

# Current and emerging treatments for relapsing multiple sclerosis in Argentinian patients: a review

Juan I Rojas  
Liliana Patrucco  
Edgardo Cristiano

Multiple Sclerosis Center of Buenos Aires, Neurology Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

**Abstract:** Multiple sclerosis (MS) is an autoimmune disease of the central nervous system. Recent developments have led to newer therapeutic options for disease treatment. A few studies have reported MS prevalence rates between 12 and 20 per 100,000 inhabitants nationwide in Argentina, and an incidence of 1.76 cases per 100,000 inhabitants per year. Considering the epidemiology of MS in Argentina, the total number of patients affected is estimated at 5,000–8,000 patients, with nearly 55%–65% of patients having a relapsing-remitting MS subtype of the disease. The aim of this review is to provide an overview of current and emerging treatments available in Argentina for patients with MS.

**Keywords:** multiple sclerosis, Argentina, treatments, disease-modifying drugs

## Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system in which environmental factors act together in a genetically susceptible individual to produce the disease.<sup>1</sup> After car accidents, the disease is the second most common cause of neurological disability, compromising the patient's quality of life, their social activities, and their environment.<sup>2</sup>

Despite the fact that much information exists about the disease in terms of epidemiology, clinical course, prognostics, health insurance, and costs, much of this information has come from developed countries; there is scarce evidence regarding MS in developing countries from South America.<sup>3</sup>

Here, we describe aspects of MS in Argentina with regard to health insurance, regulatory agencies, and finally, the disease-modifying drugs available for treatment of the condition.

Argentina is located in the southern part of South America. With an area of 2,780,400 km<sup>2</sup> and almost 40,000,000 inhabitants, Argentina is the eighth largest country in the world and the largest Spanish-speaking nation.<sup>4</sup>

The country has an extremely segmented health system, consisting of three large sectors: public, private, and managed care (the last two systems cover a population of nearly 18.3 million people, distributed among close to 300 entities of varying scope and size). Beneficiaries of the private system can freely choose their health maintenance organization, and ten of these organizations account for nearly 50% of the covered population. The public system covers 35% of the population and includes mainly uninsured people under Ministry of Health programs, high-cost programs with special reimbursement, and public hospitals. The private system includes almost

Correspondence: Juan Ignacio Rojas  
Multiple Sclerosis Center of Buenos Aires, Hospital Italiano de Buenos Aires, Perón 4272, CP1411, Buenos Aires, Argentina  
Tel +54 11 4959 0322  
Fax +54 11 4959 0322  
Email [juan.rojas@hospitalitaliano.org.ar](mailto:juan.rojas@hospitalitaliano.org.ar)

5% of the population, and the managed care system, which includes almost 60% of the population, covers employees and their families.<sup>5</sup>

In Argentina, the National Administration of Drugs, Foods, and Medical Devices is an agency created in 1992 to participate in the protection of human health by assuring the quality of the products it regulates (drugs, foodstuffs, medicinal products, diagnosis reagents, cosmetic products, dietary supplements, and household cleaning products).<sup>6</sup> The agency's professionals and technicians perform the process of authorization, registration, standardization, vigilance, and monitoring of the products used in the human medicine, food, and cosmetics fields throughout the country. The administration's main objective is to guarantee that drugs, foodstuffs, and medical devices are compliant in terms of efficacy, safety, and quality. Its work is analogous to that of the US Food and Drug Administration in the United States or the European Medicines Agency in the European Union.<sup>6</sup>

With regard to MS disease characteristics, in Argentina, a few studies report MS prevalence rates of 12–20 per 100,000 inhabitants in the region of Buenos Aires (latitude, 34°S).<sup>3,4,7</sup> The vast majority of the population in this area is of European descent (mainly Spanish and Italian), and only a minority of groups include mestizos (a Spanish term used to designate people of mixed European and Amerindian ancestry living in the region of Latin America).<sup>7,8</sup> In a study performed in Patagonia, the southern region of the country, the prevalence reported was similar to that of Buenos Aires, with almost 17.2 patients per 100,000 inhabitants in 2002 for a total surface area of 768,165 km<sup>2</sup>.<sup>9</sup> Previous studies showed that Argentina is a medium-risk area for MS.<sup>3</sup> Only one study in the country evaluated the incidence of MS.<sup>10</sup> The study was conducted on the population of a health maintenance organization in Buenos Aires between 1991 and 2007 and showed an incidence density of 1.76 cases per 100,000 inhabitants per year.<sup>10</sup> Considering the epidemiology of MS in Argentina provided by previous studies, the total number of patients affected is estimated at 5,000–8,000 patients, with nearly 55%–65% of patients having a relapsing-remitting MS (RRMS) subtype of the disease.<sup>11</sup> Regarding the cost of the disease in Argentina, a recent study evaluated this issue in affected patients.<sup>12</sup> The study showed that MS imposes a significant economic burden on the Argentinean society. The mean annual cost per patient was estimated at US\$36,025 in patients with an expanded disability status scale (EDSS) between 0 and 3 and reached US\$50,712 in patients with an EDSS 7. The economic burden increases with higher physical disability. This was accounted for by the increase in resource use of medical visits, informal

