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Review Article

Ligelizumab: A novel molecule in the management of chronic spontaneous urticaria

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ABSTRACT

The next-generation high affinity monoclonal immunoglobulin E (IgE) inhibitor Ligelizumab is being tested in clinical studies to treat chronic spontaneous urticaria (CSU). In 2020, the US Food and Drug Administration (FDA) designated Ligelizumab (QGE031) as a breakthrough therapy for patients with chronic idiopathic urticaria; however, FDA clearance has not yet been granted, despite the phase 3 trial's completion. Recent clinical investigations have shown that it has a considerable affinity for the high-affinity IgE receptor (FcRI) on the surface of immune cells, which is quite beneficial in the management of the distressing symptoms of CSU. Studies have been done comparing Ligelizumab to Omalizumab, the current standard of care for treating CSU that is refractory. While omalizumab is more effective than Ligelizumab at inhibiting IgE: CD23 interactions, Ligelizumab exhibits stronger inhibition of IgE binding to FcRI, basophil activation, IgE synthesis by B cells, and passive systemic anaphylaxis. To learn about this molecule's extended characteristics, long-term efficacy and safety, and potential uses in other dermatological disorders, more clinical data is needed.

Keywords: Chronic spontaneous urticaria, Immunoglobulin E, Ligelizumab

INTRODUCTION

Ligelizumab is a humanized immunoglobulin G1 monoclonal antibody that targets the high-affinity immunoglobulin E (IgE) receptor (FcεRI) on the surface of immune cells. It is being developed as a treatment for chronic spontaneous urticaria (CSU), a type of chronic hives (urticaria) that occurs without an identifiable cause. CSU is a debilitating condition that can significantly impact a patient's quality of life and current treatment options are often inadequate.[1] Small cutaneous venules that are surrounded by perivascular non-necrotizing cellular infiltration are indicative of CSU. It largely consists of CD4 (+) lymphocytes, with a predominance of the T helper (Th)2 subtype but includes Th1 cells and high plasma levels of cytokines produced by Th17 cells. In addition, there are monocytes, eosinophils, basophils, and neutrophils. The process is driven by endothelial cells that have been activated and chemokines produced by mast cells.[2]

Ligelizumab's mechanism of action is to block the interaction between IgE and the FcεRI, which is thought to play a central role in the pathogenesis of CSU. This results in a decrease in the production of pro-inflammatory mediators and a reduction in the severity of hives and itching. In Phase II and III clinical trials, Ligelizumab has effectively reduced CSU symptoms and improved patients' quality of life.[3]

In summary, it is a promising investigational drug that targets the high-affinity IgE receptor (FcεRI) to reduce the symptoms of CSU.

IgE receptor (FcεRI)

IgE is sensitive to several allergens and triggers an immune response through the high-affinity IgE receptor, FcRI, resulting in a mast cell-mediated immune response. IgE coupled to FcRI triggers the production of newly produced lipid mediators, cytokines, and secretory granules from mast cells and basophils, which leads to both early- and late-phase allergic reactions. Once an individual has developed IgE antibodies to certain antigen epitopes, multiple mechanisms can lead to more robust and diverse IgE responses to both the original as well as other antigens. Some of these mechanisms are mediated by CD23, which can be expressed in epithelial cells, B cells, and myeloid cells.[4,5]

MECHANISM OF ACTION

Jensen *et al.*[6] studied the structure of IgE and the mechanism of action of Ligelizumab. The inhibition of IgE binding and displacement of receptor-bound IgE were evaluated. The findings show that the IgE molecules under investigation have a generally stiff shape. A stiff Fab-Fc architecture is maintained by a symmetrical conformation of IgE that

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is induced by Ligelizumab binding to IgE. Ligelizumab reduces IgE binding without displacing receptor-bound IgE, according to analyses of effector cell activation. The findings highlight a functional activity similar to omalizumab together with disruption of CD23 binding. The findings indicate the first entire IgE structures, indicating that the IgE Fab is fixed about the Fc. Simply put, ligelizumab inhibits the binding of IgE with FcRI resulting in the non-manifestation of symptoms of CSU.

