JAMA Dermatology | Original Investigation

Benefits and Harms of Omalizumab Treatment in Adolescent and Adult Patients With Chronic Idiopathic (Spontaneous) Urticaria

A Meta-analysis of "Real-world" Evidence

Michael D. Tharp, MD; Jonathan A. Bernstein, MD; Abhishek Kavati, PhD; Benjamin Ortiz, MD; Karen MacDonald, PhD; Kris Denhaerynck, PhD; Ivo Abraham, PhD; Christopher S. Lee, PhD

IMPORTANCE Omalizumab is indicated for the management of chronic idiopathic urticaria (CIU) (also known as chronic spontaneous urticaria) in adolescents and adults with persistent hives not controlled with antihistamines. The effectiveness of omalizumab in the real-world management of CIU is largely unknown.

OBJECTIVE To quantitatively synthesize what is known about the benefits and harms of omalizumab in the real-world clinical management of CIU regarding urticaria activity, treatment response, and adverse events.

DATA SOURCES Published observational studies (January 1, 2006, to January 1, 2018) and scientific abstracts on the effectiveness of omalizumab in CIU were identified using PubMed, Embase, Web of Science, and Cochrane search engines; references were searched to identify additional studies.

STUDY SELECTION Included studies were observational in design and included at least 1 outcome in common with other studies and at a concurrent time point of exposure to omalizumab. A total of 67 articles (35.2% of those screened) were included in the analysis.

DATA EXTRACTION AND SYNTHESIS PRISMA and MOOSE guidelines were followed; independent selection and data extraction were completed by 2 observers. Random-effects meta-analyses were performed.

MAIN OUTCOMES AND MEASURES Main outcomes were change in weekly Urticaria Activity Score (UAS7; range, 0-42), change in Urticaria Activity Score (UAS; range 0-6) (higher score indicating worse outcome in both scales), complete and partial response rates (percentages), and adverse event rate (percentage).

RESULTS Omalizumab therapy was associated with an improvement in UAS7 scores (−25.6 points, 95% CI, −28.2 to −23.0; $P < .001$; 15 studies, 294 patients), an improvement in UAS scores (−4.7 points, 95% CI, −5.0 to −4.4, $P < .001$; 10 studies, 1158 patients), an average complete response rate of 72.2% (95% CI, 66.1%-78.3%; $P < .001$; 45 studies, 1158 patients) with an additional average partial response rate of 17.8% (95% CI, 11.7%-23.9%; $P < .001$; 37 studies, 908 patients), and an average adverse event rate of 4.0% (95% CI, 1.0%-7.0%; $P < .001$; any level of severity, 47 studies, 1314 patients).

CONCLUSIONS AND RELEVANCE Benefits and safety of omalizumab in the real-world treatment of CIU meet or exceed results gleaned from clinical trials. These real-world data on omalizumab in CIU may help inform both clinical treatment expectations and policy decision making.

JAMA Dermatol. 2019;155(1):29-38. doi:10.1001/jamadermatol.2018.3447
Published online November 14, 2018.

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 132

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Christopher S. Lee, PhD, Boston College Connell School of Nursing, 140 Commonwealth Ave, Chestnut Hill, MA 02467 (csleern@gmail.com).

Chronic idiopathic urticaria (CIU), also known as chronic spontaneous urticaria (CSU), is defined as the development of wheals, angioedema, or both that lasts for at least 6 weeks.[1,2] Symptoms of CIU include swelling, itching, and pain in affected areas as well as general discomfort that negatively influence patients' quality of life.[3,4] Many patients with CIU remain symptomatic for periods lasting up to 5 years despite approved or higher-than-approved doses of H1 antihistamines. Clearly, there is room for improvement in the treatment of CIU.[4]

Omalizumab is a recombinant humanized monoclonal antibody that reduces levels of free IgE and the high-affinity receptor for the Fc region of IgE that are essential in mast-cell and basophil activation in conditions like CIU. Several early, phase 2, randomized, placebo-controlled, multicenter studies of omalizumab have provided evidence of beneficial efficacy on symptoms in patients with CIU who were previously symptomatic despite the use of approved doses of H1 antihistamines.[5,6] In a pivotal phase 3 trial, omalizumab diminished signs and symptoms among patients with CIU who were symptomatic despite the use of approved doses of H1 antihistamines compared with placebo.[7]

