

Evaluation of Pharmacologic Treatments for H₁ Antihistamine-Refractory Chronic Spontaneous Urticaria

A Systematic Review and Network Meta-analysis

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 Supplemental content

IMPORTANCE The comparative benefits and harms of all available treatments for H₁ antihistamine-refractory chronic spontaneous urticaria (CSU) have not been established.

OBJECTIVE To evaluate different treatment effects of pharmacologic treatments among patients with H₁ antihistamine-refractory CSU.

DATA SOURCES Searches were conducted of MEDLINE, Embase, PubMed, Cochrane Library, Web of Science, Scopus, and CINAHL from inception to April 19, 2021, with no language restrictions. Gray literature from Google Scholar, ongoing trial registers, and preprint reports was added to the searches of electronic databases.

STUDY SELECTION Randomized clinical trials using validated measurement tools that investigated the benefits and harms of pharmacologic treatments among adolescent or adult patients with CSU who had an inadequate response to H₁ antihistamines were screened for inclusion independently by 2 investigators.

DATA EXTRACTION AND SYNTHESIS Two investigators independently extracted study data according to the predefined list of interests. A random-effects model was used to calculate the network estimates reported as standardized mean differences and odds ratios with corresponding 95% CIs.

MAIN OUTCOMES AND MEASURES The primary outcomes that reflect the patient's perspective included changes in urticaria symptoms from baseline and unacceptability of treatment (all-cause dropouts).

RESULTS Twenty-three randomized clinical trials with 2480 participants that compared 18 different interventions or dosages and placebo were included. The standardized mean differences for change in urticaria symptoms were −1.05 (95% CI, −1.37 to −0.73) for ligelizumab, 72 mg; −1.07 (95% CI, −1.39 to −0.75) for ligelizumab, 240 mg; −0.77 (95% CI, −0.91 to −0.63) for omalizumab, 300 mg; and −0.59 (95% CI, −1.10 to −0.08) for omalizumab, 600 mg. No significant differences in treatment unacceptability were observed. With respect to benefits and harms, the network estimates illustrated that the most efficacious treatments were achieved with ligelizumab, 72 or 240 mg (large beneficial effect) and omalizumab, 300 or 600 mg (moderate beneficial effect).

CONCLUSIONS AND RELEVANCE The findings in this meta-analysis suggest that the biologic agents ligelizumab, 72 or 240 mg, and omalizumab, 300 or 600 mg, can be recommended as effective treatments for patients with CSU who have had an inadequate response to H₁ antihistamines. Head-to-head trials with high methodologic quality and harmonized design and outcome definitions are needed to help inform subsequent international guidelines for the management of CSU.

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Chronic spontaneous urticaria (CSU) is the most common form of chronic urticaria, characterized by recurrent hives (wheals) and/or angioedema lasting more than 6 weeks, without any specific eliciting triggers.¹ In addition to disease severity and significant morbidity, CSU can be challenging, with significant morbidity and impaired health-related quality of life. Moreover, evidence suggests that CSU affects patients' socioeconomic status, particularly with substantial loss of productivity at school, work, or daily life, due to the unpredictable nature of the disease.² Despite the widespread use of various effective non-sedating second-generation H₁ antihistamines for the management of CSU over the past decade,³ less than half of patients receive adequate treatment with licensed doses of second-generation H₁ antihistamines.⁴

To date, studies have suggested promising or novel pharmacologic therapies for the management of H₁ antihistamine-refractory CSU.^{1,5,6} These different therapies possess anti-inflammatory, immunosuppressant, immunomodulatory, biological, and other pharmacologic qualities. However, to our knowledge, the comparative effectiveness, unacceptability of treatment, and safety profiles of all available treatments for H₁ antihistamine-refractory CSU have not been elucidated. To provide decision-making information for the pivotal clinical question, however, there is a need to establish effective pharmacologic treatments for H₁ antihistamine-refractory CSU. Therefore, we performed a comprehensive systematic review and network meta-analysis (NMA) of randomized clinical trials that investigated pharmacologic treatments for H₁ antihistamine-refractory CSU. To inform the clinical relevance of contemporary evidence, we aimed to systematically summarize all available evidence and compare different treatments that evaluated the effectiveness and safety profiles of pharmacologic treatments among patients with CSU that was refractory to treatment with H₁ antihistamines.

Methods

This systematic review and NMA was performed and is reported following guidance from the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline for reporting of NMAs.⁷ The prespecified protocol was registered on PROSPERO (CRD42020196592). Details of the methods used in this study are provided in eAppendix 1 in the Supplement.

Search Strategy and Study Selection

In brief, we searched electronic databases including MEDLINE, Embase, PubMed, Cochrane Library, Web of Science, Scopus, and CINAHL from inception to April 19, 2021, with no language restrictions. The full search strategy for each database is presented in eTable 1 in the Supplement. Gray literature from Google Scholar, ongoing trial registers, and preprint reports was added to the searches of electronic databases (eTable 2 in the Supplement). To identify all relevant articles, reference lists of included studies, reviews, and major international dermatology, allergy, and immunology conferences were also identified.

Key Points

Question What are the comparative benefits and harms of all available pharmacologic treatments for H₁ antihistamine-refractory chronic spontaneous urticaria?

Findings In this network meta-analysis of 23 randomized clinical trials including 2480 participants, the biologic agents ligelizumab, 72 or 240 mg (large beneficial effect), and omalizumab, 300 or 600 mg (moderate beneficial effect), appeared to be effective treatments for H₁ antihistamine-refractory chronic spontaneous urticaria. Alternative treatments with small beneficial effects, namely, dapsone, hydroxychloroquine, cyclosporine, and zafirlukast, can be used.

Meaning The findings of this meta-analysis may inform international guidelines for the management of chronic spontaneous urticaria that is inadequately controlled with H₁ antihistamines and further research in this clinical setting.

Eligible titles and abstracts of articles identified by the systematic search were screened independently by 2 investigators (S.N. and M.C.). Then, potentially relevant full-text articles were reviewed against the study inclusion and exclusion criteria for the final set of included studies. We included randomized clinical trials that included adolescent or adult (≥12 years) participants who were diagnosed with H₁ antihistamine-refractory CSU and used validated measurement tools for treatment assessment with a follow-up of 2 weeks onward (eTable 3 in the Supplement). For the companion trials that comprised overlapping participants and study periods, relevant information was assembled with the study that provided the most detailed information.

Outcomes and Assessment

The primary outcomes were change in urticaria symptoms (components of pruritus and hives) from baseline and unacceptability of treatment, defined as all-cause study dropouts. The secondary outcomes included (1) change in pruritus severity score from baseline, (2) change in hives severity score from baseline, (3) adverse events, and (4) serious adverse events.

We preferred to use the urticaria activity score over 7 days as the parameter for the urticaria symptom responses as per the 2017 joint guideline recommendations from the European Academy of Allergology and Clinical Immunology, Global Allergy and Asthma European Network, European Dermatology Forum, and the World Allergy Organization.¹ However, if a different measurement tool was applied, the data were extracted and weighted according to what was defined by authors of the studies evaluated.

