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Ocrelizumab as a breakthrogh in multiple sclerosis treatment

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Abstract

Multiple sclerosis is the most commonly occurring inflammatory disease of the nervous system. It is estimated that over 2 million people suffer from this disease. Currently SM is untreatable, one can only try to stop the progression of the disease or reduce severity of the symptoms.

There have been numerous studies on the effectiveness of other monoclonal antibodies in the treatment of multiple sclerosis. A drug that offers a chance for a breakthrough in the treatment of multiple sclerosis is ocrelizumab. It is a monoclonal antibody directed against B lymphocytes expressing the CD20 antigen.

Results of the studie confirm the efficacy of ocrelizumab in inhibiting ongoing nerve fiber degeneration and reducing the inflammation associated with it, as well as the near complete depletion of CD20+ B lymphocytes and partial depletion of CD20+ T lymphocytes. They also suggest that ocrelizumab is a safe and effective treatment for multiple sclerosis.

Studies conducted on the therapeutic efficacy of ocrelizumab show that its effect on disease progression is superior compared to some current drugs. Ocrelizumab also has a similar safety profile to the currently used interferon β-1a. An important feature of ocrelizumab is its efficacy in the treatment of the primary progressive form of MS, where significant therapeutic efficacy with other drugs has not been seen to date.

Key words: ocrelizumab; multiple sclerosis; ppms; rrms; monoclonal antibody

1. Introduction

Multiple sclerosis is the most commonly occurring inflammatory disease of the nervous system. It is estimated that over 2 million people suffer from this disease. Currently SM is untreatable, one can only try to stop the progression of the disease or reduce severity of the symptoms [1]. There has been an increase in the detection of SM in the recent years, which shows improvements in the diagnostic process. Over past few years survival rate of diagnosed with SM has been improved, which shows progress in the treatment of the disease. [2]

Despite of years of research the pathology of multiple sclerosis is still unknown. Over the years scientist have recognized the following as a factor which are thought to increase probability of developing symptoms of SM: genetic predisposition, abnormalities in the immune system, vitamin D deficiency, UVB, Epstein-Barr virus infection, obesity during childhood and smoking. [3]

First symptoms of multiple sclerosis develop between 20 and 40 years old, with women having the disease almost three times more often than men. A characteristic pathological feature of multiple sclerosis are periventricular inflammatory lesions, whose presence leads to the development of demyelinating plaques. These lesions are most often located in the periventricular area, the pons, and the spinal cord. [1] The cause of demyelinating lesions is an autoimmune reaction that results in the formation of inflammatory lesions and demyelination of nerve fibers. Inflammatory infiltrates contain T lymphocytes, dominated by cells expressing MHC class I CD8+, as well as B lymphocytes and plasma cells. [4] In the early stages of the disease, axons are fairly well preserved, but as the disease progresses, irreversible damage occurs.

The symptomatology of multiple sclerosis is very rich, the course of the disease is unpredictable and characterized by individual variability. This rich symptomatology and variations in the course of the disease are due to the varied localization of demyelinating lesions. The most common neurological symptoms include: visual and sensory disturbances, limb weakness, gait disturbances, bladder dysfunction and many others. Nonspecific symptoms such as spasticity, fatigue, weakness, sexual dysfunction, mood swings from depression to euphoria, and cognitive impairment also contribute to the disease picture. [5]

There are currently three main forms of multiple sclerosis: relapsing-remitting, primary progressive, and secondary progressive. The most common form, especially in the early stages of the disease, is the remission-rejection form (RRMS). It is characterized by periods of exacerbation of symptoms (flares) lasting from a few days to a few weeks, followed by remission. Usually first flares go away without leaving any permanent changes, but as the disease progresses, each flare leaves permanent neurological damage. The remission-relapsing form of the disease progresses in most patients to a secondary progressive form (SPMS), characterized by a steady progression of symptoms without periods of remission. The primary progressive form (PPMS) is characterized by a gradual increase in symptoms from the very beginning of the disease [1].

Despite the clinical differences between RRMS and progressive MS, pathological changes are seen in both, but to a greater extent in the remission-relapsing form. The composition of the inflammatory infiltrate in RRMS and progressive MS is similar, although the percentage of B cells and plasma cells is higher in progressive MS, resulting in differences in the effectiveness of therapy for each form of the disease. [6].

Multiple sclerosis is a progressive disease, so the clinical status of patients should be assessed regularly. It is particularly important to assess the patient's health status in the context of the effectiveness of the applied treatment. Many tests and scales have been developed for assessment. One of the best known and most commonly used is the Expanded Disability Status Scale (EDSS) created by J. Kurtzke [7]. The patient's condition can be assessed using tests that evaluate motor coordination e.g. The timed 25-foot walk, nine-hole peg test (9HPT), Purdue Pegboard Test [8]. The course of the disease can also be monitored using magnetic resonance imaging. The result of MRI examination is an essential element of the diagnostic process and is an important prognostic factor. This examination is the only one that allows for the intravital assessment of the entire central nervous system [9].

