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# Injection Administration Features of the Patients who Self-administer Subcutaneous Immunomodulator Injection and the Injection Site Reactions

## *Kendi Kendine Subkutan İmmünomodülatör Enjeksiyon Uygulayan Hastaların Enjeksiyon Uygulama Özellikleri ve Enjeksiyon Bölgesi Reaksiyonları*

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### Summary

**Objective:** This study aims at examining the injection administration features of the patients with multiple sclerosis who self-administer subcutaneous immunomodulator injection, and the injection site reactions they experience.

**Material and Method:** A total of 50 patients who fit the inclusion criteria for the study and volunteered to participate were included in the sample. The data was collected by a questionnaire which was developed by the researchers and based on the literature.

**Results:** In our study, 74% of the patients have reported at least one injection site reaction. Pain and redness were among the most common injection site reactions and the least common reactions were abscess and lipoatrophy. No statistical difference was found between the development of injection site reactions and injection administration features, types of the administered medications, administration period of the medications, and number of total injections. A statistically significant difference was observed between gender and the development of injection site reactions.

**Conclusion:** Injection administration features that were included in the study were not effective factors in terms of the injection site reactions. Injection site reactions were more common in women than in men. *(Turkish Journal of Neurology 2014; 20:7-12)*

**Key Words:** Multiple sclerosis, injection site reactions, immunomodulator treatment

### Özet

**Amaç:** Bu çalışmada kendi kendine subkutan immünomodülatuar enjeksiyon uygulayan hastalarda, enjeksiyon uygulama özelliklerinin ve enjeksiyon bölgesi reaksiyonlarının incelenmesi amaçlanmıştır.

**Gereç ve Yöntem:** Çalışmaya katılmayı gönüllü olarak kabul eden 50 multipl skleroz hastası, araştırmanın örneklemini oluşturmuştur. Araştırmada veriler, literatüre dayalı olarak araştırmacılar tarafından geliştirilen veri toplama formu kullanılarak toplanmıştır.

**Bulgular:** Çalışmamızda hastaların %74'ü en az bir enjeksiyon bölgesi reaksiyonu bildirmiştir. En sık görülen enjeksiyon bölgesi reaksiyonları ağrı ve kızarıklık olup, en az gelişen reaksiyonlar ise apse ve lipoatrofidir. Enjeksiyon bölgesi reaksiyonu gelişme durumu ile enjeksiyon uygulama özellikleri, kullanılan ilaç, ilacı kullanma süresi ve total enjeksiyon sayısı arasında istatistiksel olarak anlamlı bir farklılık bulunmamıştır. Ancak enjeksiyon bölgesi reaksiyonu gelişme durumu ile cinsiyet arasında istatistiksel olarak anlamlı bir farklılık bulunmuştur.

**Sonuç:** Enjeksiyon uygulama özelliklerinin, enjeksiyon bölgesi reaksiyonları üzerinde etkili olmadığı belirlenmiştir. Kadınlarda, erkeklere göre daha fazla enjeksiyon bölgesi reaksiyonu gelişmektedir. *(Türk Nöroloji Dergisi 2014; 20:7-12)*

**Anahtar Kelimeler:** Multipl skleroz, enjeksiyon bölgesi reaksiyonları, imünomodülatör tedavi

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## Introduction

Multiple Sclerosis (MS) is a chronic, progressive, and inflammatory demyelinating disease of autoimmune nature which usually starts in the early years of adulthood (1,2). During the first step treatment of the relapsing remitting MS, which is the most common type of MS (55%-85%), treatments that aim at reducing the frequency of the attacks and modifying the disease have been performed for the last 10-15 years (3-6). Medications with immunomodulatory effects that can be administered subcutaneously (SC) are interferon beta-1a (IFN β-1a; 22-44 mcg), interferon beta-1b (IFN β-1b; 8 miu), and glatiramer acetate (GA) (20 mg) (4).