Two investigators (S.N. and M.C.) independently abstracted the following prespecified data on the study and participant characteristics, specific intervention and control groups, and predefined outcomes and measurement tools. The corresponding author was contacted for clarification in cases in which the reported information was unclear or incomplete. To estimate treatment effects, the mean difference in

the change in any continuous outcome parameters from baseline was calculated. In cases in which the correlation coefficient (ρ) was not obtained, we anticipated a value of 0.7 for the correlation coefficient between the baseline and end of treatment follow-up.³ We critically appraised the methodologic quality of each included study using the Cochrane revised tool.⁸ The overall risk of bias was then classified as low, some concerns, or high.

Two investigators (S.N. and M.C.) independently graded the evidence certainty using the confidence in NMA along with the Grading of Recommended Assessment, Development, and Evaluation (GRADE) approach.^{9,10} The evidence certainty was categorized as very low, low, moderate, and high quality (the assessment criteria are provided in eAppendix 2 in the [Supplement](#)).

We further established our findings based on a contextualized approach to inform clinical interpretation in the context of clinical and methodologic viewpoints. We considered the key components to estimate the effect of the evidence findings, including magnitudes of effect size, evidence certainty, and surface under the cumulative ranking curve (SUCRA) values, to draw evidence-based conclusions. To facilitate interpretation of the clinical evidence findings, we then classified the particular treatment effects by incorporating the dimensions of safety profiles as having trivial (not substantively different from placebo), small, moderate, and large treatment effects.¹¹

Statistical Analysis

We conducted a random-effects model framework to incorporate direct and indirect treatment comparisons, which provided more conservative results in the estimated treatment effects. To rank the treatment hierarchy in the NMA, the SUCRA was calculated for each treatment comparison.¹² Higher SUCRA scores indicated a higher ranking for effectiveness and undesirable treatment. The transitivity assumption in terms of sufficient similarity between the treatment comparisons was explored. The degree of inconsistency was classified as low ($\tau^2 = 0.04$), moderate ($\tau^2 = 0.16$), and high ($\tau^2 = 0.36$).¹³ Assessment of the incoherence assumption was evaluated using a loop-specific approach, a node-splitting technique, and the design-by-treatment interaction model.^{14,15} Potential small-study effects were investigated using comparison-adjusted funnel plot symmetry.¹² In addition, we calculated the 95% prediction intervals for all NMA estimates, which accounted for a predicted range for the true treatment effect in an individual study and the expected uncertainty about the estimate of a future study.¹⁶

We planned to perform a set of subgroup analyses based on the following effect modifiers: age and sex of study participants, definition of refractory CSU, baseline CSU severity, angioedema status, autologous serum skin test status, study size, and study treatment period. We also planned to perform network meta-regression analyses by supplementing other covariates as mentioned in the adjusted NMA model. However, because of limitations in data availability and small sample sizes, statistical integration of results for the subgroup analysis, as well as the adjustment for covariates in the network meta-regression, was not possible.

To address the robustness of the results, a set of sensitivity analyses was applied based on (1) assuming a p value of 0.5 in cases with missing correlation coefficients for continuous outcomes,^{3,17} (2) including only trials with parallel group design, (3) excluding trials with an unclear definition of refractory to H₁ antihistamine dosing, and (4) excluding studies with high overall risk-of-bias assessment.

All outcomes are reported as standardized mean differences (SMDs) and odds ratios (ORs) with 95% CIs. Two-tailed P values $< .05$ were considered statistically significant. All analyses were performed using Stata, version 16.0 (StataCorp LLC).¹²

Results

Twenty-three trials were included in the NMA (eFigure 1 in the [Supplement](#)).¹⁸⁻⁴⁰ These trials investigated 18 different interventions or dosages and 1 placebo. All possible treatment nodes for each outcome of interest are illustrated in eFigure 2 in the [Supplement](#). The characteristics of all included trials are summarized in [Table 1](#); and eTable 4 and eTable 5 in the [Supplement](#). In total, 2480 participants with H₁ antihistamine-refractory CSU were identified, with mean age ranging from 32.2 to 43.8 years. The included trials were conducted in patients with CSU that was refractory to licensed-dose antihistamines (9 trials^{21,22,24,25,28,32-34,37}), up-dosed (ie, 2- to 4-fold higher-than-approved doses) antihistamines (10 trials^{18,23,26,27,29-31,35,38,39}), mixed cases (1 trial³⁶), and unclear definition (3 trials^{19,20,40}). A detailed outcome assessment is provided in eTable 6 in the [Supplement](#). Based on the overall risk-of-bias assessment, 13 trials had a low risk of bias, 10 trials had some concerns, and no trial had a high risk of bias (eTable 7 and eFigure 3 in the [Supplement](#)).

Outcomes

The NMA illustrated that cyclosporine (SMD, -0.83 ; 95% CI, -1.63 to -0.03), dapsone (SMD, -1.14 ; 95% CI, -2.06 to -0.22), hydroxychloroquine (SMD, -1.26 ; 95% CI, -1.85 to -0.66); ligelizumab, 24 mg (SMD, -0.40 ; 95% CI, -0.77 to -0.02); ligelizumab, 72 mg (SMD, -1.05 ; 95% CI, -1.37 to -0.73); ligelizumab, 240 mg (SMD, -1.07 ; 95% CI, -1.39 to -0.75); omalizumab, 150 mg (SMD, -0.37 ; 95% CI, -0.55 to -0.19); omalizumab, 300 mg (SMD, -0.77 ; 95% CI, -0.91 to -0.63); omalizumab, 600 mg (SMD, -0.59 ; 95% CI, -1.10 to -0.08); and zafirlukast (SMD, -0.46 ; 95% CI, -0.89 to -0.04) were more efficacious than placebo ([Table 2](#)). Notably, AZD1981 and methotrexate seemed to be less efficacious than placebo, and the evidence does not support the effectiveness of other treatment comparisons.

However, no significant difference among the treatment comparisons for unacceptability of treatment was observed ([Table 2](#)). According to SUCRA values with respect to the dimensions of the effectiveness and unacceptability of treatment, the top-ranked intervention was ligelizumab, 72 mg ([Figure](#); eFigure 4 in the [Supplement](#)). Overall results from pairwise analysis did not differ significantly from the findings of the network estimates, except for the effect of ligelizumab, 24 mg, and omalizumab, 75 mg, on changes in urticaria symptoms (eTable 8 and eTable 9 in the [Supplement](#)).

