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Evaluation of efficacy, safety and tolerability of fingolimod in patients with the relapsing form of multiple sclerosis – 12-month observation. A preliminary report

Ocena skuteczności, bezpieczeństwa i tolerancji fingolimodu u chorych z rzutową postacią stwardnienia rozsianego – obserwacja 12-miesięczna. Doniesienie wstępne

Zdzisław Maciejek[1], Hanna Wójcik-Drączkowska[2], Sławomir Wawrzyniak[1], Anna Niezgodzińska-Maciejek[1]

[1]Klinika Neurologiczna, 10 Wojskowy Szpital Kliniczny z Polikliniką w Bydgoszczy
[2]Katedra i Klinika Neurologii, Uniwersytet Medyczny w Gdańsku

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Abstract

Background and purpose: Oral fingolimod 0.5 mg daily was approved in the European Union in 2011 for the treatment of relapsing multiple sclerosis in the aggressive form and as a second line treatment in patients with high disease activity despite interferon beta therapy. The aim of this study was the evaluation of efficacy, safety and tolerance of fingolimod in patients with relapsing-remitting multiple sclerosis (RRMS) during a 12-month observation period.

Material and methods: The investigated group consisted of 11 patients aged between 23 and 63 years. All patients underwent immunomodulatory treatment (disease modifying drugs – DMD) or immunomodulatory treatment in combination with mitoxantrone (Mx) without a positive effect for 3-5 years. Patients received oral fingolimod 0.5 mg daily during 12 months. Disability was evaluated with Kurtzke Expanded Disability Status Scale (EDSS) scale. Safety and tolerability of fingolimod were evaluated by adverse events monitoring, laboratory tests, and ophthalmological and skin assessment.

Results: Before the initiation of fingolimod treatment all the patients progressed in disability and in MRI changes including five cases with gadolinium-enhancing lesions. During fingolimod treatment there was no new relapse in any patient and no patient stopped the treatment because of any adverse event. During the 12-month treatment, EDSS improvement was observed in seven patients, three patients were stable, and one patient progressed by 0.5 point in the EDSS.

Streszczenie

Wstęp i cel pracy: Fingolimod uzyskał w 2011 r. w Unii Europejskiej rekomendację do leczenia wysoce aktywnej postaci rzutowej stwardnienia rozsianego oraz jako lek drugiego rzutu – postaci rzutowo-remisyjnej stwardnienia rozsianego (RRMS) u chorych nieodpowiadających na leczenie interferonem beta. Celem pracy jest wstępna ocena skuteczności, bezpieczeństwa i tolerancji fingolimodu u chorych na RRMS w ciągu 12-miesięcznej obserwacji.

Materiał i metody: W badaniu wzięło udział 11 osób z RRMS w wieku od 23 do 63 lat. Wszyscy otrzymywali leczenie immunomodulacyjne bądź immunomodulacyjne z immunosupresyjnym, bez pozytywnej odpowiedzi w ciągu 3–5 lat. Chorzy stosowali fingolimod – 0,5 mg doustnie raz dziennie – przez 12 miesięcy. W trakcie leczenia oceniano niesprawność w skali niewydolności ruchowej Kurtzkego (*Expanded Disability Status Scale* – EDSS), kontrolowano badania krwi, przeprowadzono konsultacje okulistyczne i dermatologiczne.

Wyniki: We wszystkich przypadkach przed leczeniem fingolimodem stwierdzono progresję niesprawności oraz zmian radiologicznych w obrazach MRI mózgu, w tym w 5 przypadkach obecność ognisk T1-zależnych wzmacniających się po kontraście. W trakcie leczenia fingolimodem u żadnego chorego nie obserwowano nowych rzutów i nie przerwano leczenia z powodu działań niepożądanych. W 7 przypadkach stwierdzono poprawę sprawności w skali EDSS, a w 3 przypadkach stan neurologiczny nie uległ zmianie; w 1 przypadku nastąpiło pogorszenie o 0,5 pkt w EDSS.

Correspondence address: Zdzisław Maciejek, Klinika Neurologiczna, 10 Wojskowy Szpital Kliniczny z Polikliniką SPZOZ, ul. Powstańców Warszawy 5, 85-681 Bydgoszcz, e-mail: z.maciejek@wp.pl
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Conclusions: In our study patients fingolimod was effective, safe and well tolerated independently of disease activity and previous treatment.

