NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

RESEARCH ARTICLE

Arch Neuropsychiatry 2023;60:23–27
https://doi.org/10.29399/npa.28081

Clinical and Demographic Characteristics and Two-Year Efficacy and Safety Data of 508 Multiple Sclerosis Patients with Fingolimod Treatment

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ABSTRACT

Introduction: Fingolimod is the first oral immunomodulatory treatment used as secondary care therapy in the treatment of multiple sclerosis for the last 10 years. The objective of our study is to reveal the experiences of the first generic fingolimod active ingredient treatment in different centers across Turkey.

Method: The first generic fingolimod efficacy and safety data of patients followed-up in 29 different clinical multiple sclerosis units in Turkey were analyzed retrospectively. Data regarding efficacy and safety of the patients were transferred to the data system both before the treatment and on the 6th, 12th and 24th month following the treatment. The data were analyzed using the IBM SPSS 20.00. P value of <0.05 was considered to be statistically significant.

Results: A total of 508 multiple sclerosis patients, 331 of whom were women, were included in the study. Upon comparing the Expanded Disability Status values before and after the treatment, a significant decrease was observed, especially at month 6 and thereafter. Since bradycardia occurred in 11 of the patients (2.3%), the first dose had to be longer than 6 hours. During the observation of the first dose, no issues that could prevent the use of the drug occured. Side effects were seen in 49 (10.3%) patients during the course of fingolimod treatment. Respectively, the most frequent side effects were bradycardia, hypotension, headache, dizziness and tachycardia.

Conclusion: The observed results regarding efficacy and safety were similar to clinical trial data in the literature and real life data in terms of the first equivalent with fingolimod active ingredient.

Keywords: Efficacy, fingolimod, multiple sclerosis, safety

Cite this article as: Terzi M, Helvacı EM, Şen Sedat, Boz C, Çilingir V, Akçalı A, et al. Clinical and Demographic Characteristics and Two-Year Efficacy and Safety Data of 508 Multiple Sclerosis Patients with Fingolimod Treatment. Arch Neuropsychiatry 2023;60:23–27.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (1,2). Neuroinflammation and neurodegeneration occurs in the natural course of MS. The attacks and progression can be seen in this pathogenesis (3–5). The prevalence of MS, which is one of the leading causes of neurological disability in young adults, varies between 2 and 200 per 100,000 and affects approximately 2.5 million people worldwide and approximately 60 thousand people in Turkey (6,7).

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Received: 11.12.2021, **Accepted:** 20.04.2022, **Available Online Date:** 13.01.2023

Highlights

- **The first generic fingolimod active ingredient therapy was demonstrated in Turkey**
- **Retrospective analysis of efficacy and safety data was done**
- **The results were similar to the clinical trial and the real life data in the literatüre**

Immunomodulatory therapies are applied to prevent attacks and progression in MS treatment (8). Considering the clinical, radiological, demographic findings of the disease together with the comorbid factors stepped or induction treatments are exercised. First-line treatments administered by injection are generally well tolerated. However, side effects and low efficacy due to injection limit the use of injection drugs (9). Fingolimod is an oral immunomodulatory treatment that has been used in the treatment of MS for the last 10 years (10). Besides its anti-inflammatory effects the neuroprotective effects of fingolimod have been set forth as well (11,12). Fingolimod was approved to be used for the treatment of relapsing remitting MS (RRMS) patients by the Food and Drug Administration in 2010 (13). It can also be used in first line treatment in MS patients with poor prognostic features (14). Significant experience has been gained in Turkey in the last 10 years, and several fingolimod-containing drugs that have completed their bioequivalence study are being offered to patients for the last 3 years. The purpose of our study is to reveal the fingolimod experience of different centers across Turkey. In line with this purpose, a real-life data study to determine the efficacy and safety of treatment in patients using fingolimod in Turkey was planned.

