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ORIGINAL ARTICLE

# The effect of fingolimod on complete blood count, lipid panel, and relationship with clinicoradiologic features in patients with multiple sclerosis

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***ABSTRACT***

**Objectives:** This study aimed to determine the impact of fingolimod treatment on complete blood count (CBC) or lipid panel results and the association of these changes with clinical or radiologic features.

**Patients and methods:** The medical records of 214 patients (154 females, 60 males; mean age: 34.6±10.6 years; range, 16 to 65 years) with multiple sclerosis treated with fingolimod were retrospectively analyzed between January 1, 2015, and January 1, 2023. Pre- and posttreatment demographic data, disease-modifying therapies used previously, total number of attacks, annualized relapse rate, Expanded Disability Status Scale score, radiologic activation change, NEDA (no evidence of disease activity)-3, CBC, and lipid panel results were recorded, and the relationship between clinicoradiological features and laboratory changes were analyzed.

**Results:** The mean duration of exposure to fingolimod was 28.92±20.83 months. Neutrophil and lymphocyte (predominantly) counts decreased ($p=0.011$ and $p<0.001$, respectively), whereas monocyte counts did not change. Low-density lipoprotein (LDL) and total cholesterol levels were higher over 40 years of age ($p=0.021$ and $p=0.047$, respectively), and high-density lipoprotein (HDL) levels were higher in females ($p<0.001$). Total cholesterol, LDL, and HDL levels were slightly increased ($p<0.001$, $p=0.002$, and $p=0.003$, respectively). The LDL level was higher in those with an annualized relapse rate <0.3 ($p=0.003$). There were no significant differences with other clinical or radiologic parameters.

**Conclusion:** Fingolimod reduced the number of lymphocytes (more markedly) and neutrophils. It caused a slight increase within normal limits for LDL and HDL and above normal limits for total cholesterol. However, these changes were not associated with clinical or radiologic activation and usually did not require medical treatment. Therefore, close monitoring is unnecessary except in the presence of risk factors or persistent severe lymphopenia.

***Keywords:*** Complete blood count, fingolimod, high-density lipoprotein, low-density lipoprotein, total cholesterol.

Sphingosine-1-phosphate (S1P) is a lipid mediator acting as a potent extracellular signaling molecule through receptors.[1] It plays a role in many systems, particularly the immune system, central nervous system, blood-brain barrier, and cardiovascular system. With the modulation of its receptor, some agonist or antagonist effects are observed. Fingolimod (FTY720) is an analog of endogenous S1P that binds to receptors 3, 4, and 5, primarily S1P1. It is also the first orally administered disease-modifying therapy (DMT) for multiple sclerosis (MS). Fingolimod exerts an immunomodulatory effect on many immune cells, such as B cells, T cells, dendritic cells, and monocytes, through S1PR modulation.[2,3] In addition, studies indicate that the number of circulating lymphocytes, monocytes, and natural killer cells are decreased. At the same time, neutrophil counts do not change; different results indicate that transcriptional changes are induced rather than numerical changes on others,

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except for lymphocytes.[4-7] It may also contribute to the antiatherogenic effect of high-density lipoprotein (HDL) via S1P mediation.[8] However, experimental studies show both antiatherogenic and proatherogenic results. Few MS studies determined a detailed blood lipid profile change for fingolimod, yielding conflicting results. However, as a general overview, fingolimod may lead to a moderate increase in total cholesterol and HDL levels.[9,10] This study aimed to determine the effect of fingolimod on complete blood cell counts and lipid profiles and reveal the relationship between these changes and clinicoradiologic features.

## PATIENTS AND METHODS

This study was conducted by retrospectively reviewing the medical records of a total of 401 patients who had a definite diagnosis of relapsing-remitting multiple sclerosis (RRMS) according to the revised 2017 or previous McDonald diagnostic criteria. All patients were treated with 0.5 mg oral fingolimod once daily at the Department of Neurology, Bursa Uludağ University Faculty of Medicine, between January 1, 2015, and January 1, 2023.

