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Efgartigimod: The Saviour for Autoimmune Condition

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Abstract
Efgartigimod (efgartigimodalfa-fcab, Vyvgart™) is a first-in-class neonatal Fc receptor antagonist being developed by argenx for the treatment of autoimmune diseases including myasthenia gravis. It used specifically in generalized myasthenia gravis (gMG) in adults who are anti-acetylcholine receptor (AChR) antibody positive. Efgartigimod binds to the FcRn and inhibits its interaction with IgG, thereby reducing IgG recycling and increasing degradation of IgG and pathological auto antibodies, without altering other immunoglobulins and albumin levels. This results in a reduction in overall levels of IgG, including the abnormal AChR antibodies that are present in gMG. Efgartigimod was approved by the FDA in December 2021, and is administered as a single-dose intravenous infusion. The most common side effects of efgartigimod include infusion reactions, headache, and upper respiratory tract infections. Efgartigimod is a promising new treatment for gMG, and has the potential to offer significant benefits to patients who have not responded to other treatments. Further studies are needed to assess the long-term safety and efficacy of efgartigimod.[1, 2]
Key words: Efgartigimod, auto antibodies, Autoimmune, Immunoglobulins

Introduction

Myasthenia Gravis is a chronic autoimmune neuromuscular disorder that causes localised or general muscles weakness (voluntary).The pathogenesis of the myasthenia gravis includes the binding of IgG antibodies to postsynaptic acetylcholine receptors (AChRs) or other components at neuromuscular junction, resulting in impaired neuromuscular transmission by inhibiting acetylcholine-dependent signalling and inducing accelerated internalisation and degradation of AChRs. Efgartigimodalfa is a promising new treatment option for gMG. It is the first drug that specifically targets FcRn, and it has the potential to provide a more effective and durable treatment than currently available therapies. In clinical trials, efgartigimodalfa was shown to be effective in reducing the levels of pathogenic IgG antibodies and improving symptoms in patients with gMG.[1, 2]

While we are discussing about history and background of drug it came to notice that; intravenous efgartigimod, a drug developed by argenx, was first approved in the USA in December 2021 for treating generalised myasthenia gravis in adults who are anti-AChR antibody positive. It was later approved in Japan for the treatment of generalised myasthenia gravis in adults who do not have sufficient response to steroids or NSISTs. The recommended dosage of efgartigimod is 10 mg/kg (or 1200 mg for patients weighing ≥ 120 kg) administered as a 1 h intravenous infusion once weekly for 4 weeks as one treatment cycle. Patients should be monitored for signs and symptoms of hypersensitivity reactions during infusion and for 1 h thereafter. Subsequent cycles are administered based on clinical evaluation; the safety of administering efgartigimod sooner than 50 days after the

previous cycle was not studied in patients with generalised myasthenia gravis.

The agent is undergoing regulatory review for the treatment of generalised myasthenia gravis in the EU and is also undergoing phase III clinical development for immune thrombocytopenia worldwide. In addition to the intravenous formulation, argenx is developing a recombinant human hyaluronidase-based subcutaneous formulation of efgartigimod using ENHANZE® technology (licensed from Halozyme Therapeutics). Several clinical studies of subcutaneous efgartigimod are underway in healthy volunteers and in patients with autoimmune diseases, including bullous pemphigoid, chronic inflammatory demyelinating polyradiculoneuropathy, immune thrombocytopenia, myasthenia gravis, autoimmune myositis, and pemphigus.

Company agreements have been signed between argenx and BioWaInc, Lonza and argenx, Halozyme Therapeutics, Bayer Healthcare Pharmaceuticals Inc, and Zai Lab. Argenx is aiming to develop multiple subcutaneous therapeutics targeting the human neonatal Fc receptor and up to six additional targets. The company expects to redeem the priority review voucher for a future marketing application for efgartigimod to reduce the target review time.

Pharmacokinetic Properties

The intravenous formulation shows a linear pharmacokinetics and drug exposure increases Proportionally with increasing dose to 50 mg/kg, volume of distribution is 15-20 litres And a half-life of 80-120 hr. The subcutaneous formulation has a comparable half-life that of intravenous with bioavailability of approx. 50%. It belongs to a first-in-class 4 antagonists of the neonatal Fc receptor (FcRn). In the SAD (Single Ascending Dose) phase, the mean Cmax increased more than dose proportionally for the 0.2 and 2 mg/kg cohorts and then overall dose proportionally between 10 and 50 mg/kg, up to a Cmax value of 1,175 μg/ml.