METHOD

Ondokuz Mayıs University Clinical Research Ethics Committee's permission was obtained as per the decision dated 13.06.2020 and numbered 2020/420. Retrospective analysis regarding the efficacy and safety data of patients who were using Fingolimod and being followed up in 29 different clinics in Turkey, were made. Data of patients with records and clinical follow-ups in relevant centers such as were obtained from patient follow-up systems and these data were transferred to the prepared excel program. Below-mentioned data of patients with records and clinical follow-ups in relevant centers have been obtained from follow-up systems and transferred to prepared excel program: i) demographic characteristics (gender, age, height, weight, etc.), ii) blood pressure before treatment, iii) pulse rate before the first dose, iv) blood lipid profile before treatment, v) blood lymphocyte level before treatment, vi) white blood cell level before treatment, vii) attack treatment in the last month, viii) first dose treatment method, ix) problems experienced in the first dose observation, x) side effects observed during treatment, xi) Expanded Disability Status Scale (EDSS) score before and after treatment, xii) number of attacks before and after treatment, xiii) Magnetic Resonance Imaging (MRI) findings before and after treatment, xiv) 25 step walking test, xv) 9 hole peg test, xvi) PASAT and/or digit symbol test, xvii) whether any laboratory abnormality was observed after treatment, xviii) whether a serious adverse event such as malignancy status and myocardial infarction etc. was observed after treatment. Data regarding the efficacy and safety of the patients were transferred to the data system both before the treatment and on the 6th, 12th and 24th months following the treatment.

Statistical Analyses

Since the data were not normally distributed, comparisons between two independent groups were analyzed with the Mann-Whitney U test. While the comparisons of more than two groups were analyzed with the Kruskal-Wallis test, data with multiple replicates were analyzed with the Friedman test, and correlations were analyzed using Spearman rank correlations. The relationship between qualitative variables was tested with Pearson Chi-square and Fisher Chi-Square tests. Data were analyzed in IBM SPSS 20.00 program and $p<0.05$ was considered to be statistically significant.

RESULTS

A total of 508 MS patients were included in the study. 331 of them were female (65.2%). The mean age of the patients was 38.0±10.4 (Min: 16, Max: 73). 447 (92.5%) of them were in Relapsing Remitting and 36 (7.5%) were in the Relapsing Progressive clinical form (Figure 1). There was no difference between the two genders in terms of clinical and demographic characteristics of the patients (Table 1).

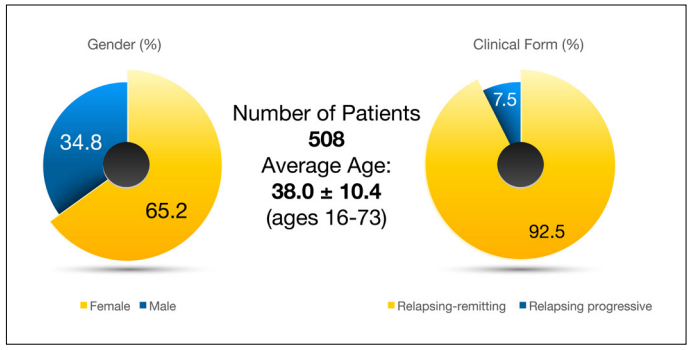

Figure 1. Age and clinical form distribution of MS patients using Vintor.

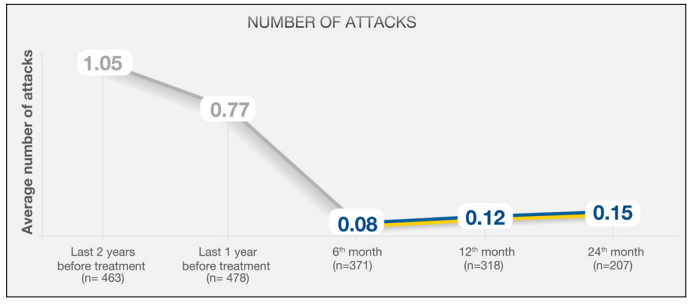

Figure 2. Average number of attacks before and after Vintor use.

Table 1. Comparison of pre-treatment clinical, demographic, and radiological characteristics of MS patients using Vintor in terms of gender

	Female (n=331)	Male (n=177)	p value
Age, year (median, range)	38 (16–64)	38 (17–73)	0.953
BMI, kg/m2 (median, range)	24.1 (14.5–29.7)	25.0 (16.3–22.8)	0.179
Diastolic, mmHg (median, range)	70 (46–107)	77 (50–106)	0.003
Systolic, mmHg (median, range)	110 (77–160)	120 (90–157)	0.000
EDSS Score (median, range)	2 (0–6)	2 (0–5)	0.225
Gd+lesion count on MRI (median, range)	2 (1–11)	2 (1–11)	0.006

