Opšti pregledi/
General reviews

MULTIPLE SCLEROSIS – CURRENT WAY OF MANAGEMENT AND AVAILABLE THERAPEUTIC AGENTS

MULTIPLA SKLEROZA – SADAŠNJI NAČINI LEČENJA I DOSTUPNA TERAPIJSKA SREDSTVA

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Abstract

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Ključne reči
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Multiple sclerosis (MS) is an autoimmune, inflammatory, demyelinating and neurodegenerative disease of the central nervous system (CNS) that causes neurological disability in young adults. Today MS has expensive and only partially efficacious therapies. Important strategy against MS is to identify biomarkers of early neuronal damage and to treat patient prior to the onset of any clinical symptoms. Treatment of MS has few aspects: first one is treating the attacks and second one is modifying the course of the disease (in relapsing-remitting forms). In progressive forms antineoplastic and immunosupresive agents are used. These agents are administrated subcutaneously or intramuscularly. These injection agents (including: steroid hormons, cell activation factors interferons, synthetic polymer of amino acids and others) are designed to reduce the frequency of relapses and some even slow disability progression. The aim is to prevent of demyelination and a reduction of axonal loss.

Elusive and often unpredictable multiple sclerosis (MS) is the most common autoimmune inflammatory demyelinating neurodegenerative disease of the central nervous system (CNS). Between 50 and 100 per 100,000 individuals are affected by this disease, although the incidence and prevalence of MS greatly varies geographically. High frequency areas of the world include Europe (with Russia), southern Canada, northern United States, New Zealand and southeast Australia. Farther from the equator – so the disease is more prevalent. MS affects two to three times more women than men. Onset usually occurs between the ages of 20 and 40 years. The disease affects mostly urban population and the Caucasoid race. Diagnosis is based on the presence of typical focal changes in the central nervous system and supporting evidence from ancillary tests, such as magnetic resonance imaging (MRI) of the brain and cerebrospinal fluid examination. Traditionally for MS diagnosis comfirmation diferent criteria are used based on number of attacs (Shumacher's, McDonald's, Poser's criteria) or on number of lesion and their location (Barkhof's criteria). The newest published criteria is Swantan criteria (Polman et al. 2011)[1].

Although the basic pathology of MS was already recognized in the 18th century from French neurologist and professor of anatomical pathology Jean-Martin Charcot, its causes and pathogenesis remain elusive. The pathological features of MS consist of inflammation, demyelination, gliosis and axon degeneration. The clinical progress can be characterized by a relapsing-remitting (RRMS) or a chronic progressive course - primary - progressive MS (PPMS), secondary - progressive MS (SPMS), progressive -relapsing MS (PRMS). There is also a benign form of MS in which after one or two attacks symptoms disappear. RRMS is characterized by recurrent attacks in which neurologic deficits appear in different parts of the nervous system and resolve completely or almost completely over a short period of time, leaving little residual deficit. Patients with a relapsing-remitting pattern account for approximately 85% of MS cases. Data indicate that approximately 50% of patients with RRMS convert to a secondary progressive pattern within 10-15 years after disease onset. This pattern may or may not include relapses, but it is characterized by continued progression over years, with increasing disability [2,3].

Treatment with disease-modifying agents is thought to slow the progression of RRMS. Unlike RRMS, SPMS without relapses does not seem to be responsive to currently available disease-modifying agents [3]. In PPMS, which accounts for approximately 10% of MS cases, function declines steadily without relapses. In PRMS, which accounts for fewer than 5% of patients with MS, occasional relapses are superimposed on progressive disease.

In MS inflammation and neuron degeneration are present from earliest stage of the disease. What precisely causes it remains controversial. Some scientists believe that the inflammation causes the degeneration and some others - one smaller group - thinks that this is a primary degenerative disorder with secondary inflammation. Whichever theory is true, we know reducing inflammation does help patients. It helps to reduce relapses, and it is believed it helps ultimately to delay or prevent the emergence of what we call secondary progressive disease. In that phase of the illness, there's less inflammation but there is progressive axonal degeneration causing progressive neurologic symptoms like leg weakness or incoordination [4].

