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TREATMENT OF MULTIPLE SCLEROSIS

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SUMMARY – Multiple sclerosis is an autoimmune inflammatory demyelinating disease of the central nervous system, characterized by multifocal inflammatory destruction of myelin, axonal damage and loss of oligodendrocytes. The disease is carried through two stages: inflammatory and degenerative. The most common form of disease in approximately 85% of the cases is RRMS (relapsing-remitting form). The treatment of MS is devided into: treatment of the acute phase of illness, prevention of new relapses and disease progression, and symptomatic treatment. Most of the changes in treatment of multiple sclerosis and most of the news in recent years concerning new drugs are used in the treatment of progression of the disease and prevention of disease relapses. Some of these drugs are registrated in most Europian countries and USA, and others are in various stages of research.

Key words: *Multiple sclerosis – therapy; Immunosuppressive agents – therapeutic use; Interferon, beta – therapeutic use*

Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system characterized by multifocal inflammatory destruction of myelin, axonal damage and loss of oligodendrocytes. In the pathogenesis of the disease, activated T-lymphocytes are involved, causing endothelial changes in the blood-brain barrier, secreting inflammatory mediators and stimulating the cascade of inflammation. In the disease development, interferon gamma plays a significant role; it is produced in activated T-cell lymphocytes (TH1 class) and activates macrophages to protease and tumor necrosis factor (TNF) production, which in turn destroy oligodendrocytes, leading to the onset and progression of the disease.

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The most common form of disease, found in approximately 85% of cases is the relapsing-remitting form (RRMF). The treatment of MS is divided into treatment of the acute phase of the disease, prevention of new relapses and disease progression, and symptomatic treatment[1].

Treatment of Multiple Sclerosis

In newly diagnosed patients and in the stage of acute exacerbation or disease relapses, we apply corticosteroids as 'pulse corticosteroid therapy' using methylprednisolone (Solumedrol®®) intravenously 500-1000 mg/day in 250 mL saline solution in short infusions (30-45 minutes) for 5 days. Along with corticosteroids, histamine blockers (H2 receptors, ranitidine), acetazolamide and potassium replacement therapy are administered for three weeks. The corticosteroid side effects are hirsutism, osteoporosis, acne, cataract, hypertension, duodenal ulcer, psychosis, and blood glucose impairment. Contraindications for the

use of corticosteroids are active inflammatory disease, poorly regulated diabetes and psychosis.

The patients in the acute stage of the disease that do not respond to corticosteroid therapy can be treated with plasmapheresis, i.e. seven successive plasmapheresis procedures every other day or intravenous immunoglobulins (IVIg) at a dose of 0.4 g/kg daily for 5 days. Side effects of immunoglobulin therapy may be related to their intravenous administration, dosage or transmission of infectious agents (e.g., hepatitis C virus) and prions. The most important side effects associated with the intravenous administration of immunoglobulins include headache, fever, shivering, facial flushing, back pain, and anaphylactic shock as the most severe one. Side effects associated with dosage of intravenously administered immunoglobulins are hematologic (neutropenia and lymphopenia, and increased plasma viscosity), dermatologic (rash, eczema and urticaria), aseptic meningitis and renal (tubular) damage[2,3].

Immunomodulators and immunosuppressants are used in the prevention of the disease relapse. Since 1993, the immunomodulatory therapy with interferons that change the natural course of the disease in MS patients has been used in the prophylactic treatment of disease exacerbation. The mechanism of action of interferons is not fully understood, but they are known to have antiviral, immunomodulatory and antiproliferative effects. They increase the number and activation of CD 8 suppressor cells, their count being reduced in MS patients, inhibiting the secretion of interferon gamma, which favors the development and progression of the disease, and inhibits the interferon gamma-induced expression of MHC class II antigen at glial cells. They also lead to lymphotoxin (LT) and TNF decrease, which impairs oligodendrocyte function and promotes astrogliosis that reduces the possibility for activated immune cells to cross the blood-brain barrier and increases TH2 cytokines, interleukin 4 (IL-4) and IL-10 by favoring their production as well as the production of transforming growth factor beta (TGF beta) in T helper cells.

