

Current Management of Chronic Spontaneous Urticaria and Emerging Phase 3 Trial Drugs

Khushi Gupta B.S.¹, Zahra Ansari B.S.², Dina Ghanim B.A.³, Michael Ghebrial B.S.⁴, Leah Thomas B.S.⁵, Chiara Tognaccini B.S.⁶, Jashin J. Wu, M.D.⁷

1. Emory School of Medicine 2. Dell Medical School 3. Kaiser Permanente Bernard J. Tyson School of Medicine 4. UC Riverside School of Medicine 5. Loma Linda University School of Medicine 6. California University of Science and Medicine 7. Department of Dermatology

Learning Objectives

- Understand the current guideline-based management of CSU.
- Identify the role of off-label therapies and their limitations.
- Describe investigational agents in phase 3 trials for CSU.

Current FDA-Approved

Omalizumab

- **MOA:** Humanized IgG₁ monoclonal antibody; binds free IgE → downregulates FcεRI on mast cells & basophils
- **Evidence:** Phase III RCT (n=323) showed 300 mg dose significantly reduced weekly hive and itch scores vs placebo [1].
- **Safety:** Well-tolerated overall; serious adverse events: 6% in 300 mg group [1].

Off-Label Therapies

Cyclosporine A

- **MOA:** Calcineurin inhibitor; suppresses T-cell activation & mast cell mediator release
- **Evidence:** 62% responding within 3 months with low dose, 20% requiring long-term therapy, and 18% not responding; guideline-supported (step 4 therapy) [2].
- **Safety:** 20 patients discontinued early due to side effects [2]. Risk of kidney impairment, elevated BP; requires lab monitoring [3].

Montelukast

- **MOA:** Leukotriene receptor antagonist; reduces mast-cell mediated inflammation.
- **Evidence:** modestly improves urticaria activity; may help in NSAID-induced CSU [4, 5, 6].
- **Safety:** Generally safe; rare neuropsychiatric events reported [4, 5].

Systemic Glucocorticoids

- **MOA:** Broad anti-inflammatory and immunosuppressive effects
- **Evidence:** Rapid symptom relief; not recommended long-term [7].
- **Safety:** Side effects in ~15%—GI upset (e.g., dyspepsia, vomiting), headache, anxiety, fatigue, sedation [7].

Investigational Drugs in Phase 3 Trials

Drug Name	Trial Numbers	Mechanism of Action	Trial Outcomes (if published)	Endpoints	Safety Findings
Ligelizumab	NCT03580356, NCT03580369	Binds free IgE, downregulates FcεRI on mast cells & basophils	UAS7 ↓: -19.3 (72mg), -19.8 (120mg) vs -10.3 placebo. UAS7=0 rates ~40% at week 24 [8].	UAS7 score reduction at week 12	Mild-moderate AEs; consistent with previous anti-IgE therapies
Remibrutinib	NCT05030311, NCT05032157	Inhibits Bruton's tyrosine kinase to block mast cell degranulation	UAS7 ↓: -20.0 to -19.4 vs -13.8 to -11.7 (P<0.001). UAS7=0: 27.9–31.1% vs 6.5–10.5%. UAS7≤6: 46.8–49.8% vs 19.6–24.8% [9].	UAS7 score reduction; % achieving UAS7=0 at week 12	Similar to placebo; petechiae in 3.8% (vs 0.3% placebo)
Fenebrutinib	NCT04538794	Inhibits Bruton's tyrosine kinase to block mast cell degranulation	Network meta-analysis suggests efficacy vs placebo; primary phase 3 data unpublished [10].	Not reported in phase 3 trials	Safety data unavailable in phase 3
Dupilumab	NCT04180488	Blocks IL-4 and IL-13 signaling, reducing type 2 inflammation	UAS7 reduction: Study A -8.5 (95% CI -13.2 to -3.9); Study B -5.8 (95% CI -11.4 to -0.3). ISS7 improved. [11].	UAS7 score reduction; itch severity score (ISS7) reduction	Similar to placebo; consistent with dupilumab's known profile

Summary

- Omalizumab is the only FDA-approved therapy for CSU with strong efficacy and safety data, while off-label options like cyclosporine A, montelukast, and systemic corticosteroids show varying benefit—with cyclosporine supported in guidelines for refractory cases, montelukast offering modest relief, and corticosteroids effective short-term but limited by side effects.
- Emerging phase 3 agents—including ligelizumab, Bruton's tyrosine kinase inhibitors (remibrutinib, fenebrutinib), and dupilumab—show promise in improving urticaria activity scores and achieving complete symptom control.
- Future management may focus on personalized, mechanism-based therapy, expanding beyond IgE blockade to include mast cell degranulation inhibition and type 2 inflammation modulation, addressing heterogeneous disease pathways.

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