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Are different degrees of lymphopenia for FTY720 associated with serious infectious-type events? No

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Abstract

Objective: *Describing the occurrence of infections in patients with relapsing-remitting multiple sclerosis (RRMS) treated with fingolimod and with different degrees of lymphopenia in our unit.* **Patients and Methods:** *Observational, descriptive, longitudinal, and retrospective study in the Hospital Centro Médico Nacional Siglo XXI. Patients with RRMS and treatment with fingolimod were grouped based on lymphocyte count and infections. Quantitative variables were expressed as mean, standard deviation, and interquartile range; qualitative variables were expressed as frequencies and percentages.* **Results:** *110 patients, 76 (69.1%) female, 34 (30.9%) male, mean age 38.3 years (17-63, SD 9.85). Mean of initial expanded disability status scale 1.59 (0-5.5, SD 1.15) with a mean diagnosis time of 63.6 months (3-252, SD 50.96). Prior to starting fingolimod, 90.09% of patients had lymphocyte count >1,000. At six months of treatment, 35.64% had lymphocyte >1,000. At twelve months 32.95% had lymphocyte from 501 to 700. At 24 months, 34.21% had lymphocyte from 701 to 1,000. Of the 110 patients, 31.8% had mild infections, of which pharyngitis was reported in 10%, gastroenteritis 2.7%, urinary tract infection 10.9%, HPV infection 0.9%, SARS-CoV-2 infection 3.6%, ophthalmic herpes 0.9%, molluscum contagiosum 0.9%, oral candidiasis 0.9%. 68.18% did not present infections of any kind, no serious infections were reported even with lymphocyte levels below 200.* **Conclusions:** *Selective lymphopenia caused by fingolimod was not associated with infections of any kind in this population even at levels of 200-500 cells/mm^3.*

Keywords: *Fingolimod. Lymphopenia. Relapsing-remitting multiple sclerosis. Sphingosine 1-phosphate.*

¿Los diferentes grados de linfopenia por FTY720 se asociaron a eventos graves de tipo infeccioso? No

Resumen

Objetivo: *Describir la ocurrencia de infecciones severas en pacientes con EMRR tratados con fingolimod y con diferentes grados de linfopenia en nuestra unidad* **Métodos:** *Estudio observacional, descriptivo, longitudinal y retrospectivo realizado en el Hospital Centro Médico Nacional Siglo XXI. Pacientes con EMRR tratados con fingolimod, se agruparon por grados de linfopenia e infecciones. Las variables cuantitativas se expresaron como media, desviación estándar y rango intercuartil; las variables cualitativas se expresaron en frecuencias y porcentajes.* **Resultados:** *110 pacientes, 76 mujeres (69.1%), 34 hombres (30.9%), media de edad 38.39 (17-63 DE 9.85). Media EDSS inicial 1.59 (0-5.5, DE 1.15), tiempo diagnóstico medio 63.67 meses (3-252, DE 50.96). Previo al inicio de fingolimod, 90.09% de los pacientes tenía linfocitos absolutos >1,000. A los 6 meses de tratamiento, 35.64% tenía >1,000 linfocitos. A los 12 meses el 32.95% tenía 501-700 linfocitos, a los*

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24 meses el 34.21% tenía 701-1,000 linfocitos. De los 110 pacientes, el 31.8% presentó infecciones leves, de las cuales se informó faringitis en 10%, gastroenteritis 2.7%, infección del tracto urinario 10.9%, infección por VPH 0.9%, infección por SARS-CoV-2 3.6%, herpes oftálmico 0.9%, molusco contagioso 0.9%, candidiasis oral 0.9%. El 68.18% no presentó infecciones de ningún tipo, no se reportó infecciones graves incluso con niveles de linfocitos inferiores a 200. **Conclusiones:** *La linfopenia selectiva causada por fingolimod no se asoció a infecciones severas en esta población incluso en niveles de 200 a 500 células/mm^3.*

Palabras clave: *Esclerosis múltiple remitente recurrente. Esfingosina 1-fosfato. Fingolimod. Linfopenia.*

Introduction

The correlation between lymphopenia and the incidence of severe infections in patients with relapsing-remitting multiple sclerosis (RRMS) treated with fingolimod have been a topic of interest and debate for a long time.

Multiple sclerosis (MS) is a chronic, inflammatory, and demyelinating central nervous system disease associated with a wide range of axonal and neuronal damage[1-4] the immune response is mainly given by T-cells, with a contribution of B cells and plasmatic cells, as well as activation of macrophages and microglia[5-9].

