Adherence to interferon β treatment in Kosovan multiple sclerosis registry

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ABSTRACT

Because of side effects, adherence to the treatment with β interferons in multiple sclerosis (MS) is low, leading to decreased treatment efficacy. This can be challenging, especially in healthcare systems where these medications are the only therapeutic option for the treatment of MS. The number of missed doses was calculated as a difference between the number of doses a patient had to withdraw from the treatment start to the cut-off date and the real number of doses taken from the MS unit. Missed doses were compared to gender, age, time since the diagnosis, time from the diagnosis to the treatment start, clinical type of MS, expanded disability status scale (EDSS), and duration of the treatment. Results showed that the adherence rate during the follow-up period was 73.8%. Patients above 40 years of age (P<0.005), higher EDSS (P<0.001), longer duration of the disease (P<0.001), longer waiting time from the diagnosis to the treatment initiation (P<0.001), and longer time on interferons (P<0.001) had lower adherence rates to the treatment. In conclusion, the findings were in correlation with studies that have used similar criteria for the determination of adherence and supported reports that adherence rate decreases with time and poses a challenge to the overall efficacy of the treatment.

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Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system, which is thought to be primarily an inflammatory disorder, followed by neurodegeneration in later stages. Long-term immunomodulatory treatment of the disease started in 1993 with interferon β-1b, soon followed by glatiramer acetate.[1] Because of political instability, subsequent war in 1998-99, and societal transition during the first decade of this century that disabled government policies and investment in high-cost medications, Kosovan patients with MS only after 2008 were able to receive treatment, in that time, only with interferon β-1b.

Still, there were no sufficient doses for all newly diagnosed patients; a limited number of only 80 doses were available until 2020. For the last four years, interferon β-1b and 1a have been available for all newly diagnosed patients. Limited doses of ocrelizumab and fingolimod can be used for patients judged to have an aggressive/active form of the disease, for switching in cases deemed to be nonresponsive to or not effective to the treatment with interferons, and for primary progressive MS (PPMS) patients in case of ocrelizumab.

Interferon β is available only in subcutaneous form. In-

jectables are often unpleasant for patients, and they can have different cutaneous or systemic side effects, which can lead to discontinuation and lower adherence rates to the treatment. Cutaneous side effects usually appear within the first months of treatment and over time progression to lipoatrophy and skin necrosis can happen.[2] Most common side effects due to cytokine release include fever, fatigue, muscle and joint aches, and headaches.[3]

The World Health Organization defines adherence to long-term therapy as "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a healthcare provider.[4] Equally, the International Society for Pharmacoeconomics and Outcomes Research defines adherence as the extent to which a patient acts in accordance with the prescribed interval and dose and dosing regimen.[5]

Adherence to the treatment with injectables is a challenge, especially in an environment where this type of treatment is the only one available for therapy. Many international reviews have highlighted this problem and estimates of adherence vary between different studies and locations, from around 40 to 88%.[6-11] Alcohol dependence, perceived cognitive difficulties, longer disease duration, mild disability status, and high education are among the factors that are associated with non-adherence.[12,13] Perceived loss of efficacy, adverse effects, problems with the injection device, and dosing frequency play also a role in adherence to the treatment.[14,15]

This study aims to present results from the Kosovan registry of multiple sclerosis regarding adherence to the injectable interferon β-1a and 1b treatment and to identify clinical features relevant to non-adherence.

Materials and Methods

An observational retrospective study was conducted in treatment-naïve patients from 2008 (when the first doses of interferon β-1b were made available to MS patients in Kosovo) until March 31, 2023. All patients were not on any other immunomodulatory treatment before interferon. MS unit within the Neurology Clinic of the University Clinical Centre of Kosovo (UCCK) is the focal point of referral, diagnosis, and treatment decisions in Kosovo, where also the distribution of interferon injectables is being made.

Each patient withdraws a box of medication from the unit which contains the dosage needed and sufficient for a month. A box of interferon β-1a contains 12 pre-prepared injections, while a box of interferon β-1b contains a dose sufficient for 15 monthly injections. We have calculated the total months of each patient on medication since the date of treatment initiation – it was equal to the total number of boxes that each patient had to take from our unit. This was named "Ideal Adherence (IA)".

Then, we extracted data from the National Registry about the number of boxes withdrawn from each patient, which we named "Real Adherence (RA)". The difference between ideal and real adherence (IA – RA) meant the number of boxes not taken within the observational period. That was equal to the number of missed doses during the treatment timeline.

