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Original Article

Comparison of the Total Side Effects of Injectable Disease-Modifying Drugs for the First-line Treatment of Relapsing-Remitting Multiple Sclerosis

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Abstract

Background: Physicians generally prescribe disease-modifying drugs (DMDs) to reduce the frequency and severity of relapses in multiple sclerosis (MS). The frequency and severity of side effects are important factors that can affect drug choice. The main purpose of this analysis was to evaluate the side effects of different types of first-line injectable DMDs and determine which drug has more complications, and which drug has the most drug discontinuation rates due to severe side effects.

Methods: Four groups of injectable DMDs were compared in 386 relapsing-remitting MS (RRMS) patients in the range of 15-60 years who were controlled with these drugs for at least two years (2017-2019) and had the Expanded Disability Status Scale (EDSS) from 0 to 5 without underlying heart and liver diseases. Eventually, the frequency of side effects was determined for each group, and the collected data were compared in each treatment group.

Results: In the present study, 31% of patients had no complications. Most of the reported complications (68.25%) were mild in severity, and only 15.5% of the patients discontinued their therapy.

Conclusion: The findings recommend that the side effects of different DMDs used for RRMS should be studied more comprehensively in clinical and post-marketing trials. Additionally, physicians should take note of these side effects of DMDs in their prescriptions to increase patients' adherence to therapy.

Keywords: Disease-modifying drugs, Multiple sclerosis, Side effects

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Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating, and debilitating autoimmune disease of the central nervous system (CNS), with predominance in the female gender. It has no effective cure and requires lifetime treatment (1). The purpose of treatment in MS is to prevent recurrence and reduce the rate of neurologic destruction (2). Neurologists generally prescribe disease-modifying drugs (DMDs) to reduce the frequency and severity of relapses in MS patients (3). Interferon (IFN) β-1a (high dose), IFN β-1a (low dose), IFN β-1b, and glatiramer acetate are a group of DMDs that are generally used for relapsing-remitting MS (RRMS). The reported side effects of IFNs include alopecia and flu-like syndrome, anemia, variation of transaminases, local reaction and cutaneous necrosis at the injection site, necrotizing vasculopathic skin lesions, neuropathy, increase in spasticity, livedo-reticularis, depression, suicidal ideation, headache, and pneumonia (4-6). Likewise, the reported side effects of glatiramer acetate include nausea, vomiting, skin rashes, cardiovascular side effects such as rapid heart rate, depression, skin color changes, weight gain, anxiety, body pain and weakness, flushing, breathing difficulties, and chest pain (7).

Considering the importance of adverse effects in clinical practice and its effect on the choice of medication, observed adverse effects following the use of DMDs manufactured in Iran (IFNβ and glatiramer) were compared in this study.

Materials and Methods

A total of 386 patients (63 males and 323 females) with

definite RRMS diagnoses consulted at Imam Khomeini clinic and Sina hospital in Hamadan city, west of Iran, were evaluated in this prospective cross-sectional study. Patients were treated with first-line injectable DMDs, including the high dose IFN β-1a, the low dose IFN β-1a, IFN β-1b, and glatiramer acetate for at least 2 years (June 2017 to June 2019). Patients were scheduled for a routine neurologist (MS Fellowship) visit at 0, 1, 3, 6, 12, and 24 months after the start of treatment. Then, 119 patients were treated with IFN β-1a low dose, 103 patients received IFN β-1a high dose, 90 patients were treated with IFN β-1b, and 74 patients were treated with glatiramer acetate.

Baseline electrocardiographic assessment, complete blood count with differential, liver function test, blood urea nitrogen creatinine, thyroid function tests, and blood pressure were checked and recorded for all patients. The mentioned lab data were collected monthly at first, and after 6 months of monthly checks, they were obtained every three months. Skin examination was carried out every 3 months for one year and then annually. Clinical course, test results, and magnetic resonance imaging findings were reviewed (at 0, 1, 3, 6, 12, and 24 months after the start of medication) by an MS fellowship and clinical pharmacist.

Inclusion criteria included patients 15–50 years of age with a clinical and laboratory-supported diagnosis of RRMS. Patients should also have a history of at least one attack and the involvement of at least two neurological systems in the physical examination and an expanded disability status scale of 0-5. Exclusion criteria included the history of severe allergic or anaphylactic reaction to any first-line injectable DMDs or other components of drug formulation, evidence of cardiac, hepatic, renal, psychiatric, neurologic, hematologic, endocrinology, and auto-immune diseases, malignancy, hypertension, diabetes mellitus, history of epilepsy, suicidal ideation, severe depression, lactation, and pregnancy. Moreover, the history of receiving corticosteroids (during the month before starting DMDs) as well as the use of other MS medications or any immunosuppressive drugs (according to 2015 McDonald criteria) were the other exclusion criteria considered in the study.

