Latin American algorithm for treatment of relapsing-remitting multiple sclerosis using disease-modifying agents

Algoritmo latino-americano para tratamento da esclerose múltipla remitente-recorrente utilizando drogas modificadoras da doença

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ABSTRACT

Objective: It is estimated that circa 50,000 individuals have relapsing-remitting multiple sclerosis in Latin America. European and North-American algorithms for the treatment of multiple sclerosis do not foresee our regional difficulties and the access of patients to treatment. **Methods:** The Latin American Multiple Sclerosis Forum is an independent and supra-institutional group of experts that has assessed the latest scientific evidence regarding efficacy and safety of disease-modifying treatments. Accesses to treatment and pharmacovigilance programs for each of the eight countries represented at the Forum were also analyzed. **Results:** A specific set of guidelines based upon evidence-based recommendations was designed for Latin America. Future perspectives of multiple sclerosis treatment were also discussed. **Conclusions:** The present paper translated an effort from representatives of eight countries discussing a matter that cannot be adapted to our region directly from purely European and North-American guidelines for treatment.

Key words: multiple sclerosis, treatment, Latin America.

RESUMO

Objetivo: Estima-se que haja aproximadamente 50.000 pessoas com a forma remitente-recorrente da esclerose múltipla na América Latina. Os algoritmos de tratamento norte-americanos e europeus não levam em consideração nossas peculiaridades regionais, nem a dificuldade no acesso ao tratamento por parte dos pacientes. **Métodos:** O Fórum Latino-americano de Esclerose Múltipla é um grupo de especialistas independente e suprainstitucional, que avaliou as mais recentes evidências científicas sobre a eficácia e a segurança das drogas modificadoras do curso da doença. Foram avaliados também o acesso ao tratamento e os programas de farmacovigilância de cada

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um dos oito países representados no Fórum. **Resultados:** Uma lista específica de recomendações baseadas em evidências científicas foi estabelecida para a América Latina. Também foram discutidas perspectivas de futuros tratamentos para esclerose múltipla. **Conclusões**: O presente estudo representou um esforço dos representantes de oito países latino-americanos em discutir um assunto que não pode ser adaptado para uso em nossa região diretamente a partir de recomendações de tratamento europeias ou norte-americanas.

Palavras-Chave: esclerose múltipla, tratamento, América Latina.

Multiple sclerosis (MS) treatment in Latin America is a dynamic process due to the approval of new drugs worldwide, with particular emphasis on oral drugs at this moment. The introduction of these drugs in Latin American countries tends to be gradual, using data from local pharmacovigilance programs and often based on studies carried out in other continents. The potential patient population in the region presenting relapsing-remitting MS (RRMS) is estimated to be of the order of 50,000 people[1], while its prevalence varies between 1.48 and 25 per 100,000 inhabitants[2-8]. The main objectives of the present study were to update the therapeutic algorithm designed in 2010[9] and to assess the use of medications in several countries of the region. The present study focused on the first, second, and third-line therapeutic options, while a detailed and updated discussion on MS diagnosis can be found elsewhere[10].

A literature search was carried out at PubMed database, using the key words 'multiple sclerosis', 'relapsing-remitting', 'drug therapy', 'disease-modifying drugs', and the internationally recognized name of each individual compound. More recent papers and systematic reviews with solid levels of evidence were selected by the group. Studies involving Latin American populations were also included.

Since 2009, the Latin American MS Forum has been meeting annually with the intention of analyzing the latest advances in MS management. The 2011 meeting took place in Brazil and included a panel of 12 independent neurologists, with experience in MS. These experts were from Argentina, Brazil, Chile, Colombia, Mexico, Peru, Uruguay, and Venezuela. Based on the selected papers, the available level of evidence of each disease-modifying drug was analyzed regarding efficacy and safety. Additionally, health system coverage of expenditure on drugs and pharmacovigilance programs was assessed in individual countries. Drugs under analysis for approval and generic medications without scientific evidence were also discussed. The panel also took into consideration treatment of children with MS. It was agreed that a recommendation would be considered to be 'approved' when at least 10 out of the 12 experts (83.3%) accepted it.