While ligelizumab exhibits a greater reduction of IgE binding to FcRI, basophil activation, and IgE generation by B cells. It is less effective than omalizumab in inhibiting IgE: CD23 interactions, according to the research of Gasser *et al*.[7]

Thus, this monoclonal antibody directed at IgE binds specifically to an epitope in the IgE Cε3 domain. It neutralizes serum IgE and inhibits the production of IgE through inhibition of IgE-FcεRI binding activity and, to a lesser extent, IgE binding to CD23.[7] This receptor inhibition strongly prevents the manifestation of CSU symptoms.

PHARMACOKINETICS

Ligelizumab is a relatively new drug and hence, details about its molecular characteristics are private as of now. However, it is known to be an IgG4 monoclonal antibody, designated as QGE031.

A study by Arm *et al*.[8] determined the pharmacokinetics of Ligelizumab (QGE031) in subjects with skin conditions. When given intravenously over 2 h, QGE031's time course in serum was characterized by a biexponential drop, with a swift initial and slower terminal elimination phase. At dosages of 1 mg/kg and above, a delayed terminal disposition phase was apparent. The pharmacokinetic (PK) profile showed a half-life of 17–23 days at dosages of 3 and 10 mg/kg. According to PK parameters such as a shorter half-life and time courses of reaction, higher levels of IgE sped up the removal of QGE031. Following subcutaneous treatment, the PK of QGE031 serum concentrations is also shown. After subcutaneous administration, QGE031 reached its maximum concentration (Cmax) in the blood 2–4 days after the previous dosage was given.

PHARMACODYNAMICS

The study by Arm *et al.* also determined the pharmacodynamics of the drug. In the intravenous research, QGE031 decreased free IgE in comparison to the placebo and caused a dose-dependent increase in total IgE. In comparison to omalizumab, free IgE decreased more quickly and to a greater degree. Suppression of free IgE was less than the LLOQ (7.8 ng/mL) at all doses of QGE031 administered. Omalizumab caused a "shallower" suppression of free IgE with a slow restoration to baseline. In contrast, QGE031 decreased free IgE more quickly, more completely, for a longer period, and with a quicker return to baseline. In comparison to the placebo, subcutaneous administration of QGE031 caused total IgE blood concentrations to rise quickly, incrementally, and consistently at all dosages. Even in participants with high IgE (>700 IU/mL), all doses of QGE031 reduced free IgE below the LLOQ (1.95 ng/mL) more effectively than omalizumab. The duration of free IgE suppression for intravenous and subcutaneous injections of QGE031 was longer for higher doses and tended to be shorter in participants with higher baseline IgE.

CLINICAL EVIDENCE

Due to the paucity of data regarding the efficacy and safety of ligelizumab compared to omalizumab and placebo in patients with moderate-to-severe CSU that was not adequately controlled with H1-antihistamines and other treatments, Maurer *et al*. formulated a trial to study the same.[1] Patients were randomly assigned to receive subcutaneous injections of either Ligelizumab or omalizumab or a placebo. Symptoms of hives, itch, and angioedema were tracked using weekly activity scores. In total, 382 patients were enrolled in the study. Significant control of hives was achieved in the Ligelizumab group as compared to the others (ClinicalTrials.gov: NCT02477332).

This study was succeeded by a Phase 2b extension study to evaluate the long-term safety and effectiveness of Ligelizumab 240 mg in patients who had the active disease after 32 weeks.[9] In the extension study, Ligelizumab demonstrated consistent effectiveness throughout 52 weeks of therapy, with more than a third of patients obtaining a symptom-free state after just 4 weeks and 84.2% reaching minimal disease activity at the end. Ligelizumab could thus be said to be significantly useful in disease control and management of symptoms.

Metz *et al*.[10] extrapolated the results obtained from the Ligelizumab Phase 2b study and extension study to determine the efficacy of Ligelizumab in counteracting the symptoms of angioedema in CSU patients. For each treatment arm, changes in the Weekly Urticaria Activity Score (UAS7), Dermatology Life Quality Index (DLQI), and Weekly Angioedema Activity Score (AAS7) were examined between each time point.

