

Reasons of Nonadherence to Treatment in Relapsing Remitting Multiple Sclerosis Patients

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ABSTRACT:

BACKGROUND:

Multiple sclerosis is a chronic disease characterized by inflammation, gliosis, and neuronal loss; the course can be relapsing-remitting or progressive.

Treatment with Disease modifying therapy may reduce the number of relapses, slowing down the progression of the disease, reducing disability and the number of hospitalizations.

AIM OF STUDY:

To assess the adherence to medication and to know the causes of non-adherence to treatment in Iraqi patients with Multiple Sclerosis.

METHODS AND MATERIALS:

Study included 178 patients with relapsing remitting multiple sclerosis from Dr. Saad Al-Witry Hospital for Neurosciences for period started from December 2018 until December 2019. Statistical analysis was tested using Pearson Chi-square test. Statistical significance was considered whenever the P value was equal or less than 0.05.

RESULTS:

It was found that 69(38.8%) patients were adherent to treatment while 109 (62.2%) were not. There was significant difference between the two groups in the treatment used (P=0.0001). There were significant differences in non-adherent group between the treatment used in terms of adverse effects, treatment cessation by physician and unavailability of treatment (P=0.015, 0.001 and 0.0001) respectively.

CONCLUSION:

Two thirds of patients were not adherent to treatment, Most common cause was adverse effect mainly in interferon group, also inconvenience and perceived lack of efficacy reported in this groups, unavailable treatment is a reason for patient used Natalizumab, treatment cessation by physician especially with Fingolimod because of side effect of drug.

KEYWORDS: Multiple sclerosis, adherence, DMTs

INTRODUCTION:

Compliance: is a passive behavior in which a patient is following a list of instructions from the doctor (taking the medication at the right time, at the right dose, on right day). Most common cause of non-compliance in MS patients was forgetting to inject⁽¹⁾.

Adherence: defined by the World Health Organization (WHO) as the extent, to which a patient behavior-taking medication, following diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider is crucial for patients to obtain the full benefits of their treatment⁽¹⁾.

Non-adherence: patients were identified as non-adherent if they missed one or more dose in the 28 days prior to completing the survey or if

they missed at least 25% of the chosen DMT doses. If they missed ≥ 1 injection of Avonex; ≥ 3 injections of Rebif, Betaferon, missed two or more tablets of fingolimod and missed one dose of natalizumab⁽¹⁾.

Causes of non-adherence

Adverse effect, Disease and treatment duration, Demographic features, MS Quality of Life scale: adherent patients reported having a better quality of life in particular, Perceived lack of efficacy is one of the most commonly reasons of treatment discontinuation. The disease course of MS patients and therapy is often effective; the patients may not understand the benefits of adherence to treatment. The effects of treatment may not become apparent immediately, Unrealistic expectation have been highly predictive of non-adherence. Therefore, it is important to explain to patient DMT therapy used to decrease disease activity and disability

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not curable (4-6). Inconvenience and needle phobia: as result of adverse effect of DMT therapy. Cognitive impairment and depression: memory impairment often results from MS (7) and may make it difficult for the patient to follow correctly the prescribed treatment regimen.

AIM OF STUDY:

The purpose of this study is to assess the adherence to medication and to know the causes of non-adherence to treatment in Iraqi patients with relapsing remitting Multiple Sclerosis (MS).

MATERIALS AND METHODS:

It is a descriptive observational cross-sectional study.

178 RRMS patients' data were collected from Dr. Saad Al-Witry Hospital for Neurosciences for period started from December 2018 until December 2019.

Patients were interviewed (for about 40-50minutes) and fully examined by neurologist. Patients were asked to fill a questionnaire (see appendix-1), which contained information about age, gender, area of residence, time since diagnosis of MS, number of relapses, Expanded Disability Status Scale (EDSS), symptoms at disease onset, type of treatment, adverse effects, reasons of discontinuation and patient opinions to improve adherence to the treatment. Patients diagnosed with RRMS according to McDonald's criteria 2017.

