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Immunomodulatory Treatments for Myasthenia Gravis: Plasma Exchange, Intravenous Immunoglobulins and Semiselective Immunoadsorption

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1. Introduction

Myasthenia Gravis (MG) is an autoimmune disorder characterized clinically by fluctuating muscle weakness and fatigability on exertion. The disease is caused by specific autoantibodies against proteins of the neuromuscular junction (NMJ) (Conti-Fine et al, 2002; Sanders & Meriggioli, 2009). Two different autoantibodies are routinely detectable, i.e. antibodies against the acetylcholine receptor (AChR) or to a muscle specific tyrosine kinase (MuSK) (Hoch et al., 2001). Anti acetylcholine receptor autoantibodies are detected in about 80-85% of patients with generalized Myasthenia Gravis. Myasthenia Gravis patients without antibodies to either acetylcholine receptor or MuSK are now defined as affected with "seronegative Myasthenia Gravis". A recent study reported that a proportion of seronegative patients has low-affinity antibodies to acetylcholine receptor, antibodies that cannot be detected by common radioimmunoassay (Leite et al., 2008).

In Myasthenia Gravis associated with anti-acetylcholine receptor antibodies the neuromuscular transmission is impaired because of the reduced number of functional acetylcholine receptors. At least three antibody-mediated mechanisms have been described to explain acetylcholine receptor impairment: accelerated endocytosis and degradation of acetylcholine receptor, functional blockade of acetylcholine-binding sites and complement-mediated damage of the post-synaptic membrane (Conti-Fine et al., 2002). The pathogenicity of anti-muscle specific tyrosine kinase antibodies is still a matter of investigation (Guptill & Sanders, 2010).

Anti-muscle specific tyrosine kinase antibodies belong to the Immunoglobulin-4 subclass of immunoglobulins and do not bind complement. Muscle specific tyrosine kinase is necessary for the agrin-mediated clustering of acetylcholine receptors on the surface of the postsynaptic membrane. It has been shown that passive transfer of immunoglobulins from anti-muscle specific tyrosine kinase positive patients can cause myasthenia when injected into mice; moreover, acetylcholine receptor density was reduced and a loss of the normal apposition between the presynaptic and postsynaptic structures has been reported (Cole et

al., 2008), Therefore, apart from the above mentioned differences, anti-acetylcholine receptor and anti-muscle specific tyrosine kinase antibodies interfere with neuromuscular transmission and hence modulation of their activity can produce clinical improvement.

Myasthenia gravis is currently treated with several therapeutic approaches with the aim to induce pharmacological remission and, when possible, complete stable remission (Richman & Agius, 2003; Mantegazza et al., 2011). These approaches include: a) symptomatic treatment with anticholinesterase inhibitors, b) corticosteroids and immunosuppressive drugs to keep autoreactivity against the antigenic targets under control, and c) thymectomy, that removes surgically a potential site of autosensitization and/or perpetuation of the autoimmune process underlying the disease.

Immunomodulation in myasthenia gravis is considered a therapeutic tool able to modulate and hence interfere with the activity of specific autoantibodies. In this regard, myasthenia gravis represents a candidate disorder for the use of these treatments since, compared with other autoimmune diseases, the pathogenetic mechanisms are well characterized, and both autoantibodies and antigenic targets have been identified.

Modulation of autoantibody activity can be obtained by either their removal from plasma by means of different apheretic techniques such as therapeutic plasma exchange (TPE) or selective immunoadsorption (IA), or by expansion of the circulating immunoglobulin pool by infusion of high dose intravenous immunoglobulins (IVIG) that interfere with their activity by means of several, and still poorly understood, biological mechanisms. Removal of immunoglobulins by TPE or expansion of the total circulating pool by intravenous immunoglobulins represent opposite approaches able to induce a rapid improvement of the patients' clinical condition. Their use has been initially proposed as a form of "rescue treatment" for myasthenia gravis patients affected with the most severe forms of the disease (i.e. patients with bulbar and or respiratory involvement, patients admitted to the intensive care for respiratory insufficiency needing mechanical ventilation). Subsequently, their long-term use as been proposed for chronic immunomodulation of patients refractory to standard immunosuppression.

