Int J Physiol Pathophysiol Pharmacol 2020;12(3):88-94
www.ijppp.org /ISSN:1944-8171/IJPPP0107934

Original Article

Effects of fingolimod treatments on alanine transaminase and aspartate transaminase levels in patients with multiple sclerosis

Saeid Sadeghi Joni[1], Masoumeh Cheshmavar[2], Pouria Shoureshi[3], Zohreh Zamani[4], Niusha Taoosi[5], Morteza Akbari[6], Mahdieh Afzali[2]

[1]Department of Radiology, Razi Hospital, Guilan University of Medical Sciences, Rasht, Iran; [2]Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran; [3]Department of Internal Medicine, Orange Park Medical Center, Florida, USA; [4]Department of Neurology, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran; [5]Islamic University of Riau, Riau, Indonesia; [6]School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Received January 15, 2020; Accepted May 1, 2020; Epub June 15, 2020; Published June 30, 2020

Abstract: Introduction: Multiple Sclerosis (MS) is a chronic neurological disorder with no known cause or cure. Fingolimod (FTY720) is an oral medication recently approved for the treatment of MS as well as other diseases with autoimmune aspects. However, the drug is not without side effects. The severity and prevalence of these side effects are not completely understood. One of the most common causes for the patient cessation of fingolimod is an increase in liver enzymes, indicating possible inflammation or damage to liver cells. Alanine transaminase (ALT) and aspartate transaminase (AST) are the most common liver enzymes used as indicators of hepatic health. Objectives: This three-month prospective cohort study selected patients who were diagnosed with relapsing-remitting MS (RRMS) and who were not taking fingolimod oral treatment. ALT and AST levels were determined for these patients at baseline and then after three months of taking FTY720 to determine if these liver enzymes were changed. Methods: 36 RRMS patients completed this study, which lasted three months. They were started on 0.5 oral FTY720 after approval from a physician and completion of an AST/ALT blood test. Baseline levels were determined and then taken again three months later. Statistical analysis of these values was performed using $P<0.05$ as a significance threshold. Results: In this sample of patients, only ALT levels were significantly increased after fingolimod treatment in the general cohort ($P=0.00$). The general cohort showed an insignificant increase in AST levels. In male and female populations separately, AST was not significantly increased. ALT was only significantly increased in men ($P=0.00$) and insignificantly increased in women. Conclusion: This study further confirms our concerns about fingolimod's possible effects on the liver. While these numbers do support the claim that the drug does on average increase ALT in patient populations, it is important to note that most of these patients have no real hepatic side effects. In addition, previous studies have cited a return to normal ALT and AST levels after cessation of fingolimod, suggesting its effects are temporary and not severely damaged in the usual patient.

Keywords: Multiple sclerosis, fingolimod, liver enzymes

Introduction

Multiple sclerosis (MS) is an autoimmune neurological disease that affects roughly young population around the world [1]. Its prevalence increases with distance from the equator. This chronic disease causes deterioration of the myelin sheath leading to neurological symptoms that can range in permanence and severity. Besides, the types of symptoms vary by patient making diagnosis often difficult and confusing for both patient and physician. These symptoms may be cognitive or physical. Increasingly severe levels of disability can result from MS pathology [2]. Currently, the only options for involved patients are managing symptoms. The most common types of pharmaceutical drug therapies utilize immunomodulation, which is effective in some patients. Fingolimod (FTY720) (Fingolid, Osveh Co. Iran),