Currently, the only treatment options for MS are to slow down the progression of the disease and to try to reduce the severity of the symptoms that are already present. The main therapeutic goal is to prevent the development of disability in the patient; therefore, treatment should be implemented immediately after diagnosis. The activity of MS is assessed on the basis of the annual incidence of episodes, the progression noted on MRI (number of new foci, their volume and distribution and the increase in atrophy) and, mentioned above, the progression of motor disability. [10]

The treatment of remission-relapsing multiple sclerosis includes first-line agents such as interferons (interferon β1a, interferon β1b, and pegylated interferon β1b) and glatiramer acetate, which have comparable efficacy, as well as oral agents such as teriflunomide and dimethyl fumarate. Among second-line drugs, used in case of contraindications or lack of improvement after first-line treatment, we distinguish mitoxantrone, fingolimod and two monoclonal antibodies - alemtuzumab and natalizumab. The mechanism of action of these monoclonal antibodies is different - alemtuzumab, which is a humanized monoclonal IgG1κ antibody against CD52 glycoprotein, causes suppression of CD3+ T cells and CD19+ B cells. Natalizumab, on the other hand, is a recombinant humanized antibody against α4 integrin, which allows blocking the infiltration of lymphocytes into the inflamed tissue, thus reducing its inflammation. [11]

There have also been numerous studies on the effectiveness of other monoclonal antibodies in the treatment of multiple sclerosis. Dacalizumab which acts by blocking the action of the receptor for interleukin 2 (known as CD25), has been successfully used in immunosuppressive therapy after kidney transplantation. Decalizumab has also been shown to be effective in the treatment of multiple sclerosis in combination with interferons. Usage of Decalizumab manifested by a significant reduction in the occurrence of lesions on imaging studies. Anti-CD20 antibodies, rituximab and ocrelizumab, which inhibit the activity of B lymphocytes expressing CD20 antigen, are also used in the treatment of multiple sclerosis. A significant decrease in the number of CD20+ B lymphocytes has been demonstrated, as well as a reduction in lesions seen on imaging studies. [12]

A drug that offers a chance for a breakthrough in the treatment of multiple sclerosis is ocrelizumab. It is a monoclonal antibody directed against B lymphocytes expressing the CD20 antigen. Ocrelizumab is used to treat both remission-relapsing and primary progressive forms of multiple sclerosis, which have so far resisted all known therapies. In the primary progressive form, okrelizumab has been shown to have a beneficial effect in delaying disability progression. [13]

Ocrelizumab binds to the CD20 antigen on the surface of lymphocytes, causing their depletion, thus inhibiting myelin destruction by hyperreactive B lymphocytes, reducing inflammation and disease activity. It reduces the number of flares and may also relieve the severity of disease symptoms already present. Additionally, it is a safe drug with no serious side effects. [14]

The regimen of okrelizumab administration includes premedication with methylprednisolone and an antihistamine. The first dose is 300mg of ocrelizumab, followed by another 300mg after two weeks, after which the regimen consists of one 600mg dose every 6 months.

Ocrelizumab was approved by the Food and Drugs Administration for the treatment of multiple sclerosis in 2017, and in Europe by the European Medicines Agency from 2018 [15] Since then, many studies have been conducted comparing both its efficacy to that of other drugs and its effectiveness in monotherapy.

2. Literature review

A 2019 study of patients at the University Hospital of Colorado looked at the results of one year of therapy with okrelizumab. A retrospective study of 100 patients diagnosed with multiple sclerosis who were prescribed ocrelizumab was conducted, and conclusions were drawn about the use of the drug based on laboratory tests, imaging, and medical history. The majority of subjects (80%) had a projection-remission form of MS, 16% secondary progressive, and 4% primary progressive. During therapy, 10% of patients developed lymphopenia <500/mm3 and 1% developed neutropenia <1000/mm3. During the infusion period, some patients (9.2% during the first and 7% during the second infusion) developed an allergic reaction, which required discontinuation of ocrelizumab. Only 2% of patients experienced a relapse. The results of the above study suggest that ocrelizumab is a safe and effective treatment for multiple sclerosis. [16]

A 2019 study by F. Barkhof et al. examines how the use of ocrelizumab affects the magnetic resonance imaging (MRI) image of the disease in patients with the relapsing-remitting (RRMS) form of MS. The results of RRMS patients using ocrelizumab, placebo, and interferon β-1a were compared. Ocrelizumab reduced the number of foci enhancing after gadolinium-containing contrast agent administration in T1-weighted imaging as early as week four compared to placebo and at week eight compared to interferon. In addition, ocrelizumab also reduced the number of lesions seen in T2-weighted images compared to both placebo and interferon between weeks 4 and 8 of use[17].

