Original Article

Assessment of clinician adherence to Fingolimod instructions and its effect on patient safety

Alaa A. Alhubaishi, PharmD, PGY1, *Lolwa M. Alsharekh,* PharmD, *Haya F. Almoharb,* B. Pharm, *Faisal A. Alqarni,* PharmD, BCPS, *Abdalhadi M. Alqahtani,* B.Parm, MSc, *Mohammed K. Alghazwni,* B. Pharm, *Modhi A. Alfuraydi,* PharmD, *Abdulmajed Z. Alsadi,* MD,SBN, *Raad Y. Altalhi,* MBBS, SBN, *Tariq M. Almutairi,* MD, MSc, *Ghadah H. Alshehri,* MSc, PhD.

ABSTRACT

الأهداف: تقييم التزام الأطباء بالاستخدام الفعال لفينجوليمود وفقًا للتوصيات الموصوفة لتقليل مخاطر السلامة، وتحديد العواقب، وتسليط الضوء على مجالات التحسين لصانعي السياسات لصالح كل من المريض ومقدم الرعاية.

المنهجية: دراسة رصدية بأثر رجعي أجريت في مستشفى الرعاية الثلاثية استهدفت مرضى التصلب المتعدد اللويحي الذين يتلقون علاج فينجوليمود في الفترة من يناير 2017 إلى ديسمبر 2021. تم تقييم التزام الأطباء بتعليمات الشركة المصنعة وتم تصنيفهم إلى جيد، ومعتدل، وضعيف بناءً على الالتزام بتعليمات فينجوليمود وإجراءات المراقبة. تم تقييم أربعة مقاييس لتقييم التزام الأطباء الى: مراقبة بطء نبضات القلب، وفحص العيون، وإنزيمات الكبد، والالتهابات. وبالإضافة إلى ذلك، تم أيضًا تقييم تأثير الالتزام على سلامة المرضى.

النتائج: تم تضمين 140 مريضا في الدراسة. كان لدى 72 مريضا (51.4%) طبيبًا غير ملتزم لإرشادات مراقبة فينجوليمود (حيث تم اتباع واحد من الارشادات أو لم يتبع أي من منها). كان لدى 65 مريضًا (46.4%) طبيبا التزاما معتدلا (حيث تم اتباع 3-2 من الارشادات). كان لدى 3 مرضى (2.10%) طبيبا ملتزما بجميع ارشادات مراقبة فينجوليمود. فيما يتعلق بمضاعفات فينجوليمود ، وجد أن 18 مريضًا يعانون من بطء دقات القلب بعد الجرعة الاولى، اربع مرضى يعانون من وذمة البقعة الصفراء في العين والالتهابات ، و6 مرضى يعانون من ارتفاع إنزيمات الكبد. وجد أن عدم التزام الطبيب لإرشادات مراقبة فينجوليمود إلى عدم إكمال العلاج وأعلى معدل للتوقف عن استخدام فينجوليمود أو التحول إلى خيارات علاجية أخرى.

الخلاصة: كان الالتزام بارشادات مراقبة فينجوليمود ضعيفًا بين الأطباء في الدراسه مما أدى إلى أعلى معدل لتبديل الدواء أو التوقف عنه.

Objectives: To assess clinicians' adherence to fingolimod's effective use according to the prescribed recommendations to reduce safety risk, identify the consequences, and highlight areas for improvement to policy makers for the benefit of both patient and care-giver.

Methods: A retrospective observational study conducted at a tertiary hospital targeting multiple sclerosis patients on fingolimod from January 2017 to December 2021. The physicians' adherence to the manufacturer's instructions was assessed and categorized into good, moderate, and poor based on adherence to fingolimod instructions and monitoring measures. Four monitoring measures were assessed: bradycardia observation, ophthalmic examination, liver enzymes, and infections. In addition, the impact of adherence on patient safety was also assessed.

Results: A total of 140 patients were included. Seventy-twopatients (51.4%) had physician with poor adherence (followed only one instruction or none). Sixty-five patients (46.4%) had 2-3 manufacture recommendations where physician's adherence was moderate. Three patients (2.10%) had all manufacturer's recommendations. In terms of fingolimod complications, 18 patients found to have bradycardia after the first does, macular oedema and infections was reported in 4 patients, and the elevation in hepatic enzymes was reported in 6 patients. Poor physician's adherence has resulted in treatment incompleteness and highest fingolimod discontinuation or switching to other treatment options.