care, professional care, sick leave, and retirement because of MS in the analyzed sample.<sup>12</sup> Regarding specific medications to treat MS, drugs are covered 100% on a case-by-case basis by national and provincial governments.<sup>5</sup>

This information has been compared with data from the rest of Latin America. A recent epidemiological review of the region demonstrated that the prevalence of MS ranges from 0.75 to 21.1 cases per 100,000 inhabitants, with the highest prevalence being reported in Brazil, Argentina, and Martinique of the West French Indies (15–21.1 cases per 100,000 inhabitants), whereas the lowest prevalence reported was in Colombia and Ecuador (0.75–5.05 cases per 100,000 inhabitants).<sup>7</sup> The distribution of population genetics could account for the observed differences in the countries of Latin America. In Argentina, for example, the population is predominantly Caucasian, whereas in Colombia and Ecuador, it is predominately mestizo. This may partially explain the higher risk for MS in the southern part of the continent when compared with the central region.<sup>7</sup>

## Current disease-modifying therapies for multiple sclerosis in Argentina

Treatment options mainly tend to halt or slow the progression of disability as well as provide a reduction in the relapse rate of affected patients.<sup>13</sup>

The current treatment options available in Argentina are discussed here (Tables 1 and 2).

### Interferon beta

Interferon beta (IFN beta) has been demonstrated to be effective in controlling disease activity in MS, but the precise mechanism of action of IFN beta remains to be defined. Its anti-inflammatory activity in MS is dominated by antiproliferative and proapoptotic effects via molecular changes that include the expression of Fas/Fas ligand, p53,

**Table 1** Current and emerging disease modifying drugs in Argentina\*

DMD	Status	Year of approval in Argentina
IFN beta-1b subcutaneously	Available	1995
IFN beta-1a intramuscularly	Available	1996
IFN beta-1a subcutaneously	Available	1997
Glatiramer acetate	Available	1997
Natalizumab	Available	2010
Fingolimod	Available	2011
Teriflunomide	Available	2013
Alemtuzumab	Under evaluation	–
BG-12	Under evaluation	–

**Note:** \*Information collected in December 2013.

**Table 2** Current approved disease-modifying drugs in relapsing multiple sclerosis in Argentina

Agent (route and frequency of administration)	Trade name (company)	Effect on disease activity relative to placebo			
		Relapse rate	MRI active lesions	Confirmed EDSS progression*	Change in T2 lesion volume
IFN beta-1b (subcutaneous injection every other day) <sup>20</sup>	Betaferon® (Schering, Berlin, Germany); Betaseron® (Bayer, Leverkusen, Germany); Extavia (Novartis, Basel, Switzerland)	Annualized, –34% ( $P=0.0001$ )	–83% ( $P<0.009$ )	–29% (not significant)	–17.3% ( $P=0.001$ )
IFN beta-1a (intramuscular injection once a week) <sup>21</sup>	Avonex® (Biogen Idec, Weston, MA, USA)	Annualized, –32% ( $P\leq 0.04$ )	–36% ( $P=0.05$ )	–37% ( $P=0.02$ )	–4% (not significant)
IFN beta-1a (subcutaneous injection, three times a week) <sup>23</sup>	Rebif® (EMD Serono/Pfizer, Darmstadt, Germany)	Mean, –32% ( $P<0.005$ )	–78% ( $P<0.0001$ )	–30% ( $P<0.05$ )	–14.7% ( $P<0.0001$ )
Glatiramer acetate (subcutaneous injection, daily) <sup>26</sup>	Copaxone® (Teva Pharmaceuticals, Petah Tikva, Israel)	Mean, –29% ( $P=0.007$ )	–35% ( $P<0.001$ )	–12% (not significant)	–8.3% ( $P=0.0011$ )
Natalizumab (intravenous infusion every 4 weeks) <sup>28</sup>	Tysabri® (Biogen Idec, Weston, MA, USA/Elan Pharmaceuticals, Dublin, Ireland)	Annualized, –68% ( $P<0.001$ )	–83% ( $P<0.0001$ )	–42% ( $P<0.001$ )	–18% ( $P<0.001$ )
Fingolimod (daily pill, 0.5 mg) <sup>35,36</sup>	Gilenya® (Novartis)	Annualized, –54% ( $P<0.001$ )	–82% ( $P<0.0001$ )	–37% ( $P<0.05$ )	–69% ( $P<0.0001$ )
Teriflunomide (daily pill, 14 mg) <sup>38,39</sup>	Aubagio® (Genzyme, Cambridge, MA, USA/Sanofi, Paris, France)	Annualized, –31.5% ( $P<0.001$ )	–80% ( $P<0.001$ )	–29.8% ( $P=0.03$ )	–76.7% ( $P<0.001$ )

