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PHARMACOLOGICAL TREATMENT OF MULTIPLE SCLEROSIS USING DISEASE-MODIFYING THERAPIES


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КАСАЛЛИКНИ ЎЗГАРТИРУВЧИ ТЕРАПИЯ ЁРДАМИДА ТАРҚОҚ СКЛЕРОЗНИ ФАРМАКОЛОГИК ДАВОЛАШ

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ФАРМАКОЛОГИЧЕСКОЕ ЛЕЧЕНИЕ РАССЕЯННОГО СКЛЕРОЗА С ИСПОЛЬЗОВАНИЕМ МОДИФИЦИРУЮЩИХ ТЕЧЕНИЕ ЗАБОЛЕВАНИЯ ПРЕПАРАТОВ

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Резюме. *Ушбу мақола кўп склероз терапиясини ўрганишга бағишланган. Кўп склероз сурункали касаллик бўлиб, ягона тўғри даволаш усули йўқлиги сабабли уни абадий даволаш мумкин емас. Иммуномодуляцион терапия кўп склерознинг такрорий шаклларини даволаш учун ишлатилиши мумкин. Касалликнинг боришини ўзгартирадиган иммуномодуляцион терапияни танлаш бўйича консенсус йўқ. Кўпгина мутахассислар беморга кўрсатма беришни ва биргаликда қарор қабул қилишни тавсия қиладилар, шу жумладан клиник изоляция қилинган синдромли ва бир нечта патологик ўзгаришларга ега беморларга иммуномодуляцион терапия таклиф етилганда.*

Калит сўзлар: *кўп склероз, дори, иммуномодуляцион терапия, бемор.*

Abstract. *This article is devoted to the study of the therapy of multiple sclerosis. Multiple sclerosis is a chronic disease, and it is not possible to cure it forever due to the absence of the only correct therapeutic method. Immunomodulatory therapy can be used to treat recurrent forms of MS. There is no consensus on the choice of immunomodulatory therapy that changes the course of the disease. Most experts recommend instructing the patient and making decisions together, including when immunomodulatory therapy is offered to patients with clinically isolated syndrome and who have more than one pathological change.*

Keywords: *multiple sclerosis, drug, immunomodulatory therapy, patient.*

Multiple sclerosis is a chronic disease, and it is not possible to cure it completely due to the absence of a definitive therapeutic method. Nevertheless, it is possible to significantly improve the patient's quality of life. The disease itself does not pose a mortal danger; therefore, the life expectancy of a patient with such a diagnosis can be similar to that of a healthy person [4, 7, 9].

However, it should be borne in mind that MS is accompanied by a number of problems that reduce the quality of life. Although the disease in most cases does not lead to disability, it provokes painful sensations, discomfort, and other troubles [2, 6, 8].

The prognosis also directly depends on the type of disease. In the primary progressive stage, there is a steady decrease in functions without periods of exacerbations and remissions. Sometimes there may be moderate functional decline — it all depends on the specific case [1, 3, 5].

Multiple sclerosis (MS) is characterized by the appearance of disseminated foci of demyelination in the brain and spinal cord. Characteristic symptoms include visual and oculomotor disorders, paresthesia, weakness, spasticity, urinary disorders, and mild cognitive symptoms. The "scattered" neurological symptoms typical of this disease, as exacerbations and re-

missions alternate, gradually lead to disability. Diagnosis based on clinical manifestations or MRI requires the presence of ≥ 2 characteristic neurological lesions that are separated both in time and in space (localization in the central nervous system). Treatment includes the use of glucocorticoids during exacerbations, immunomodulatory drugs for the prevention of exacerbations, and supportive care [3, 7, 9].

It is assumed that immune mechanisms are involved in the development of multiple sclerosis. One of the possible causes is considered to be infection with a latent virus (possibly a human herpesvirus, in particular the Epstein–Barr virus), which, when activated, triggers a secondary autoimmune response.