Fingolimod-1-phosphate, the active form of fingolimod, is an agonist of S1PR1,3,4 and 5 receptors; Its anti-inflammatory activity is through S1P lymphocyte receptors, with a joint that produces the receptor internalization and functional antagonism concludes in the decrease of lymphocyte count in blood, with a variable grade of lymphopenia (redistributive lymphopenia)[10,11].

With a daily dose, lymphocyte count decreased along two weeks, with a minimum value of 30% from initial lymphocyte count. Furthermore, selective lymphopenia keeps memory lymphocytes in blood circulation, which reduces the risk of opportunistic infections[12-14].

In the pivotal phase III study FREEDOMS the overall incidence of serious infections occurred in 1.6-2.6% of patients. Bronchitis and pneumonia were more common with fingolimod than with placebo (occurring in 41 patients [9.6%] receiving 0.5 mg of fingolimod and 49 patients [11.4%] receiving 1.25 mg of fingolimod vs. Twenty-five patients [6.0%] receiving placebo)[15-17].

Infection is defined as a process caused by the invasion of normally sterile tissues, fluids, or cavities of the body by pathogenic or potentially pathogenic microorganisms.

Mild infection: the presence of systemic inflammatory response that does not require hospital admission: nasopharyngitis, bronchitis, influenza, gastroenteritis, and urinary tract infection.

Severe infection is a systemic inflammatory response that requires hospital admission due to its high degree of mortality and sequelae: herpes virus encephalitis, disseminated herpes zoster, pulmonary tuberculosis, *Pneumocystis jirovecii pneumonia, toxoplasma gondii* infections, and progressive multifocal leukoencephalopathy.

In our country, there are no studies about Fingolimod effects on lymphocyte count, as well as the incidence of serious infectious events with the different grades of lymphopenia.

The aim of our study was to describe the occurrence of infections in patients with RRMS treated with fingolimod and with different degrees of lymphopenia in our unit. Finding different results to those reported in the pivotal studies.

Patients and methods

We implemented an observational, descriptive, longitudinal and retrospective study at the Clínica de Enfermedades Desmielinizantes, Hospital de Especialidades Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social. Patients with RRMS and treatment with fingolimod 0.5 mg orally daily dose for at least 6 months, from January 2015 to July 2021 were included. We gathered the information from medical records (age, gender, expanded disability status scale [EDSS], time from diagnosis, lymphocyte count at 6, 12, 18, and 24 months). Patients were grouped based on lymphocyte count: 0-200, 201-500, 501-700, 701-1000, and >1000, infections were also grouped into two groups; mild or severe/opportunistic. Getting the percentage of each group during the follow-up. Our population has a parametric distribution so that the quantitative variables were expressed as mean and standard deviation and interquartile range; qualitative variables were expressed as frequencies and percentages. The statistical package of social sciences (SPSS) version 24 for Windows was used.

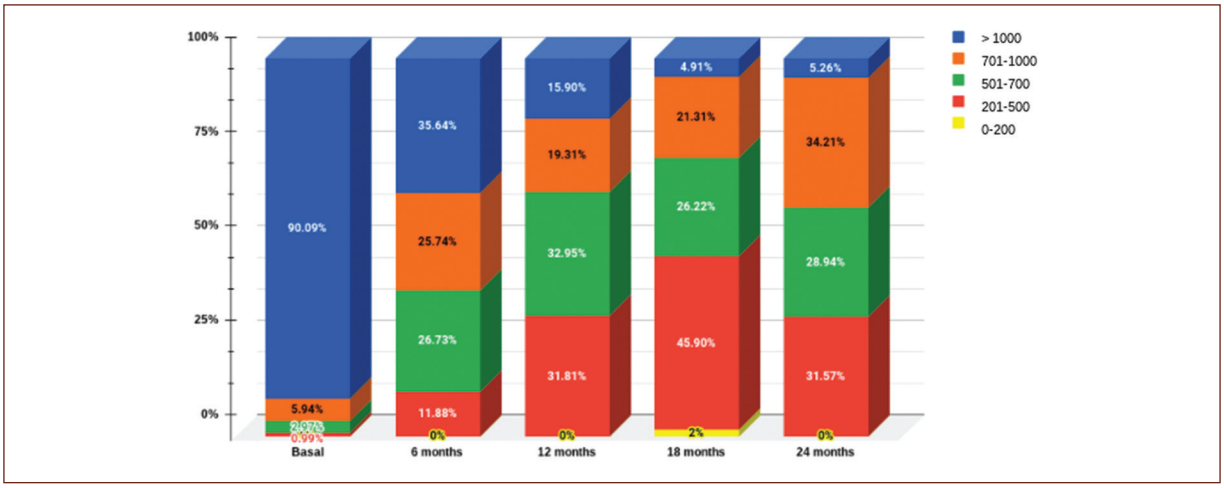

Figure 1. Lymphocyte count for 24 months.