The inclusion and exclusion criteria were defined separately for the pre-fingolimod period and the fingolimod exposure period. In this study, the term "pre-fingolimod period" referred to the one-year period before fingolimod, and the term "fingolimod exposure period" referred to the duration of exposure to fingolimod in patients who continued or discontinued fingolimod and switched to other treatments. Inclusion criteria for the pre-fingolimod period required two complete blood counts taken at least three months apart (if more than two, the most recent two before fingolimod were included) and lipid panel test performed before fingolimod. For the fingolimod exposure period, continuous use of fingolimod for at least six months was required. In addition, at least two complete blood counts and at least two lipid profiles obtained at intervals of at least three months (excluding the first six months of treatment) had to be available. Exclusion criteria for the pre-fingolimod period included a diagnosis of any endocrinological, cardiac, renal, hepatic, or hematological disease; measurements obtained during or within the first month after a relapse; and laboratory results obtained during periods without any disease-modifying therapy. For the fingolimod exposure period, patients were excluded if fingolimod therapy had been interrupted for more than four weeks, if measurements were taken during a relapse or within the first month following a relapse, or if they were using medications that could affect the laboratory results. After the evaluation of the inclusion and exclusion criteria, the study included a total of 214 nonnaive patients (154 females, 60 males; mean age: 34.6±10.6 years; range, 16 to 65 years). Measurements made in the first six months for the fingolimod exposure period were not evaluated, as drug efficacy may not have been established during this period. The measurement results included in the study after preselection according to the criteria are given in Figure 1. The analysis was performed by calculating the mean value for more than one result. The study protocol was approved by the Clinical Research Ethics Committee of Bursa Uludağ University Faculty of Medicine with the requirement for informed consent waived (Date: 14.02.2023, No: 2023-3/20). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Sex and age at diagnosis were recorded as demographic data. Disease duration from diagnosis to fingolimod initiation, disease-modifying therapies used previously, the total number of attacks, annualized relapse rate, Expanded Disability Status Scale (EDSS) scores, and progression, and radiological activation change were recorded for before (prefingolimod period) and after (fingolimod exposure period) as clinicoradiologic data. Progression was defined as a permanent increase of at least 1.5 points in individuals with an EDSS score of 0 or 1, or a permanent increase of at least 1 point in individuals with an EDSS score of at least 1.5. New gadolinium-enhancing lesions on magnetic resonance imaging or new or enlarging demyelinating lesions on T2-weighted sequences (excluding the first six months after the initiation of fingolimod treatment) were defined as radiological activation. The results were statistically analyzed and compared with changes in complete blood count and lipid panel tests in the pre-fingolimod period and fingolimod exposure period.

### Statistical analysis

Data were analyzed using IBM SPSS version 28.0 software (IBM Corp., Armonk, NY, USA). The data were examined using the Shapiro-Wilk test to determine whether they were normally distributed. The results were presented as mean ± standard deviation (SD), median (min-max), or frequency and percentage. The Kruskal-Wallis and Mann-Whitney U tests were

