

## Experience with Fingolimod as an Evidence-based Therapy in Relapsing Remitting Multiple Sclerosis: A Central American Case Series

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### Abstract

**Introduction:** Central America has an estimated Multiple Sclerosis prevalence rate between 1.0 and 7.1 cases per 100,000 inhabitants. The increase in the global Multiple Sclerosis incidence, the lack of Latin-American representation in clinical studies and the rising availability of therapies to treat this disease, makes it essential to gather regional data.

**Objective:** Obtain real-life evidence data regarding the efficacy and safety of fingolimod in the Central American region, specifically in the countries of Panama, Guatemala and Nicaragua.

**Patients and Methods:** Based on medical records, sociodemographic, clinical, efficacy and safety information of patients with Relapsing Remitting Multiple Sclerosis receiving fingolimod treatment was collected and analyzed.

**Results:** Medical records of 58 patients from Panama, Guatemala and Nicaragua with a diagnosis of Relapsing Remitting Multiple Sclerosis were included. Patients had a mean age of  $37.3 \pm 10.5$  years,  $6.98 \pm 4.99$  years of disease history, a time for diagnosis of 9 months and  $22.8 \pm 15.1$  months of treatment with fingolimod. Under this disease-modifying therapy, a 60.4% reduction in active lesions, a decrease in the number of relapses, an increase in the percentage of remissions, and a 30% reduction in the annualized relapse rate, was observed. Fingolimod's main indications were: previous treatment failure with other disease-modifying therapies mainly interferons and parenteral administration intolerance. At the time of this analysis, 22.4% of patients treated with fingolimod, experienced at least one adverse event and 92.3% of patients continue treatment with fingolimod.

**Conclusions:** The sociodemographic characteristics, as well as safety and efficacy aspects of fingolimod in the Central American population with Relapsing Remitting Multiple Sclerosis are similar to the results published in postmarketing studies and controlled clinical trials in other regions worldwide.

**Keywords:** *Relapsing Remitting Multiple Sclerosis; Central America; Real-World Evidence; Fingolimod; Safety; Efficacy*

## Abbreviations

MS: Multiple sclerosis; FTY: Fingolimod; RRMS: Relapsing-Remitting MS; EDSS: Kurtzke Expanded Disability Status Scale; MRI: Magnetic Resonance Imaging; ANOVA: Analysis of Variance; SPSS: Statistical Package for the Social Sciences; ARR: Annualized Relapse Rate

## Introduction

The epidemiology of Multiple sclerosis (MS) does not have a fixed pattern; this variability is due to several aspects [1-4]. Latin America has an MS prevalence rate between 0.85 and 21.5 cases per 100,000 inhabitants [5,6]. Specifically, the Central American region has an estimated prevalence rate between 1.0 and 7.1. The management of Relapsing Remitting MS in this region is influenced by health systems with limited resources including a disparity in the access and coverage of treatments, but also restricted complementary diagnostic testing [7], aspects that evidence the region's complexity. With some exceptions [8-10], the lack of epidemiological data and the shortage of standardized methods for information collection and analysis in the MS population [11], probably generate an underreporting of cases [10,12] that is likely to erroneously reduce the prevalence in the region. As of 2012, a regional registry has been implemented [13].

The increase in the Latin American MS incidence rate [14-16], the limited inclusion of Central American patients' in clinical trials [17] and the increase in the availability of new therapies in the region [7], require the development of regional real-world evidence studies.

Fingolimod (FTY), the first oral drug approved for treatment of relapsing-remitting MS (RRMS) [18,19], is a sphingosine receptor modulator that prevents the migration of lymphocytes from the lymph nodes [20,21]. FTY has shown efficacy in phase III clinical trials in patients with RRMS [22-24]. At the time of this analysis, FTY had been used in more than 125,000 patients, generating an exposure greater than 240,000 patients/year [25] and was approved in five Central American countries. Real-world studies suggest that FTY is an adequate treatment in a wide range of MS patients, including patients with poor prognosis (high disease activity) and patients with previous treatment failure. These studies also support the efficacy and safety results demonstrated in the pivotal studies [26,27]. This case series seeks to collect real-world evidence of RRMS patients treated with FTY in the Central American region, specifically in the countries of Panama, Guatemala and Nicaragua.