The variables used to correlate the number of missed doses were gender, age, time since the diagnosis, time from the diagnosis to the treatment start, clinical type of MS, EDSS, and duration of the treatment.

Statistical analysis

The data with a normal distribution were presented as mean ± standard deviation, while data that did not follow a normal distribution were presented as median and interquartile range. Nonparametric variables were compared using the Mann-Whitney U test for binary variables and the Kruskal-Wallis test for ordinary variables. The correlation between age and EDSS with missed doses was assessed using Pearson's correlation coefficient. Significance was determined with a P-value below 0.05. Statistical analyses were conducted using SPSS version 26.

Results

Patients enrolled are from the Kosovan National Registry of people with multiple sclerosis, diagnosed and followed up in the Neurology Clinic of the UCCK. From the total number of 560 patients with MS registered in the National Registry, 410 of them were assigned to interferon β-1a and β-1b treatment. After the expansion of treatment capabilities and improvement of budgetary availabilities, around 75% of patients receiving interferon β in Kosovo started their treatment after 2020.

By September 30th, 2023, there were 410 patients with MS to whom interferon β treatment was prescribed. Patients who refused, withdrew with their initiative, or by the medical team from the treatment, and those who were switched to other medications due to different reasons were excluded from the evaluation. Also, patients that were not taking the medication for three consecutive months were thought to be non-persistent, and therefore, were excluded from further calculation.

At last, 325 patients were on interferon β medication, of whom 218 (67.1%) were on interferon β-1b (Betaferon®), and 107 (32.9%) on interferon β-1a (Rebif®). More than one-third of patients were female (223, 68.6%). Their mean age was 38.5±11.6 and most patients were categorized as having relapsing-remitting form of MS. The mean EDSS value was 1.43±0.7. To evaluate the possible effect or correlation of functional disability to treatment adherence, patients were divided into three categories, based on EDSS. The mean duration of the disease in this cohort was 7.3±6.4 years (Table 1).

Because of the limited availability of immunomodulatory treatment in Kosovo before 2020, the overall mean gap between the time of diagnosis and treatment onset was 44.7 months; but since the treatment has become available for each newly diagnosed patient, time from diagnosis to treatment has dropped gradually (Figure 1). Most patients were less than 3 years on the treatment with interferons.

Adherence rate to the treatment was compared to gender, age, MS clinical type, functional capacity expressed through EDSS, disease duration, waiting time to the initiation of treatment, and treatment duration. Patients with older age (above 40), higher EDSS, longer duration of the disease, longer waiting time from the diagnosis to the treatment initiation, longer time on injectable treatment, and those with progressive forms of multiple sclerosis have had lower adherence rates to the treatment (Table 2, Figures 2-4). Overall adherence rate was found to be 73.8%.

Discussion

Multiple sclerosis is a chronic central nervous system disease that is believed to exert its pathology mainly through immune-mediated mechanisms. Thus, different immunomodulatory treatments continue to be at the core of treatment for this disorder. β interferons were the first disease-modifying treatment options for patients with multiple sclerosis. Clinical trials have shown that β interferons have a beneficial effect on RRMS by reducing the frequency of exacerbations, the accumulation of permanent disability, and disease activity.[16] They have also been shown to reduce relapse rates in the relapsing form of the disease.[17]

Their application in parenteral form creates adherence and persistence problems to the treatment. Even though oral and infusion forms of DMTs are widely available, β interferons and glatiramer acetate remain as first-line treatment options in many regions. Low cost is one of the factors that enables their use, especially in low- and middle-income countries, such as Kosovo.

Many studies have documented that better adherence to the treatment has been associated with lower relapse rates and better quality of life.[15,18,19] Our experience with long-term immunomodulatory treatment of MS is very limited since most patients have started their treatment after 2020. Patients who refused the medication and/or were not taking it regularly (missed three consecutive months) were categorized to be non-persistent, and therefore, were excluded from the calculation. Out of 325 patients actively taking β interferons, 85 patients have refused medication, mainly because of unwillingness to take injectables and/or cutaneous and/or systemic side effects due to the injections.

Overall, the adherence rate to the treatment in our cohort was 73.8%. This is higher than in some cohorts reported previously with similar size and follow-up. Portaccio *et al.* have reported a discontinuation rate of 46% on 225 subjects with a mean follow-up of 4.2 years.[20]

Table 1. Epidemiological and clinical features of the subjects.

