 2014, key opinion leaders from six LATAM countries answered questions regarding DMT and MS services in their countries.<sup>11</sup> One-third of them declared that more than 80% of their patients one year after DMT initiation kept the original treatment prescribed. The main reason for treatment discontinuation was tolerability to injections (pain, fear of injections, and skin reactions). These data contrast reports from other regions of the world (specifically, the North American Research Committee on Multiple Sclerosis (NARCOMS) database) in which the main reason for discontinuation was perceived lack of efficacy. A likely explanation for this finding, beyond the inherent nature of injectable drugs, is the interchangeability that has been observed in LATAM with the use of biosimilars.<sup>2,12,13</sup>

Pegylated IFNB-1a, a structural modification of IM INF beta-1a, allows a less frequent administration because of its longer half-life. However, it is currently not available in LATAM.

Another consideration about the use of IFNBs in LATAM, particularly in Caribbean populations or those with a larger proportion of individuals of African descent, is the higher risk of a diminished response to these drugs, as has been previously reported.<sup>14,15</sup>

GA is a complex drug administered by SC injection and constituted by a mixture of synthetic polypeptides with immunomodulatory properties due to its effect in peripheral antigen presentation. It is currently licensed for the treatment of relapsing MS and CIS. In its pivotal trials, GA showed a 29% reduction in ARR, as well as positive effects on

magnetic resonance imaging (MRI) lesion load and disability progression.<sup>16</sup> Owing to its efficacy results, it is currently considered as a platform therapy for patients without highly active MS. GA has been approved in several LATAM countries since 2004. However, despite worldwide experience and long-term approval in many other countries in more developed countries, GA has not been so widely distributed in LATAM.<sup>17</sup> GA was not available in Central America until very recently. Copaxone<sup>®</sup> 20 mg (GA 20 mg) is distributed by Teva in Mexico, Brazil, Argentina, Chile and Venezuela. In Peru and Colombia the medication is also available but distributed by a secondary company. GA 40 mg is also available in Mexico, Argentina, Chile, Peru and Colombia. Generic 20 mg GA is available in Mexico and Argentina, and generic 40 mg GA only in Argentina. In the above-mentioned survey,<sup>2</sup> only 35% of MS neurologists stated that GA was available in their health care systems. Over the past several years, GA biosimilars have been used, mainly in Mexico and Argentina. Because of the inherent nature of this nonbiological complex drug, the development of biosimilars for GA is more challenging and ideally requires the development of a randomized clinical trial. Once these biosimilars are commercially available, rigorous pharmacovigilance programs will be necessary to ensure that safety and efficacy is maintained.<sup>12</sup> However, these programs are nonexistent for most of the drugs in the majority of LATAM countries.

A subanalysis of the observational COPTIMIZE trial included 263 LATAM patients who were switched to GA after different IFNBs.<sup>18</sup> In this study, tolerance to GA was similar in LATAM patients compared to Canada, Western Europe (CWE) and Eastern Europe (EE). A greater reduction of ARR was observed in LATAM patients; however, their baseline ARR was much higher than among other patients. One hypothesis to explain this phenomenon was the difference in health care standards among the three regions studied. Interestingly, adverse events (AEs) were lower in LATAM patients and a larger proportion of them reported an improvement in AEs compared to previous IFNB treatment.

#### *Oral therapies*

Many of the oral medications, which favor adherence in MS patients, are now available in LATAM. Fingolimod was the first oral drug introduced in the market, with its FDA approval in 2010, followed by its use in most LATAM countries. Fingolimod 0.5 mg is an orally active sphingosine 1-phosphate receptor modulator approved for use in adults with



relapsing MS. FREEDOMS was the first randomized, placebo-controlled, double-blind Phase III trial involving a large number of RRMS patients followed for two years. Patients treated with both fingolimod doses showed a significantly reduced ARR (primary endpoint) compared to placebo, with a relative reduction of 54% and 60% for the 0.5 mg and 1.25 mg doses, respectively.<sup>19</sup> There are studies measuring safety and tolerability of fingolimod in LATAM;<sup>20</sup> overall, fingolimod was well tolerated, and its safety profile as well as efficacy were similar to those reported in the Phase 3 studies and the FIRST study. The FIRST LATAM study was conducted in Argentina, Brazil, Colombia, Mexico, Panama and Peru. Other post-marketing studies have reported similar fingolimod safety experiences in LATAM populations.<sup>21–23</sup> Overall, fingolimod 0.5 mg is well tolerated, and safe in LATAM RRMS patients. Today fingolimod as the original brand (Gilenya®) is available in Mexico, Central America and the Caribbean countries, Colombia, Ecuador, Peru, Venezuela, Chile, Argentina, Uruguay and Brazil. There are generic brands of fingolimod, mainly in Argentina.

