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Myasthenia gravis treatment

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Abstract

"Myasthenia gravis" has its origins in Greek. The terms denote muscle weakening (myasthenia) and heaviness (gravis). Myasthenia gravis (myasthenia gravis) is an autoimmune disorder marked by muscle weakness that exacerbates with activity, predominantly impacting the oculobulbar muscles and principally targeting postsynaptic nicotinic acetylcholine receptors. [1] This condition, characterized by a significantly high mortality rate due to respiratory failure, holds unique significance among neuromuscular disorders and within the broader field of neurology, as patients can enjoy perfectly normal lives with appropriate treatment. The prevalence of the condition in women is bimodal, with the highest incidence occurring between the ages of 20-30 and above 50 years. In contrast to males above the age of 50. The disease's most notable characteristic is muscle weakness, which exacerbates with tiredness and is at least partially alleviated by rest. Patients indicate improvement in the morning, with symptoms exacerbating in the evening or when fatigued [2] The manifestation of disease progresses with periods of remission and exacerbation. Remissions can last for durations ranging from a few days to several years.

Key words: Myasthenia gravis; muscle weakness; heaviness; autoimmune disorder

Principles of Treatment Evolution

In 1934, physostigmine, a cholinesterase inhibitor, was utilized for the treatment of myasthenia gravis. [3]. Indeed, Remen authored a study in 1932 indicating that neostigmine was efficacious in the treatment of myasthenia gravis. Nevertheless, this significant discovery was unrecognized by the medical world at that time. [4] In the late 1800s, the association of thymus pathology with people suffering from myasthenia gravis was contemplated. [5] Subsequently, it was determined that thymectomy was advantageous for patients, particularly those with positive acetylcholine receptor antibodies [6] The management of myasthenia gravis advanced in the 1970s. The utilization of steroids commenced subsequent to azathioprine treatment. Prednisone medication contradicted prior findings and demonstrated its efficacy in the treatment of myasthenia gravis. Plasma exchange was approved for the acute treatment of severe myasthenia gravis in 1976. Mediators were believed to influence circulation in myasthenia gravis [7] Intravenous immunoglobulin, mycophenolate mofetil, and tacrolimus were introduced as treatments around the close of the last century.

Management of Myasthenia Gravis

Cholinesterase Inhibitors

The primary therapy for myasthenia gravis are acetylcholinesterase inhibitors. These function by delaying the breakdown of acetylcholine at the neuromuscular junction [2] Pyridostigmine bromide is the most commonly utilized agent globally. The agent's action initiates within 15-30 minutes, peaks at 1-2 hours, and persists for 3-4 hours or longer. Treatment often commences with a dosage of 30-60 mg, with changes made based on therapeutic response or adverse effects. Doses of 180 mg or above are seldom beneficial. [8] Pyridostigmine is available for intravenous and intramuscular injection. Intravenous rapid-acting techniques may induce significant morbidity due to the potential for bradycardia. The advantageous impact of drug-induced inhibition may diminish over time, resulting in tolerance to the drug. The treatment of acetylcholinesterase inhibitors may be reduced as clinical efficacy diminishes, and patients may be reinstated if symptoms exacerbate throughout the tapering process. acetylcholinesterase inhibitor therapy is generally dependable; nonetheless, problems may arise. [2] The adverse effects of pyridostigmine include diarrhea, abdominal pain and cramps, nausea, heightened salivation, urinary symptoms such as urgency, and increased perspiration. Precaution is warranted in cases of obstructive lung illnesses, bradyarrhythmias, renal impairment, prostatic hypertrophy, and sudden myocardial

infarction. Cholinergic adverse effects, including abdominal pain and heightened salivation, may occur due to the elevation of acetylcholine at the neuromuscular junction generated by the medication. In the event of a significant adverse impact, the dosage of the medication should be diminished, and supplementary therapies should be incorporated. Consequently, it may be asserted that the efficacy of acetylcholinesterase inhibitors diminishes with prolonged administration. These medications offer symptomatic alleviation. [8]

Alternative Neuromuscular Conduction Augmenters

Ephedrine was initially utilized for the management of myasthenia gravis in the 1930s. Ephedrine is recognized for its direct impact on neuromuscular transmission. It has also demonstrated efficacy in congenital myasthenia gravis. [9] Despite this, it does not represent a significant therapeutic option for autoimmune myasthenia gravis. 3,4-Diaminopyridine, typically utilized for Lambert-Eaton myasthenic syndrome, may be considered for muscle-specific kinase-related myasthenia gravis, however substantial experience has not been documented. [10]

