Access and barriers to MS care in Latin America

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Abstract

Multiple sclerosis (MS), an epidemiologically emergent disorder in Latin America (LATAM), poses substantial socioeconomic challenges to a region where most countries remain as economies in development. MS is not health priority despite its economic and communitarian impact with a relatively low prevalence. MS treatments in LATAM have evolved from earlier long-term oral steroids and immunosuppression protocols, to platform disease modifying therapies (DMTs), to the current landscape with more advanced therapeutic molecules. Following FDA approval, a DMT may eventually become available in LATAM conditioned to industrial marketing interest. Most countries do not count all medications in their armamentarium. Access to therapy by the MS population in the region is low (9.5%–42.8%). Generic treatments, biosimilars, and follow-on complex non-biological drugs (CNBD) are commonly available in institutional formularies in LATAM despite their lack of supportive efficacy and safety data and reported molecular differences with the innovators. Savings to health systems thus far have been negligible. Medicine licensing agencies in LATAM, despite limitations in resources, have considerably improved their assessments by incorporating more modern criteria and methodology. Access to symptomatic management, rehabilitation procedures, and the role of patients associations are discussed.

Keywords: Multiple sclerosis, Latin America, access to therapy, healthcare

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Introduction

The increasing presence of multiple sclerosis (MS) in Latin American (LATAM) causes a complex conglomerate of challenges, including the economic burden exerted by the disease in developing economies. The socioeconomic impact of MS in the Americas constitutes a realistic public health concern in most areas of the continent, despite its relatively low prevalence in the region. While this situation is not exclusive of LATAM (similar concerns have been expressed in other parts of the developing world), the increasing cost of MS medications appears to be a global phenomenon driven by industrial price escalation and market tolerance. Considering that prices of disease modifying therapies (DMTs) and medications for symptomatic management are the main direct factors determining the costs of MS care, particularly in LATAM, this situation is confounded by the additional gravamen of other tangible and intangible costs (absence from work, rehabilitation, informal caregivers time, etc.) and the existing limitations to provide alleviating services and coverage from public health and national social security institutions (SSIs). Each country in LATAM has different health laws integrated with their own medicines licensing departments and a host of institutional systems for delivery of care. There are substantial disparities in providing quality and efficient care throughout the region. The barriers faced by MS patients and health providers in LATAM in accessing in some cases the minimum of MS management deserve discussion.

Evolution and advent of MS therapy in LATAM

There are no reports on the status of MS therapy prior to the first epidemiologic report from LATAM in modern times (in Mexico, in 1970). Empiric use of chronic oral steroids in MS was a common therapeutic approach utilized in many countries in the hemisphere. For more than two decades, immunosuppression (azathioprine) was globally used (albeit reluctantly) in relapsing and progressive disease. The first published protocol, utilizing chronic oral low-dose cyclophosphamide in
1974, was not a controlled study but remains in use in some centers in Mexico and Central America instead of more advanced and safe DMTs.

Periodic intravenous cyclophosphamide pulses were not readily adopted in LATAM, particularly protocols with intensive immunosuppression (by adding plasma exchanges and ACTH). MS was just becoming an epidemiologically emergent disease in the region; hence, complex therapies proposed at the time were generally not attempted in the Americas.

In 1993, the US Food and Drug Administration (FDA) approved beta-interferon 1-b (BIFN 1-b), initiating the modern DMT era for MS. The manufacturing US company was confronted with a massive demand for the product, which overwhelmed the available supply. The manufacturer resorted to a computerized lottery for medication assignment using the numbers of the patient’s social security numbers. This process automatically excluded non-US citizens and non-US residents. Another manufacturing company offered to European and LATAM patients, a native beta-interferon acquired from human fibroblasts (Frone®) utilized in the management of ophthalmic herpes and hepatitis B. Frone® was used in relapsing MS in Mexico, Argentina, and Brazil until the release in 1997 of beta-interferon 1-a (BIFN 1-a), a recombinant interferon engineered from mammal cells (subcutaneous 22/44 mcg three times a week). Its efficacy was supported by a major controlled clinical trial. This product became the sole DMT utilized in LATAM since BIFN 1-b and eventually low-dose BIFN 1-a (intramuscular 30 mcg once-weekly) licensed by the FDA in 1995, and glatiramer acetate (GA), approved in 1998, were late in their entrance to the Latin American market (except in Argentina where these products were approved between 1995 and 1997). Subcutaneous BIFN 1-a 22/44 mcg was finally approved by the FDA entering the US market in 2002 after the results of the EVIDENCE trial.