DISEASE-MODIFYING DRUGS

RRMS treatment is based on different therapeutic lines, which are classified according to the available evidence regarding use, efficacy, and toxicity of medications. The first line of therapy comprises Glatiramer Acetate and Interferon-beta. The second one includes Natalizumab and Fingolimod. In case of further therapeutic failure, treatment progresses to a third line, represented by Rituximab and Alemtuzumab. The fourth line includes bone marrow transplantation and high doses of cyclophosphamide. Figure presents the treatment algorithm proposed for Latin America. In addition to the abovementioned drugs, a review on Mitoxantrone, Methotrexate, and Azathioprine has also been conducted in order to make recommendations for their use in Latin America, while several aspects regarding generic medications have also been discussed.

FIRST LINE OF TREATMENT

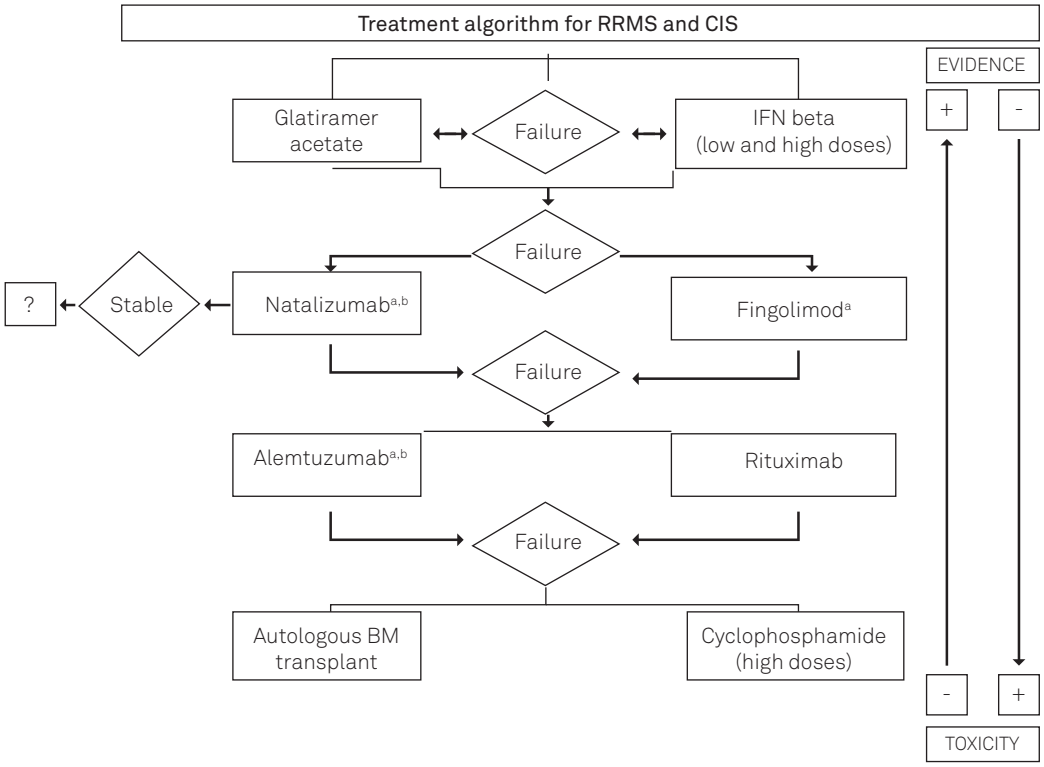
Glatiramer Acetate and Interferon-beta (low or high doses) are the first line of treatment options. Their efficacy and safety are well established and can be found in other sources[9]. Patients initially treated with low-dose interferon that present therapeutic failure must be switched to glatiramer acetate. Patients initially treated with glatiramer acetate that present therapeutic failure must be switched to high-dose interferon. There is no evidence supporting a switch between low and high doses of interferon[11].

SECOND LINE OF TREATMENT

The second line comprises Natalizumab and Fingolimod. There is no evidence allowing recommendation of one drug over the other.