Conclusion: Adherence to fingolimod instructions was poor among physicians which resulted in highest drug switching or discontinuing rate.

Neurosciences 2024; Vol. 29 (3): 184-189
doi: 10.17712/nsj.2024.3.20240040

From the Department of Pharmacy Practice (Alhubaishi, Alshehri), College of Pharmacy, Princess Nourah bint Abdulrahman University, from the Department of Pharmacy (Alsharekh, Almoharb, Alqarni, Alghazwni, Alfuraydi), Security Forces Hospital, from Clinical Research Department (Alqahtani), King Fahad Medical City, from the Department of Internal Medicine (Alsadi), Security Forces Hospital, Department of Neuroscience (Almutairi), King Faisal Specialist Hospital and Research Centre, Riyadh, and from Department of Internal Medicine (Altalhi), King Faisal Medical Complex, Taif, Kingdom of Saudi Arabia

Received 28h April 2024. Accepted 31st May 2024.

Address correspondence and reprint request to: Dr. Ghadah H. Alshehri, Department of Pharmacy Practice, College of Pharmacy, Princess Nourah bint Abdulrahman University, Riyadh, Kingdom of Saudi Arabia
E-mail: ghalshehri@pnu.edu.sa
ORCID ID: https://orcid.org/0000-0001-7807-4470

Multiple sclerosis (MS) is an acquired chronic immune-mediated inflammatory condition of the central nervous system that affects the brain and spinal cord. Multiple sclerosis mostly affect the age group between 20 and 40, with a higher prevalence in women than men.[1] The MS prevalence has increased regionally and globally. The prevalence is based on recent data which found 40.40 cases per 100,000 worldwide and 61.95 cases per 100,000 for Saudi nationals.[2] The MS is usually present with recurrent focal neurological deficits that are subacute in nature and may improve to some extent over the course of weeks to months.[3]

There are 3 different disease patterns for multiple sclerosis. Relapsing-Remitting Multiple Sclerosis (RRMS) is the most common form where episodes of flare-ups (relapses or exacerbations) are followed by periods of remission wherein symptoms improve or disappear.[4] Patients with RRMS may develop Secondary Progressive Multiple sclerosis (SPMS) which is a progressive worsening of the neurologic function over time. The third is Primary Progressive Multiple sclerosis (PPMS) where a worsening of neurological functions happens from the onset of symptoms, without early relapses and remissions.[5] The treatment of MS should be initiated to decrease the frequency of exacerbations and disease progression by using disease-modifying agents.[5] Many drugs have been approved for the management of multiple sclerosis; these can lower the frequency of relapses and delay the disability progression, and thus referred to as disease-modifying drugs (DMD).[6] The choice of disease-modifying drugs is guided by multiple factors including: patient characteristics, comorbidities, disease activity, drug safety profile, and accessibility of the drug.[7]

Fingolimod is the first oral disease-modifying therapy approved by the US Food and Drug Administration in 2010 for the treatment of patients with RRMS. Many studies have demonstrated its efficacy. In a double blind, a randomized study investigated the effect of fingolimod on (RRMS) at 2 doses: 0.18 with 0.5 mg and 0.16 with 1.25 mg of fingolimod, compared with placebo 0.40 (p<0.001 for either dose vs. placebo). Fingolimod at both doses (0.5 mg and 1.25 mg) significantly reduced the risk of disability progression over the 24-month period (hazard ratio, 0.70 and 0.68, respectively; p=0.02 vs. placebo, for both comparisons). In addition, Fingolimod doses were superior to placebo regarding MRI-related measures.[8] Moreover, a phase 3 randomized, double-blind clinical trial compared fingolimod to intramuscular interferon beta-1a. The annualized relapse rate was significantly reduced in the fingolimod group.[9]

Whilst fingolimod demonstrated efficacy in treating RRMS, its use has been associated with increased complication risks including: first-dose bradycardia, increase in liver enzymes macular edema, and risk of infections.[10–12] In addition, serious side-effects, including atrioventricular block, have also been reported.[13] As control measures to reduce the risks associated with fingolimod, the manufacturer-prescribed guideline recommended conducting a baseline safety assessment and first dose observation for signs and symptoms of bradycardia to maximize safety with fingolimod use (**Table 1**).

