Caspian Journal of Neurological Sciences
"Caspian J Neurol Sci"
http://cjns.gums.ac.ir

Non-adherence to Disease-Modifying Treatments in Patients with Multiple Sclerosis

Roudbary Seyed-Ali (MD)[1] , Yousefzadeh-Chabok Shahrokh (MD)[2] , Behzadnia Hamid (MD)[3], Bakhshayesh-Eghbali Babak (MD)[4] , Emamhadi Mohamadreza (MD) [5] , Ghayeghran Amirreza (MD)[1] , Hatamian Hamidreza (MD)[1] , Saberi Alia (MD)[4] , Andalib Sasan (PhD) [2]*

ARTICLE INFO

Article type:
Original Article

Bullet points:

- ***Disease-modifying drugs are somehow intolerable for patients with MS.***
- ***A high rate of non-adherence to DMDs in MS patients was demonstrated.***

Article history:
Received: 7 May 2017
Accepted: 10 Jul 2017
Available online: 8 Aug 2017
CJNS 2017; 3 (10): 128-134

***Corresponding author:**
Department of Neurosurgery, Poursina Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran Faculty of Medicine, Iran Email: neurosurgery95@gmail.com

ABSTRACT

Background: Multiple Sclerosis (MS) is a debilitating disease of the central nervous system. Usually, long-term MS medications are injected intramuscularly or subcutaneously, making them intolerable for many MS patients.

Objectives: In the present study, the rate and the causes of non-adherence to MS disease-modifying drugs (DMDs) were assessed in patients with MS.

Materials and Methods: Two hundred and three MS patients of Guilan MS Society were interviewed demographic and clinical data of the patients were collected.

Results: Among the 203 patients, 73.9% were female. The mean±SD age of the patients was 32.47±9.15. Non-adherence to DMDs was due to side effects (21.7%) and requests of the families (21.7%) or ineffectiveness (17.4%). Significant association was seen between the non-adherence to DMDs and gender (p=0.015) and relapses (p=0.021).

Conclusion: The evidence from the present study suggests that there is a high rate of non-adherence to DMDs in MS patients in Guilan.

Keywords: Multiple Sclerosis; Medication Adherence

➢ ***Please cite this paper as:***
Roudbary SA, Yousefzadeh-Chabok Sh, Behzadnia H, Bakhshayesh-Eghbali B, Emamhadi M, Ghayeghran A, Hatamian H, Saberi A, Andalib S. Non-adherence to Disease-Modifying Treatments in Patients with Multiple Sclerosis. Caspian J Neurol Sci 2017; 3(10): 128-134.

1. *Neurology Department, Poursina Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran*
2. *Neuroscience Research Center, Department of Neurosurgery, Poursina Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran*
3. *Department of Neurosurgery, Poursina Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran*
4. *Neuroscience Research Center, Department of Neurology, Poursina Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran*
5. *Brachial Plexus and Peripheral Nerve Injury Center, Guilan University of Medical Science, Rasht, Iran*

Introduction

Multiple Sclerosis (MS), which is a debilitating chronic disease (1), affects the brain and spinal cord (2). MS is traditionally held to be the white matter disease (3) wherein lymphocytes invade the oligodendrocytes providing the myelin sheaths (4,5); however, neurodegenerative process has recently been recognized in the MS (6). Despite the fact that etiology of MS is not properly understood, infectious agents (7) and genetic changes (8,9) are said to play roles in the complex pathobiology of MS. The symptoms of MS are diverse. Common MS symptoms include fatigue (10), visual impairment (11), ataxia and tremor (12), bladder problems (13), bowel problems (14), cognitive impairment (15), anxiety (16), and depression (17). Hearing loss, which is also a symptom in MS (18), is less prevalent. Based on the course of the disease, MS is divided into several forms. MS diagnosis is made by clinical examination and magnetic resonance imaging (MRI) (19), and lumbar puncture (20). Evoked potential test (21) and optic coherence tomography (22) can add supportive evidence to the diagnosis. There is no cure for MS yet and treatments mostly modify the course of the disease, control its symptoms during attacks and prevent relapses and reduce the complications. Several medications are used in the treatment of MS. Interferon beta-1 is a commonly used medication in the treatment of MS. It is a cytokine that is secreted as an immune response and has immunomodulatory effects on MS. Interferon beta-1b (Betaseron), interferon beta-1a (Avonex), interferon beta-1a (Rebif), and interferon beta-1b (Extavia) have been FDA approved. Nonetheless, the most common side effects are reactions in the injection site and a flu-like syndrome.

