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Editorial

Myasthenia Gravis: The Unmet Needs of a Paradigmatic Autoimmune Disease

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Editorial

Myasthenia Gravis (MG) is a paradigmatic autoimmune disease, of chronic course, with exacerbations and remissions, even in the absence of treatment. The disease may occur at any age, it can be associated with other autoimmune diseases such as thyroid gland diseases, and congenital forms are also possible. Pathophysiology is mainly characterized by the blockade of neuromuscular transmission, in the site of the Acetyl-choline receptors, which results in fatigability and/or weakness of diverse muscles of the body, including the respiratory ones. The annual incidence ranges from 0.3 to 2.8/100,000 [1]. The clinical symptoms may appear acutely or in an insidious manner. On some cases MG is detected immediately of a surgical intervention when the patient is weaned off the respiratory support. Since more than two decades ago, diagnosis has changed little in MG. With regard to treatment, new drugs are available, but a number of unmet needs remain.

We know the antigens and antibodies present in the majority of patients (AchR, musk, LRPA), which are virtually diagnostic of MG, but 10% of patients are triple seronegative. In this respect anti-titin and anti-agrin antibodies have arise as a biomarker for these seronegative forms, but these antibodies may be also present in the AchR seropositive ones, and whose clinical meaning is not clearly understood [2]. Among 667 MG sera from 13 countries, 13,4% of triple seronegative MG patients were positive for anti-titin antibodies. An attempt of clinical-immunological pattern has been reported. LRP4 antibodies were associated to late-onset myasthenia, with mild symptoms and good response to treatment. Anti-Agrin antibody MG was associated to early onset and moderate response to treatment. Patients negative for anti-AchR and anti-titin positive presented with mild limb muscle weakness, whereas the patients positive for both anti AchR and titin suffered from more severe MG with bulbar symptoms, and myasthenic crisis [3]. However the antibody titer does not correlate with the disease severity and are not indicative of better or worse outcome, so other pathophysiologic mechanisms escape to our knowledge.

The role of thymus in MG has not been elucidated yet. The presence of hyperplasia or thymoma in some cases might be a consequence more than a pathogenic element. This assertion is supported by the fact of spontaneous regression of thymomas have been reported in patients on conventional therapy [4]. Until recently, thymectomy has been performed on an empiric basis in non-thymomatous MG. The first randomized clinical trial ever published (126 patients randomized, with less than 5 year disease duration) favored thymectomy plus alternate day prednisone over alternative day predinsone alone, with fewer patients needing immunosuppressant's and lower doses of prednisone in the thymectomized group [5]. The patients were followed up for a period over 3 years. Nonetheless, further clinical trials are needed to ascertain the subset of patients who can benefit specifically of the procedure. Moreover, the effects of tymectomy are not immediate, and remissions can occur after years of the intervention. Other unanswered questions are when to perform thymectomy, and what we can expect from it.

Medical treatment is based on Cholinesterase Inhibitors (ChI), corticosteroids, and immunosuppressants. In accordance with the International Consensus Guidance [6]. ChI and prednisone are safe in pregnancy and azathioprine as well. For myasthenic crisis either IV immunoglobulin's or plasmapferesis are an effective treatment. Long-term maintenance therapy poses some caveats. Many patients need high doses of prednisone for doing well, but the potential side-effects of corticosteroids make the clinicians to substitute prednisone for immunosuppressive drugs. Azathioprine is one of the most and best tolerated immunosuppressant in MG patients, with the doses adjusted for the levels of TPMT (thio-purine-methyl-tranferase). It allows the clinicians to either tapper or with draw corticosteroids. Notwithstanding the benefits of azathioprine, there is a non-negligible risk of malignancies over time, especially in patients taking it for ten years or longer, so surveillance programs are needed. For cases in which azathioprine is not tolerated or does not work, another question arises: what other immunosuppressant should be given?; cyclosporine ?; tacrolimus?; mycophenolate?; Rituximab?. Given the lack of clinical trials, it would be very useful to create registries so as to share the experience among colleagues. The Myasthenia Gravis Foundation of America (MGFA) has created a patient registry to promote research, treatment, advocacy, and public awareness of MG (www.myasthenia.org). This registry is expected to be a source of important information for clinician and researchers.

Rituximab (Anti- CD20 monoclonal antibody) has emerged as an alternative option in cases of refractory MG, with good response in some cases. The evidence of action has only based on case reports and series (169 patients treated) [7]. Predictors of response were: positivity for anti-Musk antibodies, less severe disease, and younger age. But the fear of serious complications (ie: progressive multifocal leucoencephalopathy) limits the number of infusions.

Eculizumab is another monoclonal antibody that acts by inhibiting the terminal part of the Complement cascade, which is overactive in MG. The drug is used in paroxysmal nocturnal hemoglobinuria, and it has been recently approved by the European Commission and

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Table 1: List of unmet needs in Myasthenia gravis.

1	To elucidate the role of thymus gland in MG
2	To find out the fact that initiates immunogenicity (drugs, vaccines, infections, genetic propensity), and why immunogenicity becomes chronic. It is essential for prevention and treatment purposes.
3	New biomarkers of long-term prognosis and risk of myasthenic crisis.
4	Surveillance programs for patients on immunosuppressive drugs.
5	To establish the preference of some immunosuppressants over the rest.
6	To share information among clinicians for better indication of drugs by means of appropriate registries.
7	To learn from other autoimmune diseases

launched in Germany for refractory and generalized AchR positive MG. Eculizumab has demonstrated to be of benefit in a phase II small clinical trial (n=14) for 16 weeks, with most patients on eculizumab showing a 3 point reduction in the Quantitative Myasthenia Gravis score [8]. A posterior phase III clinical trial has confirmed the benefit of the drug (REGAIN-study or MG-301) and the long-term open-label extension study (MG-302). The improvements were observed not only in symptoms, but also in daily living activities (source: MGFA). Although there were no major side-effects in these trials the FDA warned on the serious meningococical and other infections, so the patients should be closely monitored. Another draw-back of eculizumab is its sky high price (around 400,00 USD per year).

Despite the new developments in MG, there are several unmet needs that should be addressed in further research (Table 1).

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