Real-world effectiveness of fingolimod in patients with multiple sclerosis in Bulgaria

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Introduction. Fingolimod, a sphingosine-1-phosphate receptor agonist used for the treatment of multiple sclerosis (MS). Our goal was to assess the impact of fingolimod on quality of life in patients with relapsing-remitting multiple sclerosis (RRMS) after 2 years of treatment in this real-world study.

Patients and methods. This was a 2-year, prospective, observational study conducted in Bulgaria in RRMS patients treated with fingolimod. Quality of life was assessed using the Bulgarian-language version of the MSQoL-54 scale. The primary endpoint was the change from baseline in the MSQoL-54 score after 2 years of treatment. Secondary endpoints included the change from baseline in the MSQoL-54 score after one year of treatment, furthermore the assessment of depression level using the Hamilton D-17 score.

Results. A total of 87 eligible patients were included in the study with a mean age of 38.7 ± 8.45 years. The median Expanded Disability Status Scale (EDSS) score was 3.5 points. We found statistically significant improvement in 10 subscales at month 12 and in seven subscales at month 24. The mental health composite score increased from 64.0 ± 16.69 points to 67.5 ± 15.94 points at month 24 (p = 0.012). The physical health composite score increased from 61.7 ± 17.61 to 66.3 ± 16.70 (p = 0.001). Depression level measured by the HAM-D17 decreased significantly by month 12 and month 24. The EDSS score decreased or remained stable in more than half of the patients (61.6%). We detected better quality of life in patients with a lower EDSS score.

Conclusions. Quality of life scores and the depression level are improved in RRMS patients treated with fingolimod over 2 years in real-life setting.

Key words. Depression. Fingolimod. Movement disorders. Multiple sclerosis. Quality of life. Sexual disfunction.

Introduction

Multiple sclerosis (MS) is a chronic potentially disabling immune-mediated demyelinating disease of the human central nervous system [1]. The estimated European mean annual MS incidence rate is 4.3 cases per 100.000 [2]. Data from the Bulgarian Health Insurance Fund show that around 1,500 patients are treated for MS in Bulgaria, but according to data from the Bulgarian Movement Disorders and Multiple Sclerosis Society the number of Bulgarian patients with MS is estimated to be around 3,600 [3].

Typically, recurrent acute episodes (relapses) of neurological symptoms, which are followed by a complete or partial recovery, can be observed during the relapsing remitting MS (RRMS) disease course. Approximately 50% of these patients progress to secondary progressive MS within 10 years, 90% within 25 years. Apart from these initially relapsing forms of MS 10-15% of patients present with primary progressive MS (PPMS), which is characterized by steady deterioration of impairment without prior experience of relapses [4].

Studies assessing the therapeutic effects of treatments for MS almost always focus on slowing physical disability progression, reducing relapse rate and reducing disease activity seen with magnetic resonance imaging (MRI) [5], relaying most of all in quantitative outcomes. There is a lot of data proving that disease-modifying therapies for relapsing forms of MS significantly reduce the annualized relapse rate and the number of focal gadolinium-enhancing lesions on MRI, in addition, they have a modest impact on disability progression. However, people with MS often assess broader issues, such as general health, mental health, depression as important determinants of their overall health-related quality of life (HRQoL) [6]. In people with MS, HRQoL deteriorates significantly with disease progression. Sexual dysfunction is a common, but often ignored symptom in MS [7]. The estimated prevalence of

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sexual concerns in the MS population ranges between 40% and 80%, however, relatively little research has evaluated the impact of sexual dysfunction on quality of life in comparison to other common MS symptoms [8].

Fingolimod, a sphingosine-1-phosphate receptor agonist, is the first high efficacy oral therapy for MS that has shown consistent effects on the four key measures of disease activity vs. placebo and an active comparator [9,10].

In an interim analysis of a Swiss surveillance monitoring program (SWISSASCENT) including data from 100 fingolimod patients significant improvement was seen in QoL during fingolimod treatment as well as in treatment satisfaction in all domains of the TSQM-9 scale upon switch from other DMTs to fingolimod [11]. A Phase IV *Evaluate Patient OutComes* (EPOC) study (conducted in US & Canada) aimed to test the hypothesis that therapy change to oral fingolimod improves patient-reported outcomes compared to standard-of-care disease-modifying therapy (DMT) in patients with relapsing MS; and their safety and tolerability were also assessed. For the secondary endpoints BDI-II was used for depression and SF-36 for quality-of-life [12].

