Title: Adverse Drug Reactions of Multiple Sclerosis Disease-Modifying Drugs

Authors: Maryam Salehbayat¹, Roya Abolfazli², Niayesh Mohebbi^{3,*}, Seyed Mehrdad Savar⁴, Gloria Shalviri⁵, Kheirollah Gholami⁶

1. International Campus, Tehran University of Medical Sciences, Tehran, Iran.
2. Iranian Center of Neurological Research, Tehran University of Medical Sciences, Tehran, Iran.
3. Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.
4. Research center for rational use of drugs, Tehran University of Medical Sciences, Tehran, Iran.
5. Tehran University of Medical Sciences, Tehran, Iran.
6. Pharmacoepidemiology and Pharmacovigilance Center, Food and Drug Administration, Ministry of Health, Tehran, Iran.

***Corresponding author:** Niayesh Mohebbi, Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran. E-mail address: niayesh_mohebbi@yahoo.com

To appear in: *Basic and Clinical Neuroscience*

Received date: 2021/06/23

Revised date: 2021/07/31

Accepted date: 2021/08/28

This is a “Just Accepted” manuscript, which has been examined by the peer-review process and has been accepted for publication. A “Just Accepted” manuscript is published online shortly after its acceptance, which is prior to technical editing and formatting and author proofing. *Basic and Clinical Neuroscience* provides “Just Accepted” as an optional and free service which allows authors to make their results available to the research community as soon as possible after acceptance. After a manuscript has been technically edited and formatted, it will be removed from the “Just Accepted” Web site and published as a published article. Please note that technical editing may introduce minor changes to the manuscript text and/or graphics which may affect the content, and all legal disclaimers that apply to the journal pertain.

Please cite this article as:

Salehbayat, M., Abolfazli, R., Mohebbi, N., Savar, M., Shalviri, G., & Gholami, K. H. (In Press). Adverse Drug Reactions of Multiple Sclerosis Disease-Modifying Drugs. *Basic and Clinical Neuroscience*. Just Accepted publication Sep. 12, 2021. Doi: <http://dx.doi.org/10.32598/bcn.2021.2848.2>

DOI: <http://dx.doi.org/10.32598/bcn.2021.2848.2>

Abstract:

Introduction: High frequency of adverse drug reactions (ADRs) challenges multiple sclerosis (MS) treatment. We aimed to assess the nature and frequency of ADRs induced by MS medications in an observational cross-sectional study.

Material and Methods: ADRs of all outpatients who had been visiting a neurologist and had been receiving at least one disease-modifying therapy (DMT) for MS during the last three months were investigated.

Results: A total number of 484 ADRs were detected in these patients. The preventability rate was 5.9%, and 0.61% of reactions were serious.

Discussion: The high frequency of adverse drug reactions in this study shows a strong need for planning a strategy to increase patients' adherence to treatment.

Keywords: Adverse Drug Reactions, Interferons, Neuropharmacology, Neurology, Compliance

Key Messages: It is crucial to consider the ADRs associated with MS medications.

Introduction:

Biosimilar drugs have an essential role in decreasing costs to health systems. Most MS patients in Iran use Interferon(IFN) β biosimilars as disease-modifying therapies (DMTs). Zarxio[®] and Nivestym[®], the biosimilars of NEUPOGEN[®] (filgrastim), are the only biosimilars that have been approved by the FDA. ("FDA Approved Drug Products: Nivestym," 2018; "FDA Approved Drug Products: Zarxio (filgrastim-sndz)," 2015)

Treatment regimen adherence in MS proved to be challenging. Some studies reported patient adherence rate as 60-76% for 2-5 years. (Costello, Kennedy, & Scanzillo, 2008) According to other studies, one of the biggest obstacles that could result in non-adherence is ADRs. (Abolfazli et al., 2014) Therefore, evaluation of ADR occurrence patterns and their management in these patients is vital.

This study aims to evaluate ADRs suspected to be induced by MS medications. Although there are published studies that evaluated ADRs of just one or two MS medications (Clanet et al., 2002; Jacobs et al., 1996; Jongen et al., 2011)

Materials and Methods:

In an observational cross-sectional study, a questionnaire was developed to evaluate the ADRs of all the outpatients visiting the neurology clinic of Amir A'alam hospital, Tehran, Iran, and had been receiving at least one DMT for MS during the last three months. The patients who did not consent to be enrolled were excluded from the study.

A sample size of 250 was calculated with a 5% type 1 error and using the rate of ADRs from previous studies. (Nabavi et al., 2019)

The World Health Organization's (WHO) definition of ADR was applied to mark and report an ADR. (Organization, 2000)

ADRs were detected by reviewing laboratory data, interviewing patients, and consulting a neurologist. Liver enzymes, fasting blood sugar, and lipid profile enzymes were monitored for all patients. All detected reactions were recorded on a national ADR yellow card by the same pharmacist in the next step. The causality of drug-related adverse reactions was classified through the WHO criteria. The seriousness of recorded ADRs was also determined by the WHO definition. (Organization, 2000) Moreover, the preventability of ADRs was assessed by Schumock and Thornton questionnaire. (Schumock & Thornton, 1992)

The data derived from the recorded questionnaire were analyzed using IBM SPSS 21. Chi-square and t-test were used for statistical analysis.