Table 1. Description of Randomized Clinical Trials Included in the Meta-analysis

Source	Study design (sample size)	Site	Definition of refractory CSU ^a	Treatment		Age, mean (SD), y		Female, No. (%)		Duration of CSU, y		Outcomes reported	Overall risk of bias
				Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control		
Grattan et al, ¹⁸ 2000	DB, parallel-group, MC; 4-wk treatment (N = 30)	UK	Refractory to up-dosing antihistamines	Cyclosporine, 4 mg/kg d	Placebo orally	39.0 (14.2)	37.5 (12.0)	16 (80.0)	8 (80.0)	Median, 1.0 (range, 0.25-5.0)	Median, 0.7 (range, 0.25-16.0)	Urticaria symptoms, unacceptability of treatment, adverse events	Low
Erbagci, ¹⁹ 2002	RCT; SB, crossover; 6-wk treatment (N = 30)	Turkey	NS	Montelukast, 10 mg once daily	Placebo orally	42.8 (7.7)	42.8 (7.7)	21 (70.0)	21 (70.0)	Mean (SD), 1.3 (0.8)	Mean (SD), 1.3 (0.8)	Unacceptability of treatment, adverse events	Some concerns
Bagenstose et al, ²⁰ 2004	DB, parallel-group, MC; 3-wk treatment (N = 95)	US	NS	Zafirlukast, 20 mg twice daily	Placebo orally	41.2 (12.6)	43.5 (13.3)	42 (87.5)	37 (78.7)	NR	NR	Urticaria symptoms, unacceptability of treatment, adverse events	Some concerns
Vena et al, ²¹ 2006	DB, parallel-group, MC; 8-wk (primary) treatment period (N = 99)	Italy	Refractory to licensed-dose antihistamines	Cyclosporine, 5 mg/kg/d (days 0-14), 4 mg/kg/d (days 14-27), 3 mg/kg/d (from day 28)	Placebo orally	40.6 (10.6)	41.7 (11.5)	34 (53.1)	23 (65.7)	NR	NR	Unacceptability of treatment, adverse events	Some concerns
Saini et al, ²² 2011	DB, parallel-group; 4-wk treatment (N = 90)	US, Germany	Refractory to licensed-dose antihistamines	Omalizumab, single dose of 75, 300, or 600 mg	Placebo subcutaneously	40.6 (14.4)	41.2 (16.2)	44 (63.8)	17 (81.0)	NR	NR	Urticaria symptoms, pruritus severity, hives severity, unacceptability of treatment, adverse events	Low
Kaplan et al, ²³ 2013	DB, parallel-group, MC; 24-wk treatment (N = 335)	International	Refractory to up-dosing antihistamines	Omalizumab, 300 mg subcutaneously at 4-wk intervals	Placebo subcutaneously	42.7 (13.9)	44.3 (14.7)	186 (73.8)	55 (66.3)	Mean (SD), 7.0 (8.8); median, 3.4 (range, 0.5-50.3)	Mean (SD), 8.8 (11.2); median, 4.1 (range, 0.6-54.1)	Urticaria symptoms, pruritus severity, hives severity, unacceptability of treatment, adverse events	Low risk

(continued)

Table 1. Description of Randomized Clinical Trials Included in the Meta-analysis (continued)

Source	Study design (sample size)	Site	Definition of refractory CSU ^a	Treatment		Age, mean (SD), y		Female, No. (%)		Duration of CSU, y		Outcomes reported	Overall risk of bias
				Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control		
Magerl et al, ²⁴ 2013	DB, parallel-group, MC; 4-wk treatment (N = 76)	Germany	Refractory to licensed-dose antihistamines	Miltefosine, 150 mg/d (100 mg if evidence of intolerance)	Placebo orally	45.0 (12.4)	42.6 (12.5)	28 (56.0)	14 (53.8)	NR	NR	Urticaria symptoms, pruritus severity, hives severity, unacceptability of treatment, adverse events	Low risk
Maurer et al, ²⁵ 2013	DB, parallel-group, MC; 12-wk treatment (N = 322)	International	Refractory to licensed-dose antihistamines	Omalizumab, 75, 150, or 300 mg subcutaneously at 4-wk intervals	Placebo subcutaneously	42.3 (14.0)	43.1 (12.5)	189 (77.8)	55 (69.6)	Mean (SD), 6.2 (7.8)	Mean (SD), 7.2 (10.7)	Urticaria symptoms, pruritus severity, hives severity, unacceptability of treatment, adverse events	Low
Morgan et al, ²⁶ 2014	DB, SC, crossover; 6-wk treatment (N = 22)	US	Refractory to up-dosing antihistamines	Dapsone, 100 mg orally once daily	Placebo orally once daily	41.9 (11.0)	44.8 (13.9)	2 (20.0)	3 (25.0)	Median, 1.0 (range, 0.5-5.0)	Median, 1.3 (range, 0.3-10.0)	Urticaria symptoms, pruritus severity, hives severity, unacceptability of treatment, adverse events	Some concerns
Sharma et al, ²⁷ 2014	DB, parallel-group, SC; 12-wk treatment (N = 29)	India	Refractory to up-dosing antihistamines	Methotrexate, 15 mg/wk orally	Placebo orally	34.2 (10.4)	30.1 (10.1)	8 (57.1)	9 (60.0)	Mean, 1.9 (NR)	Mean, 2.2 (NR)	Urticaria symptoms, pruritus severity, hives severity, unacceptability of treatment, adverse events	Low

(continued)

Table 1. Description of Randomized Clinical Trials Included in the Meta-analysis (continued)

Source	Study design (sample size)	Site	Definition of refractory CSU ^a	Treatment		Age, mean (SD), y		Female, No. (%)		Duration of CSU, y		Outcomes reported	Overall risk of bias
				Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control		
Saini et al, ²⁸ 2015	DB, parallel-group, MC; 24-wk treatment (N = 318)	International	Refractory to licensed-dose antihistamines	Omalizumab, 75, 150, or 300 mg subcutaneously at 4-wk intervals	Placebo subcutaneously	41.4 (14.1)	40.4 (15.6)	179 (75.2)	52 (65.0)	Mean (SD), 6.9 (9.0)	Mean (SD), 7.0 (9.7)	Urticaria symptoms, pruritus severity, hives severity, unacceptability of treatment, adverse events	Low
Harris et al, ²⁹ 2016	DB, parallel-group, MC; 20-wk treatment (N = 32)	Canada, Germany	Refractory to up-dosing antihistamines	Quilizumab, 450 mg subcutaneously at wk 0 and 4	Placebo subcutaneously	44.7 (13.2)	41.8 (12.3)	2 (13.3)	0	Mean (SD), 8.3 (13.0); median, 2.3 (NR)	Mean (SD), 14.2 (19.0); median, 6.8 (NR)	Urticaria symptoms, pruritus severity, hives severity, unacceptability of treatment, adverse events	Some concerns
Staubach et al, ³⁰ 2016	DB, parallel-group, MC; 24-wk treatment (N = 91)	Germany	Refractory to up-dosing antihistamines	Omalizumab, 300 mg subcutaneously at 4-wk intervals	Placebo subcutaneously	44.9 (range, 20-73)	41.4 (range, 20-61)	30 (68.2)	33 (70.2)	Mean (SD), 8.4 (9.3); median, 5.0 (range, 0.0-40.0)	Mean (SD), 7.4 (8.8); median, 5.0 (range, 0.0-41.0)	Urticaria symptoms, pruritus severity, hives severity, unacceptability of treatment, adverse events	Low
Boonpiyathad and Sangasapaviliya, ³¹ 2017	SB, SC, parallel-group; 12-wk treatment (N = 55)	Thailand	Refractory to up-dosing antihistamines	Hydroxy-chloroquine, 400 mg/d orally	Placebo orally	33.0 (12.1)	34.0 (11.9)	21 (87.5)	20 (83.3)	Mean (SD), 0.4 (0.4)	Mean (SD), 0.5 (0.5)	Urticaria symptoms, unacceptability of treatment, adverse events	Some concerns