In the world, recombinant beta interferons are used in the treatment of MS. The glycolyzed form is interferon 1a, which is similar to natural human interferon beta (Rebif®, Merck-Serono and Avonex®, Biogen Idec), was registered in Europe, Canada and the USA in 1998. The non-glycolyzed form is interferon beta 1b (Betaseron®, Berlex Laboratories, Betaferon, Bayer-Schering AG, and Extavia, Novartis)[4-6]. There was a number of important clinical trials that tested and compared the efficacy of these interferons in the treatment of patients suffering from various forms of MS, primarily in patients with RRMS, according to the frequency of drug usage (once a week, three times a week, or every other day), the length of drug usage (one year, two years, or several years), the way of administration (subcutaneously, s.c., or intramuscularly, i.m.), drug dosage, and disability at the beginning and at the end of drug administration on the EDSS scale (scale of disability of MS patients in which disability is scored from 0 for normal neurologic status to 10 for death). The efficacy of each beta interferon was assessed by the number of relapses, disease progression, reduction of disability on EDSS scale by 1 point, reduction in the number of active demyelinating lesions on magnetic resonance (MR), and reduction in the extent of lesions on MRI during drug administration. The best known clinical studies were as follows: the first multicenter, randomized, double blind, placebo controlled study from 1993 in RRMS patients (comparison of interferon beta 1b and placebo); PRISMS study (comparison of two different doses of beta interferon 1 a – Rebif® 22 mcg (6 MIU) s.c. three times a week and Rebif® 44 mcg (12 MIU) s.c. three times a week)[7]; SPECTRIMS (Secondary Progressive Efficacy Clinical Trial in MS); ETOMS (Early Treatment of Multiple Sclerosis with Rebif®); EVIDENCE (Evidence for Interferon Dose Effect: European-North American Comparative Efficacy trials, comparative study of Efficacy of Rebif® and Avonex®); and OWIMS (comparison of Rebif® in a dose of 22 mcg s.c. and 44 mcg s.c. once a week). The latest studies, some of which are still in progress, are INCOMIN (Independent Comparison of Interferons, following up patients treated with interferon beta 1 b 250 mcg every other day s.c. and interferon beta 1 a 30 mcg i.m. once a week, showing the more frequent usage to be more efficient); BEYOND (a study with a twofold dose of interferon beta 1 b, Betaferone®, which is still in the second phase); and BENEFIT (Betaferone® in Newly Emerging mul-

tiple sclerosis For Initial Treatment), with initial administration of interferon beta 1 b, Betaferone®, in newly detected patients in comparison with placebo. The latest study the three-year results of which have been published this year showed the use of interferon beta 1 b, Betaferone®, in the early stages of the disease, in comparison with placebo, to delay the time to clinically definitive form of disease (CDMS), to significantly reduce the number of relapses and disability, and to increase the quality of life in patients. Meta-analysis of randomized placebo controlled studies of interferons in patients with RRMS (published during the 1993-2002 period) using the Cochrane Collaboration method has shown them to mildly reduce the number of patients with disease exacerbation in the first year of treatment, with uncertain clinical efficacy after the first year of interferon administration; additional studies on the long term use of recombinant forms of beta interferon and cost-effect analysis are necessary[8-17].

The quality of MS treatment with interferon beta was assessed in the QUASIMS study that included 510 centers in 11 countries and compared treatment with different interferon beta preparations. This study showed similar efficacy of all beta interferons available, being administered either as initial or follow up therapy for RRMS[7-18].

In Croatia, there are strict criteria concerning indications and contraindications for the treatment with interferon beta. Treatment with interferon beta may be related to the occurrence of neutralizing antibodies. Immunologic studies have shown that neutralizing antibodies can extend biological lifetime of cytokines and have beneficial effect. The occurrence of neutralizing antibodies with the use of interferon may be related to the loss of efficiency. Side effects of interferon beta are 'flue-like' symptoms, skin lesions at the site of application, elevated liver enzymes, depression, and allergies. Anemia may be present with the use of Avonex® and cytopenia with Betaseron®.

