Medicinski podmladak

Medical Youth

Mini review article

INTERFERON BETA – MEDICATION WHICH STARTED THE REVOLUTION IN THE TREATMENT OF MULTIPLE SCLEROSIS

INTERFERON BETA – LEK KOJIM JE ZAPOČETA REVOLUCIJA U LEČENJU MULTIPLE SKLEROZE

Jovana Ivanović[1], Tatjana Pekmezović[2], Jelena Drulović[1,3]

[1] Faculty of Medicine, University of Belgrade, Belgrade, Serbia
[2] Institute of Epidemiology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia
[3] Clinic of Neurology, Clinical Center of Serbia, Belgrade, Serbia

Correspondence: drulovicjelena@gmail.com

Abstract

Multiple sclerosis is a chronic, inflammatory, demyelinating and neurodegenerative disease of the central nervous system. The etiology is unknown, and it is estimated that about 2.5 million people all around the world are suffering from this disease. It is the most common cause of non-traumatic disability in young adults. The clinical presentation is very variable and unpredictable. There are three basic forms of the disease – relapsing remitting, primary progressive and secondary progressive multiple sclerosis. The prognosis for these patients has changed since 1993, when the first disease modifying therapy – interferon beta, was approved. Interferon beta reduces the number of relapses, reduces the number of hyper intense lesions on T2 sequences of endocranial MRI, mildly delaying the progression of the disease. Interferon beta is also used in pediatric population. It is considered to be generally safe, since it does not increase the likelihood of developing malignancy and opportunistic infections.

Keywords:
Multiple sclerosis, interferon beta, natural history of the multiple sclerosis

Sažetak

Multipla skleroza (MS) je hronično, inflamatorno, demijelinizaciono i neurodegenerativno oboljenje centralnog nervnog sistema. Nepoznate je etiologije, a procenjuje se da je širom sveta obolelo oko 2.500.000 ljudi. Najčešći je uzrok netraumatskog invaliditeta kod mladih odraslih osoba. Klinička slika je veoma varijabilna i nepredvidiva. Postoje tri osnovne forme bolesti – relapsno remitentna, primarno progresivna i sekundarno progresivna multipla skleroza. Prognoza kod ovih pacijenata se promenila od 1993. godine kada je prvi put registrovan lek za modifikovanje prirodnog toka bolesti relapsne MS – interferon beta. Interferon beta smanjuje broj relapsa bolesti i broj hiperintenznih lezija na T2 sekvenci magnetne rezonance endokranijuma, a dovodi i do blagog usporavanja progresije bolesti. Interferon beta se koristi i u pedijatrijskoj populaciji. Uglavnom je bezbedan i ne povećava rizik za razvoj maligniteta i oportunističkih infekcija.

Ključne reči:
Multipla skleroza, interferon beta, prirodni tok multiple skleroze

The authors declare no conflicts of interest.

doi:10.5937/mp70-18871
Editorial board: podmladak.med.bg@gmail.com
e-ISSN: 2466-5525

Multiple sclerosis (MS) is chronic, inflammatory, demyelinating and neurodegenerative disease of the central nervous system. Etiology is unknown, and it is estimated that there are about 2,500,000 of people suffering from this disease. Multiple sclerosis was first described by Charcot in 1868, when he noticed triad of symptoms – nystagmus, intention tremor and scanning of speech (1). The MS is the most common cause of non-traumatic disability in young adults (2). The incidence of the disease is relatively low in childhood, increasing after 18 years of age, reaching a peak between 25 and 35 years of age, and then again decreasing. The risk of morbidity is higher in women than in men and the ratio varies between 1:2 and 1:3 (3). The etiology of MS is still unknown, and numerous studies have highlighted the importance of both genetic and environmental factors, as well as their interactions, which triggers the autoimmune process. Significant environmental factors include infections, especially Epstein-Barr virus infection, lack of ultraviolet radiation, vitamin D deficit and smoking (4). Analyzes of the mortality rate in MS patients showed that the mortality risk is higher in patients than in the general population, so these persons have a 2.7 times higher mortality risk. The death is most commonly caused by secondary complications such as infections, decubital wounds, pneumonia, sepsis, and very rarely as a direct consequence of the disease and cervical and brainstem lesions (5).

