BENEFIT FROM BETA INTERFERON IN THE TREATMENT OF MULTIPLE SCLEROSIS

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SUMMARY – Over the past twelve years, beta interferons 1a and 1b have been increasingly used as immunomodulatory agents in the treatment of multiple sclerosis as well as for prophylaxis of disease progression. In Croatia, the cost of beta interferons 1a and 1b has been covered by the Croatian Institute of Health Insurance since 1997. Despite numerous doubts about their real benefit, having in mind their price, side effects and occurrence of neutralizing antibodies, numerous clinical trials have confirmed their efficacy. The most efficient are interferon beta 1a (Rebif® in a dose of 12 MIU, subcutaneously, three times *per* week), interferon beta 1b (Betaferon® in a dose of 8 MIU, subcutaneously, every other day) and interferon beta-1a (Avonex® in a dose of 6 MIU weekly intramuscularly).

Key words: *Interferons – therapeutic use; Multiple sclerosis – drug therapy; Interferons – adverse effects; Treatment outcome; Clinical trials*

The Pathogenesis and Types of Multiple Sclerosis

Multiple sclerosis is an inflammatory autoimmune disease with demyelinization of the central nervous system characterized by multifocal inflammatory destruction of myelin, impairment of axons and loss of oligodendrocytes. Activated T-lymphocytes that cause endothelial changes of the blood-brain barrier are involved in the pathogenesis of the disease. They release inflammatory mediators and initiate the cascade of inflammation. The role of interferon gamma (IFN-γ) is important in the disease development. IFN-γ is produced by activated T-cells of class T_1-helper (TH1) and incites macrophages to the production of proteases and tumor necrosis factor (TNF) that damage oligodendrocytes, thus stimulating clinical manifestation and pro-

gression of the disease. Multiple sclerosis may take a malignant or benign course, and according to form of the disease it is divided into relapsing remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), primary progressive multiple sclerosis (PPMS) and progressive relapsing multiple sclerosis (PRMS). The most common form of the disease is RRMS, found in approximately 85% of cases.

Beta Interferon in the Treatment of Multiple Sclerosis

Over the past twelve years, beta interferon (IFN-γ) has been used in the prophylactic management of the disease progression as a beneficial immunomodulatory treatment that modifies the natural course of multiple sclerosis. The mechanism of its action is not completely understood; however, it is known that IFN-γ has an antiviral, immunomodulatory and antiproliferative effect[1]. It increases the number and activation of CD8 suppressor cells. Their number is decreased in multiple sclerosis patients. It also inhibits the secretion of IFN-γ, which enhances the manifestation and progres-

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sion of the disease. IFN-γ also inhibits gamma interferon-induced expression of major histocompatibility complex (MHC) class II antigens on the surface of glial cells. Beta interferons also have an effect on the decrease of lymphotoxins (LT) and tumor necrosis factor (TNF), which impair the oligodendrocyte function. They stimulate astrogliosis, thus decreasing the possibility of transport of activated immune cells across the blood-brain barrier. Beta interferons increase T_2-helper (TH2) cytokines, interleukin 4 (IL-4) and interleukin 10 (IL-10), stimulating their production as well as the production of the transforming growth factor beta (TGF-beta) from TH cells.

Recombinant beta interferons 1a and 1b are used in the treatment of multiple scelrosis; the glycosylated form of beta interferon 1a is more similar to the natural human beta interferon (Rebif®-Serono and Avonex®-Biogen). They have been registered on the European market, and on the market in Canada and USA since 1998. The non-glycosylated form of beta interferon 1b (Betaseron®-Berlex Laboratories and Betaferon®-Schering AG) has also been used. The first clinical trial that confirmed its activity was performed in 1993.

Interferon beta 1a is produced from mammal cells. As a result, their structure is more similar to the human beta interferon. Beta interferon 1b is produced from cultures of the bacteria *E. coli.*

The Efficacy of Multiple Sclerosis Treatment with Beta-Interferon – Clinical Trials

Numerous important clinical trials have been performed worldwide, testing and comparing the efficacy of some of the above mentioned beta interferons in the treatment of patients suffering from different forms of multiple sclerosis, most frequently RRMS. Treatment efficacy was compared between the type of beta interferon used and another beta interferon[2] or placebo according to the frequency of administration (weekly, three times *per* week, every other day), time span of administration (year, two years, many years), route of administration (subcutaneous [s.c.], intramuscular [i.m.]), drug dosage and disability at the beginning and at the end of treatment graded by the Expanded Disability Status Scale (EDSS; scale of disability grading disability of patients suffering from multiple sclerosis from 0 denoting normal neurologic finding to 10 denoting death)[3,4].

The validity of a particular type of beta interferon was measured by the number of relapses (relapse or worsening of the disease), progression of the disease,

decrease of disability by one point on EDSS scale, decrease in the number of demyelinization lesions on magnetic resonance imaging (MRI), and decrease in the extent of lesions on MRI during the treatment period.