Dimethyl fumarate (DMF) (Tecfidera®), one of the oral agents most widely used for treatment in MS, was first approved by the FDA in 2013. It has immune-modulatory properties exerted through abilities to divert cytokine production toward a Th2 profile. DMF affects the anti-oxidative stress cell machinery promoting the transcription of genes downstream to the activation of the nuclear factor (erythroid derived 2)-like2 (NRF2). NRF2 has the potential for cytoprotection on glial cells, oligodendrocytes and neurons. There have been two Phase 3 studies on BG-12 (DMF). The first one was the DEFINE trial,<sup>24</sup> which evaluated 240 mg twice a day (BID) vs 240 mg three times a day (TID) vs placebo. Relative reductions of the adjusted ARR of the low- and high-dose regimens in comparison with placebo were 53% and 48%, respectively. In the other trial (CONFIRM),<sup>25</sup> DMF was administered 240 mg BID vs 240 mg TID vs GA vs placebo, and it showed a decrease in the ARR in comparison with placebo by 44% in the lower and by 51% in the higher dosage group.

DMF was recently introduced to the LATAM market, but its distribution is limited to a small number of countries; it is distributed by Stendhal in Mexico, and Colombia, and by Biogen in Argentina, Brazil and Chile. Generic brands of DMF are available in Argentina; paradoxically, one of those brands

was available in Argentina before the original product came out on the market.

Aubagio® (teriflunomide), approved for use in RRMS in 2012, is an oral agent that inhibits the proliferation of activated T and B lymphocytes in the periphery by selectively and reversibly inhibiting dihydroorotate dehydrogenase, and the de novo pyrimidine synthesis pathway; it is available for use in a few countries in LATAM, by direct distribution by Sanofi Genzyme. In the pivotal trial TEMSO,<sup>26</sup> patients were randomized to once-daily placebo, or teriflunomide 7 mg or 14 mg; there were representing relative risk reductions rates vs placebo of 31.2% and 31.5%, respectively. The TOWER study<sup>27</sup> showed teriflunomide 14 mg dose significantly reduced ARR (36.3%), disability progression and MRI outcomes compared with placebo. There is a generic brand of teriflunomide called Terflimida® available in Argentina.

#### *Intravenous medications*

Mitoxantrone, a synthetic anthracenedione derivative, is an antineoplastic, immunomodulatory agent and was the first drug approved by the FDA in year 2000 for progressive MS and worsening RRMS.<sup>28</sup> In LATAM, it is available in 90% of the countries because of its indication for other pathologies like leukemia and cancer.<sup>2</sup> It has been used as an induction treatment for a short period of time for very aggressive MS (non-responsive, rapidly progressive, SP and very active MS) prior to treatment with other DMTs. The drug reduces disability progression and reduction in the number of new lesions and new gadolinium-enhancing lesions.

Compared to other DMTs it has a lower cost; however, its use has been limited because it has a maximum accumulative dose of 140 mg/m<sup>2</sup> due to cardiotoxic effects and has been associated with other effects such as the presence of leukemias or infections.<sup>29</sup> In LATAM when used, it is recommended in patients who have failed other therapies and who do not have access to other therapies with a safer profile. Its use is recommended for a limited time and under strict monitoring of cardiac, renal, hepatic and hematological functions.<sup>30</sup>

Natalizumab was the first monoclonal antibody approved for MS by the FDA in 2004 and then reintroduced in the market in 2006. This drug targets alpha 4 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 central nervous system (CNS).<sup>31</sup>

The AFFIRM and SENTINEL studies showed that natalizumab was effective both as monotherapy and in combination with IFNβ-1a in patients with relapsing MS. The pivotal study AFFIRM showed a relapse risk reduction of 68% compared with placebo, significant reduction of sustained disability progression (42%) and significant effects in MRI measurements.<sup>31,32</sup>

