DOI: http://dx.doi.org/10.18502/cjn.v23i3.17601

Current Journal of Neurology

Review Paper

Curr J Neurol 2024; 23(3): 176-88

Podcast

The effect of interferon beta on quality of life in patients with multiple sclerosis: A systematic review and meta-analysis study

Received: 06 Mar. 2024
Accepted: 09 May 2024

Mohammadreza Jamshidi[1], Milad Abbasian[2], Ali Ghasemnezhad[3], Atoosa Keshavarz-Motamed[4], Zehra Batool[5], Arian Tavasol[6], Mahsa Nikfarjam[6], Mohammad Moein Ashrafi[7], Atefeh Zare-Ahmadabadi[7], Seyyed Ali Jalalian[8]

[1] Department of Anesthesiology, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran
[2] Nargund College of Physiotherapy, Rajiv Gandhi University of Health Sciences, Bangalore, India
[3] School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[4] Student Research Committee, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
[5] Dr. Panjwani Center for Molecular Medicine and Drug Research, International Center for Chemical and Biological Sciences, University of Karachi, Karachi, Pakistan
[6] Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[7] School of Medicine, Yazd Branch, Islamic Azad University, Yazd, Iran
[8] School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Keywords
Multiple Sclerosis; Interferon Beta; Quality of Life

Abstract

Background: Multiple sclerosis (MS) is one of the most common progressive neurological disorders affecting young adults. This study aimed to perform a meta-analysis on the effect of interferon beta (IFN-β) on the quality of life (QOL) of patients with MS.

Methods: Using valid keywords and searching through databases like Medlib, ScienceDirect, PubMed, etc., 10 articles published between 1999 and 2020 were collected. The inclusion criteria were developed based on clinical guidelines, focusing on studies involving adults with MS treated with IFN-β, with outcomes measuring QOL. The exclusion criteria included studies not in English, those involving pediatric populations, or those lacking a control group. In the reviewed studies, 14 scales of QOL were measured at the beginning and the end of treatment with IFN-β.

How to cite this article: Jamshidi M, Abbasian M, Ghasemnezhad A, Keshavarz-Motamed A, Batool Z, Tavasol A, et al. The effect of interferon beta on quality of life in patients with multiple sclerosis: A systematic review and meta-analysis study. Curr J Neurol 2024; 23(3): 176-88.

Corresponding Author: Ali Ghasemnezhad
Email: ghasemnezhadali@gmail.com

The data were analyzed using the random effects model meta-analysis method with R software and Stata software. Publication bias was not significant. Heterogeneity was evaluated using the Q test and the I^2 index. In heterogeneous studies, subgroup analysis and meta-regression were used for meta-analysis. The random-effect model was used for analyses with I^2 of more than 50%.

Results: A total number of 1320 people with an average age of 32.40 ± 8.77 years were included in this study. On average, there was a slight decline in energy and satisfaction with sexual function scales (SSF), while a slight improvement was seen in the other 12 scales, following the treatment with IFN-β. However, no significant changes were observed in any of the QOL scales following treatment, except for health distress (HD) ($P < 0.001$), role limitation due to physical problems (RLPP) ($P < 0.001$), and role limitation due to emotional problems (RLEP) ($P = 0.037$), all of which showed a slight but natable improvement. The physical and mental components, showed significant increases of 0.189 [95% Confidence interval (CI): 0.083, 0.295, $I^2 = 0\%$] and 0.221 (95% CI 0.119, 0.324, $I^2 = 0\%$) in the scores after using IFN-β, respectively.

Conclusion: This study's results showed that treatment with IFN-β does not negatively affect the QOL of patients with MS. Moreover, this treatment can slightly improve most QOL scales associated with the disability observed in MS.

Introduction

Multiple sclerosis (MS) stands out as the most prevalent neurological disorder among young adults, characterized by central nervous system (CNS) demyelination.[1] This condition not only brings about a decrease in the speed of transmission of nerve messages, but also encompasses a spectrum of physical and mental challenges, impaired executive function, and familial dysfunction.[2] Strikingly, MS exhibits a higher incidence in women compared to men.[3] Despite ongoing research, a definitive understanding of the environmental, immunological, and genetic variables contributing to MS development remains elusive.[4]

The underlying cause of MS involves an abnormal immune system response leading to the degeneration of the myelin sheath, though the specific triggers for this response remain unknown. A complex interplay of factors, including immune system defects, genetic predisposition, infectious diseases, mental stress, biochemical characteristics, diet, vitamin deficiency, and allergic reactions, is implicated in the onset of MS.[5]

Globally, the impact of MS is substantial, with the Multiple Sclerosis Association of America reporting approximately 2.5 million cases worldwide and 200 new cases added weekly.[6] In Iran, while accurate statistical data is lacking, an estimated 57 individuals per 100000 are believed to suffer from MS.[7] The challenges MS patients face extend beyond the physical symptoms, affecting their participation in health-related activities and diminishing their overall quality of life (QOL).[8,9]

A multitude of symptoms related to physical health (PH), such as fatigue, bladder and bowel disorders, pain, visual impairment, balance and coordination problems, spasms, and sexual issues, significantly contribute to the compromised QOL of MS patients.[10] This, in turn, affects various aspects of their lives, including physical, emotional, social, and cognitive functions, not only for the patients, but also impacting their relatives.[11] Studies consistently reveal a lower QOL in MS patients than in the general population.[12,13]

Recognizing the multidimensional nature of QOL, encompassing physical, mental, and social health, becomes crucial in the context of MS.[14] Various tools, such as the "Hamburg Quality of Life Questionnaire in Multiple Sclerosis"[15] and the "Multiple Sclerosis Quality of Life-54," derived from the SF-36 questionnaire,[12] offer increased sensitivity in measuring QOL in MS patients. Notably, gender-specific differences have been observed, with psychological disorders and limitations due to physical problems having a more significant impact on QOL in men compared to women.[16,17]

In the therapeutic landscape of MS, while there is no definitive treatment, the last few decades have witnessed the effectiveness of immunosuppressive and regulating treatments in controlling the disease. Interferon beta (IFN-β) has emerged as an early contributor to altering the disease course.[18,19] IFN-β, a cytokine belonging to the IFN type I family, operates through the heterodimeric IFNAR1/IFNAR2 receptor, modulating inflammatory responses via the JAK-STAT family of signal transducers.[20] Despite the proven efficacy of IFN-β in some studies, its impact on the QOL of MS patients remains uncertain.[21,22]

However, the frequency of administration and potential side effects associated with disease-modifying agents, including interferon, raises concerns about their impact on disability outcomes and overall QOL.[23] While significant strides have been made in understanding MS, there remains a critical research gap concerning the effects of IFN-β treatment on the QOL of MS patients.

Although IFN-β has demonstrated efficacy in influencing the course of the disease, its specific effects on patients' QOL have not been comprehensively explored. This knowledge gap is pivotal, considering the multifaceted challenges MS patients face and the potential implications of treatment on their overall well-being.

The existing literature provides a broad overview of MS, encompassing its prevalence, symptoms, and the complex interplay of factors contributing to its development. However, a focused exploration into the nuanced relationship between IFN-β treatment and QOL is conspicuously absent. Understanding the impact of IFN-β on the various dimensions of QOL, such as physical, mental, and social well-being, is crucial for tailoring interventions and improving the holistic care of MS patients.

Furthermore, the limited references to studies suggesting the beneficial effect of IFN-β on QOL underscore the necessity for a comprehensive investigation. Existing evidence, though promising, lacks the depth required to inform clinical decision-making and health policy effectively. By addressing this research gap, our study aims to contribute valuable insights to the specific ways IFN-β may influence the QOL of MS patients.