**Note:** \*Definitions for EDSS progression varied slightly across studies.

**Abbreviations:** EDSS, expanded disability status scale; MRI, magnetic resonance imaging.

and Bax (proapoptotic molecules), as well as inhibition of the production of proinflammatory cytokines such as interleukin 1 (IL-1) and tumor necrosis factor.<sup>14</sup> IFN beta also has shown a decrease in the production of IL-23 and increased IL-10 production by dendritic cells. The molecule also modified the production of IL-17 via dendritic cells.<sup>15</sup> Through these anti-inflammatory activities, IFN beta controls disease activity in MS patients.<sup>14–18</sup> Subcutaneous IFN beta-1b was studied in RRMS patients in a randomized, double-blind, placebo-controlled study in 1993.<sup>19,20</sup> The study demonstrated that the relapse rate for patients receiving placebo was 1.27; for those receiving 1.6 million units, it was 1.17; and for those receiving 8 million units IFN beta-1b, it was 0.84 after 2 years. Two years later, Jacobs et al studied the efficacy of IFN beta-1a administered intramuscularly in a multicenter, randomized, placebo-controlled study.<sup>21</sup> A significant delay in time to sustained EDSS progression (–37%;  $P=0.02$ ) was observed, as well as significantly fewer exacerbations ( $P=0.03$ ) in patients treated with IFN versus those in the placebo group. Finally, in 1998, a randomized, multicenter, double-blind, placebo-controlled study evaluated the efficacy of IFN beta-1a given subcutaneously versus placebo in RRMS.<sup>22,23</sup> The relapse rate was significantly lower with the doses of IFN beta (44 and 22 µg) compared with placebo, with a risk reduction of relapses of 27% for 22 µg (95% confidence interval, 14%–39%) and

33% for 44 µg (95% confidence interval, 21–44).<sup>22,23</sup> Adverse effects of IFN beta therapy include influenza-like symptoms (fevers, chills, and myalgias) and mild abnormalities on routine laboratory evaluation, such as an elevation in liver enzymes or mild lymphopenia.<sup>22,23</sup> Rarely, severe hepatotoxicity and muscle abscesses associated with intramuscular application have been reported. When injected subcutaneously, IFN beta also often causes reactions at the site of injection, including pain, redness, induration, or rarely, skin necrosis.

In Argentina, available formulations of IFN beta approved to treat MS include the three original IFN beta formulations (subcutaneous IFN beta-1a, Rebif® [EMD Serono/Pfizer, Darmstadt, Germany]; subcutaneous IFN beta-1b, Betaferon® [Schering, Berlin, Germany]/Betaseron® [Bayer, Leverkusen, Germany]; and intramuscular IFN beta-1a, Avonex® [Biogen Idec, Weston, MA, USA]), which have been available in Argentina since 1997 for the treatment of RRMS patients, and two biosimilar formulations (subcutaneous IFN beta-1a Blastoferon® [Farmacias Ahumada, Santiago, Chile] and Inmunomas® [AMEGA biotech, San Isidro, Argentina], available since 2005 and 2011, respectively).