Results

110 patients were included; 101 completed 6 months, 88 completed 12 months, 61 completed 18 months, and 38 completed 24 months of follow-up. 76 (69.1%) patients were female and 34 (30.0%) were male, with a mean age of 38.39 years (17,63, SD 9.85). Mean initial EDSS was 1.59 (0-5.5, SD 1.15), with a mean time from diagnosis of 63.67 months (3-252, SD 50.96). In Table 1 are shown all patients characteristics.

From all 110 patients, 25 (22.7%) were naive, and prior to fingolimod treatment, 90.09% had lymphocyte count greater than 1000 cells/mcL. At 24 months, 34.21% had 701-1000 lymphocytes/mcL, and 31.57% had 201-500 cells/mcL. Figure 1 shows the proportion of patients in each lymphocyte group during the follow-up.

Of the 110 patients, 68.18% did not present infections of any kind, 31.8% presented mild infections, of which pharyngitis was reported in 10%, gastroenteritis 2.7%, urinary tract infection 10.9%, HPV infection 0.9%, SARS-CoV-2 infection 3.6%, ophthalmic herpes 0.9%, molluscum contagiosum 0.9%, and oral candidiasis 0.9%. There were no severe infections 0%; such as herpes encephalitis, progressive multifocal leukoencephalopathy, pulmonary tuberculosis, pneumocystis pneumonia, or toxoplasmosis during follow-up even with lymphocyte levels less than 200.

Table 1. Patients characteristics

Characteristics	Results (%)
Male n (%)	34 (30.9)
Female n (%)	76 (69.1)
Age *(SD)	38.39 (17-63, SD 9.85)
EDSS *(SD)	1.59 (0-5.5, SD 1.15)
Time from diagnosis * (SD)	63.67 (3-252, SD 50.96)
Previous treatments n (%)	
Naïve	25 (22.7)
6 millions interferon	23 (20.9)
8 millions interferon	18 (16.36)
12 millions interferon	8 (7.27)
Glatiramer acetate	25 (22.72)
Dimethyl fumarate	1 (0.9)
Teriflunamide	1 (0.9)
Rituximab	1 (0.9)
Mitoxantrone	1 (0.9)
Natalizumab	3 (2.72)
Ocrelizumab	1 (0.9)
Azathioprine	2 (1.80)
Immunoglobulin	1 (0.9)

*Mean.
SD: standard deviation.

Discussion

MS affects young adults between 20 and 40 years, with a greater prevalence in females[18]. In our study, the mean age was 38.39 years and females were more prevalent than males (69.1% vs 30.9% respectively), which agree with the references.

The indications of fingolimod are RRMS with EDSS between 0 and 5.5, naive patients with an aggressive disease or treatment failure[19]. All patients included in our study had these characteristics.

Fingolimod works as a functional antagonist of sphingosine phosphate receptor, which produces a selective lymphocytic redistribution concluding in lymphopenia[20-22].

In our study, 0.9% of patients had treatments that reduce lymphocyte count; whence, these patients had lymphocyte count between 201 and 500 previous fingolimod started. This group of patients completed 24 months of treatment without infections or lower lymphopenia. At 18 months, 1.63% of patients had lymphocyte count lower than 200 cells/mcL, in whom fingolimod administration was modified from daily dose to every other day, completing 48 months (maintaining this dose for 6 months) without opportunistic infections or other complications. The patients had a mean baseline EDSS of 1.59 (0-5.5, SD 1.15), after treatment with fingolimod, showed a statistically significant decrease in EDSS at 6 months with a mean EDSS of 1.2 (0-5, SD 1.13, p = 0.001). In our study, no difference was observed in the efficacy of treatment with fingolimod at alternate doses and daily doses.

The lack of severe infections/opportunistic is because of the selective lymphopenia, which prevents the migration of naive lymphocytes from lymph nodes and the retention of memory T-cells in secondary lymph tissue. Therefore, in blood circulation, there are more memory T-cells, which reduce the infection risk. We prevent severe herpesvirus infections by performing serology against varicella-zoster virus prior to the start of treatment and vaccination in seronegative subjects[23].

Conclusions

During the follow-up, the lymphocyte count was not linearly downward as it is described in references; at 24 months of treatment, 34.21% of patients had lymphocyte count between 701 and 1,000 cells/mcL, which make us conclude that lymphopenia induced by fingolimod is not duration of treatment dependent and selective lymphopenia caused by fingolimod was not associated with severe infections in this population even at levels of 200-500 cells/mm^3.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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