The rationale for our research lies in the potential implications for patient care and treatment strategies. MS patients often grapple with a myriad of physical and psychological challenges, impacting their daily lives and societal participation. If IFN-β treatment significantly enhances QOL, it could guide clinicians in prescribing optimal therapies and influence healthcare policies to improve the overall well-being of individuals with MS.

In conclusion, the current body of knowledge lacks a comprehensive understanding of the relationship between IFN-β treatment and QOL in MS patients. Our study seeks to bridge this gap by providing a nuanced exploration of the subject, thereby offering valuable insights that can inform clinical practice, enhance patient care, and contribute to the ongoing discourse surrounding the management of MS.

Materials and Methods

Searching strategy: The present study is a meta-analysis of the effect of IFN-β on QOL in patients with MS, conducted by reviewing documents and electronic resources available between 1999 and 2020. The information was used to find scientific journals and articles on PubMed, Medlib, ScienceDirect, ISI, Scopus, and Embase databases. A comprehensive search strategy was employed, using search strings such as 'multiple sclerosis' AND 'interferon beta' AND 'quality of life', with Boolean operators AND, OR, and NOT to refine the search. Keywords were standardized in MeSH.

Inclusion and exclusion criteria: The inclusion criteria were developed based on clinical guidelines. These criteria were validated through expert consensus and pilot testing. The inclusion criteria were developed through stating the objectives of the meta-analysis, and establishing Population, Intervention, Comparison, Outcome, and Study Design (PICOS) Criteria and the language of the studies.

The inclusion criteria of the present meta-analysis are as follows:

1. The study must include patients with MS who are being treated with IFN-β, (2) must study QOL in patients using the MSQOL-54 questionnaire, (3) and it must investigate the QOL before and after treatment with IFN-β.

The exclusion criteria are as follows:

1. Studies including patients with severe depression (confirmed by a psychologist or a neurologist) or with suicidal thoughts (Severe depression was defined using DSM-5 criteria and assessed with the Hamilton Depression Rating Scale, and suicidal thoughts were identified using the Beck Scale for Suicide Ideation.)
2. Qualitative and descriptive studies
3. Abstract articles, articles presented at conferences, review articles, systematic reviews, and meta-analyses
4. Studies published in non-English Journals.

Study selection: Two researchers examined the titles and abstracts of the articles using EndNote (X8; Clarivate, Philadelphia, PA, USA), and then, screened them according to the inclusion and exclusion criteria. Papers that met the requirements were further evaluated by reading the full text. In case of disagreement between the two researchers, the judgment was left to a third expert.

Data extraction and analysis: The homogeneity of all articles was evaluated. If there was significant heterogeneity, we performed subgroup analysis and meta-regression to examine the heterogeneity. The selected articles were thoroughly reviewed, and one of the researchers entered all the information into a form designed and prepared for data extraction. In cases of discrepancies, a data analyst helped the team. Then, the data were entered into Excel software

(Microsoft, Redmond, WA, USA). The data were transferred from Excel software to Review Manager (version 5.3; Cochrane Org., London, UK), and Stata software (version 14; StataCorp LLC, College Station, TX, USA) in the next step. The data collected in this study included the name of the author, year of publication, place of research, number of patients, average age, duration of follow-up, type and dose of prescribed interferon, type of study design, Expanded Disability Status Scale (EDSS) score, and change in health (CH), energy criteria (En), emotional well-being (EW), health distress (HD), health perception (HP), PH, role limitation due to emotional problems (RLEP), role limitation due to physical problems (RLPP), satisfaction with sexual function (SSF), sexual function (SF), social function (SOF), physical function (PF), cognitive function (CF), and bodily pain (BP) at the beginning and end of the treatment. These scales were also examined in physical component summary (PCS) and mental component summary (MCS). Patients were classified based on EDSS score changes at the beginning and end of the studies (improvement or stability and worsening).

Quality assessment: We used the Newcastle-Ottawa Scale (NOS) to assess the quality of the cohort studies in included in our analysis, focusing on important domains such as selection, comparability, and outcome. The NOS, which assigns stars to each of these domains-a higher number of stars indicating better quality-allows us to systematically evaluate the likelihood of bias in these investigations. We employed the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool for clinical trials. This technique made it possible to thoroughly assess all possible biases that may have arisen during the course of the study, including confounding, participant selection, and outcome measurement bias. We made sure that the studies that were part of our systematic review and meta-analysis were evaluated rigorously and consistently by using these well-established quality assessment methodologies.

Missing data: We thoroughly evaluated each included study to determine the degree and possible influence of missing data on the findings in order to address the missing data in those studies. We followed the original research procedures when they described missing data and employed certain imputation techniques. Furthermore, we used the Cochrane Risk of Bias (RoB) tool to evaluate the possibility of bias resulting from missing data. These measures were implemented to guarantee the stability of our analysis and to prevent the conclusions from being unnecessarily impacted by missing data.

Studies were combined according to the number of samples, mean, and standard deviation. We employed Standardized Mean Differences (SMDs) to account for variations in measurement scales across the included studies. The SMDs were calculated as the difference in means between pre-treatment and post-treatment with IFN-β, divided by the pooled standard deviation. The weight of each study was determined by its inverse variance. The heterogeneity was evaluated using the Q test and the I2 index. In cases where the results of the studies were heterogeneous, they were analyzed using a random-effect model for meta-analysis [A random-effects model was chosen instead of a fixed-effects model since significant heterogeneity ($I^2 > 50\%$) was present]. A P-value of < 0.05 was considered statistically significant. In order to investigate publication bias, we will visually inspect funnel plots and use statistical tests, such as Egger's and Begg's tests, to assess the symmetry of the data and ascertain whether unpublished studies may have an impact on our findings. A sensitivity analysis was performed to evaluate the stability of our meta-analysis results, involving the exclusion of studies with high RoB and the adjustment of key assumptions to determine the impact on the overall findings. Data analysis was performed in R software (R Foundation for Statistical Computing, Vienna, Austria), and Stata software.

Results

Study selection and characteristics: The initial search yielded 173 studies. After screening titles and abstracts, 50 studies underwent full-text review, resulting in 10 studies meeting all inclusion criteria. Review articles, conference papers, studies which reported irrelevant data, and non-English articles were excluded.

Out of the 173 studies reviewed (Figure 1), we identified 10 articles that met the inclusion criteria and were published between 1999 and 2020 (Table 1). These studies encompassed diverse designs, including 2 case-control studies, 10 case series, and 2 randomized controlled trials (RCTs), collectively involving 1773 participants. The average age of subjects was 34.8 ± 9.13 years, and 30% and 68% of participants were men and women, respectively.