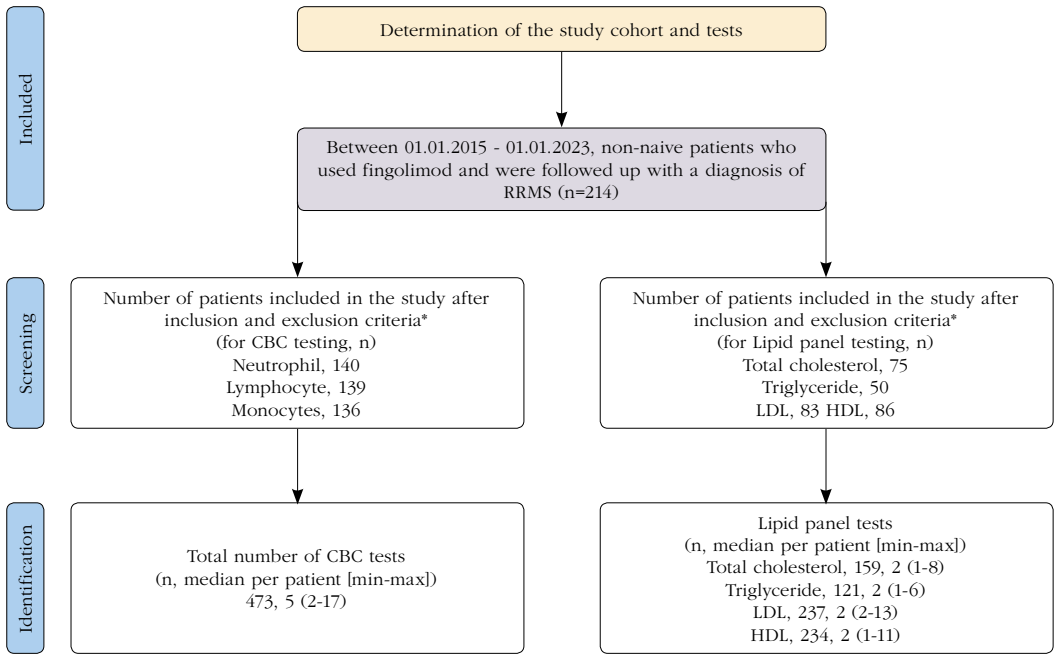


**Figure 1.** Figure 1. Determination of the study cohort and tests to be analyzed.

RRMS: Relapsing-remitting multiple sclerosis; CBC: Complete blood count; LDL: Low-density lipoprotein, HDL: High-density lipoprotein; * Number of patients meeting the condition for both the pre-fingolimod period and the fingolimod exposure period.

used for nonnormally distributed data. The Bonferroni test was used as a multiple comparison test. Paired data were analyzed using the Wilcoxon signed-rank test. Linear mixed model analyses for repeated measures were performed separately, where the CBC and lipid panels were the dependent variables, and the age, sex, disease time, annualized relapse rate (ARR), DMT count, previous DMTs, EDSS scores, radiologic activation, changes in EDSS scores, relapse-free periods, and NEDA (no evidence of disease activity)-3 variables were the independent fixed-effects. Categorical variables were compared between groups using Pearson's chi-square and Fisher's exact tests. A p-value <0.05 was considered statistically significant.

## RESULTS

The mean time from diagnosis to treatment with fingolimod was 6.48±4.34 years, and the duration of exposure to fingolimod was 28.92±20.83 months. The mean EDSS score before and after treatment was 2.42±1.4 and 2.61±1.64. One hundred forty-two of the patients had previously used a single DMT. Previous DMTs included 148 injections, 43 patients on teriflunomide, nine on dimethyl fumarate, and two induction treatments (natalizumab and mitoxantrone). Three patients discontinued their treatment for >6 months in the pre-fingolimod period. The mean number of relapses in the pre-fingolimod period was 2.39±1.35 and 0.15±0.39 in the fingolimod exposure period. The mean ARR was 0.57±0.57 before and 0.10±0.4 after treatment. One hundred eighty-three (86.3%) patients were relapse-free during the follow-up. Among 166 patients with magnetic resonance imaging before and after fingolimod, 25 (16.1%) had radiologic activation.

When the pre-fingolimod period and fingolimod exposure period CBC and lipid panels were compared, there was a decrease in neutrophil and lymphocyte counts and an increase in low-density lipoprotein (LDL), HDL, and total cholesterol levels (Figure 2). However, only total cholesterol was higher than the expected normal reference range (>200 mg/dL; Table 1). For the changes that were found to be significant (neutrophil and lymphocytes counts for CBCs; LDL, HDL, and total cholesterol levels for lipid panels), there was no difference between the previously used DMTs (Table 2). However, the effect of prior DMT use was eliminated using a linear mixed model to clarify the results, even if there was no difference between the groups. Regardless of the effect of DMTs, there was no significant association between CBCs and clinicoradiologic features at