Table No.1: Pharmacokinetic Properties of efgartigimod

Sr. No	Properties	Efgartigimod
1	Class	Monoclonal Antibody
2	Category	Anti inflammatory, Immunoglobulin- FC fragments
3	Cmax	1,175 μg/ml
4	Tmax	--
5	T half	80-120 hr.
6	Route of administration	Intravenous/ Subcutanious
7	Volume of Distribution	15-20 litres
8	Metabolism	--
9	Excretion	Urine
10	Aqueous solubility	--
11	Protein binding	FcRN receptor bound

Dose

Injection: 400 mg/20 mL (20 mg/mL) as a colourless to slightly yellow, clear to slightly opalescent solution, in a single-dose vial.

Mechanism of Working Efgartigimod binds to the neonatal Fc receptor and inhibits its interaction with IgG, thereby reducing IgG recycling and increasing degradation of IgG and pathological autoantibodies, without altering other immunoglobulins and albumin levels.[2]

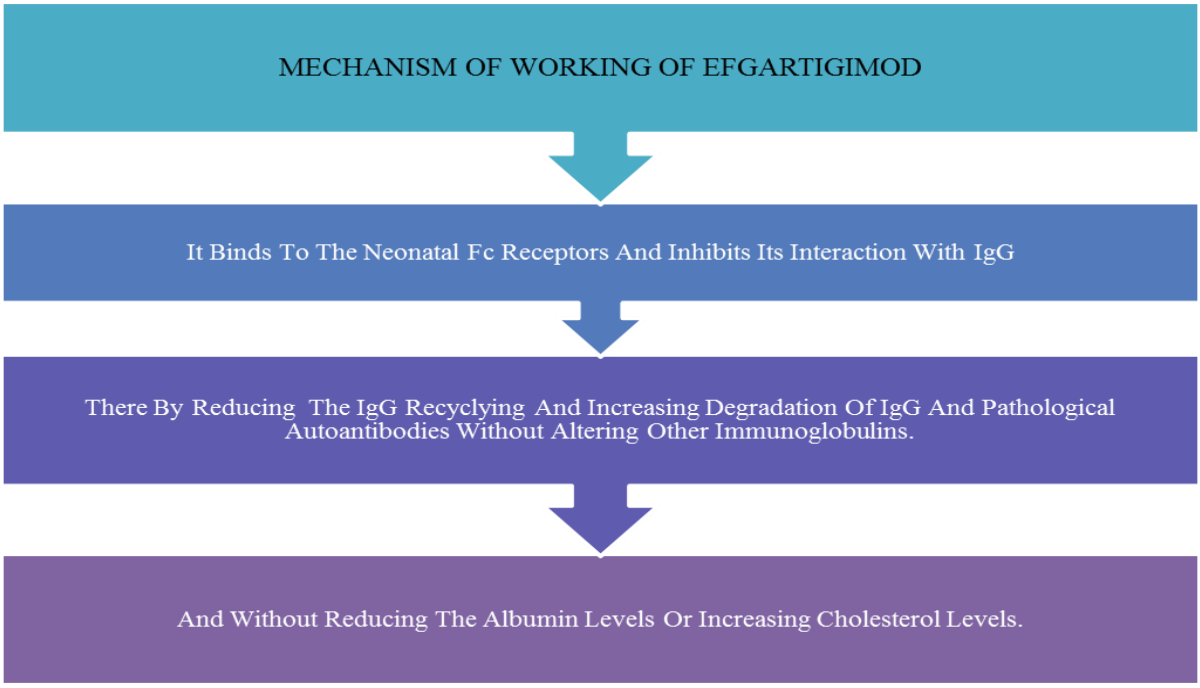

Figure 1: Mechanism of action of Efgartigimod

Medical Uses [4-8]

This drug used in treatment of;

- Myasthenia gravis

  Generalised myasthenia gravis (gMG) is a chronic, autoimmune neuromuscular disorder that can significantly impair quality of life. Intravenous efgartigimodalfa is approved for the treatment of gMG in adults who are anti-acetylcholine receptor (AChR) antibody positive. It rapidly reduced disease burden and improved muscle strength.