Multiple sclerosis is a disease characterized by a very heterogeneous and unpredictable clinical presentation, and the severity of the disease may vary from asymptomatic, proven only by autopsy, but also can lead to very rapid disability and even to fatal outcome. Despite the wide heterogeneity, three clinical forms of the disease are defined: relapse-remitting (RRMS), secondary-progressive (SPMS), and primary-progressive multiple sclerosis (PPMS) (6). The RRMS initially presents in about 80-90% of patients and is characterized by the acute disease worsening, relapse, and afterwards remission and stabile period. Relapses are defined as the worsening of already existing symptoms or appearance of a new neurological deficit lasting longer than 24 hours, in the absence of fever and infection. The frequency of relapse is variable in different patients. The phase of remission between the two relapses must last at least 30 days, and if this period is shorter, the new symptoms are considered as a worsening within a single relapse of the disease (7). The first clinical attack of the disease is called a clinically isolated syndrome which suggests demyelination (CIS). In some patients, CIS never converts to MS, but it is more common that a new disease relapse or progression occur and the diagnosis of clinically definite MS can be established. However, in 40-80% of the patients who had RRMS at the beginning of the disease, progression occurs after 6 to 22 years, with an irreversible accumulation of the neurological deficit. This form of disease is known as a secondary progressive (SPMS). Also, it is well known that a possible occurrence of relapses in SPMS exists in approximately 40% of cases (8). Primary progressive (PPMS) occurs in 10-20% of patients and is characterized by progressive and continuous accumulation of neurological deficits since the onset of the disease. The PPMS occurs usually in the elderly and this form of the disease is more common in men (9).

There is not a sufficiently specific clinical feature, neither a diagnostic procedure that can with absolute certainty verify the diagnosis of MS. The main principle which is used for establishing MS diagnosis is dissemination of neurological symptoms/signs in time and space, until recently with revised Mc Donald criteria from 2017 (10). The diagnosis is based on the following principles:

1. Objective evidence of dissemination in time and space by clinical or neuroradiological examination;

2. Objective neurological deficit typical of MS that must be detected by neurological examination;

3. Typical lesions on endocranial and spinal cord magnetic resonance (MR) - existence of hyperintensive T2-weight lesions on typical localizations: periventricular, juxtacortical, infratentorial, in the cervical spinal cord, and according to the latest criteria (sub)cortical;

4. Excluding other alternative diagnoses (demyelinating, infectious, vascular, neurodegenerative…).

The new McDonald criteria does not require the finding of visual evoked potentials (VEPs) for diagnosis, but the isoelectric focusing cerebrospinal fluid has again got a great significance, especially in patients with the first demyelinating symptoms/ signs, as well as in the diagnosis of PPMS. Based on all these principles, one of the following diagnoses should be established: MS, possible MS and not MS (10).

Almost every neurological manifestation can occur in patients with MS. The most common clinical manifestations are motor, sensory, visual neurological deficit, symptoms caused by brainstem and cerebellar lesions, bowel and bladder dysfunction, sexual dysfunction and fatigue. However, pain, cognitive and psychiatric disorders are also common. Involuntary movements, paroxysmal disorders and seizures can also occur. All these clinical manifestations significantly affect the quality of life of the diseased (11).

The MS significantly affects the quality of life of the diseased, because in most cases the first clinical manifestation occurs in young adults, between the ages of 20 and 40, who are capable of working, and at the peak of their physical, psychological, reproductive capacity. However, immunomodulatory drugs that change the natural history of the disease significantly improve the quality of life and the prognosis of MS in these patients (12).

In MS, there are three types of therapy – therapy which is used for treating relapses of the disease, disease modifying therapy and symptomatic therapy.

High-dose corticosteroids are used for MS relapse treatment, usually methylprednisolone intravenously 1000 mg daily, is administered, for three or five consecutive days. In cases of corticosteroid therapy resistant relapses, therapeutic plasma exchanges can be performed, usually five to seven procedures (13).

Symptomatic therapy includes a pharmacological and non-pharmacological approach to facilitate and eliminate the symptoms of the disease that affect the daily activities and quality of life of the patient. A non-pharmacological approach is particularly important, such as physical therapy and psychological support for patients (14).

Today, there are 15 drugs that have the ability to modify the natural history of the disease, reduce the number and severity of the relapses, and delay progression. These are immunosuppressive and immune-modulatory drugs (15). The first therapeutic line includes four interferon beta preparations, two glatiramer acetate formulations, teriflunomide and dimethyl fumarate. Escalation therapy includes fingolimod, natalizumab, alemtuzumab, ocrelizumab and mitoxantrone (16). Since 2017 and 2018, the monoclonal antibody ocrelizumab is administered in the US and European countries for the treatment of RRMS, but more significantly, ocrelizumab is the first and only approved drug for treating PPMS (17,18). Additionally, a few months ago, an oral therapy, cladribine, has been approved as a RRMS therapy, which is significant because it is the first oral drug that leads to the immune system reconstitution (19). Until March 2018 another monoclonal antibody, daclizumab, was used as escalation therapy for the treatment of RRMS, however, the drug was withdrawn after reporting 12 cases of fatal immune-mediated meningoencephalitis (20).