The principles of the current version of the Declaration of Helsinki were followed, and the institutional ethical committee approval was granted. In other words, the research protocol was approved by the Research Ethics Committee of Hamadan University of Medical Sciences with the ethics code of IR.UMSHA.REC.1397.519, and the nature of the trial and possible side effects of the drugs were explained to the patient. After a detailed discussion with the MS fellowship, patients made a final decision, and each patient signed an informed consent. All 386 patients completed their treatment without interruption. To assess side effects following the use of these drugs, a questionnaire was prepared and filled out at 0, 1, 3, 6, 12, and 24 months post-treatment. Eventually, the frequency of side effects was determined for each group, and the collected data were compared in each treatment group. Additionally, patients who experienced an MS attack during the study or for any reason discontinued or changed their medication were excluded from the study.

It should be noted that the adverse events are divided into three groups regarding their prevalence and presented as: Most common (more than 10% frequency), Common (between 1 and 10%), and Rare (below 1%).

Results

A total of 386 patients (63 males and 323 females) were included in this study. All patients were followed up for treatment at 1, 3, 6, 12, and 24 months after starting the study. First-line DMDs were well tolerated, and most of the reported complications (68.25%) were mild in severity. Side effects resulted in the discontinuation of the drug were observed in 61 patients following the administration of interferon-β (13 with high dose INF β-1a, 21 with low dose INF β-1a, and 10 with INF β-1b) and glatiramer (17 patients). In two patients, the injection of high dose INF β-1a exacerbated the disease. In one of them, the attack led to drug discontinuation, and 20 patients were eliminated from the study due to pregnancy. The most frequent side effects observed with DMDs are summarized in Table 1. Leukopenia and the rise of hepatic enzymes were the most commonly observed side effects that were acquired from the patients' lab data. Further, Tables 2, 3, 4, and 5 present complications observed with a lower prevalence following the use of DMDs.

Low Dose INFβ-1a

Table 2 depicts less frequent adverse effects observed following the use of low-dose INFβ-1a. Observed abnormal lab data observed in this group of patients were 0.7% lymphopenia, 5% anemia, and 0.6% decrease in hemoglobin. Further, a case of stroke and one case of lymphoma were found in patients taking this drug, and 29% of patients had no complications with low dose INF β1a.

High Dose INFβ-1a

Side effects with lower frequency are depicted in Table 3. Lab data observed in the administration of high-dose INFβ-1a were 10% lymphadenopathy, 5% anemia, and 2% hyperbilirubinemia. Moreover, 39% of patients had no complications with high dose INFβ-1a.

INFβ-1b

Table 4 illustrates less frequent adverse effects in patients treated with INFβ-1b. One case of livedo-reticularis was found in patients taking this drug, and 34% of patients had no complications with INFβ-1b.

Glatiramer

Table 5 presents less frequent adverse effects in patients receiving glatiramer. The administration of glatiramer exhibited proteinuria in 2% of glatiramer recipients, and

Table 1. The Most Frequent Side Effects of DMDs

Side Effects	INFβ-1a (LD)	INFβ-1a (HD)	INFβ-1b	Glatiramer	Total
Back Pain	24%	35%	14%	14%	21.7%
Alopecia	10%	40%	5%	0%	12%
Flu like syndrome	44%	49%	51%	2%	36.5%
UTI	14%	3%	0%	5%	5.5%
Dyspnea	9%	14%	14%	13%	12.5%
Vaginal infection	1%	2%	0%	5%	2%
Menstrual disease	3%	2%	0%	3%	2%
Injection site reaction	50%	6%	53%	23%	33%
Rash	2%	2%	2.8%	5%	3%
Cut of drug	17%	12%	11%	%22	15.5%
Leukopenia	12%	11%	5%	0.03%	19/75%
Rise of hepatic enzymes	25.7%	27%	6%	0%	14.6%

Note. INF: Interferon; DMDs: Disease modifying drugs; UTI: Urinary tract infection; HD: High dose; LD: Low dose.

Table 2. Side Effects of INFβ-1a (Low Dose)

Side Effects	Percent	Side Effects	Percent
Flashing	4%	Headache	2%
Itching	1%	Palpitation	2%
Weight loss	1%	Nausea/vomiting	6%
Reaction of site injection	2%	Hematuria	2%
Tremor	3%	UTI	3%
Depression	4%	Rash	2%
Suicidal thought	5%	Edema	1%
Fungal infection	1%	Amenorrhea	2%
Cellulitis	1%	Diarrhea	1%
Fever	2%	Anger	1%
Decrease of hemoglobin	0.6%	Anemia	5%
Lymphopenia	0.7%		

Note. UTI: Urinary tract infection.

Table 3. Side Effects of INFβ-1a (High Dose)

Side Effects	Percent	Side Effects	Percent
Fever	19%	Headache	58%
Injection site reaction	50%	Nausea/vomiting	20%
Depression	19%	UTI	10%
Suicidal thought	4%	Rash	4%
Infection	6%	Eye disease	4%

Note. UTI: Urinary tract infection.

Table 4. Side Effects of INFβ-1b

Side Effects	Percent	Side Effects	Percent
Flashing	8.3%	Itching	5.6%
Depression	3%	Weight loss	2.8%
Fever	3%	Reaction of site Injection	5%
Rash	3%	Tremor	5%
Joint pain	3%		

Note. INF: Interferon.