Data organized using Microsoft Excel 2016. Statistical analysis performed using the available

statistical package of SPSS-25 (Statistical Packages for Social Sciences- version 25).

Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values).

The significance of difference of different percentages (qualitative data) tested using Pearson Chi-square test (c2-test) with application of Yate's correction or Fisher Exact test whenever applicable. Statistical significance was considered whenever the P value was equal or less than 0.05 (8-13).

Inclusion criteria

1. Confirmed diagnosis of relapsing remitting MS based on medical records.
2. Taking treatment (INFB 1b SC, INFB 1a SC, INFB 1a IM, Fingolimod, and Natalizumab).
3. Treatment for at least 6 months prior to participation in the study.
4. Age over 16 years.

Exclusion criteria

1. Progressive forms of MS.
2. Confirmed diagnosis of RRMS but not taking (INFB-1b SC, INFB1a SC, INFB1a IM, Fingolimod, and Natalizumab)
3. Pregnant patient.
4. Patient discontinues treatment in period of study.

RESULTS:

178 MS patients' data were collected and the results were as follows:

1- Adherent and non-adherent patients

Among 178 RRMS cases, it was found that 69 (38.8%) patients were adherent to the DMT while 109 (61.2%) were not (figure. 1).

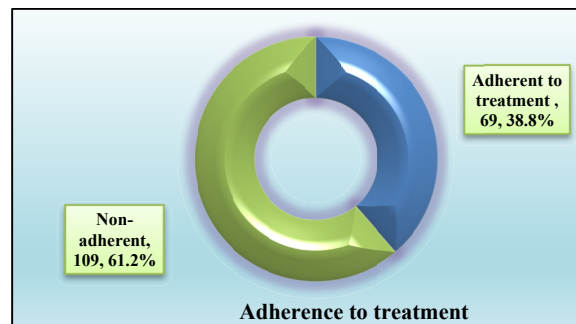


Figure 1: Number of patients and their percentages according to adherence to the DMT.

2- Demographic distribution, educational level and marital status of patients

Results shown that there was no significant

differences between the adherent and non-adherent groups (see table. 1) (P >0.05).

Table 1: Comparison between the adherent and non-adherent groups in terms of age, gender, area of residence, educational level and marital status.

		Adherent to treatment (n=69)		Non-adherent (n=109)		P value
		No	%	No	%	
Age (years)	16---19	2	2.9	1	0.9	0.154
	20---29	17	24.6	18	16.5	
	30---39	25	36.2	33	30.3	
	40---49	12	17.4	39	35.8	
	50---59	12	17.4	17	15.6	
	60---69	1	1.4	1	0.9	
	Mean±SD (Range)	36.7±10.5 (17-65)		39.0±9.7 (19-60)		
Gender	Male	15	21.7	34	31.2	0.169
	Female	54	78.3	75	68.8	
Residence	Baghdad	55	79.7	93	85.3	0.330
	Others	14	20.3	16	14.7	
Educational level	Illiterate	4	5.8	2	1.8	0.560
	Primary	17	24.6	29	26.6	
	Secondary	23	33.3	38	34.9	
	College	25	36.2	40	36.7	
Marital status	Single	13	18.8	24	22.0	0.759
	Married	54	78.3	79	72.5	
	Divorced	1	1.4	4	3.7	
	Widow	1	1.4	2	1.8	

*Significant difference between proportions using Pearson Chi-square test at 0.05 level.

3- Disease duration, Age, EDSS score, and symptoms at MS onset

There was no significant difference between the adherent and non-adherent group (table .2)

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Table 2: Difference between adherent and non-adherent groups in age at MS onset, EDSS score at MS onset, disease duration and Symptoms at MS onset.