Several therapies for MS exist, although there is no known cure. Treatment of MS has few aspects: immunomodulatory therapy (IMT) for the underlying immune disorder, inflammation control and therapies to relieve or modify symptoms. IMT is directed toward reducing the frequency of relapses and slowing progression. Currently, most disease-modifying agents have been approved for use only in relapsing forms of MS [5]. Currently available MS therapies have shown significant efficacy throughout many trials, but they produce different side-effect profiles in patients. They require regular and frequent parenteral administration and are associated with limited long-term treatment adherence. Thus, there is an important need for the development of new therapeutic strategies. Research directions on MS treatments include investigations of MS pathogenesis and heterogeneity, research of more effective, convenient, or tolerable new treatments for RRMS, development of therapies for the progressive subtypes, neuroprotection strategies, and the search for effective symptomatic treatments [6]. A number of treatments that may curtail attacks or improve function are under investigation.

Early diagnosis is important because there is growing evidence that early intervention is useful. It is known through the work of Trapp et. al., 1998 that axonal loss can be present, even in asymptomatic patients, early in the disease process [7,8,9,10]. Important strategy against MS is to identify biomarkers of early neuronal damage and to treat patient prior to the onset of any clinical symptoms. In this study the authors detect the early neuronal damage by means of serum of MS patients, a very important indication for immediate neuroprotective treatment [11]. Kolasinski et al., 2012 found a significant correlation between neurodegenerative events (detailed investigation with MRI and neuropathology). Neurodegeneration distant from the site of initial tissue damage will lead to microglia activation [12]. Lucchinetti et al., 2011 showed that cortical demyelination is already present at early stages of the disease, and, when this happens, the lesions show profound lymphocytic infiltration

similar to that seen in active white matter lesions [12]. Chio et al., 2012 showed that meningeal inflammation may drive tissue injury in the cortex and may diffuse into the cortical tissue and induse demyelination and neurodegeneration either directly or indirectly through microglia activation [12].

In addition, studies in patients with a first attack of neurologic symptoms suggestive of MS have demonstrated decreased disability and lower secondary relapse rates with treatment [6]. MS lesion and the development of clinical surrogate markers, which allow to define subsets of patients with different forms of underlying pathogenesis, is necessary. This will pave the way for an optimized treatment approach, that will likely need both to target inflammation and to focus on promotion of neuroprotection and repair [13].

One of the most common ways to manage MS is by taking an injectable therapy. There are several types of injection therapies which are administered differently — either intramuscular injection (INFβ-1a) or subcutaneous (Corticosteroids), (INFβ-1b), (Glatiramer Acetate) etc. These injection agents help reduce the frequency of relapses -some even slow disability progression.

Corticosteroids are a class of chemicals that includes steroid hormones naturally produced in the adrenal cortex of vertebrates and analogues of these hormones that are synthesized in laboratories. First known use was in 1944 and they awarded the Nobel Prize for Physiology and Medicine in 1950. Most often corticosteroids (methylprednizolone, prednisone, and dexamethasone) are administered with immunosuppressive or anti-inflammatory effect. Methylprednisolone can hasten recovery from an acute exacerbation of MS as first-line treatment.

Use of corticosteroids has several severe side-effects as for example: hyperglycemia, insulin resistance, diabetes mellitus, osteoporosis, cataract, anxiety, depression, colitis, hypertension, ictus, erectile dysfunction, hypogonadism, hypothyroidism, amenorrhoea, and retinopathy.

Plasma exchange (plasmapheresis) can be used short term for severe attacks if steroids are contraindicated or ineffective. The 2011 American Academy of Neurology (AAN) guideline for plasmapheresis in neurological diseases categorizes plasmapheresis as „probably effective" as second-line treatment for relapsing MS exacerbations that do not respond to steroids [14].

As therapies to reduce the frequency of exacerbation of the disease in most cases is used intravenously administered immunoglobulin G as a second line preparation. It neutralizes the proinflammatory cytokines and promotes remyelination [15].

Interferon beta-1a [also interferon beta-1-alpha] are available on the market from (Biogen Idec from '96); (Merck Serono from '98). Interferon beta-1a is a drug in the interferon family used to treat MS. It is produced by mammalian cells. Interferons have been shown to produce about a 18–38% reduction in the rate of MS relapses. Starting a course of interferons early may slow its progress, though this is highly controversial.

It is believed that Interferon beta based drugs achieve their beneficial effect on MS progression via their anti-inflammatory properties. Extensive studies have also deter-

mined that Interferon beta improves the integrity of the blood–brain barrier (BBB), which generally breaks down in MS patients, allowing increasing amounts of undesirable substances to reach the brain. This strengthening of the BBB may be a contributing factor to Interferon-Beta's beneficial effects. These studies were carried out in vitro and thus may not necessarily work the same way in vivo.

