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SHORT COMMUNICATION

# Overcoming therapeutic challenges: Successful management of a supposedly triple seronegative, refractory generalized myasthenia gravis patient with efgartigimod

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## Abstract

**Background and purpose:** This study was undertaken to highlight neonatal Fc receptor inhibition (efgartigimod) as a valuable therapeutic option for patients with refractory seronegative myasthenia gravis (MG) and to emphasize the concept that seronegative MG is greatly constrained by the limitations of currently available diagnostic methods and therapeutic measures.

**Methods:** We describe the first refractory, generalized MG (gMG) patient successfully treated with efgartigimod after testing negative on standard autoantibody detection tests.

**Results:** Our patient presented with severe fluctuating bulbar and generalized weakness, resulting in multiple myasthenic crises requiring intubation. After a 28-year medical history of multiple failed lines of treatment, our patient was started on efgartigimod. Over five treatment cycles, a definite improvement in her clinical condition was observed (Myasthenia Gravis Foundation of America class: IIIb to IIb; MG-Activities of Daily Living score: 11 to 0; MG-Quality of Life 15 score: 30 to 0; Quantitative MG score: 28 to 6). Standard autoantibody detection tests failed to detect known pathogenic autoantibodies, but cell-based assay (CBA) identified autoantibodies against clustered adult acetylcholine receptor (AChR).

**Conclusions:** In light of recent approvals of efgartigimod by the European Medicines Agency and US Food and Drug Administration exclusively for AChR-positive gMG forms, our case highlights evidence suggesting that such an approach might be shortsighted and could limit therapeutic options for patients with refractory seronegative gMG. Additionally, introducing more sensitive analytical techniques, exemplified by CBA, may help bridge the gap between seronegative and seropositive patients. This represents an urgent unmet need for gMG patients, as the antibody profile dramatically influences the therapeutic approach.

Stefano Carlo Previtali and Yuri Matteo Falzone share last authorship.

**KEYWORDS**
biological drugs, case report, cell-based assay, efgartigimod, FcRn inhibitors, myasthenia gravis, refractory

## INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease affecting the neuromuscular junction, in which autoantibodies disrupt the physiological nerve–muscle crosstalk. The clinical spectrum of MG ranges from ocular to generalized (generalized MG [gMG]) fatigable muscle weakness [1]. The primary treatment approach involves the use of acetylcholinesterase inhibitors and immunomodulation. However, some patients, defined as refractory, do not respond to long-term treatment with corticosteroids or multiple nonsteroidal immunosuppressive treatments, or they have intolerable side effects to these therapies [2]. These patients often require continuous administration of intravenous immunoglobulins (IVIg) or plasma exchange (PLEX), significantly affecting their quality of life (QoL). Notably, 10%–15% of patients with MG test negative for known pathogenic autoantibodies, leading to a diagnosis of seronegative MG [1]. Cell-based assay (CBA), a promising but not widely available and certified test, has been shown to improve diagnostic sensitivity in this population [3–5]. Although groundbreaking treatment advancements like eculizumab, ravulizumab, and efgartigimod for acetylcholine receptor (AChR)-positive gMG, as well as rozanolixizumab for AChR and muscle-specific kinase (MuSK)-positive gMG, have transformed the therapeutic approach to antibody-positive gMG [6–9], it is important to note that seronegative MG patients in Europe and in the United States are currently ineligible for these biological drugs. As a result, the pharmacological options available to this patient population remain limited. Addressing this limitation is a crucial step toward optimizing care for seronegative MG patients. In this report, we present the first case of a 56-year-old woman with a challenging history of refractory seronegative gMG successfully managed with efgartigimod, a first-in-class neonatal Fc receptor (FcRn) inhibitor that greatly diminishes IgG recycling, thus lowering pathogenic autoantibody levels in serum.