Use of Natalizumab is supported by level I evidence. In all countries belonging to this forum, the drug has been approved or is undergoing approval. Its efficacy and anti-inflammatory activity translate into a significant decrease in relapse rates and disability (measured on the Expanded Disability Status Scale — EDSS), as well as a decrease in gadolinium-enhancing lesions and new ones, as assessed using magnetic resonance imaging (MRI)[12,13]. Safety measures include serum assessment of JC virus (debatable importance), MRI (not less than three months before drug infusion — baseline), chest radiography, blood cell count (before each infusion, requiring neutrophils above 1,500/mm^3 and lymphocytes above 1,000/mm^3), and lymphocyte CD4/CD8 phenotype every three months.

The most serious complication of this drug treatment is the development of progressive multifocal leukoencephalopathy



[a]There are no comparative studies allowing selection of one or another second-line drug; [b]if treatment with natalizumab is to be continued, the recommendation is to obtain a new informed consent; RRMS: relapsing-remitting multiple sclerosis; IFN: interferon; BM: bone marrow; CIS: clinically isolated syndrome.

Figure. Latin American treatment algorithm for relapsing-remitting multiple sclerosis and for clinically isolated syndrome, in 2011.

(PML), with a risk that increases considerably after two years of continuous treatment[14-16]. At present, there are no biomarkers preceding the development of PML, and no evidence allowing recommendations to be made for a stabilized patient after a period of Natalizumab treatment (i.e., to continue with natalizumab or to return to a first-line therapeutic option). This decision must be based on each individual case. The experts highlighted the importance of making the risks clear to patients, if treatment with Natalizumab is to be continued, and suggested that a new informed consent should be signed by all parties.

One important precaution is to administer the drug at a recognized infusion center, with continuous monitoring by a certified doctor throughout the period of infusion (in Argentina and Brazil, the recommendation is to have immediate access to a cardiac defibrillator during infusion). Drug administration must be made on a regular basis (Natalizumab 300 mg by means of intravenous infusion every 28 days). If the patient presents any clinical changes leading to suspected relapse of PML, MRI should be performed. A washout period must be observed prior to natalizumab treatment, with at least a six-month interval if the patient has received any previous oral immunosuppressive drugs, and a one-year interval if he/she has previously been treated with intravenous immunosuppressive drugs. Natalizumab is not recommended for patients with positive serum tests for HIV and HTLV (Human T lymphotropic virus) viruses or with active tuberculosis, or for those who have at any time been treated with Rituximab. The countries represented in the Forum have adopted different pharmacovigilance programs for this drug: in Argentina, there is monitoring of prescriptions, in Colombia and Venezuela, there is a Technical Assistance Program for Tysabri® Prescribers (PATTY); while Mexico and Brazil are monitoring its use by their own national health programs.

Fingolimod was approved by the Food and Drug Administration (FDA) as a first-line treatment; however this is controversial due to the serious side effects that have been reported when using this drug. Due to the lack of long-term safety data, the experts recommend that fingolimod should be used as a second-line option when there is therapeutic failure with Glatiramer Acetate or Interferon-beta, or for patients with very active and aggressive MS or those with rapidly progressing disease. Use of Fingolimod is supported by level I evidence, published data shows that oral Fingolimod 0.5 mg/day reduced the relapse rates, as well as the new lesions and gadolinium-enhancing new lesions on MRI[17,18]. The main adverse events with this drug are cardiac (severe bradycardia and atrioventricular block), meaning that the patients need close cardiac monitoring following the first drug administration, and periodic monitoring thereafter[19]. The patient's follow-up must include periodic ophthalmological monitoring (for macular edema) and dermatological assessments (for

varicella and herpes infections). Among the additional precautions necessary during this treatment, pregnancy must be reported to pharmacovigilance programs, since the drug must be withdrawn, and vaccination with live attenuated organisms should be avoided. In the majority of countries represented in this Forum, Fingolimod is undergoing approval and no specific pharmacovigilance programs have been designed. In Argentina, this drug is controlled by the Risk Evaluation and Mitigation Strategy (REMS) pharmacovigilance program.

