Efgartigimod, an FcRn antagonist, as a potential treatment for post COVID-19 syndrome

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ABSTRACT

A significant proportion of patients who survive coronavirus disease of 2019 (COVID-19) develop a constellation of life-altering symptoms that persist long after the initial infection has resolved. This post-COVID-19 syndrome may result from the development of autoreactive IgG antibodies that cause inflammation and tissue injury. In this commentary, we suggest that efgartigimod, a drug approved for the treatment of generalized myasthenia gravis, be tested for use in patients with post-COVID-19. Efgartigimod is a humanized IgG Fc fragment containing five point mutations that significantly increase affinity for the Fc region of the neonatal crystallizable fragment receptor (FcRn). FcRn is involved in the pathogenesis of autoimmune diseases via the IgG recycling pathway because FcRn binds to autoreactive IgG antibodies and prevents the antibodies from being catabolized. Efgartigimod is a modified immunoglobulin that competitively displaces endogenous IgG from FcRn, thus increasing the level of unbound IgG, which is then catabolized and leads to decreased circulating levels of autoreactive as well as normal IgG. We suggest that efgartigimod be evaluated in a random, double-blind placebo-control trial in adults with post-COVID-19 for at least 2 months. If re-purposing this myasthenia gravis-approved drug for post-COVID-19 is successful, additional bioengineered FcRn antagonists should be tested for efficacy in patients with post-COVID-19.

Keywords: post COVID-19, Efgartigimod, Immunoglobulin G, autoreactive antibodies
the etiology of the post-COVID-19 syndrome remains to be elucidated; however, based on clinical data over the past 3 years, it has been postulated that the post-
COVID-19 syndrome could result from the induction of autoimmune diseases by SARS-CoV-2 in a subset of patients who had not previously been diagnosed with an autoimmune disease [4]. Indeed, several autoimmune diseases have occurred in patients after COVID-19 infection [5]. Specifically, infection with viruses, such as Epstein-Barr virus, cytomegalovirus, HTLV-1, hepatitis A and C viruses, and parvovirus B19, can increase the risk of autoimmune diseases [6]. It has been hypothesized that the post-COVID-19 syndrome results from an acute, dysregulated immune response that increases the likelihood of autoreactive IgG antibody development, thus producing autoimmune diseases. Clinical studies have suggested that post-COVID-19 patients have a greater probability of circulating autoantibodies, which occur in patients with autoimmune diseases compared to healthy control patients [7]; however, among the majority of self-recovered and hospitalized patients with COVID-19, the autoantibodies decay and are mostly removed from the circulation over time. These various autoreactive antibodies appear to be derived from the clonal expansion of naive B cells and the temporary loss of broad immune tolerance [8]. In view of the above findings, we postulate that the post-COVID-19 syndrome could be caused, in part, by autoreactive antibodies that produce inflammation and tissue damage. As a result, treatments that decrease the levels of autoreactive IgG antibodies should produce a beneficial effect in patients suffering from post—COVID-19.

In this commentary we propose that the drug, efgartigimod, a clinically-approved drug for the treatment of generalized myasthenia gravis, be tested for use in patients with post-COVID-19. The efficacy of efgartigimod is attributed to the ability of efgartigimod to decrease autoreactive IgG recycling, which is done by inhibiting IgG interaction with the recycling protein, neonatal crystallizable fragment receptor (FcRn), which rapidly and significantly decreases IgG levels. Efgartigimod decreases the levels of autoreactive IgG antibodies in myasthenia gravis patients and improves the quality of life [9]. After discussing the structure and function of FcRn in the recycling pathway, we will discuss the structure and mechanism of efgartigimod action, upcoming trials, adverse effects, and the pharmacokinetic profile.