Moreover, allergic reactions, hematologic disorder, and liver dysfunction might be seen after the treatment. Interferon beta is not recommended during pregnancy inasmuch as it increases the risk of abortion and decreases birth weight.

Disease-modifying treatments (DMTs) are usually expensive and should be consumed for a long time. Because DMTs require intramuscular or subcutaneous injections, they are difficult to be tolerated for a long time. In a Spanish study, 73% of patients discontinued immunomodulatory medication (23). More to the point, over a quarter of the patients stopped taking their medications, which was associated with lower education levels and previous relapses. MS treatment should be acceptable to the patient and enhance patient's adherence to long-term treatment. Little is known about the non-adherence to DMDs by MS patients in Guilan province in Iran. Hence, the present study investigated the non-adherence to these medications and its by MS patients in the Guilan province.

Materials and Methods

A cross-sectional design was used for this study, in which 203 MS patients, members of the Multiple Sclerosis Society of Guilan province, were evaluated by questionnaires regarding demographic data (age, sex, duration of illness, education, adherence or non-adherence to treatment), causes of non-adherence to treatment (type of medication, medication price, disease progression, inefficiency of medications, unavailability of medications, side effects, family request for withdrawal from treatment, physician's decision, planned cessation such as pregnancy, and missing doses and *etc.*). The inclusion criteria were a diagnosis of

relapsing remitting (RR) MS according to the revised McDonald criteria (2005) and membership in Multiple Sclerosis Society of Guilan with a history of using DMDs. Informed consent was obtained from all the patients. Data was analyzed by SPSS software (version 17), using frequency, mean, and standard deviation. The Chi-square test was used to examine the associations.

Results

Table 1 shows the demographic data of MS patients participated in the present study. Cinovex (% 42.4) and Actovex (21.9%) were the most consumed DMDs (table 2).

Table 1. Frequency distribution of some demographic factors of MS subjects

Variable		N (%)
Gender	Male	53 (26.1)
	Female	150 (73.9)
Age (years)	Less than 20	16 (7.9)
	21-30	77 (37.9)
	31-40	64 (31.5)
	More than 40	46 (22.7)
Age (years)	Mean ± SD	32.47±9.15
Disease duration (years)	Less than a year	17 (8.4)
	1<Y*≤2	29 (14.3)
	2<Y≤3	29 (14.3)
	3<Y≤5	33 (16.3)
	5<Y≤10	59 (29.1)
	10 <Y	36 (17.7)
Disease duration (months)	Mean ± SD	76.6±69.4
Educational level	Elementary school - illiterate	51 (25.1)
	High school - Diploma	89 (43.8)
	Academic education	63 (31)
Monthly income (Iranian Rials)	Less than ten million	99 (56.2)
	More than ten million	77 (43.8)
Increase in EDSS	Less than one unit	43 (21.2)
	More than one unit	160 (78.8)
Increase in EDSS	Mean ± SD	2.09±1.1

*: Disease duration

Table 2. Frequency distribution of DMDs consumed by MS patients

Type of DMD	N (%)
Cinovex	86 (42.4)
Actovex	39 (19.2)
Avonex	7 (3.4)
Resigen	26 (12.8)
Rebif	5 (2.5)
Actoferon	16 (7.9)
Betaferon	4 (2)
Ziferon	1 (0.5)
Extavia	1 (0.5)
Osvimer	10 (4.9)
Copamer	8 (3.9)
Total	203 (100)

58.1% of the patients (n=118) received DMDs regularly, while 22.7% (n=46) stopped taking the medications, and 19.2% (39) missed some of the doses. The most frequent causes of medication non-adherence were adverse effects (21.7%) and family request (21.7%) or inefficiency of the medication on the course of the disease (17.4%) (table 3).

