

Review Article

Dupilumab, a new addition to the armamentarium for the management of chronic spontaneous urticaria: A narrative review

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ABSTRACT

Chronic urticaria (CU) is a globally prevalent mast cell-driven skin disorder. Non-sedating second-generation antihistamines (nsAHs) are recommended as the first-line therapy in patients with CU and according to the guideline, non-responders to the standard dose can be given higher doses up to 4 times the standard dose. Omalizumab, an anti-immunoglobulin E antibody, is recommended for those who do not respond to higher doses of nsAH. Despite the presence of many treatment options and guidelines for their use, many patients still do not achieve adequate relief of symptoms from CU. Dupilumab, a monoclonal antibody, has been available in the market for a long time. It recently received approval from the U.S. Food and Drug Administration for the treatment of chronic spontaneous urticarial (CSU). In this review, we discussed the pharmacology, mechanism of action, and adverse effects of dupilumab in CSU.

Keywords: Non-response, Patient outcomes, Tolerability, Urticaria

INTRODUCTION

Urticaria, a prevalent skin disorder, is primarily driven by the mast cells and characterized by recurrent itchy wheals. It may or may not be associated with angioedema. When the symptoms are present for more than 6 weeks, they are called as chronic urticaria (CU). If an identifiable trigger is not present, CU is known as chronic spontaneous urticaria (CSU).^[1] CSU affects about 0.5–1.8% of the adults, adversely affecting their quality of life.^[2] Second-generation non-sedating antihistamines (nsAHs) are recommended as the first-line treatment for CSU. In patients with unsatisfactory control of symptoms, increase in dosage (up to four-fold) of second-generation non-sedating antihistamines is recommended.^[3] In patients with impaired quality of life due to refractory CSU, subcutaneous omalizumab (300 mg every 4 weeks), an anti-immunoglobulin E (IgE) monoclonal antibody can be used. In resource-limited settings or those who cannot afford omalizumab, ciclosporin (4–5 mg/kg per day during 6 months) can be a treatment option for patients not responding to up-dosing of second-generation non-sedating H1 antihistamines. During pregnancy and breastfeeding, cetirizine, levocetirizine, or desloratadine is preferred due to the availability of more safety data.^[3] Considering the incomplete response to omalizumab in about 25% of patients,^[4] there is an unmet need for effective

and targeted treatment in CSU. Recently, the U.S. Food and Drug Administration has approved dupilumab for the treatment of CSU.

Objective

In this review article, we discussed pharmacodynamics, pharmacokinetics, dose, and adverse effects of dupilumab in CU.

Research question

What is the pharmacological rationale, clinical efficacy, and safety profile of dupilumab in the management of CSU, and how does it expand current therapeutic options for patients unresponsive to conventional treatments?

METHODOLOGY

A literature search was done using PubMed, Google Scholar, and other open resources for English-language articles that mentioned CSU and its treatments. The national clinical trial database ClinicalTrials.gov was used to obtain information regarding any ongoing clinical trials. We only included clinical trial reports, case reports, and case series.

Inclusion criteria

Adult or adolescent patients (≥ 12 years) diagnosed with CSU, with or without angioedema. Studies including both

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adult and pediatric CSU cases were considered if CSU-specific data could be extracted. Treatment with dupilumab (subcutaneous, any dosage regimen). Studies combining dupilumab with other agents (e.g., omalizumab, cyclosporine) were included if dupilumab's effect was evaluable.

MECHANISM OF ACTION

Several agents including type 2 inflammatory cytokines are involved in the pathogenesis of CSU. The mechanisms for the development of CSU may include direct and/or indirect activation of mast cells and other cells including basophils and eosinophils. Upregulated FCεRI expression and cytokine production play an important role in the pathogenesis of the disease.^[5]

Dupilumab is a fully human VelocImmune-derived^[6] monoclonal IgG4 antibody. It works by blocking interleukin (IL)-4Rα which results in inhibition of both IL-4 and IL-13 signaling. These two are important mediators of type 2 inflammation in several diseases.^[7] Both are involved in promoting B-cell immunoglobulin isotype class switching to IgE, resulting in the production of IgE.^[8] IgE attaches to FCεRI, the high-affinity IgE receptor on mast cells surface. Allergen or auto-allergen cross-linking of FCεRI-bound IgE results in degranulation of mast cells and release of mediators.^[7] The mechanism of action of dupilumab in type 2 inflammation cascade is shown in Figure 1.^[9]

Dupilumab, by blocking IL-4 and IL-13 signaling pathways, aligns with the emerging understanding of type 2 inflammation as a key driver in a subset of CSU cases. This targeted approach offers a novel therapeutic avenue, especially for those whose disease is resistant to existing treatments.