In LATAM natalizumab is available in approximately 55% of the countries under different regulations and programs of pharmacovigilance.<sup>2</sup> In some countries it is considered a second-line treatment and has not been included in the basic formulary because of cost-containment measures.<sup>1</sup> Its efficacy and anti-inflammatory activity translate into a significant decrease in relapse rates and disability (measured by the EDSS), as well as a decrease in gadolinium-enhancing lesions and new T2 lesions, as assessed using MRI.<sup>29</sup> A poster presented atECTRIMS 2009 on the effects of natalizumab on relapses and MRI in Hispanic patients with relapsing MS in the AFFIRM and SENTINEL trials confirmed that efficacy is maintained across ethnic subgroups.<sup>32</sup>

The recommendation in LATAM is that 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. The principal limitation of its use is the association with progressive multifocal encephalopathy (PML) caused by John Cunningham virus (JCV) reactivation. The known PML risk factors are prior use of immunosuppressive drugs, natalizumab exposure for more than 24 months and anti-JCV seropositivity. More recently the use of the JCV antibody index has been introduced for risk stratification.<sup>29,31</sup>

As of March 2017, there have been 714 PML cases described worldwide, 711 in MS patients and three in patients with Crohn's disease.<sup>33</sup> In Mexico, there have been two documented cases of PML and there is one case report from Colombia from 2013.<sup>11,34</sup>

Despite the proven efficacy of natalizumab, in a recent survey of LATAM neuro-immunologists on the treatment of MS with monoclonal antibodies, a group of 26 physicians working at MS units in seven LATAM countries who have had experience with natalizumab treatment, most neurologists had no confidence in starting a patient with natalizumab or alemtuzumab because of its safety profile. Pharmacovigilance programs for each of these monoclonal antibodies is considered fundamental

by the neurology community.<sup>34,35</sup> The use of highly sensitive tests that can detect less than 50 copies of JCV RNA in cerebrospinal fluid (CSF) in patients with suspected PML is essential. Most of the available tests detect 100–500 copies, which often determine the existence of false negatives.

Alemtuzumab, a humanized monoclonal antibody, selectively targets CD52, a protein expressed at high levels on the surface of T and B lymphocytes but at lower levels on natural killer cells and other cell types involved in innate immunity, leading to a selective depletion of circulating T and B cells. Efficacy was shown to be high with a relapse reduction of roughly 50% compared with the active comparator high-dose, high-frequency subcutaneous IFNβ-1a in two studies (CARE-MS I and CARE-MS II).

It is available in 50 countries. In Mexico it has been available since 2013, even before it was approved by the FDA. It has also been licensed in Argentina, Guatemala, Chile, Brazil and Venezuela. The indication for alemtuzumab states that it should be generally reserved for patients who have experienced an inadequate response to two or more DMTs; however, in some countries it is licensed as a first-line therapy.<sup>11,35,36</sup>

Rituximab is a chimeric monoclonal B-cell-depleting anti-CD20 antibody approved for non-Hodgkin lymphoma and rheumatoid arthritis. It can be considered for the treatment of MS as it has shown beneficial effects in two randomized placebo-controlled Phase 2 trials: the (HERMES) trial for RRMS and the (OLYMPUS) trial for primary progressive MS. The most common side effects are infusion-related reactions, the risk of infections and hematological events (such as neutropenia). PML has been reported in rituximab-treated patients but usually following other immunosuppressive treatments in B-cell lymphoma and rarely in rheumatic diseases. It is available in LATAM and increasingly used as an off-label DMT because of its approval in other diseases. However, there are scarce real-world evidence data regarding this experience. There is a generic form of rituximab available in Mexico (Kikuzumab®); however, its license was revoked after safety issues emerged in hematological patients.<sup>37</sup>

Ocrelizumab, recently approved by the FDA for RRMS and progressive MS, is still not available in LATAM.

Immunosuppressive agents like mitoxantrone, azathioprine, cyclophosphamide, methotrexate,

mycophenolate mofetil and glucocorticoids were the first agents used against MS and were used off-label before IFNBs were approved in the 1990s. The potential beneficial effects of these agents in MS are limited by systemic adverse effects like increased risk of infections or other hematological complications. In fact, in LATAM these agents are more widely available and frequently used in patients who do not have access to other DMTs because of costs or lack of health care access. Likely explanations are the lower cost of these drugs and the more widespread access to them. There is a scarcity of data regarding the documentation of their effectiveness, however.<sup>38</sup>

### Conclusion

Despite regional recommendations regarding MS care, DMT access in LATAM is still limited by regional economical limitations and a general lack of uniform health care access. The use of biosimilars is an important issue in LATAM that warrants further vigilance and research.

### Conflicts of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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