Following the results of European studies indicating the synthetic anthrancenedione mitoxantrone was effective in “active” MS, the agent was approved in 2000 for the treatment of worsening relapsing–remitting MS (RRMS). Mitoxantrone was already available in LATAM as an oncological therapy; however, its use in MS was partially adopted in the region. The MS protocol administering 12 mg/m² intravenously every 3 months until reaching a total cumulative dose of 140 mg/m² is not generally followed in LATAM, most practitioners tending to use only a few doses then switching again to a platform DMT. In addition, mitoxantrone has remained as an off-label therapy for MS in LATAM since national licensing agencies have opted for its approval solely as an antineoplastic agent. Nevertheless, its use in LATAM has also declined due to safety concerns.

The FDA approved the first monoclonal antibody for RRMS, natalizumab, in 2004, removed it temporarily following the first cases of progressive multifocal leukoencephalopathy (PML), and finally restored it to the US market in 2006. Natalizumab became available first in Mexico in 2009, followed by Argentina, Brazil, and Costa Rica in 2010, Venezuela, Peru, and Dominican Republic in 2012, Chile in 2013, and Ecuador in 2015. Natalizumab can be prescribed only under special arrangements (usually financed by local SSIs) and in limited supply in most Central American countries, except Nicaragua. Serological antibody JCV index testing became available in these countries in 2015. Up to 2017, there have been two documented PML cases, both from Mexico.

Following their licensing by the FDA, DMT oral medications for RRMS, fingolimod (in 2010), teriflunomide (in 2012), and dimethylfumarate (in 2013), became rapidly available in LATAM. Fingolimod was launched in 2011 in Mexico, Brazil, and Argentina, and the following year in Colombia, Chile, Guatemala, Panama, Peru, Venezuela, and Dominican Republic. Teriflunomide was approved in Brazil in 2012, Argentina in 2013, and Mexico, Colombia, and Guatemala in 2014. Dimethylfumarate was licensed in Mexico and Argentina in 2015 followed by Colombia, Chile, and Uruguay in 2016.

The monoclonal antibody alemtuzumab has been available for MS in Mexico since 2013, a year earlier than its approval by the FDA. It is also licensed in Argentina, Guatemala, Chile, Brazil, and Venezuela. Starting in 2017, daclizumab and pegylated BIFN 1-a became available in Mexico through international insurance coverage, accessible only to a small fraction of the MS population.

After FDA grants licensing to a new MS therapeutic product availability in LATAM generally lags one to two years, and occasionally longer periods of time. Applications to regional licensing agencies are conditioned by marketing strategies and commercial interests of the pharmaceutical industry. Regulatory agencies throughout the Americas had in general lacked of adequate mechanisms and tools to evaluate new therapeutic molecules. The approval process of MS therapies in LATAM has gradually improved.
and refined in the last decade with the utilization of more scientific and technologically educated approaches by the regulatory authorities.

**Impact of generic therapeutic products**

Considerable discussions have ensued since the appearance of “generic” medications for MS in LATAM. Their access to the market and utilization in public health and social security institutions throughout the region has been greatly enabled in part by the unpreparedness of the licensing agencies to legally and technologically address this situation, and confounded by the lack of information and appropriate education of regulatory health officials. In many countries in the area practically half of the DMT are generic products.