PHARMACOKINETICS

Dupilumab is administered as a subcutaneous injection. Initial peak concentration (C_{max}) of dupilumab with doses of 300, 400, and 600 mg is 30.5 ± 9.39 , 41.8 ± 12.4 , and

70.1 ± 24.1 mcg/mL, respectively. The bioavailability of dupilumab after a subcutaneous dose in CSU subjects ranges between 61% and 64%. Total volume of distribution is 4.8 ± 1.3 L. It is expected to get broken down like endogenous IgG. After the last steady-state dose (300 mg Q2W), the median time to non-detectable concentration (<78 ng/mL) is 10 weeks whereas with dose of 300 mg QW, it is 13 weeks. It is available as 300 mg and 200 mg pre-filled syringes with needles and 300 mg and 200 mg pre-filled pens for subcutaneous injection.^[10]

EVIDENCE FOR EFFICACY AND SAFETY OF DUPILUMAB IN CU

In this section, available evidence for dupilumab in CU has been summarized. Table 1 shows cases reports with successful treatment of CU with dupilumab.^[11-13]

A case series followed six patients (three females, three males, average age 36) with CSU for up to 34 months. Initial disease activity, measured by UAS7, was a mean of 37.4. All patients were initially treated with dupilumab. Four out of the six patients (67%) achieved and maintained CSU remission (UAS7 remained zero) for 14–22 months after discontinuing dupilumab therapy. This suggests a potential “disease-modifying efficacy” of dupilumab. Of the two patients who did not achieve remission, one was uncontrolled and omalizumab was added. The other patient had an 18-month lapse in dupilumab treatment due to affordability issues and was later restarted on the drug through compassionate access. This small case series highlights dupilumab's potential to induce sustained remission in a significant proportion of CSU patients even after treatment cessation, indicating a possible long-term benefit beyond just symptom suppression.^[14]

EFFICACY IN CSU

Efficacy of dupilumab in treating adults and children >12 with CSU symptomatic despite H1 antihistamine therapy was assessed through the CUPID (NCT04180488) master protocol clinical trial. This encompassed three 24-week well-designed trials: CUPID Study A, B, and C studies, followed by a 12-week blinded safety follow-up.^[10]

STUDY DESIGN AND PATIENT POPULATIONS

In the CUPID A and C studies, patients who did not achieve symptomatic relief with an H1 antihistamine and did not have exposure to anti-IgE treatment were enrolled. These two studies had no difference among them, but were a part of the same clinical trial, and Study C was a confirmatory trial. In the CUPID B study, patients who did not achieve adequate symptomatic relief with both H1 antihistamine and anti-IgE treatment were enrolled. The CUPID Study B did not meet its primary endpoint, and therefore, dupilumab's efficacy in CSU is not proven. On the other hand, efficacy was confirmed in the CUPID A and CUPID C studies. A total of 284 adults

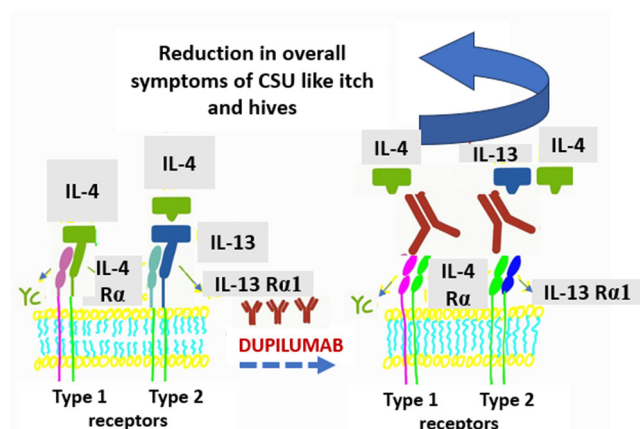


Figure 1: Mechanism of action in chronic spontaneous urticaria. CSU: Chronic spontaneous urticaria, IL: Interleukin.

Table 1: Case reports with dupilumab in chronic urticaria.