2. Therapeutic apheresis in MG

Therapeutic apheresis includes techniques able to remove different blood components. TPE is the standard procedure to separate the patient's plasma from blood cells. Plasma is obtained by means of centrifugation with computerized continuous flow cell separators or by separation with hollow fibers filters. The plasma obtained is substituted by a replacement fluid, usually 4-5% albumin solution.

The procedure is generally well tolerated; however, particular attention must be given to the patient's general clinical conditions, coagulation status and presence of cardiovascular contraindications.

Two vascular accesses are needed, the first for blood inflow, and the second one for reinfusion of blood cells mixed with the replacement fluid. A critical point is the evaluation of vascular accesses that means the availability of peripheral veins able to provide an adequate blood flow; if not, central catheters should be positioned, with higher costs and potential side effects, particularly infections when they must be left in place for several days.

A single needle approach is also feasible with some cell separators, even though more time consuming.

The use of TPE in Myasthenia Gravis was reported for the first time in 1976 (Pinching and Newsom-Davis, 1976). Since the first report, TPE has become a critical therapeutic tool for Myasthenia Gravis (Mandawat et al., 2010). Myasthenia Gravis is the best candidate disorder for treatment with TPE because of the definite role of specific autoantibodies against acetylcholine receptor or muscle specific tyrosine kinase, the two antigenic targets of the neuromuscular junction reported so far in Myasthenia Gravis.

In 1986, the National Institute of Health (NIH) held a Consensus Conference on the use of TPE in Myasthenia Gravis and concluded that TPE is effective in the short-term and that a placebo-controlled trial would not be feasible nor ethically justified (NIH, 1986; Assessment of Plasmapheresis, American Academy of Neurology 1996). Therefore, no evidence-based information is available in the literature (Cortese et al., 2011). The analysis of open studies is difficult due to their heterogeneity; indeed, exchange protocols differed among studies, treated patients were either in myasthenic crisis or prolonged worsening and the effect of ongoing treatments with steroids and disease duration are likely to have considerably influenced the results.

Methodological flaws related to these studies have been underlined in the Cochrane review on this topic (Gajdos et al., 2002). Open studies showed that TPE was effective in at least 60-70% of treated patients and that improvement was strictly related in time with plasma removal. The heterogeneity of treatment protocols in terms of number of sessions is so wide that a definite conclusion on the optimal number of sessions to be performed cannot be achieved. In some studies the number was fixed while in others patients were submitted to a number of exchange sessions apparently dependent on the achievement of a detectable clinical improvement.

In clinical practice, we adopt a conservative approach consisting of a short protocol of two exchanges performed every other day with removal of one plasma volume per session; in our hands this protocol was effective in 70% of treated patients, all affected with bulbar Myasthenia Gravis (Antozzi et al., 1991). We routinely evaluate the patient within seven days and repeat the same protocol in case of failure. We favour a conservative approach that can be effective in a short period of time instead of performing several exchanges as default. This is important considering the patient's tolerability, particularly when vascular accesses are poor. The majority of authors usually recommend three to six exchanges removing 1-1.5 plasma volumes with saline and 5% albumin replacement, performed every other day. We prefer the alternate days schedule because of the immunoglobulin backflow from the extravascular to the intravascular space.

The main indication to TPE in Myasthenia Gravis is the acute worsening of the disease (either severe generalized or bulbar) or myasthenic crisis. Other indications include worsening during the start of corticosteroids, and preparation to thymectomy in symptomatic patients. On the basis of our experience we think there is no need to perform TPE immediately before thymectomy when Myasthenia Gravis is well controlled by pharmacological treatment.

The chronic use of TPE in Myasthenia Gravis has never been addressed with a definite protocol. Nevertheless, TPE can be used at repeated intervals in selected patients in case of

frequent relapses, when the response to pharmacological treatment is unsatisfactory after an adequate clinical follow-up, or in patients that have major contraindications to long-terms corticosteroids. Limitations to the use of chronic TPE are the need for good vascular accesses and the obvious effects on several plasma components in case of intensive and prolonged protocols. Therefore, the number of sessions and interval between them must be tailored on each patient taking into account the general clinical conditions, severity of Myasthenia Gravis, and potential side effects. Because of these limitations, selective apheresis should be the technique of choice in severe immunosuppression-resistant patients requiring prolonged apheretic treatments (Antozzi et al., 1994).