It has been well-established that the protein, FcRn, plays a crucial role in the transport/trafficking of immunoglobulin G (IgG) and albumin into salvage or recycling pathways. The recycling pathway (see below) mediates the following: 1) the long serum half-life (approximately 21 days) of IgG; and 2) the relatively high levels of circulating IgG isotypes [10]. FcRn also has a role in innate and adaptive immune responses. Specifically, FcRn transports antigens into antigen-loading compartments of antigen-presenting cells [10]. FcRn is widely expressed in endothelial, epithelial, and hematopoietic cells (macrophages, monocytes, dendritic cells, neutrophils, and B cells); however, endosomes contain the majority of FcRns.

The FCGRT gene in humans is located on chromosome 19q13 and encodes a major histocompatibility complex (MHC) class I-like heavy chain (p51 [40 kDa]) that non-covalently binds to a light chain (p14 [12 kDa]), also known as beta2-microglobulin, to form the heterodimeric protein (FcRn) [10]. FcRn has one site that is glycosylated in humans. FcRn has extracellular domains (α1, α2, α3), a transmembrane region, and a cytoplasmic tail [10]. The FcRn recycling or salvage process for IgG begins with the non-specific, fluid phase pinocytosis of IgG antibodies. Upon internalization by a cell, two molecules of IgG bind to FcRn with equal affinity, which allows for saturable binding, in early sorting acidified endosomes (pH = 6.0) [11]. The acidic pH protonates amino acid residues (H310 and H435) in the CH2-Ch3 hinge domain of IgG, which allows for the formation of salt bridges that decrease IgG3 affinity for FcRn [12]. IgG molecules that are not sequestered by FcRn are delivered by late endosomes to lysosomes that are subsequently biodegraded or catabolized [10]. Upon sorting and trafficking of the FcRn-bound IgG into endosomes, IgG can then be exocytosed by the cell into the circulation as follows: 1) direct delivery of transport containers (TCs) or vesicles from sorting endosomes to the exocytosis site or area; or 2) indirect delivery through TCs that are not located near sorting endosomes that migrate relatively large distances within the cell, eventually settling above the plasma membrane [13]. Following the release of IgG, FcRn can be rapidly internalized. After exposure to the extracellular milieu where the pH is approximately 7.4, the affinity of IgG for FcRn decreases, causing release from FcRn and into the circulation, thereby completing IgG recycling [13].

One of the major characteristics of the salvage pathway, the pH-dependent binding profile of FcRn-to-IgG (the Fc portion of IgG) has a high affinity for FcRn at an acidic pH and a lower affinity at an approximately neutral pH has been exploited to create human IgGs with Fc mutations (i.e., FcRn antagonists) that have an increased affinity for FcRn at acidic and neutral pHs [9]. FcRn is involved in the pathogenesis of autoimmune diseases via the recycling pathway because FcRn maintains autoreactive IgG antibodies.

As stated earlier, there are clinical data suggesting that the etiology of the post-COVID-19 syndrome may be due to the presence of reactive autoantibodies. Therefore, we hypothesize that IgG molecules with modified Fc regions have an increased affinity for FcR at acidic and neutral pHs could be used to treat post-COVID-19 patients that express IgG autoantibodies.

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Therefore, we propose use of the drug, efgartigimod-alfa-fcab (previously designated, Argenx-113). Efgartigimod (Vyvgart) was approved in December 2021 by the United States Food and Drug Administration for the treatment of adults diagnosed with generalized myasthenia gravis, a chronic autoimmune disease, who test positive for anti-acetylcholinergic receptor (AChR) antibodies located in the neuromuscular junction or at postsynaptic sites [14]. The results of the randomized, double-blinded, placebo-controlled ADAPT trial indicated that efgartigimod, when administered as 1 intravenous infusion (10 mg) once weekly for at least 4 weeks produces a maximal decrease in total IgG and AChR antibody levels by 61.3% and 57.6%, respectively [15]. Furthermore, 68% of the patients who received efgartigimod had significant improvement compared to 30% of patients given placebo [15]. According to recent clinical studies, efgartigimod (using the same infusion schedule as the ADAPT trial) was efficacious in patients diagnosed with the chronic autoimmune diseases, idiopathic thrombocytopenia, pemphigus vulgaris, and foliaceous decreasing total IgG levels by 63.7% and 74%, respectively [16]. Furthermore, efgartigimod is being evaluated in clinical trials as a treatment for chronic inflammatory demyelinating polyradiculoneuropathy, bullous pemphigoid, and autoimmune myositis [16].