Table 3. Frequency distribution of causes of DMDs non-adherence in the MS patients

Causes of for non-adherence to DMDs	N (%)
Side effects	10 (21.7)
At the request of the family	10 (21.7)
Ineffectiveness	8 (17.4)
High cost	5 (10.9)
Physician's decision	4 (8.7)
Patient choice	4 (8.7)
Unavailability of medications	3 (6.5)
Pregnancy	2 (4.3)
Total	46 (100)

The using state of DMDs was not significantly associated with age (p=0.43), educational level (p=0.31), monthly income (p=0.47), disease duration (p=0.142), EDSS (p=0.47), and the type of medication (p=0.52). There was a statistically significant association between the gender (p=0.015), the number of relapses during the course of the disease and using state of DMDs (p=0.021). There was not any association between the medication manufacturer and medication non-adherence and missing doses (p=0.52) (table 4).

Table 4. Frequency distribution of using state of the of DMDs in the MS patients

Type of DMD	Regular consumption N (%)	Lack of regular consumption N (%)	Medication discontinuation N (%)	Total N (%)	Statistical significance
Cinovex	55 (64)	10 (11.6)	21 (24.4)	86 (100)	
Actovex	19 (48.7)	10 (25.6)	10 (25.6)	39 (100)	
Avonex	6 (85.7)	1 (14.3)	0 (0)	7 (100)	
Resigen	14 (53.8)	5 (19.2)	7 (26.9)	26 (100)	
Rebif	2 (40)	2 (40)	1 (20)	5 (100)	
Actoferon	7 (43.8)	5 (31.2)	4 (25)	16 (100)	0.52
Betaferon	3 (75)	1 (25)	0 (0)	4 (100)	
Ziferon	1 (100)	0 (0)	0 (0)	1 (100)	
Extavia	0 (0)	0 (0)	1 (100)	1 (100)	
Osvimer	7 (70)	2 (20)	1 (10)	10 (100)	
Copamer	4 (50)	3 (37.5)	1 (12.5)	8 (100)	
Total	118 (58.1)	39 (19.2)	46 (22.7)	203 (100)	

Discussion

In the present study, 58.1% of the MS patients took DMDs on a regular basis, 22.7% stopped taking the medications and 19.2% missed some doses. In a similar study, Rio *et al.* (24) reported that non-adherence to interferon beta and glatiramer acetate for controlling MS was approximately 17%. Giovannoni *et al.* (25) reported that 16% to 27% of MS patients discontinued the treatment. Meyniel *et al.* (26) reported that the percentage non-adherence to IFNb-1a (IM), IFNb-1a (SC), IFNb-1b, and glatiramer acetate was 44% after 3 years of follow-up, 43% after 2.9 years, 37% after 2.8 years, and 31% after 3.2 years. In the present study, we found that the medication manufacturer in each group was not associated with medication non-adherence or missing doses, which might indicate a close similarity between various types of MS medications approved by the Food and Drug Administration of Iran.

In this study, the medication non-adherence was due to side effects and family requests (21.7%), the inefficiency of medications on the course of the disease (17.4%), high cost (10.9%), patient choice (8.7%), and unavailability of medications (6.5). In a study by Tremlett *et al.* (23), 52.33% of the patients mentioned medication

inefficiency as a cause of non-adherence to the treatment. And, only 4.3% of the patients stopped taking medication due to side effects. By contrast, we found that the highest rates of medication non-adherence were due to side effects. Vicente *et al.* (27) suggested the lack of favorable effects of treatment (38.8%) and side effects (32.8%) as the most important causes of treatment non-adherence. Mesaroš *et al.* (28), in a 5-year follow-up in patients with MS, suggested that the absence of favorable effects (54%), pregnancy (21%) and side effects (17%) were involved in non-adherence to the medications. In addition, only 3% of the patients chose to discontinue medication. Similarly, 8.7% of the patients in our study chose to discontinue medications and 21.7% because of the family's request. Most studies reported medication discontinuation due to patient choice with low frequencies (23-27). However, Tremlett *et al.* (23) reported that non-adherence to medication due to patients' decision was seen in 17.2% of the German patients. Meyniel *et al.* (26) reported that MS medication discontinuation was higher in female than in malepatients (p=0.003). Berger *et al.* (29) examined discontinuation IFNβ-1a and reported higher discontinuation in the female patients. The present study did not find any statistically significant relationship between age groups and consumption status of DMDs, which is consistent with the findings of previous studies (23-25,27). There was no significant association between educational level and consumption status of DMDs. Berger *et al.* (29) did not find any association between educational level and medication discontinuation. The present study did not find any statistically significant association between increased EDSS score and consumption status of DMDs. Meyniel *et al.* (26) found that EDSS score changes were involved in the medication discontinuation.