## Materials and Methods

Using a standardized methodology, neurologists from secondary and tertiary treatment level hospitals in the Central American region, who also had experience in the treatment of RRMS, generated a common database. Anonymous data including safety and efficacy information along with clinical and sociodemographic characteristics, was obtained from the medical charts of RRMS patients undergoing FTY

treatment. The information was collected from the time of drug approval in each participating country until the first trimester of 2017. Subsequently, consolidation, discussion and homogenization of the collected data was achieved in a face-to-face physician’s meeting.

The main variables retrieved from medical charts and analyzed in this case series were: gender, age, country of residence, date regarding the onset of symptoms, disease diagnosis date, initial disease modifying therapy prescribed, reason for FTY initiation, Kurtzke Expanded Disability Status Scale (EDSS) score, number of relapses, presence of active lesions in magnetic resonance imaging (MRI), main adverse events reported with FTY treatment, concomitant therapies and continuity of treatment.

Absolute and relative frequencies were estimated for the categorical variables, as well as measures for central tendency (mean and median) and dispersion (standard deviation and range) for the quantitative variables. Unless indicated otherwise, these values are expressed as: absolute quantity and percentage (qualitative variable) and mean  $\pm$  standard deviation (quantitative variable). After checking for normality and equality of variances, mean comparison between groups was carried out by either t Student tests or ANOVAs. Non-compliance of normality and/or homoscedasticity assumptions cases, were evaluated with nonparametric tests followed by a *post hoc* analysis to compare significant correlations. A value of  $p < 0.05$  was considered statistically significant. Data was analyzed using SPSS v 22.0 (SPSS, Inc., Armonk, NY, USA) and Sigmaplot v 13.0 (Systat Software, San Jose, CA, USA) was used for the elaboration of the graphs.

### Results

This study included the information collected from medical charts of 58 RRMS patients, who reside in: Panama (43.2%), Guatemala (38.0%) and Nicaragua (18.8%). All patients were diagnosed with RRMS applying the McDonald 2010 criteria and received fingolimod as disease-modifying therapy. At the time of this analysis patients had an average age of 37.3 years  $\pm$  10.5, with a range between 16 and 62 years of age. *Post hoc* analysis did not demonstrate a significant difference regarding patient’s age and country of origin.

Women represented 84.5% (n = 49) of all patients included in the study; this female predominance was maintained throughout the countries analyzed (Figure 1). No difference between patient’s sex and age or the mean years following diagnosis were identified. Cases studied presented an average of 6.98  $\pm$  4.99 years of RRMS following disease diagnosis, with a range between 0.42 and 22.0 years. Panama (8.67  $\pm$  4.60) and Nicaragua (3.69  $\pm$  3.31) showed a significant difference regarding the years of disease course.