The most extensively cited clinical trials are the following: the IFNB Multiple Sclerosis Study Group, the first multicenter, randomized, double blind, placebo controlled study conducted in 1993 in RRMS patients (comparison between beta interferon 1b and placebo)[5,6]; PRISMS (Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis; (comparison between two different doses of beta interferon 1a, Rebif® 22 mcg (6 MIU) s.c. three times *per* week and Rebif® 44 mcg (12 MIU) s.c. three times *per* week[7]; SPECTRIMS (Secondary Progressive Efficacy Clinical Trial in MS)[8]; ETOMS (Early Treatment of Multiple Sclerosis with Rebif®)[9]; EVIDENCE (comparative study of the efficacy of Rebif® and Avonex®)[10]; and OWIMS (comparison of Rebif® in a dose of 22 mcg s.c. and 44 mcg s.c. weekly)[11]. According to new findings from the BENEFIT (Betaferon/Betaseron in Newly Emerging MS For Initial Treatment) study[12], interferon beta-1b 250 mcg treatment delayed the onset of clinically definitive multiple sclerosis (CDMS) by one year (363 days) in patients with first clinical signs of multiple sclerosis compared to placebo.

Analysis of the efficacy of different types of beta interferon and mechanisms of action for multiple sclerosis treatment has shown that therapy should be directed towards activation of T-cells and their differentiation into TH cells, induction of TH1 cell proliferation by IL-1, gathering of B lymphocytes and monocytes by TH1, transport of activated TH1 cells across the blood-brain barrier, and reactivation of T-cells[13,14] (Table 1).

Doubts about the Use of Beta Interferon (Efficacy, Side Effects, Price, Occurrence of Neutralizing Antibodies)

Recombinant beta interferons have been approved for the treatment of RRMS, however, discussion about their real efficacy, adverse events and price is still going on. A meta-analysis of published randomized placebo controlled trials of their use in RRMS patients (during the 1993-2002 period) by use of Cochran Collaboration has pointed out that they have been slightly decreasing the number of patients having exacerbations over the first year of treatment and that the clinical effect after the first year of treatment has been uncertain. It has also shown that new studies of the long-term use of re-

Table 1. Efficacy of different types of beta interferon

Micrograms (mcg) or dose level	Copaxone	Avonex 1X33	Rebif 3X22/3X44	Betaferon 8 MIU
% of decrease of relapses				
In 1 year	33	9.6	33/37	33
In 2 years	29	18	29/32	31
% of increase of time to first relapse			59/87	
No relapse in 1 year	24	46	69/119	56
No relapse in 2 years	45	31	70/113	93
Time to progression of disability		37	55/79	15
% of decrease of progression	4		7.7/46	
% of decrease of T2 activity in 2 years		33	67/78	
% of decrease of T1 Gd (9 months)	29		53/74	

combinant forms of beta interferon and cost-effect analyses are needed[15].

The treatment with beta interferons could also be associated with the occurrence of neutralizing antibodies. Immunologic studies have shown that neutralizing antibodies could prolong the biological life of cytokines, thus eliciting a favorable positive effect. The occurrence of neutralizing antibodies with the use of beta interferon could be associated with the loss of their efficacy.

The side effects of the above mentioned types of beta interferon are the following: flu-like symptoms, skin changes at the site of application, impaired liver function tests, depression, and allergy. Anemia may occur during Avonex® treatment[16], and cytopenia with Betaseron® treatment.

The Use of Beta Interferons in the Treatment of Multiple Sclerosis in Croatia

In Croatia, two types of beta interferons have been approved for the treatment of multiple sclerosis since 1997: Rebif®, interferon beta 1a (Serono), 22 mcg s.c. 3 times *per* week, and Betaferon®, interferon beta 1b (Schering AG), 8 MIU s.c. every other day, along with interferon beta-1a Avonex® in a dose 6 of MIU weekly i.m. The cost of interferon therapy is covered by the Croatian Institute of Health Insurance. The Institute regulatory body (Drug Committee) approves the treatment with beta interferon 1a or 1b on the basis of the following criteria: patient age 18-55, ability to walk minimum 500 meters without support (EDSS ≤4), disease duration for a minimum of one year, at least two episodes of the disease exacerbation over the past two years

before drug administration, absence of pregnancy, and absence of psychological disturbances (depression).

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Sažetak

KORIST OD LIJEČENJA MULTIPLE SKLEROZE BETA INTERFERONOM

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Posljednjih dvanaest godina u svrhu profilakse pogoršavanja bolesti, odnosno u imunomodulacijskom pristupu u liječenju bolesnika oboljelih od multiple skleroze u svijetu se rabe interferoni beta 1a i 1b. U Republici Hrvatskoj se na teret Hrvatskoga zavoda za zdravstveno osiguranje u liječenju multiple skleroze interferoni beta 1a i 1b primjenjuju od 1997. godine. Iako postoje brojne dvojbe o njihovoj stvarnoj koristi s obzirom na cijenu, nuspojave te pojavu neutralizirajućih antitijela, dosad je objavljeno više kliničkih studija koje su pokazale njihovu učinkovitost. Najučinkovitiji su interferon beta 1a (Rebif® u dozi od 44 mikrograma (mcg) subkutano, tri puta na tjedan), interferon beta 1b (Betaferon® 8 MIU subkutano svaki drugi dan) i interferon beta 1a (Avonex® 6 MIU intramuskularno jedanput na tjedan).

Ključne riječi: *Interferoni – terapijska primjena; Multipla skleroza – liječenje lijekovima; Interferoni – štetni učinci; Liječenje – ishod; Klinička ispitivanja*