While the efficacy of omalizumab for the treatment of CIU has been established, the clinical benefits and harms associated with omalizumab therapy in the real-world management of CIU are less well known, particularly since patients included in trials do not always reflect the complexity of patients with CIU seen in clinical practice. Efficacy-effectiveness gaps (ie, differences in outcomes reported in clinical trials vs real-world practice) are common and confound both clinical and policy-level decision making.[8,9]

In line with our research group's previous systematic review[10] and meta-analysis[11] of omalizumab in severe allergic asthma, we recently completed a systematic review of omalizumab in CIU.[12] The purpose of the present report is to quantitatively synthesize what is known about the benefits and harms of omalizumab as used in real-world management of CIU using meta-analytic techniques, and to provide insight into potential efficacy-effectiveness gaps.

Key Points

Question What is known about the benefits and harms of omalizumab as used in the real-world clinical management of chronic idiopathic urticaria (also known as chronic spontaneous urticaria)?

Findings In this meta-analysis of 67 published reports on real-world effectiveness, omalizumab therapy was associated with an average 25.6-point improvement in weekly Urticaria Activity Score (vs a 14.9 to 22.1 point improvement reported in clinical trials), a 4.7 point improvement in Urticaria Activity Score, a complete response rate of 72.2%, a partial response rate of 17.8%, and an average adverse event rate of 4.0% (vs 2.9%-8.0% reported in clinical trials).

Meaning Benefits and safety of omalizumab in the real-world treatment of chronic idiopathic urticaria meet or exceed the results gleaned from clinical trials.

Methods

Published observational studies and scientific abstracts on the effectiveness of omalizumab in CIU were identified using the PubMed, Embase, Web of Science, and Cochrane search engines and combinations of the search terms "chronic idiopathic urticaria," "chronic spontaneous urticaria," and "omalizumab" (as a MeSH Term and in all fields). To our knowledge, the first reports on omalizumab effectiveness in CIU were published in 2006; thus, the search was conducted for studies published from January 1, 2006, to January 1, 2018.

Reference lists of each report were searched to identify additional omalizumab studies in the context of CIU. The search process was conducted independently by 2 experts in systematic review and observational methodology (K.M. and K.D.). Studies included in this analysis were those that (1) were observational in design, (2) included at least 1 effectiveness metric in common with other studies, and (3) were judged to meet inclusion criteria by consensus of the expert reviewers. This meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),[13] and the MOOSE guidelines for Meta-analyses and Systematic Reviews of Observational Studies (see eChecklist in the Supplement).[14]

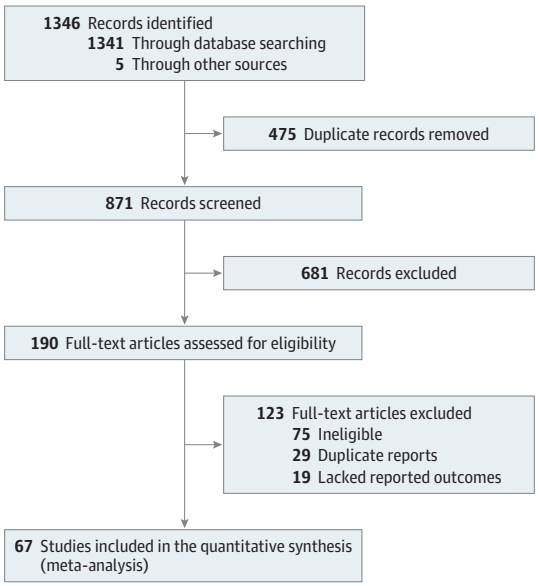
A total of 67 observational studies on the effectiveness of omalizumab in CIU (with or without angioedema) were identified (**Figure 1**).[15-81] As detailed in eTable 1 in the Supplement, there were 19 studies of patients with CIU or CSU specified, 2 of patients with chronic autoimmune urticaria (CAU), 5 of patients with chronic urticaria not otherwise specified (CU NOS), 38 of patients with CIU, CSU, or CU NOS with comorbidities, and another 3 of mixed samples of patients with urticaria. These articles on the effectiveness of omalizumab in CIU were included in our group's systematic review, which also contains additional study description, narrative analysis, and tables of evidence.[12]