As mentioned earlier, antibodies to muscle specific tyrosine kinase have been reported in a proportion of patients in which anti- acetylcholine receptor antibodies were not detectable (Sanders & Meriggioli, 2009). These patients can be differentiated on clinical grounds from those with anti- acetylcholine receptor antibodies. Their clinical picture is characterized by a typical "oculo-bulbar" involvement and more frequent respiratory compromise and occurrence of myasthenic crisis requiring mechanical ventilation (Evoli et al, 2003). The disease in these patients is frequently refractory to standard immunosuppressive regimens for variable periods of time; nevertheless, muscle specific tyrosine kinase-positive Myasthenia Gravis shows a good response to TPE (or intravenous immunoglobulins) (Guptill et al., 2011). This feature is of particular importance in the effort to overcome the prolonged bulbar involvement that frequently occurs in this subset of Myasthenia Gravis patients. Treatment protocols are similar to those adopted for acetylcholine receptor-positive Myasthenia Gravis.

3. Semiselective immunoadsorption

The ideal apheretic approach should remove only the specific autoantibody involved in the pathogenesis of the disease under treatment, leaving all the other plasma components unaltered. Such a specific approach is not yet available for clinical practice. A compromise is represented by a technique able to remove only circulating immunoglobulins (IgGs) and hence the specific autoantibody. This technique is called semiselective immunoadsorption (IA).

Different ligands are available for clinical use in immunoglobulin-mediated disorders.

The first to be introduced was protein A (Samuelsson, 2001). Protein A is a component of the staphylococcal cell wall with the particular feature of binding human immunoglobulins with high affinity; the binding is thought to be mediated by the Fc fragment of immunoglobulins. Moreover, protein A has several other features that make it an ideal candidate for semiselective immunoadsorption: the protein has a negligible interaction with other plasma components, is stable to wide variations in temperature and pH, and can be easily regenerated.

A second method involves the use of polyclonal sheep anti-human immunoglobulins that remove directly circulating immunoglobulins by means of an immunological interaction (Nakaji 2001). In both cases, plasma must be separated by centrifugation, and is then passed on-line through a set of two filters filled with either protein A or sheep anti-human immunoglobulin. The filters are operated by dedicated monitors and work alternatively; while the first filter removes immunoglobulins, the second one is washed, submitted to the

elution process to remove the adsorbed immunoglobulins, and then filled with a buffer solution, ready for the next adsorption cycle. These particular features make these techniques suitable for treatment of unlimited amounts of plasma since no replacement fluid is needed and the interaction with coagulation factors is negligible.

A different kind of semiselective immunoadsorption uses filters containing tryptophan-linked polyvinyl alcohol gel, used to treat Myasthenia Gravis patients with promising initial results in terms of clinical improvement (Grob et al., 1995; Shibuya et al., 1994). The binding is mediated by a chemical interaction and is much less selective than protein A or sheep anti-human immunoglobulin since other plasma components are retained, particularly fibrinogen and complement. A variable range of reduction of immunoglobulin and specific antibodies has been reported. The procedure does not seem to be more clinically effective than TPE and further studies should be performed to compare different methods. Moreover, these filters cannot be regenerated and therefore do not allow unlimited removal of immunoglobulins as occurs with protein A or sheep anti-human immunoglobulin.

From a technical standpoint semiselective immunoadsorption is more complicated and expensive then TPE. The procedure takes several hours since at least two plasma volumes should be treated during each session to fully exploit the binding capacity of the filters. Our treatment protocol consists of three sessions of at least two plasma volumes each, performed every other day. Again, considering the immunoglobulin backflow from the extra to the intravascular compartments we favour the alternate day regimen. Afterwards, we usually perform one maintenance session every four to six weeks; when clinical improvement between consecutive sessions remains stable and the interval between them can be increased to more than two months we usually stop semiselective immunoadsorption treatment. More intensive protocols can be performed safely if clinically needed since no replacement fluid is required and both methods do not interact with coagulation factors; in this regard, this method is particularly helpful in the treatment of patients needing oral anticoagulation.

Because of the complexity of the procedure, its duration, and costs, the indications to semiselective immunoadsorption are different from those of TPE that remains the first line apheretic option for acute exacerbations of Myasthenia Gravis. We favour the use of semiselective immunoadsorption in patients with treatment-resistant Myasthenia Gravis after adequate clinical follow-up, patients requiring frequent TPE to keep a satisfactory improvement, or patients with major contraindications to the use of high dose corticosteroids and/or other immunosuppressive drugs. In these patients, the periodic massive removal of circulating immunoglobulins can be of help in keeping symptoms under control.