## CASE PRESENTATION

At the age of 28 years, our previously healthy patient developed fluctuating bulbar and generalized weakness consistent with a postsynaptic neuromuscular junction disorder on neurophysiological evaluation (compound muscle action potential decremental response of 55% on ulnar nerve repetitive stimulation at 3 Hz). Her symptoms swiftly improved after acetylcholinesterase inhibitor administration. Although several radioimmunoassay (RIA) tests were performed, neither anti-AChR nor anti-MuSK autoantibodies were identified. Similarly, enzyme-linked immunosorbent assay for anti-low-density lipoprotein receptor-related protein 4 autoantibodies yielded a negative result, leading to a diagnosis of seronegative MG. The patient was initially treated with steroids and pyridostigmine and later underwent thymic tissue excision, but significant improvement was not achieved, with a baseline Myasthenia Gravis Foundation of America (MGFA) class of IIIb. Over the years, several attempts at introducing steroid-sparing therapies proved ineffective in preventing recurrent myasthenic crises (Figure 1), necessitating mechanical ventilation. Add-on IVIg treatment was also introduced but showed suboptimal and labile symptom control, lasting no longer than 3 weeks (Figure 1). In 2019, the patient began using noninvasive ventilation (NIV) in the form of bilevel positive airway pressure to manage nocturnal respiratory fatigue. Due to poor response to various treatment approaches, we decided to implement monthly PLEX courses, resulting in clear amelioration of symptom control lasting 2–3 weeks, with rapid clinical deterioration in the 4th week. This correlated with markedly high IgG serum levels 14 days after PLEX, suggesting rapid autoantibody synthesis. Although this strategy provided acceptable disease control, it resulted in the occurrence of severe thrombotic events (notably, deep venous thrombosis affecting the right upper limb in both 2019 and 2021) and infectious complications (a parapharyngeal abscess in 2021 and a Staphylococcus epidermidis central venous catheter-related bloodstream infection in 2022), further worsening the patient's QoL.

In October 2022, with approval from the ethics committee, the patient underwent Argenx compassionate use program for efgartigimod. Between October 2022 and June 2023, five full cycles of efgartigimod (10 mg/kg) were administered. As per recommendation, the second cycle was scheduled at an interval of 8 weeks (from the first infusion), resulting in suboptimal disease control before administration. The interval between cycles was then reduced to 7 weeks, with clinical benefit. The patient experienced rapid clinical responses in the first week of each cycle, with MG-Activities of Daily Living (MG-ADL) and MG-Quality of Life 15 (MG-QoL15) scores reaching their lowest levels by week 3. Notably, the clinical condition substantially improved between the first and fifth cycle, suggesting a prolonged, cumulative effect of efgartigimod. During this period, the patient did not require PLEX or NIV, and she was able to return to work (Figure 2). Moreover, the patient consistently improved without added risks. No infections occurred. Initial total IgG levels exceeded 10 g/L, temporarily decreased during cycles, but never dropped below 4 g/L, meeting program criteria. A serum sample collected before the initiation of efgartigimod treatment underwent a live CBA test at the Neuroimmunology Laboratory of IRCCS Mondino Foundation of Pavia, Italy, as described elsewhere [10]. This assay identified autoantibodies against clustered adult AChR.

## DISCUSSION

Our case report focuses on the diagnostic and therapeutic challenge posed by seronegative refractory gMG and delves into the potential

