Original Article

Evaluation of Association between Flu-Like Syndrome Induced by Beta Interferon Drug and Required Drug Response in Patients with Multiple Sclerosis

Abdollah Ghaferi[1], Maziar Shojaei[1], Arezoo Chouhdari[2]

[1] Department of Neurology, Faculty of medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Preventive and Community Medicine Specialist. Member of Research Council at Clinical Research Development Center and Skull base Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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Abstract

Background: Beta interferon is one of the important drugs for multiple sclerosis. Its common side effects are flu-like symptoms caused by drug injection. The purpose of this study was to evaluate the possibility of predicting the response rate of this drug based on the flu-like drug reaction.

Materials and Methods: This case-control study performed in Loghman Hakim hospital in Tehran in 2017 and 110 patients with multiple sclerosis under beta interferon treatment studied. Patients were divided into two groups with and without flu-like drug reaction. A neurology resident according to the patient's history and patient records filled in the questionnaires. The results of the two groups were compared by SPSS 16 software.

Results: A total of 110 patients including 31 patients with flu-like drug reaction and 79 non-complicated patients were evaluated. These patients included 32 males and 78 females with an average age of 35.55 years. The mean duration of beta interferon use was 4.33 years in the case group and 4.34 years in the control group. Finally, a significant correlation between the flu-like drug reaction and the optimal response in the first year treatment was found (p=0.026). In addition, cause of drug discontinuation had significant correlation with presence of flu like drug reaction (p=0.028). There was no significant correlation between the disease annual attacks rate and flu like drug reaction.

Conclusion: Flu-like drug reaction is a common complication of interferon beta drugs, which has a therapeutic difference in patients with and without this drug reaction.

Keywords: Multiple sclerosis, Beta interferon, Flu like drug, Side effect

***Corresponding Author:** Abdollah Ghaferi, Department of Neurology, Faculty of medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: drghaferi1381@gmail.com

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Introduction

Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) of unknown cause. The course is extremely variable, but most patients initially experience relapses with complete or near-complete recovery interspersed with periods of clinical remission. Although a minority of patients has only minimal symptoms, many become disabled in time because of incomplete recovery from relapses or conversion to a progressive form of the disease. MS affects

approximately 400,000 people in the United States and 2.5 million worldwide. It is a leading cause of non-traumatic disability in young adults. The disease typically begins between the ages of 20 and 40 years[1]. The incidence of MS is two or three times higher in women than in men[2].

According to the latest statistics of the Iranian multiple sclerosis society, the prevalence of multiple sclerosis in Iran is about 70,000. In the province of Tehran (capital city of Iran) in 2008, the disease was 50 per 100,000 people, and in 2015, it reached 115 per 100,000 people[3]. The point is that the disease affects young people and the active workforce of the community.

Multiple sclerosis treatments generally include treatment for acute attacks, symptomatic treatments, and modulators of disease[3]. Beta interferon is one of first step disease modifying drugs that reduce clinical attacks and new T2 lesion in MRI [4]. In addition, this drug reduce the speed of progression of disease in relapsing remitting type of disease[5]. Side effects from interferon beta included skin reactions, flu-like symptoms, fatigue, leukopenia, new or worsened depression, and new or worsened headache[6]. Flu like syndrome is one of the known side effects of this drug that include fever, muscle aches, chills and fatigue[7]. Beta interferon is used in two types 1A and B. One form of beta interferon 1A is used weekly intramuscular (avonex) and another form 3 times a week under the skin (Rebif). Beta interferon 1B is also used subcutaneously every other day (Betaferon)[8]. There are some copied biopharmaceuticals drugs of these in Iran. Cinnovex and Actovex are for Avonex, Recigen and Actorif for Rebif and Ziferon, Actoferon and Extavia for Betaferon[9]. In patients with relapsing remitting multiple sclerosis, little difference in relapse outcomes were found between beta interferon-1a SC (Rebif®) and beta interferon-1b (Betaseron®), while beta interferon-1a IM (Avonex®) was less effective than beta interferon-1a SC (Rebif®) and beta interferon-1b (Betaseron®)[10] .