Materials and methods: The age of MS onset ranges from 15 to 60 years, with typical cases occurring between 20 and 40 years; women are affected slightly more often.

In MS, focal demyelination (so-called plaques) develops, in which there are processes of oligodendroglial destruction, perivascular inflammation, and chemical changes in the lipid and protein components of myelin both within the plaque and in the surrounding area. Axonal damage is common, and neuronal cell bodies may also die or be damaged.

Results: The predominant localization of plaques scattered throughout the central nervous system (CNS) is the white matter, in particular the posterior and lateral columns (especially in the cervical segment of the spinal cord), the optic nerves, and the periventricular zone. The pathways of the midbrain, pons, and cerebellum are also affected. Involvement of the gray matter of the brain and spinal cord in the pathological process is possible but to a much lesser extent.

Although the pathological process in MS can fade unpredictably and become active again, there are several typical variants of its course:

Relapsing-remitting course: periods of exacerbation are followed by periods of complete or partial recovery of neurological deficit or stabilization of symptoms. Remissions can last for months or years. Exacerbations develop spontaneously or under the influence of trigger factors, which include infectious diseases (for example, influenza). Recurrent forms of MS include active secondary MS (defined as a clinical relapse or a new lesion observed on MRI of the brain or spinal cord).

Primary-progressive: gradual progression of the disease without periods of remission, although there may be time intervals (so-called "plateau periods") during which symptoms do not increase. It differs from the relapsing-remitting variant in the absence of clearly pronounced exacerbations.

Secondary-progressive: the disease begins with alternating exacerbations and remissions (relapsing-remitting), followed by steady progression of the process.

Progressive with exacerbations: the disease gradually progresses; however, against the background of a slow increase in symptoms, sudden obvious exacerbations develop. This is a rare variant of the course of MS.

Mild cognitive impairment is most commonly observed in clinical practice. Patients may develop apathy, reduced insight into their own condition, and impaired concentration. Disorders in the emotional sphere are often revealed, manifested by emotional lability, euphoria, or, more often, depression. Unilateral (asymmetric) optic neuritis and internuclear ophthalmoplegia develop most often. Central vision is affected more than peripheral vision.

Optic neuritis leads to visual impairment (ranging from scotoma to complete blindness), pain in the eye on movement, sometimes narrowing of the visual fields, swelling of the optic disc, and the appearance of a complete or partial afferent pupillary defect.

Internuclear ophthalmoplegia develops if the medial longitudinal fasciculus connecting the nuclei of the III, IV, and VI pairs of cranial nerves is affected. On horizontal gaze, adduction of one eyeball is reduced, with nystagmus in the other (abducting) eye; convergence is preserved. In MS, internuclear ophthalmoplegia is usually bilateral; unilateral internuclear ophthalmoplegia often occurs in ischemic stroke.

Rapid low-amplitude eye fluctuations in the primary gaze position (pendular nystagmus) are rare but characteristic of MS. Vertigo often manifests itself. There may also be intermittent numbness of half of the face or pain (resembling trigeminal neuralgia), weakness, or spasm of the facial muscles. With the development of bulbar disorders or damage to the cerebellum or corticonuclear tracts, mild dysarthria may appear. Lesions of other cranial nerves are quite unusual but may develop secondary to involvement of the brainstem in the pathological process.

Weakness is common. It is overwhelmingly associated with damage to the corticospinal tracts in the spinal cord, predominantly involving the lower extremities, with the development of spastic paraparesis.

During neurological examination, attention is drawn to increased tendon reflexes (knee and Achilles) and the presence of pathological extensor reflexes (Babinski's sign) and clonus. Due to spastic paraparesis, the patient develops a clumsy, unsteady gait; in severe forms of the disease, this may confine the patient to a wheelchair. In the later stages, painful flexor spasms may occur in response to sensory stimuli (for example, touching bed linen). Lesions in the brain or cervical spinal cord can cause hemiparesis, which sometimes becomes the reason for seeking medical attention.