Reported Outcomes

Changes in the weekly Urticaria Activity Score (UAS7) (mainly using the daily method) were reported in studies included in the present meta-analysis. The UAS7 asked respondents to rate the number of wheals they have and the intensity of pruritus daily for 1 week. Scores on the UAS7 range from 0 to 42, with higher scores indicating worse CIU.[82] Several studies also reported change in Urticaria Activity Score (UAS) collected at 1 time point; the UAS ranges from 0-6, with higher scores indicating worse CIU. Pretreatment and posttreatment scores were provided such that change in scores could be calculated if not reported. The ranges of minimally important difference on the UAS7 and UAS have been reported as 9.5 to 10.5 and 4.5 to 5.5, respectively.[83]

Several articles have reported quality of life as measured by the Dermatology Life Quality Index (DLQI).[84] The DLQI is a 10-item self-administered questionnaire. A DLQI score is calculated by summing the results of each question to a total between 0 (no effect) and 30 (extremely large effect on quality of life). The range of minimally important difference on the

Figure 1. Study Inclusion Flowchart



DLQI has been reported as 2.24 to 3.10.[85] Several additional articles reported pretreatment and posttreatment quality of life measured by the Chronic Urticaria Quality of Life Questionnaire (CU-Q_2oL). The CU-Q_2oL is a self-administered 23-item questionnaire, with 5 response options on how much patients have been troubled by each problem (from 1, not at all, to 5, very much), with higher scores (ranging from 23 to 115) indicating worse quality of life.[86]

Clinical response to omalizumab was reported in 2 different ways across studies. First, a vast majority of articles reported 3 categories of response: (1) complete response (reported in numbers of cases and most frequently defined as symptom disappearance that commonly could be followed by discontinuation of antihistamine treatment); (2) partial response (reported in numbers of cases and most frequently defined as incomplete symptom improvement, or symptom improvement followed by worsening after discontinuation of antihistamine treatment); and (3) nonresponse or refractory CIU (reported in numbers of cases with no significant improvement). Second, several articles reported response in 2 categories (response vs nonresponse) that were consistent with definitions already detailed such that results could be aggregated across studies.

Finally, adverse events were reported in most of the articles included in this meta-analysis. We synthesize the adverse event rate across studies using safety samples and the raw number of cases of adverse events as reported at any level of severity. As reported elsewhere,[12] the most common adverse events were headache, fatigue, and injection site reaction; anaphylaxis was experienced by 3 patients. See our group's systematic review for more details on specific types of adverse events.[12]

Statistical Analysis

Our approach to this meta-analysis of observational studies of omalizumab in CIU was guided by analytic and reporting criteria.[13,14] Raw published data were extracted, verified in duplicate, and combined into a single database. Two effect size types were extracted from the literature. First, continuous outcomes, such as UAS7 scores, were extracted as mean and standard deviation (SD) prior to and after treatment. When not already calculated, changes in raw scores (eg, of UAS7) as well as in standardized mean difference (ie, Cohen *d*) were computed.[87] Second, counts of events and sample sizes were extracted to calculate rates of response and adverse events. In the case of UAS7 scores only, there were 9 case studies involving 1 or 2 patients that were aggregated into a single result for inclusion in the meta-analysis after sensitivity analyses indicated that doing so would not bias estimates.

