

Myasthenia Gravis: Trend of Therapeutic Agents in the Management of the Disease

Chika J Mbah*

Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria

*Corresponding Author: Chika J Mbah, Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria.

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Abstract

Myasthenia gravis (MG) is an autoimmune disease caused by autoantibodies against the nicotinic acetylcholine receptors on the postsynaptic membrane at the neuromuscular junction. It is characterized by weakness and fatigability of the voluntary muscles. The objective of the study was to provide the trend of therapeutic agents utilized in the treatment of myasthenia gravis. The methodology utilized published works in scientific journals, official books and other medical and pharmaceutical relevant books to gather relevant information. Academic institution library as well as the internet websites offered assistance in the information gathering. The results have shown that the trend of these therapeutic agents against myasthenia gravis is acetylcholinesterase inhibitors, corticosteroids, immunosuppressants and immunomodulators and new chemical entities awaiting approval. The study suggests that drug treatment of myasthenia gravis is highly successful and has in combination with other treatment procedures very significantly reduced the mortality of patients with myasthenia gravis to near zero.

Keywords: Myasthenia Gravis (MG); Autoimmune Disease; Neuromuscular Junction (NMJ)

Introduction

Myasthenia gravis (MG) an autoimmune disease is a neuromuscular junction (NMJ) disorder caused by autoantibodies against the nicotinic acetylcholine receptor (AChR) located in the postsynaptic muscle endplate membrane [1,2]. The autoantibodies implicated in AChR myasthenia gravis are immunoglobulin G1 (IgG1) and immunoglobulin G3 (IgG3) respectively [3]. The autoimmune disorder is characterized by weakness and fatigability of the voluntary muscle arising from the distortion and simplification of the postsynaptic muscle membrane and consequent attachment of antibodies and complement to the membrane. The fundamental defect is a decline in the number of available acetylcholine (ACh) receptors at the postsynaptic muscle membrane. The mechanism of the decline involves immune activation against acetylcholine receptors (complement-mediated lysis, cross-linking) and functional blockade of postsynaptic receptors [4]. In addition, thymus abnormalities have been found to be involved in the pathogenesis of the disease.

A large number of drugs have the potential to induce myasthenia gravis. Some of such drugs include but not limited to D-penicillamine, aminoglycoside, fluoroquinolones, tetracyclines, timolol, betaxolol, general anesthetics, chloroquine, sulfonamides, quinidine, barbiturates, gabapentin, phenytoin and calcium channel blockers.

The symptoms of myasthenia gravis are specific muscular weakness and fatigability. Ocular symptoms such as ptosis, diplopia, or blurred vision seem to be first manifestation of the disease. Ptosis (weakness of levator palpebrae) which may be unilateral, is a common presenting feature and it is often fluctuating in nature. Weakness can be increased by factors such as exertion, hot temperatures, infections, emotional upsets, certain drugs previously mentioned, surgery and pregnancy.

The diagnosis of myasthenia gravis involves clinical demonstration of fatigability while the electrodiagnostic, pharmacological and serological tests are adjunct to the diagnosis [5]. Such tests include edrophonium (tensilon) test (only carried out where diagnosis of myasthenia gravis is required urgently and there are facilities for full resuscitation); ice test (performed when ptosis is present); electrophysiological tests (repetitive nerve stimulation and single fibre electromyography); AChR antibody in serum test (specific for myasthenia gravis and regarded as a 'diagnostic gold standard'); computed tomography tests (diseases associated with myasthenia gravis namely diabetes mellitus, thyroid disease, rheumatoid disease etc.) and MRI tests (structural or inflammatory brain stem lesion, chest MRI etc).

Myasthenia gravis has been classified according to the aetiology of the disease (acquired autoimmune, transient neonatal, drug-induced, congenital myasthenic syndromes), age of onset (transient neonatal or adult autoimmune), presence or absence of anti-AChR antibodies (seropositive or seronegative) and severity (grade 0 to grade 4) [6]. Grade 0 (asymptomatic), Grade 1 (ocular signs and symptoms); Grade 2 (mild generalized weakness); Grade 3 (moderate generalized weakness, bulbar dysfunction, or both) and Grade 4 (severe generalized weakness, respiratory dysfunction, or both).