Efgartigimod is a humanized IgG Fc fragment of the ZA allotype. Structurally, efgartigimod is a homodimer composed of 2 identical polypeptide chains containing 227 amino acids linked together by 2 intra-chain S-S bonds [14]. Efgartigimod was created using the proprietary abdeg antibodies that enhance the degradation of IgG (abdeg) technology licensed to Argenx (Boston, MA, USA), which allows for introduction of the following 5-point mutations in an IgG molecule: M252Y; S254T; T256E; H433K; and N434F [14]. These alterations significantly increase the affinity of efgartigimod for the Fc regions of FcRn compared to normal IgG antibodies at acid and near neutral pHs [9]. One molecule of FcRn binds two efgartigimod molecules. The in vitro equilibrium dissociation constant of efgartigimod for human Fc at pH 6,0 and 7.4 were 14 and 320 nM, respectively [9]. This property allows efgartigimod to competitively displace IgG from FcRn, which increases the level of unbound IgG. IgG is subsequently catabolized in cells, thereby greatly decreasing the circulating levels of autoactive, as well as normal IgG [9]. Efgartigimod produces a similar decrease in the levels of IgG1, IgG2, and IgG3, whereas the decrease in IgG4 is less than the other IgGs [9]. It usually takes 8-9 weeks for total IgG levels to return to basal levels after the last dose of efgartigimod [9]. Furthermore, the plasma levels of IgG (normal and autoactive) do not increase above basal levels after discontinuation of efgartigimod therapy [9]. Clinical trial data indicate that efgartigimod does not significantly alter the circulating levels of albumin and IgA, IgM, and IgD antibodies because the circulating levels are not maintained by FcRn-dependent recycling [9].

Overall, clinical data clearly indicate that the inhibition of IgG binding to FcRn by efgartigimod is specific, rapid, and prolonged. Currently, there are no data indicating that efgartigimod (10 mg/kg) significantly affects the number of B cells or the function of innate and adaptive immunity [17]. A recent in vitro study reported that an IgG variant containing the same five-point mutations as efgartigimod decreased the binding of this IgG molecule complement factor, C1q, and FcgR, which recognize antigens complexed with IgG antibodies [18]. It is unknown, however, if efgartigimod has a lower binding affinity to these proteins compared to normal IgG.

We propose that efgartigimod be evaluated using a random, double-blind, placebo-controlled trial design as a treatment for adults (≥18 years; n=100-200) who have met the following criteria: 1) a documented history of significant, intolerable symptoms and impairments; 2) symptoms that cannot be explained by another diagnosis; and 3) a previous SARS-CoV-2-positive test based on real-time PCR results. All patients will be fully informed of the potential adverse effects produced by efgartigimod and an increase in the likelihood of re-infection with COVID-19. The vaccination status of the patients will be obtained prior to treatment because the use of efgartigimod in myasthenia gravis patients has been reported to decrease the protective levels of antibodies to tetanus toxin, varicella zoster virus, pneumococcal capsular polysaccharide, and total IgG levels to a similar magnitude, although the level of protective antibodies returned to baseline after cessation of treatment [19, 20]. Furthermore, prior to participation in the trial all patients will undergo a thorough medical examination to exclude other diagnoses. Patients with a history of autoimmune disease before being infected with SARS-CoV-2 will be excluded from participation. Before treatment, 1, 2, 3, and 4 weeks after treatment, and 2 months after cessation, patients will be screened for the presence of antinuclear antibodies and the significant, persistent production of an autoantibody panel associated with autoimmune diseases in the following order based on information from Quest Diagnostics: 1) suspected autoimmune disease; 2) suspected autoimmune rheumatic disease; and 3) autoimmune diseases not included in a multiplex 11-antibody panel. The frequency and magnitude of signs and symptoms will be assessed using the same time scale as indicated for autoantibody testing (Long COVID Symptom and Impact Tools) [21], which represents the first validated and reliable method for monitoring the symptoms and impact of long COVID.