One of the most commonly experienced side effects of the SC administered immunomodulator treatment is the injection site reactions. In the literature, several findings emerge from various studies investigating the frequencies and the types of these reactions. In the multicenter, double-masked, randomized and placebo-controlled trial that was carried out by the European Study group, the injection site reactions were reported at a rate of 43.6%, injection site inflammations at 50.0%, and necrosis at 4.7% of the patients with secondary progressive MS (n=360) who were administered 8 million IU IFN β-1b treatment SC every other day (7). In their multicenter, randomized, comparative, parallel-group, and open-label study, REGARD study group compared patients with relapsing remitting MS (n=460) who were administered 44 µg SC IFN β-1a (three times per week) and 20 mg SC GA (once per day) treatments. The injection site reactions observed in this study were erythema (IFN β-1a: 32%, GA: 30%), pain (IFN β-1a: 12%, GA: 14%), pruritus (IFN β-1a: 2%, GA: 20%), bruising (IFN β-1a: 9%, GA: 10%), swelling (IFN β-1a: 1%, GA: 11%), and induration (IFN β-1a: 2%, GA: 7%) (8).

Since this is a long-term treatment which needs to be administered frequently (GA is administered every day, IFN β-1b every other day, and IFN β-1a tree times a week), it is recommended that patients administer the injections themselves. For this purpose, the pharmaceutical companies carry out support programs for nurses on injection training. It is reported that the self-administration of injection provides the MS patients the maximum independence and reduces the risk of missed injections (9). However, it is indicated that the self-administration also cause injection skin reactions, which may lead to non-compliance in the early periods of treatment due to disturbance and ultimately encourage them to stop the treatment (10-14). In the literature, it is suggested that the injection administration features of the patients who experience such reactions should be monitored and certain recommendations for the prevention of these reactions should be made (15). However, no study comparing the relationship between the injection site reactions and the injection administration features could be found in the literature.

This study aims at examining the injection administration techniques of the patients with MS who self-administer SC immunomodulator injections and the injection site reactions they experience.

## Materials and Methods

### Design and Participants

This study was designed and carried out as a cross-sectional and descriptive investigation. The study group included all patients who self-administered SC immunomodulator injections and admit to the MS outpatient clinics of a training hospital in Ankara between September 2008 and February 2010. During the period of the study, a total of 118 MS patients came to the outpatient clinics. Sixty-five of these patients were found to be compliant with the inclusion criteria of the study. Finally, 50 MS patients who volunteered to participate in the study constituted the study group. The study was approved by the ethical committee of the Gülhane Military Medical Academy.

Inclusion criteria of the study were the following:

- Patients who self-administered SC immunomodulator injections for a minimum of 3 months;
- Patients who had received injection training at least once from the training nurses who were trained on SC injection administration at the support programs carried out by pharmaceutical companies.

### Instruments

The research data were collected by a questionnaire which was developed by the researchers based on the literature and expert opinion. The questionnaire form consisted of three parts and a total of 21 questions. The first part (6 questions) was related to the socio-demographic features of the patients and the characteristics of their diseases; the second part (13 questions) was related to the characteristics of the SC immunomodulator medications and the injection administration methods; and the third part (2 questions) was related to the injection site reactions described by the patients. The questionnaire forms were filled by the researcher during the individual interviews performed with the patients. All injection sites were evaluated by the same researcher by inspection and palpation methods.

### Data Analysis

Data were transferred to the computer and analyzed using SPSS for Windows Version 15.0 (SPSS Inc., Chicago, IL., USA) package program. Means, standard deviations, frequencies, and percentages were calculated following the descriptive statistics. Chi-square and Mann-Whitney U test were used to analyze the differences between some variables and injection site reactions. For the statistical significance evaluation $p<0.05$ was accepted.

## Results

### Sample Characteristics

Among the patients who participated in the study, 60% were women, the average age was 36.16±9.18; 54% were high school graduates and 76% were married. Sixty-four percent of the patients, 24% of patients, and 12% of patients had been using IFN β-1a 22/44µg, IFN β-1b and GA 20 mg in the order (Table 1). Ninety percent of the patients were using auto-injectors, and 66% had received injection training only once within the framework of the support programs carried out by pharmaceutical companies.