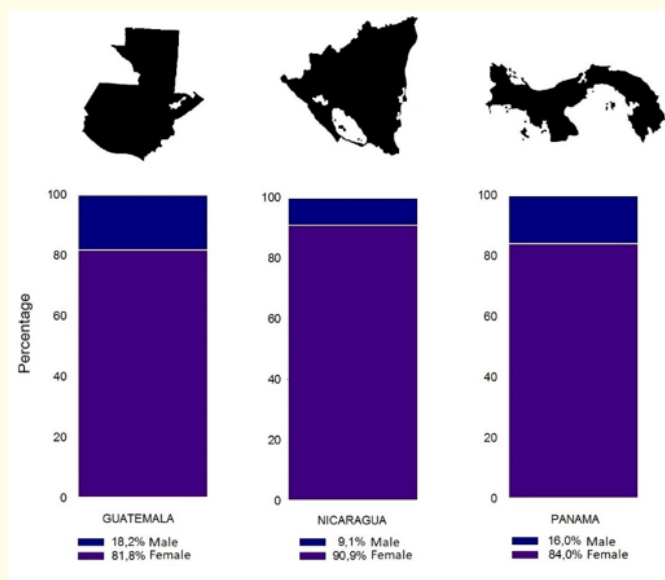
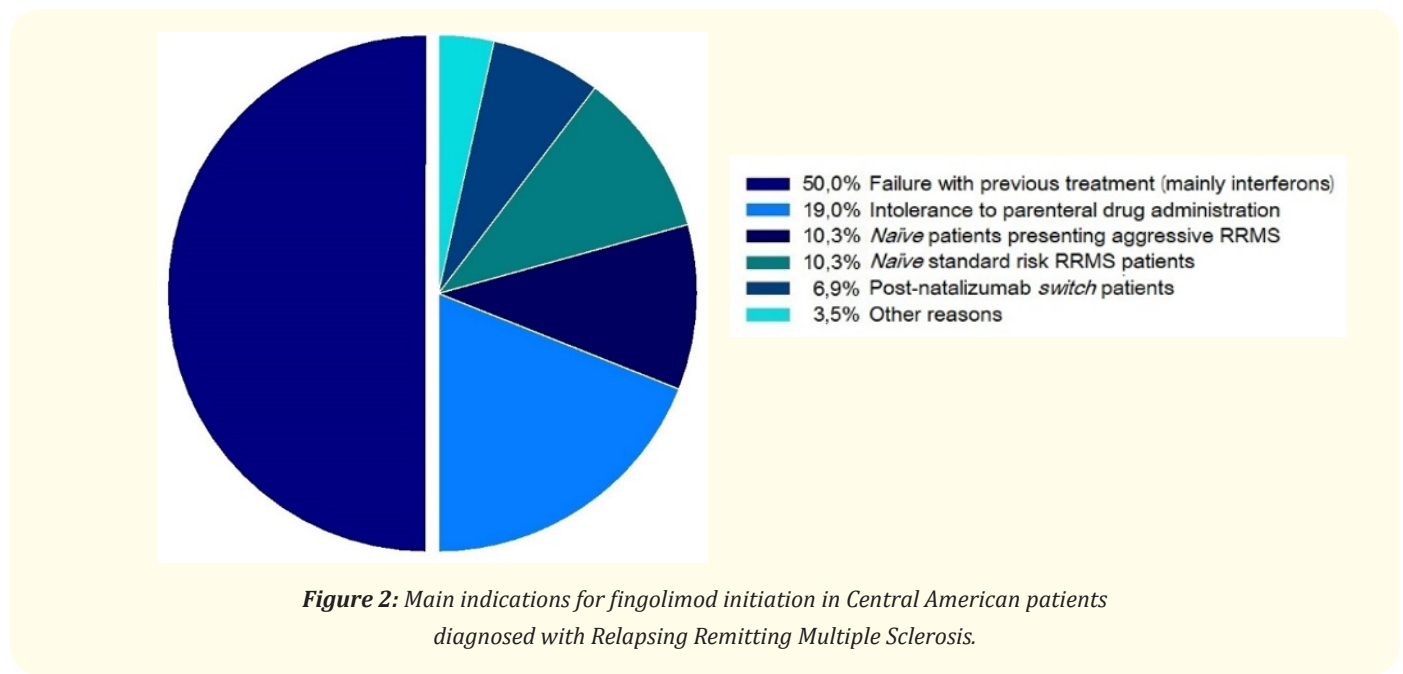


Figure 1: Sex ratio by country of Central American Relapsing Remitting Multiple Sclerosis patients in treatment with fingolimod.

Without demonstrating a significant difference between countries, the average time for RRMS diagnosis was  $9.25 \pm 14.6$ , with a range between 0 and 60.9 months. The average baseline EDSS score was  $2.54 \pm 1.66$  (range 0.0 - 6.0), and  $3.26 \pm 1.88$  (range 0.0 - 7.0) the year before starting FTY treatment. More than three-fourths of patients (75.9%), presented gadolinium enhancing lesions before starting with fingolimod.

By the end of this analysis, patients had been on fingolimod treatment for  $22.8 \pm 15.1$  months (range 0.97-72.2). FTY main indications were: failure with previous treatment prescription (mainly interferons), intolerance to parenteral drug administration, naive patients presenting aggressive RRMS, standard risk RRMS patients and *post*-natalizumab switch patients (Figure 2).