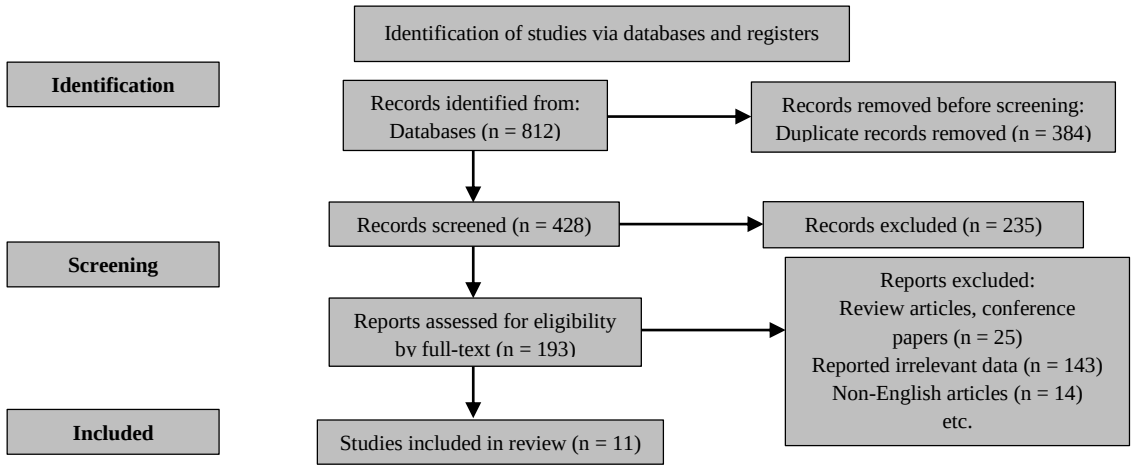

Figure 1. Study selection flowchart

In their studies, De Giglio et al.[24] and Freeman et al.[33] adopted the randomized controlled trial design, involving 46 and 346 participants, respectively. De Giglio et al. implemented IFN B 1b for 2 years,[24] while Freeman et al. employed IFN B 1b for 3 years.[33] Simone et al.[25] and Rice et al.[34] performed case-control studies. Simone et al.[25] utilized IFN-β 1a for 2 years with 41 participants, while Rice et al.[34] used IFN B 1b for 3.5 years with 54 participants. Most studies (10 out of 14) fell under the case series category, covering a range of designs. For instance, Arnoldus et al.[26] conducted a case series for over 6 months with 51 participants, using a combination of IFN-β 1a and 1b.

Study quality was evaluated using the Cochrane RoB tool, with results indicating 6 high-quality studies and 4 studies with some concerns. Detailed quality assessments are provided in tables 2 and 3.

Variability in interferon types, duration, and sample sizes

Various IFN-β types were utilized across the tudies, such as IFN-β 1a, IFN-β 1b, or a combination of both. The duration of interventions ranged from 6 months to 3 years.

The sample sizes across studies ranged from 23 participants in the study by Mokhber et al.[27] to 383 in the study by Pakdaman et al.[31] This diversity in sample sizes contributes to the generalizability of the findings, with larger samples potentially providing more robust results.

The interferon types utilized in the studies were IFN-β-1a in 8 articles, IFN-β-1b in 3 articles, and a combination of IFN-β-1a and -1b in the remaining 3 articles. The duration of the studies ranged from 6 months to 3 years. Moreover, 7 studies employed the MSQoL-54 questionnaire, while the remaining 7 used the SF-36 questionnaire. The distribution bias, assessed through the funnel diagram, appeared symmetrical (Figure 2), with a calculated P-value of 0.131.

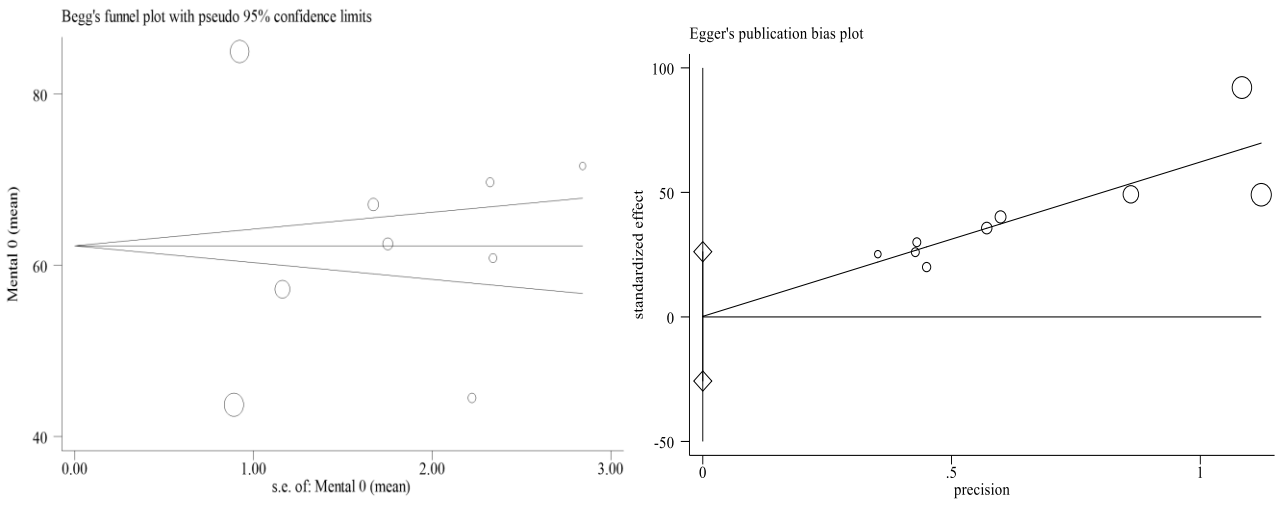

Figure 2. Publication bias diagram in the reviewed studies (The circles show the weight of the studies.)

Table 1. Attributes of the reviewed articles

References	n	Place	Age (mean ± SD)	IFNB type	EDSS	Scales	Duration	Questionnaire	Study design
Patti et al.[21]	304	Catania	-	IFN-β 1a Patients started IFNβ-1a therapy within 1 month of enrolment; after 2 years, 152 (38.5%) out of 394 were treated with Avonex (Group A); 152 (38.5%) with Rebif 44 (Group B); and 90 (23%) did not take any medication (Group C)	1.8	CH, En, EW, HD, HP, RLEP, RLPP, SF, SoF, SSF, PF, BP, CF & PCS, MCS	2 years	MSQoL-54	Prospective cohort
De Giglio et al.[24]	46	Rome	30.4 ± 7.0	IFN B 1b Women with RRMS were randomly assigned (1:1:1) to receive subcutaneous IFN-b-1a (Rebif, Merck Serono, Geneva, Switzerland) 44 mcg 3 times a week (tiw) (group 1), subcutaneous IFN-b-1a 44 mcg tiw plus ethinyl estradiol 20 mcg and desogestrel 150 mcg (Mercilon, MSD Italia SRL, Rome, Italy) (group 2) or subcutaneous IFN-b-1a 44 mcg tiw plus ethinyl estradiol 40 mcg and desogestrel 125 mcg (Gracial, Organon Italia S.p.A., Rome, Italy) (group 3)	1.7	CH, En, EW, HD, HP, PH, RLEP, RLPP, SF, SoF, SSF, CF	2 years	MSQoL-54	RCT
Simone et al.[25]	41	Bari	36.8 ± 11.5	IFN-β 1a	3	CH, En, EW, HD, HP, PH, RLEP, RLPP, SF, SoF, SSF, PF, BP & PCS, MCS	2 years	MSQoL-54	Clinical trial
Arnoldus et al.[26]	51	Amsterdam	35.1± 8.8	IFN-β 1a & 1b Of the 51 patients, 36 were treated with IFN-b-1b, consisting of a subcutaneous injection of 8 million international units on alternate days, and 15 with IFN-b-1a, which was administered by intramuscular injection of 30mg weekly.	3	CH, EW, SoF, PF, BP, MCS	6 months	SF-36	Clinical trial
Mokhber et al.[27]	60	Mashhad	29.8 ± 7.5	IFN-β 1a & 1b (Avonex, Rebif, Betaferon) Avonex was administered 30µg once per week via intramuscular injection. Rebif was administered 44µg 3 times per week via subcutaneous injection. Betaferon was administered 0.25mg every other day via subcutaneous injection.	1.5	En, EW, HD, RLEP, RLPP, SF, SoF, PF, BP & PCS, MCS	1 year	MSQoL-54	Clinical trial
Jongen et al.[28]	204	Nijmegen	-	IFN-β 1a INFb-1a (AvonexÒ) was commercially available and administered intramuscularly once a week.	2.4	PCS, MCS	2 years	MSQoL-54	Clinical trial
Vermersch et al.[29]	121	Lille	38.5 ± 9.4	IFN-β 1a IFN-b1a (Avonex1) was administered as a once-weekly intra-muscular injection of 30 mg (6.0 million units).	3.1	CH, En, RLEP, SoF, PH, BP & PCS, MCS	1 year	SF-36	Clinical trial
Abolfazli et al.[30]	77	Tehran	30.5 ± 8.9	IFN-β 1a Patients were equally distributed in either Avonex or CinnoVex groups according to the neurologist's consultation (at inclusion time, selected patients in either group did not differ in EDSS, demographics, or QOL). QOL assessment was conducted 4 times in a 12-month period, at baseline (stage 1) and at months 4 (stage 2), 8 (stage 3), and 12 (stage 4) following recruitment and by means of MSQOL54.	1.9	CH, En, EW, HD, HP, PH, RLPP, SF, SoF, SSF, PF, BP & PCS, MCS	2.5 years	MSQoL-54	Clinical trial
Pakdaman et al.[31]	383	Tehran	28.7 ± 5.4	IFN-β 1a Eligible patients received HSA-free subcutaneous IFN-β 1a IFNβ-1a (44 µg subcutaneous injection, 3 times a week) for 1 year and were prospectively followed-up at 6 and 12 months.	2.5	CH, En, EW, RLEP, RLPP, SoF, PF, BP & PCS, MCS	1 years	SF-36 & MusiQoL	Prospective cohort