- Bullous pemphigoid

  Pemphigus comprises a group of rare autoimmune blistering skin disorders and is is characterised by IgG auto antibodies targeting desmoglein (Dsg)-3, which is associated with mucosal lesions Efgartigimod, an FcRn inhibitor, rapidly improves the condition of patients with pemphigus by reducing serum anti-Dsg autoantibody levels It binds to the IgG binding site of FcRn, thereby reducing the levels of circulating IgG without affecting levels of albumin or other immunoglobulins.

- Chronic inflammatory demyelinating polyradiculoneuropathy

  Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare and serious autoimmune disease of the peripheral nervous system. In patients with this disorder, some antibodies of the immune system are thought to damage the nervous system. These antibodies are IgG antibodies that are long-lasting, because they are recycled and kept in the body after attaching to a protein in cells called FcRn. Efgartigimod is an investigational antibody fragment designed to reduce disease-causing immunoglobulin G (IgG) antibodies and block the IgG recycling process. This allows the

damaging IgGs to be broken down and removed from the body more quickly, stopping further damage to peripheral nerves.

- Immune thrombocytopenia

  Primary immune thrombocytopenia (ITP) is an acquired autoimmune bleeding disorder, characterised by a low platelet count (<100 × 109 /L) in the absence of other causes associated with thrombocytopenia. Efgartigimod induced a rapid reduction of total IgG levels (up to 63.7% mean change from baseline), which was associated with clinically relevant increases in platelet counts and a reduced proportion of patients with bleeding.

- Autoimmune myositis

  Autoimmune myositis is characterised by inflammatory and degenerative changes in the muscles or in the skin and muscles (dermatomyositis) particularly those in the neck, shoulders, hips and back. Clinical study designs to evaluate subcutaneous efgartigimod use in patients with myositis are being finalised

Adverse Effects [9-13]

Efgartigimod is a well-tolerated drug that has shown minimal or no side effects in patients treated with it. Between September 5, 2018 and November 26, 2019, 167 patients were enrolled, randomly assigned, and treated with efgartigimod and placebo. Among these patients, 77% were acetylcholine receptor antibody-positive, and more of those in the efgartigimod group were MG-ADL responders. Of these patients, 77% had treatment-emergent adverse events, with the most frequent being headache and nasopharyngitis. Four patients in each treatment group discontinued treatment during the study, and there were no deaths.

Efgartigimod showed a rapid decrease in total immunoglobulin G (IgG) and anti-AChR autoantibody levels, and 75% showed a rapid and long-lasting disease improvement. However, efgartigimodalfa-fcab may increase the risk of infection. The most common infections observed in Study 1 were urinary tract infection (10% of efgartigimodalfa-fcab-treated patients compared to 5% of placebo-treated patients) and respiratory tract infections (33% of efgartigimodalfa-fcab-treated patients compared to 29% of placebo-treated patients). A higher frequency of patients who received efgartigimodalfa-fcab compared to placebo were observed to have below normal levels for white blood cell counts (12 versus 5%, respectively), lymphocyte counts (28 versus 19%, respectively), and neutrophil counts (13 versus 6%, respectively).

Intravenous efgartigimodalfa is generally well-tolerated in patients with gMG, as demonstrated in the ADAPT and ADAPT+ trials, with most adverse events being mild to moderate in severity. In the ADAPT trial, AEs occurred in 77% of 84 efgartigimodalfa recipients versus 84% of 83 placebo recipients. The most common (≥10%) AEs with efgartigimodalfa occurring at a higher nominal rate than placebo included headache (29% vs 28%), upper respiratory tract infections (11% vs 5%) and urinary tract infections (10% vs 5%). Overall, serious AEs occurred in 5% and 8% of patients in the efgartigimodalfa and placebo groups, respectively, and 4% of patients from each group discontinued treatment due to an AE.

Infection-related AEs occurred in 46% of efgartigimodalfa recipients and 37% of placebo recipients, with most being mild to moderate in severity. Infusion-related reactions occurred in 4% and 10% of patients in the efgartigimodalfa and placebo groups, respectively, with all being mild to moderate in severity.