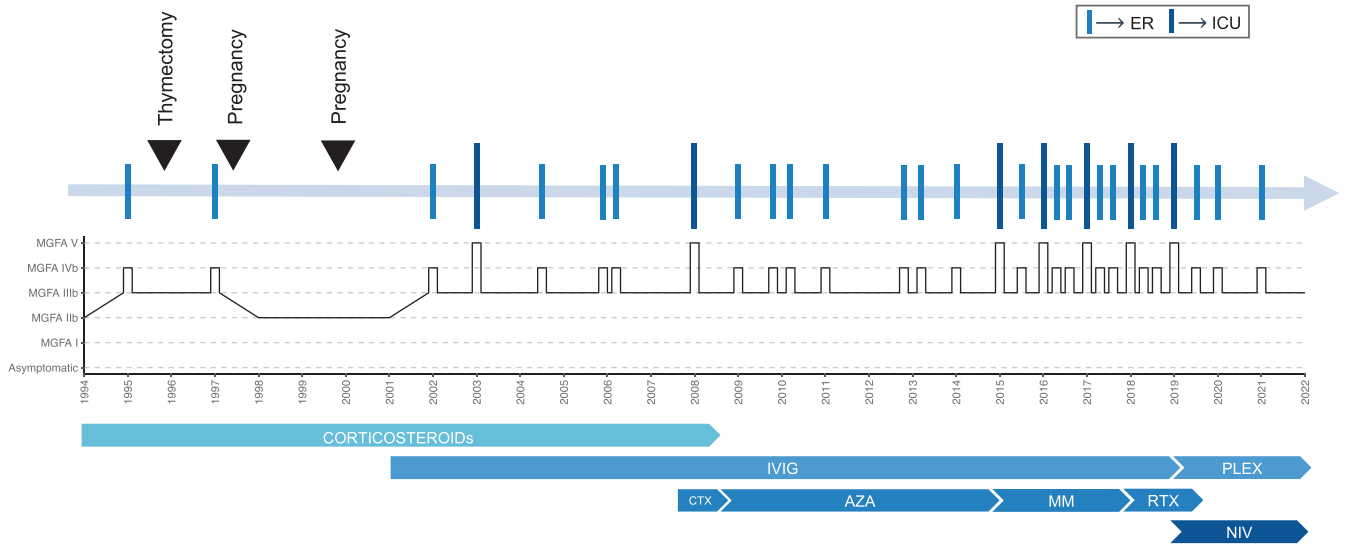


**FIGURE 1** Timeline of Myasthenia Gravis Foundation of America (MGFA) class and therapeutic interventions since diagnosis. The figure displays the MGFA class and therapeutic interventions attempted over the years. After an initial period of effective symptom control with corticosteroid therapy, during which two uneventful pregnancies were carried out, the patient experienced multiple admissions to the emergency room and received treatments for myasthenic crises. Every intensive care unit (ICU) admission resulted in intubation and mechanical ventilation. AZA, azathioprine; CTX, cyclophosphamide; ER, emergency room; IVIG, intravenous immunoglobulins; MM, mycophenolate mofetil; NIV, noninvasive ventilation; PLEX, plasma exchange; RTX, rituximab.

efficacy of FcRn inhibitors (efgartigimod) to address the needs of this specific patient population. The ADAPT trial included MG patients with diverse therapy responses and autoantibody profiles but without mention of refractory status and encompassed 16 seronegative cases treated with efgartigimod [8]. Despite a small sample size and a higher-than-expected placebo effect in the seronegative group (possibly playing a role in the decision by the US Food and Drug Administration and European Medicines Agency not to approve efgartigimod for this patient subgroup), post hoc analysis of the ADAPT trial and interim findings from the ADAPT+ open-label expansion trial revealed a similar treatment effect in seronegative patients compared to the AChR-positive group, suggesting that efgartigimod might be effective in this population [8, 11]. It is important to note that the study design and inclusion criteria make the results less directly applicable to refractory patients. Nevertheless, based on these encouraging results, Japanese regulatory institutions decided to expand efgartigimod eligibility to MG patients regardless of antibody status [12]. During the ADAPT trial, patients had to wait 8 weeks from the first infusion to start another cycle. However, after conducting a risk–benefit assessment, we decided to shorten this period to 7 weeks due to our patient's clinical deterioration in the third treatment-free week. This modification appeared to be effective, safe, and well tolerated, suggesting the possibility of tailoring the efgartigimod dosing regimen based on individual patient characteristics. An 8-week interval was again attempted between the third and fourth cycle, but significant symptom worsening was observed, as reflected by MGFA class and MG-ADL, MG-QoL15, and Quantitative MG scores (Figure 2).