A few experiences have been reported in the literature confirming the efficacy of semiselective immunoadsorption in the management of Myasthenia Gravis patients (Benny et al., 1999; Haas et al., 2002). During the last decade we submitted to semiselective immunoadsorption 19 treatment-resistant Myasthenia Gravis patients; the severity of the disease ranged from severe generalized to bulbar. Patients were periodically treated for a mean of 16 months. Improvement up to minimal manifestations or pharmacological remission was recorded in 18 out of 19. It is of interest that semiselective immunoadsorption was effective in 6 patients after failure of TPE or intravenous immunoglobulins. The mean corticosteroid reduction at the end of the treatment period was 42%.

The absence of detectable anti-acetylcholine receptor or anti muscle specific tyrosine kinase antibodies is not a contraindication to start semiselective immunoadsorption that was indeed dramatically effective in a "double-negative" patient. In this regard, the presence of low affinity antibodies in double-negative patients with Myasthenia Gravis might explain the clinical response to TPE of these patients (Leite et al., 2008).

After treatment of two plasma volumes we observed a mean 71% of total immunoglobulin and 82% reduction of specific autoantibodies (mean of 51 sessions) (Antozzi et al., 1994; Berta et al., 1994). Both immunoglobulin and anti-acetylcholine receptor antibody levels increase after treatment, but their synthesis does not seem to be increased by repeated removal; on the contrary, the time course of autoantibody recovery is consistent with immunoglobulin half-life. Moreover, as shown by Goldammer and colleagues, the synthesis of free light chains, a marker of current antibody synthesis, is not increased by semiselective immunoadsorption (Goldammer et al., 2002).

The effect of semiselective immunoadsorption, and its superiority compared with TPE, is likely related to the massive removal of immunoglobulin to an extent that cannot be achieved with standard TPE.

We also measured the potential influence of semiselective immunoadsorption on different circulating cytokines in patients affected with Myasthenia Gravis and found increased levels of Interleukin-10 and reduced levels of Interleukin-18 in post-IA plasma samples (Baggi et al., 2008). Interestingly, Interleukin-18 plays a role in the pathogenesis of experimental Myasthenia Gravis since the in vivo blockade of Interleukin-18 activity suppressed the clinical manifestations of the disease (Im et al., 2001); moreover, serum levels of Interleukin-18 were found to be increased in Myasthenia Gravis patients and clinical improvement correlated with its reduction (Jander & Stoll, 2002). Therefore, the effects of semiselective immunoadsorption on the immunological homeostasis might be wider and more complex than the mere mechanical removal of circulating antibodies, and deserve further laboratory investigations.

Research on semiselective immunoadsorption involves the investigation of new selective and specific techniques able to provide antigen-specific depletion of immunoglobulin, at least for anti-acetylcholine receptor antibodies. This approach has been investigated in vitro by means of immunoadsorbent columns carrying immobilized human acetylcholine receptor recombinant fragments. The immobilization of recombinant proteins on Sepharose beads and incubation with a seropositive Myasthenia Gravis sera resulted in a significant reduction in the concentration of specific autoantibodies in these sera (Zisimopoulou et al., 2008). Investigation on the scaling up of both production of recombinant proteins and their conjugation are needed to determine the feasibility of specific semiselective immunoadsorption in the human disease.

4. High dose intravenous immunoglobulins

Intravenous immunoglobulins, purified from human plasma, is a solution containing a wide range of antibodies against pathogens and antigens. Intravenous immunoglobulins were initially used in patients affected with hypogammaglobulinemia, given through the intramuscular route because of the high risk of anaphylactoid reactions. Subsequently, by means of improved purification techniques, intravenous immunoglobulins have become

suitable for intravenous administration, with the advantage that larger doses can be administered in a shorter period of time.

In 1981, Imbach reported the effect of intravenous immunoglobulins in children with idiopathic thrombocytopenic purpura, with dramatic increase of platelets after intravenous immunoglobulins infusion (Imbach et al., 1981). Since that observation, the use of intravenous immunoglobulins has been extended to several neurological and non neurological autoimmune and inflammatory disorders (Elovaara et al., 2008; Donofrio et al., 2009).

