Evaluation of long-term efficacy of disease-modifying agents in patients with relapsing-remitting multiple sclerosis

Anita Risonjić[1], Hana Smajlović[1], Anisa Šero[1], Ena Šaranović[1], Nudžejma Veladžić[1], Maida Rakanović-Todić[2], Lejla Burnazović-Ristić[2], Sanita Maleškić Kapo[2], Enra Mehmedika-Suljić[3]

[1]Faculty of Medicine, University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[2]Department of Pharmacology and Toxicology, Faculty of Medicine, University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[3]Clinic of Neurology, University clinical centre Sarajevo, Sarajevo, Bosnia and Herzegovina

ABSTRACT

Objective. Disease-modifying therapy (DMT) still remains a fundamental treatment for relapsing-remitting multiple sclerosis. However, data about their resudual effect and relapse severity after the discontinuation of treatment remain scarce. The objective of this study was to evaluate the presence of residual effect of metenkefalin and tridecactide, as a novel disease-modifying agent (DMT), in treatment of relapsing-remitting multiple sclerosis (RRMS).

Materials and methods. A retrospective observational study was conducted to examine number and severity of relapses in a two-year period after the discontinuation of DMT. Data of total of 40 patients were included in the study analysis. Of that number, 32 received combination of metenkefalin and tridecactide, while 8 patients received interferon-β–1b (IFN-β-1b). The objective parameter for relapse severity was Expanded Disability Status Scale (EDSS) score.

Results. 8 out of 40 patients who received DMT were hospitalized for relapses in a two-year period after the end of treatment. All of them after discountinuation of treatment with combination of metenkefalin and tridecactide. The median age of patients was 41.38±10.1 years (range from 26 to 60 years). Two thirds of these patients (6 patients) had only one relapse. The median time from the end of the treatment to relapse was 8.15±3.65 months (range from 1.5 from 14.7 months). The median value of EDSS score during the relapses was 3.25 (3.0-4.25) and it was significantly higher than the median value of EDSS score at the end of metenkefalin and tridecactide treatment [2.5(1.38-3.0)] (p=0.041; p>0.05).

Conclusion. The results of our study indicate some residual effect of metenkefalin and tridecactide treatment on relapse rate that should be further explored.

Keywords: multiple sclerosis, disease-modifying therapy, metenkefalin and tridecactide, relapse

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*Corresponding author
Maida Rakanović-Todić
Department of Pharmacology and Toxicology
Faculty of Medicine
University of Sarajevo
Čekaluša 90, 71000 Sarajevo
Bosnia and Herzegovina
E-mail: maida.todic@mf.unsa.ba

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by demyelination and axonal loss. It is the most common disabling neurological disease of young adults. The etiology of MS is unknown, but it is suggested to be an autoimmune disorder. Environmental and genetic factors play a partial role in the development of MS (1, 2).

Four disease courses have been identified in MS: relapsing-remitting MS (RRMS), primary-progressive MS (PPMS), secondary-progressive MS (SPMS) and progressive-relapsing MS. Among these four the most common is RRMS (approximately 85% initial diagnoses of MS) which is characterized by clearly defined attacks of worsening neurological function called relapses. These relapses are followed by remission which represent a partial or complete recovery periods (2).

The treatment management can be divided into relapses treatment, disease-modifying and symptomatic treatment. Disease-modifying therapy (DMT) remains to be the main treatment for RRMS associated with improved long-term outcomes and disease control (1, 3). It is recommended to include DMT as early as possible in order to reduce disease progression and burden of disease. Anyway, treatment algorithms distinguish between first- and second-line agents considering the benefit-risk profile of the agents and clinical indicators of the disease, however, due to insufficient data, no clear recommendations have been established for the choice of one DMT agent over another. The choice of DMT is left to the practicing neurologist. Currently, several disease-modifying agents are available, with mutual therapeutic aims which include lowering frequency and duration of relapses, decreasing the persistence of effects of relapses, preventing of disability progression and consequently improving quality of life.

During our study only two DMT were available to the patients, 1) metenkefalin and tridecactide in combina-

tion, and 2) IFN-β-1b. Enkorten® (ENK) is a novel drug with immunomodulatory and anti-inflammatory activity which is registered in Bosnia and Herzegovina. It is a combination of two neuropeptides, metenkefalin and tridecactide (adrenocorticotropic hormone 1-13) which exert cytoprotective anti-inflammatory effects (4, 5). Interferon beta (INF-β) was one of the first approved DMT for MS. It is considered that IFN-β-1b increases the production of anti-inflammatory cytokines (IL-4 and IL-10) and suppresses the production of proinflammatory cytokines (TNF-tumor necrosis factor).