is an immunomodulatory drug that has recently been approved for the treatment of multiple sclerosis [3, 4]. It was the first oral medication approved for the treatment of MS, specifically for relapsing-remitting MS (RRMS). There are other drugs on the market that are given intravenously or through injection for the management of RRMS. Fingolimod led the way for oral MS treatment, making it easier for patients to manage their symptoms at home. Fingolimod is the first sphingosine 1-phosphate (S1P) receptor modulator to be approved as a treatment for any malady [5]. Fingolimod acts on the S1P1 receptor as an agonist leading to subsequent downregulation of the receptor's expression [6]. Fingolimod has been shown clinically effective in preventing this exodus of lymphocytes from the lymphoid tissues, leaving them unable to access the CNS as readily [7]. This lack of lymphocytic penetration is thought to prevent further myelin sheath damaged by the immune system. Fingolimod crosses the blood-brain barrier (BBB), allowing it to take effect directly in the CNS [8]. The drug is also an oral medication, making it much easier to take daily in comparison to other MS drugs. Patient compliance for oral drugs is much higher than more invasive ones. So far, the results have been promising. The patient populations targeted by fingolimod are those who have been diagnosed with RRMS. In patients with 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 certain cases [9-11]. While the drug is not a miracle cure, it does seem to produce some noticeable results. However, it is not without risk. The side effects range from manageable to life-threatening. Heart conditions have been the most serious concern of health providers and researchers. Because sphingolipids are cardiovascular protectants and have been shown to promote regular heart rate, the downregulation of S1P1 receptors can lead to cardiovascular side effects [12]. There have been cases reported of severe herpetic viral infections and macular edema [4, 13-15]. There have also been reports of aggressive skin cancer running rampant [16]. However, the most common side effects are unremarkable and usually mild [11]. There is still much unknown about how fingolimod might affect other neurological functioning, which is a concern for patients taking the drug for extended amounts of time [17].

Fingolimod is well-cited as producing lymphopenia because it is for this reason that fingolimod is used for MS treatment [18, 19]. In vitro, fingolimod has shown increased populations of regulatory T cell populations [20]. There have also been studies citing a decrease in these regulatory T cells after application of fingolimod, or no significant change [21]. These effects are expected and involved in the drugs target plan of action. However, physicians should be concerned about how fingolimod is acting in other parts of the body. In this case, the area of question is the liver. In the current study, we measured the effect of FTY720, also known as fingolimod, on aspartate transaminase (AST) and alanine transaminase (ALT) levels in MS patients. ALT and AST are both enzymes commonly used to determine liver health. The ratio of AST to ALT can either be elevated or low, in each case predicting a different set of possible liver conditions such as fatty liver disease (either alcoholic or nonalcoholic) and hepatitis B/C. Because of the very recent development, approval, and use of this drug in humans, it is imperative to monitor possible harmful side effects. Liver side effects are common concerns for any new drug on the market, especially one given for a chronic condition such as MS. Also, increases in these transaminase enzymes have been cited by all of the major fingolimod clinical trials [11, 13, 22, 23]. Increased levels of AST and ALT suggest liver cell damage, because when these cells are injured or inflamed, they leak higher amounts of these enzymes into the body. If in fact, these increases are suggestive of harm to liver cells, rather than a result of some pathway that has yet to be understood between fingolimod and production of liver enzymes, then treating MS patients with fingolimod may be doing more harm than good.

Methods and materials

Patients

36 patients with the mean age of 34.24±8.43 diagnosed with relapsing-remitting MS (RRMS) by neurologists according to McDonald's criteria [24] were invited to participate in this three-month cohort study. Based on the sample size calculation, 36 patients were calculat-

ed. We recruited patients until our study population completed.

Patients were recruited from Eka Hospital Pekanbaru. The study was approved ethically by the ethical committee of Islamic University of Riau with the ethical code of IUR108-REC1-117. Those patients between 18 to 40 years of age who had 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) were selected for this study. Oral FTY720 0.5 mg was given to all patients under the doctor's permission daily. Before the treatment was initiated, volunteers were asked if they were smokers, alcohol/drug abusers, had vaccination with the liver attenuated vaccine within two months before the study, asthma, pulmonary problems, EKG abnormalities, macular edema or any kind of eye disease and 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, natalizumab treatment within 6 months prior to randomization, prescription drugs within 4 weeks prior, or over-the-counter drugs within 2 weeks before baseline were additional exclusion criteria. All the patients signed the written informed consent and also the ethics committee approved the study.

