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Classical and Promising Therapies in the Management of Patients with Neuromyelitis Optica Spectrum Disorders

Vesselin Karabinov*

Department of Clinic of Neurology, National Heart Hospital, Bulgaria

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***Corresponding author:** Vesselin Karabinov, Department of Clinic of Neurology, National Heart Hospital 65 Konyovitsa Str 1000 Sofia, Bulgaria

Abstract

Neuromyelitis Optica is a severe, autoimmune disease of the central nervous system and in untreated patient leads to blindness and severe disability. It has a different prevalence rate worldwide. The prevalence of NMOSD in various studies ranges from 0.5 to 10 per 100 000. The highest prevalence is in the Asian region. Usually, recovery from an attack is incomplete. Until now, there was a lack of data with a high degree of confidence about the therapeutic strategies being implemented. Data from recent clinical trials on the efficacy of new biological therapies have shown very good results in reducing the incidence of attacks and delaying the progression of disability. Positive results have led to the approval of a drug for the treatment of neuromyelitis optica.

Keywords: Neuromyelitis optica; Treatment; Novel therapies

Abbreviations: NMO: Neuromyelitis Optica; NMOSD: Neuromyelitis Optica Spectrum Disorders; MOG: Myelin-Oligodendrocyte Glycoprotein; EMA: European Medicines Agency; FDA: Food and Drug Administration

Introduction

Neuromyelitis Optica (NMO) is a severe, autoimmune disease of the central nervous system and in untreated patient leads to blindness and severe disability. It has been described by Eugene Devic in 1894 and includes cases with single-phase or relapsing course of optic neuritis and transversal myelitis. There are earlier descriptions in the literature in the works of the German ophthalmologist Friedrich Albin Schanz, which outline most of the clinical and pathological features of the disease and on which the works of Devic and Gault are based [1]. In Japan, in 1891, Tane Michi Aoyama describes a case of a patient with symptoms of NMO [2]. The term Neuromyelitis Optica Spectrum Disorders (NMOSD) is currently accepted. NMOSD was proposed in 2007 and aims to group patients with aquaporin 4 antibodies (AQP4 Ab, NMO-IgG) with clinical manifestation only of episodes of transverse myelitis without optical neuritis and those with optical neuritis without transverse myelitis that are thought to have NMO. Following the description of NMO specific antibodies (AQP4 Ab, NMO-IgG) by Vanda Lennon in 2004, the diagnosis of the disease and the early differential diagnosis has improved significantly [3]. Some patients with clinical signs of NMOSD are seronegative. Recently, some studies report that in part of them antibodies against Myelin-Oligodendrocyte Glycoprotein (MOG Ab) are detected [4].

NMOSD has a different prevalence rate worldwide. The prevalence of NMOSD in various studies ranges from 0.5 to 10 per 100 000. The highest prevalence is in the Asian region. The disease usually developed around the age of 20 or 40, but the first attack can occur in childhood as well as in adults. Women are more commonly affected. The ratio of women to men is about 4: 1, the largest in Japan is 10: 1 [5-7]. Until now, there was a lack of data with a high degree of confidence about the therapeutic strategies being implemented due to the low incidence of the disease, the severity of the attacks, the early disability and the death of untreated patients. It should be noted that there was no registered drug with indication of NMOSD.

The purpose of this manuscript is to summarize the therapeutic approach in the treatment of NMOSD by focusing on emerging new therapies.

Treatment

The therapeutic strategy for patients with NMOSD is focused on four areas:

a. Treatment of attacks;

b. Preventive immunosuppressive treatment;

c. Symptomatic therapy;

d. Physical therapy and rehabilitation.

The treatment of the attacks is carried out with pulse therapy with corticosteroids: methylprednisolone 1g per day for five days and then switch to oral prednisone 1mg / kg / d. for 6 to 12 months with a gradual dose reduction. In patients who do not respond to pulse therapy, the dose of methylprednisolone may be increased to two grams daily. Plasmapheresis is used in patients with poor response to high doses of corticosteroids [4]. Plasmapheresis may be the first-line therapy in patients with severe neurological deficits, for example in transversal myelitis and in patients who have had a poor response to previous corticosteroid treatment. In our clinic, we use plasmapheresis as the first-line therapy in the treatment of attacks without serious side effects and complications. Different studies also show that the early use of plasmapheresis is associated with a better outcome [4,8].

Immunosuppressive therapy is accepted to prevent relapses. Currently, the most widely used are prednisone, azathioprine, mitoxantrone, rituximab, mycophenolate, methotrexate, cyclophosphamide, immunoglobulins and plasmapheresis. The choice of a particular therapy depends mainly on the availability, the side effects and the experience of the treating physician with the particular option. The most common strategy is to initiate treatment after an attack with oral corticosteroids, then add the selected immunosuppressant and gradually withdraw the corticosteroid of great importance is the symptomatic treatment of pain, stiffness, pelvic-reservoir disorders, fatigue. Treatment of residual symptoms significantly improves the quality of life. It is very important to carry out rehabilitation in patients with NMOSD, since even the first attack of transverse myelitis can lead to severe disability and, as a rule, recovery after an attack is incomplete.