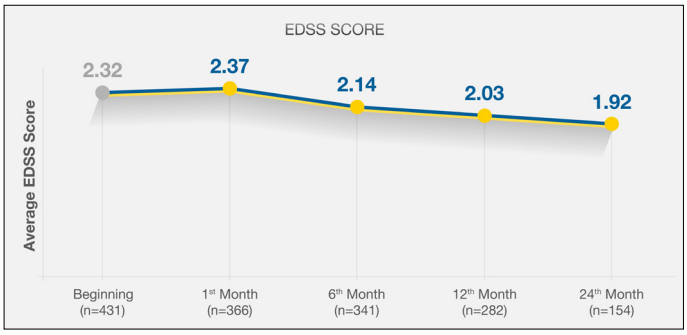

Figure 3. Average EDSS values before and after Vintor use.

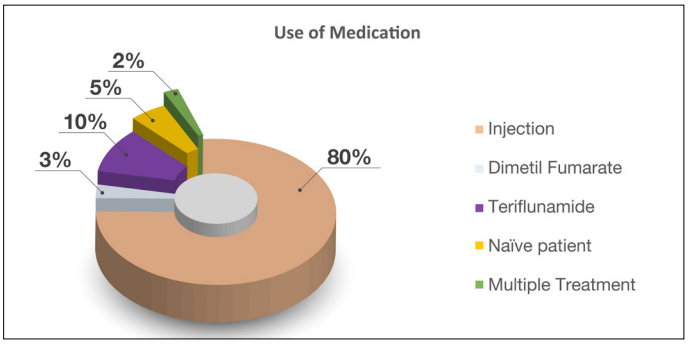

Figure 4. Distribution of immunomodulatory treatment used by patients before Vintor use.

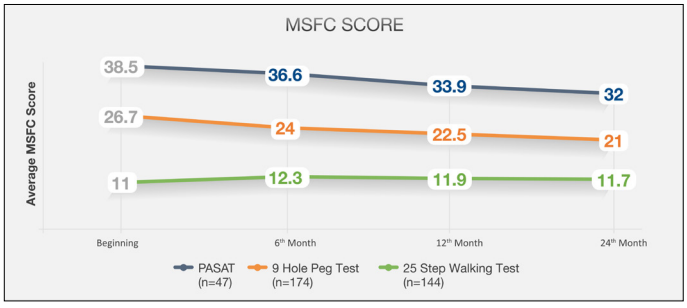

Figure 5. Average MSFC values before and after Vintor use.

No radiological activation (a new T_2 lesion or an enhancing lesion) was observed in 442 (95.3%) of 464 patients who completed their 2nd year of treatment. The mean number of attacks within one year prior to fingolimod treatment was 0.8±0.8. The mean number of attacks after treatment was 0.1±0.3 at 6 months, 0.1±0.3 at 12 months, and 0.2±0.4 at 24 months (Figure 2). The mean EDSS of the patients was 2±1.4 (Min: 0, Max: 6) before fingolimod treatment. The mean EDSS was 1.9±1.9 at 6 months, 1.8±1.4 at 12 months, and 1.7±1.5 at 24 months after treatment (Figure 3).

The treatments used before fingolimod were as follows, after injection treatment in 382 (79.6%), 46 (9.6%) after teriflunamide treatment, 16 (3.3%) after dimethyl fumarate treatment, 12 (2.5%) had more than one transitioned from first-line treatment. In 24 patients (5%), fingolimod was preferred as the first treatment and no other treatment was used before (Figure 4). 145 (30%) of the patients who started to receive fingolimod treatment had an attack under the drug they used one month before starting the treatment. 339 (70%) of the patients started to use fingolimod after clinical or radiological worsening within the last 6 months.

No significant changes statistically were observed in the Multiple Sclerosis Functional Composite (Digit symbol test, 25-step walking test, PASAT) test at the 6th, 12th, and 24th months compared to the pre-treatment period (Figure 5).