Serum ALT-AST measurements

Before study initiation, 3 ml of venous blood samples were collected in the MS clinic of Eka hospital from every patient carefully using routine venipuncture method. In order to avoid the effects of physical activity on ALT and AST levels, blood samplings were performed early in the morning without previous physical activity. The blood AST and ALT levels were measured by recruiting plasma content and then storing at -80°C. For measuring plasma levels of ALT and AST we utilized enzyme-linked immunosorbent assay (ELISA) commercial kits purchased from Kehua (Shanghai, China). After the first blood sampling, treatment with FTY720 was initiated immediately. At the end of the three months therapeutic period with FTY720, patients were called again to the MS clinic for final measurements of hepatic enzymes, ALT and AST, by blood sampling. The levels of blood ALT and AST were measured with an auto-analyzer as mentioned above.

Statistical analysis was performed using SPSS for hardware (version 24). Our data was normal according to Smirnov Test-sample Kolmovorov-One. Furthermore, paired-sample T-test and independent sample T-test was used for other statistical analysis. All tests were two-tailed and $P<0.05$ was considered as a significant threshold.

Results

37 patients (28 female and 9 male) with the mean age of 34.24±8.43 were asked to participate in this three months cohort study. One woman was excluded from the study due to complications from FTY720, which were cardiovascular and skin related.

Based on measurements and laboratory results, the mean blood ALT level in the entire study population before initiation of treatment with FTY720 (ALT1) was 20.41±11.25 U/L and after the therapeutic period (ALT2) was 25.88±14.58 U/L. This is meaningfully higher than before treatment (P=0.00). Although the mean blood AST level before the treatment (AST1) was 20.41±5.52 U/L among patients and afterward (AST2) became 22.11± 6.53 U/L, which is higher than before, it was not statistically considerable (P=0.12). The mean blood ALT level among men and women before FTY720 therapy was 30.22±15.17 U/L and 17.14±7.44 U/L respectively. After three months these values reached 40.66±15.77 U/L and 20.96±10.44 U/L in men and women respectively. This increase was not statistically significant in women (P=0.10). The increase in male ALT levels was significant (P=0.00). The same measurements for mean blood level of AST among men and women were 23.66±6.67 U/L and 19.33±4.73 U/L before fingolimod and 28.11±7.84 U/L and 20.11±4.68 U/L after treatment. Statistical analysis reveals that neither male nor female cohorts were significantly increased, although the male cohort just barely missed the significance threshold (P=0.07). The augment in women blood AST was also not significant because of the *P*-value (P= 0.52). The elevation of both ALT and AST blood levels are more considerable among men than in women (**Table 2**). Other statistics are described in **Table 1**. It should also be mention-

Table 1. Descriptive statistics

	N	Minimum	Maximum	Mean	Std. Deviation
age.male	8	27.00	54.00	38.5000	9.11827
age.female	33	22.00	51.00	33.2121	8.06519
age.total	41	22.00	54.00	34.2439	8.43143
EDSS.male	8	1.00	2.00	1.2500	.37796
EDSS.female	33	1.00	5.00	1.6515	.92267
EDSS.total	41	1.00	5.00	1.5732	.85558
age.at.onset.total	41	18.00	48.00	28.5366	7.51697
age.at.onset.male	8	23.00	49.00	34.7500	8.79529
age.at.onet.female	33	18.00	41.00	27.3030	6.56451
Valid N (listwise)	8				

Table 2. ALT and AST levels before and after therapies

	Male (Mean ± SD) (U/L)	Female (Mean ± SD) (U/L)	Total (Mean ± SD) (U/L)
ALT_1	30.22±15.17	17.14±7.44	20.41±11.25
ALT_2	40.66±15.77	20.96±10.44	25.88±14.58
ALT_1-ALT_2	10.44±5.87	3.81±11.71	5.47±10.87
95% CI	14.96-(-5.92)	8.44-0.81	-9.15-(-1.79)
P-value	0.00	0.10	0.00
AST_1	23.66±6.67	19.33±4.73	20.41±5.52
AST_2	28.11±7.84	20.11±4.68	22.11±6.53
AST_1-AST_2	-4.44±6.46	-0.77±6.32	-1.69±6.46
95% CI	-9.42-0.52	-3.27-1.72	-3.88-0.49
P-value	0.07	0.52	0.12

(ALT_1 and AST_1: before therapies, ALT_2 and AST_2: after therapies).

ed that the patients with increased liver function tests were refereed to internists for further treatments.