## Glatiramer acetate

Glatiramer acetate (GA) is a synthetic copolymer made up of four amino acids (L-glutamic acid, L-lysine, L-alanine, and

L-tyrosine).<sup>19</sup> Molecular research has shown that GA could act by a direct mechanism to control immunological activity in MS patients. GA is processed by antigen-presenting cells. Through class I and class II presentation pathways, GA is later presented to cluster of differentiation (CD)8+ and CD4+ T cells. A CD8+ T-cell response results in modification of antigen-presenting cell subsets.<sup>24</sup> Presentation by modified antigen-presenting cells subsequently results in the generation of CD4+ T-regulatory cells, a direct killing of Th1 CD4+ T cells, and deviation toward Th2 response involved in the immunological regulation achieved in MS patients with GA.<sup>24–26</sup> A multicenter, randomized, double-blind, placebo-controlled trial evaluated the efficacy of GA in RRMS. A relapse rate of more than 2 years was significantly reduced in patients under GA versus placebo (1.19±0.13 versus 1.68±0.13; –29%;  $P=0.007$ ).<sup>26</sup> Adverse effects of GA include injection-site reactions (eg, pain, redness, and induration), although these are generally mild. A few patients treated with GA in the pivotal trial (15.2%) experienced an immediate postinjection reaction, which consists of flushing and/or chest pain together with a variable secondary symptom complex including palpitations, anxiety, and/or dyspnea.<sup>26</sup>

In Argentina, available formulations of GA approved in the treatment of MS include the original form of Copaxone® (Teva Pharmaceuticals, Petah Tikva, Israel), available for use in Argentina since 1997 for the treatment of RRMS patients, and Escadra® (MR PHARMA S.A., Buenos Aires, Argentina), a biosimilar formulation of GA available since 2012.

## Natalizumab

Natalizumab is a humanized monoclonal antibody that is directed against the  $\alpha 4\beta 1$ -integrin molecule on mononuclear white blood cells, including lymphocytes.<sup>27</sup> In the Phase III trial of natalizumab versus placebo (Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis [AFFIRM] study),<sup>28</sup> there was a 67% decrease in relapse rate and a 50% reduction in the accumulation of persistent new disability in the natalizumab-treated group. A post hoc analysis of that study focusing on a stringent definition of disease-free activity (a composite of the absence of activity in clinical aspects, plus absence of activity on magnetic resonance image measures) yielded proportions of 37% (natalizumab) versus 7% (placebo).<sup>29</sup> Natalizumab was withdrawn after two cases of progressive multifocal leukoencephalopathy (PML) in the extension phase of the Safety and Efficacy of Natalizumab in Combination with IFN beta-1a in Patients with Relapsing Remitting Multiple Sclerosis (SENTINEL) study and then reintroduced after the establishment of intensive surveillance regimens with

long-term safety data reporting.<sup>30</sup> Real-world data demonstrated that being able to stratify John Cunningham virus (JCV) status was useful in stratifying the risk of PML. If negative, PML is unlikely to occur (although it is not impossible).<sup>31</sup> Nearly 6,000 patients from the AFFIRM, Tysabri® Global Observation Program in Safety-US, JCV Antibody Program in Patients with Relapsing Multiple Sclerosis Receiving or Considering Treatment with Tysabri (STRATIFY-1), and the Swedish MS registries had baseline blood samples available for anti-JCV antibody testing to stratify the risk of PML in patients treated with natalizumab.<sup>32</sup>

In Argentina, the STRATIFY program is currently available for the follow-up of MS patients under natalizumab to identify the presence of anti-JCV and the titers, if present, in order to stratify the risk of PML.

Tysabri® (natalizumab; Biogen Idec, Weston, MA, USA/ Elan Pharmaceuticals, Dublin, Ireland) was approved in Argentina by local authorities in 2010 and has been available for the treatment of MS patients since then.