Currently, there are no data regarding the use of efgartigimod during pregnancy, thus pregnant women will not be included in the trial. Also, it remains to be determined whether efgartigimod is safe and efficacious in pediatric patients. In a healthcare setting, patients will receive efgartigimod (10 mg/kg intravenously) or placebo over a period of 1 hour once a week for 4 consecutive weeks with close monitoring. If a patient cannot tolerate treatment at any time due to drug-related
adverse effects, the patient will be removed from the trial. The primary efficacy endpoint will be a statistically significant decrease in the magnitude and frequency of signs and symptoms compared to patients given placebo intravenously.

The most common adverse effects produced by efgartigimod (10 mg/kg) were headaches, and upper respiratory and urinary tract infections compared to placebo [14]. Patients were also more likely to have a lower number of white blood cells, including neutrophils and lymphocytes [14]. The majority of the infections and lower blood cell counts were mild-to-moderate in severity [14]. Efgartigimod should not be given to patients diagnosed with an active infection and withdrawn in patients who develop an infection during treatment [14]. During treatment, live-attenuated or live vaccines should not be administered due to the efgartigimod-induced decrease in IgG levels [14]. Mild-to-moderate rashes, dyspnea, and angioedema have been reported and should be monitored during the 1 h administration period and 1 h after cessation of treatment [14]. Approximately 20% of patients had antibodies to efgartigimod and approximately 7% of patients had neutralizing antibodies in a clinical study [14]; however, due to the small number of patients, the effect of immunogenicity on the efficacy and safety of efgartigimod remain to be elucidated. Overall, efgartigimod has been reported to be well-tolerated in patients with myasthenia gravis, ITP, and pemphigus vulgaris and pemphigus foliaceus.

Efgartigimod has a terminal half-life of 80-120 h and a volume of distribution of 15-20 liters [14]. Two hours after administration, approximately 0.01% of a 10 mg/kg dose of efgartigimod was detected in the urine [9]. Due to the large protein structure of efgartigimod, it is likely that efgartigimod will be metabolized by various proteolytic enzymes to smaller, inactive peptides [14]. Efgartigimod has not been reported to be a substrate, inhibitor, or inducer of CYP450 enzymes [14]. Therefore, the pharmacokinetic profile of efgartigimod is unlikely to be affected by such drugs, and efgartigimod should not significantly alter the pharmacokinetic profile of drugs that are metabolized by CYP450 [14]; however, efgartigimod could decrease the levels of drugs that bind to FcRn, such as monoclonal antibodies, immunoglobulins, and Fc-based proteins [14].

Current data indicate that the pharmacokinetic profile of efgartigimod is not significantly altered by age, gender, or ethnicity [14]. It is not known whether hepatic impairment affects the plasma levels of efgartigimod; however, given the above information, one would predict that the efgartigimod levels will not be significantly altered. In patients with mild renal impairment, no dose adjustment is required and due to inadequate data in patients with moderate renal impairment, it is unknown whether the dose of efgartigimod will need to be adjusted [14].

In conclusion, we postulate that efgartigimod could ameliorate symptoms and improve the quality of life in post-COVID-19 patients who have developed autoreactive antibodies. It is possible that efgartigimod could be used in the treatment of other post-viral illnesses characterized by the presence of autoreactive antibodies. Finally, we hypothesize that other bioengineered FcRn antagonists could be efficacious in treating post-COVID-19 patients.

CONFLICTS OF INTEREST
The authors have no conflicts of interest to declare.

REFERENCES