Today, fifteen drugs have been approved by Food and Drug Administration (FDA) making the choice of therapy more complex, but data about their prolonged efficacy and relapse severity after the discontinuation of treatment remain scarce (6). Therefore, we considered that there was a research interest to document whether relapses would be observed in patients treated any kind of DMT available, including small number of patients who completed treatment with IFN-β-1b.

The objective of this study was to evaluate if there is prolonged (residual) effect of combination of metenkefalin and tridecactide in treatment of RRMS.

Materials and methods

A retrospective observational study was conducted to examine number and severity of relapses in two-year period after the discontinuation of DMT.

This study included 40 patients aged 18-60 years with clinically confirmed diagnosis of RRMS in accordance with the McDonald Diagnostic Criteria (2010), in two-year period after the discontinuation of DMT. Two DMTs were locally available for treatment during the study period: 1) metenkefalin and tridecactide, 2) IFN-β-1b. Of that number, 32 received combination of metenkefalin and tridecactide during the period from 2012 to 2013 and 8 patients received IFN-β-1b during the period from 2010 to 2012 at Neurology Clinic of University Clinical Centre in Sarajevo, Bosnia and Herzegovina.

The treatment with metenkefalin and tridecactide was applied in accordance to intensive relapse treating scheme as follows: first week 3 X 12 mg (2 mg of tridecactide and 10 mg of met-enkephalin), second week 3 X 12 mg, third week 3 X 6 mg (1 mg of tridecactide and 5 mg of met-enkephalin). The treatment with IFN-β-1b lasted 18 months according to standard dosing scheme for RRMS.

Relapses as outcome in this study were defined as nearly appearing neurological symptoms in the absence of fever or infections that last for more than 24 hours. The objective parameter for relapse severity was Expanded Disability Status Scale (EDSS) score. EDSS quantifies

disability and status of eight functional systems and ranges from 0 (normal neurological examination) to 10 (death due to MS) as the most serious outcome (5 is referring to walking without aid for 200 meters). The annualized relapse rate (ARR) was calculated as the total number of relapses divided by the total person-time at risk of relapse.

Data were statistically analyzed in computer software SPSS (Statistical Package for Social Sciences©, version 17.0, SPSS Inc, Chicago, Illinois, USA). Data for a total of 40 patients were included in the descriptive analysis. Comparison for EDSS score was performed by Mann-Whitney U test for variables without normal distribution.

Results

Demographic and clinical characteristic of enrolled patients (n=40) are presented in the table 1. 32 patients were on treatment with metenkefalin and tridecactide and 8 patients were treated with IFN-β-1b as a DMT.

Only patients who received combination developed relapse, 20% of treated patients were hospitalized for relapses in a two-year period after the end of treatment.

Table 1. Patient characteristics

Gender	
Female	23
Male	17
Received Therapy	
Combination of metenkefalin and tridecactide	32
IFN-β-1b	8
Patients with relapses	
Combination of metenkefalin and tridecactide	8
IFN-β-1b	0

Table 2. Characteristics of patients with relapse (n=8)

Gender	
Female	4
Male	4
Number of relapses	
One relapse	6
Two relapses	1
Three relapses	1
Age (years)	41±10.1
Min.	26
Max.	60

Demographic and clinical characteristics of patients who experienced relapses are shown in Table 2. Equal number of male and female patients had relapse. The greatest number of the patients with relapses, 75% of them had one relapse, 12.5% patients developed two relapses and 12.5% patients had three relapses.

The median time from the end of the treatment to relapse was 8.15±3.65 months (range from 1.5 to 14.7 months).

For metenkefalin and tridecactide post-discontinuation period the calculated ARR was 0.125. In the same group the median value of EDSS score during the relapses was 3.25 (range 3.0-4.25) and it was significantly higher than the median value of EDSS score at the end of metenkefalin and tridecactide treatment 2.5 (1.38-3.0)] (p=0.041; p<0.05) (Figure 1).