(continued)

Table 1. Description of Randomized Clinical Trials Included in the Meta-analysis (continued)

Source	Study design (sample size)	Site	Definition of refractory CSU ^a	Treatment		Age, mean (SD), y		Female, No. (%)		Duration of CSU, y		Outcomes reported	Overall risk of bias
				Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control		
Hide et al, ³² 2017	DB, parallel-group, MC; 12-wk treatment (N = 218)	Japan, Korea	Refractory to licensed-dose antihistamines	Omalizumab, 150 or 300 mg subcutaneously at 4-wk intervals	Placebo subcutaneously	43.6 (12.2)	42.5 (14.3)	83 (57.6)	48 (64.9)	Mean (SD), 4.0 (4.7)	Mean (SD), 4.7 (6.2)	Urticaria symptoms, pruritus severity, hives severity, unacceptability of treatment, adverse events	Low
Metz et al, ³³ 2017	DB, parallel-group, MC; 12-wk treatment (N = 30)	Germany	Refractory to licensed-dose antihistamines	Omalizumab, 300 mg subcutaneously at 4-wk intervals	Placebo subcutaneously	37.5 (11.0)	41.1 (8.0)	18 (90.0)	8 (80.0)	NR	NR	Urticaria symptoms, pruritus severity, hives severity, unacceptability of treatment, adverse events	Low
Jörg et al, ³⁴ 2018	DB, parallel-group, SC; 16-wk treatment (N = 30)	Switzerland	Refractory to licensed-dose antihistamines	Omalizumab, 300 mg subcutaneously at 4-wk intervals	Placebo subcutaneously	41.8 (15.2)	42.4 (13.3)	8 (40.0)	8 (80.0)	Mean (SD), 1.8 (1.4)	Mean (SD), 3.1 (3.2)	Urticaria symptoms, unacceptability of treatment, adverse events	Some concerns
Sánchez et al, ³⁵ 2018	OL, parallel-group, MC; 16-wk treatment (N = 35)	Colombia	Refractory to up-dosing antihistamines	Omalizumab, 300 mg subcutaneously at 4-wk intervals	Cyclosporine, 3 mg/kg/d (range, 100-250 mg)	NR	NR	NR	NR	NR	NR	Unacceptability of treatment, adverse events	Some concerns
Maurer et al, ³⁶ 2019	DB, parallel-group, MC; 20-wk treatment (N = 340)	International	Mixed (57.1% refractory to up-dosing antihistamines)	Ligelizumab, 24, 72, or 240 mg; omalizumab, 300 mg subcutaneously at 4-wk intervals	Placebo subcutaneously	Ligelizumab, 43.8 (12.1); omalizumab, 41.8 (13.1)	45.4 (11.2)	Ligelizumab, 159 (75.0); omalizumab, 66 (77.6)	31 (72.1)	Ligelizumab, mean (SD), 3.8 (5.2); omalizumab, 5.1 (7.5)	Mean (SD), 3.6 (3.5)	Urticaria symptoms, pruritus severity, hives severity, unacceptability of treatment, adverse events	Low

(continued)

Table 1. Description of Randomized Clinical Trials Included in the Meta-analysis (continued)

Source	Study design (sample size)	Site	Definition of refractory CSU ^a	Treatment		Age, mean (SD), y		Female, No. (%)		Duration of CSU, y		Outcomes reported	Overall risk of bias
				Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control		
Oliver et al, ³⁷ 2019	DB, parallel-group, SC; 4-wk treatment (N = 28)	US	Refractory to licensed-dose antihistamines	AZD1981 (CRTh2 antagonist), 40 mg 3 times/d	Placebo orally	41.8 (12.3)	45.2 (12.5)	10 (71.4)	10 (83.3)	NR	NR	Urticaria symptoms, pruritus severity, hives severity, unacceptability of treatment, adverse events	Low
Pathania et al, ³⁸ 2019	OL, parallel-group, noninferiority, SC; 12-wk treatment (N = 80)	India	Refractory to up-dosing antihistamines	Cyclosporine started at 3 mg/kg/d, divided twice daily	Azathioprine started at 1 mg/kg/d, divided twice daily	36.0 (9.4)	36.7 (9.7)	24 (60.0)	24 (60.0)	Mean (SD), 5.2 (4.9)	Mean (SD), 6.6 (5.8)	Urticaria symptoms, unacceptability of treatment, adverse events	Some concerns
Leducq et al, ³⁹ 2020	DB, parallel-group, MC; 18-wk treatment (N = 75)	France	Refractory to up-dosing antihistamines	Methotrexate, 0.2 mg/kg/wk as a single dose orally for 8 weeks (increased to 2.5 mg/kg/wk in case of inadequate control)	Placebo orally	46.4 (12.6)	45.0 (13.2)	28 (71.8)	29 (80.6)	Mean (SD), 3.8 (2.6)	Mean (SD), 3.7 (4.6)	Pruritus severity (VAS), unacceptability of treatment, adverse events	Low
Maul et al, ⁴⁰ 2021	DB, parallel-group, SC; 4-wk treatment (N = 20)	Switzerland	NS	Canakinumab, 150 mg subcutaneously once at baseline	Placebo subcutaneously	42.2 (17.9)	38.7 (9.6)	6 (60.0)	6 (60.0)	Mean (SD), 2.7 (2.6)	Mean (SD), 9.4 (6.4)	Urticaria symptoms, unacceptability of treatment, adverse events	Some concerns

Abbreviations: CSU, chronic spontaneous urticaria; DB, double-blind; MC, multicenter; NR, not reported; NS, not specified; OL, open-label; SB, single-blind; SC, single-center; VAS, visual analog scale.

^a Up-dosed indicates 2- to 4-fold higher-than-approved doses.

Table 2. League Table of Treatment Response for Urticaria Symptoms (Lower Left Portion, Standardized Mean Differences [95% CI]) and Unacceptability of Treatment (Upper Right Portion, Odds Ratio [95% CI]) for H₁ Antihistamine-Refractory Chronic Spontaneous Urticaria^a