Discussion

In this sample of 39 MS patients, only ALT levels were significantly increased after fingolimod (FTY720) treatment in the general cohort. The general cohort showed an insignificant increase in AST levels. In male and female populations separately, AST was not significantly increased. ALT was only significantly increased in men (P=0.00) and insignificantly increased in women. To summarize, all cohorts showed increased levels of both ALT and AST but only ALT was statistically significant (P=0.00). These results are in agreement with the majority of medical literature published about fingolimod use in humans. The effects of fingolimod on platelet counts have been studied before [25]. FTY720's safety profile cites an increase in liver enzymes as a possible side effect of taking the drug [23, 26]. In a phase 3 trial 0.5 mg, fingolimod treatment caused an increase in ALT enzyme levels and was cited as a significant side effect along with the aforementioned set of symptoms mentioned in this paper [11]. In patients who took fingolimod oral treatment for 12 months, ALT and AST levels elevated to a peak value at around 3 months and remained at that level until 12 months [22]. It is important to note that this present study measured ALT and AST levels only three months after treatment was initiated, perhaps leaving the peak values undetermined for most patients. Many fingolimod trials suggest physician monitoring of transaminase levels not only at the start of treatment but perhaps after 1, 3, 6, 9, and 12 months as well [5]. The significant risk of elevated liver enzymes may outweigh the benefits of fingolimod treatment for certain patients, especially those patients who already have significant liver disease before starting treatment. One of the most common reasons a patient might be taken off fingolimod is an increase in liver enzymes [27]. ALT increase is the most common change in liver enzymes produced by fingolimod, representing 6.5% of all adverse effects in one study, 4.6% more than those accounted for in interferon β-1a treated patients, another common MS treatment option [28]. Manni and colleagues have performed a study on 225 RRMS patients who had been under treatments with fingolimod. They observed a significant increase in ALT and AST levels of patients especially in males [29]. These results are in line with our study. We also showed that the levels of ALT and AST are increased after 3 months follow up of RRMS patients. Symptoms of hepatic dysfunction cited in these patients include unexplained nausea, vomiting, abdominal pain, fatigue, and jaundice. However, the observed increase in liver enzymes is usually without symptoms and will return to normal after discontinuation of fingolimod [28, 30]. The mechanism for the increase in liver enzymes, especially that of

ALT, is still not known. To assess what risk this increase poses, it will be important to determine if fingolimod is directly causing an increase in these enzymes or if the drug is harming liver cells leading to these abnormal test results. One possibility is that the drug's metabolism somehow interferes with liver function or interacts with the production of liver enzymes in some obscure pathway. The drug's metabolism is rather unusual compared to other drugs in that the common drug-clearing enzymes are not involved, suggesting this as a possible area for future research [31].

The validity of AST and ALT as predictors of hepatic injury is not completely sound, in that many times these levels can be outside of the normal range without any apparent injury to the liver and vary significantly between different demographic populations [32]. In diagnosing chronic liver disease (CLD), using the AST/ALT ratio as a diagnostic tool for cirrhosis yielded 81.3% sensitivity and only 55.3% specificity [33]. While these numbers are certainly useful, they are not without error, especially in cases where the numbers are only slightly out of the normal range [34]. It is interesting to note that outside of the MS realm, FTY720 is being used in other settings. One of these areas of research involves fingolimod being used to repair and prevent liver damage in rodents. In rats, FTY720 was shown to prevent ischemic injury in normal and cirrhotic rat livers [35]. FTY720 has also been used to prevent liver graft injury in rats [36]. Similar results of immunosuppression preventing liver damage have been shown in mice models as well [37, 38]. These two dichotomies seem strange: that fingolimod can be researched in one respect as a way to prevent liver damage and in another regard be seen as a possible cause of liver damage. Nevertheless, FTY720 has been shown in rare cases to cause symptoms associated with liver damage in conjunction with elevated transaminase levels. Patients with previous histories of liver conditions should be wary of taking the drug in case it exacerbates any pre-existing problems. Also, patients should be monitored closely for enzyme levels that are outside of the normal range and be made aware of possible symptoms of liver damage. As researchers learn more about FTY720 as a substance not only in the immune system and CNS but in the entire body, hopefully the true reason for these increases can be understood. ALT and AST are the most common enzymes used to indicate liver health and the relationship between fingolimod and γ-glutamyltransferase (GGT), another liver enzyme, has been established previously. It must also be noted that liver enzymes are not sufficient to evaluate liver functions. We could suggest that fingolimod should be administrated carefully in patients with former liver problems or routine check of liver enzymes should also be performed for susceptible patients.