THIRD LINE OF TREATMENT

Alemtuzumab is approved in several Latin American countries for treatment of hematological diseases, but its indication for MS still awaits results from phase III clinical trials. Its use as a third-option drug for very aggressive RRMS is supported by level I evidence, with reports presenting relapse rate reduction, decreased brain atrophy measurements, and EDSS improvement[20,21]. The recommended dose is from 12 to 24 mg/day administered by means of intravenous infusion, requiring two to three infusions per year. The precautions for use of Alemtuzumab are similar to the abovementioned ones for Natalizumab[22]. The main adverse event related to this drug is autoimmune disease (thrombocytopenic purpura, hyperthyroidism, hypothyroidism, and thyroiditis). The medication has not yet been approved for use in MS and, therefore, there are no specific implemented programs for pharmacovigilance, although they are to be expected.

Rituximab is approved in all countries represented in the Forum for diseases other than MS (hematological diseases and rheumatoid arthritis)[9], and its use in MS is justifiable only in isolated cases[23]. The recommended dose is two pulses of 1,000 mg/day administered by means of intravenous infusion on days 0 and 15. The cycle should be repeated after six months 24. This drug must not be prescribed for HIV-positive patients.

USE OF OTHER DRUGS IN SPECIAL SITUATIONS

Mitoxantrone is approved in the majority of the countries represented in the Forum and has been used as an induction treatment for very aggressive MS (non-responsive, rapidly progressive, secondary progressive and very active MS), prior to treatment with first-line drugs[25]. In these cases, this drug reduces relapse rates and the disability assessed by the EDSS score, thereby delaying disease progression. Its efficacy is supported by level I evidence[26]. MRI shows a reduction in the number of new lesions and new gadolinium-enhancing ones[27].

Several studies have shown beneficial effects in the secondary progressive form of the disease, although the therapeutic schemes used in them have varied considerably, thus making it particularly difficult to compare data among different studies[28-30]. Risks associated with Mitoxantrone treatment include the development of leukemia, cardiotoxicity (12 to 25% of the cases), and infections if the dose exceeds 60 mg/m^2. However, the latter cannot be taken as an absolute statement, since the dose must be determined individually, according to the patient's characteristics, the disease itself, and previous treatments. For example, administration of Methylprednisolone may mask the development of cardiotoxicity. This toxicity and the different criteria used to define 'very aggressive' and 'very active' forms of MS have severely limited use of this drug for rescue therapy in some countries[31-34], but the Forum does not recommend its use in a regular manner. Strict cardiological follow-up must be carried out for further two years beyond the end of therapy, including echocardiography, assessment of ventricular ejection fraction, and cardiac Holter. The monitoring should also include blood cell counts on a regular basis for at least two years after the drug has been suspended, and cases of leukemia must be notified. Use of Mitoxantrone is subject to each country's national pharmacovigilance program.

Methotrexate has different recommendations in the countries represented in the Forum. While in Argentina it is used solely as part of combined therapies for non-responsive patients, some neurologists in Brazil may use this drug for no longer than two years (consecutive or with interruptions), although the Brazilian protocol does not include this drug for MS treatment. Use of Methotrexate for MS is supported by level IV evidence. The medication has been approved and is available in all countries of the Forum. A literature review on this drug[35] showed that it presents considerable adverse events with the recommended 7.5 mg/week dose, while no significant therapeutic effect can be observed in relation to placebo or other medications[36]. Therefore, the Forum does not recommend using methotrexate for MS. The experts highlighted that, if the drug is to be used at all, fertile female patients must use efficient contraceptive methods. In the Latin American countries represented in the Forum, use of this drug is subject to the individual national pharmacovigilance program.