As described above, studies assessing the therapeutic effects of treatments for MS usually focus on reducing relapse rate, slowing physical disability progression, and reducing disease activity seen with MRI. In their everyday lives people with MS often experience other issues and symptoms that affect their overall health-related quality of life.

Patients and methods

Study design and patients

This was a prospective, non-interventional, observational study to collect data from patients with RRMS under fingolimod treatment (as part of their routine clinical treatment) for overall quality of life, the Expanded Disability Status Scale (EDSS), patients' reported outcomes and as performed per standard clinical practice. The study aimed to enroll 96 patients. All patients were followed for up to 24 months. Patients received standard medical care during the study with no additional laboratory tests or medical procedures being performed; only patient-reported outcomes were assessed. The assessments were performed at baseline (1 day), at month 12 and at month 24.

The eligible patients were aged 18-60 years, with a diagnosis of RRMS defined by McDonald criteria (2010), the EDSS score of 0-5.5 and only patients with disease activity were observed during the 12 months prior to screening. An additional inclusion criterion was previously participating in a treatment with DMT (IFN b-1a or 1b, or glatiramer acetate) before the fingolimod treatment. Pre-existing major psychiatric disorders, anti-depressive therapy within one month before the enrollment was an exclusion criterion. All patients were provided a written informed consent prior to enrollment.

Data collection

Health-related quality of life was assessed using the validated, Bulgarian-language version of the MSQOL-54 questionnaire, which comprises 12 subscales along with two summary scores, and two additional single-item measures. The subscales are: physical function, role limitations (physical), role limitations (emotional), pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life and sexual function. The summary scores are the physical health composite summary and the mental health composite summary. The single item measures are satisfaction with sexual function and change in health. Higher scores indicate better quality of life. This questionnaire was filled at baseline, at month 12 and at month 24 after treatment initiation.

Depression was measured with the Hamilton Depression Rating Scale (HAM-D17). This is a widely used clinician-administered depression assessment scale. The short, 17-item version of the test was used to assess the severity of and change in depressive symptoms. The score ranges from 0 to 25 and lower scores indicate milder depression.

The EDSS is the most widely used scale to measure the disability of patients diagnosed with MS. A higher EDSS score represents higher neurological impairment.

Further collected data included concomitant medications, number and frequency of relapses, previous hospitalizations, and occurrence of adverse events during the study.

Statistical methods

Two study populations were assessed: the safety population was defined as all enrolled patients who received study medication and the efficacy population was defined as all patients from the safety population who have at least one valid post-baseline efficacy data value.

The primary endpoint of the study was the change from baseline in the MSQOL-54 score till month 24 of the treatment with fingolimod compared by using a paired-sample t-test; otherwise, the nonparametric Wilcoxon test was applied. The secondary endpoints of the study (changes in the MSQOL-54 score from baseline and after 12 months of treatment with fingolimod, changes in the sexual function score of the relevant scales of the MSQOL-54, changes in the HAM-D17 score, changes in the EDSS score) were analyzed similarly to the primary endpoint.

Subgroup analyses were performed by age at enrollment (<40 years old; ≥ 40 years old), by the EDSS score at baseline (<3 points; ≥ 3 points) and by gender (male; female). Associations between quantitative variables (age at enrollment, the baseline EDSS score) and QoL results were measured by the Spearman correlation.

Statistical significance level was set up at $p < 0.05$. All analyses were performed using the IBM SPSS Statistics® package (version 26).

Standard protocol approvals, registrations, and patient consents

Statement of approval was obtained from Ethics Committee for Multicenter Trials in Bulgaria. The statement number: KI-148/25.11.2015.

Written informed consent was obtained from all participants in the study. The informed consent form was approved by Bulgarian Drug Agency (NIS-0001/27.01.2016) and Ethics Committee for Multicenter Trials (KI-148/25.11.2015).

Results

Patient disposition and baseline characteristics

A total of 93 MS patients were enrolled in the study and 87 patients had at least one valid post-baseline data value. In the efficacy population there were 41 (47.1%) males and 46 (52.9%) females and the mean ± SD age was 38.7 ± 8.45 years. Most of the patients reported two relapses and two hospitalizations per year at baseline and the median EDSS score was 3.5 points (ranging from 2 to 4.5). Detailed baseline characteristics are presented in table I.

Table I. Baseline demographics and disease characteristics in the efficacy population.