Several mechanisms have been described for the effect of beta interferon, including the regulation of the secretion of cytokines and signaling molecules (including CD86, CD40 and PD-L2), preventing the migration of inflammatory cells to the central nervous system and preventing activation and proliferation of T_lymphocyte[11]. Like other, multiple sclerosis drugs, beta interferon drugs are considered as expensive drugs that cost a lot to the health system of the country. For example Avonex that is one of the cheapest multiple sclerosis drugs had median average cost 62394 $ per patient per year in 2013 in the United States[12]. The efficacy of each modifying drug in the studied population is expressed relative to the control population and the efficacy of each drug in each patient is not predicChart. According to the latest guide provided in the European Journal of Neurology, if a severe drug reaction is seen, the drug is displaced with a drug of the same level. If the clinical progression of disease or the discovery of disease progresses in the patient's brain MRI detected then the drug changed to higher level drugs[13] .

Therefore, in fact, the suitability of a drug in each particular patient is evident over time, trying to anticipate the effectiveness of the drug in each patient as soon as possible after the onset of the drug prescription is needed. According to the flu-like drug reaction is a common complication of beta-interferon drugs and does not occur in all patients, which is observed rapidly after the first injection[14,15], it seems that if this drug side effect has relation with these drug effectiveness, this prediction could be a great help to treat multiple sclerosis patients. The purpose of this study was to evaluate the possibility of predicting the response rate of this drug based on the flu-like drug reaction.

Methods

This case-control study was conducted in Loghman Hakim hospital in Tehran, capital of Iran in 2017. In this study, the dependent variable was a desirable therapeutic response. The optimal therapeutic response was the absence of multiple sclerosis attacks in one year or just a sensory isolation attack. Patients divided into two groups, with and without flulike side effects of drug. For efficacy of beta interferon, the difference between patients who received drug and control group based on previous studies was about 30%[16]. According to this difference by using MedCalc software, the sample size for the case group (having flu-like syndrome) was at least 30 and for the control group (no flu-like syndrome) was at least 80. In this study,

multiple sclerosis patients who have been diagnosed with McDonald's criteria and who have been taking interferon beta for at least 1 year entered to my study. The diagnosis of flu-like syndrome was based on the presence of fever, muscle aches, chills and fatigue in the patients. These symptoms should be repeated at each injection, and occurs within an hour to 24 hours after injection, and at least two of these four symptoms in the patient are required to diagnose the flu-like syndrome. A neurology resident in a face-to-face interview recorded each patient's information. The questionnaire included demographic data of patients, the presence or absence of flu-like syndrome, the number and type of multiple sclerosis attacks in order to determine the optimal response based on the records of the clinic and the patient's hospitalization and need for housing during the flu-like syndrome for each patient. The inclusion criteria was patient satisfaction to participate in the study, definitive nature of multiple sclerosis based on McDonald's criteria and neurologist confirmation who is associate professor. Exclusion criteria includes patient dissatisfaction for participation in the study, the patient was not in type of relapsing-remitting MS during drug use, unreliability of history , The lack of use of interferon at the onset of the disease and using concomitant immunosuppressive drugs or during the month before the onset of interferon beta. After data collection, data was analyzed by using SPSS16 software. This research project at the Ethics Committee of Shahid Beheshti University of Medical Sciences was reviewed and approved. The assigned ethics code was IR.SBMU.RETECH.REC.1396.233.

Results

A total of 110 patients (32 males (29.1%) and 78 females (70.9%)) with a mean age of 33.55±8.29 (mean ± SD) who were between 19 to 55 years of age were studied finally. The patients consisted of 31 cases and 79 patients. The case group included patients who had flu like drug reaction as defined by the criteria, and the control group did not have this drug complication.

In the case group, the mean age was 32.9 and the mean age in control group was 33.8. Of these, nine patients had a history of multiple sclerosis in the first-degree family. The average duration of disease (from the time of diagnosis of disease in the patients) in the case group was 5.85±3.26 years, and this mean in the control group was 6.08±4.04 years. The mean duration of beta interferon use in the case group was 4.33±2.34 years and this mean in the control group was 4.34±2.40 years.

The most commonly used beta interferon was Cinnovex in both groups (58.1% in the case group and 58.2% in the control group). In the second place, in the two groups were Recigen (19.4% in the case group and 12.7% in the control group) (Chart 1 and 2).