Therefore, this study is aimed at assessing clinicians' adherence to fingolimod's effective use according to the prescribed recommendations to reduce safety risk, identify the consequences, and highlight areas for improvement to policy makers for the benefit of both patient and care-giver.

Methods. ***The Study design and setting.*** This is a retrospective observational study conducted at a tertiary hospital targeting patients with MS who were started on fingolimod from January 2017 to December 2021. Criteria for inclusion included being an adult at least 18 years of age and diagnosed with relapsing remitting multiple sclerosis who had received fingolimod treatment for a minimum of 6 months, while the exclusion criteria included being under the age of 18 whose diagnosis involved other types of MS such as primary progressive, secondary progressive, or progressive–relapsing MS. To identify prior research, searches were run in the PubMed database using keywords such as fingolimod, clinician adherence, monitoring guideline and Saudi Arabia. This study follows the Strengthening the Reporting of Observational studies in Epidemiology "STROBE" checklist statement as recommended by Enhancing the QUAlity and Transparency Of health Research "EQUATOR" guidance.

Ethical approval. The study was approved by the Security Forces Hospital (SHF) (Ref.# H-01-R-069). All methods were performed in accordance with the relevant guidelines and regulations.

Data collection. Study data were collected from patient records and managed using a Microsoft Excel

Disclosure. The authors declare no conflicting interests, support or funding from any drug company. The research was funded by Princess Nourah bint Abdulrahman University Researchers Supporting Project number (PNURSP2024R315), Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia.

Table 1 - Drug manufacturer's recommendations to reduce risks associated with fingolimod.

Monitoring parameter	When
Bradycardia	At least 6 hours after first dose
Pulse and blood pressure	Hourly during observation
Electrocardiograms (ECGs)	Prior to dosing and at end of observation
Ophthalmic examinations	Before and 3–4 months after treatment
Liver transaminase and bilirubin levels	Before initiation of therapy and within 6 months of initiation
Complete blood cells (CBC)	During treatment and for 2 months after discontinuation

Table 2 - Multiple sclerosis patients characteristic on fingolimod.

Variables	Frequency (n)	Percent (%)
Age (Mean (SD))	34.82 (11.36)	
Gender		
Male	56	40.0
Female	84	60.0
Comorbidities		
Diabetes mellitus	4	2.86
Blood disorder	2	1.43
Skin cancer	1	0.71
Arrhythmia	4	2.86

sheet. The data included patients' demographic information, comorbidities, vital signs, medication known to cause bradycardia, and laboratory data. Based on the manufacturer's instructions, patients' data were collected and sectioned to: (a) data that need to be observed before initiating the first dose of fingolimod; and (b) data that need to be observed as follow-up after initiating the first dose of fingolimod. All major clinician adherence point parameters were documented (**Table 1**).

Outcomes. The primary endpoint was to assess the adherence level among clinicians to applying the instructions recommended by the manufacturer of Fingolimod. To assess the primary endpoint, the first dose of Fingolimod and the applied assessment by clinicians will be recorded at the start of therapy and during follow-ups when required. The level of adherence among clinicians will be classified into 3 categories: good, moderate, and poor.

The secondary endpoint was to evaluate the impact of adherence to the manufacturer's instructions on patient safety. To assess this secondary endpoint, the clinician's adherence will be followed in a retrospective manner to assess patient safety by recording patient compliance and any incidence with signs and/or symptoms of bradyarrhythmia and Atrioventricular (AV) block, infections, macular edema, and elevations in liver function tests that could lead to medication failure.

Outcome definition(s). The outcomes defined as the following: Good adherence: when all the instructions are applied (4 out of 4), moderate adherence: when more than half of the instructions are applied (2 to 3 points), poor adherence: when less than half of the instructions are applied (one or none), bradycardia: it was defined as a heart rate below 60 heartbeats per minute, AV block: this was defined as partial or complete interruption of impulse transmission from the atria to the ventricles, infections: defined as elevation of WBC >11.0× 109/L or Lymphocyte %>40, positive latent infection screening or the presence of varicella-zoster antibodies or opportunistic infections diagnosis, macular edema: defined as swelling in part of the retina observed via dilated eye exam and pictures of the retina, abnormal liver-related biomarkers were defined according to the Saudi journal of gastroenterology as alanine aminotransferase (ALT) values of more than 40 U/L, or aspartate aminotransferase (AST) values of more than 40 U/L or albumin values of less than 35 g/L, treatment incompleteness: defined as switching to another treatment option or discontinuing of fingolimod by the physician, patient compliance: defined as when the patient during the follow-ups reported good ability to take the drug as prescribed by the physician in terms of the correct dose, route, timing, and frequency.