There was a statistically significant association between the number of attacks during the course of disease and consumption of DMDs in the present study. In fact, what is evident in all the previous studies (23,25-27) is that a major cause of non-adherence to medication discontinuation among patients was lack of an appropriate response or inadequate response, or the side effects of the medications. Rio *et al.* (24) reported ineffectiveness and medication side effects as the main causes of non-adherence to treatment in 56% of the patients. The education level and even unfavorable economic status were not common causes of non-adherence to treatment in this study. There was no significant relationship between monthly income and consumption status of DMDs.

Conclusion

Altogether, the evidence from the present study suggests that there was a high rate of non-adherence to DMDs in the studied MS patients and the most prevalent cause of this event is the side effects of DMDs. On this account, it is necessary to heighten the knowledge of MS patients about the disease.

Conflict of Interest

The authors have no conflict of interest.

References

1. Andalib S, Talebi M, Sakhinia E, Farhoudi M, Sadeghi-Bazargani H, Emamhadi MR, et al. Mitochondrial DNA G13708A Variation and Multiple Sclerosis: Is There an Association? Revue Neurologique 2017; 173(3):164-168.

2. Andalib S, Talebi M, Sakhinia E, Farhoudi M, Sadeghi-Bazargani H, Gjedde A. Mitochondrial DNA T4216C and A4917G Variations in Multiple Sclerosis. J Neurol Sci 2015; 356(1–2):55-60.
3. Mashinchi S, Mashinchi S, Arefhosseini SR, Ebrahimi Mameghani M, Yousefzadeh S, Saberi A. Pattern of Diet and Supplement Consumption among Multiple Sclerotic Patients Pre and Post Diagnosis and their Attitudes toward the Effects of these Parameters on Disease Progression. Journal of Guilan University of Medical Sciences 2012; 21(84):1-14. [Text in Persian]
4. Minagar A, Toledo EG, Alexander JS, Kelley RE. Pathogenesis of Brain and Spinal Cord Atrophy in Multiple Sclerosis. J Neuroimaging 2004; 14(s3):5S-10S.
5. Andalib S, Talebi M, Sakhinia E, Farhoudi M, Sadeghi-Bazargani H, Gjedde A. Lack of Association between Mitochondrial DNA G15257A and G15812A Variations and Multiple Sclerosis. J Neurol Sci 2015; 356(1–2):102-106.
6. Trapp BD, Nave K-A. Multiple Sclerosis: an Immune or Neurodegenerative Disorder? Annu Rev Neurosci 2008; 31247-269.
7. Ascherio A, Munger KL. Environmental Risk Factors for Multiple Sclerosis. Part I: the Role of Infection. Ann Neurol 2007; 61(4):288-299.
8. Andalib S, Talebi M, Sakhinia E, Farhoudi M, Sadeghi-Bazargani H, Motavallian A, et al. Multiple Sclerosis and Mitochondrial Gene Variations: a Review. J Neurol Sci 2013; 330(1):10-15.
9. Andalib S, Emamhadi M, Yousefzadeh-Chabok S, Salari A, Emami Sigaroudi A, Seyedi Vafaee M. MtDNA T4216C Variation in Multiple Sclerosis: a Systematic Review and Meta-analysis. Acta Neurol Belg 2016; 116(4):439–443.
10. Flachenecker P, Kümpfel T, Kallmann B, Gottschalk M, Grauer O, Rieckmann P, et al. Fatigue in Multiple Sclerosis: a Comparison of Different Rating Scales and Correlation to Clinical Parameters. Mult Scler J 2002; 8(6):523-526.
11. Kale N. Management of Optic Neuritis as a Clinically First Event of Multiple Sclerosis. Curr Opin Ophthalmol 2012; 23(6):472-6.
12. Mills RJ, Yap L, Young CA. Treatment for Ataxia in Multiple Sclerosis. The Cochrane Database of Systematic Reviews 2007; (1):CD005029.
13. Lúcio AC, Perissinoto MC, Natalin RA, Prudente A, Damasceno BP, D'Ancona CAL. A Comparative Study of Pelvic Floor Muscle Training in Women with Multiple Sclerosis: Its Impact on Lower Urinary Tract Symptoms and Quality of Life. Clinics 2011; 66(9):1563-1568.
14. Preziosi G, Raptis DA, Storrie J, Raeburn A, Fowler CJ, Emmanuel A. Bowel Biofeedback Treatment in Patients with Multiple Sclerosis and Bowel Symptoms. Dis Colon Rectum 2011; 54(9):1114-21.
15. Amato MP, Langdon D, Montalban X, Benedict RH, DeLuca J, Krupp LB, et al. Treatment of Cognitive Impairment in Multiple Sclerosis: Position Paper. J Neurol2013; 260(6):1452-68.
16. Ghojazadeh M, Taghizadeh M, Abdi S, Azami-Aghdash S, Andalib S, Farhoudi M. Fear of Disease Progression in Patients with Multiple Sclerosis: Associations of Anxiety, Depression, Quality of Life, Social Support and Knowledge. J Clin Res Gov 2014; 3(2):141-146.
17. Chwastiak L, Ehde DM, Gibbons LE, Sullivan M, Bowen JD, Kraft GH. Depressive Symptoms and Severity of Illness in Multiple Sclerosis: Epidemiologic Study of a Large Community Sample. Am J Psychiatry 2002; 159(11):1862-1868.
18. Saberi A, Hatamian HR, Nemati S, Banan R. Hearing statement in Multiple Sclerosis: a Case Control Study Using Auditory Brainstem Responses and Otoacoustic Emissions. Acta Med Iran 2012; 50(10):679-683.
19. Barkhof F, Filippi M, Miller DH, Scheltens P, Campi A, Polman CH, et al. Comparison of MRI Criteria at First Presentation to Predict Conversion to Clinically Definite Multiple Sclerosis. Brain 1997; 120(11):2059-2069.
20. Gajofatto A, Calabrese M, Benedetti MD, Monaco S. Clinical, MRI, and CSF Markers of Disability Progression in Multiple Sclerosis. Dis markers 2013; 35(6):687-699.
21. Parisi V, Pierelli F, Restuccia R, Spadaro M, Parisi L, Colacino G, et al. Impaired VEP