At the time of visit of these 110 patients, 84 (76.3%) patients were Relapsing-remitting (RRMS) type and 26 (23.6%) patients were secondary progressive (SPMS) type. With details, 3 of the 31 patients (9.6%) in the case group were SPMS type and in the control group 23 of 79 (29.1%) patients were SPMS type and the rest of the patients in both group were RRMS (Chart 3).

In the case group, 41.9% of the patients still were

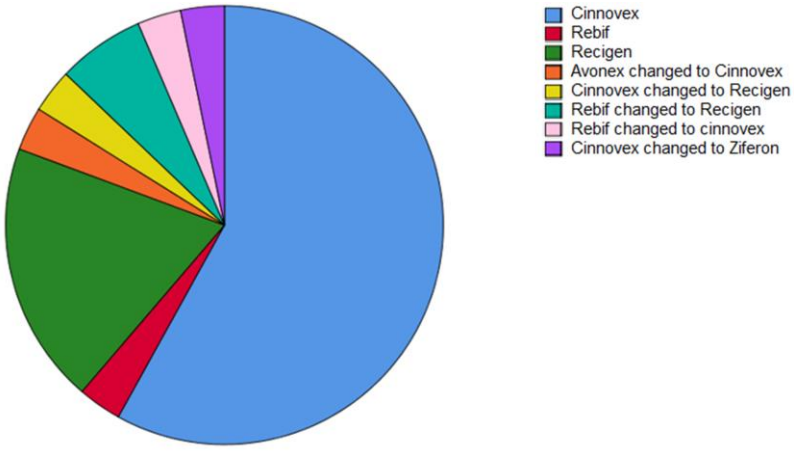

Chart 1: Type of beta interferon in case group.

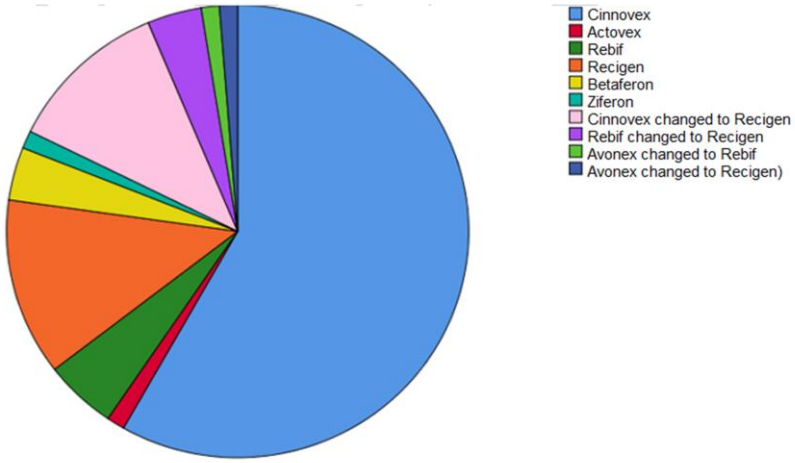

Chart 2: Type of beta interferon in control group.