The mechanism by which intravenous immunoglobulins exert their clinical effect in several autoimmune disorders is still unknown but several hypothesis have been proposed, including Fc receptor blockade of the reticuloendothelial system, modulation of the idiotypic-anti-idiotypic network, enhancement of regulatory T cells, inhibition of complement deposition, modulation of cytokines, growth factors and adhesion molecules, modulation of apoptosis and macrophages, and immune regulation of both B-cell and T-cell immune function (Ballow, 2011). The mechanism of action is likely to vary according to the disease. As far as Myasthenia Gravis is concerned, intravenous immunoglobulins might be effective particularly due to their influence on the idiotypic network and inhibition of complement deposition, according to the pathogenesis of the disease. Nevertheless, as for other autoimmune disorders, recent findings suggest an effect of intravenous immunoglobulins also on T cell immunoregulatory function (Maddur et al., 2010).

Intravenous immunoglobulins are given intravenously, the dose usually being 400 mg/kg body weight for 3-5 days. The infusion is generally well tolerated but potential adverse events must always be taken into consideration. Patients may experience anaphylaxis and anaphylactoid reactions, mild reactions including headache, fever and rash; renal failure, stroke and possible myocardial infarction have also been reported. Anaphylaxis may occur in the IgA-deficient patient. Hematological complications include hemolitic anemia and intravascular hemolysis. Thromboembolic complications have also been reported and attention should be paid to the patient's general conditions and risk factors (older age, hyperviscosity syndromes, underlying cardiovascular disorders, previous thromboembolic events). In patients at risk, high dose therapy should not be given in a short period of time, should be followed be adequate hydration, and higher daily doses should be avoided.

Several open studies on the efficacy of intravenous immunoglobulins in Myasthenia Gravis have been reported in the literature and despite the heterogeneity of patients included, clinical assessment and outcome evaluation, improvement in about 70% of treated patients has been reported. These studies are summarized in the Cochrane review devoted to this topic (Gajdos et al., 2008). A randomized placebo controlled trial reported the efficacy of intravenous immunoglobulins in worsening Myasthenia Gravis patients; the primary outcome was the Quantitative MG Score (QMG) assessed at baseline and at 14 and 28 days. Improvement was statistically significant at 14 days while the Quantitative MG Score at 28 days failed to reach statistic significance (Zinman et al., 2007).

The use of TPE in Myasthenia Gravis was first considered in comparison with intravenous immunoglobulin, that represents an alternative to TPE and share the same indications.

One randomized trial comparing the two treatments has been reported by the Myasthenia Gravis Clinical Study Group in France in 1997 (Gajdos et al., 1997). The study compared TPE

and intravenous immunoglobulin in 87 patients with acute forms of the disease and concluded that intravenous immunoglobulins (400 mg/kg for 3 or 5 days) was as effective as TPE (3 sessions of 1.5 plasma volumes each). Criticism to this study included the lack of a control arm, the nonblinding of the plasmaexchange group, and the lack of stratification according to the antibody status. No significant superiority of 2 g/kg over 1 g/kg intravenous immunoglobulins was observed in the treatment of Myasthenia Gravis exacerbations (Gajdos et al., 2005).

Recently, the effect of intravenous immunoglobulins and TPE was compared by means of a randomized study including 84 patients, providing Class I evidence that intravenous immunoglobulins and TPE have compararable efficacy and are equally tolerated in patients with moderate to severe Myasthenia Gravis within two weeks of treatment (Barth et al., 2011).

Therefore, the general recommendation is that intravenous immunoglobulins are a safe and effective alternative treatment option to TPE as a short term treatment for acute exacerbation of Myasthenia Gravis. Moreover, they can be easily administered particularly when TPE is not available, or feasible due to inadequate vascular access, in patients with contraindications to extracorporeal circulation, and in children.

As already reported for TPE, also intravenous immunoglobulins have been used to prepare patients for thymectomy (Jensen & Bril, 2008). However, it is our opinion that the same considerations reported above for TPE are valid also for intravenous immunoglobulins, and that their administration before surgery should be limited to patients with Myasthenia Gravis conditions not adequately controlled by the ongoing treatment, particularly when bulbar symptoms and signs are present.