Figure 1 Value of EDSS at the end of metenkefalin and tridecactide treatment and during relapses
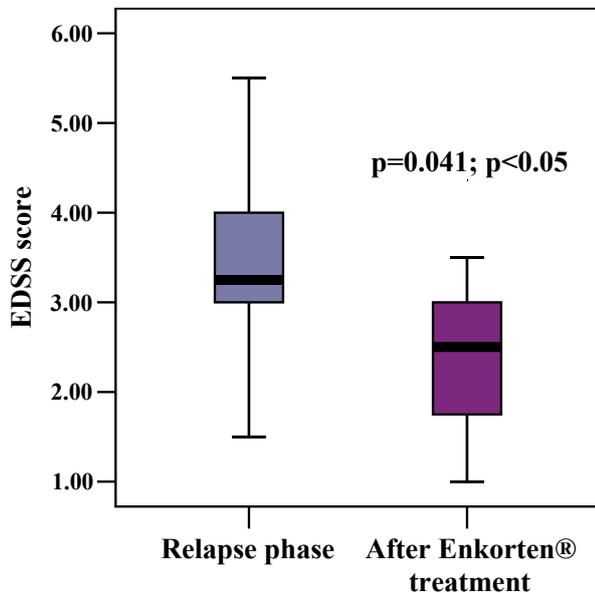
Discussion

In clinical practice discontinuation of DMT is usually undertaken due to the occurrence of side effects and poor tolerance of the drug, or a decrease in the effectiveness of the treatment itself. We were interested to explore the residual effect of the treatment with metenkefalin and tridecactide, and if there is a need for strict clinical monitoring after treatment discontinuation. Results of our study indicate that combination of metenkefalin and tridecactide as a disease-modifying therapy was not accompanied by a high relapse rate after treatment discontinuation. 75% of patients, who received this combination, were relapse-free in a two-year period after the discontinuation of therapy. The

results of Phase II and Phase III clinical trials are showing that 85% of enrolled patients were without relapse during treatment with metenkefalin and tridecactide (4, 5). Likewise, 72% of patients in the experimental group did not experience any relapses during the 12 months of Phase II clinical trial, compared to 42.3% in the control group.

All the 8 patients treated with IFN-β-1b in our study did not have any relapse in a two-year period after the end of therapy. The results of several prominent studies that have demonstrated that IFN-β-1b is efficient in reducing both relapse rate and MRI lesions (7, 8). Despite the development of new DMTs, this agent remains significant contributor in the treatment of RRMS thanks to well known risk-benefit ratio (8), but also in terms of costs and health outcomes (9).

The effects of DMT has been well investigated. Observed annualized relapse rate reduction during the treatment with IFN beta-1b is 34%, while for newer DMT agents such as natalizumab, alemtuzumab and mitoxantrone, it was over 60% (10). Anyway, a disease course after discontinuation of DMT is poorly explored, while the observed effects are diverse. Newer agents have been more investigated, given clearer implications about the wash-out period when replacing treatments. In order to reduce the risk of relapse, a maximum period of 3 months is recommended between natalizumab discontinuation and starting treatment with fingolimod (11)

Berger et al. (2015) described a case series of four RRMS patients that developed severe relapse two to four months after fingolimod treatment discontinuation (12). In Italian multicenter TY-STOP study (13), that enrolled 130 patients that completed 24 doses of natalizumab, authors stratified patients who completed follow-up data (n=124) into three groups, those who continued natalizumab treatment, group that changed to different treatment option, and those that discontinued natalizumab. Study detected a protective effect of natalizumab continuation on the risk of relapse compared with discontinuation of natalizumab (OR, 4.40; 95% CI, 1.72-11.23), and discontinuation with changing of DMT (OR, 3.28; 95% CI, 0.99-10.79). The calculated mean annualized relapse rate for natalizumab continuation was 0.24, while rate of 0.73 followed any type of discontinuation of natalizumab including stopping and changing treatment (n=81).

Relapse frequency has a predictive value, especially in early-stage multiple sclerosis. Studies have shown that patients, who had more frequent relapses within 2-5 year from onset of the disease, have poorer prognosis. Extension of inter-relapse interval is one of the main aims of every disease-modifying therapy. Achievement of this aim leads to better quality of patient's life and it

is assumed that it has a positive prognostic value (14, 15). Our findings demonstrate that patients who used metenkefalin and tridecactide combination were without a relapse for more than 8 months in average.

Not registering relapses in patients treated IFN-β-1b could be due to small number of patients who received IFN-β-1b (8 patients). Secondly, patients received IFN-β-1b for a much longer period than patients who were receiving the combination.

Previous studies suggested factors that can affect the frequency of relapse, for instance smoking is associated with an increased relapse rate during treatment with IFN-β (16). Data about such factors are not available in our study.

Conclusion

The results of our study indicate some residual effect of metenkefalin and tridecactide treatment on relapse rate. This leaves the hope for further investigations. Therefore, further research is needed to answer the question about effectiveness ad usefulness of metenkefalin and tridecactide combination in patients with RRMS.

Declaration of interest

The authors declare that they have no conflict of interest.

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