Key words: fingolimod, multiple sclerosis – relapsing-remitting form (RRMS).

Wnioski: Leczenie fingolimodem było efektywne, bezpieczne i dobrze tolerowane niezależnie od aktywności choroby oraz wcześniejszego leczenia.

Słowa kluczowe: fingolimod, stwardnienie rozsiane – postać rzutowo-remisyjna (RRMS).

Introduction

Multiple sclerosis (MS) is a major diagnostic and therapeutic problem. The progress that has been made in this field over the past several years is a consequence of the introduction of new diagnostic techniques and new immunomodulatory drugs inhibiting the inflammatory process and reducing accompanying neuronal and axonal damage [1,2]. Physicians currently treating MS patients must decide which cases would benefit from immunomodulatory treatment (interferon beta, glatiramer acetate) and when a switch to second-line drugs (fingolimod, natalizumab) would be advisable following lack of favourable response to first-line drugs [2,3]. Based on recent data encompassing 5-year observation of the effects of immunomodulatory therapy of MS, only 33% of patients respond positively to therapy. A change of treatment is advisable in 37% of cases and introduction of second-line drugs – in 12% of cases [4]. If no positive response to interferon beta or glatiramer acetate therapy is noted, the treatment of choice is the escalation of therapy [3]. Second-line drugs include fingolimod and natalizumab [1,3,5,6].

In 2010, fingolimod was approved in the United States for the treatment of the relapsing form of MS (relapsing-remitting multiple sclerosis – RRMS). In 2011, the drug was approved for use in the European Union, though only for very active forms of the disease and as second-line treatment of RRMS in patients who do not respond positively to interferon beta therapy. The drug is available in the 0.5 mg dose, to be taken orally once daily [7]. On 1 January 2013, fingolimod was included in Poland's drug reimbursement scheme within the framework of the National Health Fund's programme of MS therapy as second-line treatment of RRMS in patients failing first-line treatment (interferons beta).

Fingolimod promotes retention of lymphocytes CD4+ in the lymph nodes. The fingolimod-induced redistribution of lymphocytes is selective in nature: naive T cells which are highly implicated in the pathogenesis of MS and immune memory, including over 90% of IL-17-producing T lymphocytes, become 'trapped' in the lymph nodes, while effector lymphocytes, which play a major role in defence against infections, enter the circulation [7]. Phase II and III clinical trials conducted to date (FREEDOMS and TRANSFORMS) in patients treated with fingolimod have demonstrated a significant reduction in the relapse rate, an increase in the proportion of relapse-free patients, a reduction in gadolinium-enhancing lesions and a decrease in brain atrophy compared to the control group. It should be stressed that serious adverse events (herpes and varicella-zoster infections) occurred only in individuals receiving a higher dose of the drug. Other adverse events included mild herpes outbreaks, upper respiratory or urinary tract infections, bradycardia, atrioventricular block, hypertension, increased liver enzyme activity and reduced lymphocyte count in peripheral blood which is attributable to the mechanism of action of fingolimod [7-9].

The TRANSFORMS trial demonstrated a greater reduction of the relapse rate in the fingolimod-treated group vs. interferon beta-treated group, along with a greater proportion of relapse-free patients and greater reduction of gadolinium-enhancing lesions. The extended phase of the trial showed a sustained efficacy benefit of fingolimod therapy. A significant reduction in the number of new T2- and T1-weighted lesions was found in the group of patients initially treated with interferon beta after switching to fingolimod [8]. A very important element of both phases of the TRANSFORMS trial was the assessment of brain volume, with a significant reduction in brain atrophy observed in fingolimod-treated groups as opposed to the interferon beta-treated group [8].

The year 2011 also saw the publication of results of a fingolimod efficacy trial conducted in groups of patients suffering from very active RRMS selected from among participants of the FREEDOMS and TRANSFORMS clinical trials [10]. A comparison of groups treated with fingolimod, placebo or interferon beta 1-a demonstrated the greatest benefits of treatment among fingolimod-treated patients.

Summing up, fingolimod treatment was proven to be effective regardless of the level of activity of the disease or prior therapy – also when fingolimod was used in first-line treatment [10].

The aim of the present study was to perform a preliminary assessment of the efficacy, safety and tolerance of fingolimod as a second-line drug in patients with the relapsing form of MS over a 12-month observation period.