Interferons, including interferon beta, are anti-inflammatory cytokines which have a complex mechanism of action - increasing the expression and concentration of anti-inflammatory mediators, reducing the expression of proinflammatory cytokines, decreasing the migration of inflammatory cells through the blood brain barrier, increasing the production of neuronal growth factors and increasing the number CD56 + NK cells (21).

Possibility that MS can be very severe illness has been recognized a long time ago, so attempts to modify the natural history of this disease are promoted from 1981 when Jacobs et al. applied interferon beta intrathecally in 34 RRMS patients, since they thought that interferon beta had immunomodulatory effects, and this has been proven due to the fact that treated patients had statistically significant lower relapse rates than the control group of untreated patients (22).

In 1984, Knobler et al. administered interferon alpha for six months in 24 RRMS patients, and showed that treated patients had a lower relapse rate and milder neurological deficit than a placebo-controlled group of patients (23).

In 1993, the results of a clinical study which involved 372 RRMS patients were published, and it was concluded that patients treated with interferon beta had a lower number of disease exacerbations, with milder relapses leading to a smaller neurological deficit compared to the untreated cohort of patients (24). Knobler et al. have published very significant results in 1993 after six years follow-up of RRMS patients treated with interferon beta and presented the long-term safety of this drug and no serious life-threatening adverse events. The only serious adverse event observed during the six-year follow-up was suicide attempt in one treated patient, but it was estimated that this event was not associated with study drug (25). Due to previous reported positive results, on July 23, 1993, Interferon beta 1b (Betaseron) was approved as the first immune-modulatory therapy for the RRMS, and was a gold standard and the first choice therapy for modifying the natural history of the disease. Since that time, a number of randomized clinical studies have been conducted to assess the efficacy and safety of interferon beta and its effects on the natural history of the disease. Majority of studies were conducted over 2-3 years and evaluated only the short-term effects of the drug. In 1996, Jacobs et al. published the results of a randomized placebo-controlled study involving 301 patients with RRMS and showed that the intramuscular application of interferon beta 1a decreases the accumulation of physical deficits, then decreases the number and severity of MS relapses, and also decrease the number of active lesions on brain MRI (26). It has also been shown that the drug application reduces the number of MS relapses by 1/3 (27). However, the majority of clinical studies are related to the short-term effects of interferon beta therapy, and studies that estimate the long-term effect of the drug on the natural history of the disease are rare.

The first study on long-term effects of interferon beta therapy on the natural history of MS was performed by Trojano et al. who followed 1504 RRMS patients for seven years, out of which 1103 treated and 401 untreated, and showed that interferon beta therapy statistically significantly delayed the time to achieve secondary progression as well as the degree of neurological deficit quantified with EDSS score (28) 4.0, and 6.0 (29). On the other hand, Shirani and her associates published the results of their research in 2012 after a five-year follow-up of 868 treated RRMS patients compared to the untreated cohort of patients. Contrary to previous results, they concluded that there was no statistically significant influence of interferon beta therapy on progression of MS (30). However, in the same year, Bergamaschi et al. similarly to the Trojano study, showed that interferon beta statistically significantly slowed the progression of the disease (31). In 2013, Drulovic and colleagues conducted a prospective cohort study with 419 RRMS patients (236 interferon beta treated patients and 183 treatment naïve patients) which were followed up for seven years and demonstrated that the use of interferon beta therapy slowed the disease progression and delayed the time to reach SPMS. The time to reach EDSS 4.0 (time point when patient's gait become restricted) in cohort of treated patients compared to untreated patients was prolonged for 4.4 years, and time to reach EDSS 6.0 (neurological deficit when the patient has to use unilateral assistance to walk at least 100 meters) was postponed for 2.2 years (32).

Interferon beta is a very important medication because it is also used in the pediatric population due to its effectiveness, and because of its safety profile, since it does not have any serious adverse events. The results of

the study published last year, in which 67 children with RRMS and average age of 14.2 years, were followed-up for two years, showed that the treated children in 49.1% of cases were relapse-free and 76.8% of children had no disease progression and increasing of EDSS score. There were no serious adverse events, and the most common symptoms were flu-like symptoms, skin reactions, and elevation of liver enzymes (33).

Efficacy of interferon beta was also evaluated in patients with clinically isolated syndrome which suggests demyelination and it was shown that early treatment initiation reduces the possibility of developing clinically definite MS (34).