Statistical analysis. Data analysis was performed using the SPSS 25.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were reported as dichotomous, polychotomous, and as frequencies and percentages to explore the distribution of clinical characteristics and outcomes among patients. Continuous variables were presented as median with standard deviation (SD) to compare lab results between the first dose group and the follow-up group. The chi-squared or Fisher's exact test, as appropriate, was used to compare the categorical variables between groups. For all tests, no imputation was done, and a *p*-value of 0.05 or lower was regarded as statistically significant.

Results.

Demographic and clinical characteristics. Of the whole cohort, Sixty percent of the patients were

Table 3 - Clinician adherence categories based on following manufacturer's recommendations.

Clinician adherence classification	Number of clinicians	Percentage
Poor adherence (1 or no recommendation was followed)	72	(51.43)
Moderate adherence (2-3 recommendations were followed)	65	(46.43)
Full adherence (all recommendations were followed)	3	(2.10)

Table 4 - Clinician adherence to applying each manufacturer's recommendation point.

Variables	Applied or not	n (%)
Observe all patients for bradycardia for at least 6 hours; monitor pulse and blood pressure hourly. Electrocardiograms (ECGs) prior to dosing and at the end of observation period required.	Yes	113 (80.7)
	No	27 (19.3)
Ophthalmic examinations before and 3–4 months after start of treatment to assess for macular edema.	Yes	22 (15.7)
	No	118 (84.3)
Liver transaminases (aspartate transaminase and alanine transaminase) plus total bilirubin levels should be available before initiation of therapy and obtained within 6 months of Fingolimod initiation.	Yes	77 (55.0)
	No	63 (45.0)
Obtain complete blood cells, monitor for infection during treatment and for 2 months after discontinuation.	Yes	12 (8.6)
	No	128 (91.4)

Table 5 - Fingolimod complications reported during study of monitored patients.

Complication	Number of patients affected
Bradycardia with first dose	18 out of 113 monitored patients
Macular edema	4 out of 22 monitored patients
Infection Urinary tract infection	4 out of 12 monitored patients
Liver enzyme elevation AST (Mean ± SD) (U/L) 87±99.1 ALT (Mean ± SD) (U/L) 158±163.4 Total bilirubin (Mean ± SD) (ummol/l) 11.5±11.3	6 out of 77 monitored patients

Table 6 - The impact of clinician adherence to fingolimod instructions on patient treatment.

Impact of clinician adherence	Poor adherence	Moderate adherence	Full adherence	*P*-value
Treatment incompleteness	10	4	3	0.0001*
Non-compliance	65	64	2	0.024*

female and 40% were male with a mean age of 34.82 years. There were 4 patients (2.86%) who had a history of diabetes mellitus, and 4 patients with a history of arrhythmia. Two patients (1.43%) had a history of blood disorder, and one patient had skin cancer (**Table 2**).

Clinician adherence to manufacturer's recommendations. During the study, 140 patients with MS met the inclusion criteria. Based on the classification of clinician adherence, a higher proportion of patients had poor clinician adherence (72 patients, 51.4%) wherein clinicians either did not follow the manufacturer's recommendations or followed only one. Sixty-five patients (46.4%) received 2-3 manufacturer's recommendations wherein clinician adherence was classified as moderate. Only 3 patients (2.10%) received all manufacturer's recommendations and clinicians in this case fully adhered (**Table 3**). Fingolimod administration requires 4 major follow-up parameters, namely: heart rate, ophthalmic examinations, liver function test, and CBC. Regard clinician adherence to applying each recommendation, heart rate was followed for at least 6 hours along with Electrocardiograms (ECGs) prior to dosing, and at the end of the observation period it was found that for 113 patients (80.7%) their clinician followed this recommendation, while for 27 patients (19.3%) this recommendation was not followed by their clinician. Ophthalmic examinations before and 3–4 months after treatment initiation to assess for macular edema were screened appropriately based on recommendation for only 22 patients (15.7%), while for 118 patients (84.3%) it was not followed (**Table 4**). Regarding the third recommendation point which is measuring the liver transaminases (aspartate transaminase and alanine transaminase) plus total bilirubin levels that should be obtained within 6 months of fingolimod initiation, the results showed that in 77 patients (55.0%) these were monitored, while for 63 patients (45.0%) there were no liver transaminases results. Lastly, obtaining complete blood cells to monitor for infection during treatment and for 2 months after discontinuation was

the last recommended point to be followed in patients using fingolimod; only in 12 patients (8.6%) were this recommendation followed, while for 128 patients (91.4%) it was not.