Pla	0.53 (0.01 to 34.69)	0.22 (0.01 to 6.07)	1.00 (0.02 to 61.04)	0.53 (0.18 to 1.59)	2.56 (0.07 to 94.25)	1.33 (0.22 to 8.18)	0.37 (0.08 to 1.72)	0.45 (0.13 to 1.58)	0.81 (0.26 to 2.59)	1.38 (0.30 to 6.36)	0.64 (0.19 to 2.18)	1.00 (0.02 to 57.07)	0.83 (0.38 to 1.80)	0.91 (0.44 to 1.88)	0.64 (0.38 to 1.05)	0.29 (0.03 to 2.83)	0.37 (0.05 to 2.75)	0.46 (0.08 to 2.45)
-0.61 (-1.53 to 0.31)	Aza	0.42 (0.00 to 86.78)	1.89 (0.01 to 665.37)	1.00 (0.02 to 56.54)	4.83 (0.02 to 1208.43)	2.52 (0.03 to 240.31)	0.70 (0.01 to 59.80)	0.85 (0.01 to 66.36)	1.54 (0.02 to 116.91)	2.60 (0.03 to 223.13)	1.21 (0.02 to 4.31)	1.89 (0.01 to 634.86)	1.57 (0.02 to 109.24)	1.73 (0.02 to 119.69)	1.20 (0.02 to 80.64)	0.54 (0.00 to 63.00)	0.70 (0.01 to 72.15)	0.86 (0.01 to 78.03)
0.41 (-0.35 to 1.17)	1.02	AZD	4.50 (0.02 to 880.67)	2.38 (0.07 to 77.73)	11.50 (0.09 to 1535.40)	6.00 (0.14 to 260.83)	1.67 (0.04 to 63.96)	2.02 (0.06 to 69.57)	3.66 (0.11 to 121.83)	6.19 (0.16 to 236.78)	2.88 (0.08 to 97.98)	4.50 (0.02 to 835.86)	3.73 (0.12 to 111.57)	4.12 (0.14 to 121.52)	2.86 (0.10 to 81.25)	1.29 (0.02 to 72.08)	1.66 (0.03 to 79.61)	2.05 (0.05 to 83.79)
-0.17 (-1.05 to 0.72)	0.45 (-0.83 to 1.72)	Can	0.53 (0.01 to 37.33)	0.53 (0.01 to 606.76)	2.56 (0.01 to 606.76)	1.33 (0.01 to 119.29)	0.37 (0.00 to 29.87)	0.45 (0.01 to 33.11)	0.81 (0.01 to 58.31)	1.38 (0.03 to 110.59)	0.64 (0.01 to 46.70)	1.00 (0.00 to 319.64)	0.83 (0.00 to 54.46)	0.91 (0.01 to 59.45)	0.64 (0.01 to 40.05)	0.29 (0.00 to 31.72)	0.37 (0.00 to 35.86)	0.46 (0.01 to 38.71)
-0.83 (-1.63 to 0.24)	-0.22 (-0.68 to 0.24)	Cyc	-0.66 (-2.34 to -0.53)	4.83 (0.11 to 209.66)	4.83 (0.11 to 209.66)	2.52 (0.30 to 21.00)	0.70 (0.11 to 4.54)	0.85 (0.16 to 4.41)	1.54 (0.32 to 7.43)	2.60 (0.39 to 17.10)	1.21 (0.23 to 6.27)	1.89 (0.03 to 124.81)	1.57 (0.42 to 5.85)	1.73 (0.47 to 6.32)	1.20 (0.37 to 3.94)	0.54 (0.04 to 6.77)	0.70 (0.07 to 6.88)	0.86 (0.12 to 6.42)
-1.14 (-2.06 to -0.22)	-0.53 (-1.83 to 0.77)	Dap	-0.98 (-2.75 to -0.36)	-0.31 (-1.53 to 0.90)	0.52 (0.01 to 29.59)	0.15 (0.00 to 7.32)	0.18 (0.00 to 8.02)	0.32 (0.01 to 14.08)	0.32 (0.01 to 27.10)	0.54 (0.01 to 11.31)	0.25 (0.01 to 1.31)	0.39 (0.00 to 88.34)	0.32 (0.01 to 13.01)	0.36 (0.01 to 14.18)	0.25 (0.01 to 9.51)	0.11 (0.00 to 8.05)	0.14 (0.00 to 9.55)	0.18 (0.00 to 9.55)
-1.26 (-1.85 to -0.66)	-0.65 (-1.74 to 0.45)	Hyd	-1.09 (-2.63 to -0.70)	-0.43 (-1.42 to 0.57)	0.28 (0.03 to 2.99)	0.34 (0.04 to 3.06)	0.61 (0.07 to 5.26)	0.61 (0.07 to 5.26)	1.03 (0.10 to 11.08)	1.03 (0.10 to 11.08)	0.48 (0.05 to 4.29)	0.75 (0.01 to 63.10)	0.62 (0.09 to 4.48)	0.69 (0.10 to 4.83)	0.48 (0.07 to 3.14)	0.21 (0.01 to 4.00)	0.28 (0.02 to 4.15)	0.34 (0.03 to 4.06)
-0.40 (-0.77 to -0.02)	0.21 (-0.78 to 1.21)	Lig24	-0.23 (-1.65 to 0.04)	0.43 (-0.45 to 1.32)	0.75 (0.25 to 1.74)	0.86 (0.16 to 1.56)	Lig24	1.21 (0.23 to 6.28)	2.19 (0.45 to 10.58)	3.70 (0.42 to 32.33)	1.72 (0.24 to 12.27)	2.69 (0.04 to 203.54)	2.24 (0.43 to 11.64)	2.46 (0.48 to 12.71)	1.71 (0.38 to 7.71)	0.77 (0.05 to 11.60)	0.99 (0.08 to 12.44)	1.23 (0.13 to 11.94)
-1.05 (-1.39 to -0.73)	-0.44 (-1.42 to 0.53)	Lig72	-0.89 (-1.83 to 0.06)	-0.22 (-1.08 to 0.64)	0.09 (-0.88 to 1.06)	0.20 (-0.47 to 0.88)	-0.66 (-1.05 to -0.26)	Lig72	1.81 (0.49 to 6.66)	3.06 (0.42 to 22.11)	1.42 (0.25 to 0.21)	2.22 (0.03 to 153.33)	1.84 (0.46 to 7.43)	2.03 (0.51 to 8.10)	1.41 (0.42 to 4.78)	0.64 (0.05 to 8.26)	0.82 (0.08 to 8.76)	1.01 (0.12 to 8.25)
-1.07 (-1.39 to -0.75)	-0.46 (-1.43 to 0.52)	Lig240	-0.90 (-1.84 to 0.04)	-0.24 (-1.10 to 0.62)	0.08 (-0.90 to 1.05)	0.19 (-0.49 to 0.86)	-0.67 (-1.07 to -0.28)	Lig240	1.69 (0.25 to 11.54)	1.69 (0.25 to 11.54)	0.79 (0.15 to 4.25)	1.23 (0.02 to 82.56)	1.02 (0.27 to 3.78)	1.12 (0.31 to 4.12)	0.78 (0.25 to 2.40)	0.35 (0.03 to 4.37)	0.45 (0.04 to 4.61)	0.56 (0.07 to 4.32)
-0.31 (-0.80 to 0.09)	0.30 (-0.74 to 1.35)	Mil	-0.14 (-1.15 to 0.87)	0.52 (-0.42 to 1.46)	0.84 (-0.21 to 1.88)	0.95 (0.18 to 1.72)	0.09 (-0.53 to 0.71)	Mil	0.76 (0.17 to 1.35)	0.76 (0.17 to 1.35)	0.46 (0.07 to 3.31)	0.73 (0.01 to 54.93)	0.60 (0.11 to 50.98)	0.67 (0.12 to 3.62)	0.46 (0.09 to 2.32)	0.21 (0.01 to 3.28)	0.27 (0.02 to 3.36)	0.33 (0.03 to 3.22)
0.61 (-0.14 to 1.37)	1.22 (-0.03 to 2.41)	Met	0.78 (-0.87 to 1.27)	1.44 (0.34 to 2.54)	1.76 (0.57 to 2.95)	1.87 (0.91 to 2.83)	1.01 (0.16 to 1.85)	Met	1.68 (0.86 to 2.50)	0.92 (0.02 to 1.82)	0.92 (0.02 to 1.82)	1.56 (0.02 to 107.19)	1.30 (0.30 to 5.55)	1.43 (0.34 to 5.95)	1.00 (0.26 to 3.76)	0.45 (0.03 to 6.03)	0.58 (0.05 to 6.09)	0.71 (0.09 to 5.72)
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Mon	0.83 (0.01 to 50.98)	0.91 (0.02 to 55.64)	0.64 (0.01 to 37.47)	0.29 (0.00 to 29.92)	0.37 (0.00 to 33.76)	0.46 (0.01 to 36.38)
-0.17 (-0.37 to 0.03)	0.44 (-0.50 to 1.38)	Oma75	-0.58 (-1.37 to 0.20)	0.66 (-0.17 to 1.48)	0.97 (0.03 to 1.91)	1.08 (0.46 to 1.71)	0.22 (-0.19 to 0.63)	Oma75	0.89 (0.54 to 1.25)	0.13 (-0.40 to 0.66)	-0.79 (-1.57 to -0.00)	NA	1.10 (0.48 to 2.55)	1.10 (0.36 to 1.65)	0.77 (0.26 to 3.76)	0.35 (0.04 to 6.03)	0.45 (0.05 to 3.83)	0.55 (0.09 to 5.72)
-0.37 (-0.55 to -0.19)	0.24 (-0.70 to 1.18)	Omal150	-0.78 (-1.56 to 0.00)	0.46 (-0.36 to 1.28)	0.77 (0.16 to 1.71)	0.89 (0.27 to 1.51)	0.03 (-0.38 to 0.43)	Omal150	0.70 (0.35 to 1.05)	-0.06 (-0.59 to 0.46)	-0.98 (-1.76 to -0.20)	NA	-0.20 (-0.41 to 0.02)	0.70 (0.33 to 1.45)	0.31 (0.03 to 3.25)	0.40 (0.05 to 3.41)	0.50 (0.08 to 3.11)	0.50 (0.08 to 3.11)