Conclusion

This study concludes that MS patients taking oral fingolimod 0.5 mg daily for only three months are at significant risk for elevated ALT levels, and to a lesser degree AST levels. These findings are following previous studies done in human populations. This study recognizes its short time-span with caution. It is most likely true that these elevated levels are not the peak values for most patients and by citing previous literature on the topic, it seems most likely that levels would peak around the three months or so into treatment. Therefore, a timetable of 1, 3, 6, 9 and 12 months, which is recommended by Novartis Pharmaceuticals UK Ltd, seems appropriate for patients not experiencing any adverse side-effects. It is still unclear what the mechanism is behind this relationship. The results demonstrated in these patient populations also shed some doubt on studies currently being done in rodents to establish fingolimod as a possible preventer of liver damage and rejection.

Disclosure of conflict of interest

None.

Address correspondence to: Mahdieh Afzali, Department of Neurology, School of Medicine, Isfahan University of Medical Sciences, Hezar Jarib Blvd., Isfahan, Iran. Tel: +989133314544; E-mail: m.afzali2219@gmail.com

References

[1] Chung KK, Altmann D, Barkhof F, Miszkiel K, Brex PA, O'Riordan J, Ebner M, Prados F, Cardoso MJ and Vercauteren T. A 30-year clinical and magnetic resonance imaging observa-