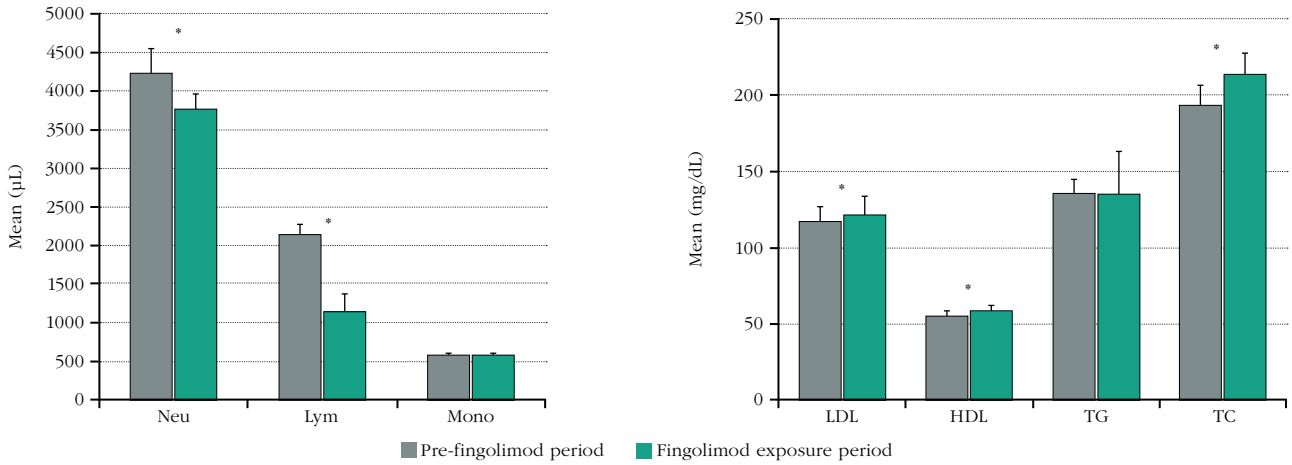


**Figure 2.** Comparison of CBC and lipid panel tests between the pre-fingolimod period and the fingolimod exposure period.

Neu: Neutrophil; Lym: Lymphocyte; Mono: Monocytes; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride; TC: Total cholesterol; CBC: Complete blood count; * p<0.05.

baseline and during follow-up. Levels of LDL and total cholesterol were higher in patients aged >40 years than in those aged <20 years (p=0.021 and p=0.047, respectively). The HDL level was lower in males (p<0.001), and the LDL level was higher in those with an ARR <0.3 (overall p=0.003, *vs.* 0.3-0.5 p=0.046, *vs.* >0.5 p=0.008). Although there was a significant difference between the ARRs for total cholesterol level, no difference was found between the groups according to the pairwise comparison. No patients developed atherosclerotic disease on a proatherogenic basis during the follow-up period. All significance analysis results are provided in Table 3.

When the effect of fingolimod on the lipid panel was evaluated, the proportion of patients with normal LDL, total cholesterol, and triglyceride levels (<100, <200, and <150 mg/dL, respectively) decreased significantly with fingolimod. In contrast, the proportion of patients with elevated serum lipid levels increased. On the contrary, the proportion of patients with low HDL levels (<35 mg/dL) decreased after treatment, whereas the proportion of patients with normal or elevated HDL levels (except >80 mg/dL for females) increased (Table 4).

## DISCUSSION

Fingolimod regulates the circulation and function of lymphocytes through SP1 receptors. In monocytes or granulocytes, it is emphasized that it generally does not change the number in circulation but changes its effects.[1] The SP1 is involved in many mechanisms, such as the immune system, central nervous system, blood-brain barrier, and

**TABLE 1**
Complete blood count and lipid panel changes with fingolimod use

| | Pre-fingolimod period | Fingolimod exposure period | Rate of change | |
|---|---|---|---|---|
| | Mean±SD | Mean±SD | % | *p* |
| Neutrophil count | 4238±1819 | 3819±1125 | –9.8 | **0.011** |
| Lymphocyte count | 2124±818 | 1140±1120 | –44 | **<0.001** |
| Monocyte count | 562±167 | 561±211 | NC | 0.578 |
| LDL level | 118.06±36.35 | 125.77±39.19 | +6.5 | **0.002** |
| HDL level | 53.7±15.16 | 56.44±13.18 | +5.1 | **0.003** |
| Total cholesterol level | 191.13±42 | 213.19±46.66 | +11.5 | **<0.001** |
| Triglyceride level | 124.62±68.06 | 135.45±94.30 | NC | 0.502 |

SD: Standard deviation; LDL: Low-density lipoprotein, HDL: High-density lipoprotein.