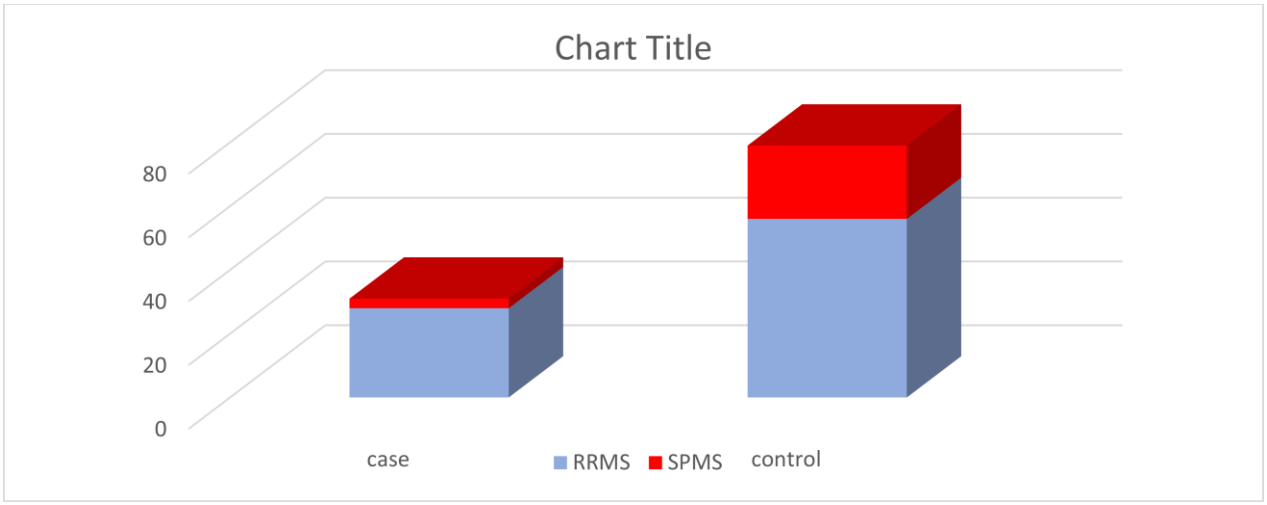

Chart 3: The population of patients studied by type of disease during the visit.

continuing beta interferon, which was 30.4% in the control group. The next frequent drug at the time of visit for both group was Fingolimod (35.5% in the case group and 22.8% in the control group). The use of natalizumab, rituximab and Azathoprine in the control group was higher in our patients (Chart 4 and 5).

In the case group, the majority of patients had to use analgesic for each injection to relieve and tolerate flu like symptoms. In 30% of them they used two times analgesic for tolerate interferon. Mostly, they injected interferon before sleep for better tolerance and reduce use of analgesic. The most commonly used analgesic was acetaminophen (32.3% of patients). The use of Ibuprofen and other forms of this drug also included 32.4% of patients. Our patients mentioned that reducing the severity of flu like symptoms during years of injection was low.

We reviewed the efficacy of interferon in the first year of treatment and compared it between two groups. The absence of any clinical attack or just one sensory attack in the first year was optimal response in the first year. Totally 93 patients of 110 patients (84.5%) responded favorably. This rate was 96.8% in the case group (30 out of 31 patients) and 79.7% in the control group (63 out of 79 patients) (Chart 6).

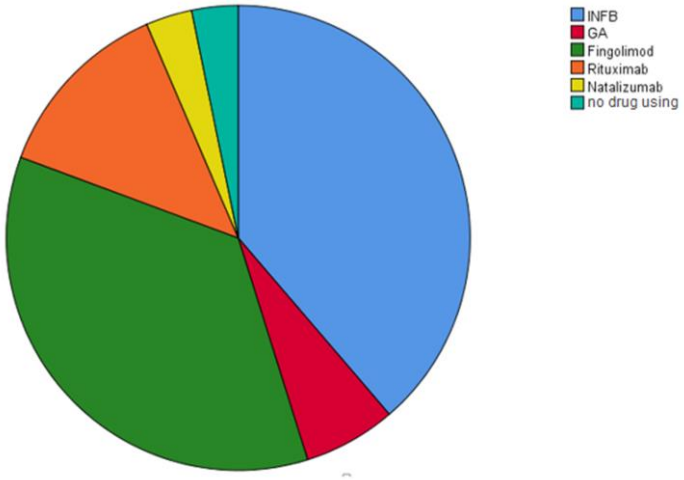

Chart 4: Type of disease modifying drugs in the case group (at visit time).

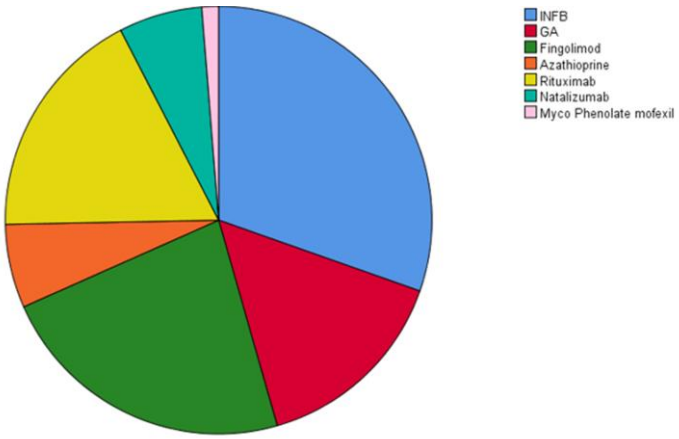

Chart 5: Type of disease modifying drugs in the control group (at visit time).