(continued)

Table 2. League Table of Treatment Response for Urticaria Symptoms (Lower Left Portion, Standardized Mean Differences [95% CI]) and Unacceptability of Treatment (Upper Right Portion, Odds Ratio [95% CI]) for H₁ Antihistamine-Refractory Chronic Spontaneous Urticaria^a (continued)

	-0.77 (-0.91 to -0.63) ^b	-0.16 (-1.09 to 0.77)	-1.18 (-1.95 to -0.41) ^b	-0.60 (-1.50 to 0.29)	0.06 (-0.75 to 0.87)	0.37 (-0.56 to 1.30)	0.49 (-0.12 to 1.09)	-0.37 (-0.74 to -0.00) ^b	0.28 (-0.03 to 0.59)	0.30 (-0.01 to 0.61)	-0.46 (-0.97 to 0.05)	-1.38 (-2.15 to -0.61) ^b	NA	-0.40 (-0.58 to -0.22) ^b	Oma300 (-0.33 to 0.69)	0.45 (0.05 to 0.85)	0.58 (0.07 to 1.09)	0.72 (0.12 to 1.15)
	-0.59 (-1.10 to -0.08) ^b	0.02 (-1.03 to 1.07)	-1.00 (-1.92 to -0.08) ^b	-0.42 (-1.45 to 0.60)	0.24 (-0.71 to 1.19)	0.55 (-0.50 to 1.61)	0.67 (-0.12 to 1.45)	-0.19 (-0.82 to 0.43)	0.46 (-0.13 to 1.06)	0.48 (-0.11 to 1.07)	-0.28 (-0.99 to 0.43)	-1.20 (-2.12 to -0.29) ^b	NA	-0.42 (-0.93 to 0.10)	0.18 (-0.33 to 0.69)	Oma600 (-0.68 to 1.08)	1.29 (0.06 to 27.15)	1.59 (0.09 to 27.30)
	-0.39 (-1.10 to 0.32)	0.22 (-0.94 to 1.38)	-0.80 (-1.84 to 0.24)	-0.23 (-1.36 to 0.91)	0.44 (-0.63 to 1.51)	0.75 (-0.41 to 1.92)	0.87 (-0.06 to 1.79)	0.01 (-0.80 to 0.81)	0.66 (-0.12 to 1.44)	0.68 (-0.10 to 1.46)	-0.08 (-0.95 to 0.78)	-1.00 (-2.04 to 0.04)	NA	-0.22 (-0.96 to 0.52)	0.38 (-0.35 to 1.10)	0.20 (-0.68 to 1.08)	Qui (0.09 to 16.95)	1.23 (0.09 to 16.95)
	-0.46 (-0.89 to -0.04) ^b	0.15 (-0.87 to 1.16)	-0.87 (-1.74 to 0.00) ^b	-0.30 (-1.28 to 0.69)	0.37 (-0.54 to 1.27)	0.68 (-0.33 to 1.69)	0.79 (0.06 to 1.52) ^b	-0.07 (-0.63 to 0.50)	0.59 (0.06 to 1.12) ^b	0.61 (0.07 to 1.14) ^b	-0.16 (-0.81 to -0.49)	-1.08 (-1.94 to -0.21) ^b	NA	-0.29 (-0.76 to 0.18)	0.31 (-0.14 to 0.75)	0.13 (-0.54 to 0.79)	-0.07 (-0.90 to 0.76)	Zaf (0.09 to 16.95)

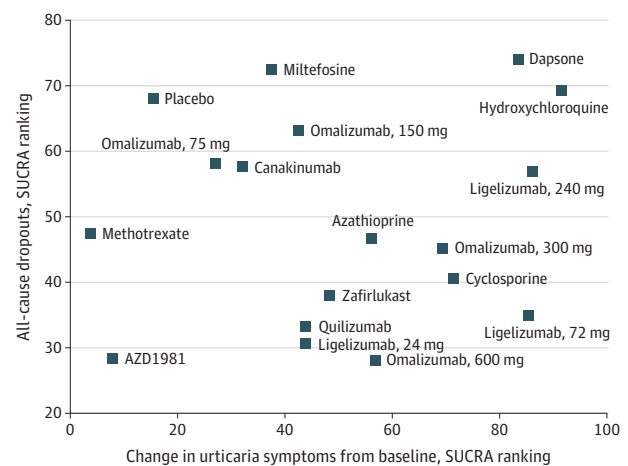
Abbreviations: Aza, azathioprine; AZD, AZD1981; Can, canakinumab; Cyc, cyclosporine; Dap, dapsone; Hyd, hydroxychloroquine; Lig24, ligelizumab, 24 mg; Lig72, ligelizumab, 72 mg; Lig240, ligelizumab, 240 mg; Mil, miltefosine; Met, methotrexate; Mon, montelukast; NA, not applicable; Oma75, omalizumab, 75 mg; Oma150, omalizumab, 150 mg; Oma300, omalizumab, 300 mg; Oma600, omalizumab, 600 mg; Pla, placebo; Qui, quilizumab; Zaf, zafirlukast.