cardiovascular system. Agonist or antagonist effects can be observed with its modulation. The S1P is present in endothelial cells, atrial myocytes, smooth muscle cells, and many cells involved in the immune system, including T and B cells, macroglia, and microglia. It has crucial roles in lymph node exit mechanism, neural cell migration/function, vessel formation, endothelial barrier, cardiovascular and nervous system development, and lymphoid tissue expression. Drug-drug interactions are unlikely, practically unnoticed, and take 30 to 60 days to return to previous levels after cessation.[11-13] In this study, the neutrophil and lymphocyte (more prominently) counts decreased. In contrast, the monocyte count did not change, independently of all other parameters evaluated with fingolimod treatment for an median of 26 months. This demonstrated that fingolimod provided an immunologically relevant cell traffic inhibitory effect. However, the lack of correlation between changes in cell number and clinicoradiologic outcomes suggested that the effect was achieved through modulation of these immunologic cells rather than numerical reduction.

The effect on lipid profile still needs to be clarified. Although there is generally believed to be a moderate increase in LDL and HDL levels, it is emphasized that this is not significant. Seventy percent of plasma S1P is transported by apolipoprotein M, which is part of HDL, and experimental studies suggest that S1P may contribute to the antiatherogenic effects of HDL.[8,14] On the other hand, fingolimod may inhibit adipogenesis and stimulate adipose tissue lipolysis.[15] There are also important clues indicating that it reduces the development of atherosclerosis, although the results of several experimental studies suggest that it may have a proatherogenic effect.[16-19] The mechanism of atherosclerosis prevention is thought to be mediated through the modulation of lymphocyte function because it has been shown to cause little or no change in blood cholesterol or triglyceride levels. A limited number of small cohort studies evaluating blood cholesterol changes with fingolimod in patients with MS reported results with moderate increases or no significant changes. Except for a few studies showing that disability may be associated with high LDL levels and low inflammatory activity with high HDL levels, most studies did not perform a detailed assessment of lipid profiles concerning clinical or radiologic changes.[9,10,20,21] There was no change in triglyceride levels in the present study. Still, there was a slight

**TABLE 2**
Complete blood count and lipid panel changes compared to previous DMT treatments

| | Rate of change between pre-fingolimod and exposure period (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Neutrophil | | Lymphocyte | | LDL | | HDL | | Total cholesterol | |
| Previous DMT | Median | Min-Max | Median | Min-Max | Median | Min-Max | Median | Min-Max | Median | Min-Max |
| IFNβ-1a, IM, 30 µg (once a week) | −0.11 | −0.56 to 0.26 | −0.65 | −0.76 to −0.2 | 0.11 | 0 to 0.33 | 0 | −0.12 to 0.17 | 0.19 | 0.12 to 0.26 |
| IFN β-1b, SC, 0.25 mg (every other day) | −0.17 | −0.54 to 0.17 | −0.55 | −0.87 to 0.33 | 0.1 | −0.09 to 0.99 | 0.24 | 0 to 0.91 | 0.06 | −0.01 to 0.38 |
| IFN β-1a, SC, 44 µg (three times a week) | −0.04 | −0.64 to 0.81 | −0.43 | −0.87 to 3.41 | 0.13 | −0.23 to 0.66 | 0.1 | −0.26 to 1 | 0.15 | −0.02 to 0.31 |
| Glatiramer acetate (three times a week) | −0.07 | −0.73 to 2.16 | −0.61 | −0.88 to 1.71 | 0.04 | −0.31 to 0.52 | 0.05 | −0.52 to 0.53 | 0.11 | −0.17 to 0.74 |
| Teriflunomide | −0.01 | −0.38 to 1.28 | −0.58 | −0.76 to 0.03 | 0.12 | −0.2 to 0.42 | 0.09 | −0.28 to 0.36 | 0.09 | 0 to 0.25 |
| Dimethyl fumarate | −0.11 | −0.71 to 0.44 | −0.47 | −0.76 to 0.03 | 0 | −0.12 to 0.04 | 0 | −0.18 to 0.07 | 0.07 | −0.03 to 0.2 |
| *p* value | | 0.421 | | 0.104 | | 0.259 | | 0.156 | | 0.838 |

DMT: Disease-modifying therapy; IFNβ: Interferon beta; IM: Intramuscular; SC: Subcutaneous; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; Data were compared with the Kruskal-Wallis test.

