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Case report

Beneficial effect of tocilizumab in myasthenia gravis refractory to rituximab

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Abstract

Muscle fatigue associated with myasthenia gravis is caused by autoantibodies interfering with neuromuscular transmission. Immunomodulating treatment is widely used in moderate to severe myasthenia, although the use of newer biological drugs except rituximab is rare. We describe the effect of tocilizumab, a blocker of interleukin-6 signalling, in two female myasthenia patients with high titres of serum acetylcholine receptor antibodies and insufficient response to rituximab. The first patient had been treated with high dose immunoglobulins regularly for several years and the second patient had been treated both with different oral immune suppressants and immunoglobulins before testing a low dose of rituximab without significant clinical effect. Subsequent treatment with tocilizumab resulted in clinical improvement within a few months. The first patient was switched back to rituximab, which resulted in worsening until tocilizumab was restarted. Tocilizumab can be a therapeutic option in cases not responding to rituximab.

Keywords: Myasthenia gravis; Immunomodulatory therapy; Rituximab; Tocilizumab

1. Introduction

Myasthenia gravis (MG) is an autoimmune neuromuscular disease caused by antibodies that disrupt acetylcholine signalling at the neuromuscular junction, leading to fluctuating fatigability and weakness of the ocular, bulbar, respiratory and/or limb muscles [1,2]. In most cases autoantibodies are directed at the acetylcholine receptor (AChRab). AChRab positive MG principally occurs in three different forms: early onset MG (EOMG), late onset MG (LOMG) and thymoma-associated MG [1,2].

The medical treatment of MG consists of symptom relieving acetylcholine esterase inhibitors, but also entails targeting of underlying autoimmune inflammation. This can be achieved by surgically removing the thymus in cases of EOMG and thymoma-associated MG and/or the use of immune suppressants [3]. The latter group traditionally consists of corticosteroids and oral agents such as azathioprine, mycophenolate mofetil and cyclosporine; all having certain risks of adverse effects and some considered to have a long induction time, while repeated infusions with intravenous immunoglobulins (IvIg) can provide more rapid effects. Evidence of efficacy of newer biological drugs in MG has emerged more recently. Eculizumab, a C5a complement blocker, has shown promising results in a phase II trial [4]. A phase III trial with eculizumab was recently completed, but detailed outcomes have not yet been made available. In addition, rituximab, an anti-CD20 B cell depleting drug, has shown promising effects in several published case series, recently summarized in a meta-analysis [5]. However, not all patients respond to these treatments and there is a need to explore additional therapeutic options.

Tocilizumab is an anti-interleukin-6-receptor humanized monoclonal antibody introduced in Japan in 2005 as a treatment for Castleman's disease, but later receiving approval by EMA (2009) and FDA (2010) for rheumatoid arthritis and juvenile idiopathic arthritis [6]. Experimental studies have shown that interleukin-6 (IL-6) stimulates the production of autoantibodies from plasma cells [7], which makes it an interesting candidate drug for antibody-mediated diseases. In fact, tocilizumab has shown promising effects in neuromyelitis optica (NMO), an autoimmune condition caused by autoantibodies towards the aquaporin-4 water transportation channel [8,9]. A further development of tocilizumab, named SA237, is currently being

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tested in two phase III NMO trials. Collectively, this makes anti-IL-6 therapy an interesting option in MG, also supported by the clinical outcomes in the two patients treated with tocilizumab for refractory MG reported here.