After treatment with fingolimod, the percentage of patients with active lesions determined by MRI was 15.5% compared to the initial 75.9% ( $p < 0.001$ ). In addition, a reduction in the number of relapses was observed, 72.4% of the patients remained free of exacerbations during the treatment with FTY.

Regarding the average number of relapses, the patients analyzed showed a total number of relapses before FTY initiation of  $3.36 \pm 3.69$  (range 0-28),  $1.72 \pm 1.23$  (range 0 - 7) in the year prior to FTY initiation and  $0.59 \pm 1.11$  (range 0 - 4) after starting FTY. Statistical differences were evident comparing the three periods. Before beginning FTY treatment, the annualized relapse rate (ARR) (number of outbreaks/years of illness) identified was  $1.47 \pm 2.17$ . The ARR decreased to  $0.97 \pm 1.08$  after starting medication with FTY.

Naive patients with RRMS who started treatment with fingolimod showed a lower disability score compared to those who initiated with interferon beta preparations ( $1.79 \pm 1.55$  vs  $3.56 \pm 1.98$ ) ( $p < 0.005$ ). This difference between groups was not present at the time of the baseline EDSS score determinations (before any treatment initiation). Regarding the EDSS score before the use of fingolimod, no differences were observed between the analyzed countries.

There is a positive correlation between the time elapsed from symptom onset and the initiation with fingolimod with a higher degree of disability (Spearman coefficient  $r_s = 0.428$ ,  $p < 0.001$ ). Patients who presented longer periods of time from symptom onset to the initiation with fingolimod generally showed greater disability. In this same manner, the univariate logistic regression analysis revealed

a statistically significant association between the delay in fingolimod treatment introduction (in months) and an increase probability of having a EDSS score greater than 3; each month of postponement in fingolimod initiation, represents a 2% increase in the probability of having an EDSS score  $\geq 3$  (OR 1.02 95% CI 1.005 to 1.031,  $p = 0.005$ ).

Based on the last record available before FTY initiation; the time (months) from disease diagnosis to the onset of FTY treatment was lower in patients with active lesions determined by MRI, in comparison to those without the presence of active inflammation areas (25.0 months vs 42.0 months). However, this tendency was not statistically significant.

Of the analyzed cases, thirteen patients (22.4%) experienced at least one adverse event during FTY treatment. A total of 15 adverse events were identified and none was considered serious. In all patients, the reduction in heart rate induced by the first dose was transient and asymptomatic. The most frequent adverse events were: lymphocytopenia, infections, reversible hepatotoxicity and headache (Figure 3).