**TABLE 3**
The p-values of the linear mixed models for repeated measures for CBCs and lipid profiles (the interaction effect with previous DMT was evaluated for each variable)

| | CBC and lipid panel | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Variables | N | L | M | L/N | LDL | HDL | TC | TG |
| Age (year) | 0.169 | 0.343 | 0.789 | 0.639 | **0.003** | 0.165 | **0.009** | 0.255 |
| Previous DMT | 0.592 | 0.160 | 0.989 | 0.393 | 0.147 | 0.835 | 0.412 | 0.996 |
| Interaction | 0.350 | 0.798 | 0.944 | 0.785 | 0.663 | 0.723 | 0.621 | 0.855 |
| Sex (Female/Male) | 0.069 | 0.841 | 0.136 | 0.553 | 0.823 | **<0.001** | 0.073 | 0.281 |
| Previous DMT | 0.299 | 0.047 | 0.963 | 0.141 | 0.176 | 0.215 | 0.166 | 0.930 |
| Interaction | 0.399 | 0.564 | 0.635 | 0.373 | 0.357 | 0.362 | 0.547 | 0.734 |
| Disease time (month) | 0.083 | 0.805 | 0.912 | 0.861 | 0.348 | 0.061 | 0.325 | 0.621 |
| Previous DMT | 0.691 | 0.078 | 0.782 | 0.433 | 0.028 | 0.238 | 0.115 | 0.995 |
| Interaction | 0.485 | 0.407 | 0.573 | 0.930 | 0.747 | 0.510 | 0.448 | 0.695 |
| ARR | 0.601 | 0.757 | 0.689 | 0.557 | **0.003** | 0.601 | 0.019* | 0.521 |
| Previous DMT | 0.158 | 0.051 | 0.801 | 0.463 | 0.007 | 0.526 | 0.077 | 0.993 |
| Interaction | 0.225 | 0.159 | 0.409 | 0.769 | 0.972 | 0.535 | 0.952 | 0.872 |
| EDSS | 0.291 | 0.328 | 0.827 | 0.676 | 0.114 | 0.301 | 0.591 | 0.417 |
| Previous DMT | 0.715 | 0.089 | 0.861 | 0.311 | 0.011 | 0.566 | 0.066 | 0.977 |
| Interaction | 0.735 | 0.446 | 0.882 | 0.562 | 0.857 | 0.780 | 0.915 | 0.723 |
| MRI activation | 0.895 | 0.335 | 0.333 | 0.444 | 0.102 | 0.903 | 0.095 | 0.439 |
| Previous DMT | 0.709 | 0.108 | 0.971 | 0.622 | 0.148 | 0.978 | 0.306 | 0.980 |
| Interaction | 0.882 | 0.850 | 0.656 | 0.567 | 0.851 | 0.555 | 0.449 | 0.973 |
| EDSS progression | 0.975 | 0.130 | 0.064 | 0.426 | 0.862 | 0.844 | 0.589 | 0.465 |
| Previous DMT | 0.800 | 0.082 | 0.887 | 0.319 | 0.081 | 0.848 | 0.211 | 0.976 |
| Interaction | 0.317 | 0.191 | 0.576 | 0.794 | 0.567 | 0.352 | 0.239 | 0.333 |
| Relaps-free | 0.089 | 0.099 | 0.582 | 0.806 | 0.574 | 0.138 | 0.404 | 0.866 |
| Previous DMT | 0.596 | 0.274 | 0.923 | 0.632 | 0.197 | 0.537 | 0.436 | 0.999 |
| Interaction | 0.458 | 0.424 | 0.553 | 0.940 | 0.879 | 0.577 | 0.469 | 0.134 |
| NEDA-3 | 0.346 | 0.434 | 0.987 | 0.415 | 0.473 | 0.468 | 0.357 | 0.705 |
| Previous DMT | 0.447 | 0.138 | 0.910 | 0.422 | 0.098 | 0.851 | 0.431 | 0.961 |
| Interaction | 0.051 | 0.866 | 0.297 | 0.490 | 0.906 | 0.117 | 0.472 | 0.420 |

