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# Safety and Efficacy of Fingolimod and Natalizumab in Multiple Sclerosis After the Failure of First-Line Therapy: Single Center Experience Based on the Treatment of Forty-Four Patients

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
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**Background:** In Poland, natalizumab or fingolimod treatment can be delivered as a second-line therapy to those patients with relapsing-remitting multiple sclerosis (RRMS) who demonstrated no response to interferon or glatiramer acetate treatment for a minimum of one year.

The objective of this study was to evaluate the impact of second-line therapy on the frequency of relapses, the disability progression, and the occurrence of side effects.

**Material/Methods:** Analysis covered 44 RRMS patients switched from first- to second-line therapy. The annualized relapse rate, disability progression (assessed with Expanded Disability Status Scale, EDSS) and MRI results (new or enlarged T2 lesions and new Gd-positive lesions) before and after switching were compared. The occurrence of adverse events was also assessed.





**Results:** The annualized relapse rate for second-line therapy was significantly lower than for first-line therapy ( $0.35 \pm 0.74$  vs.  $2.13 \pm 0.87$ ,  $p=0.00005$ ). Median of EDSS progression with first-line therapy was significantly higher than that with natalizumab or fingolimod treatment ( $p=0.00002$ ).

The mean number of new or enlarged T2 and Gd+ lesions in MRI after one-year second-line treatment was significantly lower in comparison to lesions in MRI performed at the end of the first-line therapy (for T2: 0.61 vs. 4.56,  $p=0.0004$ ; for Gd+: 0.13 vs. 1.98,  $p=0.0009$ ). No significant differences in the clinical data, MRI results, and side effects between fingolimod and natalizumab patients have been observed.

**Conclusions:** Treatment with natalizumab or fingolimod as a second-line therapy in RRMS patients is safe and effective. Less restrictive criteria for switching should be considered.

**MeSH Keywords:** **Drug Therapy, Combination • Multiple Sclerosis • Multiple Sclerosis, Relapsing-Remitting**

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## Background

In the treatment of patients with relapsing-remitting multiple sclerosis (RRMS) there is a strong emphasis on the need for optimization and personalization of the therapy. No evidence for disease activity (NEDA) [1,2], defined with respect to clinical criteria, and results of magnetic resonance imaging (MRI) are proposed as therapeutic objectives.

Injectable medications, such as interferons and glatiramer acetate (GA), have been used for more than twenty years, affected the course of the therapy, and have been characterized with moderate efficacy and a good safety profile [3]. In recent years, new forms of previously used injectable medications have been introduced: GA 40 mg three times a week [4], peginterferon beta-1a [5]; and new substances: fingolimod [6], natalizumab [7,8], teriflunomide [9], and dimethyl fumarate [10,11]. The new medications are characterized as having better efficacy but greater risk of side effects. Therefore, it is important to adjust medications based on expected efficacy for each patient at each stage of the disease individually, based on a thorough clinical and radiological evaluation and considering the safety of the administered therapy.

In Poland, treatment of patients with RRMS is reimbursed under the medication program of the National Health Fund (Narodowy Fundusz Zdrowia, or NFZ), which specifies the first-line treatment. In Poland, this is based on injectable medications (interferons and GA). For patients in whom the first-line therapy proves ineffective for a minimum period of one year, a second-line program has been created. Within the program, two medications are available: natalizumab and fingolimod.

The objective of this study is to evaluate the effects of treatment with second-line medications by means of the analysis of the impact of the therapy on the frequency of relapses, the degree of disability, and the occurrence of side effects.