Novel and emerging therapies

In recent years studies using biological therapy with NMOSD have been conducted. Monoclonal antibodies directed against components of the immune response are used. As a result of these new studies, on July 27, 2019, The U.S. Food and Drug Administration (FDA) has registered Eculizumab (Soliris) as a medication for treatment of NMOSD in AQP4 Ab-positive adult patients [9]. One month later, the drug was approved by the European Medicines Agency (EMA) with the same indication. The efficacy of the drug was demonstrated in a study of 143 patients who were randomized to receive Eculizumab or placebo. A 94% reduction of relapses was reported in the Eculizumab group compared to the placebo group over the 48-week study period. There has also been a reduction in the need for hospitalization and the need for corticosteroid and plasmapheresis treatment. Eculizumab has been warned by healthcare professionals and patients that life-threatening and fatal meningococcal infections have occurred, in patients treated with Eculizumab and that such infections can quickly become life-threatening or fatal if not recognized and treated early. Patients should be monitored for early signs of meningococcal infections and immediately examined for suspected infection. The use of the drug should be discontinued in patients treated for serious meningococcal infections. Healthcare professionals should pay more attention when administering Eculizumab to patients with another infection. No cases of meningococcal infection were observed in the NMOSD clinical trial. The most commonly reported adverse reactions in the study are upper respiratory tract infections, nasopharyngitis, diarrhea, back pain, dizziness, influenza, arthralgia, pharyngitis [9,10].

The N-MOmentum clinical trial is currently underway. This is the largest international, multicenter, placebo-controlled trial for NMOSD with 231 randomized patients, both with AQP4 Ab and seronegative. The study examined the efficacy and safety of Inebilizumab with NMOSD. Inebilizumab is a humanized monoclonal antibody against CD19 leukocytes, which causes rapid reduction of B lymphocyte counts, including antibody-producing plasma cells. Preliminary results indicate that the study fulfills both its primary endpoint and most of the secondary endpoints. The results to date have shown a significant reduction in the risk of NMOSD attacks, a reduction in the degree of disability as measured by Expanded Disability Status Scale (EDSS), reduction of hospitalizations, and reduction of new lesions in the central nervous system. Inebilizumab reduced the risk of NMOSD attack by 77% compared with placebo in AQP4-Ab seropositive patients after 28 weeks of treatment (HR: 0.227; $p < 0.0001$). A similar effect on relapse risk (73% reduction) was observed in the general population of Inebilizumab-treated patients, including AQP4-Ab seronegative patients (HR: 0.272; $p < 0.0001$). At the end of the randomized control period (RCP), 89% of seropositive patients with AQP4-Ab treated with Inebilizumab were attack-free, compared with 58% in the placebo group. Inebilizumab also demonstrates statistically significant benefits in key secondary endpoints: reduction of baseline EDSS impairment, reduction of NMOSD-related hospitalizations and reduction of active MRI lesions. Visual acuity, also a secondary endpoint, shows no statistically significant difference.

Another promising drug is also in an advanced stage of testing in the SAkuraSky study. A phase III, multicenter, double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of Satralizumab in patients with NMOSD. The study involved about 90 patients with NMO and NMOSD. Satralizumab is a humanized investigational recycling anti-IL-6 receptor monoclonal antibody. The preliminary results show that, Satralizumab significantly reduced the risk of relapse by 62%

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(hazard ratio = 0.38 [95% confidence interval: 0.16-0.88], p = 0.0184 [stratified log test]) in patients with NMOSD, both in AQP4 Ab positive and AQP4 Ab negative. The proportion of patients with no attack at 48 and 96 weeks was 88.9% and 77.6% in patients with Satralizumab and 66.0% and 58.7%, respectively, in the placebo group. In the subgroup with negative AQP4 Ab status, Satralizumab showed a 34% risk reduction (N = 28, hazard ratio = 0.66 [95% confidence interval: 0.20-2.23]) of attacks compared with placebo. In patients with Satralizumab, 84.4% and 56.3% had no attacks at 48 and 96 weeks, respectively, in the placebo group, the ratio was 75.5% and 67.1%, respectively. During treatment, for a period of approximately 2 years, Satralizumab shows a favorable safety profile. The proportion of patients experiencing serious adverse events, including serious infections, was similar in patients treated with Satralizumab or placebo. No deaths or anaphylactic reactions were observed.

Conclusion

NMOSD is a relatively rare but serious and progressive disease. The emergence of new biological agents and encouraging data from clinical trials hope for both patients and medical professionals for breaking through and starting a new era in therapeutic approaches and interrupting the relentless progression of disability. More studies and long-term and real-life data gathering are needed.

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