^a Treatment response for urticaria symptoms is shown below and to the left of the drug names across the table, and unacceptability of treatment is shown above and to the right of the drug names. Network meta-analysis results are expressed as standardized mean differences (SMDs) (95% CIs) for urticaria symptoms and odds

ratios (ORs) (95% CIs) for unacceptability of treatment. For change in urticaria symptoms, SMDs less than 0 indicate that the treatment specified in the row is more effective than that specified in the column. To obtain SMDs for comparisons in the opposite direction, negative values should be converted to positive values and vice versa. For unacceptability of treatment, ORs greater than 1 indicate that treatment specified in the column is more all-cause dropout than that specified in the row. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken to obtain ORs for comparisons in the opposite direction.

^b Statistically significant.

Figure. Cluster Ranking Plot for Effectiveness and Unacceptability of Treatment (All-Cause Dropouts) of Pharmacologic Treatments for Histamine, Antihistamine-Refractory Chronic Spontaneous Urticaria in Network Meta-analyses



For effectiveness, a higher surface under the cumulative ranking curve (SUCRA) score denotes better treatment for change in urticaria symptoms from baseline. For unacceptability of treatment, a higher score denotes undesirable treatment with a higher risk of all-cause dropouts.

For the change in pruritus and hives severity scores from baseline compared with placebo, network estimates and cluster ranking plot also suggested that ligelizumab, 72 and 240 mg, seem to be the 2 top-ranked interventions (eTable 10 and eFigure 4 and eFigure 5 in the [Supplement](#)). Based on the safety profiles, individuals receiving cyclosporine (OR, 3.45; 95% CI, 1.71-6.97), miltefosine (OR, 3.88; 95% CI, 1.20-12.57), and omalizumab, 150 mg (OR, 1.44; 95% CI, 1.02-2.03), experienced a statistically significantly higher risk of adverse events compared with placebo, but ligelizumab, 24 mg (OR, 0.44; 95% CI, 0.21-0.93), had a protective effect (eTable 11 in the [Supplement](#)). However, we did not find any significant differences among all treatment comparisons for the serious adverse events outcome (eTable 11 in the [Supplement](#)). With respect to the SUCRA values, cyclosporine was ranked as the top undesirable treatment, with a higher risk of adverse events and serious adverse events (eFigure 4 and eFigure 6 in the [Supplement](#)).

Findings from the pairwise meta-analysis were almost identical to the network estimates (eTables 12-15 in the [Supplement](#)), except for the change in pruritus severity (for methotrexate), hives severity (for ligelizumab, 24 mg, and omalizumab, 75 mg), and adverse events (for cyclosporine and omalizumab, 150 mg).

Further Analyses

Post hoc analysis excluding studies with high overall risk-of-bias assessment could not be performed because no included studies were at high risk. Findings from other sensitivity analyses were robust and did not change substantially from the main findings (eTable 16 in the [Supplement](#)). However, there was no association after using a correlation coefficient of 0.5 for the network estimates change in urticaria symptoms (for dapsone and zafirlukast) and pruritus severity (for dapsone).

Table 3. Classification of Pharmacologic Treatments Based on Network Meta-analysis for Use of H₁ Antihistamines in Patients With Refractory CSU

Treatment comparison (reference: placebo)	SMD (95% CI)	Corresponding 95% prediction interval	SUCRA score	Magnitude of effect size ^a	Evidence certainty ^b	Classification of treatment
Ligelizumab, 72 mg	-1.05 (-1.37 to -0.73)	-1.42 to -0.68	85.0	Large	Moderate	Large beneficial outcome
Ligelizumab, 240 mg	-1.07 (-1.39 to -0.75)	-1.43 to -0.70	85.9	Large	Moderate	
Omalizumab, 300 mg	-0.77 (-0.91 to -0.63)	-0.97 to -0.57	69.3	Medium	High	Moderate beneficial outcome
Omalizumab, 600 mg	-0.59 (-1.10 to -0.08)	-1.16 to -0.02	56.8	Medium	Moderate	
Cyclosporine	-0.83 (-1.63 to -0.03)	-1.70 to 0.04	71.2	Large	Low	Small beneficial outcome
Dapsone	-1.14 (-2.06 to -0.22)	-2.14 to -0.14	83.4	Large	Low	
Hydroxychloroquine	-1.26 (-1.85 to -0.66)	-1.91 to -0.60	91.1	Large	Low	
Ligelizumab, 24 mg	-0.40 (-0.77 to -0.02)	-0.82 to 0.03	43.7	Small	Low	
Omalizumab, 150 mg	-0.37 (-0.55 to -0.19)	-0.61 to -0.13	42.3	Small	High	
Zafirlukast	-0.46 (-0.89 to -0.04)	-0.94 to 0.01	48.2	Small	Very low	
Azathioprine	-0.61 (-1.53 to 0.31)	-1.61 to 0.39	56.0	Not estimated (NS)	Low	Trivial to no response (not different from placebo)
Canakinumab	-0.17 (-1.05 to 0.72)	-1.13 to 0.80	31.9	Not estimated (NS)	Low	
Miltefosine	-0.31 (-0.80 to 0.09)	-0.85 to 0.24	37.5	Not estimated (NS)	Moderate	
Omalizumab, 75 mg	-0.17 (-0.37 to 0.03)	-0.43 to 0.08	27.0	Not estimated (NS)	High	
Quilizumab	-0.39 (-1.10 to 0.32)	-1.17 to 0.39	43.8	Not estimated (NS)	Moderate	
AZD1981	0.41 (-0.35 to 1.17)	-0.42 to 1.24	7.8	Not estimated (NS)	Low	
Methotrexate	0.61 (-0.14 to 1.37)	-0.21 to 1.44	3.8	Not estimated (NS)	Moderate	Small harmful outcome
Montelukast	NA	NA	NA	NA	NA	

Abbreviations: CSU, chronic spontaneous urticaria; NA, not applicable; NS, nonstatistically significant; SMD, standardized mean difference; SUCRA, surface under the cumulative ranking curve.

^a For meaningful interpretation of treatment effects, SMD rankings are less than

-0.2 (very small), -0.2 to -0.4 (small), -0.5 to -0.7 (medium), and -0.8 or higher (large).

^b eTable 18 and eAppendix 2 in the [Supplement](#) provide full details of criteria for downgrading quality of evidence.