It means the undesirable response was 20.3% in the patients who had not flu like the one drug reaction compared with undesirable response of 3% in the group with flu like drug reaction. In order to compare the two groups with respect to that "optimal response" is a qualitative variable, the Chi-square test was used and

Because p-value was 0.026 <0.05, there was a significant difference between patients who had or had not flu like drug reaction for the first year beta interferon favorable response. Because the duration of drug use was different in patients who studied, patients compared with an average annual attack rate. In the case group, the average number of annual attacks was 0.199 with a range of 0 to 0.66 attacks per year, and in the control group, the number of attacks was 0.258 per year, with a range of 0 to 0.66 attacks per year. For a better interpretation, and because “annual attack rate” is a quantitative variable, the T-test was used which the p-value was 0.293.So we did not find significant relation between annual attack rate and presence of flu like drug reaction. We also compared the cause of discontinuation in the two groups. 41.9% of the patients in the case group and 30.4% of the patients in the control group were continuing usage one type of beta interferon drugs

Beta interferon drugs for 35.5% of patients in the case group and 27.8% of the patients in the control group changed to one of second-line drugs by their neurologist due to clinical attacks or MRI findings. 15.2% of patients in the control group, but none of the patients in the case group discontinued beta interferon

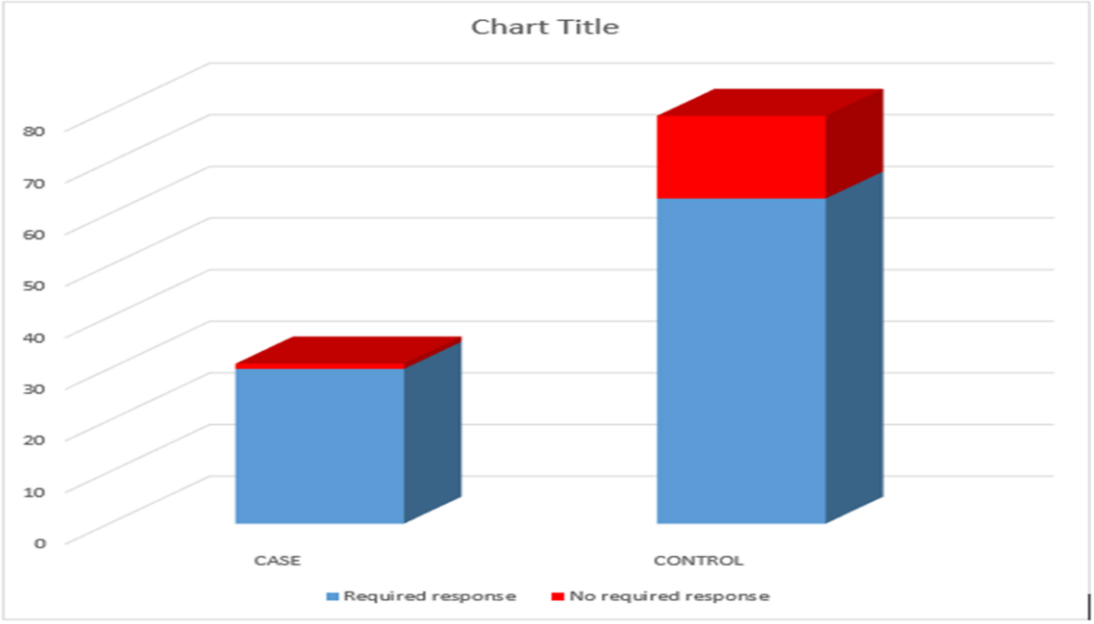

Chart 6: Desired response rate in the first year after the start of treatment.