2. Case report

Case 1 is a woman born in 1994 with severe MG since the onset in 2005. She also suffers from mild cognitive impairment and epilepsy. Her MG symptoms were generalized from onset. AChRab titres initially were negative, within a few months increasing to high levels (>200 nmol/L). Neurophysiology showed a disturbed neuromuscular transmission typical of MG on repetitive nerve stimulation (RNS) and single fibre-electromyography (SF-EMG). The first year she had only minor relief of repeated IvIg infusions, prednisolone 20–30 mg/daily and pyridostigmine up to a dose of 420 mg/daily. A transsternal thymectomy was performed in 2007 showing follicular hyperplasia. The following years her symptoms were somewhat controlled with regular IvIg and daily prednisolone at doses between 7.5 and 20 mg, however, with regular worsening in association with hormonal cycles. She opted to discontinue IvIg due to discomfort with repeated infusions in 2009. Treatment with oral immunosuppressive agents was not considered because of the patient's young age. Due to continued moderate-severe MG symptoms in 2014 she received a low dose of rituximab (100 mg single dose) without clinical improvement, as judged by evaluation with the quantitative MG status (QMG) score. The QMG score consists of 13 domains reflecting muscle fatigability in ocular, bulbar and extremities, where each muscle group is graded from 0 (no fatigability) to 3 (severe fatigability) [10]. Six months later a trial with tocilizumab given as a monthly infusion at 8 mg/kg body weight (total dose 320 mg; body weight 37 kg) was started. In total three IV infusions were administered, with a clear clinical effect as shown by a reduced QMG score associated with a modest lowering of her serum AChRab titre (Fig. 1). In order to exclude that the first dose of rituximab had been insufficient, she was then given a second infusion with 500 mg. Three months later the patient reported subjective worsening and her QMG had increased. Tocilizumab was then reinstated from March 2015, given as a subcutaneous injection of 162 mg every 2 weeks. She again displayed a beneficial response with lowered QMG ratings combined with much reduced fluctuations in relation to hormonal cycles. The daily dose of pyridostigmine was reduced from 180 to 120 mg per day. No adverse events have been recorded. The progression of symptoms over time in relation to her treatment and serum AChRab titres is shown in Fig. 1.

Case 2 is a woman born in 1932 with a history of asthma/chronic obstructive lung disease, hypertension, hypothyroidism after goitre operation and B12 deficiency. Since several years her lung condition has required treatment with oxygen. At 50 years of age she developed generalized MG. Neurophysiology with RNS and SF-EMG was consistent with MG and she displayed AChRab in serum. A transsternal thymectomy was performed in 1984 showing follicular medullary hyperplasia. Since 1984 she received pyridostigmine between 360 and 420 mg daily. Her symptoms since disease onset have been mostly unchanged with moderate MG fatigability, except for a few episodes of clinical worsening, in spite of different treatment strategies. These included long term corticosteroids, azathioprine (terminated due to elevation of amylase), mycophenolate mofetil (caused dizziness), cyclosporine (adverse effects on kidneys and pancreas) and repeated doses of 25 g IvIg every 8 to 12 weeks. A low dose of rituximab (100 mg) was tried without any clinical improvement inspite of B cells being reduced to the detection limit. Treatment with tocilizumab given as IV infusion (400 mg, body weight 72 kg) was started in May 2015 and switched to subcutaneous weekly injections (dose 162 mg) in March 2016. The pyridostigmine dose was unchanged at 360 mg daily. Still greatly affected by her pulmonary condition, she has displayed a distinct improvement in muscle strength both on subjective symptoms and on objective QMG testing, especially regarding neck strength. No clear effect on AChRab titres was evident. No adverse events have been recorded. The temporal profile of QMG scores in relation to her treatment and serum AChRab titres is shown in Fig. 1.

3. Discussion

In these two patients with refractive MG and high titres of AChRab in serum treatment with tocilizumab resulted in distinct clinical improvement. Traditional immune suppressant therapies used in MG, such as azathioprine, mycophenolate mofetil, cyclosporine, have a broad action on the immune system. However, not all patients benefit and others may have treatment-associated side effects. There is therefore a need to develop alternative treatment strategies for these patients. In this sense both eculizumab and rituximab are interesting candidates. Eculizumab interferes with the complement cascade, which can limit damage caused by complement fixing autoantibodies at the neuromuscular junction, while rituximab eliminates CD20 expressing B cells. The exact mode of action of rituximab has not been clarified in detail, but may be related to the antigen presenting capacity of B cells or their capacity to produce cytokines such as IL-6 or GM-CSF that stimulate the autoreactive immune response [11–13]. However, neither eculizumab nor rituximab is likely to directly affect the production of autoantibodies. Recent data in NMO suggest that production of autoantibodies by plasma blasts is driven by IL-6 and that interfering with IL-6 signalling results in reduced relapse rates [7–9]. Tocilizumab is a humanized monoclonal antibody against the interleukin-6 receptor that has shown clinical efficacy administered either as monotherapy or in combination with conventional disease modifying drugs such as methotrexate in adult patients with moderate to severe rheumatoid arthritis, for reference see [6]. The tolerability of tocilizumab is usually beneficial, but more severe adverse events such as perforated diverticulitis have been reported [14–16]. In a recent comparison of the effect and tolerability of tocilizumab, methotrexate or the combination of both for early rheumatoid arthritis, nasopharyngitis was the most common adverse event and was equally distributed between treatment arms [17]. The total number of reported adverse events was numerically lowest in the tocilizumab alone arm and the rate of