Several clinical studies have also evaluated the effects of interferon beta therapy on disease activity and disease progression in patients with SPMS, but these studies have not shown that the therapy affects the progression of the disease, although some benefit from therapy, such as a decrease in the volume of hyperintense lesions on the T2 sequence on brain MRI has been detected (35,36). In 2010, Rojas et al. performed a systematic review of the literature and presented the results of previous studies which were estimating the efficacy of interferon beta therapy in patients with PPMS, but there were no evidence that there was a significant difference in slowing progression between cohorts of treated and untreated PPMS patients (37).

The patients most frequently tolerate therapy with interferon beta well and have high adherence, which is usually between 87.5-97.1% (38). The most common adverse effects are flu-like symptoms, headache, local skin reactions, and transaminase elevation. Adverse effects are almost always mild, and serious adverse events have not been described, except that in the earlier studies it has been shown that interferon beta therapy may exacerbate or induce depression. However, these data are inconsistent since it is not possible to prove whether the depression is a part of the disease or it is caused by therapy (39).

Considering the efficacy and safety of interferon beta, despite the increasing number of new and more effective medications which are nowadays available for MS treatment, interferon beta is maintained as one of the first choice therapies in patients with RRMS.

References

1. Charcot JM. Disseminated sclerosis: its symptomatology. Lectures on the disease of the nervous system. *New Sydenham Society, London*, 1877; 209–217.
2. Duddy M. Epidemiology in multiple sclerosis has had its day: there are no more unanswered questions – Yes. *Mult Scler* 2012; 18:140-141.
3. Mayr WT, Pittock SJ, McClelland RL, Jorgensen NW, Noseworthy JH, Rodriguez M. Incidence and prevalence of multiple sclerosis in Olmsted Country, Minnesota, 1985-2000. *Neurology Psychiatr* 2013; 84:141-7.
4. Ascherio A, Munger K. Environmental Risk Factors for Multiple Sclerosis. Part II: Noninfectious factors. *Ann Neurol* 2007; 61:504-13.
5. Pekmezovic T, Jarebinski M, Drulovic J, Stojsavljevic N, Levic Z. Survival of multiple sclerosis patients in the Belgrade population. *Neuroepidemiology* 2002; 21:235-40.
6. Drulović J, Mostarica Stojković M, Pekmezović T,Pravica V, Filipović S, Kisić Tepavčević D, et al. (2013). *Multipla skleroza*. Beograd: Medicinski fakultet u Beogradu.
7. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005; 58:840-6.
8. Koch M, Kingwell E, Rieckmann P, Tremlett H. The natural history of secondary progressive multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2010; 81:1039-43.
9. Dujmovic I, Mesaros S, Pekmezovic T, Levic Z, Drulovic J. Primary progressive multiple sclerosis: clinical and paraclinical characteristics with application of the new diagnostic criteria. *Eur J Neurol* 2004; 11:439-44.
10. Thompson A, Banwell B, Barkhof F, Carroll W, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2017; 162-173.
11. Dackovic J, Stojsavljevic N. Simptomi i znaci multiple skleroze. U: *Acta Clinica: Multipla skleroza* 2011; 11:61-72.
12. Duddy M, Haghikia A, Cocco E, Eggers C, Dulovic J, Carmona O, et al. Managing MS in a changing treatment landscape. *J Neurol* 2011; 258:728-39.
13. Fox RJ, Kinkel RP. High dose of methylprednisolone in the treatment of multiple sclerosis. In: Cohen JA, Rudick RA, eds. Multiple Sclerosis Therapeutics, London: *Informa Healthcare,* 3rd Edition; 2007: 515-33.
14. Frohman TC, Castro W, Shah A, Courtney A, Ortstadt J, Davis SL, et al. Symptomatic therapy in multiple sclerosis. *Ther Adv Neurol Disord* 2011; 4:83-98.
15. Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler* 2018; 24(2): 96-120.
16. Wingerchuk D, Weinshenker B. Disease modifying therapies for relapsing multiple sclerosis. *BMJ* 2016; 354:i3518.
17. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *N Engl J Med.* 2017; 376(3):221-234.
18. Montalban X, Hauser SL, Kappos L, Arnold DL, Bar-Or A, Comi G et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. *N Engl J Med.* 2017; 376 209-220.
19. Jacobs BM, Ammoscato F, Giovannoni G, Baker D, Schmierer K. Cladribine: mechanisms and

