Am J Clin Exp Immunol 2019;8(2):9-15
www.ajcei.us /ISSN:2164-7712/AJCEI0091754

Original Article

Effect of fingolimod on white blood cell, lymphocyte and neutrophil counts in MS patients

Aryan Rafiee Zadeh[1], Sara Parsa[2], Nooshin Tavoosi[3], Mohsen Farshi[1], Mohammad Farid Masaeli[1]

[1]School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran; [2]School of Medicine, Islamic Azad University, Najafabad Branch, Isfahan, Iran; [3]Department of Midwifery, School of Nursing and Midwifery, Shahrekord University of Medical Sciences, Shahrekord, Iran

Received January 24, 2019; Accepted March 15, 2019; Epub April 15, 2019; Published April 30, 2019

Abstract: Introduction: Fingolimod is an immunomodulating oral treatment used for treating relapsing-remitting multiple sclerosis (RRMS). The exact mechanism for its action in preventing relapses is unknown. Also, its affect on immune cell populations remains unestablished. Objectives: This study will measure the changes in cell populations of WBCs, lymphocytes, and neutrophils in MS patients after one month of treatment. Methods: 66 MS patients from Isfahan Province with RRMS were chosen based on certain exclusion criteria and eligibility for fingolimod oral treatment. Initial cell counts for WBC, lymphocyte, and neutrophil cell populations were achieved. Fingolimod .5 mg daily treatment was then initiated under the supervision of a physician. After one month of treatment, cell counts were repeated. Statistical analysis was performed using SPSS. Results: Both lymphocyte and WBC mean cell counts were significantly decreased in this patient cohort. Neutrophil average cell counts were significantly increased in this 66 patient cohort. Only the decrease of WBC populations was significant for both male and female cohorts individually. Only female sub-cohorts were significantly changed for neutrophils and lymphocytes, increased and decreased respectively. Male sub-cohorts maintained the same directionality but failed to produce statistical significance. Conclusion: While fingolimod has been effectively proven as reducing lymphocyte cells in most patient populations, its effects on neutrophils have not been studied in abundance. Also, there may be sex-related differences in responses to fingolimod treatment with regards to lymphocytes and neutrophils, suggesting a possible difference in RRMS pathogenesis between males and females.

Keywords: Multiple sclerosis, fingolimod, neutrophils, lymphocytes

Introduction

Multiple Sclerosis (MS) is a chronic autoimmune disease that causes deterioration of the myelin sheath and leads to increasing escalation of neurological symptoms. Both physical and cognitive symptoms are frequently observed in MS patients [1]. The disease can lead to increasing levels of disability. Currently, there is no definite understanding of the pathology of MS or a method for curing it [2]. Immunomodulation utilizing drugs is the most common type of therapies for MS [3]. Fingolimod, clinical name GilenyaTM, is an immunomodulatory drug that has recently been approved for the treatment of multiple sclerosis [4]. There are of course other therapeutic options in treating MS which are mostly consisted of injectable drugs and most of them need to be injected under close observation of health care personals because of possible drug reactions. Oral intake of Fingolimod made it an easy option of MS treatment among other therapeutic options and brings a better patient's compliance for drug intake [5]. Fingolimod is a modulator of sphingosine 1-phosphate (S1P) receptor [6]. Fingolimod acts on the S1P1 receptor as an agonist, thereby causing subsequent downregulation of the receptor's expression. Stimulation of S1P1 receptor can cause lymphocytes to leave the lymphoid tissues, and by this mean, they will enter circulation [7]. Fingolimod treatment leads to less expression of these receptors, which causes a decrease in the number of lymphocytes in the central nervous system (CNS) [8]. These lymphocytes are then unable to cause an immune response in the CNS, preventing further myelin sheath damage. CNS effects of Fingolimod are mediated through its mechanism of crossing the blood-brain barrier (BBB) [9].

