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Treatment satisfaction with disease-modifying therapy in relapsing-remitting multiple sclerosis in Iraq

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ABSTRACT

Multiple sclerosis (MS) is a chronic, inflammatory, immune-mediated disease of the central nervous system (CNS). More than 2 million people worldwide have MS. The goal of the present study was to compare Iraqi patients' treatment satisfaction with three different disease-modifying therapies (DMTs), administered orally, subcutaneously, and by slow infusion; namely, fingolimod, interferon beta-1b (IFNβ-1b), and natalizumab, respectively. As well as to assess the individual differences among these therapies about their effectiveness, convenience and global satisfaction also to assess the role of certain predictors on treatment satisfaction. Patient satisfaction with medication assessed by the Treatment Satisfaction Questionnaire for Medication (TSQM-9) which comprises three components medication effectiveness, convenience, and global satisfaction. For The treatment satisfaction outcomes, the IFNβ-1b using patients had the lowest score for all TSQM-9 subscales. The most consistent differences among the groups were related to the convenience of the medication, with oral fingolimod have the highest scores and natalizumab the second. Regarding global satisfaction, natalizumab using group reported significantly higher satisfaction, as compared to both IFNβ-1b and fingolimod using groups. In conclusion, Iraqi relapsing-remitting MS patients are more satisfied with the natalizumab than with IFNβ-1b or fingolimod. Some predictors such as age, EDSS and duration of treatment, correlate with the level of satisfaction with different treatments.

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INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory, immune-mediated disease of the central nervous system (CNS) (Milo and Miller, 2014) mainly affects young adults (Heydarpour *et al.,* 2015). It is characterized pathologically by perivascular infiltrates of mononuclear cells, demyelination, axonal loss and gliosis with the formation of multiple plaques, and clinically by a variety of neurological signs and symptoms (Milo and Miller, 2014). More than 2 million people worldwide had MS (Heydarpour *et al.,* 2015) mainly young adult with an onset age of 20–50 years and meant of 30 years, although it may also develop in childhood and after the age of 60, and it is 2:1 to 3:1 times more common in women: men (Leray *et al.,* 2016). MS prevalence is higher in areas farther away from the equator and differs by different populations and geographic areas (Sahraian *et al.,* 2010). Iraq as a part of the Middle East area considered as an MS medium risk prevalence area (Hasan, 2011) but by latest epidemiological studies have indicated that the Arabian Gulf region has a high prevalence of MS (Bohlega *et*

al., 2013). The etiology of MS involves both genetic and environmental factors (Chen *et al.,* 2016). The environmental factors responsible for predisposition to MS remains elusive (Chen *et al.,* 2016) mainly involve viral infections, smoking, and vitamin D level, gut microbiota and obesity (Koch *et al.,* 2013). MS not considered a hereditary disease. However, genetic factors are known to contribute to the MS risk. MS has an overall familial recurrence rate of 20% (Kamm *et al.,* 2014). During the early stages of the disease, pathology dominated by focal inflammatory white matter lesions or plaques and a variable extent of axonal loss and reactive gliosis (Kamm *et al.,* 2014). In progressive disease courses, classical active white matter plaques are rare, and the pathophysiology involves diffuse grey and white matter atrophy (Lassmann *et al.,* 2012). The MS subtypes according to 2013 revisions may: (Lublin, 2014) 1. Clinically isolated syndrome(CIS) is a first symptomatic episode of CNS dysfunction due to inflammatory demyelination that could be MS but has yet to fulfil the diagnostic criteria of DIT (Miller *et al.,* 2012). 2. Radiologically isolated syndrome (RIS) has been added to the revised MS classification scheme (Katz Sand, 2015) and defined as persons with MRI findings suggestive of MS but with normal neurological findings or symptoms (Granberg *et al.,* 2013). 3. Relapsing-remitting MS(RRMS)*:* the most common form, affecting about 85% of MS patients. It marked by flare-ups of symptoms followed by periods of remission when symptoms improve or disappear (Reynolds *et al.,* 2011, Goldenberg, 2012). 4. Primary progressive MS(PPMS): affects approximately 10% of MS patients. Symptoms continue to worsen gradually from the beginning. There are no relapses or remissions, but there may be occasional plateaus (Goldenberg, 2012, Reynolds *et al.,* 2011). 5. Secondary progressive MS(SPMS): may develop in some patients with relapsing-remitting disease. The disease course continues to worsen with or without periods of remission or levelling off of symptom severity (plateaus) (Goldenberg, 2012, Reynolds *et al.,* 2011). Several immunomodulatory and immunosuppressive therapeutic agents are available for relapsing forms of MS. Disease-modifying therapies introduced in the 1990s, the beta interferons, have an established track record of efficacy and safety, although they require parenteral administration. Newer DMTs including monoclonal antibodies, such as natalizumab, and oral therapies, such as fingolimod, are shown to be highly efficacious. Satisfaction with medication can define as the patient's evaluation of the process of taking the medication, its short-term effects and the longer term outcomes associated with it. It used as an outcome in many clinical trials involving a wide variety of disease conditions such as type 2 diabetes, schizophrenia, or a migraine and in comparing for drugs with similar efficacy but different routes of administration, dose regimens or side effect profiles (Delestras *et al.,* 2013). Satisfaction is a predictor of adherence to treatment, and when patients adhere to therapy in the long-term, relapse rates can be reduced and functional, cognitive abilities and quality of life can be enhanced (Becker *et al.,* 2018).