Results:

In total, 250 patients (185 (74%) women and 65(26 %) men) were enrolled in the study. The mean ($\pm$ SD) age of patients was 30.6 ($\pm$ 5.3) years, ranging from 21 to 46.

A total number of 484 ADRs were detected from 191 (76.4%) patients, including 42 males and 149 females. The frequency of ADR occurrence was higher in females than males (80.5% vs. 64.4%). Forty patients reported one ADR, 70 showed two, and 82 had more than two ADRs.

Table 1 shows generic names of preparations and different brand names and routes of administration and recorded ADRs. The mean ($\pm$ SD) duration of using DMTs was 25.7 $\pm$ 23.1 months ranged from 3.0 to 102.0 months. One hundred ninety-six ADRs (40.4%) happened in the first hour after medication administration, and 214 ADRs (44.2%) were initiated 1-3 hours after using medications.

Among 484 detected ADRs, three cases were recognized as serious and 29 cases (5.9%) as preventable ADRs. The causality assessment of ADRs revealed that 65.2% of ADRs were detected as possible, followed by 22.9% as certain, 11.5% as unlikely, and 0.2% as probable. Regarding the outcome of recognized ADRs, 94.21% of patients recovered, 4.96% had unknown outcomes, and 0.83% did not recover.

The main actions taken against ADRs were symptomatic therapies (79.5%). Other measures taken were continuing the treatment (20.04%), and drug withdrawal in 2 detected ADRs (0.41%). There was one fulminant hepatitis case induced by Rebif[®] and a seizure induced by Cinnovex[®] that led to medication withdrawal. There was also a seizure reported by taking Actoferon[®] as a serious ADR that did not lead to discontinuation of the medicine.

The percentage of ADRs was significantly different among various brand names of INF β -1a that were administered intramuscularly ($p=0.01$), but it was not the case for the ones administered subcutaneously ($p=0.56$).

There was no relationship between age and ADR occurrence ($p=0.076$). Gender had a significant association with ADR; females experienced ADRs more than males ($p=0.009$). Statistical analyses showed that age and gender had no significant relationship with seriousness ($P=0.51$, and 0.55) or preventability ($p=0.5$, and 0.41).

Discussion:

Flu-like symptoms (38%) and headache (26.4%) were the most commonly observed ADRs in this study. In line with two other studies performed by Patti et al. in 2006 and Beer et al. in 2011, there was a lower rate of ISR with IM IFN β 1a compared with SC IFN β formulation.(Beer et al., 2011; Patti et al., 2006)

Also, it should be mentioned that the ADR frequency of the investigated biosimilars may vary a lot in different studies. For instance, Flu-like symptoms vary between 39.3% and 75.4% for Avonex[®]. (Nabavi et al., 2019; Pakdaman et al., 2018) Also, the overall ADR rate reaches as high as 98.9% for Avonex[®], 92.5% for Cinnovex[®] in an interventional study.(Pakdaman et al., 2018) Therefore, what this article highlights is which medications are prescribed more frequently and how different is the adverse reaction profile among them and not the exact numbers.

Tolerability of medication use is critical for increasing the adherence of patients to the treatment. Patient education regarding common ADRs and management of these ADRs is crucial for patients' compliance.

Conflict of interest statement:

Non to report.

Acknowledgment :

The study was not funded by any organizations.

Generic Name	Total No. of patients with ADR	ADR occurrence (% of users)	Brand names (Route)	No. of users	No. of patients with ADR	No. of detected ADRs (%)	Adverse drug reactions – n (%)				
							Flu-like symptoms	Headache	ISP	Palpitation	Dry mouth
IFNβ-1a	180(72%)	141(78.3%)	Actorif [®] (SC)	4	4	4(100)	2 (50)	1 (25)	2 (50)	0 (0)	0 (0)
			Recigen [®] (SC)	11	11	11(100)	3 (27.2)	3 (27.2)	1 (9.0)	0 (0)	0 (0)
			Rebif [®] (SC)	55	47	47(85.5)	32 (58.1)	22 (40)	21 (38.1)	2 (3.6)	7 (12.7)
			Actovex [®] (IM)	16	13	13(81.2)	8 (50)	4 (25)	2 (12.5)	1 (6.2)	0 (0)
			Cinnovex [®] (IM)	61	48	48(78.6)	19 (31.1)	11 (18.0)	8 (13.1)	7 (11.4)	0 (0)
			Avonex [®] (IM)	33	18	18(54.5)	10 (30.3)	5 (15.1)	1 (3.0)	3 (9.0)	0 (0)
IFNβ-1b	60(24%)	42(70%)	Ziferon [®] (SC)	6	6	6(100)	3 (50)	3 (50)	2 (33.3)	0 (0)	0 (0)
			Actoferon [®] (SC)	6	5	5(83.3)	3 (50)	4 (66.6)	1 (16.6)	0 (0)	0 (0)
			Betaferon [®] (SC)	45	30	30(66.6)	15 (33.3)	10 (22.2)	12 (26.6)	2 (4.4)	0 (0)