The first biosimilar to compete with the brand innovator BIFN 1-b, was Uribeta® (Probiomed), Mexican product released in 2004. This medication was promptly incorporated into the formulary of the Mexican Institute of Social Security, the largest health institution in the country. Soon a number of additional biosimilar medications were produced in Mexico, Argentina and Uruguay, most remaining effectively competitive in the Latin American market (Table 1).

A common concern in LATAM is the frequent replacement in the official formularies (public health and social security institutions) of innovator DMTs by similar generic products without adhering to a consistent therapeutic schedule. In some clinics at one visit the patient may receive the original medication and a generic the following appointment; both medications simply identified by the institutional code, not the registered mark. Health providers are commonly required to prescribe in generic form, i.e. “beta-interferon 1-a, 44 mcg, subcutaneously 3 times a week,” not, for example, Rebif® (innovator) or as Emaxem® (biosimilar). The product provided is unknown to the recipient as well as the prescriber in most cases. This situation potentially compromises pharmacodynamics, efficacy, and eventually the potential acquisition of NEDA. Immunogenic aspects like neutralizing antibodies have not been studied in comparative studies. While the cost of biosimilars and generic CNBDs has not resulted in measurable savings for the institutions in LATAM, in some instances follow-on products would cost more to governmental and medical insurance entities than the original brands.

Glatopa®, the generic CNBD glatiramer acetate (equivalent to the innovator Copaxone®) was approved by the FDA in 2015 but has not been promoted in LATAM; however, Probiomed, the Mexican company with the largest line of generic medications for MS has produced Probioglat® (similar to Copaxone®), already available in the formularies of the SSIs in Mexico and being promoted in other countries in LATAM.

The major hindrance posed to all the biosimilar and generic CNBD manufactured in LATAM is the lack of data supporting clinical efficacy and safety. All these therapeutic molecules were approved basically unchallenged by the regulatory process mostly by presenting and adjudicating to each product the phase 3 clinical trial results obtained by the innovator studies. Biological studies on potency and molecular characteristics between innovator BIFN

| Table 1. Innovative and follow-on biosimilar and complex non-biological drugs. |
|-----------------------------------|----------------------------------|
| Reference medication | Generic product |
| **Biosimilars** | |
| • Betaferon®/Betaseron® | • Uribeta® (MX) |
| • Rebif® | • Emaxem® (MX) |
| • Avonex® | • Xerfelan® (MX) |
| • Rituxan® | • Neuraxa® (MX) |
| **Complex non-biological drugs** | • Blastoferon® (ARG) |
| • Copaxone® | • BetaIFN Clausen® (URU) |
| | • Jumtab® (MX) |
| | • Kikuzumab® (MX) |
| | • Probioglat® (MX) |

MX: Mexico; ARG: Argentina; URU: Uruguay.
1-a, 30 mcg and 44 mcg, and corresponding follow-on interferons, one each from Mexico, Uruguay, and Iran, revealed substantial differences in biological and immunologic behavior suggesting that despite some generic products are purportedly chemical “copies,” these molecules in fact are not similar therapeutic agents, but constitute in reality new drugs. These observations may have legal and regulatory implications. There are very few comparative studies between innovators and follow-on medications. Multicenter pharmacological studies in LATAM have shown reduced bioavailability of biosimilar BIFN 1-a (30 mcg) compared to the innovator. A small head-to-head study in Iran comparing a BIFN 1-a 30 mcg version (Cinnovex®) with the original brand product-disclosed no differences in efficacy and safety issues. The Iranian generic is not available in LATAM; similar studies have not been performed in this region hence duplication of these findings is lacking.

A potential template to address the concern of validity of clinical studies involving non-innovator medications is illustrated by the GATE trial (glatiramer acetate clinical trial to assess equivalence with Copaxone®), a randomized, double-blind, active and placebo-controlled phase 3 trial, comparing Glatopa®, the generic CNBD, with the brand innovator Copaxone® and placebo. This was the first MS pivotal study of a follow-on DMT medication trial demonstrating clinical equivalence with the generic product and the first time magnetic resonance imaging (MRI)-related outcomes were utilized as the primary endpoint to measure anti-inflammatory activity of the investigational drug.