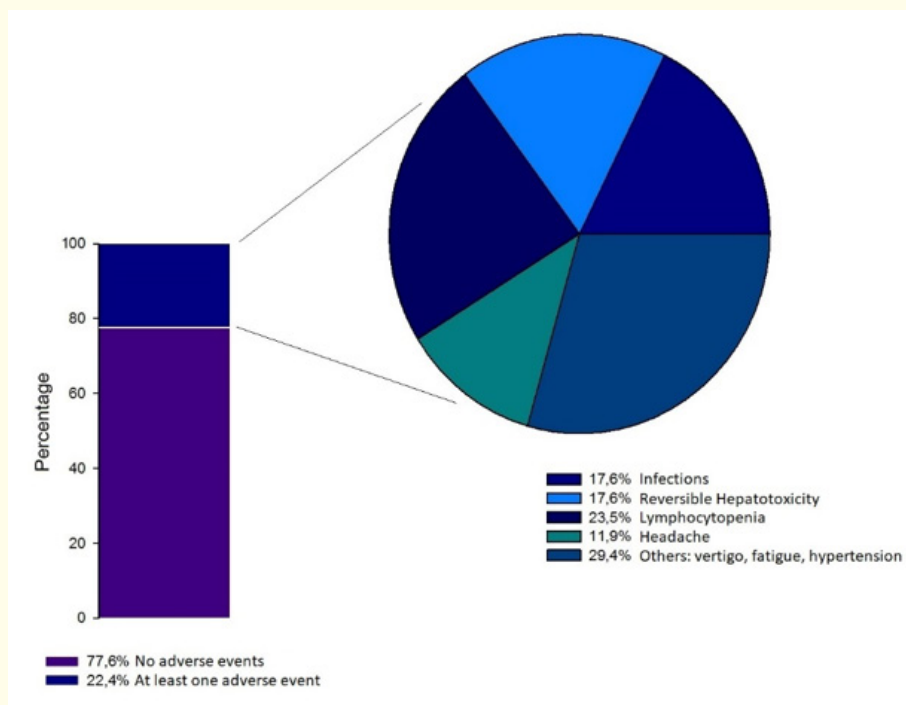


Figure 3: Main adverse events presented by Central American Relapsing Remitting Multiple Sclerosis patients in treatment with fingolimod.

In five patients (8.6%), a temporary withdrawal of treatment was reported. The reasons for this suspension were: pregnancy ( $n = 2$ ), adverse events ( $n = 2$ ) and diagnostic reassessment ( $n = 1$ ). By the end of this analysis, 92.3% of the patients continue on treatment with fingolimod. The main reasons for definitive suspension were: adverse events ( $n = 2$ ), suboptimal therapeutic response ( $n = 1$ ) and pregnancy ( $n = 1$ ).

Regarding concomitant medication use in this population, it was determined that vitamin D constitutes the main concomitant treatment, present in 31.1% of cases (Figure 4).

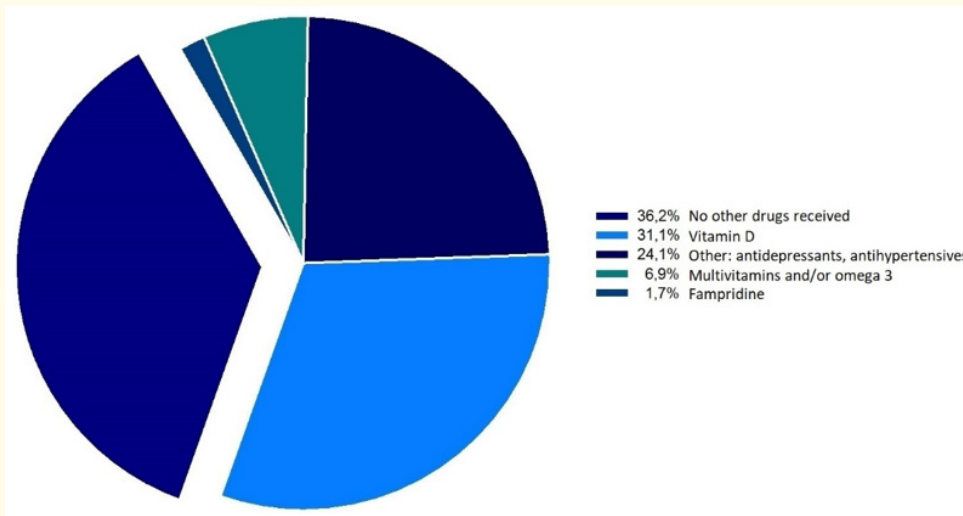


Figure 4: Concomitant medications used by Central American Relapsing Remitting Multiple Sclerosis patients in treatment with fingolimod.

## Discussion

Modern medical clinical practice implicates a complex and coordinated interaction between training, experience, research, international guidelines adherence and clinical judgment. Decision making in clinical practice, should consider not only data from traditional randomized controlled clinical trials, but should take into consideration real-world data or studies that reflect medical treatment in a specific region. Information from real-life studies should be considered and analyzed with data from clinical trials to provide a more complete picture of the effectiveness and results of a specific intervention [28]. This case series constitutes the first Central America regional study that describes real-life experience with a disease-modifying therapy, in Relapsing Remitting Multiple Sclerosis patients.

The average age of Central American RRMS patients treated with FTY (37.3 years  $\pm$  10.5) is within the range reported in postmarketing studies [27,29]. As in other real-life studies, the higher proportion of women observed in the analyzed cases [27,30,31], may be related with the disease's epidemiology [32,33].