Conditions that may mimic myasthenia gravis include Lambert Eaton syndrome (autoimmune disorder of the neuromuscular junction that affect presynaptic release of acetylcholine), botulism, acquired neuromyotonia, congenital myasthenia, drug induced myasthenia gravis, metabolic and toxic myopathies, and brain stem diseases.

Myasthenic crisis (exacerbation of myasthenia), a condition that leads to paralysis of respiratory muscles, can be caused by infections, initial high dose steroid therapy, or an inadequate treatment.

Treatment of myasthenia gravis involves use of therapeutic agents (drugs) such as acetylcholinesterase inhibitors (improve neuromuscular transmission), corticosteroids and immunosuppressants (interfering with autoantibody activity on neuromuscular junction, intravenous immunoglobulins (modulating circulating autoantibodies) and procedures such as plasmapheresis and thymectomy [7]. Initial treatment usually starts with use of the acetylcholinesterase inhibitor or in combination with corticosteroid. Short-term treatment using immunomodulating agents may be effective in the early stages of treatment or later during an exacerbation. However, for long-term treatment steroid and immunosuppressants are included in the dosage regimen. New therapeutic agents that are potential agents for the treatment of myasthenia gravis have been reported [3]. It has been suggested that treatment of the disease could be individualized according to the patient's age, degree of functional impairment, gender and severity of disease.

Procedures used in the management of myasthenia gravis

Plasmapheresis

Plasmapheresis is a method of removing blood plasma from the body and it provides rapid but temporary improvement in cases of myasthenia gravis by reducing the amount of ACh receptor antibodies [8]. It is indicated for patients with serious myasthenia gravis or myasthenic crisis; preparing patients with severe myasthenia gravis before thymectomy; symptoms of the disorder worsening during tapering or initiation of immunosuppressive therapy. Plasmapheresis procedures are double filtration plasmapheresis, immunoadsorption plasmapheresis and plasma exchange [9,10].

Thymectomy

Thymectomy is a surgical procedure that is helpful in the treatment of myasthenia gravis. The procedure is inevitable for patients with thymoma however, for non-thymoma myasthenia gravis, thymectomy may increase the likelihood of disease remission or improvement [11].

Trend of therapeutic agents

Acetylcholinesterase inhibitors were the first therapeutic agents used in myasthenia gravis [12]. Subsequently, corticosteroids [13], immunosuppressants [14], intravenous immunoglobulin [15] were found to be useful in treatment. Potential new therapeutic agents are awaiting approval.

Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors act by inhibiting acetylcholinesterase, thereby increasing the concentration of acetylcholine to react with the AChR resulting in the improvement of transmission at the neuromuscular junction. They do not interfere with the immune processes that cause and perpetuate the disease but are involved in the management of symptoms throughout the disease course. An excess of acetylcholine at the neuromuscular junction may worsen the disease by desensitizing ACH receptors, a phenomenon called cholinergic crisis. Typical examples of such drugs are neostigmine bromide, physostigmine and pyridostigmine bromide [16]. Neostigmine, an orally administered anticholinesterase, was first used in myasthenia gravis in 1935. Pyridostigmine bromide is the most often used drug in this pharmacological class and can be administered orally (tablet or syrup) or parenterally (intramuscular or intravenous injections). Neostigmine has shorter duration of action, less efficacious and more frequently cause muscarinic side effects when compared to pyridostigmine bromide. Other AChE inhibitors are (i) ambenonium chloride- rarely used because of its long duration of action and greater tendency to accumulate. (ii) edrophonium- very short-acting AChE inhibitor and is used mainly for diagnostic purposes.