DMT: Disease-modifying therapy; CBC: Complete blood count; N: Neutrophil; L: Lymphocyte; M: Monocyte; L/N: Lymphocyte/neutrophil ratio; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TC: Total cholesterol; TG: Triglyceride. Significant p-values were given in bold; * No significant difference between subgroups.

increase in LDL and HDL levels (within normal limits) and a more marked increase in total cholesterol level that exceeded the normal limit. Fingolimod produced this effect by increasing the proportion of patients with LDL levels >130 and total cholesterol level >200 (predominantly >240). For HDL, on the contrary, it reduced the low HDL level. After eliminating the effect of all DMTs, LDL and total cholesterol levels were higher in older age, and HDL levels were lower in males, as expected independent of all variables. The LDL levels were unexpectedly higher in patients with low ARR. This difference may be related to genetic or environmental variables or suggests that the previously shown favorable effect of HDL and unfavorable effect of LDL on inflammation in patients with MS may not apply to patients treated with fingolimod. On the other hand, the absence of any correlation between the lipid panel and all other clinical and radiologic changes, even NEDA-3, showed that this effect on ARR was not associated with disease progression and did not require close attention in follow-up. Similarly, the lack of correlation between CBCs and changes in any clinicoradiologic parameters indicated that fingolimod exerted its effect by cell modification

**TABLE 4**
Effect of fingolimod on the proportion of different lipid panel groups

| | | | Pre-fingolimod period | | Fingolimod exposure period | | Rate of change |
|---|---|---|---|---|---|---|---|
| | | mg/dL | n | % | n | % | % |
| LDL | | <100 | 26 | 31 | 20 | 24 | –22.5 |
| | | 100-130 | 31 | 38 | 29 | 35 | –7.8 |
| | | >130 | 26 | 31 | 34 | 41 | +32.3 |
| HDL | Female | <35 | 2 | 3 | - | - | –100 |
| | | 35-80 | 57 | 92 | 60 | 97 | +5.4 |
| | | >80 | 3 | 5 | 2 | 3 | –40 |
| | Male | <35 | 6 | 25 | 4 | 17 | –32 |
| | | 35-60 | 17 | 71 | 18 | 75 | +5.6 |
| | | >60 | 1 | 4 | 2 | 8 | +100 |
| TC | | <200 | 50 | 67 | 30 | 40 | –40.3 |
| | | 200-240 | 17 | 23 | 25 | 33 | +43.5 |
| | | >240 | 8 | 10 | 20 | 27 | +170 |
| TG | | <150 | 40 | 80 | 35 | 70 | –12.5 |
| | | 150-200 | 4 | 8 | 10 | 20 | +150 |
| | | >200 | 6 | 12 | 5 | 10 | –16.6 |

LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TC: Total cholesterol; TG: Triglyceride. Fingolimod increased the group of patients with LDL levels >130 mg/dL or total cholesterol >200 mg/dL, but there was no significant difference between groups for HDL.

and regulating the immune system function rather than reducing the total number of lymphocytes or neutrophils. Furthermore, the level of lymphopenia may not be a measurement parameter for the efficacy of fingolimod.

The main limitations of this study were the retrospective setting and analysis. Although we excluded drug and disease states, the study did not evaluate other potentially confounding variables, such as body mass index or dietary changes.

In conclusion, fingolimod caused a marked decrease in lymphocytes count and a moderate decrease in neutrophils count, independent of other clinical features. It caused a slight increase in total cholesterol, LDL, and HDL levels. Age and sex were other factors that influenced these lipid changes, which did not require additional medical treatment. There was no significant correlation between clinical and radiologic parameters and CBC or lipid panels. Therefore, very close follow-up is generally not required, except for persistent severe lymphopenia.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions:** Idea/concept, design, writing the article: F.S.; Control/supervision: O.F.T.; Data collection and/or processing: F.S., S.H.L., G.O.; Analysis and/or interpretation: F.S., G.O., E.R.K.; Literature review: F.S., S.H.L., E.R.K.; Critical review: E.R.K., O.F.T.; Materials: F.S., E.R.K., O.F.T.

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