mysteries in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2018; 1-6.
20. Biogen, 2018. Biogen and AbbVie announce the voluntary world wide withdrawal of marketing authorizations for Zinbryta® (daclizumab) for relapsing multiple sclerosis [online]. Available: http://media.biogen.com/press-release/autoimmune-diseases/biogen%C2%A0and-abbvie-announce%C2%A0-voluntary%C2%A0worldwide-withdrawal-marketi [Accessed 5 March 2018].
21. Kieseier BC. The mechanism of action of interferon-β in relapsing multiple sclerosis. *CNS Drugs*. 2011;25(6):491-502.
22. Jacobs L, O'Malley J, Freeman A, Ekes R. Intrathecal interferon reduces exacerbations of multiple sclerosis. *Science* 1981; 214: 1026-1028.
23. Knobler RL, Panitch HS, BrahenySL,Sipe JC, Rice GP, Huddlestone JR, et al. Systemic alpha-interferon therapy of multiple sclerosis. *Neurology* 1984;34:1273-1279.
24. The IFN B Multiple Sclerosis Study Group. Interferon beta lb is effective in relapsing remitting multiple sclerosis: Clinical results of a multicenter randomized double blind, placebo-controlled trial. *Neurology* 1993; 43:655-661.
25. Knobler RL, Greenstein JI, Johnson KP, Lublin FD, Panitch HS, Conway K et al. Systemic recombinant human interferon-beta treatment of relapsing-remitting multiple sclerosis: pilot study analysis and six-year follow-up. *J Interferon Res* 1993; 13(5):333-40.
26. Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol* 1996; 39:285–94.
27. The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. *Neurology* 1995; 45:1277–85.
28. Kurtzke JF. Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33:1444–52.
29. Trojano M, Pellegrini F, Fuiani A, Paolicelli D, Zipoli V, Zimatore GB, et al. New natural history of interferon-beta-treated relapsing multiple sclerosis. *AnnNeurol* 2007; 61:300–6.
30. Shirani A, Zhao Y, Karim ME, Evans C, Kingwell E, van der Kop ML, et al. Association between use of interferon beta and progression of disability in patients with relapsing-remitting multiple sclerosis. *JAMA* 2012; 308:247–56.
31. Bergamaschi R, Quaglini S, Tavazzi E, Amato MP, Paolicelli D, Zipoli V, et al. Immunomodulatory therapies delay disease progression in multiple sclerosis. *Multiple Sclerosis* 2016 Nov; 22(13):1732-1740.
32. Drulović J, Kostić J, Mesaroš Š, Dujmović Bašuroski I, Stojsavljević N, Kisić-Tepavčević D, Pekmezović T. Interferone-beta and disability progression in relapsing-remitting multiple sclerosis. *Clin Neurol Neurosurg* 2013; 115: 65-69.
33. Gärtner J, Brück W, Weddige A, Hummel H, Norenberg C, Bugge JP. Interferon beta-1b in treatment-naïve paediatric patients with relapsing-remitting multiple sclerosis: Two-year results from the BETAPAEDIC study. *Mult Scler J Exp Transl Clin* 2017; 3(4):1-9.
34. Comi G, De Stefano N, Freedman MS, Barkof F, Uitdehaag BM, de Vos M, et al. Subcutaneous interferon beta-1a in the treatment of clinically isolated syndromes: 3-year and 5-year results of the phase III dosing. Frequency-blind multicentre REFLEXION study. *J Neurol Neurosurg Psychiatry* 2017; 88(4):285-294.
35. European Study Group on Interferon-1b in Secondary Progressive MS. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. *Lancet* 1998; 352(9139):1491-1497.
36. The North American Study Group on Interferon beta-1b in Secondary Progressive MS. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. *Neurology* 2004; 63(10):1788-1795.
37. Rojas JI, Romano M, Ciapponi A, Patruccio L, Cristiano E. Interferon Beta for primary progressive multiple sclerosis. *Cochrane Database Syst Rev.* 2010; 20:(1).
38. Bayas A, Ouallet JC, Kallmann B, Hupperts R, Fulda U, Marhardt K; SMART study group. Adherence to, and effectiveness of, subcutaneous interferon beta-1a administered by RebiSmart® in patients with relapsing multiple sclerosis: results of the 1-year, observational SMART study. *Expert Opin Drug Deliv* 2015; 12(8): 1239-1250.
39. Hupperts R, Becker V, Friedrich J, Gobbi C, Salgado AV, Sperling B et al. Multiple sclerosis patients treated with intramuscular IFN-β-1a autoinjector in a real-world setting: prospective evaluation of treatment persistence, adherence, quality of life and satisfaction. *Expert Opin Drug Deliv* 2015; 12(1):15-25.