	Interferon β-1a (n=107)	Interferon β-1b (n=218)	Overall (n=325)
Gender			
Female	75	148	223
Male	32	70	102
Age (years)			
<30	36	57	93
31-40	34	57	91
>41	37	104	141
EDSS			
<4	82	130	212
4-6	24	48	72
>6	1	32	33
Missing		8	8
MS type			
RRMS	101	165	266
SPMS	5	36	41
PPMS	1	8	9
Undefined	0	9	9
Disease duration (years)			
<4	37	76	
4-6	37	27	
>6	33	107	
Missing		8	
Treatment duration (months)			
0-12	8	17	25
13-24	19	34	53
25-36	23	101	124
37-48	57	2	59
49-60	0	7	7
>60	0	49	49
Missing		8	8
Waiting time for treatment (months)			
≤6	33	85	
7-12	19	29	
13-24	8	12	
>24	47	84	
Missing		8	

EDSS, expanded disability status scale; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis.

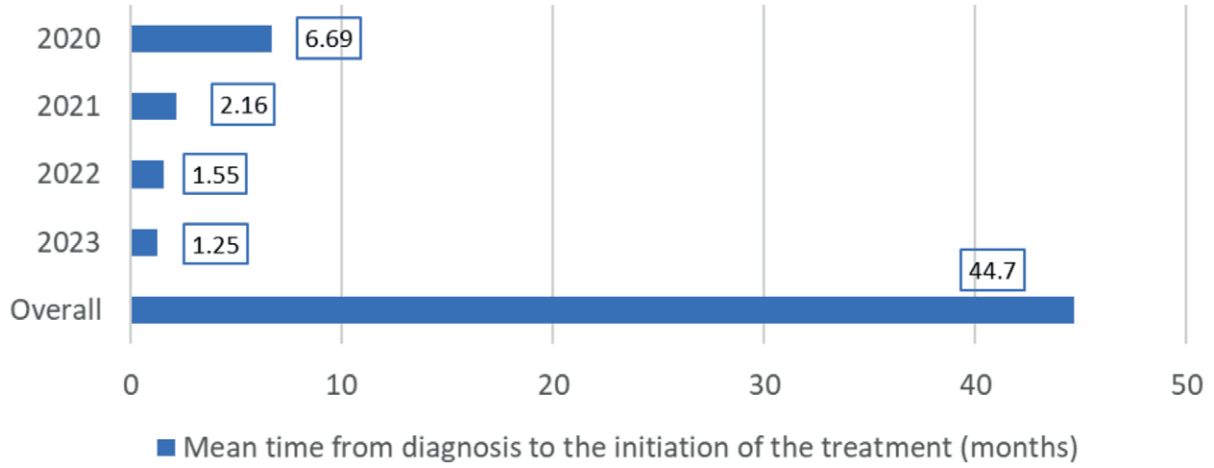

Figure 1. Waiting time to the initiation of treatment.

Table 2. Correlation of missed doses to the gender, age, expanded disability status scale, multiple sclerosis type, treatment duration, and waiting time for treatment.

	Difference between ideal and real adherence (missed doses) Median (interquartile range)	*P value
Gender		
Female	9 (4-14)	
Male	9 (4-14)	0.462
Age (years)		
<30	7 (2-12)	
31-40	9 (4-14)	<0.005
>41	10 (5-15)	
EDSS		
<4	8 (3.5-12.5)	
4-6	11 (7-15)	<0.001
>6	12 (5.5-18.5)	
MS type		
RRMS	8 (3.5-12.5)	
SPMS	11 (7.5-14.5)	0.19
PPMS	10 (3-17)	
Disease duration (years)		
<4	5 (1-9)	
4-6	8.5 (5-12)	<0.001
>6	11.5 (2-21)	
Treatment duration (months)		
0-12	2 (1-3)	
13-24	5 (3-7)	
25-36	10 (7-13)	
37-48	8 (4.5-11.5)	<0.001
49-60	21 (8-34)	
>60	34.5 (19.5-49.5)	
Waiting time for treatment (months)		
≤6	5 (0.5-9.5)	
7-12	12 (8-16)	
13-24	8.5 (3.5-13.5)	<0.001
>24	10 (5.5-14.5)	

EDSS, expanded disability status scale; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis.