Table 1. Attributes of the reviewed articles (continue)

References	n	Place	Age (mean ± SD)	IFNB type	EDSS	Scales	Duration	Questionnaire	Study design
Zecca et al.[32]	33	Lugano	43.5	IFN-β 1a Im IFNB-1a 30mcg was administered once a week by an autoinjection device (Avonex Pen™). Progressive titration with prefilled Avonex® syringes was allowed during the first 4 weeks of treatment.	2	PCS, MCS	1 year	SF-36	Clinical trial

EDSS: Expanded Disability Status Scale; RCT: Randomized Controlled Trial; RRMS: Relapsing-remitting multiple sclerosis; IFN-β: Interferon beta; PCS: Physical component summary; MCS: Mental component summary; RLEP: Role limitation due to emotional problems; RLPP: Role limitation due to physical problems; SD: Standard deviation

Table 2. Quality Assessment of Cohort Studies Using the Newcastle-Ottawa Scale (NOS)

	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Patti et al.[21]	*	*	*	*	**	*	*	*
Pakdaman et al.[31]	*	*	*	*		*	*	*

Table 3. Quality Assessment of Clinical Trial Studies Using Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I)

References	Bias due to confounding	Bias in selection of participants in the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Abolfazli et al.[30]	Moderate	Low	Low	Low	Moderate	NI	Low
Arnoldus et al.[26]	Serious	Low	Low	Low	Moderate	NI	Low
De Giglio et al.[24]	Low	Low	Low	Low	Moderate	Low	Low
Zecca et al.[32]	Moderate	NI	Low	Low	Moderate	NI	Low
Jongen et al.[28]	NI	Low	Low	Low	Low	NI	Low
Mokhber et al.[27]	Low	Low	Low	Low	Low	Low	Low
Simone et al.[25]	Low	Low	Low	Low	Low	NI	Low
Vermersch et al.[29]	Low	Low	Low	Low	Moderate	NI	Low

Comprehensive insights from QOL scales

In our meta-analysis, the SMDs of each QOL questionnaire parameter were calculated using the data related to before and after IFN-β medication use. Additionally, table 4 provides detailed insights into the initial and final average scores for various QOL scales, contributing to a more nuanced understanding of the outcomes. Due to differences in the questionnaires used in the included studies, the results are presented in 3 categories: MSQOL-54, SF-36 questionnaire, and overall results, which included both questionnaires.

The pooled results of the MSQOL-54 showed that there was a significant increase in the following scales after using IFN-β: CH [SMD 95% Confidence interval (CI) = 0.509 (0.131, 0.886), I^2 = 81.6%], EW [SMD (95% CI) = 0.219 (0.051, 0.387), I^2=21.9%], HD [SMD (95% CI) = 0.356 (0.195, 0.517), I^2 = 14.9%], RLEP [SMD (95% CI) = 0.299 (0.068, 0.530), I^2 = 56.6%], and RLPP [SMD (95% CI) = 0.275 (0.129, 0.421), I^2 = 0%].

Moreover, the overall physical and mental components of this questionnaire were improved significantly after IFN-β medication use.

However, no significant change was observed in any of the scales of the SF-36 questionnaire. This can be due to the small number of studies included in this questionnaire.

In the overall part of the analysis, participants exhibited a statistically significant increase in "Role Limitation due to Emotional Problems," with a mean difference of 0.193 (95% CI: 0.012, 0.373), a P-value of 0.037, and an I-squared of 52.4%. "Role Limitation due to Physical Problems" showed a significant increase of 0.244 (95% CI: 0.124, 0.365) with an I-squared of 0%. The "Health Distress" scale demonstrated a remarkable increase of 0.356 (95% CI: 0.195, 0.517; I^2 = 14.9%) (P < 0.001).

Despite statistical significance in some scales, the clinical implications of these changes require further discussion. For instance, the observed increase in the "health distress" scale may suggest a paradoxical perception of participants' health status. On the other hand, the lack of statistical significance in specific scales, such as "satisfaction with sexual function," prompts consideration of potential factors influencing these outcomes. Notably, the scores of the summary components, including the physical and mental components, showed significant increases of 0.189 (95% CI: 0.083, 0.295; I^2 = 0%) and 0.221 (95% CI: 0.119, 0.324; I^2 = 0%) after using IFN-β, respectively (Figures 3 and 4).

Subsequent analyses revealed a decrease in the energy and SSF, although none of these changes were statistically significant.

In addition, as shown in figure 2, the analysis for publication bias using Egger's and Begg's tests showed that the publication bias is not significant (P = 0.404).