Random-effects meta-analyses were performed to quantify pooled effectiveness estimates because this approach takes into account both within-study variance (ie, standard error) and between-study variance (ie, τ^2). Studies were weighted by the inverse of within-study variance plus the between-study variance as calculated by the DerSimonian and Laird method.[88] Weighted pooled effectiveness estimates and 95% confidence interval (CIs) are reported. In addition, *z* scores (weighted mean divided by the standard error of the weighted mean) and associated *P* values are provided for each measure to judge the precision of the pooled estimate across studies. Variation in effectiveness estimates across studies attributed to heterogeneity was quantified using Q and its *P* value as well as I^2, a metric ranging from 0% (ie, all of the heterogeneity is spurious) to 100% (ie, all of the heterogeneity is real). Predictive intervals also were calculated to present the expected range of effects that may be observed in similar studies.[89]

Traditional meta-analytic approaches are problematic when rates approach the limits of 0% or 100%, as several did in this analysis. Accordingly, the Stata command *metaprop* was used in this analysis, which pools proportions and uses the exact binomial method, with Freeman-Tukey double arcsine transformation, to compute precise 95% CIs.[90] Only studies that included more than 1 patient were included in the analyses of rates (clinical response and adverse events) so that CIs could be computed. There also are advantages to using multivariate meta-analysis (ie, simultaneously modeling 2 related outcomes) including being able to incorporate multiple outcomes into 1 model as opposed to conducting multiple meta-analyses wherein the outcomes are considered independent.[91] Hence, we used multivariate meta-analysis[92] for the clinical response to omalizumab wherein we report simultaneous estimates of complete and partial response using the *mvmeta* Stata command. Where possible, we also compared effectiveness estimates by sample inclusion (ie, CIU or CSU specified, CAU, CU NOS, CIU/CSU or CAU with comorbidities, or mixed samples) using a random-effects test for heterogeneity between subgroups. All analyses were performed using Comprehensive Meta-Analysis software, version 3.0 or StataMP, version 15.

Results

Changes in Urticaria Activity

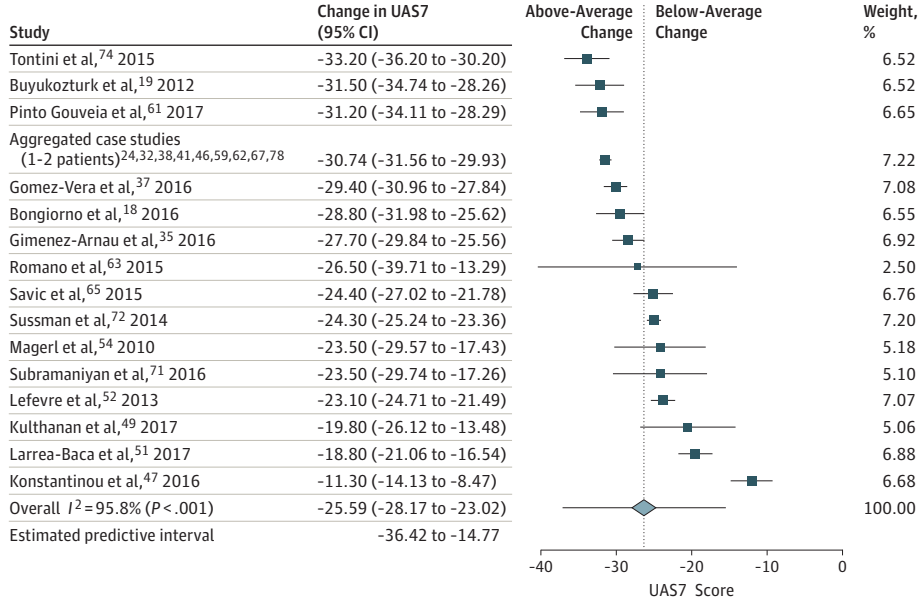
Data on change in UAS7 in response to omalizumab in CIU were available from 15 studies, and aggregated results were avail-

Table. Meta-analysis of Benefits and Harms Summary of Omalizumab Treatment

Characteristic	Patients, No.	Estimate (95% CI)	*z* Score	I^2, %
Change in UAS7	294	−25.6 (−23.0 to −28.2)	19.5	95.8
Change in UAS	245	−4.7 (−4.4 to −5.0)	27.6	75.1
Change in DLQI	84	−13.9 (−10.0 to −17.9)	6.9	94.8
Change in CU-Q_2oL	70	−42.3 (−18.9 to −65.8)	3.5	97.8
Complete response rate, %	1158	76.0 (70.0 to 82.0)	27.0	74.4
Partial response rate, %	908	15.0 (10.0 to 22.0)	7.6	73.8
Adverse events rate, %	1314	4.0 (1.0 to 7.0)	3.6	76.6

Abbreviations: CU-Q_2oL, Chronic Urticaria Quality of Life Questionnaire; DLQI, Dermatology Life Quality Index; UAS, urticaria activity score; UAS7, weekly urticaria activity score.