after Photostress Response in Multiple Sclerosis Patients Previously Affected by Optic Neuritis. Electroencephalogr Clin Neurophysiol 1998; 108(1):73-79.
22. Talebi M, Nikanfar M, Sorkhabi R, Sharifipour E, Bahrebar M, Kiavar A, et al. Optic Coherence Tomography Findings in Relapsing-remitting Multiple Sclerosis Patients of the Northwest of Iran. Iranian Journal of Neurology 2013; 12(3):81-86.
23. Tremlett H, Van der Mei I, Pittas F, Blizzard L, Paley G, Dwyer T, et al. Adherence to the Immunomodulatory Drugs for Multiple Sclerosis: Contrasting Factors Affect Stopping Drug and Missing Doses. Pharmacoepidemiol Drug Saf 2008; 17(6):565-76.
24. Río J, Porcel J, Téllez N, Sánchez-Betancourt A, Tintoré Ma, Arévalo MJ, et al. Factors Related with Treatment Adherence to Interferon b and Glatiramer Acetate Therapy in Multiple Sclerosis. Mult Scler J 2005; 11(3):306-309.
25. Giovannoni G, Southam E, Waubant E. Systematic Review of Disease-modifying Therapies to Assess Unmet Needs in Multiple Sclerosis: Tolerability and Adherence. Mult Scler J 2012; 18(7):932-946.
26. Meyniel C, Spelman T, Jokubaitis VG, Trojano M, Izquierdo G, Grand'Maison F, et al. Country, Sex, EDSS Change and Therapy Choice Independently Predict Treatment Discontinuation in Multiple Sclerosis and Clinically Isolated Syndrome. PloS one 2012; 7(6):e38661.
27. Vicente IC, Ara CJ, Huarte LR, Navarro AH, Serrano MN, Rabanaque HM. Discontinuation and Long-term Adherence to beta Interferon Therapy in Patients with Multiple Sclerosis. Farm Hosp 2011; 36(2):77-83. [Text in Spanish]
28. Mesaroš Š, Stojsavljević N, Dujmović-Bašuroski I, Dejanović I, Pekmezović T, Drulović J. Long-term Adherence to Interferon-beta Treatment in a Cohort of RRMS Patients in Belgrade, Serbia. Clin Neurol Neurosurg 2012; 114(8):1145-1148.
29. Berger JR. Functional Improvement and Symptom Management in Multiple Sclerosis: Clinical Efficacy of Current Therapies. Am J Manag Care 2011; 17S146-53.