Unlike other real-world studies, in this investigation, the illness shows a considerably lower disease course years when compared to what is described in other regions [30,34]. Statistical differences regarding years of disease course, were found among the analyzed countries, specifically between Panama and Nicaragua, this is probably attributed to the time for diagnosis of RRMS patients. In this study, the average time between initial signs and symptoms and RRMS diagnosis is close to a year, but in some cases diagnosis was delayed up to 5 years. This situation promotes Central American countries to improve access regarding diagnostic tools and to implement continuous medical education programs, with the objective of reducing the time for diagnosis.

Without demonstrating a statistical difference between analyzed countries, in this case series, RRMS patients who started treatment with fingolimod presented, on average, an EDSS score of  $3.26 \pm 1.88$ , defined by other authors as borderline between mild and moderate disability [35]. In pivotal studies and in most postmarketing studies, the degree of patients' disability quantified by the EDSS score before the initiation of FTY was mild (less than 3) [22,24,29,31,34]. Regarding the statement above, this may be related to the delay in diagnosis and in which an earlier intervention with FTY in the Central American RRMS population could offer an increased benefit for the patients.

An earlier intervention in Central American RRMS population is supported by the identified correlation and the hypothesis of a temporary therapeutic window, in which treatments can be more effective in the early phase of the disease before disability reaches an EDSS score of 3 [36].

As described in other investigations, in this case series, the main prescribing indications for initiation with fingolimod were: therapeutic failure with other disease-modifying therapies, mainly interferons, and parenteral administration intolerance [27,30]. In accordance with pivotal trials and real-world data, this analysis demonstrates: a decrease in the total number of relapses, a high percentage of patients free from acute flares, a reduction in the number of active lesions determined by MRI, and a decrease in the ARR after FTY treatment [23,24,37,38]. Likewise, a lower disability was observed in RRMS patients who started fingolimod as first treatment, compared to those who initiated therapy with interferon beta [22,28,29,39].

As in other real-world evidence studies and pivotal trials, the first dose of FTY in the Central American RRMS population was well tolerated and did not generate any reports of relevant adverse events of cardiovascular nature [17,40]. The main adverse events identified, reasons for treatment suspension both temporary and permanent, and the percentage of patients who continued FTY treatment after 18 months were very similar to those reported in other studies [27,30,31,38].

### Conclusion

This case series corroborates that clinical and sociodemographic characteristics, as well as the main aspects of efficacy and safety related to the use of fingolimod in the Central American RRMS population, are analogous to data reported in postmarketing studies and controlled clinical trials, in other regions worldwide. Aspects such as number of relapses, ARR, progression of disability, MRI lesion activity, adverse events and first dose considerations, do not show considerable differences with what is described in published scientific literature. Observed differences are probably related to endogenous characteristics of the region, such as heterogeneity and socioeconomic situation. The information obtained in this study is not only relevant for the medical clinical community and the population with RRMS, but also confirms the usefulness of fingolimod as an adequate therapeutic alternative for RRMS patients in the Central American region.

### Conflict of Interest

Gracia-García, has been lecturer for Novartis and Sanofi-Genzyme; Treviño-Frenk, has been consultant and/or lecturer for Sanofi Genzyme, Novartis, TEVA, Merck and Stendhal; Diaz-Jiménez, has been speaker and received educational grants from Novartis; Benzadón-Cohen, has been coinvestigator in pharmaceutical research protocols and has given lectures for Novartis, Sanofi-Aventis, Sanofi-Genzyme and MSD; Chinchilla-Weinstok, has received support for attending educational activities, has been part of Advisory Boards, lecturer and coinvestigator in pharmaceutical research protocols for Stendhal, Novartis, Bayer, Sanofi-Genzyme, Merck, Roche, Bayer, Pfizer and MSD; Echeverri-McCandless, has been coinvestigator in pharmaceutical research protocols, has given lectures and has received support for medical education activities participation from Abbott, Merck Sharp and Dohme, Sanofi Aventis and Roche; Garro-Zúñiga, has been lecturer for Novartis and has received support for assistance to medical education activities; Parajeles-Vindas, has been lecturer and received support from Novartis, Sanofi-Genzyme, Merck and Stendhal for medical education activities attendance; Rodríguez-Moreno, has received support from Novartis, Asofarma, Bayer and Stendhal for medical education activities attendance; Vargas-Howell, has been coinvestigator in pharmaceutical research protocols, has given lectures and has received support for medical education activities participation from Pfizer, Biogen, Merck, Novartis, GSK, Asofarma, Abbott, Bayer, Stendhal and Sanofi; Sanabria-Castro, A, has been scientific advisor for Novartis and consultant for Roche.