The long term use of intravenous immunoglobulins has been proposed but evidence based data supporting the efficacy of their chronic administration are lacking. However, open studies on a very limited number of patients reported improvement for up to 2 years (Achiron et al., 2000). It must be underlined that no control patients were included and that patients received concomitant immunosuppression. It is therefore opinion of the Cochrane review and of the European Task Force of the European Federation of Neurological Societies (Gajdos et al., 2008; Elovaara et al., 2009) that there is still insufficient evidence on the role of intravenous immunoglobulins in the long term management of Myasthenia Gravis.

As mentioned before for TPE, patients with anti-muscle specific tyrosine kinase antibodies show a positive response to intravenous immunoglobulins as reported in open studies on the clinical features of patients affected with this subgroup of Myasthenia Gravis (Guptill et al., 2011). Moreover, the controlled study reported by Zinman and coworkers (Zinman et al., 2007) included patients with muscle specific tyrosine kinase-associated Myasthenia Gravis; even though the results were not given for each antibody subgroup, the overall results indicate improvement also in patients without anti-acetylcholine receptor antibodies. This is particularly important for muscle specific tyrosine kinase-positive Myasthenia Gravis in case of respiratory insufficiency, when TPE is not available or not feasible.

5. Conclusions and future perspective

TPE, semiselective immunoadsorption and intravenous immunoglobulins represent different approaches able to modulate the activity of specific autoantibodies in Myasthenia

Gravis. TPE and intravenous immunoglobulins share the same indications, i.e. treatment of severe patients with a recent exacerbation of the disease. Even though evidence based data are rather limited (particularly for TPE), there is general agreement on the efficacy of both treatments in the acute, severe forms of the disease.

There is no evidence of the superiority of TPE versus intravenous immunoglobulins emerging from the studies reported; however, some authors favour the use of TPE as a first line approach particularly in patients with respiratory insufficiency; it is also opinion of some experts in the field that TPE is probably more rapid than intravenous immunoglobulins in promoting clinical improvement, but these observations remain personal opinions of physician with expertise in treatment of Myasthenia Gravis, opinions that should be confirmed by clinical studies.

Different considerations regard semiselective immunoadsorption, that is a more complicated, time consuming and expensive technique compared with TPE. Nevertheless, in selected, treatment-resistant patients (particularly those requiring repeated apheresis or showing no response to TPE or intravenous immunoglobulins) semiselective immunoadsorption can be of considerable help in the long-term management of the disease. The future of semiselective immunoadsorption is represented by the investigation of new ligands, as reported above on the in vitro activity of recombinant fragments of the acetylcholine receptor.

Several aspects regarding the use of TPE and intravenous immunoglobulins, as emerged from meta-analyses performed in the last ten years, need further investigation. In particular the use of immunomodulating therapies in the long-term management of Myasthenia Gravis, in combination with immunosuppressive drugs in order to reduce the burden corticosteroids as much as possible and hence reduce side effects. Protocols on the investigation of the optimal dosage should also be designed.

Recently, the subcutaneous administration of intravenous immunoglobulins has been proposed (Misbah et al., 2009); this route does not require a venous access and seems to be associated with fewer sided effects; on the other hand, frequent administrations are needed because the volumes infused intravenously cannot be given by the subcutaneous route. Studies are still preliminary and mainly performed in patients with inflammatory peripheral neuropathies, experiences that might be transferred to other autoimmune neurological disorders, including Myasthenia Gravis.

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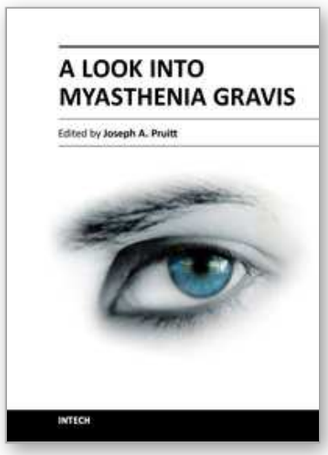
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Myasthenia gravis is presently an incurable antibody-mediated autoimmune disorder characterized by generalized voluntary skeletal muscle weakness. The cause of the weakness is a defect at the neuromuscular junction level, in which autoimmune antibodies block the receptors responsible for initiating muscular contraction. Literally translated from its Latin and Greek etymological roots, myasthenia gravis means "grave muscle weakness". Fortunately, advances in modern medicine have resulted in a reduction of the truly "grave" outcomes for those inflicted but, without a cure, the gravity surrounding the disease remains

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