Administration of Azathioprine has been approved in all countries in this Forum, although there are differences in its recommendations. In Argentina and Colombia, it is used for RRMS patients undergoing combined therapy (associated with low-dose interferon) as a third-line treatment. In Colombia, the recommendation from the Colombian Neurological Society[37] is to maintain this treatment for no longer than two years. In Brazil, azathioprine is an option for patients who cannot tolerate injectable drugs; while in Chile and Uruguay, it is used as a second-line therapy. In Mexico and Peru this drug is used for secondary progressive MS or for patients with very active disease (in Peru it is also used if patients do not have access to immunomodulatory drugs); and in Venezuela, it is not recommended at all. There are few systematic reviews regarding the efficacy and

safety of azathioprine and its use is based on level II evidence and type C recommendation[38-40]. Based upon these data, the Forum does not recommend use of azathioprine in a systematic manner and, if the drug is to be used, then clinical and laboratorial monitoring (blood cell count and liver function) must be performed every three to six months. Regarding pharmacovigilance on azathioprine, all countries use their general national program for it.

Cyclophosphamide is recommended as a rescue therapy in RRMS cases that are resistant to previously discussed treatments, as well as in rapidly progressive or 'very active' MS, or in those in which the patient has poor prognosis. The 2007 Cochrane review[41,42] showed that, in general, the published studies are limited to small groups of patients, and very few trials have followed the recommendations for randomization, double-blinding and placebo control, thus giving the drug level II evidence, with type C recommendation. With the exception of the previously mentioned situations, the Forum does not recommend cyclophosphamide, because of its severe adverse effects, which include sepsis (including five recorded cases of death), alopecia, amenorrhea and cystitis[43], and neutrophil ablation[44,45].

The experts advised against use of generic medications due to the lack of data supporting their bioequivalence and bioavailability. Furthermore, it is not possible to establish the efficacy and safety of generic medications available in some countries represented in the Forum (Argentina, Mexico, Peru, and Uruguay), since there are no published papers in indexed journals. Considering the ever-growing availability of these products in Latin America and for political and administrative issues relating to approval of these drugs, the experts highlighted risks involved in the indiscriminate use of original and generic medications for treating patients with MS.

PHARMACOVIGILANCE SYSTEMS AND MULTIPLE SCLEROSIS TREATMENT COVERAGE IN LATIN AMERICA

Each country presented their pharmacovigilance systems and coverage programs for expenditures relating to MS treatment (Table 1).

Being aware of new drugs development and of the importance of seeking comprehensive and trustworthy pharmacovigilance data, the Forum proposed that a supranational database with information on drug safety and efficacy should be created, with the aim of long-term data collection.

PEDIATRIC MULTIPLE SCLEROSIS

Although a relatively rare condition, pediatric MS (Ped-MS) is important because of its impact on a stage of life involving growth and development. It may represent up to 10% of MS cases. In general, it is manifested as RRMS with a higher relapse rate than that observed in adult patients. However, at present, there are no data on clinical trials carried out with disease-modifying agents among children and adolescents with MS that could provide level

Table 1. Pharmacovigilance systems and expenditure coverage for drugs in Latin.

Country	Covered population	Source of coverage	Pharmacovigilance program
Argentina	Total	Public System Private System	Optional information from doctors and compulsory ones from the pharmaceutical industry to ANMAT; special natalizumab program developed for the country by the pharmaceutical company.
Brazil	Total	Public Health System	National program for reporting adverse events (ANVISA).
Chile	Total	Plan for Specific Health Guarantees	National program carried out by CENIMEF. There is no compulsory reporting. It is foreseen that special programs for recently developed drugs (natalizumab, fingolimod) will be implemented.
Colombia	Total	Law 100, Compulsory Health from the Social Security Institute	National program (RIPS). PATTY program for natalizumab.
Mexico	~80% of all patients with RRMS (not for SPMS)	Social Security	National program (COFEPRIS).
Peru[a]	25%	Social Security (clinically defined forms of MS, no CIS)	Adverse events reported by the pharmaceutical industry to the National Pharmacovigilance Service at DIGEMID. A special program for natalizumab is envisaged.
	2%	Military and police personnel (RRMS)	
	10–15%	Private System	
Uruguay	Total	National Resource Funds	National program (National Pharmacovigilance Center).
Venezuela	90%	Venezuelan Institute of Social Security	National program (National Pharmacovigilance Center). PATTY program for natalizumab.
	10%	Military Health	