Corticosteroids

Corticosteroids are first-choice drugs when immunosuppression is required. Prednisone is the most commonly used because of its potent immunosuppressive activity and low anti-edemigen activity [17]. Prednisolone is also used at 10 - 20 mg/day dose level.

Immunosuppressive drugs

Immunosuppressants are used to treat myasthenia gravis either as single drugs or in combination with corticosteroids as "steroid-sparing agents." They also act as alternative therapeutic agents to corticosteroids in patients that experience adverse reactions to corticosteroids. Typical examples are azathioprine, cyclosporin A, cyclophosphamide, mycophenolate mofetil, tacrolimus and methotrexate [18]. Azathioprine is the first drug of choice as immunosuppressive drug for myasthenia gravis probably because of its steroid-sparing property and its preferential effect on T cell replication [19]. Cyclosporin A, cyclophosphamide and methotrexate are third-line therapeutic agents and are effective in patients intolerant or resistant to other immunosuppressants [20,21]. Mycophenolate mofetil and tacrolimus are newer immunosuppressive drugs that could act as second-line immunosuppressive therapeutic agents for myasthenia gravis [22,23].

Intravenous immunoglobulin (IVIg)

Intravenous immunoglobulin has been found to be effective in the treatment of myasthenia gravis [24,25]. It is also indicated for severe myasthenia gravis, myasthenic crisis and intractable myasthenia [26].

Potential new therapeutic agents

The following new chemical substances are currently being studied as potential new therapeutic agents:

- (i) Eculizumab is a C₅ monoclonal antibody directed at the complement protein C₅ to prevent the formation of the terminal complement complex, C_{5b-9}. It is reserved for patients with disease refractory to first-line treatments [27].
- (ii) Rituximab is a humanized monoclonal antibody that causes prolonged B-cell depletion and has shown indication against refractory myasthenia gravis [28,29].
- (iii) Etanercept is a blocker of tumor necrosis factor- α (TNF α) activity and has shown some therapeutic activity against corticosteroid-dependent autoimmune myasthenia gravis [30,31].
- (iv) Complement inhibitors obstruct complement activation by specific autoantibodies involved in attacking neuromuscular junction membrane end plates and therefore are potential agents for the treatment of myasthenia gravis [32].

- (v) Monarsen (antisense oligonucleotide, EN101) is an oral drug involve in modulating AChE expression by interacting with specific complementary mRNA and are able to cause targeted gene transcription inhibition [33]. It causes a reduction in production of the acetylcholinesterase.
- (vi) Rozanolixizumab (UCB7665) is a humanized anti-human neonatal Fc receptor (FcRn) monoclonal antibody designed to reduce the levels of pathogenic IgG in autoimmune diseases. It is considered a potential therapeutic agent in patients with moderate to severe myasthenia gravis and is currently undergoing phase II trial [34].
- (vii) Efgartigimod (ARGX-113), an FcRn monoclonal antibody considered to be an effective therapeutic agent against myasthenia gravis and is currently undergoing phase III trial [35].

Conclusion

Acetylcholine receptor (AChR) impairment has been explained by three antibody-mediated mechanisms namely accelerated endocytosis and degradation of AChR; functional blockade of ACh-binding sites; and complement-mediated damage of the postsynaptic membrane. The trend of therapeutic agents in the treatment of myasthenia gravis can be categorized as acetylcholinesterase inhibitors, corticosteroids, immunosuppressants, immunomodulating agents, biological and cellular therapies. Corticosteroids and immunosuppressants are usually employed on chronic therapeutic regimen, whereas immunomodulating agents are for short-term therapies.

Plasma-exchange (PE) and intravenous immunoglobulins (IVIg) are generally used to induce a rapid improvement in patients with exacerbation of the disease. These beneficial effects are rapid, but only temporary. Finally, innovation in the treatment myasthenia gravis depends mainly on using new effective therapies, reduction of side effects, therapeutic schedules optimized for chronic immunosuppression, drugs with higher specificities that selectively target the critical immunopathological steps (AChR sensitization to autoantibody production).

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