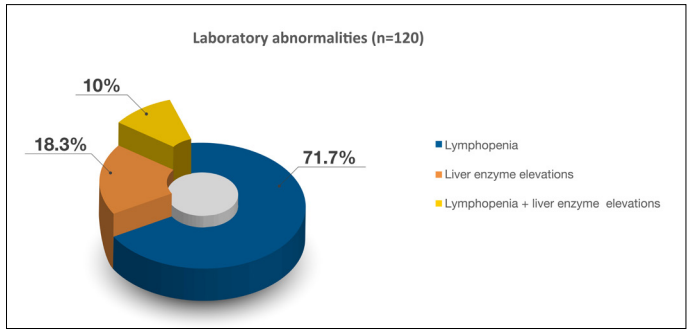

Figure 6. Distribution of laboratory abnormalities seen after Vintor use.

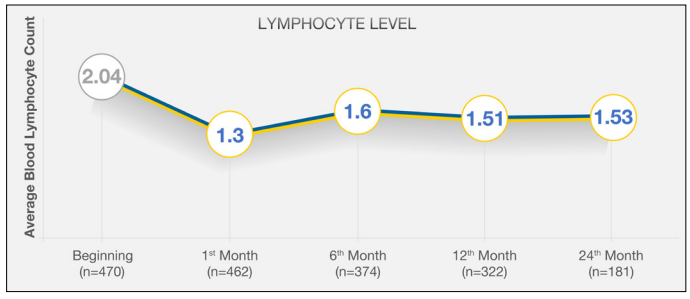

Figure 7. Mean lymphocyte values before and after Vintor use.

Observation regarding the first dose of Fingolimod was performed on 354 (71.8%) sitting patients while 139 (28.2%) of patients were lying down. The first dose observation had to last longer than 6 hours because of bradycardia in 11 of the patients (2.3%). No problem was seen that could prevent the use of the drug in the first dose observation. No significant correlation was observed between age and gender and first dose observation (p=0.351). Side effects were observed in 49 (10.3%) of the patients during the fingolimod treatment period. Observed side effects were bradycardia, hypotension, headache, dizziness and tachycardia in order of frequency. While 6 of 49 patients had to be discontinued due to side effects such as headache, dizziness, bradycardia, hypotension, bruising, itching, tachycardia, the side effects observed in other patients did not require discontinuation of treatment.

Laboratory abnormalities were observed in 141 (29.2%) of the patients during fingolimod treatment. In terms of laboratory abnormalities, lymphopenia (lymphocyte <0.5 bin/uL) (was observed in 86 patients, liver enzyme elevations were observed in 22 patients, and both lymphopenia and liver enzyme elevations were observed in 12 of the patients. A history of myocardial infarction (MI) was observed in only one of the patients at the 11th month of treatment, and the drug was discontinued in this patient (Figure 6).

The mean blood lymphocyte was 2.0±1.0, and the mean white blood cell was 7.6±6.2 before the treatment. The mean blood lymphocyte level decreased in the first month of the treatment and it was observed that it remained stable at a certain level in the 2-year follow-up (Figure 7).

DISCUSSION

MS is a central nervous system disease that usually affects the young adult age group and can progress through attacks. Over the course of the natural progress of the disease, it is observed that during the periods, where inflammation is prominent, the response for immunomodulatory

treatments is superior (1). With the developments in injection, oral and parenteral treatments in the treatment of MS, the variety offered to patients today seems to be quite good. Fingolimod treatment is used in the first-line treatment in RRMS patients who do not respond to first-line treatments as well as in some RRMS patients with poor prognosis. It is seen that there has been an increase in generic products containing fingolimod in Turkey in the last 3 years. Furthermore, the products are started to be offered to patients. We conducted the first real-life data study with a generic product in the field of MS in Turkey with the first generic fingolimod, which has been observed to have similar efficacy and safety in practical application. In our study, which included 508 MS patients, it was observed that the results were similar to the findings obtained with real-life data previously conducted with the original molecule in 2016 (15). In our study, approximately two-thirds of the patients were female and 92% had RRMS in clinical form. Clinical and radiological features of female and male patients were similar before treatment. A significant portion of the patients switched to fingolimod treatment due to ineffectiveness of other immunomodulatory treatments they used before fingolimod.