## Material and Methods

The study involved 44 patients (31 women and 13 men) aged on average 38.36 years (SD: 9.81) with RRMS treated under the NFZ program for MS treatment after the failure of the first-line therapy. All patients were diagnosed for MS according to McDonald's 2010 criteria [12]. Prior to the qualification for a second-line treatment, 15 patients had been treated with interferon beta-1b, 6 patients with interferon beta-1a SC (subcutaneous), 8 patients with interferon beta 1a IM (intramuscular), and 15 patients with GA. An annual relapse rate and the average Expanded Disability Status Scale (EDSS) score during first-line treatment was calculated for the whole group. All patients had met the criteria for ineffectiveness of the first-line

treatment and had entered into the second-line program according to NFZ criteria: no response to a complete, lasting minimum one-year cycle of treatment with interferon beta or GA, defined as the fulfillment of these two criteria:

1. The number and severity of relapses: a) two or more moderate relapses requiring administration of steroids (an increase of one to two points in EDSS score or of two points in one or two EDSS functional-system scores, or of one point in a minimum of four EDSS functional-system scores), or a severe relapse after five months of treatment (an increase in EDSS score higher than in the definition of a moderate relapse).
2. Lesions demonstrated in MRI performed after 12 months of the therapy: minimum three new T2-weighted lesions or minimum two Gd+ lesions.

Thirty patients had fingolimod administered in oral daily doses of 0.5 mg and 14 patients had natalizumab administered intravenously every 28 days in doses of 300 mg. Fingolimod was started as soon as the following contraindications had been excluded: hypersensitivity to fingolimod or its ingredients; known immunodeficiency syndrome; patients with higher risk of opportunistic infections, including patients with immunosuppression (including patients currently taking immunosuppressive drugs or patients with compromised resistance to infections as a result of the previous treatment); severe active infections; active chronic infections (hepatitis, tuberculosis); known active cancer diseases excluding basal cell carcinoma; severe hepatic impairment (Child-Pugh score: class C); patients with coronary heart disease; sick sinus syndrome with a history of myocardial infarction and treated with Ia or III anti-arrhythmic medications; patients with no history of varicella or who had not been vaccinated against varicella-zoster virus (VZV) and have no antibodies against it; and patients with secondary progressive MS (SPMS). The treatment with fingolimod was initiated on an inpatient basis with ECG and heart rate (RR) monitoring for a minimum of six hours following the start of the therapy. The therapy was monitored according to the following scheme: morphology; liver values at one month, and then at three, six, nine, and 12 months following the initiation of the therapy; ophthalmic examination after three to four months; dermatological examination after 12 months, and periodic check-ups of RR.

Natalizumab was started as soon as the contraindications had been excluded: pregnancy, breast feeding, progressive form, the increased risk of opportunistic infections, and the presence of anti-JCV (John Cunningham Virus) antibodies. All patients were declared to have read the information about the program and PML risk stratification, gave their informed consent to treatment, and received a medical warning card. For the purpose of qualification for the treatment with natalizumab, necessary laboratory tests were carried out (morphology, liver and kidney parameters, general urinalysis, pregnancy test). Monitoring of

patients treated with natalizumab at each administration of the dose (every 28 days) included: neurological status, mental condition, cognitive functions, morphology, kidney values, liver values, general urinalysis, and JVC every six months.

All patients who qualified for the study had MRI of the head performed after 12 months from the start of the therapy.

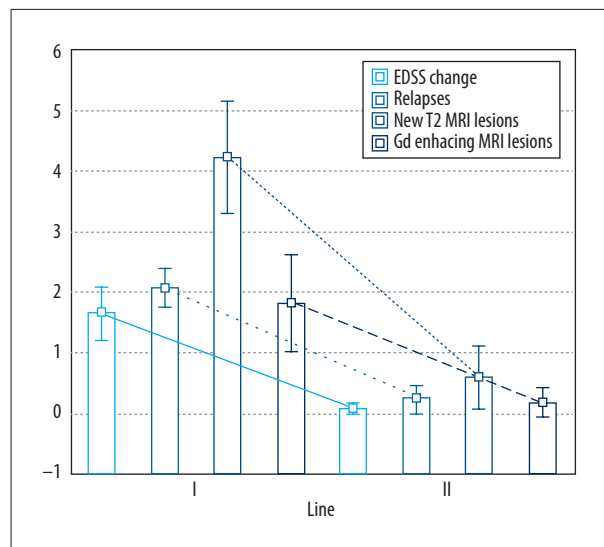
The efficacy was evaluated after each 12 months of therapy. Lack of efficacy was defined as the transition into SP or meeting two criteria of these three:

1. The number and severity of relapses: a) two or more moderate relapses requiring administration of steroids (an increase of one to two points in EDSS score or of two points in one or two EDSS functional-system scores, or of one point in minimum four EDSS functional-system scores), or a severe relapse after five months of treatment (an increase in EDSS score higher than in the definition of a moderate relapse).
2. The progression of the disease despite the treatment, i.e., decline in neurological status continued for a minimum of three months, expressed by at least: an increase of two points in EDSS score with EDSS up to 3.5, or an increase of one point with EDSS score up to four.
3. Lesions demonstrated in MRI performed after 12 months of the therapy with a minimum of three new T2-weighted lesions or a minimum of two Gd+ lesions.

The annual relapse rate during 12-month second-line therapy was calculated.

The safety of the therapy was evaluated by means of analysis of the following: the development of severe infections during therapy; the development of cancer; a significant increase in transaminases ( $3 \times \text{ULN}$ ); an increased concentration of bilirubin; kidney abnormalities; and in case of fingolimod also cardiac events (cardiac failure, rhythm and conduction disturbances); severe sleep apnea; macular edema; or prolonged decrease of lymphocytes  $<0.2 \times 10^9/\text{L}$ .

Clinical data (mean annual relapse rate and median EDSS growth) during first-line therapy and second-line therapy as well as MRI results were compared. The evaluation of MRI results took into account the presence of new or larger T2-weighted lesions and the number of Gd+ lesions in examinations performed after each 12-month period of the therapy (the number of new T2-weighted and Gd+ lesions in the examination performed at the end of the first-line treatment/initiation of second-line treatment was compared with the examination that took place a year earlier, and the number of new T2-weighted and Gd+ lesions in second-line examination was compared with the examination at the end of first-line treatment/initiation of the second-line treatment). MRI after 12 months of the second-line treatment was performed in 31 patients. The



**Figure 1.** Clinical and radiological indices during first and second line therapy.

number of relapses, progression in EDSS score, and lesions in MRI were also compared between patients treated with fingolimod and natalizumab.

### Statistics

The distribution was tested for compliance by means of Shapiro-Wilk test. Wilcoxon test was used to compare the measurements, Student's t-test or UMV was used to compare the groups and chi-square test was used to compare quality variables.

### Results

The mean duration of the first-line therapy was 36.3 months (range 12–108; SD 27.5, 25–75Q: 12–51), and of the second-line therapy 16.3 months (range 8–31; SD 6.36, 25–75Q: 12–18);  $p=0.00005$ .

There were no significant differences in terms of the average age of the patients, the mean therapy time, and the clinical condition assessed according to EDSS between the group qualified for the treatment with fingolimod and the group qualified for the treatment with natalizumab.

The annual relapse rate in the first-line therapy group was significantly higher than in the second-line therapy group (mean 2.13; SD: 0.87; median 2, 25–75Q: 1.5–2.8 95% CI 1–3.8 vs. mean 0.35; SD: 0.74, median 0, 25–75Q: 0–0.67, 95% CI: 0–1.41);  $p=0.00005$  (Figure 1).

During first-line therapy, EDSS change was observed in 36 patients; the median increase was 1.5 points (range 0–4.5).

When entering patients into first-line treatment, median EDSS was 2.5 (range 1.0–4.5); at the end of the first-line therapy it was 4.0 (range 1.0–6.0). During second-line therapy changes in EDSS were observed in 8 patients (range 0–1.5; median 0 points). The difference in the increase of points during second-line treatment was significantly higher than during first-line therapy ( $p=0.00002$ ) (Figure 1).