Fingolimod has produced promising results in MS patients thus far. In patients with relapsing-remitting MS (RRMS), remission has been achieved, and in cases where the drug has been used on non-remitting forms of MS, symptoms have been made less severe in some instances [10]. The most serious of these are heart conditions due to the protective effect of sphingolipids on the cardiovascular system [11]. Other side effects which have been documented to be along with fingolimod therapy include herpetic viral infections, macular edema and aggressive skin cancer [12, 13]. However, the most common side effects are unremarkable and usually mild and typical of most medications [14]. There is still so much unknown about how fingolimod might affect other neurological functioning, which is a concern for patients taking the drug for extended amounts of time. The effects of fingolimod on lymphocytes are well recognized, and lymphopenia is the commonly reported effect. This study addresses fingolimod's effects on white blood cells explicitly, and lymphocytes and neutrophils specifically. Lymphocytes include T and B cells. Neutrophils are the most abundant type of white blood cells and are phagocytic, an essential element of the immune system. The extensive research done on lymphocytic populations is not matched in neutrophil population studies. This study not only seeks to reinforce previous findings of lymphocytes and white blood cells overall but to add to the literature on fingolimod information about neutrophil population effects.

Methods and materials

Patients

This one-month cohort study contained a total of 66 MS patients with the mean age of 32.65 ± 8.12 diagnosed with RRMS based on McDonald's criteria by expert neurologists in Al-Zahra hospital, Isfahan. Our inclusion criteria were having one or more documented relapses in the previous year or at least 2 relapses during the previous 2 years or at least one baseline gadolinium (Gd)-enhancing T1 lesion on magnetic resonance imaging (MRI). All 66 patients signed the written informed consent, and the ethics committee approved the study. Our study initiated with blood collection from all patients for cell analysis and then immediately afterward, oral fingolimod 0.5 mg daily was prescribed for all patients under doctor's permission. Smoking, alcohol/drug abuse, Infection, high neutrophil count, having vaccination with liver attenuated vaccine within two months before study, having EKG or any other cardiovascular problems, having macular edema or any eye disease, having skin lesions or skin cancer, having one documented relapse or corticosteroid treatment within 30 days prior to the study initiation, intake of aspirin or any other anticoagulant within 2 weeks prior and natalizumab treatment within 6 months prior to randomization shaped our exclusion criteria.

Cell counts

Before fingolimod treatment of 0.5 mg daily was initiated, we collected 3 ml of venous blood samples from all MS patients utilizing usual venipuncture. The blood samples were all stored in tubes containing EDTA as an anticoagulant for further cell count analysis. The whole blood white blood cells (WBCs), lymphocytes and neutrophils were determined using an AcT Diff Coulter Counter (Beckman Coulter, Inc. Fullerton, CA) standardized with Coulter 4C-ES Cell Control (Beckman Coulter). It should be noted that all the commercial experiment kits that were used for the analyses were bought from the same company. Immediately after the first blood sampling, all patients received fingolimod 0.5 mg daily under doctor's permission for one month. At the end of fingolimod therapeutic period, patients were recalled to IMSS for final blood sampling and cell counting. At this time, 3 ml of venous blood was collected, and whole blood WBCs, lymphocytes and neutrophils were counted again as described above.

Statistical analysis was performed using SPSS for hardware (version 20). Our data were normalized according to Smirnov Test-sample Kolmogorov-One. Furthermore, paired sample T-test and independent sample T-test were used for other statistical analysis. All tests were two-tailed and $P < 0.05$ was considered as a significant threshold.

Results

66 patients (55 female and 11 male) with the mean age of 32.65 ± 8.12 were registered in this one-month cohort study. WBC: As the laboratory results show, the mean total num-

Table 1. Descriptive statistics

	N	Minimum	Maximum	Mean	Std. Deviation
Age	60	19	54	32.65	8.12
Age male	10	27	54	36.90	8.87
Age female	49	19	51	31.75	7.85
Age at onset total	60	18	49	29.68	7.94
Age at onset male	10	23	49	33.00	8.70
Age at onset female	50	18	48	29.02	7.70
EDSS total	60	1	5	1.60	.78
EDSS male	10	1	2	1.25	.35
EDSS female	50	1	5	1.68	.83
Valid N (listwise)	0				

ber WBC count before treatment initiation is 7,327.42 ± 2,517.30 in all patients (WBC1) and after the one month therapeutic period with fingolimod, the total mean WBC count amongst this cohort is 4,032.58 ± 1,166.48 (WBC2). This data indicates a considerable decrease in the mean WBC counts in the blood (P = 0.00). Although the mean blood WBC counts in male and female patients before study treatment with fingolimod was 8,156.36 ± 3,205.99 and 7,161.64 ± 2,357.18 and after one month follow up, the mean blood WBC became 4,261.82 ± 1,198.64 and 3,986.73 ± 1,165.74 in men and women. These results show a significant decrease in blood WBC both in men and women (P = 0.00). Patients statistics are described in **Table 1**.