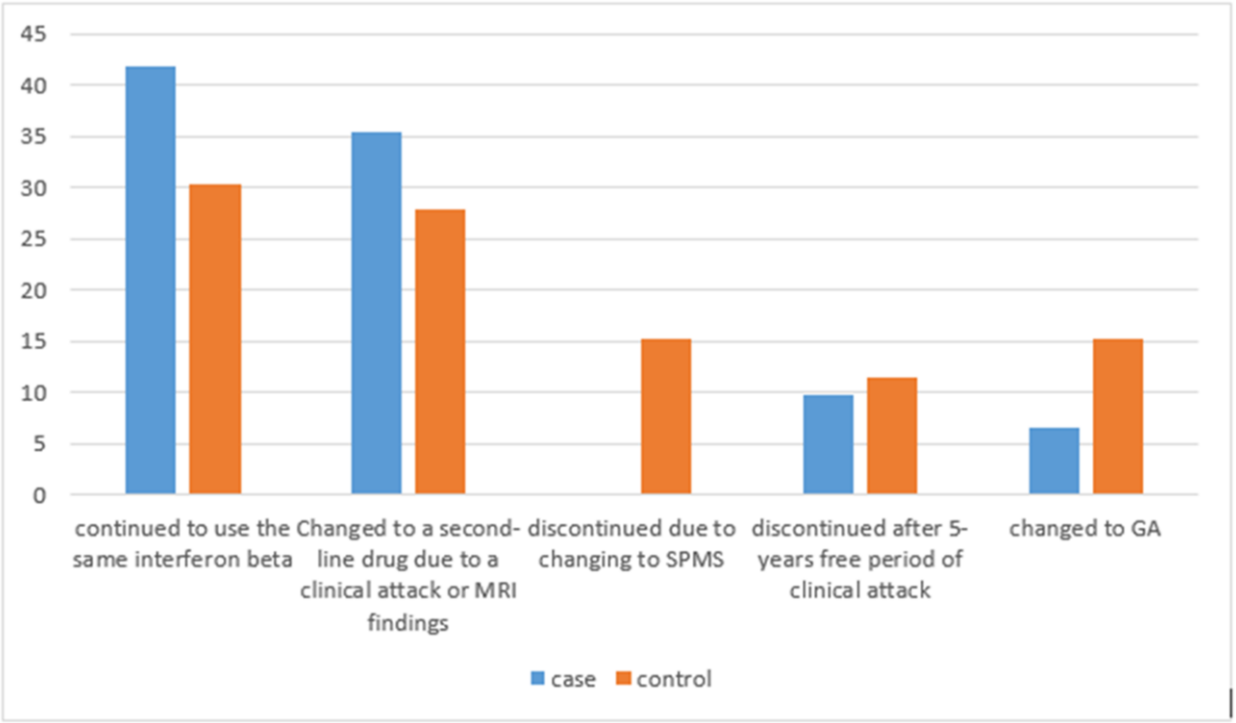

Chart 7: Comparison of the cause of Interferon beta treatment discontinuation in case and control groups.

due to secondary progressive type transformation (one of the patients in the case group that was in SP type at our visit time discontinued beta interferon because of its 5 years absence of clinical attack). 9.7% of patients in the case group and 11.4% of the patients in the control group discontinued drugs because of 5-years duration of being free of clinical attack by their neurologist order. Unfortunately four patients who were discontinued beta interferon for this reaseon came back to clinic after one or two years with

cord plaques and had paraparesis.Finally drugs for 6.5% of patients in the case group and 15.2% of the patients in the control group had been changed to Glatiramer acetate, especially due to pregnancy (Chart 7).

For comparison of two groups in the cause of discontinuation beta interferon Chi-square test were used (p=0.028). Therefore, there was a significant relationship between the flu like drug side effect and the cause of discontinuation of beta interferon.

Discussion

As noted above, multiple sclerosis is a disease of the central nervous system that affects the young generation and is a cause of the disability of the young and active generation of the population. The most common type is relapsing remitting type of disease. The purpose of disease modifying drugs is to reduce the number of disease attacks and prevent changing to progressive type. Beta interferon drug is one of the first line disease modifying drugs that due to the lower complications of the medications can used in the beginning of the disease[13]. The response to treatment varies from patient to patient. Our goal was to predict the response to interferon treatment from the beginning of the treatment based on the patient's bedside. One of the common side effects of the drug is flu-like symptoms that does not occur in all patients[6], and our question can use this drug side effect as a predictor of drug response. In this study, 110 patients with MS who had been treated with beta interferon since the start of the diagnosis were studied. A total of 31 patients had flu like drug reaction (case group). The mean age was 33.55±8.29 at the age range of 19 to 55 years old. In the case group, the mean age was 32.9 and in control group was 33.8. Mean duration of disease in the case group (from the time of diagnosis of disease) was 5.85±3.26 years, and this mean in the control group was 6.08±4.04 years.