Author	Intervention	Outcome
Zhu <i>et al.</i> (2022) ^[11]	Dupilumab 600 mg for week 1 and 300 mg at week 3, 6, 10, 16, and 24	Complete response 4 months after the last treatment with dupilumab
Puxkandl <i>et al.</i> (2023) ^[12]	Dupilumab 600 mg was given as initial dose then 300 mg every 2 weeks	Complete control of clinical symptoms
Sun <i>et al.</i> (2022) ^[13]	Rescue therapy in chronic urticaria patients (600-mg SC initial dose, then 300 mg every 2 weeks)	Significant improvement in symptoms after first dose (UAS7: 0). IgE levels normalized on subsequent investigations. Significant improvement in the quality of life; condition remained stable for 24 months on maintenance treatment

IgE: Immunoglobulin E

and children >12 years of age with CSU were enrolled in CUPID Study A and Study C. All these were symptomatic patients despite treatment with H1 antihistamine and had no exposure to anti-IgE treatment.^[10]

Dupilumab was administered based on the body weight of the patient. For patients with 30–<60 kg, 400 mg (two injections of 200 mg) was administered as the initial dose and the subsequent dose was 200 mg every 2 weeks. For patients with a body weight of >60 kg, 600 mg (two injections of 300 mg) was given as an initial dose and subsequently 300 mg was administered every 2 weeks.

The primary endpoint of the study was the change from baseline in the 7-day Itch Severity Score (ISS7) at Week 24. The ISS7 is a cumulative score (0–21) derived from daily itch severity ratings over a week. Change from baseline in the UAS7 at week 24 was the key secondary endpoint.

Dupilumab consistently outperformed placebo in both studies. For the primary endpoint (Itch Severity - ISS7), both Study A and Study C showed a greater reduction in ISS7 from baseline with dupilumab compared to placebo. The least square (LS) mean difference for dupilumab versus placebo was -4.42 in Study A and -2.37 in Study C, indicating a significant improvement in itch severity with dupilumab.

For secondary Endpoints (Overall Urticaria Activity - UAS7 and Hive Severity - HSS7), dupilumab led to a more substantial reduction in UAS7 from baseline than placebo in both studies (LS mean difference of -9.04 in Study A and -4.34 in Study C). Similarly, dupilumab resulted in a greater reduction in HSS7 from baseline compared to placebo (LS mean difference of -4.69 in Study A and -2.01 in Study C).

The number of patients achieving UAS7 score of ≤6 (minimal disease activity) and UAS7 = 0 (complete response/no disease activity) at week 24 in the dupilumab group was significantly higher compared to the placebo group in both studies. The odds ratios, consistently above 2.7, suggested that patients on dupilumab were more likely to achieve these response levels.

CUPID study A

CUPID Study A demonstrated significant improvements in itch severity (ISS7) and overall urticaria activity (UAS7) from baseline at Week 12 in the dupilumab group compared

to placebo. For ISS7, the LS mean difference (dupilumab vs. placebo) was -2.53, indicating reduced itch severity with dupilumab. For UAS7, the LS mean difference was -5.44 (95% CI: -9.77, -1.11), showing improved overall urticaria activity with dupilumab. Furthermore, the number of patients in the dupilumab group achieving UAS7 score of ≤6 at week 12 was higher than placebo (35.3% vs. 17.6%) with an odds ratio of 2.79 (95% CI: 1.22, 6.40), suggesting that patients on dupilumab were more likely to achieve a response.

CUPID study B

In this study, 108 adults and children >12 with CSU were enrolled. These patients were either inadequate responders to H1 antihistamine and anti-IgE therapy ($n = 104$) or did not tolerate anti-IgE treatment ($n = 4$).

At the time of enrolment, the patients in Study B had high disease activity. Mean ISS7, USA7, and mean Hive Severity Score over 7 days (HSS7) were 16, 31.5, and 15.4, respectively. At baseline, a total of 69.4% patients had UAS7 score of ≥28. Median total IgE level at the start of treatment was 77 IU/mL (Q1, Q3: 20, 204.5).

In this study, dupilumab did not achieve a significant difference for the primary endpoint.^[13] This means that for patients who had already failed anti-IgE treatments, dupilumab did not show a statistically significant benefit in reducing itch severity in this study.

CUPID C study

Dupilumab led to a greater reduction in ISS7 from baseline compared to placebo (LS mean change: -8.6 vs. -6.1; $P = 0.02$). Patients on dupilumab experienced a more substantial decrease in urticaria activity score over 7 days (UAS7) than those on placebo (LS mean change: -15.9 vs. -11.2; $P = 0.02$). A significantly higher proportion of patients achieved well-controlled disease status in the dupilumab group versus placebo (41% vs. 23%; odds ratio = 2.7, $P = 0.005$). Complete response was significantly more with dupilumab than placebo (30% vs. 18%; odds ratio = 2.7, $P = 0.02$).