The goals of this study were to compare Iraqi patients' treatment satisfaction with three different DMTs, administered orally, subcutaneously, and by slow infusion; namely, fingolimod, IFNβ-1b, and natalizumab, respectively, as well as to assess the individual differences among these therapies with regard to their effectiveness, convenience and global satisfaction, and to assess the role of certain predictors on treatment satisfaction.

METHODS

Subjects and measures

Subjects in this cross-sectional study selected from the multiple sclerosis Center, Baghdad teaching hospital/Medical City from November 2017 to March 2018. After approval from the college of pharmacy/ University of Baghdad committee, and Multiple Sclerosis Center in Baghdad Teaching Hospital/Medical City committee; the study was carried out on 200 subjects already diagnosed with relapsing-remitting multiple sclerosis RRMS according to the revised McDonald criteria (Polman *et al.,* 2011). Inclusion criteria include; patient aged 18 years or older, diagnosed with MS for at least one year, on the same medication for at least three months and can communicate. Exclusion criteria include pregnant or breast feeding females, patient with relapse, or patients diagnosed with another subtype of MS. Subjects were classified into 3 groups based on their treatment: Group 1 (n=70) were receiving IFNβ-1b subcutaneously; group 2 (n=60) were receiving fingolimod orally, and group 3 (n=70) were receiving natalizumab by slow infusion.

Each patient has received a complete neurological examination by a specialist neurologist, and expanded disability status scale (EDSS) (Meyer-Moock *et al.,* 2014) ratings and complete a patient-reported outcome (PRO) were measured.

Patients' satisfaction with treatment was assessed using the treatment satisfaction questionnaire for medication (TSQM-9) (Bharmal *et al.,* 2009). TSQM-9 is a psychometrically validated measure of patient satisfaction with medication which comprises three subscales medication effectiveness, convenience, and global satisfaction. The effectiveness subscale evaluates the patient's satisfaction

about the ability of the therapy to treat the condition and relieve symptoms and the length of time it takes for the medication to start working. The convenience subscale assesses the ease of planning, administration and following a schedule. The global satisfaction subscale measures the patient's confidence that the medication is a good thing and that the advantages of taking it outweigh the disadvantages. Each TSQM-9 subscale consists of three items, and each response measured on a Likert scale ranging from 1 (low) to 7 (high) then subscale scores were transformed to a range from (0 to 100), and the higher scores indicating, the greater satisfaction (Foley *et al.,* 2017).

Statistical analysis

Anderson darling test was used to asses if continuous variables follow a normal distribution if the variables follow normal distribution then mean and the standard deviation used and if did not follow normal distribution then median and interquartile range (25% to 75% percentile range) was used to present the data. Discrete variables were presented using their number and percentage; chi-square test was used to analyze the discrete variable (or Fisher exact test when chi-square was not valid. Fisher-Freeman-Halton exact test of independence used for (n *x* k) table [an extension for classical (2*x*2) Fisher exact test], if the expected frequency was less than 5%. One way ANOVA was used to analyze the differences between more than two groups. Pairwise comparisons were made using a post hoc Tukey test. Linear regression analysis was used to assess the relationship between different variables; Person's regression used if the variables follow a normal distribution, Spearman's correlation used if the variables do not follow a normal distribution. Scatter's plot was used to present the regression analysis. The negative sign of the correlation coefficient (r) indicates an inverse relationship, while, a positive sign indicates a direct relationship. SPSS ®22.0.0 (Chicago, IL) software package used for the statistical analysis, the *P* value was considered to be significant if less than 0.05.