Material and methods

The clinical material consisted of 11 patients with RRMS (8 women and 3 men) aged between 23 and 63 years (mean age: 40.4 ± 13.4). The average age of MS onset was 28.7 ± 11.6 years. The mean duration of the disease was 11.4 ± 4.3 years. The diagnosis was made on the basis of criteria proposed by McDonald *et al.* [11]. Before the commencement of fingolimod treatment, all the patients received immunomodulatory therapy (disease modifying drugs – DMD) based on interferon beta or glatiramer acetate – or combination treatment, i.e. immunomodulatory therapy followed by immunosuppressive treatment with mitoxantrone (Mx) or inversely, for several (3-5) years, often with two or more drugs, following lack of positive response to the first or second immunomodulating drug used. Because of failure of immunomodulatory and/or immunosuppressive treatments, an attempt was made to introduce fingolimod therapy in accordance with drug registration guidelines in place in the European Union. None of the patients had any contraindications to fingolimod treatment. It should also be noted that flingolimod in a second-line treatment indication was not reimbursed until January 2013, which means it was administered at the patients' own expense in all the cases under analysis. The clinical data of the patients are listed in Table 1.

As shown in Table 1, the duration of the disease exceeded 10 years in the majority of cases. Detailed clinical characteristics of the study group are given in Table 2.

Fingolimod treatment was commenced with the procedure comprising one-day hospital stay including electrocardiogram (ECG) and Holter monitoring during the initial six hours after the administration of the first dose of the drug, and blood pressure and pulse measurements performed every hour for 6 hours. Laboratory blood tests were conducted to assess complete blood count, liver enzymes and the presence of antibodies against the varicella-zoster virus (in patients who had not previously had chickenpox). Afterwards the patients received one 0.5 mg tablet of fingolimod daily, orally, for the forthcoming months. By now, the duration of drug therapy in the study group has exceeded 12 months. Throughout the treatment process, the patients were evaluated ophthalmologically and dermatologically, and assessed clinically in the Kurtzke Expanded Disability Status Scale (EDSS): initially once per month (for the first six months of treatment) and then every three months. Laboratory parameters were also monitored, focusing on complete blood count (lymphocyte count), transaminase (AspAT, AlAT)

Table 1. Background of demographic and clinical features of investigated group

Initials	Age (years)	Sex (F/M)	Age of MS onset (years)	MS duration (years)	EDSS at onset	EDSS after DMD or Mx and DMD
B.R.	52	F	42	10	1.5	4.5
J.M.	50	F	30	20	1.0	4.0
Z.Z.	23	M	19	4	1.0	2.0
A.G.	28	M	18	10	2.0	4.5
E.G.	29	F	17	12	2.0	5.0
G.J.	32	F	22	10	3.0	5.5
Z.K.	58	M	44	14	1.0	5.0
B.T.M.	63	F	51	12	3.0	6.0
A.F.	31	F	23	8	2.0	3.5
B.G.	38	F	26	9	2.0	2.0
S.Ż.	41	F	24	17	1.0	4.5

F – female, M – male, MS – multiple sclerosis, EDSS – Expanded Disability Status Scale, Mx – mitoxantrone, DMD – disease modifying drugs

Table 2. Clinical characteristics of investigated group

Initials	Symptoms at onset	Number of relapses before DMD treatment	Number of relapses during and after DMD treatment	DMD or DMD and Mx treatment	MRI after DMD treatment	MRI Gd+after DMD treatment
B.R.	Pyramidal syndrome (paraparesis)	2	2 4	Avonex Copaxone	Progression of lesions	No
J.M.	Sensory signs	2	3 3	Betaferon Mitoxantrone	Progression of lesions	No
Z.Z.	Optic neuritis, right-sided pyramidal syndrome	2	1 3	Betaferon	Progression of lesions	No
A.G.	Pyramidal syndrome (paraparesis)	2	3 5	Betaferon Mitoxantrone	Progression of lesions	No
E.G.	Pyramidal syndrome (paraparesis)	2	3 3 1 2	Rebif Avonex Tysabri	Progression of lesions	Yes
G.J.	Sensory signs, pyramidal syndrome (paraparesis)	2	2 1 1 0	Copaxone Avonex Betaferon Mitoxantrone	Progression of lesions	Yes
Z.K.	Sensory signs, pyramidal and cerebellar syndrome	2	2 1	Rebif Mitoxantrone	Progression of lesions	Yes
B.T.M.	Pyramidal syndrome (paraparesis) and cerebellar syndrome	2	3	Mitoxantrone + Copaxone	Progression of lesions	No
A.F.	Optic neuritis	2	2	Rebif	Progression of lesions	Yes
B.G.	Pyramidal and cerebellar syndrome	2	0 4	Avonex	Progression of lesions	Yes
S.Ż.	Optic neuritis	7		No medication	Progression of lesions	No