Table 4. Evaluating the areas of quality of life (QOL) at the beginning (Q0) and the end (Q1) of the studies

Scales	MSQOL-54	P	SF-36	P	Overall	P
CH	0.509 [0.131, 0.886]	0.008	0.038 [-0.173, 0.250]	0.723	0.273 [-0.051, 0.596]	0.098
Energy	-0.070 [-0.435, 0.295]	0.707	0.004 [-0.207, 0.216]	0.968	-0.027 [-0.239, 0.184]	0.800
EW	0.219 [0.051, 0.387]	0.011	-0.037 [-0.289, 0.215]	0.772	0.145 [-0.034, 0.323]	0.112
HD	0.356 [0.195, 0.517]	< 0.001	-	-	0.356 [0.195, 0.517]	< 0.001
HP	0.427 [-0.500, 1.353]	0.367	0.098 [-0.154, 0.350]	0.445	0.335 [-0.300, 0.971]	0.301
RLEP	0.299 [0.068, 0.530]	0.011	0.010 [-0.202, 0.221]	0.928	0.193 [0.012, 0.373]	0.037
RLPP	0.275 [0.129, 0.421]	< 0.001	0.188 [-0.049, 0.425]	0.120	0.244 [0.124, 0.365]	< 0.001
Sexual function	0.040 [-0.135, 0.216]	0.652	-	-	0.040 [-0.135, 0.216]	0.652
Social function	0.131 [-0.015, 0.276]	0.078	-0.072 [-0.283, 0.140]	0.507	0.066 [-0.540, 0.186]	0.283
SSF	-0.075 [-0.436, 0.286]	0.684	-	-	-0.075 [-0.436, 0.286]	0.684
Physical function	0.112 [-0.034, 0.257]	0.132	-0.067 [-0.278, 0.145]	0.535	0.054 [-0.065, 0.174]	0.373
Cognitive function	0.239 [-0.066, 0.544]	0.125	-	-	0.239 [-0.066, 0.544]	0.125
BP	0.101 [-0.045, 0.247]	0.175	0.079 [-0.142, 0.300]	0.483	0.093 [-0.027, 0.213]	0.129
Summary components						
Physical	0.233 [0.116, 0.350]	< 0.001	-0.015 [-0.267, 0.237]	0.905	0.189 [0.083, 0.295]	< 0.001
Mental	0.254 [0.137, 0.370]	< 0.001	0.115 [-0.096, 0.324]	0.285	0.221 [0.119, 0.324]	< 0.001

RLEP: Role limitation due to emotional problems; RLPP: Role limitation due to physical problems; CH: Change in health; EW: Emotional well-being; HD: Health distress; HP: Health Perception; SSF: Satisfaction with sexual function; BP: Bodily pain

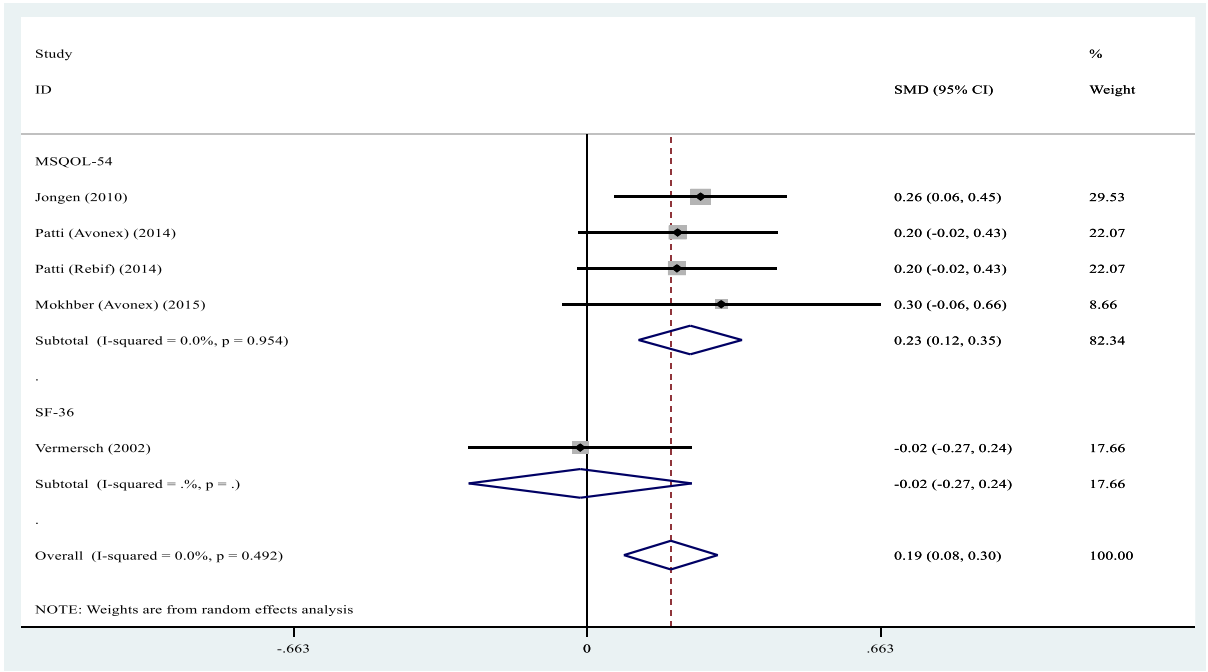

Figure 3. The forest plot of the standardized mean difference of the physical component of quality of life (QOL) before and after using beta interferon as assessed by the MSQOL-54 and SF-36 questionnaires

Furthermore, the results of quality assessment of the included studies are presented in tables 2 and 3.

Discussion

In the examination of 14 selected studies encompassing diverse designs and 1773 participants, the study revealed a comprehensive overview of the impact of IFN-β on QOL in MS patients. The average age of participants was 34.8 ± 9.13 years, and most studies fell under the case series category.

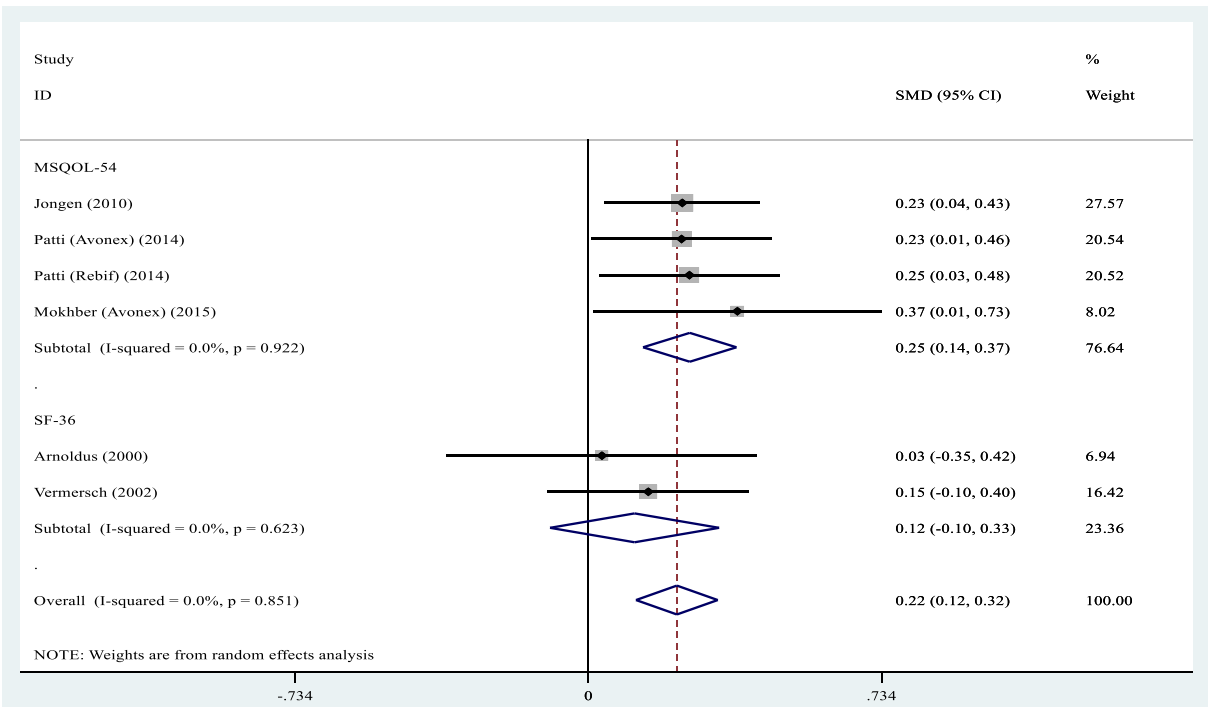

Figure 4. The forest plot of the standardized mean difference of the mental component of quality of life (QOL) before and after using beta interferon as assessed by the MSQOL-54 and SF-36 questionnaires

Variability in IFN-β types, duration, and sample sizes was evident, contributing to the generalizability of findings. While specific QOL scales exhibited statistically significant changes, such as an increase in the "Health Distress," "RLEP," and "RLPP" scales, others displayed non-significant alterations, prompting considerations of clinical relevance. Stability in the physical and mental aspects of QOL over time was noted, as indicated by significant changes in the PCS and MCS.