Treatment of Overdose[14-15]

A dose over 10% was considered an overdose in the clinical studies. No safety related issues were reported and all participants completed the

trials at doses up to 25 mg/kg administered weekly for 4 weeks.

There are no known specific signs and symptoms of overdose with efgartigimodalfa. In the event of an overdose the adverse events are not expected to be different from those observed at the 7 recommended doses. Patients should be monitored for adverse reactions, and appropriate symptomatic and supportive treatment initiated. There is no specific antidote for overdose with efgartigimodalfa.

Contraindications

Hypersensitivity to the active substance or to any of the excipients used in formulation of drug. There are no possible contraindications given for the drug.

Interactions[16-17]

There are no specific drug interaction studies performed for Efgartigimod. Efgartigimod binds to the neonatal Fc receptor and inhibits its interaction with IgG, thereby reducing IgG recycling and increasing degradation of IgG and pathological autoantibodies and hence it interacts with the drugs or molecules binding to neonatal Fc receptor. Efgartigimodalfa-fcab is not metabolised by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely to occur.

Drug Interactions with Other Drugs or Biological Products may be possible.

Efgartigimod reduces the activity of the immune system. Hence, when a patient is taking concurrent treatment of efgartigimod with any other immunostimulant, it can decrease the activity of another drug. When Efgartigimod is given with the immunosuppressant, it can synergistically increase the activity of another drug.

Efgartigimod severely interact with immunosuppressants and vaccines like adenovirus vaccine, bcg vaccine, cholera vaccine, dengue vaccine, influenza and h1n1 vaccine, encephalitis vaccine, measle virus vaccine , mumps virus vaccine, polio vaccine, rotavirus vaccine, rubella vaccine, etc.

Marketed Formulation Survey [16, 17]

Table No.2: Marketed Formulation Survey

Sr. No	Name of market formulation	Type of dosage form	Company	Cost
1	VYVGART Hytrulo Efgartigimodalfa (180 mg/1mL) + Hyaluronidase (human recombinant) (2000 U/1mL)	Subcutaneous	Argenx	Argenx has not yet published the price of the VyvgartHytrulo.
2	Vyvgart Injection	Intravenous	Argenx	$6,400.16 for 20 milliliters

Current Status [18-20]

Intravenous efgartigimod received its first approval on 17 December 2021 for the treatment of generalised myasthenia gravis in adults who are anti-AChR antibody positive in the USA. Subsequently, efgartigimod was approved in Japan on 20 January 2022 for the treatment of generalised myasthenia gravis in

adults who do not have sufficient response to steroids or NSISTs.

Patents

Table No.3: List of Patent

Sr. No	Application Number	Country of Patent	Date/Year	Legal Status
1	FIC20230003I1	Finland	2023-01-19	_
2	NO2022049I1	Norway	2022-11-23	_
3	DK14827372T	Denmark	2014-12-23	_
4	WO2015100299A1	WIPO (PCT)	2014-12-23	Application filling
5	BR112016014810A	Brazil	2014-12-23	Search and examination
6	KR1020167020339A	South Korea	2014-12-23	IP Right grant
7	MX2016008399A	Mexico	2014-12-23	IP Right grant
8	US11505585B2	United States	2017-11-22	Active
9	JP2019002272A	Japan	2019-01-10	Granted
10	FR23C1004I1	France	2023-01-12	Active

Conclusion

In conclusion Efgartigimod is a promising new treatment for myasthenia gravis. It is well-tolerated and has been shown to be effective in reducing the levels of pathogenic autoantibodies and improving symptoms. Further studies are needed to confirm the long-term safety and efficacy of efgartigimod. Here are some additional things to know about efgartigimod: It is a new class of medication, and its long-term safety and efficacy are not yet fully known. Efgartigimod can cause some side effects, including infusion reactions, headache, and fatigue. Efgartigimod is not recommended for pregnant or breastfeeding women. Efgartigimod is not currently approved for use in children.

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14. *HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use VYVGART HYTRULO safely and effectively. See full prescribing information for VYVGART HYTRULO. VYVGART ® HYTRULO (efgartigimodalfa and hyaluronidase-qvfc) injection, for subcutaneous use Initial U.S. Approval: 2023 [Internet]. Argenx.com. [cited 2023 Jul 18]. Available from: https://www.argenx.com/product/vyvgart-hytrulo-prescribing-information.pdf*
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