DMD – disease modifying drugs, Mx – mitoxantrone, MRI – magnetic resonance imaging, Gd+ – gadolinium-enhancing lesion

activity, creatinine and plasma lipids. Due to the limited number of patients observation outcomes were presented for each of the patients individually.

Results

Results of the study are presented in Table 3.

It should be noted that in 11 cases second-line treatment was introduced in patients when their physical performance deteriorated, either during or after immunomodulatory treatment. Seven out of 11 patients had a marked disability (EDSS 4.0-6.0). In all the reported cases there had been a progression in physical disability, assessed by EDSS, and in radiological damage, evaluated by brain magnetic resonance imaging (MRI), before the introduction of fingolimod treatment. In five cases, T1-weighted lesions enhancing after contrast medium administration had been identified.

Table 3. Clinical characteristics of patients treated with fingolimod before and after 12-month treatment

Initials	Clinical symptoms before treatment	EDSS before treatment	EDSS after 12-month treatment
B.R.	Pyramidal and cerebellar syndrome (bilateral)	4.5	4.0
J.M.	Bilateral pyramidal syndrome, superficial sensation disorders	4.0	4.0
Z.Z.	Right-sided pyramidal syndrome, superficial sensation disorders	2.0	2.0
A.G.	Pyramidal and cerebellar syndrome (bilateral)	4.5	4.5
E.G.	Pyramidal and cerebellar syndrome (bilateral)	6.0	5.0
G.J.	Pyramidal and cerebellar syndrome (bilateral)	6.0	5.0
Z.K.	Pyramidal and cerebellar syndrome (bilateral)	6.0	5.0
B.T.M.	Pyramidal and cerebellar syndrome (bilateral)	6.0	5.5
A.F.	Visual disturbances, pyramidal and cerebellar syndrome (bilateral)	3.5	4.0
B.G.	Pyramidal and cerebellar syndrome (bilateral)	3.0	2.5
S.Ż.	Visual disturbances, pyramidal and cerebellar syndrome (bilateral)	4.5	4.0

EDSS – Expanded Disability Status Scale

In seven cases, an improvement in physical performance assessed by EDSS was seen during the 12-month observation period. In three cases, the patients' neurological condition remained stable, whereas in one case there was a deterioration by 0.5 point (in the visual system). During the minimum of 12 months of fingolimod treatment there were no new relapses of the disease or serious adverse events. One patient developed a urinary infection, while three patients were diagnosed with elevated serum cholesterol levels. Lymphopenia was found in seven out of 11 patients, however none of the cases required drug discontinuation. It must also be emphasized that the study patients had no cardiac dysrhythmia or macular oedema. Similarly, no significant increases in liver enzyme activity were identified. None of the patients showed a more pronounced susceptibility to herpes infections.

Discussion

Ever since fingolimod was approved by the U.S. Food and Drug Administration in 2010, treatment with the drug has been prescribed to a total of 52 000 patients every year. To date, fingolimod has been approved for MS therapy in 65 countries across the world. To enhance the safety profile of the drug taken orally at a dose of 0.5 mg daily, the following actions are recommended: monitoring of peripheral blood CBC values for six months from the start of therapy, monitoring of liver enzyme activity, bilirubin concentration, ECG testing. Patients who have not had chickenpox, or who have not been vaccinated for chickenpox, should undergo serological tests. If no antibodies are identified, consideration should be given to vaccinating the patient against the disease (and administering the drug a month after vaccination). The patient's pulse and blood pressure should be monitored prior to and for six hours after the administration of the first dose of the drug. Vaccination with attenuated vaccines should be avoided during the period of treatment. The European Union guidelines recommend lymphocyte count monitoring and discontinuation of treatment if the lymphocyte count drops below 0.2×10^9/L. Ophthalmological examination should be performed within 3-4 months from the initiation of fingolimod treatment and every time the patient reports any visual disturbances; the guidance applies, in particular, to diabetics and patients with a history of uveitis. If there are appropriate indications, spirometry should be performed. The activity of liver enzymes should also be monitored at regular intervals (in the EU: at 1, 3 and 6 months of treatment). Women of reproductive age are advised to use effective contraception [1,6,12,13].