In advanced stages of MS, a combination of cerebellar ataxia and spasticity leads to disability;

other manifestations of cerebellar damage include slurred speech, scanning speech (slow pronunciation with stutters at the beginning of a word or syllable), and Charcot's triad (intention tremor, scanning speech, and nystagmus).

Spinal cord lesions in typical cases cause impaired bladder function (for example, urinary urgency, partial urinary retention, incontinence). Constipation may also develop, along with erectile dysfunction in men and loss of genital sensitivity in women. In the later stages of the process, urinary and fecal incontinence may occur.

Multiple sclerosis is suspected in patients with optic neuritis, internuclear ophthalmoplegia, or other symptoms suggestive of MS, especially if the lesions are multifocal or intermittent. If MS is suspected, MRI examination of the brain and spinal cord is prescribed.

MRI is the most sensitive neuroimaging method for diagnosing MS and allows it to be differentiated from other treatable diseases that can mimic MS, in particular non-demyelinating lesions at the spinal cord–brainstem junction (for example, subarachnoid cysts and tumors of the foramen magnum). Gadolinium contrast makes it possible to differentiate plaques in the phase of active inflammation from old plaques. In addition, MRI scanners with high magnetic field strength (from 3 to 7 Tesla) make it possible to distinguish perivenular plaques caused by multiple sclerosis from non-specific white matter lesions.

The course of multiple sclerosis is diverse and unpredictable. In most patients, especially if the onset of MS was represented by optic neuritis, remissions can last from several months to more than 10 years.

Most patients with clinically isolated syndrome eventually develop MS, with subsequent symptoms appearing or lesions being detected by MRI examination, as a rule, within 5 years after the appearance of the first symptoms. Life expectancy is reduced only in the most severe cases.

Treatment with disease-modifying therapies can delay such progression of the disease. If the patient has a radiologically isolated syndrome, there is a risk of developing MS, but further investigation of this risk is necessary.

The goals of multiple sclerosis treatment include the following:

1. Reducing the duration of exacerbations
2. Reducing the frequency of exacerbations
3. Relieving the severity of symptoms
4. Delaying the onset of disability, in particular preserving the patient's ability to walk (which is especially important)

The treatment of exacerbations and relapses is provided through the use of corticosteroids, administered in short courses, to treat the acute onset of symptoms or exacerbations that cause objective disorders sufficient to impair function (for example, loss of vision, strength, or coordination).

Plasmapheresis may be used if corticosteroids are ineffective in alleviating the severity of exacerbation. Plasma exchange can be used for any relapsing form of MS (relapsing-remitting, progressive-relapsing, secondary-progressive). However, it is not used in primary progressive MS.

In severe, difficult-to-treat disease, plasmapheresis and hematopoietic stem cell transplantation may be effective.

The use of immunomodulatory therapy can reduce the frequency of exacerbations and delay the onset of disability. Recidgen interferon beta-1a 44 mcg (12 million IU) / 0.5 ml is a natural amino acid sequence of human IFN-beta1a, obtained by genetic engineering using a culture of Chinese hamster ovary cells. Indications: relapsing-remitting course of MS.

Contraindications: initiation of treatment during pregnancy; hypersensitivity to natural or recombinant interferon beta or to any of the excipients listed in the composition; hypersensitivity to glatiramer acetate; severe depressive disorders and/or suicidal ideation; age restrictions in accordance with the instructions for use.

These therapies inhibit the proliferation and activation of autoreactive T lymphocytes, as well as the migration of activated T and B cells across the blood-brain barrier into the central nervous system; they also shift the cytokine balance toward reducing the synthesis of inflammatory cytokines and increasing anti-inflammatory ones. In addition, IFN-β and GA (glatiramer acetate) have a neuroprotective effect in the central nervous system, affecting the synthesis of neurotrophic factors that determine the growth and differentiation of neurons and oligodendrocytes.