	Total (n = 87)
Age, mean (SD), years	38.7 (8.45)
Females, n (%)	46 (52.9%)
EDSS score, mean (range)	3.2 (2-4.5)
Number of relapses per year, n (%)	
1	8 (9.4%)
2	73 (85.9%)
3	4 (4.7%)
Number of hospitalizations per year, n (%)	
1	9 (10.8%)
2	71 (85.5%)
3	3 (3.6%)

EDSS: Expanded Disability Status Scale; SD: standard deviation.

Quality of life at 12-month treatment with fingolimod

The mental health composite score was 63.2 ± 16.11 at baseline and 66.6 ± 16.98 at month 12, resulting in a statistically significant mean change from baseline (p = 0.001). The physical component score was 61.2 ± 16.98 at baseline and 66.5 ± 15.46 at month 12 and this change was statistically significant ($p < 0.001$). Similarly, a statistically significant change was noted at 12 months of treatment in the subscales physical health score, role limitations due to physical problems, role limitations due to emotional problems, pain, emotional well-being, social function, health distress, change in health and satisfaction with sexual function (Table II; Fig. 1a and b).

Quality of life at 24-month treatment with fingolimod

The mental health composite score was 64.0 ± 16.69 at baseline and 67.5 ± 15.94 at month 24, resulting in a statistically significant mean change from baseline (p = 0.012). The physical component score was 61.7 ± 17.61 at baseline and 66.3 ± 16.70 at month 24 and this change was statistically significant (p = 0.001). Similarly, statistically significant change was noted at 24 months of treatment in the physical health score, role limitations due to physical problems, pain, energy, and change in health subscales (Table II; Fig. 1a and b).

Figure 1. a) Physical health composite score; b) Mental health composite score.

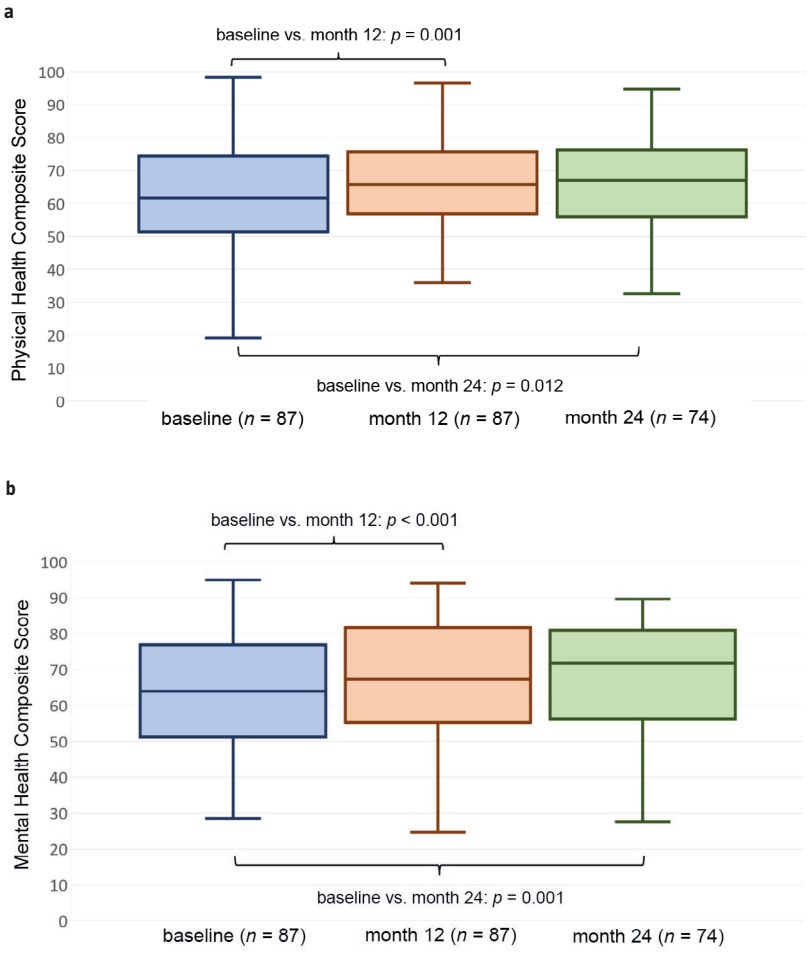


Table II. Mean MSQoL-54 physical health composite scores, mental health composite scores, HAM-D17 scores and EDSS scores by visits.