Figure 2. Change in Weekly Urticaria Activity Score (UAS7) Following Omalizumab Treatment



This forest plot represents the mean (95% CI) change in UAS7 results (squares [horizontal lines]) within individual studies. The size of each square represents the weight, by random effects analysis, of the contribution of each study; exact percentage weights are listed in the Weight column. The overall meta-analytic summary mean (95% CI) is represented by the vertical line (diamond), and the estimated predictive interval, by the solid horizontal lines extending from this diamond.

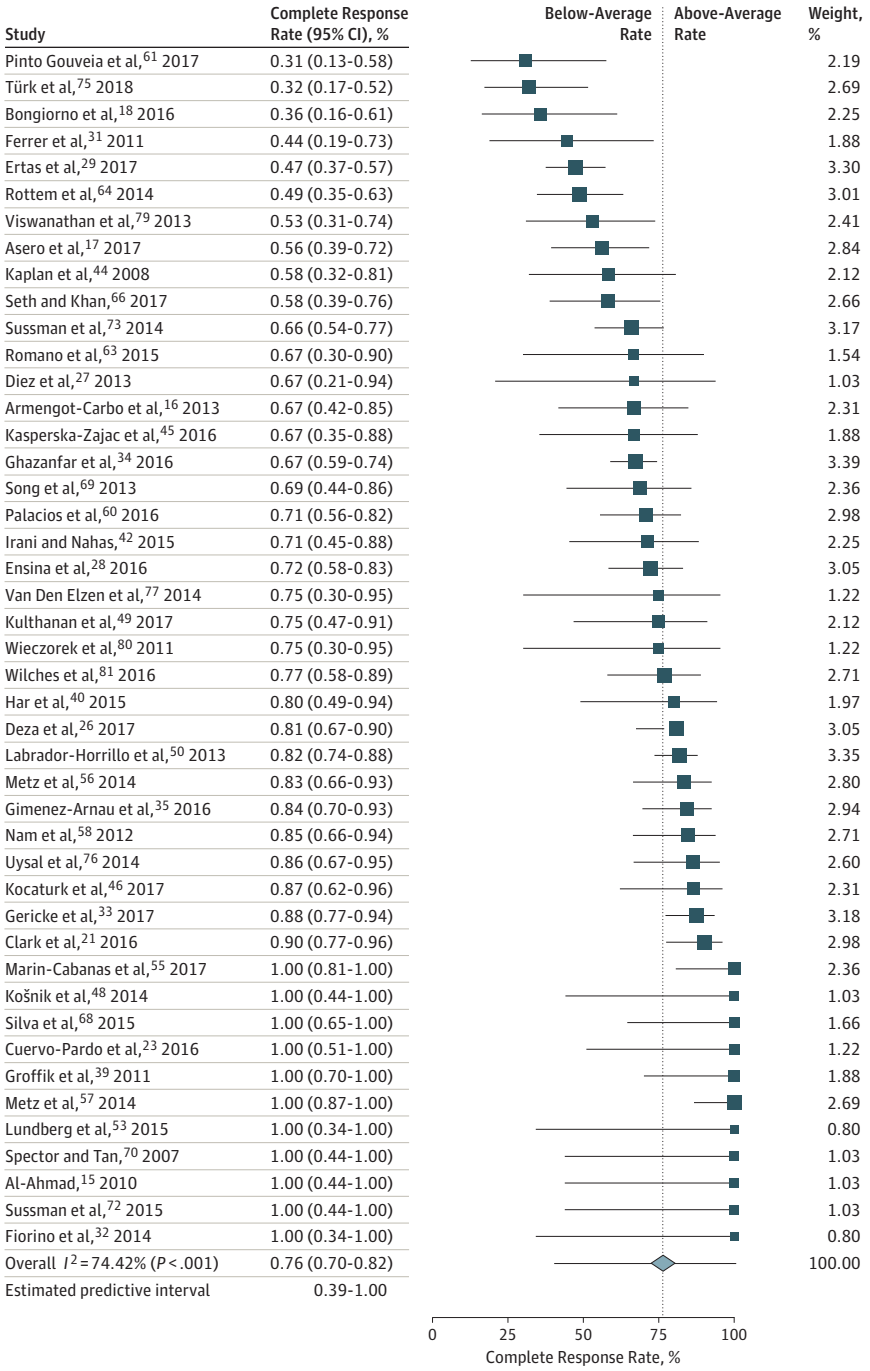
able from 9 single- or double-patient case studies, collectively involving 294 patients (**Table** and **Figure 2**; eTable 2 in the Supplement). Across studies, omalizumab therapy was associated with a 25.6-point reduction in UAS7 scores (95% CI, 23.0-point to 28.2-point reduction; z = 19.47; P < .001). There was significant (Q_{15} = 357.89, P < .001) and substantive (I^2 = 95.8%) heterogeneity in the improvement in UAS7 scores observed across studies; but, omalizumab was equally effective in reducing UAS7 scores across study subgroups (between-group Q = 0.5, P = .79; eFigure 1 in the Supplement). Using standardized mean differences, omalizumab had a large effect in improving urticaria activity as measured by the UAS7 (Cohen d = −4.4; 95% CI, −3.4 to −5.4); z = −8.8, P < .001; Q = 91.5, P < .001; I^2 = 84.7%) (data not shown).