The AAS7 score in CSU patients with angioedema at baseline changed the most from baseline with Ligelizumab. The main study's treatment phase and the follow-up periods both saw increases in the mean changes from baseline (CFB) AAS7 scores. Over 92.5% of patients achieved angioedema-free status after the extension trial treatment term, suggesting that the effectiveness of retreatment with Ligelizumab 240 mg may be suggestive of a persistent response on prolonged therapy. Effective therapies can enhance the quality of life, according to the Phase 2b study's quick start of action and therapeutic benefits. This implies the necessity to investigate anti-IgE therapy's effectiveness as an early intervention for patients with newly developed CSU and concurrent angioedema, and

in this aspect, Ligelizumab could be a very effective method of therapy.

Patients with CSU also report poorer sleep, which lowers their quality of life in terms of their health. Sleep disruption is reported by 50% of patients with poorly managed CSU, which can result in issues with depression, anxiety, social interactions, and employment.[11] Thus, the randomized, double-blind, and placebo-controlled Phase 2b core trial (NCT02477332) conducted by Giménez-Arnau *et al*.,[1,12] enrolled patients with moderate-to-severe CSU in age from 18 to 64. Patients were randomly assigned to receive Ligelizumab (72 or 240 mg), omalizumab (300 mg), or a placebo. The study continuously evaluated the patients' Sleep Interference Scores (SIS7), Weekly Activity Interference Score (AIS7), DLQI scores, and Overall Work Impairment. Overall Work Impairment was also assessed to determine the impact of CSU on the patient's work productivity. Patients in the Ligelizumab treatment arms had low SIS7 throughout the drug-free follow-up phase, and they maintained these low scores throughout the extension study. The DLQI-measured increase in quality of life was likewise substantial, with the Ligelizumab 240 mg group showing the greatest improvement. The Ligelizumab 240 mg arm showed the greatest improvement in DLQI ratings, which persisted through the completion of the treatment period. The changes in atopic dermatitis-specific impact on sleep scores (AIS7) were also substantial, with the Ligelizumab 240 mg arm showing the greatest improvement by Week 20. These results imply that Ligelizumab has the potential to be a very strong therapeutic choice for people with this ailment.

ADVERSE PROFILE

According to the findings of the study conducted by Maurer *et al*.,[9] Ligelizumab was well tolerated and posed no serious safety issues. About 95.4% of the screened patients were given Ligelizumab in the extension trial, and 84.1% of them suffered adverse effects of any kind, the majority of which were mild (41.6%) or moderate (35.8%) in type. During the extension phase, nasopharyngitis (25.2%), headache (12.8%), upper respiratory tract infection (10.2%), and urticaria (10.2%) were the most prevalent treatment emergent adverse events (TEAE) (occurring in 10% of patients). Most of these incidents ended on their own and without medical intervention. During the extension phase, 6.6% of patients (15 out of 226 patients) encountered at least one treatment-emergent severe adverse event (26 SAEs in total), 25 of which were reported as unrelated to the therapy and one, a hypersensitivity event, as linked to the medication. An independent adjudication committee later determined that the incident was anaphylactic (difficulty breathing and persistent, moderate-severity throat tightness) and treatment-related, resulting in treatment withdrawal, which was resolved 2 days later. About 11.1% of patients (25/226) reported having an adverse response at the injection site.

PEARL 1 (NCT03580369) and PEARL 2 (NCT03580356),[13] two identical Phase 3 trials that are now underway, will examine two lower doses of Ligelizumab that are anticipated to produce comparably potent clinical effects in addition to long-term safety and effectiveness. The twin trials are intended to demonstrate superior effectiveness over placebo and omalizumab in adult and adolescent patients with CSU who remain symptomatic despite H1-antihistamine therapy. Over 2000 adult and adolescent patients from 48 different nations were randomly assigned to receive Ligelizumab 72 mg, Ligelizumab 120 mg, omalizumab 300 mg, or a placebo over a year. The change in UAS over 7 days (UAS7) at week 12 as compared to baseline is the trial's main goal. The PEARL 1 and PEARL 2 studies' top-line findings, which Novartis released on December 20, 2021, however, revealed that the main endpoint of superiority for Ligelizumab compared to placebo was reached at week 12, but the results were not comparable to omalizumab.