Therapeutics Targeting the Immune System

Corticosteroids

Corticosteroids and other immunosuppressant are the primary therapeutic intervention. These drugs are the preferred immunosuppressant for the treatment of mild to severe myasthenia gravis, particularly when acetylcholinesterase inhibitor therapy is ineffective. The primary treatment for myasthenia gravis is prednisolone. Corticosteroids, when administered in suitable quantities, yield symptomatic improvement in 70-80% of patients within a timeframe of 4 to 8 weeks [1] The mechanism of steroids involves the regulation of lymphocyte proliferation and differentiation, together with the inhibition of macrophage activity and cytokine production. In ocular myasthenia gravis, treatment commences with a low dosage and is then escalated. Typically, a dosage of 20-40 mg per day (0.50-0.75 mg/kg/day) is used. The recommended maximum dosage for generalized myasthenia gravis is 1 mg/kg/day, often 60 mg/day. Muscle weakness may temporarily exacerbate 1 to 10 days after initiating prednisolone, which can be commenced at low dosages and escalated at intervals of several days. The condition may worsen with the total cessation of prednisolone [2] In geriatric patients, it is advisable to maintain medication at a reduced dosage due to the elevated morbidity and death rates associated with exacerbations. The cessation of prednisolone therapy should be avoided in muscle-specific kinase-positive myasthenia gravis and myasthenia gravis associated with thymoma. muscle-specific kinase myasthenia gravis exhibits a favorable response to corticosteroids. The need for corticosteroids may be elevated in muscle-specific kinase myasthenia gravis, and the response may be delayed. Side effects of corticosteroids include hypertension, hyperglycemia, hypercholesterolemia, cataracts, and osteoporosis [11]

Alternative Immunosuppressant

Azathioprine

Azathioprine, possessing a more favorable safety profile than alternative medications, is often the medicine of choice in myasthenia gravis. It is utilized independently or in conjunction with corticosteroids. This drug is a purine analog that obstructs nucleic acid synthesis. [12] Its impact on the immune system primarily targets the reduction of B and T cell populations. This hypothesis posits a direct impact on nucleic acid production. The advised dosage is 2-2.5 mg/kg. The efficacy manifests within 6 to 12 months. The drug's efficacy in clinical settings was correlated with a reduction in white blood cell count and an increase in mean red blood cell volume [13] If either of these is not reported, the dose may be increased to its maximum. Adverse effects include toxicity to the liver and leukocytes. The association between prolonged use under 10 years and an elevated risk of cancer has not been substantiated [1]

Mycophenolate Mofetil

Mycophenolate mofetil has been an increasingly common medication for the treatment of myasthenia gravis. Many neurologists recommend mycophenolate, which reduces corticosteroid dosage, enhances efficacy, and lowers acetylcholine receptor antibody levels for generalized myasthenia gravis and progressive ocular myasthenia. [14] Mycophenolate undergoes hydrolysis to form mycophenolic acid. This inhibits inosine monophosphate dehydrogenase, a crucial enzyme in the de novo purine production process. [15] It inhibits T and B lymphocyte proliferation by obstructing guanosine production. Mycophenolate is administered at a standard dosage of 1 g bi-daily; however, there is no evidence to suggest that increased dosages yield greater efficacy. Significant side effects include persistent diarrhea, hemolytic anemia, edema, opportunistic infections, and teratogenicity.

Methotrexate

A definitive consensus about the use of methotrexate in myasthenia gravis is lacking. The efficacy of methotrexate was endorsed; however, no protective benefit from steroids was observed after one year of treatment. [16] It resembles azathioprine regarding the reduction of the steroid dosage. Methotrexate is a specific inhibitor of dihydrofolate reductase. The therapy of this medicine involves a maximum dosage of 20 mg per week, supplemented with folate and leucovorin. Alongside manageable side effects like hepatotoxicity, leukopenia, anemia, infections, and vomiting, severe adverse effects such as renal failure and pulmonary fibrosis may occur.

Tacrolimus

Tacrolimus, favored globally for its immunosuppressive properties, continues to be widely utilized in the Far East. Contrary to earlier beliefs, it has been demonstrated that there is no effect from the usage of low-dose prednisolone. The recommended dosage of this medication is 0.035 mg/kg administered bi-daily. [17] It is a calcineurin inhibitor that regulates T cell activity, which in turn supports antibody-producing B cells [18] It may also

enhance T regulatory cells. Tacrolimus augments muscular contraction via modulating intracellular calcium release channels, hence rapidly enhancing muscle contraction. Frequent side effects include diarrhea, tremors, and paresthesia. The primary adverse impact is nephrotoxicity [2]

Cyclosporine

The alternative steroid-sparing immunosuppressant favored for myasthenia gravis is cyclosporine, a cyclic undecapeptide; nevertheless, this therapy is often unsuitable for many patients due to its nephrotoxic effects. [19] It is a calcineurin inhibitor that specifically obstructs the transcription of proinflammatory cytokines including Interleukin-2 in T cells. The efficacy of azathioprine is observed within around 4-6 weeks. A dosage of 5 mg/kg/day in two divided doses is recommended. The application of this treatment for myasthenia gravis is constrained by dose-dependent adverse effects, including nephrotoxicity, opportunistic infections, bone marrow suppression, gingival hyperplasia, hyperkalemia, and hypertension.