QOL remains a pivotal aspect of health, particularly for patients with MS. Existing literature consistently underscores the profound impact of MS on HRQOL, surpassing the effects observed in other chronic diseases.[23-26] Disparities between MS patients and their healthy counterparts across various QOL parameters indicate a substantial decline in QOL, even among those in the early stages of the disease.[13,35] Notably, impaired physical functions and social limitations emerge as primary contributors to the diminished QOL, with a significant proportion of patients facing challenges in performing their personal and professional responsibilities as the disease progresses.[26]

Several studies, including a comprehensive examination in Canada, have illustrated the pervasive influence of MS on QOL.[35] It is imperative to recognize the far-reaching consequences, wherein nearly half of MS patients experience limitations in fulfilling personal and professional obligations within a decade of disease onset.[26] QOL assessments, integral to evaluating the effectiveness of diverse treatment methods,[23,36-38] demonstrate the potential of disease-modifying treatments, such as IFN-β, to positively impact various aspects of patients' QOL.[26,29,39-41]

The significant heterogeneity among the reviewed studies prompted using a random-effect model. Factors contributing to this heterogeneity encompass diverse study methodologies, variations in QOL measurement tools, disparate observation periods, divergent clinical characteristics of study subjects, differences in healthcare systems, and the utilization of different types of IFN-β.

In addressing this heterogeneity, our meta-analysis sought to consolidate findings from prior studies, specifically exploring the impact of IFN-β on the QOL of MS patients. Contrary to concerns, the meta-analysis reveals that IFN-β treatment does not adversely affect the QOL of MS patients. IFN-β treatment positively influences multiple QOL scales, with significant effects observed in CH, HD, PH, RLEP, RLPP, SF, CF, and BP, with HD, RLEP, and RLPP exhibiting statistically significant changes. Noteworthy improvements are also evident in PCS and MCS.

These findings align with that of numerous studies in the field.[24,27,29,34] For instance, studies by Putzki et al.,[42] Jongen et al.,[28] Bermel et al.,[43] and Freeman et al.[33] consistently underscore the positive impact of IFN-β treatment on disease regression and enhanced QOL, thus supporting our meta-analysis results.[28,42,43] However, beyond the statistical significance lies the imperative need for a comprehensive clinical interpretation of these findings. The minor positive effects of IFN-β on QOL invite reflection on the multifaceted nature of MS and the intricate interplay between treatment, symptomatology, and patients' lived experiences. This underscores the need for an in-depth exploration of the reasons underlying the observed outcomes and the implications of these findings for clinical practice.

While the disease-modifying therapies (DMTs) of IFN β-1b and IFN β-1a have gained approval for treating relapsing-remitting MS, the precise mechanisms underlying the therapeutic efficacy of IFN-β in individuals with MS remain intricate and not fully elucidated. Our study sought to unravel the nuanced impact of IFN-β on multiple facets of the disease, moving beyond a mere summarization of findings to a critical analysis of the immunological processes involved.

IFN-β operates at the intersection of complex immune pathways, orchestrating a delicate balance between Th1/Th17 and Th2 responses. Within the intricate milieu of the CNS, IFN-β induces an anti-inflammatory shift in the T helper two response, contributing to the overall modulation of immune responses.[44] The observed decline in dendritic cells and the downregulation of antigen presentation by microglial cells and monocytes in the CNS and peripheral blood underscore the profound immunomodulatory effects of IFN-β.[45]

Crucially, the treatment with IFN-β extends its influence to regulatory T cells, manipulating their subpopulations. This includes an increase in naive CD4+ regulatory T cells, a decline in memory regulatory T cells, and the restoration of CD4 regulatory T-cell function. Such immunological nuances are pivotal in preserving immunological self-tolerance by regulatory T cells. Furthermore, IFN-β's upregulation of interleukin-10 (IL-10), an anti-inflammatory and tolerogenic cytokine, introduces an additional layer of complexity to its

immunomodulatory effects, decreasing the risk of autoimmune diseases.[20,46]

However, the beneficial effects of IFN-β extend beyond its immunomodulatory prowess. IFN-β emerges as a multifaceted therapeutic agent, demonstrating its potential to prevent MS attacks, ameliorate patients' physical condition, and enhance their overall QOL. Notably, cognitive improvements induced by IFN-β treatment directly impact patients' QOL and may alter the disease trajectory.

Moreover, the systemic impact of IFN-β on the immune system is not confined to its anti-inflammatory effects; it potentially contributes to a holistic improvement in overall patient health.[47] This broader perspective underscores the interconnectedness of immunological modulation and its downstream implications for the well-being of individuals with MS.

The impact of immunological therapy on QOL in MS patients is a multifaceted domain marked by varied outcomes. The study by Simone et al. notably highlighted the adverse effect of IFN-β on the QOL, particularly affecting the psychological dimension while showing a minor adverse impact on clinical disability.[25] Discrepancies in study outcomes prompt a nuanced exploration, with factors such as specific IFN-β treatment variations (dosage, duration, needle intolerance, fatigue, patient adherence, satisfaction with treatment, and side effects) potentially contributing to these differences.[48]

In our study, although statistical significance was not achieved, we observed the negative effect of IFN-β on various areas, including EN and SSF.[27] It is imperative to acknowledge that each subscale may or may not align with the combined improvement, and our findings echo the broader literature on the intricate interplay of IFN-β on different aspects of QOL.[27] The present study aligns with previous research, demonstrating a more apparent positive effect of IFN-β on MCS compared to PCS, contradicting the findings of Rice et al.[34] and Jongen et al.,[28] but consistent with the results of Arroyo et al.[49] and Patti et al.[21]

Mental health disorders, including depression, are prevalent in MS patients, potentially exerting a negative impact on their QOL. The diagnosis of a chronic disease with an unpredictable course, coupled with brain lesions and corticosteroid treatment side effects, may contribute to these mental health challenges.[50]

The increase in the CH scale following IFN-β treatment is noteworthy, suggesting a potential dual effect. Firstly, the relative stabilization of the disease with the initiation of IFN-β treatment may contribute to this observed improvement. Secondly, the mental health benefits stemming from increased care and the introduction of medication may collectively contribute to enhancing patients' perceived QOL.

While IFN-β treatment may enhance efficacy for patients, its potential negative impact on QOL due to serious side effects is a critical consideration.[25,29] Although our study did not directly investigate this relationship, Arnoldus et al. found that patients with more side effects had significantly worse results in several QOL scales after a 6-month follow-up.[26] Studies consistently demonstrate a correlation between disability, assessed by the EDSS, and QOL in MS patients.