While a Swedish study with 259 patients on injectables showed only 31% adherence at the end of a third year.[21] Main reasons for discontinuation were reported to be perceived lack of effectiveness and side effects. The first reason for the higher adherence rate in our cohort might be that patients who have refused, withdrawn, and/or were switched to other medications were excluded from the evaluation. Only patients who continued actively to take β interferons and those whose medications were not discontinued or switched to another option by doctor were subjected to this study.

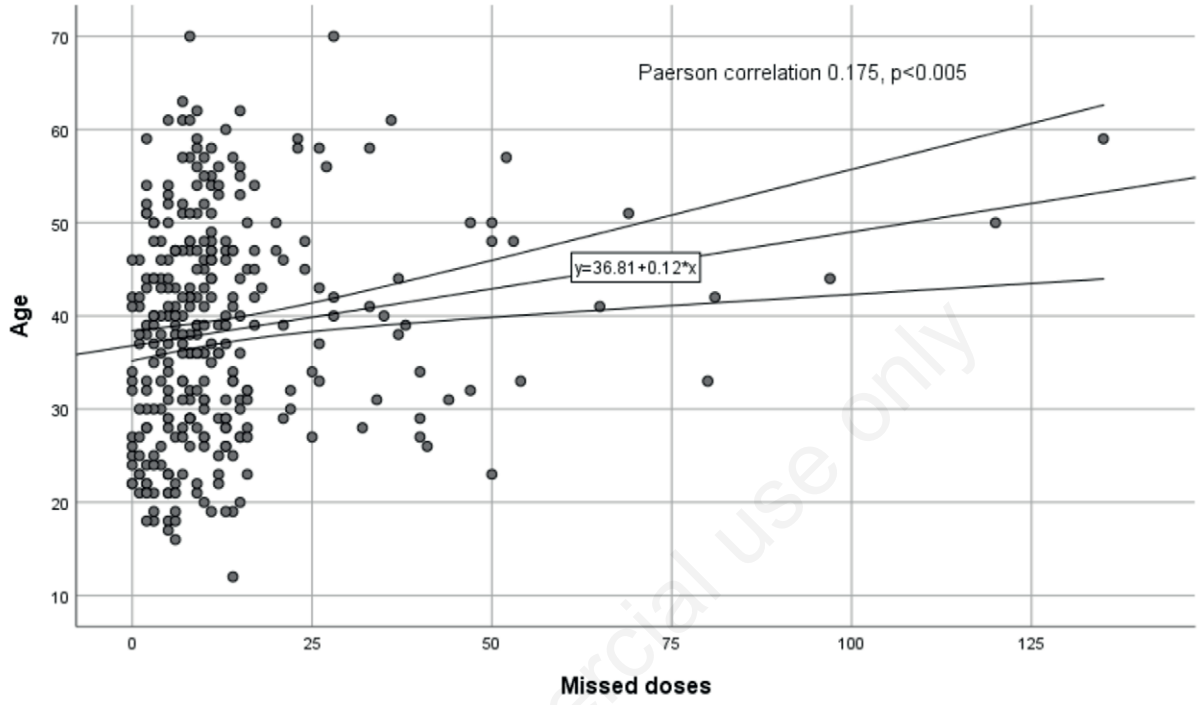

Figure 2. Distribution of missed doses in correlation to the age.