In clinical settings, the pivotal aspect of diagnosing and managing MG revolves around autoantibody testing. A positive outcome not only confirms the clinical suspicion of MG but also directly influences therapeutic approaches. The standard AChR RIA test can identify autoantibodies in ~80%–85% of patients with MG and exhibits a high specificity [13]. Despite new autoantigen identification, 10%–15% of patients test negative for known pathogenic autoantibodies and are classified as seronegative [1]. Although it is possible that other unknown antigens play a role in this population, it is a common opinion that standard testing methods are inadequate at detecting autoantibodies in most seronegative MG patients [14]. A recent breakthrough has been the development of CBA, a highly sensitive autoantibody detection test using human embryonic kidney 293 T cells genetically modified to express specific antigens in their original conformation. This has led to the detection of "clustered" AChR autoantibodies, improving detection yield [3]. However, CBA is a more complex, less standardized test and is currently primarily available in specialized research centers. According to literature, ~20% of seronegative patients tested positive on CBA for AChR antibodies and 13% tested positive for anti-MuSK antibodies [3, 13, 15, 16], blurring the line between seronegative and seropositive MG. Our case, describing a patient who tested negative for autoantibodies on standard assays despite multiple determinations, adds to this line of evidence and provides further demonstration of the potential value of CBA in this population. The favorable clinical response we observed with both PLEX and efgartigimod reinforces the hypothesis that individuals categorized as seronegative may still harbor circulating pathogenic antibodies, which might differ in terms of quantity, avidity, and affinity when compared to other patient subgroups. Reducing these pathogenic antibodies can potentially modify the course of the disease, irrespective of their downstream effector mechanisms.