Data on change in UAS scores in response to omalizumab in CIU were available from 10 studies collectively involving 245 patients (Table; eFigure 2 and eTable 2 in the Supplement). Across studies, omalizumab therapy was associated with a 4.7-point reduction in UAS scores (95% CI, 4.4-point to 5.0-point reduction; z = 27.63, P < .001). There was significant (Q_9 = 36.14, P < .001) and substantive (I^2 = 75.1%) heterogeneity in the improvement in UAS scores observed across studies as well as significant differences across study subgroups (between-group Q = 11.1, P = .004). Specifically, omalizumab was more effective in reducing UAS scores in samples of patients with CU NOS (6.0-point reduction; 95% CI, 5.2-point to 6.8-point reduction; z = 14.0, P < .001) compared with samples of patients with CAU (5.0-point reduction; 95% CI, 4.5-point to 5.5-point reduction; z = 19.6, P < .001), and compared with samples where patients had CIU/CSU with comorbidities (4.6-point reduction; 95% CI, 4.5-point to 4.8-point reduction, z = 61.5, P < .001) (eFigure 3 in the Supplement). Using standardized mean differences overall, omalizumab had a large effect in improving urticaria activity as measured by the UAS (Cohen's d = −3.4 (95% CI = -2.5 to −4.4); z = −7.2, P < .001; Q = 57.4, P < .001; I^2 = 84.3%) (data not shown).

Changes in Quality of Life

Data on change in DLQI scores following omalizumab treatment of CIU were available from 6 studies collectively involving 84 patients (Table; eTable 2 in the Supplement). Across studies, omalizumab therapy was associated with a 13.9-point reduction in DLQI scores (95% CI, 10.0-point to 17.9-point reduction; z = 6.9, P < .001). There was significant (Q_5 = 96.3, P < .001) and substantive (I^2 = 94.8%) heterogeneity in the improvement in DLQI scores observed across

Figure 3. Urticaria Complete Response Rate Following Omalizumab Treatment



This forest plot represents the mean (95% CI) complete response rate (squares [horizontal lines]) found within individual studies. The size of each square represents the weight, by random effects analysis, of the contribution of each study; exact percentage weights are listed in the Weight column. The overall meta-analytic summary mean (95% CI) is represented by the vertical line (diamond), and the estimated predictive interval, by the solid horizontal lines extending from this diamond.

studies. Data on change in CU-Q_2oL scores in following omalizumab treatment of CIU were available from 3 studies collectively involving 70 patients (Table; eTable 2 in the Supplement). Across studies, omalizumab therapy was associated with a 42.3-point improvement in CU-Q_2oL scores (95% CI, 18.9-point to 65.8-point reduction; z = 3.5, P < .001). There was significant (Q_2 = 97.3, P < .001) and substantive (I^2 = 97.8%) heterogeneity in the improvement in CU-Q_2oL scores observed across studies.