Lymphocytes: On the other hand, the mean blood lymphocytes among all patients before the study (lymph1) was 30.79 ± 10.43, and the measurements after treatment with fingolimod (lymph2) yield 16.18 ± 7.78 which is meaningfully lower than before (P = 0.00). AS measurements indicate, the mean blood lymphocytes among men and women before fingolimod treatment were 28.60 ± 11.61 and 31.27 ± 10.23. After one month the mean blood lymphocytes decreased to 19.28 ± 10.10 and 15.52 ± 7.13 in men and women. Such augments in mean blood lymphocytes were although statistically significant in women MS patients (P = 0.00), but the results indicate an inconsiderable decrease in mean blood lymphocytes in men (P = 0.10).

Neutrophils

Furthermore, total blood neutrophils among study population before fingolimod prescription (neut1) was 60.80 ± 11.49 and after total neutrophil counts (neut2) became 71.29 ± 11.57, that indicates a statistically higher neutrophils count in our study population (P = 0.00). Based on laboratory results, the mean blood neutrophils in men and women were 63.85 ± 13.09 and 60.15 ± 11.15, and at the end of the study, the mean blood neutrophils became 69.55 ± 12.15 and 71.66 ± 11.54 in men and women MS patients participated in our study. These laboratory measurements indicate a significant increase in mean blood neutrophils in women (P = 0.00) but a statistically insignificant increase in men mean blood neutrophils (P = 0.45) (**Table 2**).

Discussion

In this sample of 66 patients, we found significant decreases in white blood cell and lymphocyte counts and significant increases in neutrophil counts after one month of fingolimod treatment. It is important to note that these statistically significant changes were found in the entire cohort. When males and females were analyzed separately, the results were slightly different. In the case of white blood cells, both male and female cohorts separately showed statistically significant decreases. The decrease seen in both male and female lymphocyte count averages was only statistically significant in females. Finally, the increase seen in neutrophils was only significant in the female cohort. This suggests that the changes in these specific WBC populations may be more drastic for female patients taking the drug than in males. The pathways behind RRMS are even more misunderstood. However, there is some evidence that the pathways for RRMS may differ between males and females, and specifically in the role neutrophils and B cells have [15].

These specific cell populations each have different immune function and show that fingolimod's mechanisms are vast and intricate. By looking at the overall function of these cell populations and how fingolimod is changing their numbers, the drug's actual action in the case of MS can be further understood. White blood cells encompass many different types of im-

Table 2. Amounts of WBC, Lymphocytes, and Neutrophils, before (WBC1, Lymph1 and Neut1) and after (WBC2, Lymph2 and Neut2) fingolimod treatments

	Male (Mean ± SD)	Female (Mean ± SD)	Total (Mean ± SD)
WBC1	8,156.36 ± 3,205.99	7,161.64 ± 2,357.18	7,327.42 ± 2,517.30
WBC2	4,261.82 ± 1,198.64	3,986.73 ± 1,165.74	4,032.58 ± 1,166.48
WBC1-WBC2	3,894.54 ± 2,868.75	3,174.90 ± 2,042.20	3,294.84 ± 2,191.79
95% CI	1,967.28 - 5,821.80	2,622.82 - 3,726.99	2,756.03 - 3,833.65
P-value	0.00	0.00	0.00
Lymph1	28.60 ± 11.61	31.27 ± 10.23	30.79 ± 10.43
Lymph2	19.28 ± 10.10	15.52 ± 7.13	16.18 ± 7.78
Lymph1-Lymph2	9.31 ± 15.28	15.75 ± 10.28	14.60 ± 11.45
95% CI	-0.94 - 19.58	12.85 - 18.64	11.70 - 17.51
P-value	0.07	0.00	0.00
Neut1	63.85 ± 13.09	60.15 ± 11.15	60.80 ± 11.49
Neut2	69.55 ± 12.15	71.66 ± 11.54	71.29 ± 11.57
Neut1-Neut2	-5.70 ± 16.84	-11.50 ± 14.97	-10.49 ± 15.33
95% CI	-17.01 - 5.61	-15.67 - (-7.33)	-14.35 - (-6.62)
P-value	0.28	0.00	0.00