			Extavia® (SC)	3	1	1(33.3)	1 (33.3)	0 (0)	0 (0)	1 (33.3)	0 (0)
Glatiramer	8(3.2%)	6(75%)	Copamer® (SC)	8	6	6(75)	0 (0)	1 (12.5)	0 (0)	6 (75)	0 (0)
Mitoxantrone	2(0.8%)	2(100%)	Novantrone® (IV)	2	2	2(100)	0 (0)	2 (100)	0 (0)	2 (100)	0 (0)

Table 1. Generic names of preparations, different brand names, and recorded ADRs.(IFN: Interferon, No.: Number, ADR: Adverse drug reaction, SC: Subcutaneous, IM: Intramuscular, IV: Intravenous, ISP: Injection site pain)

References:

- Abolfazli, R., Elyasi, A., Javadi, M. R., Gholami, K., Torkamandi, H., Amir-Shahkarami, M., . . . Nasr, Z. (2014). Knowledge and attitude assessment of Iranian multiple sclerosis patients receiving interferon beta. *Iran J Neurol*, 13(3), 160-167. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/25422736>
- Beer, K., Müller, M., Hew-Winzeler, A. M., Bont, A., Maire, P., You, X., . . . Curtius, D. (2011). The prevalence of injection-site reactions with disease-modifying therapies and their effect on adherence in patients with multiple sclerosis: an observational study. *BMC neurology*, 11(1), 1.
- Clanet, M., Radue, E. W., Kappos, L., Hartung, H. P., Hohlfeld, R., Sandberg-Wollheim, M., . . . European, I.-a. D.-C. S. I. (2002). A randomized, double-blind, dose-comparison study of weekly interferon beta-1a in relapsing MS. *Neurology*, 59(10), 1507-1517. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/12451189>
- Costello, K., Kennedy, P., & Scanzillo, J. (2008). Recognizing non-adherence in patients with multiple sclerosis and maintaining treatment adherence in the long term. *Medscape J Med*, 10(9), 225. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/19008986>
- FDA Approved Drug Products: Nivestym. (2018). Retrieved from <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=761080>
- FDA Approved Drug Products: Zarxio (filgrastim-sndz). (2015). Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125553orig1s000toc.cfm
- Jacobs, L. D., Cookfair, D. L., Rudick, R. A., Herndon, R. M., Richert, J. R., Salazar, A. M., . . . Simon, J. H. (1996). Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Annals of neurology*, 39(3), 285-294.
- Jongen, P. J., Sindic, C., Sanders, E., Hawkins, S., Linssen, W., van Munster, E., . . . Quality of Life in Avonex-treated Relapsing Multiple Sclerosis Patients Study, G. (2011). Adverse events of interferon beta-1a: a prospective multi-centre international ICH-GCP-based CRO-supported external validation study in daily practice. *PLoS One*, 6(10), e26568. doi:10.1371/journal.pone.0026568
- Nabavi, S. M., Abolfazli, R., Etemadrezai, A., Hosseini, H., Moradi, N., Shahriari, S., . . . Soltanzadeh, A. (2019). A Comparison Study of Efficacy and Safety of a Biosimilar Form of Intramuscular Betaeta-interferon I-a Versus the Reference Product: A Randomized Controlled Clinical Trial in Iran. *Iran J Pharm Res*, 18(3), 1632-1638. doi:10.22037/ijpr.2019.14503.12441
- Organization, W. H. (2000). The Uppsala Monitoring Centre(the UMC), WHO Collaborating Centre forInternational Drug Monitoring. Safety monitory of medical products, guidelines for setting up and running a pharmacovigilancecenter. 28.

- Pakdaman, H., Abbasi, M., Gharagozli, K., Ashrafi, F., Delavar Kasmaei, H., & Amini Harandi, A. (2018). A randomized double-blind trial of comparative efficacy and safety of Avonex and CinnoVex for treatment of relapsing-remitting multiple sclerosis. *Neurol Sci*, 39(12), 2107-2113. doi:10.1007/s10072-018-3550-8
- Patti, F., Pappalardo, A., Florio, C., Politi, G., Fiorilla, T., Reggio, E., & Reggio, A. (2006). Effects of interferon beta-1a and-1b over time: 6-year results of an observational head-to-head study. *Acta neurologica scandinavica*, 113(4), 241-247.
- Schumock, G. T., & Thornton, J. (1992). Focusing on the preventability of adverse drug reactions. *Hospital pharmacy*, 27(6), 538-538.