## Fingolimod

Fingolimod is an oral sphingosine 1-phosphate receptor modulator that was approved for the treatment of MS in 2010 in North America and 2011 in Europe.<sup>33,34</sup> Its mechanism of action is thought to be through an active phosphorylated metabolite, FTY720-P, which resembles sphingosine 1-phosphate and alters lymphocyte trafficking through receptor subtype sphingosine 1-phosphate 1.<sup>35</sup> The consequent molecular process modulates the actin cytoskeleton of cells, thereby affecting pseudopodia formation and the migration of lymphocytes, process outgrowth, endothelial cell migration, angiogenesis, and endothelial permeability barriers.<sup>35</sup> Phase III clinical trial results with fingolimod have demonstrated efficacy in patients with RRMS. The 12-month, double-blind trial assessing injectable IFN beta-1a (30 mg/week) versus fingolimod (0.5 or 1.25 mg/day) in RRMS (TRANSFORMS trial), showed an annualized relapse rate (ARR) of 0.16 for 0.5 mg/day fingolimod, 0.20 for 1.25 mg/day fingolimod, and 0.33 for IFN beta-1a ( $P<0.001$  for each fingolimod dose versus IFN beta-1a). The Phase III Efficacy and Safety of Fingolimod in Patients With Relapsing-remitting Multiple Sclerosis (FREEDOMS) trial was a 24-month, double-blind, randomized study that included 1,272 patients with RRMS.<sup>36</sup> The ARR was 0.18 for 0.5 mg/day fingolimod, 0.16 for 1.25 mg/day fingolimod, and 0.40 for placebo ( $P<0.001$  for each dose versus placebo). In this study, fingolimod also decreased the risk for disability progression (hazard ratio, 0.70; 95% confidence interval for 0.5 mg/day fingolimod). Main adverse events

in Phase III clinical trials with fingolimod were related to the bradycardia induced during the first 6 hours of the first intake of medication that led to the implementation of blood pressure and heart rate monitoring in all patients in Argentina during this period. Other related adverse events included headache, macular edema in patients with history of diabetes and uveitis, and lower respiratory tract infections.<sup>33,36</sup>

In Argentina, Gilenya® (fingolimod; Novartis, Basel, Switzerland) was approved in April 2011.

## Teriflunomide

Teriflunomide is an oral reversible inhibitor of dihydroorotate dehydrogenase, a mitochondrial membrane protein essential to pyrimidine synthesis.<sup>37</sup> Dihydro-orotate dehydrogenase blocks de novo pyrimidine synthesis, leading to an inhibition of the proliferation of autoreactive B and T cells.<sup>37</sup> The Phase III clinical Teriflunomide Multiple Sclerosis Oral (TEMSO) study<sup>38</sup> demonstrated a significant reduction in ARR and disability progression with teriflunomide compared with placebo. Patients in the study were randomized to teriflunomide 7 or 14 mg/day or placebo. The adjusted ARRs with teriflunomide at 7 and 14 mg/day were 0.370 and 0.369, respectively, compared with 0.539 for placebo ( $P<0.001$  for both comparisons). The 14 mg/day dose of teriflunomide was associated with a 29.8% reduction in the risk for sustained disability progression ( $P=0.028$ ). Two additional studies, the Teriflunomide Oral in People with Relapsing-Remitting Multiple Sclerosis (TOWER)<sup>39</sup> and a Study Comparing the Effectiveness and Safety of Teriflunomide and IFN beta-1a in Patients with Relapsing Multiple Sclerosis compared teriflunomide with placebo and IFN beta-1a 44 µg subcutaneous, respectively.<sup>40</sup> Both studies showed that teriflunomide 7 and 14 mg was superior to placebo in reducing ARRs, but no differences were found between teriflunomide and IFN beta-1a subcutaneous 44 µg regarding ARRs. Main adverse events reported were an increase of liver enzymes, neutropenia, rhabdomyolysis, and trigeminal neuralgia.

Aubagio® (teriflunomide; Genzyme, Cambridge, MA, USA/Sanofi, Paris, France) was approved for use in Argentina in March 2013 and is currently available to treat RRMS.

## Emerging disease-modifying therapies for multiple sclerosis in Argentina

### Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody against CD52, a glycoprotein antigen found on the surface of mature lymphocytes and monocytes.<sup>41</sup> Its mechanism of action is