		Adherent to treatment (n=69)		Non-adherent (n=109)		P value	
		No	%	No	%		
Age at MS onset (years)	10---19	7	10.1	6	5.5	0.144	
	20---29	33	47.8	34	31.2		
	30---39	17	24.6	40	36.7		
	40---49	10	14.5	25	22.9		
	50---59	1	1.4	3	2.8		
	60---69	1	1.4	1	0.9		
	Mean±SD (Range)	30.5±9.9 (14-63)		33.6±9.4 (17-60)			
EDSS score at MS onset	<3.5 score	40	58.0	66	60.6	0.440	
	3.5---6	28	40.6	43	39.4		
	>6 score	1	1.4	-	-		
	Mean±SD (Range)	3.2±1.5 (1.0-7.0)		2.8±1.2 (1.0-6.0)			
Disease duration (years)	1---4	35		50.7	52	47.7	0.507
	5---9	20		29.0	40	36.7	
	=>10y	14		20.3	17	15.6	
	Mean±SD (Range)	6.2±5.0 (1-21)		5.5±3.6 (1-17)			
Symptoms at MS onset	Sensory	19		27.5	32	29.4	0.653
	Motor	17		24.6	26	23.9	
	Optic pathway	22		31.9	27	24.8	
	Brain stem/ Cerebellar	11		15.9	24	22.0	

*Significant difference between proportions using Pearson Chi-square test at 0.05 level.

4- Number of relapses, EDSS score in the last visit and disease modifying therapy used the two groups in the disease modifying therapy used (P=0.0001) (table .3) (P<0.05).
There was a significant difference between

Table 3: Differences between adherent and non-adherent groups in no. of relapses, EDSS score in last visit and disease modifying therapy used.

		Adherent to treatment (n=69)		Non-adherent (n=109)		P value
		No	%	No	%	
Number of relapses	No	27	39.1	34	31.2	0.511
	1---2	27	39.1	51	46.8	
	3 & more	15	21.7	24	22.0	
	Mean±SD (Range)	1.8±2.5 (0-15)		1.5±1.6 (0-7)		
EDSS score in the last visit	<3.5 score	24	34.8	26	23.9	0.563
	3.5---6	42	60.9	72	66.1	
	>6 score	3	4.3	11	10.1	
	Mean±SD (Range)	3.9±1.7 (1.0-6.5)		4.4±1.6 (1.0-9.0)		
Drug treatment used	INFB-1b SC	20	29.0	48	44.0	0.0001*
	INFB-1a SC	8	11.6	24	22.0	
	INFB-1a IM	8	11.6	16	14.7	
	Fingolimod	8	11.6	12	11.0	
	Natalizumab	25	36.2	9	8.3	

*Significant difference between proportions using Pearson Chi-square test at 0.05 level.

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5. Reasons of non-adherence

Table 4: Reasons of non-adherence among non-adherent group (n=109).

Reasons of non-adherence (n=109);	No	%
Adverse effects	46	42.2
Treatment unavailable	27	24.8
Inconveniences	26	23.9
Perceived lack of efficacy	15	13.8
Treatment cessation by Physician	10	9.2

6. Reasons of non-adherence among the disease modifying therapy used treatment cessation by physicians and unavailability of treatment (P=0.015, 0.0001 and 0.001) respectively (P<0.05). (Table. 5)
There were significant differences between the DMTs used in terms of adverse effects,

Table 5: Comparison between reasons of non-adherence among the disease modifying therapies used.

Drug treatment used	Adverse effects				P value
	Yes		No		
	No	%	No	%	
INFB-1b SC	24	50.0	24	50.0	0.015*
INFB-1a SC	13	54.2	11	45.8	
INFB-1a IM	7	43.7	9	56.3	
Fingolimod	2	16.7	10	83.3	
Natalizumab	-	-	9	100	
	Treatment unavailable				
INFB-1b SC	3	6.3	45	93.7	0.0001*
INFB-1a SC	4	16.7	20	83.3	
INFB-1a IM	7	43.7	9	56.3	
Fingolimod	5	41.7	7	58.3	
Natalizumab	8	88.9	1	11.1	
	Inconveniences				
INFB-1b SC	15	31.3	33	68.7	0.078
INFB-1a SC	7	29.2	17	70.8	
INFB-1a IM	4	25.0	12	75.0	
Fingolimod	-	-	12	100	
Natalizumab	-	-	9	100	
	Perceived lack of efficacy				
INFB-1b SC	9	18.7	39	81.3	0.162
INFB-1a SC	5	20.8	19	79.2	
INFB-1a IM	-	-	16	100	
Fingolimod	-	-	12	100	
Natalizumab	1	11.1	8	88.9	
	Treatment cessation by physician				
INFB-1b SC	4	8.3	44	91.7	0.001*
INFB-1a SC	-	-	24	100	
INFB-1a IM	1	6.3	15	93.7	
Fingolimod	5	41.7	7	58.3	
Natalizumab	-	-	9	100	