The number of new or enlarged T2-weighted lesions in MRI after one year of the second-line treatment was significantly lower in comparison to the number of new or enlarged T2-weighted lesions in MRI performed at the end of the first-line therapy (mean 0.61; median 0; range 0–3, 25–75Q: 0–2 vs. mean 4.56; median 4; range 0–12, 25–75Q: 2.5–6);  $p=0.0004$  (Figure 1).

The number of Gd+ lesions in MRI after one year of the second-line treatment was significantly lower in comparison to the number of Gd+ lesions in MRI performed at the end of the first-line therapy (mean 0.13; median 0; range 0–2, 25–75Q: 0–0 vs. mean 1.98; median 2; range 0–10, 25–75Q: 0–3);  $p=0.0009$  (Figure 1).

During second-line therapy, four patients developed zoster infections and three patients developed herpes infections, all successfully treated with standard medications. Apart from the above, no significant side effects listed in the methodology section were observed. Three patients treated with natalizumab suffered from JCV seroconversion after 12 months of treatment.

Due to the inefficiency of the treatment (relapses, progression of disability evaluated according to EDSS, the development of new lesions in MRI), the therapy was stopped in four patients (two treated with natalizumab, two treated with fingolimod) after 12 months.

No statistically significant differences in the annual relapse rate, change of EDSS points, the presence of new or enlarged T2-weighted lesions, or new Gd+ lesions between the group treated with fingolimod and the group treated with natalizumab were observed.

## Discussion

The decision about the right moment to introduce escalation therapy in patients with MS undergoing injectable first-line therapy of proven but limited efficacy is an important and difficult one. The suggested therapeutic objective of NEDA leaves no tolerance for relapses, disability progression evaluated according to EDSS, or the development of new lesions in MRI [1,2].

In recent years, new chemical substances have been introduced as a second-line treatment. In Poland, the availability of

therapies is regulated by NFZ regulations, according to which second-line therapy is currently restricted to two medications (natalizumab, fingolimod) and only in patients who suffered relapses and developed new lesions observed in MRI during first-line treatment in a minimum 12-month period. The efficacy of escalating treatment with these two medications has been confirmed by numerous studies [13–17].

Our study patients showed significant improvement during second-line treatment in all studied parameters (relapse occurrence, EDSS progression, the development of new T2-weighted and Gd+ lesions) in comparison to the results achieved in patients during first-line therapy.

The criteria for therapy escalation applied for our patients differed from NEDA, which (together with the improvement observed in patients during second-line therapy) would seem to challenge the NEDA's high stringency, and raise the question of whether second-line therapy should not be started earlier. On the other hand, one must not forget about safety issues. Second-line medications may cause a greater number of side effects than first-line medications. Fingolimod may cause cardiac events, ocular complications, and increase the risk of infections [6]. Therapy with natalizumab increases the risk of PML in JCV+ patients [18]. Therefore, strict initiation and monitoring rules should be applied. In our study, no significant side effects, apart from the infections successfully treated with standard medications, were observed.

In the literature there are publications about risk-predicting algorithms for individual response to therapy and the potential need for escalation. Researchers keep looking for biomarkers to estimate the risk of disease progression and the response to the applied therapy. Canadian recommendations concerning therapy optimization are based on the evaluation of the relapses, new lesions in MRI, and EDSS progression [19]. The Canadian authors propose the evaluation of first-line therapy every six or 12 months, and changing the therapy if a minimum of one severe relapse, significant EDSS progression, or new lesions in MRI occurs (minimum three T2-weighted or Gd+ lesions). They also point to the necessity of therapy escalation in patients who suffer from less severe relapses with a slight radiologic progression (two new T2-weighted or Gd+ lesions) or slight EDSS progression. According to Canadian criteria, the escalation should take place when the activity occurs in one of the domains: relapse occurrence, EDSS progression, or new lesions in MRI. In Poland, to enter patients into second-line treatment, there must be a combination of relapses and new lesions in MRI. Freedman et al. indicated the possibility of a temporary escalation – for a period of one or two years, to minimize the risk of long-term exposure to the second-line treatment medications. However, they stressed that the escalation should be permanent in patients with aggressive forms of the disease and suboptimal