Patient safety outcomes. Fingolimod complications were reported based on the monitored patients, as presented in **Table 4**. Out of the patients that were followed 18 patients found to have bradycardia after the first does, macular oedema and, non-complicated urinary tract infection was reported in 4 patients, and the elevation in hepatic enzymes was reported in 6 patients (**Table 5**).

In terms of the impact of clinician adherence to manufacturer's recommendations on patient safety, the result was either treatment incompleteness or patient noncompliance. A total of 17 patients (12.2%) did not complete fingolimod treatment of whom the majority (10 patients) were followed by clinicians with poor adherence to manufacturer's recommendations. On the other hand, a total of 131 patients (93.6%) were noncompliant with their treatment plan. The majority were followed by clinicians in the poor to moderate adherence category (**Table 6**).

Discussion. A comparison with the relevant literature is challenging, as this is the first study of its kind in Saudi Arabia to have assessed clinician adherence to fingolimod treatment guidelines. Generally, the adherence to guidelines is low among health care professionals, even though many evidence-based practice guidelines exist and are recommended for use in all medical fields.[14] A cross sectional study reported a poor adherence rate to clinical guidelines among physicians treating hypertension patients at 4 district hospitals in South Africa, which further linked this to the physicians characteristics such as age and clinical experience.[15] Another study, based in Sudan, showed that most of the clinicians were not adhering to the guidelines.[16] In Saudi Arabia, the adherence to clinical guidelines was found to be a matter of concern. The adherence among primary health care physicians to hypertension management guidelines was found to be inadequate as reported in study based on the southwest of Saudi Arabia. However, a recent study investigating the physician's adherence to antihypertensive treatment guidelines illustrate that the pattern of hypertension treatment was in line with published hypertension treatment guidelines.[17]

In this study, we aim to evaluate clinician adherence to manufacturer's recommendations as to the use of fingolimod in patients with RRMS. This study showed a low adherence among physicians to the manufacturer's monitoring recommendations on the use of fingolimod. Considering all adherence parameter guidelines, clinicians demonstrated full adherence in 2.10%, moderate adherence in 46.4%, and low adherence in 51.4%. Full adherence was evident in terms of observing the patient's heart rate, blood pressure and ECG, which can be explained by the physician's awareness of cardiovascular safety complication associated with fingolimod. On the other hand, physicians were not fully adhering to monitoring parameters related to liver enzyme, ophthalmic examination, and CBC counts.

We observed that bradycardia, hypotension, macular edema, elevation of liver enzymes, and infections appeared in the population when clinicians did not apply all the recommended precautions. The appearance of these serious events highlights the necessity of clinicians' commitment to applying all the recommended precautions to be able to intervene during the observation period to prevent serious patient harm and avoid treatment incompleteness or patient non-compliance.

The study findings highlighted the link between clinician adherence to fingolimod monitoring parameters and patient adherence to fingolimod treatment. Our study showed that physician non-adherence to the recommended fingolimod monitoring parameters has a negative impact on the patient's ability to adhere to fingolimod treatment. In contrast to our finding, patient adherence to fingolimod treatment was found to be superior when compared to self-injected disease-modifying therapies.[18] Another study has reported that most patients demonstrated optimal adherence to fingolimod treatment.[19] However, none of these studies have investigated the link between clinician adherence to fingolimod manufacturer's recommendation points on the one hand and patient adherence on the other.

Our study aimed to investigate clinician adherence to fingolimod manufacturer's recommendations using a standard approach to collect data from patient records. That being said, this study also has certain limitations that should be considered when interpreting its findings. The study was conducted in a single centre. Therefore, our findings might not be generalizable across all of Saudi Arabia's health care organizations. In addition, the retrospective review of patient records relies exclusively on information recorded in those records which could undermine the comprehensiveness of the data collected. For future studies, there is a need to collect data about clinical experience and the seniority of the clinicians involved which may positively influence the level of adherence to fingolimod monitoring recommendations.