RESULTS

The socio-demographic characteristics and TSQM-9 subscales scores for subjects participated in the study are provided in Table 1. The socio-demographic characteristics and TSQM-9 subscales scores by the type of treatment provided in Table 2.

Subjects using IFNβ-1b are older (39.4 ± 8.7 years; P=0.002) and on the treatment for a longer duration (71.8± 64.3 months; P<0.001), while they have lower EDSS score (2.5 ± 1.7; P=0.023), as compared to the other therapies. There was a statistically significant difference about all of the TSQM-9 components [effectiveness (P=0.022), convenience (P<0.001), and global satisfaction (P=0.001)], among the three study groups. Moreover, IFNβ-1b using subjects had the lowest score for all TSQM-9 subscales. There were no statistically significant differences between the remaining measured characteristics among the subjects of the study. Table 3 provides pairwise comparisons for the three studied groups regarding age, EDSS, duration of treatment and TSQM-9 scores. Regarding age, the difference was significant between IFNβ-1b and natalizumab using groups (P=0.001). While the difference in EDSS score was significant between IFNβ-1b and fingolimod using groups (P=0.025). The difference in duration of treatment was significant between IFNβ-1b and fingolimod (P<0.001), and between IFNβ-1b and natalizumab (P<0.001) using groups. The most consistent differences in TSQM-9 score were related to the convenience of the medication; the difference was significant between each pair of the studied groups (P=0.001 or more). Regarding global satisfaction, natalizumab using group has reported significantly higher satisfaction compared to both IFNβ-1b (P=002), and fingolimod (P=007) using groups.

Univariate linear regression analysis was used to assess the correlation between different predictors and the TSQM-9 scores in each of the three studied groups. Concerning IFNβ-1b using group, age was directly correlated with the global satisfaction (r=0.287; P=0.016), while EDSS was inversely correlated with both effectiveness (r=-0.367; P=0.002), and global satisfaction (r=-0.390; P=<0.001) (Table 4). For fingolimod using group, treatment duration directly correlated with the convenience (r=0261; P=0.044), and global satisfaction (r=0261; P=0.044) while EDSS was inversely correlated (r=-0.406; P=0.001) with the effectiveness subscale (Table 5). For natalizumab using group, age was inversely correlated with the global satisfaction (r=-0.336; P=0.004), while EDSS was inversely correlated with all of effectiveness (r=-0.326; P=0.006), convenience (r=-0.398; P<0.001), and global satisfaction (r=-0.425; P<0.001) subscales of TSQM-9 (Table 6).

DISCUSSION

For the 200 participants, the age of the subjects in this study was (36.4 ± 9.9) years, with disease duration (7.1 ± 5.4) years, two third of them were women (67.5%). Thus, Iraqi MS patients follow the worldwide trends regarding the onset time of disease, and the female: male ratio (Leray *et al.,* 2016).

Most of the subjects in this study reside in the middle region of Iraq (90%), while subjects reside in the south and north regions represent only small

Table 1: Socio-demographic characteristics and TSQM-9 scores for participants

Variables	Value
Age (years), mean ± SD	36.4 ± 9.9
Gender, number, %	
Female	135, 67.5%
Male	65, 32.5%
Married, number, %	134, 67%
Education (college), number, %	81, 40.5%
Zone of residence	
South regions	13, 6.5%
Middle regions	180, 90%
North regions	7, 3.5%
Smoker, number, %	25, 12.5%
Duration of MS (years), mean ± SD	7.1 ± 5.4
≥ 5 years	125, 62.5%
EDSS, mean ± SD	3.0 ± 2.1
TSQM-9 score	
Effectiveness	76.8 ± 14.6
Convenience	73.2 ± 13.1
Global satisfaction	73.7 ± 18.3

EDSS: expanded disability status scale, MS: multiple sclerosis, SD: standard deviation, TSQM-9: Treatment Satisfaction Questionnaire for Medication-9

Table 2: Socio-demographic characteristics and TSQM-9 scores for patients with their type of treatment

