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AU1) Previous sentence OK as edited? (“SSI programs provide health coverage to only some segments of the community, namely “actively economic populations”: workers who receive a salary and their direct family members.”) If not, please clarify meaning.

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MULTIPLE SCLEROSIS CARE IN LATIN AMERICA

Before the advent of diagnostic criteria for multiple sclerosis (MS), it was reported that the prevalence of MS in Mexico was “one of the lowest in the world” (1.6/100,000).¹ The notion that MS was a rare neurologic disease among those living in the tropics of the Americas and Southern latitudes was widely accepted. The geopolitical boundaries of the region identified as Latin America (LA) extend from the southern border of United States with Mexico (32° North latitude) to the Argentinian and Chilean Patagonia in South America (56° South latitude). The largest Spanish-speaking island countries in the Caribbean—Cuba, Dominican Republic, and Puerto Rico—are also traditionally considered part of LA. The continental mass includes 17 countries with a population of more than 550 million. Due to centuries of racial intermixing, it is a heterogeneous and genetically complex population. The blended cultures of native Amerindians with white Caucasian Europeans and black Africans has resulted in the predominant ethnic Latin American Mestizo. The influence of African genetics is notable in many areas of the subcontinent and the Caribbean. A common observation across LA is the absence of identification of MS in non-mixed Amerindians²; the reason for this phenomenon is unclear.

The rise in MS frequency in LA appears to be compounded by the advent of MRI technology to the region, the relative increase of neurologists, modern medical education, enhanced public awareness, and development of self-advocacy and patient groups. The current estimated prevalences in LA by Grupo Colaborativo Multicéntrico para el Estudio de la Esclerosis Múltiple en América Latina y el Caribe (GEEMAL),³ a multicenter collaborative group for the study of MS in LA and the Caribbean, show substantial zonal variations fluctuating from low to medium rates (≥ 5 to 25/100,000). Prevalence figures are based on data reported by GEEMAL. An extensive systematic review has addressed these epidemiologic aspects and raised interest in the role of environmental and genetic factors.⁴

The presence of MS in LA has had a notable socioeconomic impact; costs involved in diagnosis acquisition,

medications, and long-term care of the disease are challenging for a region where developing health systems are not designed or prepared to adopt MS care as part of their budgetary or societal responsibilities. This has resulted in limited access to US Food and Drug Administration (FDA)– or European Medicines Agency–approved disease-modifying therapies (DMT). The current therapeutic armamentarium—interferon- β (IFN- β)-1b, IFN- β -1a, glatiramer acetate, mitoxantrone, natalizumab, and the oral preparations fingolimod, teriflunomide, and dimethyl fumarate—is not completely available in most countries. Oral and IV steroids are universally utilized in acute relapses but access to symptomatic medications and rehabilitation facilities is limited while complementary and alternative therapies based on cultural beliefs are common. Utilization of third-party carrier insurance is rare. The core of national health care in all countries in LA is provided by their respective Health Ministry or Secretariat through public clinics, public hospitals, and national Social Security Institutes (SSI).

Public sanitary or health secretariats depend on national budgets assigned by the executive branch, while SSI organizations draw greater financial resources since their economic design is attached to labor, industry, and government contributions. This sociologic and administrative dichotomy does not facilitate access to care for patients with MS or other neurologic diseases.

SSI programs provide health coverage to only some segments of the community, namely “actively economic populations”: workers who receive a salary and their direct family members. Established SSI services are scarce, partially fulfilling services to beneficiaries in Argentina, Brazil, Chile, Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Panama, and Venezuela. Coverage for medications, rehabilitation, equipment, and disability benefits varies markedly among countries. Discrepancies in Latin American access to health care for MS are illustrated by the diverse level of coverage offered by SSI in the region. The causal differences are driven by national economic standings and by population numbers. Illustrative examples of these regional variables are outlined.

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The Caja Costarricense del Seguro Social (Costa Rica's Social Security) benefits 4.7 million people by national law, which is the entire population of the country. However, MS prevalence has been reported as 6/100,000. Despite this degree of coverage, patients with MS in Costa Rica would have access through the SSI to only 2 DMT, both interferon products.

The SSI in the Republic of El Salvador, Central America, has just recently included only IFN- β -1b in its formulary, despite this DMT being available internationally following FDA approval in 1993. The SSI in El Salvador provides services to less than 20% of a 6.2 million population. The reported MS prevalence is 3.0/100,000. The Mexican Institute of Social Security provides services to 27% of the national population (≥ 30 million out of a total population of 110 million). About 10% of Mexicans are recipients of health programs from military, bureaucratic, and private institutions. An estimated 63% of the population lacks health coverage. MS zonal prevalence in Mexico fluctuates from 12 to 30/100,000. The Mexican SSIs provide all first-line injectable therapies, interferons (IFN- β -1b and the 2 forms of IFN- β -1a) and glatiramer acetate. However, natalizumab, second-line therapy for relapsing MS, has not been included in the basic formulary due to cost-containment measures. However, it was approved by the national regulatory offices in 2010. The new oral medications fingolimod, teriflunomide, and dimethyl fumarate have also been licensed in Mexico but they are not available through its SSI system.

Concomitantly, generic products—biosimilar to interferon and glatiramer acetate—have been integrated into the SSI formularies, usually offered by locally producing pharmaceutical companies at a lower price than the original brands. Acquisition of generics by SSI limits the prescribing options for institutional neurologists. The argument for the relative economic savings does not consider the need for controlled studies establishing their efficacy, immunogenicity, and safety profiles. In every LA country, institutional transactions for medications are done via legal commercial bidding competitions. Prices of MS medications in the LA market also vary according to local import tax regulations.

Delegates from the Latin American Committee for Treatment and Research in MS (LACTRIMS) from 19 countries⁵ reported access to first-line DMT below 35%, options of a second-line agent (natalizumab) existing in 11 countries (47.3%), and oral medication (fingolimod) in 4 (21.0%).

Immunosuppressant medications (mitoxantrone, cyclophosphamide, azathioprine) were used in all countries (100%) in different phases of the disease and for different clinical types, frequently switching

intermittently to a bona fide DMT. This therapeutic schema is apparently due to the frequent unavailability of the prescribed DMT at the institutional pharmacy level.

Regulatory offices in LA licensing new medications and biotechnological products lack the expertise and technical tools required to assess efficiency and enforce pharmacovigilance of both innovative and follow-on therapeutic molecules.

LA populations are rarely included in clinical trials so LACTRIMS encourages participation of investigators in multicenter studies. Pharmacogenomic responses to DMT by these populations have not been explored. Education of health officials and their collaboration with national study and support groups is fundamental in elevating MS care in health systems priorities. Adequate access to MS care is a realistic concern in LA. Insufficient or inconsistent utilization of therapeutic disease modification may negatively influence long-term prognosis for substantial segments of the population. Redesigning administrative goals and adequate utilization of economic resources at the disposal of health systems would potentially result in better efficiency in the care of individuals with MS and disability management across LA.

AUTHOR CONTRIBUTIONS

Dr. Victor M. Rivera: study concept and design and supervision. Dr. Marco Tulio Medina: study concept and design. Dr. Reyna M. Duron: critical revision of the manuscript for important intellectual content. Dr. Miguel Angel Macias: acquisition of data.

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