Limitations: Acknowledging the inherent limitations and potential biases associated with the diverse study designs is crucial. Firstly, the variability in sample sizes across studies, ranging from 23 to 383 participants, introduces a potential source of bias. Studies with smaller sample sizes may have increased susceptibility to random variations, impacting the robustness and generalizability of their findings. Additionally, the heterogeneity in the duration of interventions, from 6 months to 3 years, poses a challenge in directly comparing outcomes, potentially influencing the observed effects of IFN-β treatment. One notable constraint is the potential influence of response shift on longitudinal studies, wherein changes in individuals' perceptions of their QOL over time could introduce bias, potentially leading to an underestimation of treatment effectiveness.

This phenomenon underscores the complexity of assessing the long-term impact of IFN-β treatments on MS patients' QOL. Additionally, the diversity in the selection of measures across studies evaluating the effects of IFN-β on QOL introduces challenges in comparative analyses due to the mixed results obtained. The varied nature of these measures, coupled with limited understanding regarding their sensitivity and responsiveness, underscores the need for future research to adopt standardized, MS-specific measures that offer heightened sensitivity. This step is crucial for enhancing the comparability of studies and improving the precision of QOL assessments. Moreover, the current research acknowledges the necessity of investigating the

impact of IFN-β side effects on patient's QOL, which warrants a thorough exploration to ensure more robust and reliable conclusions. Furthermore, using different questionnaires, such as MSQoL-54 and SF-36, introduces a degree of measurement variability that could affect the consistency of results. Finally, the geographic concentration raises concerns about the generalizability of the findings to a more diverse and global population of individuals with MS.

Addressing these limitations would significantly contribute to refining the validity and generalizability of the study's findings. Despite these constraints, the study substantially contributes to the existing literature on the subject. However, a more comprehensive comparison and synthesis of findings with previous research would fortify the overall argument. The discussion falls short in thoroughly exploring the similarities and differences between the current study and prior investigations, hindering a deeper understanding of the nuanced aspects of IFN-β treatment impact on MS patients' QOL. Furthermore, the conclusion would benefit from incorporating suggestions for future research directions and potential areas of investigation. Offering recommendations for further studies or identifying gaps in current knowledge would impart a more forward-looking dimension to the conclusion, thereby enhancing the overall strength of the paper.

Conclusion

In conclusion, this comprehensive meta-analysis examined 14 studies spanning diverse designs, encompassing case-control studies, case series studies, and RCTs, with a collective participation of 1773 individuals. The research covered a significant period from 1999 to 2020. It explored the impact of various forms of IFN-β treatments on the QOL of MS patients. The variability in IFN-β types, intervention durations, and sample sizes contributed to the generalizability of findings, revealing statistically significant improvements in specific QOL scales. Longitudinal analyses indicated notable increases in RLPP, RLEP, and HD. The study highlighted the progress in the physical and mental aspects of QOL. Moreover, an in-depth exploration of the impact of disability status underscored the clinical relevance of maintaining or improving the disability status. While acknowledging limitations, such as response shift and varied QOL measures, this study provides valuable insights, emphasizing the need for standardized measures and future investigations into the impact of IFN-β side effects.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

We would like to thank our colleagues and mentors for their encouragement and constructive feedback during this research. There was no funding source for this research. The authors report no conflict of interest.

References

1. Fletcher SG, Castro-Borrero W, Remington G, Treadaway K, Lemack GE, Frohman EM. Sexual dysfunction in patients with multiple sclerosis: A multidisciplinary approach to evaluation and management. Nat Clin Pract Urol 2009; 6(2): 96-107.
2. Mahmoodi GH, Nasiri E, Niaz Azari K. Evaluating mental (Psychological) health in MS patients from Mozandran Province in 1386 (2007). J Mazandaran Univ Med Sci 2009; 18(68): 70-3.
3. World Health Organization and Multiple Sclerosis International Federation. Atlas: multiple sclerosis resources in the world 2008. Geneva, Switzerland: World Health Organization; 2008.
4. Rudick RA, Miller D, Clough JD, Gragg LA, Farmer RG. Quality of life in multiple sclerosis. Comparison with inflammatory bowel disease and rheumatoid arthritis. Arch Neurol 1992; 49(12): 1237-42.
5. Pakniya N, Bahmani B, Dadkhah A, Azimian M, Naghiyaee M, MasudiSani R. Effectiveness of cognitive existential approach on decreasing demoralization in women with multiple sclerosis. Iranian Rehabilitation Journal 2015; 13(4): 28-33. [In Persian].
6. Abedini M, Paksersht M, Rafiei A, Valadan R, Amjadi O, Khajavi R, et al. Demographic and clinical characteristics of multiple sclerosis. J Mazandaran Univ Med Sci 2016; 25(132): 13-22. [In Persian].
7. Morgante L. Hope in multiple sclerosis: A nursing perspective. Int J MS Care 2000; 2(2): 9-15.
8. Fischer JS, LaRocca NG, Miller DM, Ritvo PG, Andrews H, Paty D. Recent developments in the assessment of quality of life in multiple sclerosis (MS). Mult Scler 1999; 5(4): 251-9.
9. Motl R, Mcauley E, Snook E. Physical activity and quality of life in multiple sclerosis: possible roles of social support, self-efficacy, and functional limitations. Rehabilitation Psychology 2007; 52: 143-51.
10. Janssens AC, van Doorn PA, de Boer JB, Kalkers NF, van der Meche FG, Passchier J, et al. Anxiety and depression influence the relation between disability status and quality of life in multiple sclerosis. Mult Scler 2003; 9(4): 397-403.
11. Bonomi AE, Patrick DL, Bushnell DM, Martin M. Validation of the United States' version of the World Health Organization Quality of Life (WHOQOL) instrument. J Clin Epidemiol 2000; 53(1): 1-12.
12. Idiman E, Uzunel F, Ozakbas S, Yozbatiran N, Oguz M, Callioglu B, et al. Cross-cultural adaptation and validation of multiple sclerosis quality of life questionnaire (MSQOL-54) in a Turkish multiple sclerosis sample. J Neurol Sci 2006; 240(1-2): 77-80.
13. Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW. A health-related quality of life measure for multiple sclerosis. Qual Life Res 1995; 4(3): 187-206.
14. Gold SM, Heesen C, Schulz H, Guder U, Monch A, Gbadamosi J, et al. Disease specific quality of life instruments in