Evidence for the transitivity assumption was inconclusive owing to limited data and imbalanced treatment comparisons (Table 1; eTable 4 and eTable 5 in the [Supplement](#)). However, all outcome analyses revealed low between-trial heterogeneity ($\tau^2 < 0.04$), except for the unacceptability of treatment, which showed moderate heterogeneity ($\tau^2 = 0.19$). No evidence of inconsistency between the direct and indirect effects for all outcomes was recognized (eTable 17 in the [Supplement](#)). Nonetheless, the comparison-adjusted funnel plot symmetry indicated evidence of small-study effects in most outcomes, except for the change in pruritus severity score (eFigure 7 in the [Supplement](#)).

Evidence certainty for most treatment comparisons was limited mainly because of limitations in evidence findings owing to within-study bias, reporting bias, imprecision, and transitivity (heterogeneity) (eTable 18 in the [Supplement](#)). Across all outcomes, we judged that ligelizumab, 72 or 240 mg, and omalizumab, 75, 150, 300, or 600 mg, had moderate- or high-certainty evidence, whereas other treatments were downgraded to low or very low certainty (Table 3; eTable 18 in the [Supplement](#)).

Taken together, by applying the multidimensional contextualized clinical and methodologic approach, ligelizumab, 72 or 240 mg, was classified as having a large beneficial effect and omalizumab, 300 or 600 mg, was classified as having a moderate beneficial effect (Table 3). Dapsone; hydroxychloroquine; cyclosporine; ligelizumab, 24 mg; omalizumab, 150 mg; and zafirlukast were classified as having a small beneficial effect. However, evidence findings do not support other treatments for H₁ antihistamine-refractory CSU.

Discussion

In this systematic review and NMA, we combined direct and indirect evidence from 23 randomized clinical trials of 2480 participants with H₁ antihistamine-refractory CSU. Based on clinically meaningful evidence by classification of pharmacologic treatment and tradeoff safety profiles of comparisons, the findings of this NMA suggest that ligelizumab, 72 or 240 mg, and omalizumab, 300 or 600 mg, were the most efficacious treatments for H₁ antihistamine-refractory CSU. With respect to the magnitude of effect size and evidence certainty, dapsone; hydroxychloroquine; cyclosporine; ligelizumab, 24 mg; omalizumab, 150 mg; and zafirlukast seem to have a small beneficial effect. However, the use of other treatments is not recommended because of the lack of efficacy or higher risk of adverse outcomes.

Compared with existing primary randomized clinical trials and pairwise meta-analyses, our findings were expanded by comparing 18 different treatment interventions or dosages and placebo in a single framework to investigate the benefits and harms of treatment for H₁ antihistamine-refractory CSU. With respect to study limitations and evidence certainty, a review by Kulthanan et al⁴¹ suggested that cyclosporine is effective, but its clinical utility could be limited by safety profiles. These findings are also supported by our network estimates that the use of cyclosporine increased the risk of adverse events. As a result, we judged the use of cyclosporine as providing a small beneficial effect. Taken together, our network estimates and the review by Patil et al⁴² also noted no significant benefit of

methotrexate for the treatment of CSU in individuals who are refractory to H₁ antihistamine therapy.

In addition, our findings are in line with those from previous pairwise meta-analyses regarding the benefits and safety of omalizumab (the first approved biologic agent for the treatment of CSU), particularly at a dosage of 300 mg in both clinical trials and real-world settings.⁴³⁻⁴⁶ We also highlight information on the use of the novel biologic ligelizumab, in which phase 3 studies are ongoing and recently received the US Food and Drug Administration breakthrough therapy designation in H₁ antihistamine-refractory CSU. Theoretically, mast cells are the primary effector cells that contribute to the pathogenesis of CSU. As expected, the blockade of mast cell activation by the biologics omalizumab and ligelizumab via reduction of free immunoglobulin E can direct and address the mechanisms for hive formation, which is supported by our findings, and provides better outcomes in terms of benefits and harms compared with other treatment comparisons.

Implications for Practice and Future Research

To form the implications for practice and judgment of which pharmacologic treatment is most clinically useful, we formally combined the effectiveness noted in randomized clinical trials with reasonable unacceptability and safety profiles into a single overall summary. Collectively, ligelizumab, 72 or 240 mg (large beneficial effect), and omalizumab, 300 or 600 mg (moderate beneficial effect), can be recommended as first-line treatment owing to their magnitude of effect sizes, evidence certainty, SUCRA values, and the uncertainty of evidence in the forecasts. Dapsone, hydroxychloroquine, cyclosporine, and zafirlukast can be recommended as alternative treatments (small beneficial effects). However, the potentially higher probability of unacceptability of treatment and adverse effects of dapsone, hydroxychloroquine, and cyclosporine should be considered in decision-making.

Based on our comprehensive search approach, however, increased second-generation H₁ antihistamine dose trials as recommended by the 2017 European Academy of Allergology and Clinical Immunology, Global Allergy and Asthma European Network, European Dermatology Forum, and the World Allergy Organization guideline¹ were criticized for methodologic limitations and did not meet our study eligibility criteria. These trials were mainly based on chronic inducible urticaria and were not well defined in terms of refractory CSU.⁴⁷⁻⁵⁰ Hence, according to current evidence, it is unclear whether the up-dosing of second-generation H₁ antihistamines is effective for H₁ antihistamine-refractory CSU.⁵¹

To help inform subsequent international guidelines for the management of CSU, there is a need for head-to-head trials with

high methodologic quality and harmonized design and outcome definitions, which will yield improved network estimates. To date, the results of promising trials of novel biologics are required to establish the effectiveness of such treatments for CSU patients. Moreover, we advocate that evidence from cost-effectiveness research and large collaborative pharmacoepidemiologic studies using real-world evidence is also required, which will inform guidelines, provide policy-based decisions, and help clinicians to optimize effective treatment for people living with CSU.

Strengths and Limitations

To our knowledge, this study is the first application of NMA that sheds unified hierarchies of evidence for H₁ antihistamine-refractory CSU. The strength of our analysis is its comprehensive systematic review, robust design, and focus on clinically relevant symptoms of urticaria. To compare and confirm the potential benefit of higher doses, differences in treatment effects across doses were also investigated in this study.

However, NMA has several limitations. First, treatment comparison nodes were based on a single trial or trials with small sample sizes; thus, the evidence certainty of our analysis is limited by the inherent limitations of individual included trials. Second, although our analyses indicated low between-trial heterogeneity in most outcomes, the genuine variation across the included trials, for instance, the definition of refractory CSU, cannot be ruled out. These issues could have contributed to the assumption of transitivity. Third, poorly reported or 0 events in the safety profiles should be stated, resulting in a less-precise estimation of treatment harms. Fourth, network estimates based on different subpopulations and network meta-regression to estimate the effect modifiers for all outcomes of interest were not possible because of a lack of information and multicollinearity. Fifth, despite a comprehensive search approach, potential small-study effects exist and might contribute to some of the network effect estimates we observed. Sixth, the limited interconnections in the findings from the network estimates should be acknowledged. In this respect, our findings should be interpreted with caution.

Conclusions

Overall, results of this systematic review and NMA suggest that biologics, namely ligelizumab, 72 or 240 mg (large beneficial effect), and omalizumab, 300 or 600 mg (moderate beneficial effect), are effective pharmacologic treatments with respect to the benefits and harms of H₁ antihistamine-refractory CSU.

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