The own studies reported here involved patients pretreated with at least one immunomodulatory drug before being enrolled in fingolimod treatment. In three cases, treatment was followed by mitoxantrone therapy. An improvement in physical performance evaluated in the EDSS scale was observed in seven out of 11 patients over the 12-month observation period. The remaining

patients, with the exception of one (deterioration of visual acuity), were neurologically stable. Throughout the 12 months of observation there were no new relapses of the disease or serious adverse events. Most members of the patient group under discussion had highly active disease, and failed to respond to immunomodulatory therapy and, in some cases, to immunosuppressive therapy. The outcomes of the own studies are consistent with published results of clinical trials conducted in groups of patients with highly active RRMS [10,13]. The studies comprised three groups of patients. The first group consisted of patients with one or more relapses in the year preceding the clinical trial. The second group included patients with one relapse and at least one gadolinium-enhancing lesion (Gd+) or nine T2-weighted lesions identified by MRI. The third group consisted of previously untreated patients with three or two relapses during the year preceding the year of clinical trial enrolment and at least one Gd+ lesion verified by MRI. The effects of therapy achieved in the group of patients treated with fingolimod 0.5 mg daily were compared to patients receiving placebo or interferon beta 1-a intramuscularly at a dose of 30 μg per week. The greatest benefits of treatment were demonstrated in the group treated with fingolimod vs. placebo or interferon beta 1-a.

The 2012 Annual Meeting of the American Academy of Neurology in New Orleans saw the presentation of 7-year data from a phase II extension study of fingolimod treatment (1.25 mg vs. 5 mg, once daily) in relapsing MS. The findings included sustained beneficial effect, i.e. reduced activity of the disease, compared to the group in which treatment was not continued, and good tolerance of the drug. No new relapses of the disease were confirmed in 55% and 66% of patients who completed 7-year fingolimod treatment, while 83% of patients were free of contrast-enhanced lesions. Adverse events included nasopharyngitis (40.9%), headaches (31.3%), herpes (16 cases) and skin malignancies (14 cases). The overall tolerance of the drug was good. No atrioventricular conduction disorders were observed during the 7-year observation period [14].

The 2012 Meeting of the European Neurological Society in Prague featured a presentation of results of the study conducted by Kappos *et al*. to provide a preliminary assessment of safety and tolerance of fingolimod 0.5 mg taken orally once daily during the first four months of therapy (FIRST study). The multi-centre trial involved a total of 2417 RRMS patients including diabetics, individuals suffering from bronchial asthma and certain cardiac diseases, aged up to 65 years, with disability status up to 6.5 points assessed by EDSS [15]. Clinical data were obtained for 94.4% of patients. Adverse events occurred in 75.3% of patients. The most common were: nasopharyngitis (14.8%), headaches (11.3%), lymphopenia (9.4%) and fatigue (6.6%). Infections developed in 34.3% of patients, with herpes virus infections (chiefly orolabial herpes) accounting for 4.9% of cases. Serious adverse events were confirmed in 4.1% of patients. Sixteen patients (0.7%) developed macular oedema, while 9 patients (0.4%) were diagnosed with skin cancer (other than melanoma). A total of 16 patients discontinued treatment due to abnormal liver test results. The type and incidence of adverse events did not differ from those identified during the initial six months of therapy in previous clinical trials [15].

The findings of the preliminary studies, including low proportion of patients who discontinued treatment, show that fingolimod is well tolerated across a broad spectrum of RRMS forms.

Conclusions

Fingolimod treatment was effective regardless of the activity of the disease and prior immunomodulatory and immunosuppressive therapy. It is worth emphasizing that the study reported above is the first preliminary observation of fingolimod treatment in patients with the relapsing form of MS, conducted in line with the current criteria regulating the introduction of second-line drug.

Disclosure

Authors report no conflict of interest.

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