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## Bibliography

1. Williams R, et al. "Multiple Sclerosis: It Epidemiological, Genetic, and Health Care Impact". *Journal of Epidemiology and Community Health* 49.6 (1995): 563-569.
2. Compston A, et al. "Multiple Sclerosis". *Lancet* 372.9648 (2008): 1502-1517.
3. Belbasis L, et al. "Environmental Risk Factors and Multiple Sclerosis: An Umbrella Review of Systematic Reviews and Meta-Analyses". *The Lancet Neurology* 14.3 (2015): 263-273.
4. Simpson S, et al. "Latitude Is Significantly Associated with the Prevalence of Multiple Sclerosis: A Meta-Analysis". *Journal of Neurology, Neurosurgery and Psychiatry* 82.10 (2011): 1132-1141.
5. Browne P, et al. "Atlas of Multiple Sclerosis 2013: A Growing Global Problem with Widespread Inequity". *Neurology* 83.11 (2014): 1022-1024.
6. Cristiano E, et al. "The Epidemiology of Multiple Sclerosis in Latin America and the Caribbean: A Systematic Review". *Multiple Sclerosis Journal* 19.7 (2013): 844-854.
7. Rivera MV, et al. "Multiple Sclerosis Care in Latin America". *Neurology* 82.18 (2014): 1660-1661.
8. Gracia F, et al. "Prevalence and Incidence of Multiple Sclerosis in Panama (2000-2005)". *Neuroepidemiology* 32.4 (2009): 287-293.
9. Rivera MV. "Multiple Sclerosis in Latin America: Reality and Challenge". *Neuroepidemiology* 32.4 (2009): 294-295.
10. Melcon M, et al. "Towards Establishing MS Prevalence in Latin America and the Caribbean". *Multiple Sclerosis Journal* 19.2 (2013): 145-152.
11. Ojeda E, et al. "Prevalence and Clinical Features of Multiple Sclerosis in Latin America". *Clinical Neurology and Neurosurgery* 115.4 (2013): 381-387.
12. Gracia F, et al. "Esclerosis Múltiple En América Central y El Caribe: Estado Actual y Recomendaciones Clínicas". *Revista Mexicana de Neurociencia* 18.2 (2017): 76-88.
13. "Registro Centroamericano y del Caribe de Esclerosis Múltiple (RECEM)". Instituto Conmemorativo Gorgas de Estudios de la Salud (2017).
14. Correale J. "MS in Latin America". *International MS Journal* 15.1 (2008): 3-5.
15. Luetic G. "MS in Latin America". *International MS Journal* 15.1 (2008): 6-11.
16. Gonzalez O and J Sotelo. "Is the Frequency of Multiple Sclerosis Increasing in Mexico?" *Journal of Neurology, Neurosurgery, and Psychiatry* 59.5 (1995): 528-530.
17. Chinea-Martinez AR, et al. "Efficacy and Safety of Fingolimod in Hispanic Patients with Multiple Sclerosis: Pooled Clinical Trial Analyses". *Advances in Therapy* 31.10 (2014): 1072-1081.
18. Brinkmann V, et al. "Fingolimod (FTY720): Discovery and Development of an Oral Drug to Treat Multiple Sclerosis". *Nature Reviews Drug Discovery* 9.11 (2010): 883-897.
19. FDA US Food and Drug Administration. Highlights of Prescribing Information. Gilenya (fingolimod) prescribing information (2014).