responses to treatment. In Poland, there is no possibility for de-escalation, and the criteria for introducing second-line therapy are much stricter than those proposed by Freedman et al. Patients with more aggressive forms of the disease are qualified. De-escalation of the therapy might be considered in patients who respond to the treatment but develop intolerance to the treatment, or patients treated with natalizumab who develop JCV seroconversion. There are no clear guidelines for patients for whom second-line therapy proved ineffective. In our study, it proved ineffective for three patients. As a “third-line” therapy, immunosuppressive medications (such as mitoxantrone and cyclophosphamide) or newly introduced medications of proven high effectiveness (alemtuzumab) can be used. We decided to treat our patients with mitoxantrone. In patients with strong disease activity, it has been proposed to use these medications as an induction therapy, prior to interferons.

Rio et al. have created a points-based model of response to treatment based on the one-year evaluation of relapse occurrence, EDSS disability progression, and new lesions in MRI in patients treated with interferons [20,21]. Points were granted if during a 12-month period a minimum of one relapse occurred, a minimum of two new lesions in MRI developed (T2-weighted or Gd+), or EDSS progression by one point took place. In a modified-Rio scale, points are granted for relapses (one point if one relapse occurred during 12 months, two points if a minimum of two relapses occurred) and the development of new lesions in MRI (minimum of four T2-weighted or Gd+ lesions). The criterion of EDSS evaluation has been abandoned [22,21]. Patients with two or three points in these scales were considered non-responsive to therapy and declared candidates for escalation [20,22]. In both scales, one isolated relapse without activity in MRI does not indicate a lack of response to the administered therapy. Similarly, isolated lesions in MRI do not justify the declaration of unresponsiveness.

The same situation applies to our patients – to acknowledge the failure of the first-line therapy, clinical activity (relapses) must be accompanied by radiological symptoms (new lesions in MRI). Rio scale (similarly to modified-Rio scale) provides for a long-term response to treatment on the basis of the first year of treatment. High specificity (72%) and accuracy (65%) of the modified-Rio scale in predicting EDSS disability progression

during a four-year period of observation [21] was shown. We reviewed the therapy of our patients every 12 months. In our investigated group, the ineffectiveness of the therapy (according to the study criteria) after one year of a first-line therapy was observed in 10 patients (22.78%); in others, the ineffectiveness was declared in the following years of injectable medications (on average after 42 months).

It is worth emphasizing that NFZ does not reimburse for treatment with new oral medications (DMF, teriflunomide) or new forms of injectable medications (peginterferon). We are waiting for the possibility of using them in patients who do not tolerate injectable medications, who do not respond to the therapy, or who have a mild disease activity – who do not meet the criteria for inclusion into second-line treatment. Patients who do respond to treatment with interferons, but developed antibodies against interferons, could also be potential candidates for new oral medications or GA.

However, one must note that the results of treatment with new medications come mostly from clinical trials where the medications are compared against placebo. There are very few head-to-head trials.

Our research was limited by the small number of patients and relatively short observation period for patients treated with a second-line therapy; hence our results should be treated as provisional observations. On the other hand, we are waiting for modification of criteria for introducing second-line treatment, and reimbursement of new medications, which will give us the ability to administer modern therapies to patients in Poland who have multiple sclerosis.

## Conclusions

Therapy with natalizumab and fingolimod achieved comparable results in terms of efficacy and safety during a one-year observation period in patients with RRSM after failure of treatment with interferon and GA.

The possibility of more flexible and personalized therapy, including new therapeutic options, should be examined further.

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