Variables	Interferon beta-1b	Fingolimod	Natalizumab	p-value
Age (years), mean ± SD	39.4 ± 8.7	36.2 ± 10.8	33.6 ± 9.4	0.002
Gender, number, %				
Female	43, 61.4%	38, 63.3%	54, 77.1%	0.099
Male	27, 38.6%	22, 36.7%	16, 22.9%	
Married, number, %	53, 75.7%	37, 61.7%	44, 62.9%	0.156
Education (college), number, %	30, 42.9%	23, 38.3%	28, 40.0%	0.867
Smoker, number, %	11, 15.7%	6, 10.0%	8, 11.4%	0.583
Duration of MS (years), mean ± SD	5.99± 5.36	8.12 ± 6.05	7.47 ± 4.81	0.069
≥ 5 years	36, 51.4%	42, 70%	47, 67.1%	0.057
Duration of current treatment (months), mean ± SD	71.8± 64.3	7.08 ± 4.42	19.14± 10.59	<0.001
EDSS, mean ± SD	2.5 ± 1.7	3.5 ± 2.2	3.2 ± 2.2	0.023
TSQM-9 score				
Effectiveness	74.6± 13.0	74.8 ± 15.1	80.6 ± 15.0	0.022
Convenience	65.3± 10.6	83.5 ± 8.6	72.2 ± 12.6	<0.001
Global satisfaction	69.7± 17.1	70.6 ± 19.6	80.2 ± 16.8	0.001

EDSS: Expanded Disability Status Scale, MS: multiple sclerosis, SD: standard deviation, TSQM-9: Treatment Satisfaction Questionnaire for Medication-9

proportion (6.5% and 3.5%, respectively). Generally speaking, climatic factors increase the risk for MS in populations living in areas above latitude 40°N and down latitude 40°S (Mayer, 1981). Iraq is a country located in the Middle East, at latitudes 37°.25'-29°5'. Therefore, the ease of access to the Multiple Sclerosis Center in Baghdad (in the middle of Iraq) may account for the predominance of subjects who reside in the middle region, and not due to climatic factors or latitudinal gradient. This study had shown that the mean of the EDSS of subjects having RRMS was (3.0 ± 2.1). This result is consistent with findings of a larger retrospective study carried out in the same centre, which had shown that the mean of the EDSS of Iraqi subjects having RRMS was (3.5 ± 1.69) (Mohammed *et al.,* 2018).

Subjects using IFNβ-1b therapy were older with longer duration of treatment than those on fingolimod or natalizumab therapy. Moreover, EDSS was lower in the IFNβ-1b treated group as compared to fingolimod or natalizumab treated groups. Pairwise comparison of the three study groups had shown that the difference was significant between IFNβ-1b and fingolimod treated

Table 3: Pairwise comparison of demographic and TSQM-9 scores between each pair of therapy

Variables	Interferon beta vs Fingolimod	Interferon beta vs Natalizumab	Fingolimod vs Natalizumab
Age (years)	0.143	0.001	0.272
EDSS	0.025	0.103	0.787
Duration of current treatment	<0.001	<0.001	0.181
TSQM-9 score			
Effectiveness	0.996	0.036	0.057
Convenience	<0.001	0.001	<0.001
Global satisfaction	0.952	0.002	0.007

EDSS: Expanded Disability Status Scale, TSQM-9: Treatment Satisfaction Questionnaire for Medication-9

Table 4: correlation between TSQM-9 score with various predictors for interferon beta receiving MS patients

Predictors	TSQM-9 scores					
	Effectiveness		Convenience		Global satisfaction	
	r	p-value	r	p-value	r	p-value
Age	0.107	0.380	0.083	0.494	0.287	0.016
Education	0.062	0.611	0.041	0.737	-0.077	0.525
MS duration	0.003	0.978	0.146	0.229	0.125	0.302
Treatment duration	0.003	0.978	0.146	0.229	0.125	0.302
EDSS	-0.367	0.002	-0.095	0.436	-0.390	<0.001

EDSS: Expanded disability status scale, MS: multiple sclerosis, TSQM-9: Treatment Satisfaction Questionnaire for Medication-9

groups. This may be because IFNβ-1b treated subjects had a longer duration of treatment.

This study examined treatment satisfaction in Iraqi subjects with MS across oral, injectable and infusion therapies. The three TSQM-9 components (effectiveness, convenience and global satisfaction) were found to be significantly different among the three treatment groups, and IFNβ-1b using subjects had the lowest score for all TSQM-9 components. Pairwise comparisons among the three study groups about the TSQM-9 components had shown that oral fingolimod using group had significantly higher convenience scores as compared with injectable IFNβ-1b and natalizumab using groups. These findings are augmenting the findings of other studies which had shown that orally administered DMT is more convenient to MS patients over the injectable treatments (Spessotto *et al.,* 2016, Wilson *et al.,* 2015).