Although the duration of disease is about the same, at the time of visit, patients in the case group were 9.6% of the SPMS type, while this in the control group was 29.1%. It is suggested that a more complete and precise study of this issue should be considered.

The mean duration of beta interferon used in the case group was 4.33±2.34 years and this mean in the control group was 4.34±2.40 years. The most common used beta interferon in both groups was Cinnovex. The difference between two groups was finally found to be significantly different in terms of the optimal responses in the first year (p=0.026). The author's opinion is that this difference is important from this point of view, one year after drug beginning the patient evaluate routinely. However, in our review, there was no significant association with annual attack rate and flu like drug reaction (p=0.293).

We compared the cause of beta interferon discontinuation in two groups, which included 5 types 1. Continuing beta interferon 2. Changed to second line drug due to MRI finding or clinical attack. 3. Termination of the drug due to converting to secondary progressive type 4. Change to GA a first line drug due to pregnancy or drug intolerance. 5. five years attack free and drug discontinuation (by their neurologist order). These were compared in two groups with the Chi-square test, which is due to the p=0.028. There was a significant relationship between the side effects of flu-like drugs and the cause of discontinuation of interferon beta.

The second type (the changing of the drug to the second line drugs due to the MRI finding or clinical attack) in the control group was lower (27.8 vs 35.5)! We believe more rate of converting to secondary progressive form of disease in the control group should be considered and considering no response to second line drugs in SPMS by their neurologist.

A study exact similar to our study which studied prediction of beta interferon efficacy based on flu like reaction drug side effect was not found in valid sources. Generally, they tried to find laboratory ways to predict the efficacy of the drug. Similarly what was done in 2006 by Nakatsuji Y et al, in Japan who studied 22 multiple sclerosis patient who on Betaferon treatment. Results showed an increase in serum level of IL-6 in response to IFN-beta administration was associated with headache, arthralgia, and relapse rate before treatment, and disability score at the initiation of the therapy. Significant association of change of serum TNF-alpha with age and headache was observed. The important finding in this study was that patients with a transient increase in IL-6 in response to IFN-beta showed a slow disease progression. This result suggests that this transient increase in the serum

IL-6 predicts favorable response to IFN-beta treatment[17]. In 2008, Wiesemann et al, in Germany examined 120 MS patients treated with different types of interferon beta. They found a significant upregulation of IL-10 and IL-5 serum cytokine levels during IFN-beta therapy. However, clinical response was only associated with IL-10 serum levels (p=0.038; positive predictive value 0.95, negative predictive value 0.43) but not with IL-5[18]. In the year 2000 Montalban et al, in Spain studied on 20 multiple sclerosis patients requiring beta interferon treatment based on guideline. In their study, they finally demonstrated that IL-6 levels are lower in MS patients having at least one C allele at position -174 of IL-6 gene, which in turn determined a reduced probability of beta interferon related Flu like syndrome[19]. In 2015, Bertoli et al, in Italy examined the genomics related to the production of IL-6 and TNF-α in 190 multiple-sclerosis-receiving beta interferon patients with different flu-like responses. They found that patients carrying at least one copy of the C allele at position -174 in the promoter of IL-6 gene produced lower levels of IL-6 and were less prone to develop FLS, which was also less severe. On the contrary, the polymorphism of TNF-α had no effect on FLS[20] .

Our study limitations were low number of patients and being retrospective study. They were compared based on patients' clinical attack and they used different type of beta interferon. We suggest more complete prospective study which investigate more factors to compare patients such as patients MRI, patients EDSS, type of attacks, and more. It is suggested, until accurate studies be performed, for patients who treated with beta interferon and do not have flu like the one drug reaction more closely follow up should be done. Changing drug should be considered if necessary.The final point is that Unfortunately four patients who discontinued beta interferon due to 5 years being attack free came back to clinic after one or two years with cord plaques and had paraparesis so detailed study should be made about it and take care for discontinue drug.

Conclusion

Based on the research findings indicating the relationship between the efficacy of beta interferon drugs and their flu like drug reaction in multiple sclerosis patients this drug reaction should be monitored in these patient and who don't have flu like drug drug reaction should be considered as patients with lower drug response so closer follow up is needed.

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