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Commentary

Adverse Drug Reactions of Multiple Sclerosis Disease-modifying Drugs

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ABSTRACT

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

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

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

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

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Highlights

- Adverse drug reactions (ADRs) are common in MS patients using disease modifying therapies.
- Such ADRs are more common in women than men.
- Various brand names of biosimilar disease-modifying therapy (DMT)s may have a different ADR profile.

Plain Language Summary

Multiple sclerosis (MS) is a condition that can be managed by using disease modifying medications. Such medication could trigger an adverse reaction in the patients., affecting their commitment to the treatment. By identifying these adverse reactions and educating the MS patients about these reactions and how the adverse effects can be managed, healthcare providers can improve the treatment process. This study recorded the adverse drug reactions in 250 MS patients who were receiving the medication for at least three months. Most of the patients (76.4%) experienced some kind of adverse reaction. A bigger proportion of women experienced adverse reactions than men. About 84% of these reactions occurred within the first 3 hours of receiving the medication. Depending on the medication's brand name, the rate of adverse drug reactions were different in some cases. The results of this study point out the fact that experiencing adverse drug reactions is common in MS patients and these experiences could be different for each medication with a different brand name. Therefore, it is important for the healthcare providers to inform the patients about such reactions and the patients should seek all the information they need to manage these adverse effects by consulting their physician.

1. Introduction

Biosimilar drugs play an essential role in decreasing costs to health systems. Most multiple sclerosis (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 approved by the Food and Drug Administration (FDA) (FDA, 2018; FDA, 2015). Treatment regimen adherence in MS has proved to be challenging. Some studies reported patient adherence rate as 60%-76% for 2-5 years. (Costello et al., 2008) According to other studies, one of the biggest obstacles that can result in non-adherence is adverse drug reactions (ADRs). (Abolfazli et al., 2014) Therefore, it is vital to evaluate the patterns ADR occurrence.

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

2. Materials and Methods

In an observational cross-sectional study, a questionnaire was developed to evaluate the ADRs of all the outpatients referred to the Neurology Clinic of Amir A'alam Hospital, Tehran, Iran, who had received at least one DMT for MS during the last three months. The patients who did not consent to enroll were excluded from the study.

A sample size of 250 people was calculated with a type 1 error of 5% 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 (WHO, 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 in the next step were recorded by the same pharmacist on a national ADR yellow card. The causality of drug-related adverse reactions was classified according to the WHO criteria. The seriousness of recorded ADRs was also determined by the WHO definition (WHO, 2000). Moreover, the preventability of ADRs was assessed by the Schumock and Thornton questionnaire (Schumock & Thornton, 1992).

Table 1. Generic names of preparations, different brand names, and recorded ADRs

Generic Name	No. (%)		Brand Names (Route)	No.		No. (%)					
							Adverse Drug Reactions				
	Patients With ADR	ADR Occurrence,		Users	Patients With ADR	Detected ADRs	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
			Recigen® (SC)	11	11	11(100)	3(27.2)	3(27.2)	1(9.0)	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
			Cinnovex® (IM)	61	48	48(78.6)	19(31.1)	11(18.0)	8(13.1)	7(11.4)	0
			Avonex® (IM)	33	18	18(54.5)	10(30.3)	5(15.1)	1(3.0)	3(9.0)	0
IFNβ-1b	60(24)	42(70)	Ziferon® (SC)	6	6	6(100)	3(50)	3(50)	2(33.3)	0	0
			Actoferon® (SC)	6	5	5(83.3)	3(50)	4(66.6)	1(16.6)	0	0
			Betaferon® (SC)	45	30	30(66.6)	15(33.3)	10(22.2)	12(26.6)	2(4.4)	0
			Extavia® (SC)	3	1	1(33.3)	1(33.3)	0(0)	0	1(33.3)	0
Glatiramer	8(3.2)	6(75)	Copamer® (SC)	8	6	6(75)	0	1(12.5)	0	6(75)	0
Mitoxantrone	2(0.8)	2(100)	Novantrone® (IV)	2	2	2(100)	0	2(100)	0	2(100)	0

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Abbreviations: IFN: Interferon; ADR: Adverse drug reaction; SC: Subcutaneous; IM: Intramuscular; IV: Intravenous; ISP: Injection site pain.

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

3. Results

A total of 250 patients (185 women [74%] and 65 men [26 %]) were enrolled in the study. The Mean±SD age of patients was 30.6±5.3 years, ranging from 21 to 46.

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

Table 1 presents generic names of preparations, and different brand names and routes of administration and recorded ADRs. The Mean±SD duration of using DMTs was 25.7±23.1 months ranging 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%). A case of Rebif®-induced fulminant hepatitis and a case of Cinnovex®-induced seizure existed that led to medication withdrawal. A seizure

was also 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 not for those administered subcutaneously (P=0.56).

No relationship was observed between age and ADR occurrence (P=0.076). Gender had a significant relationship with ADR; women experienced ADRs more than men (P=0.009). Statistical analyses showed that age and gender had no significant relationship with seriousness (P=0.51, 0.55) or preventability (P=0.5, 0.41).

4. Discussion

Flu-like symptoms (38%) and headache (26.4%) were the most commonly observed ADRs in this study. Consistent with two other studies conducted by (Patti et al., 2006) and (Beer et al., 2011) a lower rate of injection-site reactions (ISR) with intramuscular interferon beta-1a (IM IFNβ1a) was observed compared to subcutaneous (SC) IFNβ formulation (Beer et al., 2011; Patti et al., 2006).

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

5. Conclusion

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

Ethical Considerations

Compliance with ethical guidelines

This study was evaluated and approved by the Research Ethics Committee (REC) of Tehran University of Medical Sciences in accordance with the national and international ethical standards for biomedical research (Project No.: 32449).

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Authors' contributions

Conceptualization and supervision: Niayesh Mohebbi and Kheirollah Gholami; Methodology: Niayesh Mohebbi and Maryam Salehbayat; Investigation and data collection: Maryam Salehbayat, Roya Abolfazli, and Gloria Shalviri; Data curation and writing the original draft: Seyed Mehrdad Savar; Review and editing: All authors.

Conflict of interest

The authors declared no conflict of interest.

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