thought to be mediated by prolonged T-cell depletion and modulation of the lymphocyte repertoire caused by pulsed administration of the medication. Specifically, a distinctive pattern of T- and B-cell repopulation begins within weeks of administration, leading to a change in the balance of the immune system. Alemtuzumab was studied in a Phase II Study Comparing Low- and High-Dose Alemtuzumab and High-Dose Rebif® in Patients With Early, Active Relapsing-Remitting Multiple Sclerosis (CAMMS223), a 3-year, Phase II, rater-blinded trial. The patients were randomized to subcutaneous IFN beta-1a (44 mg three times per week) or annual intravenous cycles of alemtuzumab (12 or 24 mg/day) for 36 months.<sup>42</sup> Alemtuzumab was associated with a significantly reduced rate of sustained disability accumulation versus IFN beta-1a (9.0% versus 26.2%;  $P<0.001$ ). The mean EDSS score improved by 0.39 points with alemtuzumab and worsened by 0.38 points with IFN beta-1a ( $P<0.001$ ). Two Phase III trials of alemtuzumab (Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis I [CARE-MS I] and Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis II [CARE-MS II]) were recently presented. CARE-MS I compared alemtuzumab (12 mg/day for 5 days initially and for 3 days the year after) versus subcutaneous IFN beta-1a (44 mg three times per week) in patients with RRMS who had not received prior disease-modifying therapy. This study showed that alemtuzumab resulted in a 55% reduction in relapse rate versus IFN beta-1a over the course of 2 years ( $P<0.0001$ ).<sup>43</sup> CARE-MS II compared alemtuzumab with IFN beta-1a subcutaneously in patients with RRMS who relapsed on prior therapy. The study showed a 49% reduction in relapse rate in patients receiving alemtuzumab 12 mg compared with IFN beta-1a subcutaneously ( $P<0.0001$ ).<sup>43</sup> The coprimary end point showed a 42% reduction in the risk for sustained disability measured by EDSS ( $P=0.008$ ). The main adverse events reported included thyroid disorders (23% versus 3%), immune thrombocytopenic purpura (3% versus 1%), and infections (66% versus 47%).<sup>42</sup>

Currently, Lemtrada (alemtuzumab; Genzyme, Cambridge, MA, USA) is under consideration for approval in Argentina, and a compassionate program is under use to provide MS patients with alemtuzumab.

### BG-12 (dimethyl fumarate)

BG-12 is a fumaric acid ester with immunomodulatory properties. It produces a decrease in leukocyte passage through the blood–brain barrier, causing a neuroprotective effect by the activation of antioxidative pathways.<sup>44</sup>

Determination of the Efficacy and Safety of Oral Fumarate in RRMS (DEFINE) was a Phase III, randomized,

double-blind, placebo-controlled, dose-comparison study of BG-12 in 1,234 RRMS patients.<sup>45</sup> Patients were randomized either to BG-12 at a dose of either 240 mg/twice a day or 240 mg/three times a day or to placebo. Both BG-12 doses were associated with a significant decrease in the proportion of patients who relapsed at 2 years compared with placebo ( $P < 0.0001$ ). Both BG-12 doses were significantly superior to placebo in reducing ARR and were also superior to placebo in slowing the rate of disability progression, as measured by EDSS scores at 2 years. Results were observed in a second randomized, double-blind, placebo-controlled trial with placebo and a comparative group of GA.<sup>45</sup>

Main adverse events occurring more often with BG-12 versus placebo were abdominal pain, flushing, and hot flush.<sup>45</sup> BG-12 has been approved and is currently in use for RRMS patients in the United States.

In Argentina, Tecfidera® (BG-12; Biogen Idec) is under consideration for approval to treat of RRMS patients.

Laquinimod and monoclonal antibodies such as rituximab, daclizumab, ocrelizumab, and ofatumumab are completing Phase III clinical trials; results are therefore expected to undergo regulatory evaluation in Argentina.

## Conclusion

Argentina is a medium-risk country for MS, with a prevalence estimated at 12–20 cases per 100,000 inhabitants and an incidence of 1.7 cases per 100,000 inhabitants per year. Current and emerging disease-modifying treatments for MS are available to treat MS patients in Argentina to obtain freedom from disease and improve long-term outcomes. Physicians should be aware of their efficacy and safety profiles to be able to choose the best treatment option for each patient, according to the presentation and progression of the disease.

## Disclosure

JIR has received honoraria from Novartis as a scientific advisor and has received travel grants and attended courses and conferences on behalf of Merck-Serono Argentina and Novartis Argentina. LP has received honoraria for scientific and research grants from Teva Tuteur, Merck Serono, Biogen Idec, and Bayer Schering. EC has received fees for consultations as a scientific advisory board member and for travel to meetings, conferences, and clinical trials from Avanir, Bayer, Biogen, Merck, Novartis, and Teva. The authors declare no other conflicts of interest.

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