	n	Mean (SD)
MSQoL-54 PCS		
Baseline	87	61.16 (16.98)
Month 12	87	65.51 (15.46)
Month 24	74	66.32 (16.7)
MSQoL-54 MCS		
Baseline	87	63.17 (16.11)
Month 12	87	66.6 (16.98)
Month 24	74	67.55 (15.94)
HAM-D17		
Baseline	87	4.93 (4.41)
Month 12	87	3.97 (2.86)
Month 24	75	3.41 (2.57)
EDSS		
Baseline	87	3.19 (0.744)
Month 12	87	3.24 (0.758)
Month 24	73	3.29 (0.845)

EDSS: Expanded Disability Status Scale; HAM-D17: Hamilton depression rating scale; MCS: mental health composite score; MSQoL-54: Multiple Sclerosis Quality of Life-54; PCS: physical health composite score; SD: standard deviation.

Depression and sexual functioning

The mean + SD HAM-D17 score was 4.93 ± 4.41 at baseline, 3.97 ± 2.86 at month 12 and this change was statistically significant (p = 0.029). Similarly, a statistically significant (p = 0.038) decrease was observed between the mean baseline value (4.76 ± 4.50) and the month 24 value (3.41 ± 2.57) (Table II; Fig. 2).

In the baseline versus month 12 comparison, we found a statistically significant improvement in the satisfaction with sexual function subscale. It was increased from the mean 66.6 ± 30.54 points to 70.9 ± 27.40 points (p = 0.028), but the change in the sexual function subscale was not significant (p = 0.184). In the baseline versus month 24 comparison, we did not find statistically significant differences (sexual function scale p = 0.35; satisfaction with sexual function scale p = 0.424).

Expanded Disability Status Scale

The mean EDSS score increased from 3.19 ± 0.744 points to 3.24 ± 0.758 at months 12, however this increase was not statistically significant (p = 0.302). In the baseline versus month 24 comparison, the EDSS score increased to 3.29 ± 0.845 (p = 0.013). At 24 months the EDSS score decrease was observed in nine patients (12.3%), increase was detected in 28 patients (38.4%) and a stable EDSS score was recorded in 36 patients (49.3%) (Table II).

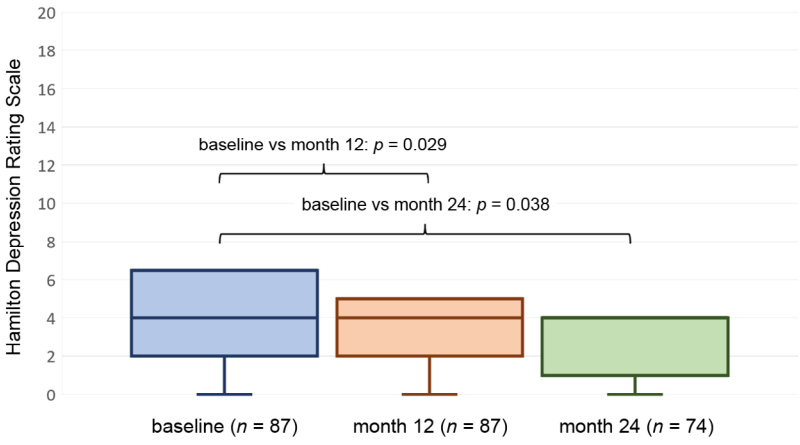
Subgroup analyses

In the subgroup analysis we found that the satisfaction with sexual function improvement was higher in the females compared to males (p = 0.028, the change from baseline is 9.38 points and –3.21 points, respectively) at month 24.

We also found a statistically significant difference between patients stratified by age in the satisfaction with sexual function subscale (p = 0.042). An improvement was detected in the group of patients younger than 40 years (mean change from baseline compared with score at month 24: 9.03 points), whereas in the group of patients older than 40 years a decrease was observed (mean change from baseline at months 24: –4.39 points).

Investigating the study objectives using subgroups characterized by EDSS points at baseline, we found significant improvements in 9 subscales at month 12 and in 12 subscales at month 24 in the MSQoL-54 scale. All significant results were higher in the EDSS <3 points subgroup.

Figure 2. Hamilton depression rate scale.



Safety

A total of five patients, (5.4% of enrolled patients) who took at least one treatment of fingolimod reported adverse events. A total of 16 events were reported and the vast majority of these were recorded as serious adverse events (15 events in 4 patients). The lead event in this category was relapse of MS. All serious adverse events related to the relapse of MS.