Symptomatic management
MS requires of comprehensive and highly individualized symptomatic treatment since disease manifestations and comorbidities commonly contribute to disability and reduced quality of life. More than 65 different international trade brands and generic products, utilized in the management of the multiple symptoms ascribed or derived from MS, are generally available in LATAM to manage depression, fatigue, neuropathic pain, gait disturbance, spasticity, neurogenic bladder and bowel, erectile dysfunction, etc. Considering how symptomatic the disease may be, some patients would actually require one or several medications adding considerably to the direct gravamen of the cost care. Often the affected individual is unable to afford these therapies. Certain onerous medications, i.e. onabotulinumtoxin A injections for spasticity and dalfampridine for gait disturbance, are rarely employed despite of being available in some South American countries. Encouraged by law changes in some countries, oral cannabinoids offered for pain and spasticity are gradually entering the pharmaceutical scenario.

Access to MS care services
Treating MS is a complex endeavor considering that multiple tangible and intangible factors play a role in the management of disease, independent of medication therapy. These challenges are notorious in LATAM considering the majority of the countries in the continent remain in the phase of economic development, hence facing substantial limitations in providing adequate and organized health care, particularly addressing an emergent disorder like MS. In general the disease is not properly recognized by sanitary officials as a health burden in the region, therefore not considered as a priority disease deserving institutional support.

Most of the MS care in LATAM is provided by public health and social security institutions. Although private practice entities also provide attention to the MS patient, in general their scope is not integrated into a multidisciplinary fashion. While the presence of MS in LATAM has carried a notable socioeconomic impact involving large costs for diagnosis acquisition and access to DMT, compounded by symptomatic management and rehabilitation expenses, the diverse health systems in the hemisphere are not prepared to adopt MS care as part of their financial (or societal) responsibilities.

Some factors adjudicated to explain increasing MS identification in the Americas include modern neurological education and access to MRI studies in the area. Despite progress the MS population remains underserved in these respects. The World Health Organization (WHO), utilizing data from the European region and North America, considers a ratio of five neurologists/100,000 inhabitants as “service adequate.” This ratio, however, is suboptimal across LATAM: in Argentina is 2.9/1003, in Mexico and Brazil 1.2/1003, in Ecuador 1/1003, and in Bolivia, Nicaragua, and Honduras <1/1003. Only a very small fraction of neurological specialists in LATAM are considered “MS specialists” (i.e. by formal post-neurological residency training or Fellowship in MS).

Data on available MRI units per country from the Organization for Economic Collaboration and Development (OECD) lists only two LATAM countries: Chile in 20th place (9.43 units/million population) and Mexico in 27th (2.25 units/million population).
Japan leads with 51.67, followed by US with 38.9 units/million population.

Rehabilitation services are available in most secondary and tertiary level hospitals and institutional clinics in practically any major city in the continent; however, exceptionally few are targeted to the neurorehabilitation of the person with MS. Neurocognitive rehabilitation in the other hand, promoted by the Relevamiento Latinoamericano Cognitivo Conductual en EM (RELACCEM), a collaborative group involving Argentina, Chile, Colombia, Mexico, Uruguay, and Venezuela, is provided to at least 48% of MS patients in those countries.

Nursing in LATAM remains as a technical career reaching formal licensure in just a few countries. Nurses taking care of MS patients in this region have been trained or tutored institutionally. As late as 2017, there were still no nurses from LATAM certified by the International Organization of MS Nurses.

There are 15 MS patient associations in LATAM integrated as federation in Mexico and as individual private social entities in the rest of the continent. These groups maintain inconsistent communication with the MS International Federation since only the Argentinian, Brazilian, Chilean, and Uruguayan societies are full members. These associations do not influence licensing of MS medications in their respective countries. Local neurologists act as their clinical advisors in most cases.