multiple sclerosis: validation of the Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS). Mult Scler 2001; 7(2): 119-30.
15. Miller A, Dishon S. Health-related quality of life in multiple sclerosis: The impact of disability, gender and employment status. Qual Life Res 2006; 15(2): 259-71.
16. Khodaveisi M, Rahmati M, Falahinia G, Karami M, Molavi Vardanjani M. The Effect of Orem's Self Care Model on physical quality of life in patients with multiple sclerosis. Scientific Journal of Nursing, Midwifery and Paramedical Faculty 2018; 3(4): 24-35. [In Persian].
17. Casetta I, Riise T, Wamme NM, Economou NT, De Gennaro R, Fazio P, et al. Gender differences in health-related quality of life in multiple sclerosis. Mult Scler 2009; 15(11): 1339-46.
18. Javed A, Reder AT. Therapeutic role of beta-interferons in multiple sclerosis. Pharmacol Ther 2006; 110(1): 35-56.
19. Rudick RA, Goelz SE. Beta-interferon for multiple sclerosis. Exp Cell Res 2011; 317(9): 1301-11.
20. Cohan SL, Hendin BA, Reder AT, Smoot K, Avila R, Mendoza JP, et al. Interferons and multiple sclerosis: lessons from 25 years of clinical and real-world experience with intramuscular interferon beta-1a (Avonex). CNS Drugs 2021; 35(7): 743-67.
21. Patti F, Pappalardo A, Montanari E, Pesci I, Barletta V, Pozzilli C. Interferon-beta-1a treatment has a positive effect on quality of life of relapsing-remitting multiple sclerosis: results from a longitudinal study. J Neurol Sci 2014; 337(1-2): 180-5.
22. Goodin DS, Traboulsee A, Knappertz V, Reder AT, Li D, Langdon D, et al. Relationship between early clinical characteristics and long term disability outcomes: 16 year cohort study (follow-up) of the pivotal interferon beta-1b trial in multiple sclerosis. J Neurol Neurosurg Psychiatry 2012; 83(3): 282-7.
23. Nortvedt MW, Riise T, Myhr KM, Nyland HI. Quality of life in multiple sclerosis: measuring the disease effects more broadly. Neurology 1999; 53(5): 1098-103.
24. De Giglio L, Marinelli F, Barletta VT, Pagano VA, De Angelis F, Fanelli F, et al. Effect on cognition of estroprogestins combined with interferon beta in multiple sclerosis: Analysis of secondary outcomes from a randomised controlled trial. CNS Drugs 2017; 31(2): 161-8.
25. Simone IL, Ceccarelli A, Tortorella C, Bellacosa A, Pellegrini F, Plasmati I, et al. Influence of interferon beta treatment on quality of life in multiple sclerosis patients. Health Qual Life Outcomes 2006; 4: 96.
26. Arnoldus JH, Killestein J, Pfennings LE, Jelles B, Uitdehaag BM, Polman CH. Quality of life during the first 6 months of interferon-beta treatment in patients with MS. Mult Scler 2000; 6(5): 338-42.
27. Mokhber N, Azarpazhooh A, Orouji E, Khorram B, Modares GM, Kakhi S, et al. Therapeutic effect of Avonex, Rebif and Betaferon on quality of life in multiple sclerosis. Psychiatry Clin Neurosci 2015; 69(10): 649-57.
28. Jongen PJ, Sindic C, Carton H, Zwanikken C, Lemmens W, Borm G. Improvement of health-related quality of life in relapsing remitting multiple sclerosis patients after 2 years of treatment with intramuscular interferon-beta-1a. J Neurol 2010; 257(4): 584-9.
29. Vermersch P, de Seze J, Delisse B, Lemaire S, Stojkovic T. Quality of life in multiple sclerosis: influence of interferon-beta1 a (Avonex) treatment. Mult Scler 2002; 8(5): 377-81.
30. Abolfazli R, Hosseini A, Gholami K, Javadi MR, Torkamandi H, Emami S. Quality of life assessment in patients with multiple sclerosis receiving interferon beta-1a: A comparative longitudinal study of Avonex and Its Biosimilar CinnoVex. ISRN Neurol 2012; 2012: 786526.
31. Pakdaman H, Amini HA, Gharagozli K, Abbasi M, Tabassi A, Ashrafi F, et al. Health-related quality of life in patients with relapsing-remitting multiple sclerosis treated with subcutaneous interferon beta-1a in Iran. Int J Neurosci 2017; 127(6): 501-7.
32. Zecca C, Pavelek Z, Prikrylova K, Ghielmetti M, Beeler A, Gobbi C. Tolerability, treatment satisfaction and quality of life outcomes in stable multiple sclerosis patients switched from injectable therapies to auto injected intramuscular interferon beta 1a: The SFERA study. Mult Scler Relat Disord 2019; 30: 104-9.
33. Freeman JA, Thompson AJ, Fitzpatrick R, Hutchinson M, Miltenburger C, Beckmann K, et al. Interferon-beta1b in the treatment of secondary progressive MS: impact on quality of life. Neurology 2001; 57(10): 1870-5.
34. Rice GP, Oger J, Duquette P, Francis GS, Belanger M, Laplante S, et al. Treatment with interferon beta-1b improves quality of life in multiple sclerosis. Can J Neurol Sci 1999; 26(4): 276-82.
35. Burden of illness of multiple sclerosis: Part II: Quality of life. The Canadian Burden of Illness Study Group. Can J Neurol Sci 1998; 25(1): 31-8.
36. Benedict RH, Wahlig E, Bakshi R, Fishman I, Munschauer F, Zivadinov R, et al. Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. J Neurol Sci 2005; 231(1-2): 29-34.
37. Zivadinov R, Zorzon M, Tommasi MA, Nasuelli D, Bernardi M, Monti-Bragadin L, et al. A longitudinal study of quality of life and side effects in patients with multiple sclerosis treated with interferon beta-1a. J Neurol Sci 2003; 216(1): 113-8.
38. Tepavcevic DK, Pekmezovic T, Drulovic J. Quality of life assessment in patients with multiple sclerosis. Vojnosanit Pregl 2009; 66(8): 645-50. [In Serbian].
39. Rudick RA, Miller DM. Health-related quality of life in multiple sclerosis: Current evidence, measurement and effects of disease severity and treatment. CNS Drugs 2008; 22(10): 827-39.
40. Cohen JA, Cutter GR, Fischer JS, Goodman AD, Heidenreich FR, Kooijmans MF, et al. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. Neurology 2002; 59(5): 679-87.
41. Lily O, McFadden E, Hensor E, Johnson M, Ford H. Disease-specific quality of life in multiple sclerosis: the effect of disease modifying treatment. Mult Scler 2006; 12(6): 808-13.
42. Putzki N, Fischer J, Gottwald K, Reifschneider G, Ries S, Siever A, et al. Quality of life in 1000 patients with early relapsing-remitting multiple sclerosis. Eur J Neurol 2009; 16(6): 713-20.
43. Bermel RA, Weinstock-Guttman B, Bourdette D, Foulds P, You X, Rudick RA. Intramuscular interferon beta-1a therapy in patients with relapsing-remitting multiple sclerosis: A 15-year follow-up study. Mult Scler 2010; 16(5): 588-96.
44. Filipi M, Jack S. Interferons in the Treatment of Multiple Sclerosis: A Clinical Efficacy, Safety, and Tolerability Update. Int J MS Care 2020; 22(4): 165-72.
45. Rommer PS, Milo R, Han MH, Satyanarayan S, Sellner J, Hauer L, et al. Immunological aspects of approved MS therapeutics. Front Immunol 2019; 10: 1564.
46. Jakimovski D, Kolb C, Ramanathan M, Zivadinov R, Weinstock-Guttman B. Interferon beta for multiple sclerosis. Cold Spring Harb Perspect Med 2018; 8(11).
47. Mokhber N, Azarpazhooh A, Orouji E, Rao SM, Khorram B, Sahraian MA, et al. Cognitive dysfunction in patients with multiple sclerosis treated with different types of interferon beta: A randomized clinical trial. J Neurol Sci 2014; 342(1-2): 16-20.
48. Centonze D, Fantozzi R, Buttari F, Grimaldi LME, Totaro R, Corea F, et al. Multicenter interventional phase iv study for the assessment of the effects on patient's satisfaction of peg IFN Beta-1a (Pre-filled Pen) in subjects with relapsing-remitting multiple sclerosis unsatisfied with other injectable subcutaneous interferons (PLATINUM Study). Front Neurol 2021; 12: 637615.
49. Arroyo GR, Kita M, Crayton H, Havrdova E, Margolin DH, Lake SL, et al. Alemtuzumab improves quality-of-life outcomes compared with subcutaneous interferon beta-1a in patients with active relapsing-remitting multiple sclerosis. Mult Scler 2017; 23(10): 1367-76.
50. Rodgers J, Bland R. Psychiatric manifestations of multiple sclerosis: A review. Can J Psychiatry 1996; 41(7): 441-5.