The injectable, IFNβ-1b and natalizumab, were associated with lower convenience scores; this may explain by the frequent injectable doses per week (IFNβ-1b), local reactions and pain that may influence treatment satisfaction (Fernández *et al.,* 2017). Many clinical studies had shown that switching from injectable DMT to oral fingolimod was associated with improvement in patients' satisfaction regarding effectiveness, side effects and convenience, leading to better control of disease progression (Fox *et al.,* 2014, Calkwood *et al.,* 2014). Better patients' satisfaction achieved upon switching from injectable to oral therapies, had been reported in other medical illnesses such as thromboembolism prophylaxis (Peidro-Garces *et al.,* 2013), iron chelation (Osborne *et al.,* 2007), and oncology (Jensen *et al.,* 2008).

One of the main aims of the study was to assess the relative contribution of certain sociodemographic and clinical predictors on TSQM-9 components. Univariate regression analysis had been used to study the correlation between TSQM-9 components and these predictors. Factors that positively correlated with one or more of these subscales would increase the TSQM-9 score, and hence, patients' satisfaction with treatment, and vice versa.

The study had shown that EDSS negatively correlated with TSQM effectiveness and global satisfaction subscales in IFNβ-1b using group; with effectiveness subscale in fingolimod using group, and with all of the TSQM-9 components in natalizumab using group. This negative correlation between EDSS scores and TSMQ scores is consistent with the general idea that treatment satisfaction for a given treatment is highly dependent on the perception of efficacy (Turner *et al.,* 2007).

Fernandez *et al.* had reported a similar negative correlation between EDSS scores and TSQM scores with injectable DMT (Fernández *et al.,* 2017).

Age was negatively correlated with global satisfaction subscale in natalizumab using group, while it is positively correlated with the same subscale in

Table 5: Correlation between TSQM-9 score with various predictors for fingolimod receiving patients

Predictors	TSQM-9 scores					
	Effectiveness		Convenience		Global satisfaction	
	r	p-value	r	p-value	r	p-value
Age	-0.231	0.076	-0.048	0.716	0.026	0.841
Education	0.245	0.060	0.102	0.437	0.234	0.072
MS duration	-0.217	0.095	-0.206	0.115	-0.122	0.354
Treatment duration	0.196	0.133	0.261	0.044	0.265	0.041
EDSS	-0.406	0.001	-0.144	0.273	-0.163	0.212

EDSS: Expanded disability status scale, MS: multiple sclerosis, TSQM-9: Treatment Satisfaction Questionnaire for Medication-9

Table 6: Correlation between TSQM-9 score with various predictors for natalizumab receiving patients

Predictors	TSQM-9 scores					
	Effectiveness		Convenience		Global satisfaction	
	r	p-value	r	p-value	r	p-value
Age	-0.192	0.111	-0.216	0.072	-0.336	0.004
Education	0.127	0.295	0.091	0.452	0.196	0.104
MS duration	-0.117	0.335	-0.183	0.130	-0.215	0.074
Treatment duration	0.086	0.479	0.159	0.188	0.235	0.050
EDSS	-0.326	0.006	-0.398	<0.001	-0.425	<0.001

EDSS: Expanded disability status scale, MS: multiple sclerosis, TSQM-9: Treatment Satisfaction Questionnaire for Medication-9

IFNβ-1b using group. TSQM global satisfaction score is used to evaluate the general satisfaction or dissatisfaction with treatments that patients are taking. The efficacy of immunomodulatory DMTs decreases with age (Weideman *et al.,* 2017).

The positive correlation between age and global satisfaction scores in IFNβ-1b using group is unexpected but may attribute to a wrong idea that treatment with the more frequent dosing may counteract the reduced efficacy with age. Finally, duration of treatment positively correlated with convenience and global satisfaction in fingolimod using group. The mean duration of treatment of fingolimod using group was (7.08 ± 4.42 months); thus, clinical outcomes and subsequently treatment satisfaction with treatment would improve with increasing the duration of treatment.

CONCLUSION

Iraqi MS patients are more satisfied with the natalizumab than with IFNβ-1b and fingolimod. Some predictors such as age, EDSS and duration of treatment, correlate with the level of satisfaction with different treatments.

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