During the first placebo-controlled phase 3 trials namely the FREEDOMS and FREEDOMS-2, fingolimod was examined for the first time. Within the context of these studies, 0.5 mg and 1.25 mg doses of treatment were administered to MS patients for 24 months (16). In the FREEDOMS study, the annual attack rate in the group receiving 0.5 mg of fingolimod was found to be significantly lower than in the placebo group. In the MRI branch of the study, in terms of the presence of newly developed or enlarged lesions in T2-weighted sections within 24 months, it was found that the group receiving 0.5 mg of fingolimod had a significantly positive effect on lesion burden compared to the placebo group. In the same study, positive effect of fingolimod on brain atrophy was shown within 2 years of treatment. Results from the FREEDOMS-2 study indicated that efficacy was similar to the results obtained from the FREEDOMS study (16,17). In our study, a similar effect of fingolimod on the annual attack rate was found (17,18).

In our study, it was observed that there was a significant decrease in the mean number of attacks post-treatment, starting from the 6th month, and this decrease continued for two years. Similar to our study, the data of 1361 patients were analyzed in a real-life study in Turkey conducted by Terzi et al. in 2016. Based on the results of the study, the annual attack rate decreases by 88% in the 2nd year after switching to fingolimod treatment (15). According to the results of the analysis of the (PANGAEA) study, again similar to our study, it is seen that after the patients receiving IFN β or Glatiramer Acetate switched to receiving fingolimod treatment, the annual frequency of attacks decreased by approximately 80% in the 4th year (19).

In terms of mean EDSS, it was observed that there was a decrease in EDSS from the 6th month of treatment and this situation remained stable for two years thereafter. In a study conducted in Turkey by İlki et al. on fingolimod real-life data in children with relapsing Multiple Sclerosis, results similar to our study were reported in terms of attack frequency and EDSS. While the median annual attack frequency of patients was 1.9 before fingolimod use, it was observed to be zero with fingolimod treatment (9). The positive effect of fingolimod on relapse and progression, which are the most important efficacy parameters in MS treatment, can be considered as an indicator of the positive response to the treatment. During the two-year treatment period of the patients, the digit symbol test, 25-step walk test and nine-hole peg test were also evaluated in terms of efficacy. It was observed that there was no deterioration in these parameters within 2 years. All these efficacy data derived showed that the results obtained with fingolimod were similar to the real-life data results obtained with the original molecule within Turkey as well as the data obtained from clinical studies and real-life data across the world.

Similar results were observed in both clinical studies and real-life data studies in terms of safety parameters. In our study, even though bradycardia was observed in the first dose administrations, a situation requiring drug discontinuation was not encountered. When the literature was evaluated in terms of side effects, it was concluded that, similar to our study, no side effects were observed due to the use of fingolimod, except for problems such as first dose bradycardia and lymphopenia, and no side effects were observed during the first dose monitoring (9,18,20). Lymphopenia was the most common laboratory finding in laboratory parameters as expected. In our study, that being said, serious lymphopenia requiring drug discontinuation in patients was not encountered.

Conclusion

In conclusion, the observed efficacy and safety results were similar to clinical trial data both in the literature and real life data in terms of the first equivalent with fingolimod active ingredient. In MS patients; fingolimod treatment can be used effectively and safely, considering the clinical and radiological findings of the patients.

Limitations

Since MSFC was not applied to all patients, it was not possible to obtain a significant finding in MSFC values.

Acknowledgements: *We would like to thank Hadi Çelikay, Gülşah Topbaş, Müjgan Bartu, Ezgi Bedir, Narin Zekir, Yasemin Törüm, Şeyma Alacaçayır for their support to this study.*

Thanks to SANOVEL for funding the publication process.

Ethics Committee Approval: Ondokuz Mayıs University Clinical Research Ethics Committee's permission was obtained as per the decision dated 13.06.2020 and numbered 2020/420.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- MT, EMH, SŞ; Design- MT, SŞ, EMH; Supervision- MT, EMH, SŞ; Resource- (-); Materials- MT; Data Collection and/or Processing-CB, VÇ, AA, YB, CU, RT, NY, HE, SB, MS, DK, SG, BPB, BÖ, SM, NKİ, SÖ, ŞY, SS, ŞAT, MÇ, MFY, TKY, AÖS, ŞFG, EG, AÜ, NB, KA, MKT, BK, GS; Analysis and/or Interpretation- YT; Literature Search- MT, EMH, SŞ; Writing- MT, EMH; Critical Reviews- SŞ.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: Support provided by SANOVEL.

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