Among other medications used in therapy of MS, mention should be made of the immunomodulator Copaxone® (glatiramer acetate) in a dosage of 20 mg s.c. once a day[18], which is on the Croatian Institute for Health Insurance list since September 2006, along with immunosuppressants (Novartone, mitoxantron hydrocloride in a dosage of 8-12 mg/m^2 i.v., Azatioprine® Imuran®, cyclophosphamide Cytoxan®, cyclosporine A and methotrexate). Currently, highest expectations are put on therapy with mitoxantrone hydrochloride, a synthetic anaplastic agent with anti-inflammatory effect. This medication is prescribed for SPMS, and has been confirmed to reduce clinical symptoms and lesion activity on MRI. The dosage of medication is cumulative, and because of its cardiotoxicity it has a strictly limited total life dose of up to 120-140 mg i.v.[1].

Additionally, full irradiation of lymphatic nodes can be performed over a 5-6 weeks.

Recently, new studies on the use of stem cell transplantation in the treatment of severe forms of MS (SPMS and PPMS) are emerging. This form of treatment has been previously administered for other autoimmune diseases such as systemic sclerosis and rheumatoid arthritis[19,20].

Monoclonal antibodies (Mabs) that also belong to the class of biotechnological medications show promising results in the treatment of autoimmune and inflammatory diseases such as MS. Since they enable selective modulation of defined molecules, they are an attractive therapeutic option.

For different types of MS, a large number of monoclonal antibodies are currently studied: anti T 11, anti T12, anti T 4, anti CD3, anti CD4, anti CD 25, anti CD20, and widely known anti CD52 (alemtuzumab), clinical studies of which are in progress[21,22]. One of the monoclonal antibodies, anti alpha 4 integrin (natalizumab, Tysabri®), is already registered in America and Europe for the treatment of rapidly progressive forms of MS. Studies which confirm its efficacy are AFFIRM (compares efficiency of Tysabri® 300 mg i.v. every four weeks *vs.* placebo every four weeks) and SENTINEL (Tysabri® in recommended dose is added to therapy with Avonex® in half of all patients, while in the other half placebo is combined with Avonex® for 120 weeks). Patients that received Tysabri® had a significantly lower number and frequency of disease relapses, reduced disability and lower number of active lesions on MR[23-25].

Today, orally administered drugs for use in MS are also investigated, the best known of which is cladribine (2-chloro-2-deoxyadenosine, CdA), a synthetic purine analog[26]. As for symptomatic treatment, the management of spasticity, slackness, dysfunction of miction, equilibrium, vertigo, tremor, pain and mood changes is of highest importance.

Conclusion

Due to the large number of clinical studies of new drugs for MS, it appears optimistic to expect a discovery of increasingly effective medications for MS therapy. Research is directed towards enhancement of currently available medications (new formulations of drugs already in use, e.g., beta interferon 1a, which is less immunogenic, pegylated interferon beta preparations that have better pharmacokinetic properties and can be administered less often), improved possibilities of administration (by improving auto injectors), research of oral drugs, usage of combination of drugs, and better collaboration between patients and physicians, which is also very important for successful treatment.