Cyclophosphamide

Cyclophosphamide is another medication with steroid-sparing qualities for the therapy of myasthenia gravis (myasthenia gravis). There exist oral and intravenous formulations for patients with treatment resistance. [20] Through the liver's cytochrome P450 oxidase system, cyclophosphamide is converted to phosphoramide mustard, which delivers alkyl radicals into DNA and disrupts cellular reproduction. This mechanism is likely cytotoxic to lymphocytes. Other concerns include hemorrhagic cystitis, diarrhea, nausea, and vomiting, which can be severe.

Rituximab

It is a monoclonal antibody that specifically binds to the CD20 transmembrane antigen on B cells. In muscle-specific kinase positive myasthenia gravis, which exhibits inadequate response to first immunological therapies, safety and efficacy are seen; low disease severity and younger age are markers of favorable therapy response. The standard dosing of Rituxan is 375 mg/m² administered once weekly for a duration of four weeks. Administered dosages are provided biannually. [21] Multiple infusion-related responses may manifest (e.g., fever, headache, nausea). It can be mitigated with premedication and by reducing the infusion rate. The most severe adverse effect linked to this medication is progressive multifocal leukoencephalopathy. [22]

Eculizumab

The modulation of the complement system has been a topic of discussion for numerous years for the treatment of myasthenia gravis (myasthenia gravis). Only a single agent was deemed suitable for therapy. [23] Favorable outcomes of the phase 3 study were noted among individuals who did not derive advantages from immunosuppressive medication. The FDA has cleared it for use in individuals with acetylcholine receptor antibody-positive generalized myasthenia gravis. Eculizumab is one of the most costly medications, with an annual expense of approximately $400,000. [24]

Non-Therapeutic Management of Myasthenia Gravis

Plasmapheresis

The application of plasma exchange exhibits a rapid therapeutic effect in fatigue conditions. [2] It is utilized to alleviate weakness and enhance muscle function prior to surgeries, following thymectomy, and during myasthenic crises. The mechanism of action of plasmapheresis involves the removal of pathogenic antibodies and potential supportive protein structures from the bloodstream. [1] The therapy process typically comprises five exchanges. The primary benefit of this treatment compared to alternative treatments is the swift effect that manifests within days. Typically, following the second plasma exchange, patients exhibit a therapeutic response, at minimum halting disease progression. Plasma exchange yields superior outcomes compared to intravenous immunoglobulin in Musk-positive patients. Patients may experience paresthesias due to citrate-induced hypocalcemia during the infusion, and hypotension may arise at the commencement of the exchange [25] A significant drawback is its brief period of efficacy. This treatment is costly and is associated with coagulation problems and hemodynamic imbalance. Central line insertion.

Intravenous Immunoglobulin

Intravenous immunoglobulin therapy, comprising Ig antibodies derived from pooled human plasma, is another form of antibody-mediated treatment. The typical treatment consists of 2 g/kg administered over a duration of 5 days. Research assessing the impacts of plasmapheresis and intravenous immunoglobulin therapy in myasthenic crises indicates that plasmapheresis yields superior clinical outcomes. Ancak, intravenous immunoglobulin'nin yan etki ve komplikasyonlarının daha az olduğu tespit edilmiştir. [2] Some of the benign side effects of intravenous immunoglobulin include dizziness, cold, and headache. Occasionally, significant issues arise with intravenous immunoglobulin. Anaphylactic reactions occur in patients with immunoglobulin A deficiency, which may affect 1 in 1,000 persons. This highlights the impact of intravenous immunoglobulin on the immune system through numerous routes. They influence the autoimmune phase by multiple mechanisms, including as competing with autoantibodies, inhibiting cytokines, interacting with the Fc receptor on macrophages or immunoglobulins on B cells, and recognizing antigens by sensitized T cells. [26]

Thymectomy

Thymectomy is one of the initial treatments for persons with myasthenia gravis (myasthenia gravis). Thymoma occurs at a rate of 10-15%, with incidence increasing with age. Thymectomy is indicated for all myasthenia gravis patients with thymoma. In individuals with tumor-associated myasthenia gravis, this procedure is conducted to

excise the thymic tumor and to address the myasthenia gravis itself. The fundamental principle is to excise the thymus tissue, the primary site of antibody synthesis, and to diminish the concentration of acetylcholine receptor antibodies in the bloodstream. This surgical treatment is indicated for individuals under 60 years of age and in the early stages of the condition. Thymectomy is advised for generalized acetylcholine receptor positive myasthenia gravis and seronegative myasthenia gravis. It is not recommended in muscle-specific kinase-positive myasthenia gravis [2]

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