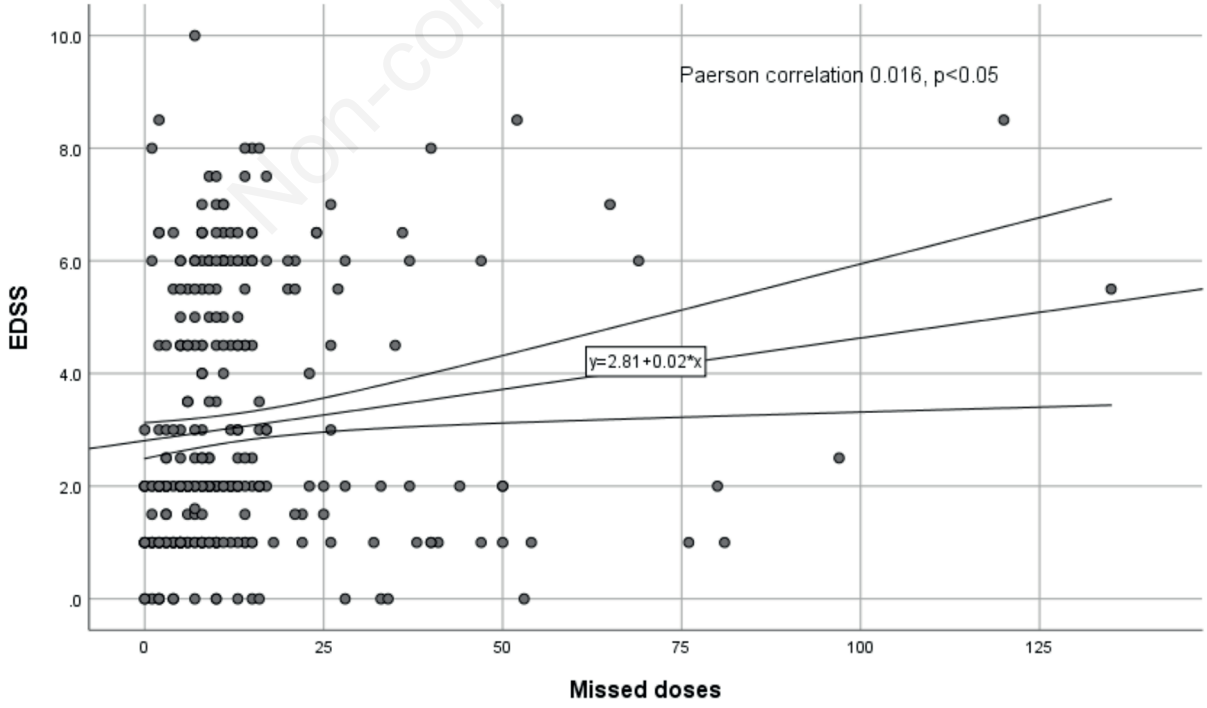

Figure 3. Distribution of missed doses in correlation to the expanded disability status scale.

Studies with longer follow-ups have demonstrated that around half of the patients have discontinued treatment after 13 years of mean follow-up, with a 16% drop after the first year.[22] Around 80% of our patients were less than 4 years on the treatment with β interferons. Shorter treatment time might be a second reason for higher adherence. Longer treatment with β interferons has been associated also with less adherence in our cohort.

Circumstances in our country might be the third explanation for higher adherence rates. Interferon β-1a and 1b are the only first-line treatments in Kosovo. High-efficacy DMTs are available in only limited amounts and are reserved for highly active RRMS (ocrelizumab and fingolimod) or PPMS (ocrelizumab). The inability of patients to choose between different DMTs with diverse modes of application might create an impression of the necessity to take the medication regularly, knowing that there might not be another option should he/she discontinues it. Limited resources for the doctors to switch medications suggest stricter imposition of interferons to their patients.

However, due to the lack of homogeneity in definitions and methods of calculation of adherence, it is difficult to make comparisons between different studies. Use of very strict demands that have estimated adherence rates to 75% in patients with RRMS in a study in Spain,[19] yielded very similar results to ours. Two other studies that considered a patient adherent if more than 80% of medication was taken by him/her, calculated adherence rate to be 83.6% and 77.9%, respectively.[12,23]

Younger age in our cohort was associated with a higher adherence rate. Some studies did not report an association with age or have reported that older age has modestly decreased non-adherence.[12,13,24] Since the longer duration of the disease is associated with lower adherence, we judge that it contributes indirectly to the decrease of adherence in older patients. Several studies have shown that higher levels of disability, as measured by the EDSS, are associated with lower adherence to the β interferon treatment.[13,22,24,25] Those with EDSS of 4,5 and above were found to be most likely to have a lower degree of adherence, as is the case in our cohort.

The longer duration of the disease increases the possibility of the progression of the disease to the progressive form and thus, to the accumulation of disability. It contributes additionally to the lower adherence and persistence to the treatment.[13] In addition to disability, factors such are fatigue and inflammation have been found to have an additional impact on adherence.[25,26]

Before 2020, most of the patients diagnosed with multiple sclerosis in Kosovo were not able to start with the disease-modifying treatment immediately after the diagnosis. The importance of the early start of disease-modifying therapies for the treatment of multiple sclerosis is well established.[27,28] Early initiation of the treatment may have advantages in terms of disability progression and transition from clinically isolated syndrome to definite multiple sclerosis. Our patients have lost important time, in many cases years, until the treatment had started. This delay in treatment caused significant disability accumulation over time, progression in the secondary progressive form of the disease, and minimized the potential benefit of the treatment Therefore, a longer waiting time for the treatment initiation was associated with a lower adherence rate in our cohort. We judge that starting the treatment in the later stages of the disease, when disability was more prominent and the expectations of patients for the reversal of disability were