No statistical difference was found between the development of the injection site reactions and the age groups ($\chi^2=0.914$, $p<0.05$), whereas a statistical significance was observed between

the gender and the development of the injection site reactions ($\chi^2$=9.921, p<0.05). In women more injection site reactions were detected than in men.

**Injection Administration Features**

In our study, it was observed that not all injection sites could be used by 30.6% of the patients due to the difficulty of injection in certain sites (arms and gluteal regions), and pain and/or sensitivity experienced in these sites. It was also observed that since they were afraid of injections, 22% of the patients had their injections administered by other people (patients' relatives), and 8% never used the injection sites in alternation (Table 2).

It was determined that 24% of the people who administered the injections did not wash their hands and clean the injection site before the injections, and 14% made the administration right after taking the medication out of the refrigerator and allowing it to reach the room temperature.

**Injection Site Reactions**

In our study, 74% of the patients (n=37) have reported at least one injection site reaction. The reported post-injection skin reactions were as follows: erythema (IFN ß-1a: 40.6%, IFN ß-1b: 50%, GA: 50%), pain (IFN ß-1a: 34.4%, IFN ß-1b: 33.3%, GA: 50%), induration (IFN ß-1a: 21.9%, IFN ß-1b: 50%, GA: 33.3 %), ecchymosis (IFN ß-1a: 15.6%, IFN ß-1b: 8.3%, GA: 33.3%), lipoatrophy (GA: 33.3%), and abscess (IFN ß-1a: 3.1%). Injection site reactions which developed for each individual medication are presented in Table 3. In addition, during the evaluation performed

**Table 1. Usage properties for individual medications**

| | IFN β-1a 22/44µg (n=32) | IFN β-1b (n=12) | GA (n=6) |
|---|---|---|---|
| | Mean±SD | Mean±SD | Mean±SD |
| Duration of the usage of the medication (months) | 34.0±28.4 | 25.8±18.8 | 37.1±28.4 |
| Total numbers of injections | 408.0±345.6 | 495.6±445.2 | 111.3.0±942.0 |

IFN β-1a:interferon beta-1a, GA:glatiramer acetate

**Table 2. Reaction development status and injection administration features**

| Features | Reaction development status | | | | Total | |
|---|---|---|---|---|---|---|
| | Yes | | No | | | |
| | n | % | n | % | n | % |
| Usage of the injection site: | | | | | | |
| Patients that use the whole injection site | 27 | 54.0 | 10 | 20.0 | 37 | 74.0 |
| Patients that do not use the whole injection site | 9 | 18.0 | 4 | 8.0 | 13 | 26.0 |
| Alternate usage of the injection sites: | | | | | | |
| Yes | 30 | 60.0 | 16 | 32.0 | 46 | 92.0 |
| No | 3 | 6.0 | 1 | 2.0 | 4 | 8.0 |
| NSAI drug usage before the injections: | | | | | | |
| Yes | 23 | 46.0 | 6 | 12.0 | 29 | 58.0 |
| No | 13 | 26.0 | 8 | 16.0 | 21 | 42.0 |
| Person who administers the injection: | | | | | | |
| Patients | 20 | 40.0 | 19 | 38.0 | 39 | 78.0 |
| Patient's relatives | 5 | 10.0 | 6 | 12.0 | 11 | 22.0 |
| Hands washing habits of the person who administers the injection: | | | | | | |
| Yes | 18 | 36.0 | 12 | 24.0 | 30 | 60.0 |
| No | 5 | 10.0 | 7 | 14.0 | 12 | 24.0 |
| Sometimes | 4 | 8.0 | 4 | 8.0 | 8 | 16.0 |
| Cleaning of the injection site: | | | | | | |
| Yes | 15 | 30.0 | 17 | 34.0 | 32 | 64.0 |
| No | 7 | 14.0 | 5 | 10.0 | 12 | 24.0 |
| Sometimes | 4 | 8.0 | 2 | 6.0 | 6 | 12.0 |
| Waiting time for temperature change of the medication | | | | | | |
| 0 | | | | | | |
| 2-15 min | 4 | 8.0 | 3 | 6.0 | 7 | 14.0 |
| 16-30 min | 8 | 16.0 | 5 | 10.0 | 13 | 26.0 |
| 31 min and above | 8 | 16.0 | 7 | 14.0 | 15 | 30.0 |
| | 7 | 14.0 | 8 | 16.0 | 15 | 30.0 |