tional study of multiple sclerosis and clinically isolated syndromes. Ann Neurol 2020; 87: 63-74.
[2] Filippi M, Brück W, Chard D, Fazekas F, Geurts JJ, Enzinger C, Hametner S, Kuhlmann T, Preziosa P and Rovira À. Association between pathological and MRI findings in multiple sclerosis. Lancet Neurol 2019; 18: 198-210.
[3] Zadeh AR, Ghadimi K, Ataei A, Askari M, Sheikhinia N, Tavoosi N and Falahatian M. Mechanism and adverse effects of multiple sclerosis drugs: a review article. Part 2. Int J Physiol Pathophysiol Pharmacol 2019; 11: 105-114.
[4] Zadeh AR, Askari M, Azadani NN, Ataei A, Ghadimi K, Tavoosi N and Falahatian M. Mechanism and adverse effects of multiple sclerosis drugs: a review article. Part 1. Int J Physiol Pathophysiol Pharmacol 2019; 11: 95-104.
[5] Chun J, Kihara Y, Jonnalagadda D and Blaho VA. Fingolimod: lessons learned and new opportunities for treating multiple sclerosis and other disorders. Annu Rev Pharmacol Toxicol 2019; 59: 149-70.
[6] Brunkhorst R, Vutukuri R and Pfeilschifter W. Fingolimod for the treatment of neurological diseases-state of play and future perspectives. Front Cell Neurosci 2014; 8: 283.
[7] Paolicelli D, Manni A, D'onghia M, Direnzo V, Iaffaldano P, Zoccolella S, Di Lecce V, Tortorella C, Specchia G and Trojano M. Lymphocyte subsets as biomarkers of therapeutic response in fingolimod treated relapsing multiple sclerosis patients. J Neuroimmunol 2017; 303: 75-80.
[8] Anthony DC, Sibson NR, Losey P, Meier DP and Leppert D. Investigation of immune and CNS-mediated effects of fingolimod in the focal delayed-type hypersensitivity multiple sclerosis model. Neuropharmacology 2014; 79: 534-541.
[9] Muris AH, Rolf L, Damoiseaux J, Koeman E and Hupperts R. Fingolimod in active multiple sclerosis: an impressive decrease in Gd-enhancing lesions. BMC Neurol 2014; 14: 164.
[10] Sorensen PS. Effects of fingolimod in relapsing-remitting multiple sclerosis. Lancet Neurol 2014; 13: 526-527.
[11] Calabresi PA, Radue EW, Goodin D, Jeffery D, Rammohan KW, Reder AT, Vollmer T, Agius MA, Kappos L, Stites T, Li B, Cappiello L, von Rosenstiel P and Lublin FD. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol 2014; 13: 545-556.
[12] Simula S, Laitinen T, Laitinen TM, Tarkiainen T, Hartikainen P and Hartikainen JE. Effect of fingolimod on cardiac autonomic regulation in patients with multiple sclerosis. Mult Scler 2016; 22: 1080-1085.
[13] Ward MD, Jones DE and Goldman MD. Overview and safety of fingolimod hydrochloride use in patients with multiple sclerosis. Expert Opin Drug Saf 2014; 13: 989-998.
[14] Niemelä E, Desai D, Niemi R, Doroszko M, Özliseli E, Kemppainen K, Rahman NA, Sahlgren C, Törnquist K, Eriksson JE and Rosenholm JM. Nanoparticles carrying fingolimod and methotrexate enables targeted induction of apoptosis and immobilization of invasive thyroid cancer. Eur J Pharm Biopharm 2020; 148: 1-9.
[15] Gross CM, Baumgartner A, Rauer S and Stich O. Multiple sclerosis rebound following herpes zoster infection and suspension of fingolimod. Neurology 2012; 79: 2006-2007.
[16] Sato DK and Callegaro D. Oral fingolimod to treat multiple sclerosis: see your cardiologist first. Arq Neuropsiquiatr 2014; 72: 651-652.
[17] Landi D, Vollaro S, Pellegrino G, Mulas D, Ghazaryan A, Falato E, Pasqualetti P, Rossini PM and Filippi MM. Oral fingolimod reduces glutamate-mediated intracortical excitability in relapsing-remitting multiple sclerosis. Clin Neurophysiol 2015; 126: 165-9.
[18] Johnson TA, Evans BL, Durafourt BA, Blain M, Lapierre Y, Bar-Or A and Antel JP. Reduction of the peripheral blood CD56(bright) NK lymphocyte subset in FTY720-treated multiple sclerosis patients. J Immunol 2011; 187: 570-579.
[19] Francis G, Kappos L, O'Connor P, Collins W, Tang D, Mercier F and Cohen JA. Temporal profile of lymphocyte counts and relationship with infections with fingolimod therapy. Mult Scler 2014; 20: 471-480.
[20] Dominguez-Villar M, Raddassi K, Danielsen AC, Guarnaccia J and Hafler DA. Fingolimod modulates T cell phenotype and regulatory T cell plasticity in vivo. J Autoimmun 2019; 96: 40-49.
[21] Eken A, Duhen R, Singh AK, Fry M, Buckner JH, Kita M, Bettelli E and Oukka M. S1P 1 deletion differentially affects TH17 and regulatory T cells. Sci Rep 2017; 7: 12905.
[22] Kira J, Itoyama Y, Kikuchi S, Hao Q, Kurosawa T, Nagato K, Tsumiyama I, von Rosenstiel P, Zhang-Auberson L and Saida T. Fingolimod (FTY720) therapy in Japanese patients with relapsing multiple sclerosis over 12 months: results of a phase 2 observational extension. BMC Neurol 2014; 14: 21.
[23] Saida T, Kikuchi S, Itoyama Y, Hao Q, Kurosawa T, Nagato K, Tang D, Zhang-Auberson L and Kira J. A randomized, controlled trial of fingolimod (FTY720) in Japanese patients with mul-