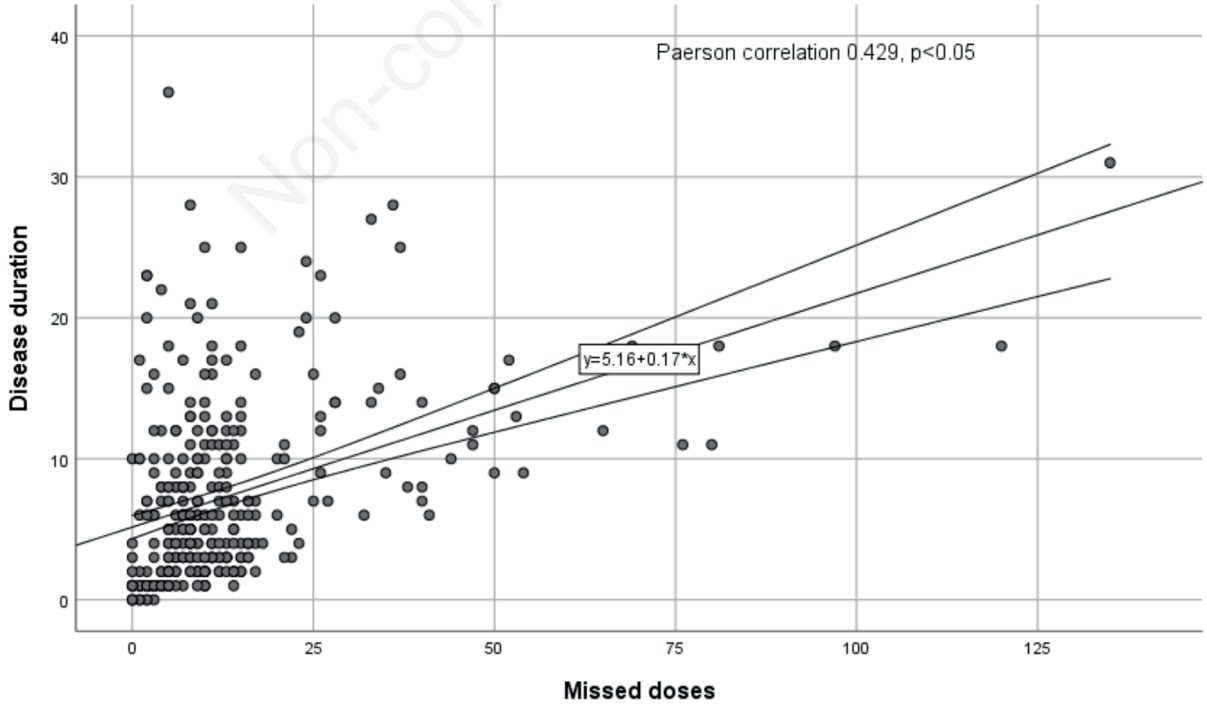

Figure 4. Distribution of missed doses in correlation to the disease duration.

high, created disappointment among patients, leading to lower adherence and abandonment of the treatment.

A study conducted in Switzerland found that 23% of individuals with MS had started DMTs after one year from diagnosis.[28] More than 75% of patients have started DMTs within two months of diagnosis. The introduction of diagnostic and treatment guidelines, and novel treatment options have contributed to the early start of DMTs. In our case, the availability of β interferons for the immediate start of treatment after the definite diagnosis, the facility of reaching the MS unit, and the centralized distribution of treatment by this unit, contributed to a sharp decrease in waiting time for the treatment, which is not longer than 45 days since the first address to the unit.

In summary, the adherence rate in our cohort is similar to the studies where the criteria for the determination of adherence is stricter. Comparison of non-adherence to other countries is difficult because of the difference in the economic and social circumstances, as well as regarding the availability of different disease-modifying treatment options. Our study aims to report adherence rates to the β interferon treatment. The reasons for non-adherence were not addressed, and it can be a topic for additional evaluation. Studies with adequate design, size, and follow-up are needed to collect strict clinical data for accurate adherence and persistence rates. Prompt identification of the reasons for non-adherence will enable their timely address and improvement in adherence and efficacy of the treatment.

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