Interferon beta-1b [also interferon beta-1- beta] is a drug in the interferon family used to treat the relapsing-remitting and secondary-progressive forms of MS. Interferon beta-1b is produced in modified E. coli. It is approved for use after the first MS event. It is administered by sub-cutaneous injection and has been shown to slow the advance of the affliction as well as reduce the frequency of attacks.

Glatiramer acetate (licensed in 1996) is a random chain (polymer, synthetic tetrapeptid) of amino acids - Glutamic acid, Lysine, Alanine and Tyrosine (hence GLATiramer). It is synthesized in solution from these amino acids a ratio of approximately 5 parts Alanine to 3 of Lysine, 1.5 of Glutamic acid and 1 of Tyrosine using N-carboxyamino acid anhydrides. It was originally designed to mimic a protein in myelin, called myelin basic protein, with the intention of inducing experimental autoimmune encephalomyelitis (EAE - an animal model of MS). Quite to the contrary, it was found to suppress the disease and as a result came to be trialed in human MS. For this reason, it was originally believed to act as a decoy by drawing the immune system's attack away from the myelin. Nowadays, researchers are no longer at all sure how works. There are some evidences that it converts the body's immune response from a Th1 type to a Th2 one, promotes suppressor T cells or acts as an altered peptide ligand. Glatiramer acetate is self-administered by daily sub-cutaneous injections. Glatiramer acetate was licensed for the treatment of RRMS in the USA by the Federal Drugs Authority (FDA) in December 1996. It has been approved in Canada and most of Europe by the national drug regulation organizations and EMA.(European Medicines Agency)

Although the clinical definition of multiple sclerosis requires two or more episodes of symptoms and signs, glatiramer acetate is approved for treatment after single episodes. It is also used to treat relapsing-remitting multiple sclerosis. The most common side effects of Glatiramer acetate are redness, pain, swelling, itching, or a lump at the site of injection, flushing, rash, shortness of breath, and chest pain. These reactions are usually mild and seldom require professional treatment. A permanent indentation under the skin at the injection site may occur, due to a local destruction of fat tissue.

Treatment and management of multiple sclerosis should be targeted toward relieving symptoms of the disease, treating acute exacerbations, shortening the duration of an acute relapse, reducing frequency of relapses, and preventing disease progression. Drugs approved for use in MS that reduce the frequency of exacerbations or slow disability progression are referred to as disease-modifying drugs (DMDs). These DMDs can be further classified as immunomodulating (or receptor modulating) or immunosuppressives. Some immunosuppressants are also FDA-approved as antineoplastic agents. Drugs that treat MS-related symptoms (eg, acute exacerbations, cognitive dysfunction, fatigue, spasticity, bowel and bladder problems, and pain) but do not modify the course of the disease are referred to as symptom-management medications [5]. The recent studies found that over 60% of MS patients use complementary and alternative medicine (diet, gymnastics, yoga) possibly because conventional treatments lack effectiveness.

The future of MS treatment should be aimed at combining anti-inflammatory agent and such with a neuroprotektive effect. Combination of both interferon and glatiramer acetate at the same time was better that taking either agent alone [16].

Sažetak

Multipla skleroza (MS) je autoimunsko, zapaljenjsko i neurodegenerativno oboljenje centralnog nervnog sistema (CNS) koje uzrokuje neurološku slabost kod mlađih odraslih osoba. Danas se u lečenju MS koriste skupi i samo delimično efikasni lekovi. U borbi protiv MS važno je identifikovati biomarkere ranog oštećenja neurona i lečiti obolele pre pojave kliničkih simptoma. Lečenje MS ima nekoliko aspekata: prvi je tretiranje akutnih napada, a drugi je modifikovanje toka bolesti (kod relapsno-remitentnog oblika). Za lečenje progresivne forme bolesti koriste se antineoplastični i imunosupresivni lekovi. Ovi lekovi (uključujući tu steroidne hormone, faktore koji aktiviraju ćelije interferone, sintetičke analoge amino kiselina i drugi) se ubrizgavaju potkožno ili intramuskularno, a kreirani su da smanje učestalost relapsa, neki čak i da smanje progresiju bolesti. Cilj je da se spreči demijelinizacija i smanji gubitak aksona.

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