*Significant difference between proportions using Pearson Chi-square test at 0.05 level.

DISCUSSION:

This study was aimed to evaluate the effect of age marital status, gender, education, area of residence on adherence to DMT. There were no significant differences between the two groups. Interestingly, several other studies in USA, Poland and Turkey also found there was no

significant differences between adherent and non-adherent groups in terms of age, gender, level of education (table 3.1) ⁽¹⁴⁻¹⁶⁾.

Age at MS onset was no significant different between the two groups as the studies have shown that MS starts as the age of 20-40 years ⁽¹⁷⁾.

Rio et al. observed that the EDSS score at entry was the main factor that predicted discontinuation of therapy, disagree with our result possible related to our patients delay in consultation of neurologist therefore present with increase EDSS in both groups ⁽⁵⁾. The disease duration had no effect on adherence as some studies stated that the non-adherent percent increases with time table 3.2 ^(14,15). MS symptoms also did not affect adherence similar to our findings it was found that there was no significant different in MS symptoms between adherents and non-adherent groups ⁽⁴⁾. A study carried out in 2015 in Turkey showed that the relapse rate has no correlation with adherence to the DMTs ⁽¹⁶⁾.

Furthermore a study carried out in Lithuania in 2017 found that there was a significant difference between adherent and non-adherent groups in the EDSS score on the day of examination ⁽¹⁸⁾. Possibly because of the large sample size in their study and frequent change in treatment to our patients because drug was unavailable frequently.

DMTs adverse effect were the most common reason for non-adherence cited by patients. It is well established by other studies (group randomized pilot trial (Bruce, Bruce, Lynch, et al., 2016 and Devonshire et al, multinational 2011) that is adverse effects is one of the most common reasons of non-adherence of MS patients to the DMTs ^(19,20). However, the study addressed the issue of treatment unavailability in Governmental hospitals, which was the second cause of non-adherence; this reason was attributed to the low to middle range financial situation of most patients included in this study and to the expensive prices of these DMTs. In other study, show costs of DMTs as a reason of non-adherence in 14.1% of cases ⁽²⁰⁾.

Other cause of discontinuation was the treatment cessation by physician among the DMTs used; it was most common in patients on Gilenya (41.7%). Patients who are using Gilenya reported to suffer from macular edema ⁽²¹⁾ or lymphopenia ⁽²²⁾.

Other causes of DMTs discontinuation were inconveniences and perceived lack of efficacy, interestingly there were no significant

differences among the DMTs used in terms of these two groups.

Alroughani et al. who found that in Kuwait patients who did not adhere to DMTs had inconvenience 32.9% and perceived lack of efficacy 25.9% as a reason of non-adherence more than adverse effect 23.5% mostly because of long duration of their study ⁽²³⁾.

CONCLUSION:

In our study, about two thirds of patients were not adherent to treatment. There were significant differences in non-adherent group between treatment used in terms of adverse effect, treatment unavailability, and treatment cessation by physician, no significant difference in terms of inconvenience and perceived lack of efficacy. Most common cause of non-adherence was adverse effect mainly in interferon groups. There was no significant difference between adherent and non-adherent groups in term age, gender, marital status, residence, and education level, number of relapses, disease duration and Expanded Disability Status Scale in the first and last visit.

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