by the researcher in 48% of the patients erythema, in 16% ecchymosis, and in 2% abscess and lipoatrophy was also detected, and 14.0% of the patients complained of pain during palpation.

In our study, no statistically significant difference was found between the development of the injection site reactions and the alternate usage of the injection sites ($\chi^2$=0.45, p>0.05), the persons who administered the injections ($\chi^2$=2.501, p>0.05), hand washing before the injections ($\chi^2$=0.067, p>0.05), cleaning the site ($\chi^2$=0.043, p>0.05), non-steroidal anti-inflammatory (NSAI) drug usage before the injections ($\chi^2$=0.331, p>0.05), and waiting time for temperature change of the medication ($\chi^2$=9.121, p>0.05) (Table 2). In addition no statistical difference was found between the development of the injection site reactions and the type of the administered medications ($\chi^2$2.205, p>0.05), the administration period of the medications (z=-0.281, p>0.05), and the number of total injections (z=-0.079, p>0.05) (Table 1 and Table 3).

## Discussion

Within the framework of the nurse support programs (Betaseron Education, Training and Assistance Nurse Program, MS Lifelines, Shared Solutions) carried out by the companies that produce immunomodulator drugs with the intention of reducing the injection site reactions and increasing the patients' compliance to the treatment, the training on the correct injection techniques is provided to the patients through home visits and telephone counseling. All patients in our study have received training and counseling services within the scope of these programs. In the literature, it is reported that these training programs have a positive effect on the compliance of the MS patients to the treatment (16-19). However, in our study it was observed that some patients still experienced difficulties regarding the performance of auto-injections; some of them had their injections administered by other people; and some exhibited improper behavioral patterns (such as not washing their hands and not cleaning the sites before the injections, not using the injection sites alternately, not using all injection sites or administrating the medication before it reaches room temperature) with regards to the injection administration. These findings reveal the necessity of reevaluation of the nursing services provided to the patients in terms of the sustainability of the injection training.

It is reported that the proportion of injection site reactions for SC IFN-β-1a was between 13% and 89%, for SC IFN-β-1b was between 22%-96%, and for GA was between 7%-90% in a systematic review study (20). In our study, in 74% of the patients (n=37) (IFN ß-1a: 71.9%, IFN ß-1b: 83.3%, GA: 66.6%) at least one type of an injection site reaction was detected; this is a value within the ranges reported in the literature.

The most common reactions that were described by the patients and detected by the researcher were erythema, pain, induration, ecchymosis, lipoatrophy, and abscess, in this order. In our study, 50% of the patients who received IFN ß-1b treatment experienced erythema and induration, pain in 33.3%, and ecchymosis and pruritus was observed in 8.3%. In their study, where the reported injection site reactions were examined in the patients who received IFN ß-1b treatment, Gaines & Varricchio (1998) demonstrated that in 57% of the patients (n=1443) experienced erythema, in 30% pain, in 12% ecchymosis, in 8% pruritus and in 4% infections (21). Our findings are similar to the findings of this study.

Lipoatrophy, which was one of the most important injection site reactions observed in our study, was detected in 33.3% of the patients (n=2) who used GA. Edgar, Brunet, Fenton, McBride & Gren (2004) examined the injection site reactions in the patients who used GA detected lipoatrophy in 45% of the patients (n=76) in their study (22). We believe that the difference between these findings is related to the sample size.