References

1. Chofflon M. Mechanisms of action for treatments in multiple sclerosis. Biodrugs 2005;19:299-308
2. Isaacs A, Lindemann J. Virus interference. The interferon. Proc R Soc Lond (Biol) 1957;147:258-67
3. Iz rada struène grupe za lijekove Ministarstva zdravstva Republike Hrvatske. Pharmaca 1997;35:49-60
4. The IFNB MS Study Group.Interferon beta -1b is effective in RRMS : clinical results of a multicentre, randomized, double-blind, plecebo-controlled trial. Neurology 1993;43:665-61
5. Filippini G, Munari L, Incorvaia B, Ebers GC, Polman C, D´Amico R. Interferons in relapsing rmitting multiple sclerosis: a systematic review. Lancet 2003;361:545-52
6. Sharief MK. Dose and frequency of administration of interferon-beta affect its efficacy in multiple sclerosis. Clin drug Investig 2003;23:551-9
7. The PRISMS Study Group (Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis). Randomised double-blind placebo controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis . Lancet 1988;352:1498-504
8. Jacobs LD, Cookfair DL, Rudick RA. Results of a phase III trialof intramuscular recombinant beta interferon as treatmentof multiple sclerosis. Ann Neurol 1994;36:256 ???
9. Jacobs LD, Cookfair DL, Rudick RA. Intramuscular interferon-beta 1a for a disease progression in relapsing multiple sclerosis. Ann Neurol 1996;39:258-94
10. IFNB MS Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I MRI analysis results of a multicentre, randomized, double-blind, placebo-controlled trial. Neurology 1993;43:662-667
11. Kappos L. New aspects in the treatment of multiple sclerosis with interferon beta 1b. J Neurol 2004;251(Suppl 4):I V/1;DOI 10.1007/00415-004-1401-4
12. Durelli L. Is multiple sclerosis a disease that requires frequent beta interferon dosing? J Neurol 2004;251(Suppl 4): IV/13-IV/24;DOI 10.1007/00415-004-1404-1
13. Comi G, Filippi M, Barkhof F, Durelli L, Edan G, Fernandez O et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet 2001; 357:1576-82
14. Galetta SL. The Controlled High Risk Avonex Multiple Sclerosis Trial (CHAMPS study). J Neuroophthalmol 2001;21:292-5
15. Kappos L, Polman CH , Freedman MS, Edan G, Hartung HP, Miller DH et al. Treatment with interferon beta-1b delays conversion t clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology 2006;67:1242-9
16. Kappos L, Freedman MS, Polman CH, Edan G, Hartung HP, Miller DH et al. Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis:a 3-year follow-up analysis of the BENEFIT study. Lancet 2007;370:389-97
17. Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP et al. Extended use of glatiramer acetat (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. Copolymer 1 Multiple Sclerosis Study Group. Neurology 1998;50:701-8
18. Tyndall A, Saccardi R. Haematopoetic stem cell transplantation in the treatment of severe autoimune disease;results from phase I/II studies, prospective randomized trials and future direction.Br Soc Immunol Clin Exp Immunol 2005;141:1-9
19. Mancardi GL. Autologus haematopoetic stem cell transplantation . neurol sci 2005;26:S19.
20. Hohlfeld R, Wekerle H. Drug insight : using monocvlonal antibodies to treat multiple sclerosis. Nature Clin Pract Neurol 2005;1:34-44
21. O´Leary S, Beavin J, Bishop C, Capolino L, Greinel e, Hudson E. Practical guidelines for administering natalizumab:a nursing perspective. Int MS Care 2007;9:1-8
22. Cannella B, Raine CS. The adhesion molecule and cytokine profile of multiple sclerosis lesions. Ann Neurol 1995;37:424-35
23. Tysabri® (natalizumab) (package insert). Cambridge, MA: Biogen Idec, Inc. 2006
24. Yednock TA, Cannon C, Fritz LC, Sanchez-Madrid F, Steinman L, Karin N. Prevention of experimental autoimmune encephalomyelitis by antibodies against alpha 4 beta 1 integrin. Nature 1992;356:63-6
25. Polman CH, O´Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH et al. A randomized, placebo- controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354:899-910
26. Post-hos analysis of the AFFIRM study. Cambridge, MA: Biogen Idec, Inc. 2005
27. Sipe JC. Cladribine for multiple sclerosis: review and current status. Expert Rev Neurother 2005;5:721-7

Sažetak

LIJEČENJE MULTIPLE SKLEROZE

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Multipla skleroza (MS) je upalna autoimuna demijelinizacijska bolest središnjega živčanog sustava obilježena multifokalnom upalnom destrukcijom mijelina, oštećenjem aksona i gubitkom oligodendrocita. Bolest se odvija kroz dvije faze, upalnu i degenerativnu. Najčešći oblik bolesti, u otprilike 85% slučajeva je RRMS (relapsno-remitentni oblik).

Liječenje MS dijeli se na liječenje akutne faze bolesti, prevenciju novih recidiva i progresije bolesti te simptomatsko liječenje. Posljednjih godina najviše promjena i novih lijekova u liječenju multiple skleroze rabi se u liječenju odnosno sprječavanju progresije bolesti te prevenciji recidiva bolesti. Neki od tih lijekova su registrirani u većini europskih zemalja i u Americi, a drugi su u različitim fazama istraživanja.

Ključne riječi: *Multipla skleroza – terapija; Imunosupresivi – terapijska primjena; Interferon, beta – terapijska primjena*