America, according to country, in 2011.
MS: multiple sclerosis; RRMS: remitting-relapsing multiple sclerosis; ANMAT: Drug, Food and Medical Technology Administration; ANVISA: National Agency for Sanitary Vigilance; CENIMEF: National Database Center for Drugs and Pharmacovigilance; COFEPRIS: Federal Committee for Protection Against Sanitary Risks; DIGEMID: General Direction for Medications, Supplies, and Drugs; PATTY: Technical Assistance Program for Tysabri® Prescribers; RIPS: Individual Registration for the Health Service; CIS: clinically isolated syndrome; SP: Secondary Progressive MS; [a]The Peruvian Health System cares for 60% of the population in the country, but does not cover MS treatment.

I evidence[46]. The available evidence come from observational studies including case series[47]. In the absence of specific clinical trials regarding treatment of clinically isolated syndrome (CIS) and RR disease in children and adolescents, the treatment is based upon clinical experience and uses information from treatment of adults with MS[46].

None of the presently available disease-modifying agents for treating adults has been formally approved for treatment of children and adolescents[46]. However, the main choices are first-line treatments (one of the immunomodulatory drugs, i.e., interferon or glatiramer acetate), which appear to be safe and well tolerated in younger patients[47]. As is the case with adults, in Ped-MS it may be necessary to escalate the treatment, but experience with second[48,49], third[50], and fourth[51] lines of therapy in children and adolescents is limited and based upon anecdotal evidence.

The experts assessed the situation of pediatric patients in different countries, regarding specialists caring for these cases (general neurologists, pediatricians, and neuropediatricians) and medications that are prescribed in daily practice. It was observed that in Argentina, Ped-MS is usually treated by neuropediatricians, although cities in its countryside may not have such specialists, therefore general neurologists may treat them. The drugs used for these patients are interferon and glatiramer acetate. All immunomodulatory drugs accepted for adults were also approved for children in Brazil, where neurologists caring for adults with MS usually are also responsible for Ped-MS, unless there is a neuropediatrician in the group. The same medications used for adults are also recommended for Ped-MS in Colombia, but for those younger than 15 years of age and for those with weight lower than 40 kg, the recommendation is to start treatment using one third of the adult dose of interferon.

Patients are cared for by neurologists who are specialists in MS, together with neuropediatricians. At the time of the present work, Chile had only eight reported cases of Ped-MS, all of them undergoing treatment with interferon. In Mexico, all cases of Ped-MS are treated by neuropediatricians (the majority of cases using Interferon-beta and a few cases, Glatiramer Acetate). The few detected cases of Ped-MS in Peru were referred to general neuropediatricians or neurologists with experience in treating MS. There is no medication specifically approved for Peruvian children, but all detected cases are undergoing treatment with interferon. Pediatric patients in Uruguay are treated by neuropediatricians up to the age of 15 years, and by neurologists thereafter. The main prescribed treatment is Interferon beta 1-b and, in lower proportion, Interferon beta 1-a and Glatiramer Acetate. Treatment of pediatric cases in Venezuela (approximately 60 cases) is carried out by neuropediatricians, who prescribe all present available drugs. A recent case of Natalizumab treatment in a patient younger than 18 years-old was mentioned by the Venezuelan panelist.

NEW CONCEPTS AND THERAPEUTIC AIMS

The experts discussed new concepts relating to MS treatment. Drugs developed more recently have made it possible to aim towards new therapeutic outcomes, such as reaching disease remission or having a patient classified as 'free from disease activity' (absence of relapses and of disability progression, with stable MRI)[52]. This concept was based on the possibility of establishing the disease activity level in a more trustworthy manner, measured using new MRI techniques (functional MRI and magnetic transference image).