Thus, more extensive research is required to appropriately determine the safety profile of this drug at pharmacological and supra-pharmacological doses.

USAGE

The US Food and Drug Administration granted Breakthrough Therapy Designation to Ligelizumab for the treatment of CSU on January 14, 2021, recognizing the significant unmet need for new treatment options and the potential of Ligelizumab to address this need. Ligelizumab is currently in late-stage clinical development and is being evaluated in Phase III clinical trials as a potential treatment option for patients with CSU.

CONCLUSION

Ligelizumab, developed by Novartis, has been claimed to perform better as opposed to omalizumab and other commonly employed monoclonal antibodies in the improvement of the distressing symptoms of CSU. This potent IgE receptor inhibitor with a trustworthy safety profile and strong anti-pruritic actions has demonstrated commendable improvement in the disease severity and other associated distressing symptoms among CSU patients. Howsoever, further large-scale clinical studies are required to research the varied applications and subtle effects of this topical medication on the microbiota of the human skin.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Maurer M, Giménez-Arnau AM, Sussman G, Metz M, Baker DR, Bauer A, *et al*. Ligelizumab for chronic spontaneous urticaria. N Engl J Med 2019;381:1321-32.
2. Grattan C. Autoimmune chronic spontaneous urticaria. J Allergy Clin Immunol 2018;141:1165-6.
3. Trischler J, Bottoli I, Janocha R, Heusser C, Jaumont X, Lowe P, *et al*. Ligelizumab treatment for severe asthma: Learnings from the clinical development programme. Clin Transl Immunology 2021;10:e1255.
4. Galli SJ, Tsai M. IgE and mast cells in allergic disease. Nat Med 2012;18:693-704.
5. Gould HJ, Sutton BJ. IgE in allergy and asthma today. Nat Rev Immunol 2008;8:205-17.
6. Jensen RK, Jabs F, Miehe M, Mølgaard B, Pfützner W, Möbs C, *et al*. Structure of intact IgE and the mechanism of ligelizumab revealed by electron microscopy. Allergy 2020;75:1956-65.
7. Gasser P, Tarchevskaya SS, Guntern P, Brigger D, Ruppli R, Zbaren N, *et al*. The mechanistic and functional profile of the therapeutic anti-IgE antibody ligelizumab differs from omalizumab. Nat Commun 2020;11:165.
8. Arm JP, Bottoli I, Skerjanec A, Floch D, Groenewegen A, Maahs S, *et al*. Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects. Clin Exp Allergy 2014;44:1371-85.
9. Maurer M, Giménez-Arnau A, Bernstein JA, Chu CY, Danilycheva I, Hide M, *et al*. Sustained safety and efficacy of ligelizumab in patients with chronic spontaneous urticaria: A one-year extension study. Allergy 2022;77:2175-84.
10. Metz M, Bernstein JA, Giménez-Arnau AM, Hide M, Maurer M, Sitz K, *et al*. Ligelizumab improves angioedema, disease severity and quality-of-life in patients with chronic spontaneous urticaria. World Allergy Organ J 2022;15:100716.
11. Maurer M, Abuzakouk M, Bérard F, Canonica W, Elberink HO, Giménez-Arnau A, *et al*. The burden of chronic spontaneous urticaria is substantial: Real-world evidence from ASSURE-CSU. Allergy 2017;72:2005-16.
12. Giménez-Arnau A, Maurer M, Bernstein J, Staubach P, Barbier N, Hua E, *et al*. Ligelizumab improves sleep interference and disease burden in patients with chronic spontaneous urticaria. Clin Transl Allergy 2022;12:e12121.
13. Clinicaltrials.gov. A Phase III Study of Safety and Efficacy of Ligelizumab in the Treatment of CSU in Adolescents and Adults Inadequately Controlled With H1-antihistamines. Bethesda, Maryland: Clinicaltrials.gov.; 2022.

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