Recidgen is supplied in the form of pre-filled subcutaneous syringes containing 44 micrograms / 0.5 ml of human recombinant IFN-beta1a.

The initial injection was carried out in the treatment room of the medical facility. In accordance with the instructions for use, it was recommended to administer the drug at the same time, preferably in the evening, on certain days of the week with an interval of at least 48 hours (for example, at 8:00 p.m. on Mondays, Wednesdays, and Fridays).

For the first two weeks, the drug was administered at a dose of 0.1 ml (according to the marking on the syringe). The drug remaining in the syringe was not used. In the third and fourth weeks, the drug was administered at a dose of 0.25 ml from the syringe (according to the marking on the syringe).

At the second, third, and sixth months of treatment, a clinical and laboratory assessment of the patient's condition was carried out.

The EDSS score was determined. The following indicators were analyzed:

- complete blood count with platelet count;

• biochemical blood analysis (urea, creatinine, total protein, bilirubin, ALT, AST, amylase, glucose);

• general urine analysis.

From the fifth week onward, in the absence of deviations from the norm, the dose was increased to 0.5 ml (the entire syringe — 44 mcg). The mode of administration of the drug remained the same.

The most common side effects of interferons are flu-like syndrome and depression (which tend to decrease over time), the formation of neutralizing antibodies after several months of therapy, and cytopenia.

Since most people are reluctant to self-inject, oral immunomodulatory drugs are increasingly used as first-line therapy for recurrent forms of MS.

Immunomodulatory therapy can be used to treat recurrent forms of MS. There is no consensus on the choice of disease-modifying immunomodulatory therapy. Most experts recommend educating the patient and engaging in shared decision-making, including when immunomodulatory therapy is offered to patients with clinically isolated syndrome who have more than one pathological change (according to imaging studies).

Encouragement and support are beneficial for patients with multiple sclerosis. Regular physical exercise is recommended (for example, stationary cycling, treadmill walking, swimming, stretching, and balance exercises), with or without physiotherapy, even for patients in the progressive stages of MS, since exercise trains the heart and muscles, reduces spasticity, prevents contractures and the risk of falls, and has positive psychological effects.

Conclusion:

Patients should, if possible, maintain a lifestyle as close as possible to normal and active behavior, while avoiding excessive load, fatigue, and overheating. It is necessary to give up smoking. Vaccination does not increase the risk of exacerbation.

Weakened patients need to prevent bedsores and urinary tract infections; sometimes periodic self-catheterization of the bladder is necessary. It is impossible to fully recover from multiple sclerosis, but timely medical care, accurate diagnosis, and properly selected therapy increase the chances of halting its progression and achieving long-term remission.

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ФАРМАКОЛОГИЧЕСКОЕ ЛЕЧЕНИЕ РАССЕЯННОГО СКЛЕРОЗА С ИСПОЛЬЗОВАНИЕМ МОДИФИЦИРУЮЩИХ ТЕЧЕНИЕ ЗАБОЛЕВАНИЯ ПРЕПАРАТОВ

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Резюме. *Данная статья посвящена изучению терапии рассеянного склероза. Рассеянный склероз — хроническое заболевание, и излечить его навсегда невозможно из-за отсутствия единственно правильного метода лечения. Иммуномодулирующая терапия может применяться для лечения рецидивирующих форм рассеянного склероза. Единого мнения относительно выбора иммуномодулирующей терапии, изменяющей течение заболевания, нет. Большинство экспертов рекомендуют инструктировать пациента и принимать решения совместно, в том числе, когда иммуномодулирующая терапия предлагается пациентам с клинически изолированным синдромом и имеющим более одного патологического изменения.*

Ключевые слова: *рассеянный склероз, лекарственный препарат, иммуномодулирующая терапия, пациент.*