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Title: 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. 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 (±SD) age of patients was 30.6 (± 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 (±SD) duration of using DMTs was 25.7 ± 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 IFNβ1a compared with 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 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:

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| Generic Name | Total No. of patients with ADR (% of users) | ADR occurrence (% of users) | Brand names (Route) | 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(100)                   | 2 (50)           | 1 (25)   | 2 (50) | 0 (0)       | 0 (0)     |
|              |                                           |                             | Recigen® (SC)       | 11                      | 11(100)                  | 3 (27.2)         | 3 (27.2) | 1 (9.0) | 0 (0)       | 0 (0)     |
|              |                                           |                             | Rebi® (SC)          | 55                      | 47(85.5)                 | 32 (58.1)        | 22 (40)  | 21 (38.1)| 2 (3.6)     | 7 (12.7)  |
|              |                                           |                             | Actovex® (IM)       | 16                      | 13(81.2)                 | 8 (50)           | 4 (25)   | 2 (12.5)| 1 (6.2)     | 0 (0)     |
|              |                                           |                             | Cinnovex® (IM)      | 61                      | 48(78.6)                 | 19 (31.1)        | 11 (18.0)| 8 (13.1)| 7 (11.4)    | 0 (0)     |
|              |                                           |                             | Avonex® (IM)        | 33                      | 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(100)                   | 3 (50)           | 3 (50)   | 2 (33.3)| 0 (0)       | 0 (0)     |
|              |                                           |                             | Actoferon® (SC)     | 6                       | 5(83.3)                  | 3 (50)           | 4 (66.6) | 1 (16.6)| 0 (0)       | 0 (0)     |
|              |                                           |                             | Betaferon® (SC)     | 45                      | 30(66.6)                 | 15 (33.3)        | 10 (22.2)| 12 (26.6)| 2 (4.4)     | 0 (0)     |
| | Extavia®, (SC) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Glatiramer | 8(3.2%) | 6(75%) | Copamer®, (SC) | 8 | 6 | 6(75) | 0 (0) | 1 (12.5) |
| Mitoxantrone | 2(0.8%) | 2(100%) | Novantrone®, (IV) | 2 | 2 | 2(100) | 0 (0) | 2 (100) |

| | IFN: Interferon, No.: Number, ADR: Adverse drug reaction, SC: Subcutaneous, IM: Intramuscular, IV: Intravenous, ISP: Injection site pain | |

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