20. Huwiler A., *et al.* "Physiology and Pathophysiology of Sphingolipid Metabolism and Signaling". *Biochimica et Biophysica Acta* 1485.2-3 (2000): 63-99.
21. Matloubian M., *et al.* "Lymphocyte Egress from Thymus and Peripheral Lymphoid Organs Is Dependent on S1P Receptor 1". *Nature* 427.6972 (2004): 355-360.
22. Cohen JA., *et al.* "Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis". *New England Journal of Medicine* 362.5 (2010): 402-415.
23. Calabresi PA., *et al.* "Safety and Efficacy of Fingolimod in Patients with Relapsing-Remitting Multiple Sclerosis (FREEDOMS II): A Double-Blind, Randomised, Placebo-Controlled, Phase 3 Trial". *The Lancet Neurology* 13.6 (2014): 545-556.
24. Kappos L., *et al.* "A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis". *New England Journal of Medicine* 362.5 (2010): 387-401.
25. Novartis. Novartis Patient Exposure on file (2017).
26. Khatri BO. "Fingolimod in the Treatment of Relapsing-Remitting Multiple Sclerosis: Long-Term Experience and an Update on the Clinical Evidence". *Therapeutic Advances in Neurological Disorders* 9.2 (2016): 130-147.
27. Lapierre Y., *et al.* "Canadian Experience with Fingolimod: Adherence to Treatment and Monitoring". *Canadian Journal of Neurological Sciences* 43.2 (2016): 278-283.
28. Correale J., *et al.* "Use of Fingolimod in the Management of Relapsing-Remitting Multiple Sclerosis: Experience from Latin America". *Advances in Therapy* 32.7 (2015): 612-625.
29. Prosperini L., *et al.* "Real-World Effectiveness of Natalizumab and Fingolimod Compared with Self-Injectable Drugs in Non-Responders and in Treatment-Naïve Patients with Multiple Sclerosis". *Journal of Neurology* 264.2 (2017): 284-294.
30. Hersh CM., *et al.* "Experience with Fingolimod in Clinical Practice". *International Journal of Neuroscience* 125.9 (2015): 678-685.
31. Baroncini D., *et al.* "A Real-World Experience with Fingolimod in Active RRMS Patients Naïve to Second-Line Agents: A 2 Years, Intention-to-Treat, Observational, Single Center Study". *Multiple Sclerosis and Demyelinating Disorders* 1.1 (2016): 4.
32. Boström I., *et al.* "Sex Ratio of Multiple Sclerosis in the National Swedish MS Register (SMSreg)". *Multiple Sclerosis Journal* 19.1 (2013): 46-52.
33. Orton SM., *et al.* "Sex Ratio of Multiple Sclerosis in Canada: A Longitudinal Study". *The Lancet Neurology* 5.11 (2006): 932-936.
34. Totaro R., *et al.* "Fingolimod Treatment in Relapsing-Remitting Multiple Sclerosis Patients: A Prospective Observational Multicenter Postmarketing Study". *Multiple Sclerosis International* (2015): 763418.
35. Kurtzke JF. "Rating Neurologic Impairment in Multiple Sclerosis: An Expanded Disability Status Scale (EDSS)". *Neurology* 33.11 (1983): 1444-1452.
36. Stangel M., *et al.* "Towards the Implementation of 'no Evidence of Disease Activity' in Multiple Sclerosis Treatment: The Multiple Sclerosis Decision Model". *Therapeutic Advances in Neurological Disorders* 8.1 (2015): 3-13.
37. Tichá V., *et al.* "Real-World Outcomes in Fingolimod-Treated Patients with Multiple Sclerosis in the Czech Republic: Results from the 12-Month GOLEMS Study". *Clinical Drug Investigation* 37.2 (2017): 175-186.

38. Rasenack M., *et al.* "Efficacy and Safety of Fingolimod in an Unselected Patient Population". *PLOS One* 11.1 (2016): e0146190.
39. Khatri B., *et al.* "Comparison of Fingolimod with Interferon Beta-1a in Relapsing-Remitting Multiple Sclerosis: A Randomised Extension of the TRANSFORMS Study". *The Lancet Neurology* 10.6 (2011): 520-529.
40. Linker RA and Guillaume Wendt. "Cardiac Safety Profile of First Dose of Fingolimod for Relapsing-Remitting Multiple Sclerosis in Real-World Settings: Data from a German Prospective Multi-Center Observational Study". *Neurology and Therapy* 5.2 (2016): 193-201.

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