In essence, the data from both CUPID Study A and Study C strongly support the efficacy of dupilumab in significantly

reducing itch severity, overall urticaria activity, and hive severity and in achieving higher rates of disease control in patients with CSU, compared to placebo.

SAFETY PROFILE

There was no difference in the incidence of treatment-emergent adverse events with dupilumab as compared to placebo. The profile of dupilumab was generally consistent with its previously established safety records. Common adverse effects, including hypersensitivity reactions, conjunctivitis, keratitis, psoriasis, arthralgia, parasitic infections, eosinophilic conditions, and concurrent administration of live vaccines are contraindicated.^[13] Serious adverse events are infrequent, but continuous evaluation of long-term safety and tolerability remains inevitable.

CONTRAINDICATIONS

Dupilumab should be avoided in patients with known hypersensitivity reactions. It is not indicated for the treatment of other forms of urticaria than CSU. It should not be used for the treatment of acute bronchospasm, status asthmaticus, or psoriasis.^[13]

DRUG INTERACTIONS

An increase in levels of some cytokines during chronic inflammation can change the formation of CYP450 enzyme. Considering the possibility of modulation of some cytokines by dupilumab, while starting or stopping it in those receiving CYP450 substrates, especially narrow therapeutic index drugs, clinicians should be careful. For example, monitoring of warfarin's effect should be considered. Similarly, measurement of concentration for drugs such as cyclosporine and modification of the CYP450 substrate should be considered.^[13]

USE OF DUPILUMAB IN SPECIAL POPULATIONS

As per the population pharmacokinetic assessment, age had no effect on dupilumab clearance in adults and children from 6 to 17 years of age. In children from 6 months to 5 years of age, an increase in clearance was seen with age.^[13]

There were no differences in pharmacokinetics between elderly and younger adults.^[13]

Twelve children between 12 and 17 years of age with CSU were part of CUPID. Steady-state trough levels of six children receiving dupilumab 300 mg every 2 weeks or 200 mg every 2 weeks had the same range as adults with CSU receiving dupilumab 300 mg every 2 weeks.^[13]

Phase 3 clinical trials (LIBERTY-CSU CUPID Studies A and C) have consistently demonstrated its efficacy in significantly reducing both itch severity (ISS7) and overall urticaria activity (UAS7) compared to placebo. A substantial proportion of patients treated with dupilumab achieved

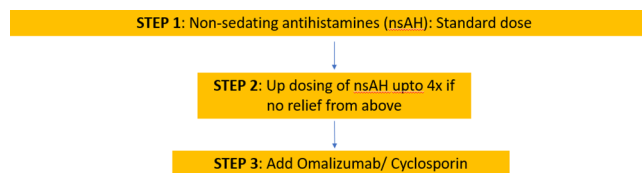


Figure 2: Therapeutic ladder for chronic urticaria.

well-controlled or even complete disease remission, indicating a meaningful improvement in their quality of life. Importantly, the safety profile of dupilumab in CSU studies has been consistent with its established safety profile across other approved indications, such as atopic dermatitis and asthma. Common adverse events were generally mild. These adverse events included reactions at the injection site. The sequential treatment strategy for CU is presented in the preceding section as Figure 2.^[3]

Possible place of dupilumab in the therapeutic ladder of CSU: Considering the cost, dupilumab may have its place in the following patient populations of CSU

1. Those with contraindications for the use of omalizumab and cyclosporin
2. Patients with CSU with comorbidities such as atopic dermatitis, eosinophilic phenotype of asthma, chronic rhinosinusitis with nasal polyp, eosinophilic esophagitis, prurigo nodularis, inadequately controlled and eosinophilic phenotype of chronic obstructive pulmonary disease, and bullous pemphigoid.

CONCLUSION

Dupilumab represents a significant advancement, particularly for patients who remain symptomatic despite conventional H1-antihistamine therapy. It offers a valuable new option for adults and adolescents aged 12 years and older suffering from uncontrolled CSU. Its demonstrated efficacy in alleviating debilitating itch and hives, coupled with a favorable safety profile, makes it a promising therapeutic addition for patients seeking better disease control and improved quality of life. Continued research may further elucidate its long-term benefits and optimal integration into CSU management algorithms.

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