The panelists also highlighted the importance of correlating the image with the clinical manifestations, including a neurocognitive assessment on MS patients. Even if the most used scale for measuring disease progression is EDSS, the MS Functional Composite was suggested to be always applied if the treatment unit has properly trained professionals, thus allowing better assessment of cognitive deterioration. The Brief Repeatable Battery is another useful tool for assessing cognition, has been validated in Latin America[53], and a variety of neuropsychological tests can be considered for patients' assessment[54]. It can be applied by neurologists specially trained for using it, and systematic use of this battery could help in screening cognitive decline. If necessary, the neurologist should refer the patient to a neuropsychologist for further testing. The Mini-Mental State Examination, on the other hand, has no use for neurocognitive assessment of MS patients. Beyond neurocognitive testing, it was also recommended that regular assessment of quality of life should be made as part of the patients' follow-up. For this purpose, the experts suggested that the MS Quality of Life Scale should be used, which is more specific than the Short Form (36) Health Survey (SF-36) .

The present work may have had some limitations. Part of the literature review used here is related to clinical trials carried out mainly among European and North-American subjects, who may have different epidemiological characteristics and comorbidities to those of a Latin American population. Even inside Latin America, there may be differences depending on the abovementioned variables for each country. However, there are Latin American published papers that are not PubMed indexed and, therefore, their information may be underrepresented in our analysis. In accordance with the Forum objectives, the experts focused on the therapeutic aspects of MS in Latin America and did not discuss some general points, such as induction therapy, which is hardly ever used in the countries represented in this meeting. Lastly, some studies used here for assessing drug efficacy have methodological differences, which make it difficult to establish comparisons.

Decision-making in relation to RRMS is becoming more complex because of the growing availability of drugs and the lack of studies comparing them directly among each other. The experts have designed a therapeutic algorithm based on scientific evidence, including recommendations

on disease-modifying drugs recently or undergoing approval processes. The analysis on the risk-benefit profile of each drug takes into consideration the efficacy and safety of the compound and the specific characteristics of Latin American patients (high prevalence of tuberculosis and HTLV). This work took into consideration monitoring through pharmacovigilance programs and recommended wide access to all available treatments. The panel proposed that a supranational pharmacovigilance database should be created, with the aim of enabling wide-ranging data gathering and, hence, fast decision-making in the future, based on experience.

COMMENTS FROM EXPERTS

RRMS treatment in Latin America must take into consideration the epidemiological characteristics of patients from this region, as well as the political and administrative circumstances that affect therapeutic decisions. These issues include the high prevalence of HTLV and tuberculosis, the fact that some countries lack approval for widely used drugs in other countries, the introduction of generic medications, and the degree of expenditure coverage by the health systems. For some countries in which the patient population undergoing treatment is small, joint work by regional forums enables optimization of clinical experience, access to pharmacovigilance data, and knowledge on the disease, thus ultimately resulting in better clinical practices based upon the latest available scientific evidence.

PERSPECTIVES FOR THE NEXT FIVE YEARS

The first oral treatment for MS (Fingolimod) was recently approved by the FDA (USA) in September 2010 and by the European Medicines Agency (EMA) in January 2011. Nonetheless, until a time is reached when more data regarding long-term safety are available, it is likely that different formulations of interferon-beta and Glatiramer Acetate will continue to be the preferred first-line treatments for patients with less active MS. The extension of Natalizumab treatment beyond two years will possibly depend on evidence of usefulness in JC virus detection assays. This may be of prognostic value in relation to the likelihood of developing PML, but the availability of this assay in Latin America also has to be taken into consideration. Phase III trials were recently concluded for cladribine, and the results led to treatment rejection for MS by the FDA. The therapeutic panorama may also be modified through approval of other drugs for MS, which currently under phase III clinical investigations include Alemtuzumab, Teriflunomide, Laquinimod, BG-12, Daclizumab and pegylated IFN β-1a.

CONCLUSIONS

Diagnostic and therapeutic aspects of MS in Latin America differ from those used in Europe and in the United States due to several aspects, including epidemiological, economical, and sanitation factors. The availability and coverage of drug-related expenditure by the public healthcare systems are not uniform. The Forum recommended that all medication currently approved for treatment of MS needs to be available for Latin American patients, independently of their economic and social conditions. Results from this Forum might ultimately be used by physicians and health care authorities, while discussing drug availability in Latin American countries. Finally, a supranational database should be created to enable retrieval of long-term pharmacovigilance data from the region.

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