DMT approval in LATAM countries does not necessarily reflect accessibility to the treatments. Multinational studies indicate that less than 35% of MS patients in LATAM (9.5% in Dominican Republic) have access to DMT despite the medication being commercially available after approval by their local regulatory agencies. These studies showed almost a similar utilization rate between intravenous gamma-globulin and plasma exchange with steroids in the management of acute relapses, and the common use of chemotherapeutic agents in substitution of bona fide DMT. This therapeutic option is perhaps motivated by the cost and frequent unreliability in supply of established DMTs (Table 2).

Access to therapy in Mexico remains low (≥42.8%), despite healthcare and services provided by the Public Health Ministry, four large SSIs, and private practices to more than 21,000 identified MS patients in the country. Mexico along with Argentina, Brazil, Chile, and Colombia are the only countries in the region where all FDA-approved DMTs, up to the first quarter of 2017, are theoretically available.

Public sanitary or health secretariats depend on national budgets assigned by the executive branch while SSIs have stronger financial resources since its economic structure is supported by labor, industry and government contributions. Traditionally, SSIs may be able to provide more DMTs and services to MS patients than public health systems. Still some countries, i.e. Republic of El Salvador’s national SSI, offers only three DMTs, and under limited bureaucratic supply to its eligible beneficiaries.

The impact of MS in mental and health-related quality of life among MS caregivers have been studies in Mexico demonstrating a strong association with anxiety, depression and decreased satisfaction with life, signaling the need to develop supportive interventions for Latino MS caregivers.

Adding to expenditures is the traditional tendency in LATAM to treat relapses through hospitalization care. The concept of outpatient management of MS exacerbations is yet to evolve within the general management options of MS in the region. The cost

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**Table 2.** Therapeutic armamentarium in 19 countries* of LATAM (modified and updated from Gracia et al.).

| Availability                  | % (n)  |
|------------------------------|--------|
| Treatment of relapse          |        |
| Methylprednisolone            | 100 (19)|
| IV gamma-globulin             | 100 (19)|
| Plasmapheresis                | 94.7 (18)|
| **Immunomodulators**          |        |
| Interferons                   | 100 (19)|
| Glatiram acetate              | 36.8 (7)|
| Biosimilars                   | 36.8 (7)|
| Natalizumab                   | 57.8 (11)|
| Alemtuzumab                   | 31.5 (6)|
| **Immunosuppressors**         |        |
| Azathioprine                  | 100 (19)|
| Cyclophosphamide              | 100 (19)|
| Mitoxantrone                  | 94.7 (18)|
| **Oral medications (3)**     |        |
| At least one medication       | 21.5 (4)|
| All three medications         | 26.3 (5)|

*Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, and Paraguay.
of a single relapse in Mexicans with RRMS has been estimated to be about one-third of the yearly cost of any platform DMT. \(^{32}\) Data from Argentina and Brazil reveal an extraordinary rise in the burden and cost of management as the disease becomes progressive and Expanded Disability Status Scale worsens. \(^{30,33}\)

The foundation in 1999 of the Latin American Committee for Treatment and Research in MS (LACTRIMS) created a continental organism that has gradually become the most significant stimulus for clinical education and epidemiologic studies in the region,\(^{34}\) development of therapeutic guidelines,\(^{35-39}\) and the most effective regional advocate for patients.\(^{40}\) MS care is complex and expensive. Adequate and universal access to therapies by this population poses a great challenge to health systems in the Americas where the price of each medication’s depends of local and importation tax laws and institutional bidding. Administrative goals and mechanisms of care delivery require to be redesigned. Transparent discussions and more opportunities for price negotiation between industry and health officials should ideally include participation and advice from MS professionals and national academic associations, contributing with evidence-based information and considerations on cost-effectiveness.

There is no evidence of an association between research and development costs and the price of medications. A more comprehensive utilization of economic resources by the health systems would potentially result in better efficiency in the care of individuals with MS in LATAM.

**Conflicts of interest**
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