**Table 3. Reactions developed to each medication**

| Reactions | Medications | | | | | |
|---|---|---|---|---|---|---|
| | IFN β-1a 22/44µg (n=32) | | IFN β-1b (n=12) | | GA (n=6) | |
| | n | % | n | % | n | % |
| Reaction development status | | | | | | |
| Yes | 23 | 71.9 | 10 | 83.3 | 4 | 66.6 |
| No | 9 | 28.1 | 2 | 16.7 | 2 | 33.3 |
| Reactions Type[a] | | | | | | |
| Erythema | 13 | 40.6 | 6 | 50.0 | 3 | 50.0 |
| Pain | 11 | 34.4 | 4 | 33.3 | 3 | 50.0 |
| Induration | 7 | 21.9 | 6 | 50.0 | 2 | 33.3 |
| Swelling | 5 | 15.6 | 2 | 16.6 | 2 | 33.3 |
| Ecchymosis | 5 | 15.6 | 1 | 8.3 | 2 | 33.3 |
| Pruritus | 1 | 3.1 | 1 | 8.3 | 1 | 16.6 |
| Lipoatrophy | - | - | - | - | 2 | 33.3 |
| Abscess | 1 | 3.1 | - | - | - | - |

[a]: n is a multiple, as multiple answers were allowed Interferon beta-1a, GA:glatiramer acetate

In our study, in 40.6% of the patients who used IFN ß-1a, erythema, in 34.4% pain, in 21.9% induration, in 15.6% swelling, in 21.9% ecchymosis, and in 3.1% pruritus was observed. In addition, in one patient who used interferon IFN ß-1a, abscess was detected as another important injection site reaction. According to the study of Pohl, Rostasy, Gärtner & Hanefeld (2005), out of 71% of the patients (n=51) who used IFN ß-1a erythema, abscess in 6%, and necrosis in 6% were observed (23). In our study, however, induration, swelling, ecchymosis and pruritus were also observed at the injection sites.

In our study, it was demonstrated that gender is associated with the injection site reactions, that is, the injection site reactions are more common in women compared to men. Also in the literature it is reported that women carried a greater risk in terms of the injection site reactions. It is suggested that this arises due to the differences between male and female cutaneous structures (21,24,25).

Several factors such as the administration of the injection under non-sterile conditions, using medications which are not at room temperature, using the same injection site for every administration, injection of the medication into the intradermal tissue, not changing the needle after the medication is drawn into the injector or exposure of the recently used injection sites to sun rays or ultraviolet rays, constitute the risk factors for the development of the injection site reactions (15,26). Alternated usage of the injection sites, usage of medications at room temperature, washing the hands and cleaning the injection site before the administration, usage of auto-injectors and NSAI drugs are suggested for prevention of the injection site reactions (13,27-29). In our study, it was demonstrated that 14% of the patients administered the medication without allowing it to warm up to room temperature, 8% did not use the injection sites in alternation, and 24% did not wash their hands and clean the injection sites before the injections. However, no relationship was found between the injection site reactions and washing hands and cleaning the site before the injections, NSAI drugs usage, alternate usage of the injection sites, and waiting time for temperature change of the medication. Although it is reported that these variables are important in the prevention of injection site reactions, they were not observed as effective factors in our study. This may be due to the high auto-injector usage rate (90%) and the sample size of our study. It is reported that the auto-injectors reduce the injection site reactions risk compared to the conventional injectors (13,30,31).

## Conclusion

This study focused on the injection administration features and the injection site reactions in the patients with MS who administered self-injection. In this study, in 74% of the patients at least one type of an injection site reaction was detected. While temporary pain and erythema were observed as the most common reactions, abscess and lipoatrophy were the most serious and least frequently observed reactions. Injection site reaction development rates were higher in women compared to men. Although it is reported that the injection administration features are important in prevention of the injection site reactions, in our study it was found that these were not determining factors of the injection site reactions.

We suggest applying this research on a greater sample size and examination of other possible factors which may be impose an effect on the reactions.

### Limitations

All data were collected by patient self-reporting in this study because of the lack of an objective standard measurement tool, which could be used for the evaluation of the injection site reactions.

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