Table 5. Side Effects of Glatiramer

Side Effects	Percent	Side Effects	Percent
Lipoatrophy	2%	Palpitation	5.3%
Bruise	8%	Edema	11%
Rash	5%	Body pain	12%
Erythema of site injection	5%	Headache	44%

33% of patients had no complications with glatiramer.

Total Side Effects of DMDs

The findings of this study are comparable with other studies regarding the overall percentage of complications of DMDs to help physicians understand the common side effects of these medications (Table 6).

The Severity of Side Effects of DMDs

Knowing the severity and incidence of complications can be very helpful to a physician's decision to either continue or discontinue medication. It should be noted that mild clinical complications in this study were complications that can be tolerated without the need for any medication. Moderate clinical complications were supposed to require an action such as hospitalization, prescribing a medication to reduce complications, change in the dose of the main drug, or temporary interruption to control it, but the drug did not discontinue completely. Severe clinical complications were complications that can lead to the discontinuation of the main medication completely due to their intolerability. According to this definition, the complications were generally mild (68.25%), and DMDs were well tolerated (Table 7).

Discussion

MS is a degenerative disease of the CNS and a common cause of adult disability (8). Neurologists generally prescribe DMDs to reduce the recurrence rate of MS attacks and the progression of this disease.

Different types of first-line injectable DMDs are used to

Table 6. Total Side Effects of DMDs

SEs	INF β 1a (LD)	INF β 1a (HD)	INF β 1b	Glatiramer	Total
Mild cardiovascular SEs	8%	Not observed	12%	18%	9.5%
Severe cardiovascular SEs	3%	1%	3%	5%	3%
Dermatologic	35%	40%	20%	7%	25.5%
Metabolic	6%	Not observed	8%	3%	4.25%
Local	6%	50%	53%	23%	32.25%
Neuro-psychological SEs	4.5%	23%	3%	Not observed	7.6%
Infection	4%	6%	3%	22%	9.5%
Genitourinary	6%	2.5%	6%	16%	7.6%
Gastrointestinal	6%	20%	2%	5%	8.25%
Respiratory	40%	60%	30%	7%	34.25%
Skeletal	25%	35%	14%	20%	23.5%
CNS	20%	19%	15%	20%	18.5%
Hematological SEs	35%	40%	10%	1%	21.5%

Note. INF: Interferon; DMDs: Disease-modifying drugs; SEs: Side effects; CNS: Central nervous system.
Mild Cardiovascular side effects include palpitation, bradycardia, tachycardia, and edema. Severe cardiovascular side effects include heart failure. Dermatologic side effects include rash, itching, and alopecia. Metabolic side effects include weight gain, weight loss, and flushing. Local side effects include injection site reactions, lipoatrophy, and bruise. Neuro-psychological side effects are depression, suicidal thoughts, and anger. Infectious side effects include fungal infection, cellulitis, and *Jirovecii* virus infection. Genitourinary side effects include amenorrhea, urinary tract infection, vaginal infections, menstrual disease, and hematuria. Gastrointestinal side effects are diarrhea, nausea, and vomiting. Respiratory side effects included dyspnea, flu-like syndromes, and lung infection. Skeletal side effects include body pain, back pain, and joint pain. CNS side effects include headache and tremors. Other side effects include wounds, fever, leukopenia, and a rise in hepatic enzymes.

Table 7. The severity of Clinical Side Effects of DMDs

DMDs	Mild Side Effects	Moderate Side Effects	Severe Side Effects
INFβ-1a LD	60%	23%	17%
INFβ-1a HD	72%	16%	12%
INFβ-1b	70%	19%	11%
Glatiramer	71%	7%	22%
Total	68.25%	16.25%	15.5%

Note. INF: Interferon; DMDs: Disease-modifying drugs; HD: High dose; LD: Low dose.

control the course of this disease, including IFNβ-1a (low dose and high dose), IFNβ-1b, and glatiramer acetate. The side effects of DMDs are widespread and include hematology, hepatic, gastrointestinal, cardiac, dermal complications, and the like. The frequency of side effects can be a factor in drug selection. No studies have been found to examine all side effects of the first-line injectable DMDs used in RRMS, so this study is the first neurological report to describe all side effects of these drugs together. In previous studies, the side effects of these drugs have been studied separately, so we decided to investigate the incidence rate of adverse effects of all first-line injectable DMDs used for controlling the course of RRMS to help reduce these complications. Most of the side effects of DMDs in the current study were flu-like symptoms with INFβ and injection site reactions with glatiramer.

These complications are similar to common complications reported in valid pharmaceutical information sources and in other studies. Several studies have shown that interferon can cause flu-like symptoms. In agreement with our findings, Río et al in 2005 reported that flu-like symptom is the most common adverse effect of INF-β (9). Consistent with our results, Caporro et al indicated that the most common adverse effect of glatiramer is injection site reaction (10).

Conclusion

In conclusion, this study recommends that physicians should pay attention to these general side effects of first-line DMDs in their prescriptions.

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Competing Interests

None.

Ethical Approval

The study protocol was approved by the Research Ethics Committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1397.519).

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