tiple sclerosis. Mult Scler 2012; 18: 1269-1277.
[24] Habek M, Pavičić T, Ruška B, Pavlović I, Gabelić T, Barun B, Adamec I, Crnošija L and Skorić MK. Establishing the diagnosis of multiple sclerosis in croatian patients with clinically isolated syndrome: 2010 versus 2017 McDonald criteria. Mult Scler Relat Disord 2018; 25: 99-103.
[25] Farrokhi M, Beni AA, Etemadifar M, Rezaei A, Rivard L, Zadeh AR, Sedaghat N and Ghadimi M. Effect of fingolimod on platelet count among multiple sclerosis patients. Int J Prev Med 2015; 6: 125.
[26] Harrison K. Fingolimod for multiple sclerosis: a review for the specialist nurse. Br J Nurs 2014; 23: 582-589.
[27] Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, Selmaj K, Agoropoulou C, Leyk M, Zhang-Auberson L and Burtin P; FREEDOMS Study Group. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010; 362: 387-401.
[28] Fazekas F, Berger T, Fabjan TH, Ledinek AH, Jakab G, Komoly S, Kraus J, Kurca E, Kyriakides T, Lisy L, Milanov I, Panayiotou P, Jazbec SS, Talab R, Traykov L, Turcani P, Vass K, Vella N and Havrdova E. Fingolimod in the treatment algorithm of relapsing remitting multiple sclerosis: a statement of the central and east european (CEE) MS expert group. Wien Med Wochenschr 2012; 162: 354-366.
[29] Manni A, Direnzo V, Iaffaldano A, Di Lecce V, Tortorella C, Zoccolella S, Iaffaldano P, Trojano M and Paolicelli D. Gender differences in safety issues during fingolimod therapy: evidence from a real-life relapsing multiple sclerosis cohort. Brain Behav 2017; 7: e00804.
[30] David OJ, Kovarik JM and Schmouder RL. Clinical pharmacokinetics of fingolimod. Clin Pharmacokinet 2012; 51: 15-28.
[31] Jin Y, Zollinger M, Borell H, Zimmerlin A and Patten CJ. CYP4F enzymes are responsible for the elimination of fingolimod (FTY720), a novel treatment of relapsing multiple sclerosis. Drug Metab Dispos 2011; 39: 191-198.
[32] Peveling-Oberhag J and Zeuzem S. "Liver enzymes"--interpretation of laboratory values. Versicherungsmedizin 2010; 62: 73-77.
[33] Giannini E, Risso D, Botta F, Chiarbonello B, Fasoli A, Malfatti F, Romagnoli P, Testa E, Ceppa P and Testa R. Validity and clinical utility of the aspartate aminotransferase-alanine aminotransferase ratio in assessing disease severity and prognosis in patients with hepatitis C virus-related chronic liver disease. Arch Intern Med 2003; 163: 218-224.
[34] Park GJ, Lin BP, Ngu MC, Jones DB and Katelaris PH. Aspartate aminotransferase: alanine aminotransferase ratio in chronic hepatitis C infection: is it a useful predictor of cirrhosis? J Gastroenterol Hepatol 2000; 15: 386-390.
[35] Man K, Ng KT, Lee TK, Lo CM, Sun CK, Li XL, Zhao Y, Ho JW and Fan ST. FTY720 attenuates hepatic ischemia-reperfusion injury in normal and cirrhotic livers. Am J Transplant 2005; 5: 40-49.
[36] Zhao Y, Man K, Lo CM, Ng KT, Li XL, Sun CK, Lee TK, Dai XW and Fan ST. Attenuation of small-for-size liver graft injury by FTY720: significance of cell-survival Akt signaling pathway. Am J Transplant 2004; 4: 1399-1407.
[37] Kong Y, Wang H, Wang S and Tang N. FTY720, a sphingosine-1 phosphate receptor modulator, improves liver fibrosis in a mouse model by impairing the motility of bone marrow-derived mesenchymal stem cells. Inflammation 2014; 37: 1326-1336.
[38] Yin XD, Jia PJ, Pang Y and He JH. Protective effect of FTY720 on several markers of liver injury induced by concanavalin a in mice. Curr Ther Res Clin Exp 2012; 73: 140-149.