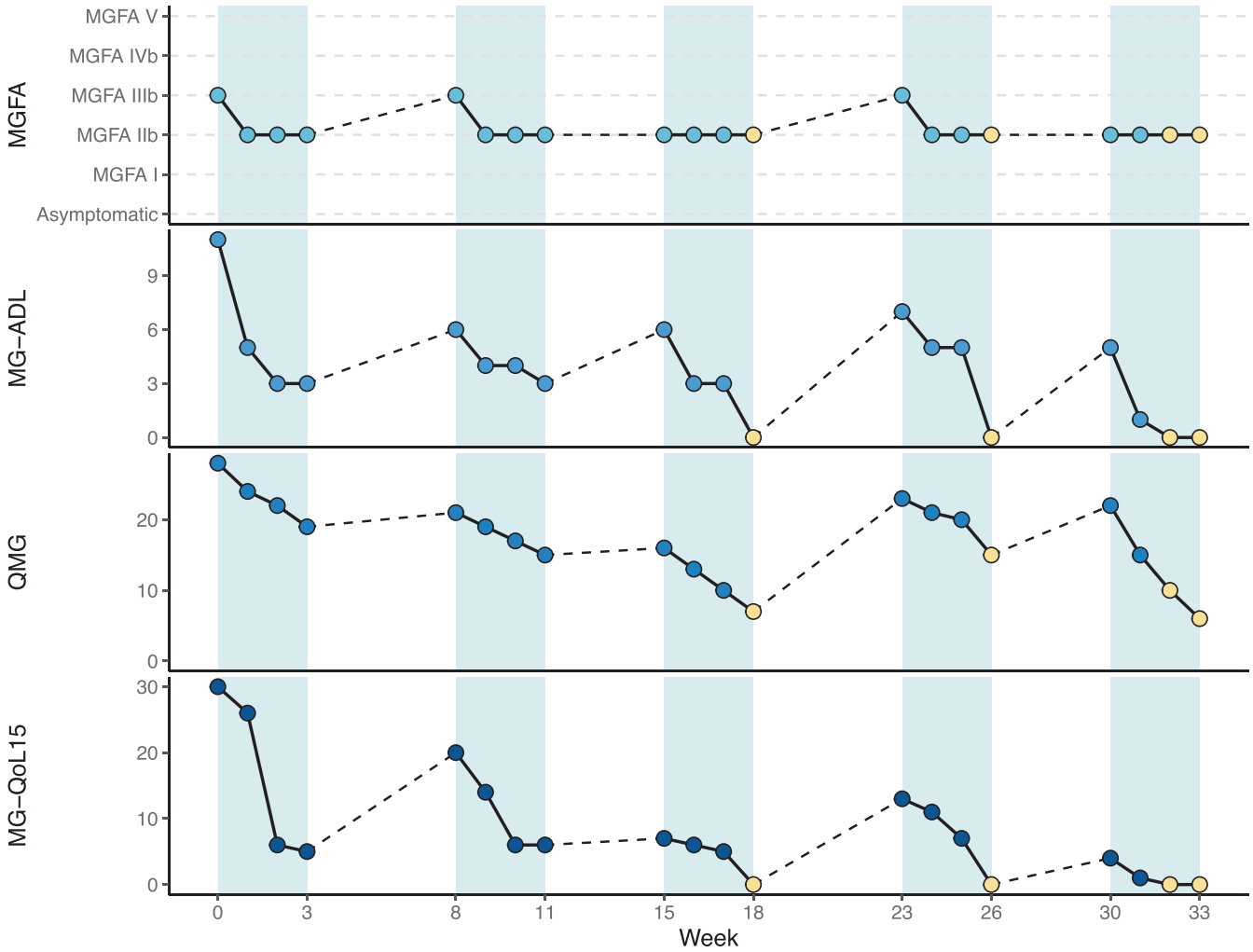


**FIGURE 2** Change in Myasthenia Gravis Foundation of America class (MGFA), MG-Activities of Daily Living (MG-ADL), Quantitative MG (QMG), and MG-Quality of Life 15 (MG-QoL15) during cycles I–V of efgartigimod. Shaded areas represent treatment cycles, unshaded areas represent inter-cycle intervals. As per recommendation, the second and fourth cycles were started 8 weeks after the previous one, with a significant worsening in clinical scores. Yellow points represent evaluations at which an MGFA postintervention status of MM-3 was achieved.

Our report brings attention to a potential limitation of the current approach in the treatment of refractory seronegative gMG patients. With recent approvals of FcRn inhibitors (efgartigimod and rozanolixizumab) exclusively for antibody-positive gMG forms, there is evidence to suggest that this approach may be shortsighted and limit therapeutic options for seronegative patients. The case emphasizes the crucial need to improve diagnostic test sensitivity, such as CBA, which could bridge the gap between seronegative and seropositive patients. This would enable a more accurate and personalized approach to treatment. Our findings are in line with other reports suggesting the potential efficacy of newly developed drugs even in seronegative MG patients, at least on standard testing, although prolonged longitudinal data assessing safety and efficacy are lacking [11, 17]. The advancements in diagnostic tools and a more comprehensive approach to MG management will lead to improved outcomes and better QoL for patients across different serological profiles.

In the current medical landscape, beyond efficacy and tolerability, cost-effectiveness has become a crucial factor in therapeutic management decisions. Recent literature suggests that efgartigimod, while potentially ameliorating QoL of myasthenic patients, comes with an incremental cost that exceeds conventional thresholds for cost-effectiveness [18]. Drawing inspiration from the history of our patient, we argue that the enduring clinical efficacy of this treatment could lead to a significant reduction in the use of concurrent therapies and the need for repeated hospitalizations. This, in turn, has the potential to substantially decrease the social and health care costs associated with their overall management. We firmly believe that well-designed studies evaluating the cost-effectiveness of efgartigimod are needed.

## AUTHOR CONTRIBUTIONS

**Stefano Carlo Previtali:** Supervision; writing – review and editing; conceptualization; writing – original draft; investigation. **Massimo**

**Filippi:** Supervision; writing – review and editing; investigation. **Matteo Gastaldi:** Investigation; writing – review and editing. **Yuri Matteo Falzone:** Supervision; conceptualization; writing – review and editing; writing – original draft; investigation. **Christian Laurini:** Writing – original draft; visualization; investigation. **Benedetta Sorrenti:** Writing – original draft; visualization; investigation. **Luca Bosco:** Investigation; writing – review and editing. **Marina Scarlato:** Writing – review and editing; investigation. **Camilla Mirella Maria Strano:** Writing – review and editing; investigation.

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## CONFLICT OF INTEREST STATEMENT

SCP is PI in clinical trials for Argenx, Jannsen, Dyne, Biomarin; Scientific Board Member for Argenx, Wave, Esperare.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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