mune cells; however, the general trend of decreased immune cell counts suggests a decreased immune response, and hopefully a decreased autoimmune response. Lymphocytes are more specifically involved in autoimmunity [16]. There is evidence that T cells are explicitly made for self-antigens by the body, and this may lead to an autoimmune response, in the case of MS the attack on myelin and axons [17, 18]. It is the actual activation of these self-reactive T cells, which is usually prevented in healthy individuals, that leads to autoimmunity under most models of MS pathogenesis [19]. There is also a question as to how and why these T cells enter the CNS to affect CNS tissues actively, but it seems that certain phases in T cell development are more conducive to crossing the BBB [20]. B cells have long been thought of as circumstantial participants in this pathway, but recently humoral attacks have been suggested as a possibility for autoimmunity in MS [21]. No matter what the actual pathway is, it is most likely that both of these types of lymphocytes are actively involved in pathogenesis and any decrease in their numbers is helpful to ameliorating symptoms.

The observed increase in average neutrophil count observed in this study is particularly strange. This seems counterintuitive to the goal of fingolimod treatment. Neutrophils are phagocytic immune cells, responsible for the initial quick phase of inflammation [22]. In experimental autoimmune encephalomyelitis (EAE) a decreased amount of circulating neutrophils was correlated with delayed and decreased severity of demyelination [23]. Neutrophils seem repeatedly implicated in neuroinflammation in EAE [24]. If neutrophil populations are increased in fingolimod taking patients, or most significantly in women, it could be a source of inefficacy by the drug. Also, the differences observed in neutrophil and lymphocyte changes in this study suggest a possible difference in disease mechanisms for RRMS.

Fingolimod has been shown to cause a decrease in white blood cell counts, including populations of monocytes specifically [25]. However, studies have been mostly focused on measuring its affects in lymphocyte populations specifically. Fingolimod is a drug that intends to reduce the number of lymphocytes leaving the lymphoid tissues into the circulation by downregulation of S1P1 receptor expression. Therefore, its reduction in lymphocytes was expected in this study. Its efficacy in performing this task has been demonstrated in patient populations [26-28]. Initially and continually, its ability to reduce lymphocyte traffic has been reproduced in animal models as well [29, 30]. Most notably, changes in T cell subsets have been confirmed, but its effect on B cell subsets is also thought to be effective in reducing RRMS progression [31]. Fingolimod may lower the proportion of memory B cells in

circulation and cause an influx of naïve memory B cells, further supporting the hypothesis that B cell immunity is also an essential factor in RRMS [32]. Patient cohorts treated with fingolimod have shown differing decreases in lymphocyte counts based on weight as well as gender, with similar patterns observed in this study with regards to women experiencing a more severe decrease [33]. Also, there is some evidence that T cell populations overall are not affected after long periods on fingolimod, but that the proportion of CD4+ to other T cells is increased [34, 35]. In the case of this study, specific types of lymphocytes were not tested for and the period of study was only one month.

The extent to which neutrophil populations are affected by fingolimod has not been researched extensively. Therefore, the increase observed in this study needs to be recreated to verify its validity. There are no other studies to our knowledge that reported an increased population of neutrophils in patients after fingolimod treatment. In mice, fingolimod does not seem to elicit any change in neutrophil populations or an even decreased average count [36, 37]. The same results have been produced in other animal models [38, 39]. This is an area that needs to be further investigated by physicians with access to large samples of MS patients. The role of neutrophils in autoimmunity and fingolimod action should not be ignored. The results of this study suggest that neutrophil populations may be increased in patient populations, with special attention being placed on female patients as susceptible to this increase.

Conclusion

This study strengthens the evidence that fingolimod is effective in reducing white blood cell and lymphocyte counts in MS patients with RRMS. However, it suggests that neutrophil populations may be increased, most significantly in female patients. Perhaps, this is due to the slight differences in RRMS pathology that occur between sexes. Further analysis of patient populations needs to be done to conclude if this increase is reproducible or if neutrophil populations are unchanged in patients taking oral fingolimod treatment.

Disclosure of conflict of interest

None.

Address correspondence to: Mohammad Farid Masaeli, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. Tel: +98913404-6017; E-mail: faridmsl90@gmail.com

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