In conclusion, adherence to fingolimod instructions and monitoring measures was significantly low among clinicians. This poor adherence led to higher drug switching or discontinuing rate compared to the moderate or full adherence clinician group. Our study advocates for the implementation of regulations and protocols to guarantee the utilization of updated guidelines. Additionally, we propose establishing regular clinical audits is deemed crucial for strengthening the governance system for all involved entities to ensure the safety of MS patients.

Acknowledgement. *We would like to thank Princess Nourah bint Abdulrahman University for funding our study under the University's Researchers Supporting Project number (PNURSP2024R315).*

References

1. NICE guideline [NG220]. 2022. 2022. Multiple sclerosis in adults: management. https://www.nice.org.uk/guidance/ng220
2. AlJumah M, Bunyan R, Al Otaibi H, Al Towaijri G, Karim A, Al Malik Y, et al. Rising prevalence of multiple sclerosis in Saudi Arabia, a descriptive study. ***BMC Neurol*** 2020; 20: 49.
3. Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. ***Eur J Neurol*** 2018; 25: 215-237.
4. National Clinical Guideline Centre (UK). Multiple Sclerosis: Management of Multiple Sclerosis in Primary and Secondary Care. London (UK): National Institute for Health and Care Excellence (UK); 2014.
5. Saguil A, Kane S, Farnell E. Multiple sclerosis: a primary care perspective. ***Am Fam Physician*** 2014; 90: 644-652.
6. Tramacere I, Del Giovane C, Salanti G, D'Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. ***Cochrane Database Syst Rev*** 2015; 2015: CD011381.
7. Rae-Grant A, Day GS, Marrie RA, Rabinstein A, Cree BAC, Gronseth GS, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. ***Neurology*** 2018; 90: 777-788.
8. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. ***N Engl J Med*** 2010; 362: 387-401.
9. Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. ***N Engl J Med*** 2010; 362: 402-415.
10. ©Novartis. MEDICATION GUIDE GILENYA® (je-LEN-yah) (fingolimod) capsules. https://www.novartis.com/sg-en/sites/novartis_sg/files/Gilenya-Dec2020.SIN-app220321.pdf.
11. Gajofatto A, Turatti M, Monaco S, Benedetti MD. Clinical efficacy, safety, and tolerability of fingolimod for the treatment of relapsing-remitting multiple sclerosis. ***Drug Healthc Patient Saf*** 2015; 7: 157-167.
12. Arvin AM, Wolinsky JS, Kappos L, Morris MI, Reder AT, Tornatore C, et al. Varicella-zoster virus infections in patients treated with fingolimod: risk assessment and consensus recommendations for management. ***JAMA Neurol*** 2015; 72: 31-39.
13. Brown B, Weiss JL, Kolodny S, Meng X, Williams IM, Osborne JA. Analysis of cardiac monitoring and safety data in patients initiating fingolimod treatment in the home or in clinic. ***BMC Neurol*** 2019; 19: 287.
14. Kennedy PJ, Leathley CM, Hughes CF. Clinical practice variation. ***Med J Aust*** 2010; 193: S97-D99.
15. Adedeji AR, Tumbo J, Govender I. Adherence of doctors to a clinical guideline for hypertension in Bojanala district, North-West Province, South Africa. ***Afr J Prim Health Care Fam Med*** 2015; 7: 776.
16. Abdelgadir HS, Elfadul MM, Hamid NH, Noma M. Adherence of doctors to hypertension clinical guidelines in academy charity teaching hospital, Khartoum, Sudan. ***BMC Health Serv Res*** 2019; 19: 309.
17. Dhanaraj E, Raval A, Yadav R, Bhansali A, Tiwari P. Prescription Pattern of Antihypertensive Agents in T2DM Patients Visiting Tertiary Care Centre in North India. ***Int J Hypertens*** 2012; 2012: 520915.
18. Agashivala N, Wu N, Abouzaid S, Wu Y, Kim E, Boulanger L, et al. Compliance to fingolimod and other disease modifying treatments in multiple sclerosis patients, a retrospective cohort study. ***BMC Neurol*** 2013; 13: 138.
19. Zimmer A, Coslovsky M, Abraham I, Décard BF. Adherence to fingolimod in multiple sclerosis: an investigator-initiated, prospective, observational, single-center cohort study. ***Patient Prefer Adherence*** 2017; 11: 1815-1830.