None of the adverse events were suspected to relate to the study drug. All affected patients were completely recovered from all the events.

Discussion

The aim of this study was to gather real world evidence from the Bulgarian cohort of RRMS patients and to observe the use of fingolimod as a treatment option once the first line DMT failed without circling around different first line DMTs that will not add value to the patient's management of the disease (the first option of the second line).

As a relatively small number of research evaluates the depression, sexual dysfunction and other PROs in the MS population, this study will add knowledge of the impact of these usually ignored symptoms on MS patients' general quality of life. The study provides 2 years' prospective data on the usual therapeutic effects in terms of symptom control and evaluates the influence on improving quality of life.

We found a significant improvement in the QoL assessed by the MSQoL-54 scale at both months 12 and 24. Our results support a previous observation that second-line treatments may have a greater impact on patients' quality of life than first-line therapies [13].

It is a well-known fact that HRQoL scores correlate with health outcomes of the MS (e.g., EDSS) and low quality of life is a predictor of long-term disability [13]. This previous observation is supported by our findings that higher scores were observed on several subscales of the MSQOL-54 in patients with baseline EDSS < 3 points.

Depression is a major issue in MS patients, its lifetime prevalence can reach as much as 50% [14]. In our study the Hamilton D-17 score was applied to assess the depression levels of the patients and we found a significant improvement. In line with our result, another study reported that fingolimod treatment was associated with an improvement in depressive symptoms in MS patients who had switched from another treatment [15].

Although a statistically significant increase was observed at the 24-month visit in the EDSS score, in the majority of the patients a stable or decreased EDSS score was seen, which pattern was also observed in another study [16].

Our study has several important limitations and some of them result from the observational study design. A further limitation is that we did not collect laboratory test results and medical examina-

tion records in the study and as a result many patient-specific patterns remain unexplored. The same limitation may be a consequence of the very low number of reported side effects compared to other studies. Lastly, it should be highlighted that the small sample size could influence our results.

In summary, we collected real-world data, and this non-interventional study provides useful information for further improvement of patient care for MS patients.

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Eficacia en la vida real del fingolimod en pacientes con esclerosis múltiple en Bulgaria

Introducción. El fingolimod es un agonista del receptor de esfingosina-1-fosfato utilizado para el tratamiento de la esclerosis múltiple (EM). Nuestro objetivo era evaluar los resultados del fingolimod en la calidad de vida de los pacientes con EM recurrente-remitente tras dos años de tratamiento en este estudio de la vida real.

Pacientes y métodos. Se trata de un estudio observacional prospectivo de dos años de duración realizado en Bulgaria en pacientes con EM recurrente-remitente tratados con fingolimod. Se evaluó la calidad de vida mediante la versión en búlgaro de la escala *Multiple Sclerosis Quality of Life-54* (MSQoL-54). El criterio de valoración principal fue el cambio respecto al valor inicial en la puntuación en la MSQoL-54 tras dos años de tratamiento. Los criterios de valoración secundarios fueron el cambio respecto al valor inicial en la puntuación en la MSQoL-54 tras un año de tratamiento, además de la evaluación del nivel de depresión mediante la puntuación de la escala de puntuación de la depresión de Hamilton (HAM-D17).

Resultados. En el estudio se incluyó a 87 pacientes elegibles con una edad media de 38,7 ± 8,45 años. La mediana de la puntuación en la *Expanded Disability Status Scale* (EDSS) fue de 3,5 puntos. Se halló una mejora estadísticamente significativa en 10 subescalas en el mes 12 y en siete subescalas en el mes 24. La puntuación combinada de salud mental aumentó de 64 ± 16,69 puntos a 67,5 ± 15,94 puntos en el mes 24 (p = 0,012). La puntuación combinada de salud física aumentó de 61,7 ± 17,61 a 66,3 ± 16,7 (p = 0,001). El nivel de depresión medido por la HAM-D17 disminuyó considerablemente en el mes 12 y en el mes 24. La puntuación de la EDSS disminuyó o se mantuvo estable en más de la mitad de los pacientes (61,6%). Detectamos una mejor calidad de vida en los pacientes con una puntuación más baja en la EDSS.

Conclusiones. Las puntuaciones de calidad de vida y el nivel de depresión mejoraron en los pacientes con EM recurrente-remitente tratados con fingolimod durante dos años en un entorno real.

Palabras clave. Calidad de vida. Depresión. Disfunción sexual. Esclerosis múltiple. Fingolimod. Trastornos del movimiento.

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