Ocrelizumab significantly reduces disease activity by inhibiting CD20+ B lymphocytes. A 2018 study conducted in Hannover, Germany, tested whether the drug is also able to inhibit the activity of CD20+ T lymphocytes. For this purpose, blood from patients diagnosed with MS was tested before starting therapy with okrelizumab and two weeks after starting therapy using flow cytometry. The results show that already after one dose (300mg) of ocrelizumab there is an effective depletion of both CD20+ B cells and CD20+ T cells. The results of the study demonstrate the high efficacy of the drug against both lymphocyte populations, which contributes to its high effectiveness in the treatment of MS. [18]

The efficacy of ocrelizumab can also be assessed by the presence of markers of neural tissue degeneration i.e. neurofilament light chains (NFL) found in cerebrospinal fluid (PMR) and plasma. In 2019, a study was conducted on 100 patients diagnosed with projection MS who

were treated with okrelizumab 600mg every 24 weeks. CSF samples were collected twice at 12-week intervals before the start of therapy, at week 12, 24, and 52 after the first administration of the drug. The results of the study confirm the correlation of NFL levels in both PMR and plasma with the amount of gadolinium deposits seen in T1-weighted images and new or enlarging lesions seen in T2-weighted sequences. Ocrelizumab significantly reduced NFL levels in PMR and plasma, as well as the number of CD20+ B cells and CD20+ T cells in PMR. The results of this study confirm the efficacy of ocrelizumab in inhibiting ongoing nerve fiber degeneration and reducing the inflammation associated with it, as well as the near complete depletion of CD20+ B lymphocytes and partial depletion of CD20+ T lymphocytes. [19]

In 2017, Hauser and colleagues published a paper comparing the efficacy of okrelizumab therapy and interferon β-1a therapy in patients with the remission-rejection form of multiple sclerosis. The researchers used the results of a clinical examination, magnetic resonance imaging, and a questionnaire completed by the patient to compare the effectiveness of the two therapies. The clinical examination assessed the deterioration of patients' performance status and the improvement in performance status. There was a difference in the rate of disability progression between the groups. Patients treated with ocrelizumab showed a slower rate of disability deterioration than patients treated with interferon β-1a. After 12 weeks of therapy, it was found that 9.6% of the okrelizumab-treated patients had deteriorated, whereas this percentage was 13.6% in the interferon-treated group.

The second aspect that was compared was the effect of therapy on patients' improvement. It was found that after 12 weeks of therapy, 20.7% of patients treated with ocrelizumab reported an improvement in performance status, whereas in the group of patients treated with interferon β-1a this was reported by 15.6% of patients. In both cases, statistical analysis of the data showed statistical significance of these changes. Analysis of the results of the questionnaires completed by the patients did not show a statistically significant difference between the results of the groups compared. Differences between groups were also found when comparing the results of magnetic resonance imaging. Patients treated with ocrelizumab had fewer areas of gadolinium contrast enhancement in T1-weighted images compared with patients treated with β-1a interferon. The difference was significant at 94% fewer lesions in patients treated with okrelizumab. The incidence of adverse events during treatment with okrelizumab and interferon β-1a was comparable, with adverse events reported by 80.1% of study participants taking okrelizumab and 80.9% of participants taking interferon β-1a. The most common adverse reactions reported by study participants were post-injection reactions, nasopharyngitis, and upper respiratory tract infections. By comparison, in another study examining the effects of ocrelizumab, side effects were reported by 95.1% of participants taking the drug. [20] The side effects themselves were similar in both studies, with problems related to the injection of the drug ranking first. [19]
A study by Montalban and colleagues [14] evaluated the therapeutic efficacy of ocrelizumab in patients with the primary progressive form of multiple sclerosis. The results of the group of patients taking ocrelizumab were compared to those of patients taking placebo. It was found that the rate of disability progression was lower in the group of patients taking the drug than in those taking placebo. At 12 weeks, disability progression occurred in 32.9% of patients taking ocrelizumab, compared with 39.3% in the placebo group. After 120 weeks, the time to walk 25 steps was assessed in study participants. The averaged result for both groups was compared with the result before the start of the study. In the group taking Ocrelizumab, time increased by an average of 38.9%, compared to a 55.1% increase in average time in the group of patients taking placebo.

3. Conclusion

Studies conducted to date on the therapeutic efficacy of ocrelizumab show that its effect on disease progression is superior compared to some current drugs. Ocrelizumab also has a similar safety profile to the currently used interferon β-1a. An important feature of ocrelizumab is its efficacy in the treatment of the primary progressive form of MS, where significant therapeutic efficacy with other drugs has not been seen to date.

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