Clinical Response to Omalizumab

Data on complete response was available from 45 studies involving 1158 patients (Table and **Figure 3**; eTable 2 in the Supplement). Across studies, the average complete response rate was 76.0% (95% CI, 70.0%-82.0%; z = 27.0, P < .001). Although there was significant heterogeneity in complete response rates across studies (Q = 172.0, P < .001, I^2 = 74.4%), there were no significant differences in complete response rate across study subgroups (between-subgroup Q_4 = 3.48, P = .48)

(eFigure 4 in the Supplement). Based on the same 45 studies, the average nonresponse rate was 7.0% (95% CI, 5.0%-10.0%; $z = 8.9$, $P < .001$). Although there was significant heterogeneity in nonresponse rates across studies ($Q = 71.9$, $P < .001$, $I^2 = 37.4\%$), there were no significant differences in nonresponse rates across study subgroups (between-subgroup $Q_4 = 7.2$, $P = .130$) (data not shown).

Data on partial response was available from 37 studies involving 908 patients (Table; eTable 2 and eFigure 5 in the Supplement). Across studies, the average partial response rate was 15.0% (95% CI, 10.0%-22.0%; z = 7.6, $P < .001$). Although there was significant heterogeneity in partial response rates across studies ($Q = 137.3$, $P < .001$, $I^2 = 73.8\%$), there were no significant differences in partial response rates across study subgroups (between-subgroup $Q_4 = 3.8$, $P = .44$) (data not shown). When modeled jointly using multivariate metaregression, the complete response rate was 72.2% (95% CI, 66.1%-78.3%; $z = 23.3$, $P < .001$, $I^2 = 5\%$), and the partial response rate was 17.8% (95% CI, 11.7%-23.9%; $z = 5.7$, $P < .001$, $I^2 = 4\%$) (eFigure 6 in the Supplement).

Adverse Events Following Omalizumab Treatment

Data on adverse events was available from 47 studies involving 1314 patients (Table and **Figure 4**; eTable 2 in the Supplement). Across studies, the average adverse event rate (any level of seriousness/severity) was 4.0% (95% CI, 1.0%-7.0%; $z = 3.6$, $P < .001$). There was significant heterogeneity in adverse event rates across studies ($Q = 196.1$, $P < .001$, $I^2 = 76.6\%$). The adverse event rate was lower in studies of patients with mixed urticaria compared with other study subgroups (between-subgroup $Q_3 = 14.5$, $P < .001$) (eFigure 7 in the Supplement).

Discussion

The objective of this meta-analysis was to quantitatively synthesize what is known about the benefits and harms of omalizumab as used in the real-world clinical management of CIU. Synthesizing results from 67 published reports, we have provided evidence that omalizumab therapy results in large and significant improvements in UAS7, UAS, DLQI, and CU-Q_2oL scores. We also have provided evidence that omalizumab therapy is associated with complete and partial response rates of approximately 72.2% and 17.8%, respectively, when examined simultaneously. Finally, we have provided evidence that across real-world studies of omalizumab in CIU, the average adverse event rate at any level of severity is 4%. The results of this meta-analysis of observational research must be interpreted with an understanding of (1) what is already known about omalizumab in CIU from trials, (2) what these results add to our understanding of real-world use of omalizumab in CIU, and (3) what can be expected in clinical practice.

In the pivotal trial of omalizumab in CIU,[7] patients experienced a 17.9- to 20.7-point average reduction in UAS7 scores and an 8.3- to 10.2-point average reduction in DLQI scores. In the ASTERIA I trial,[93] patients had a 14.9- to 22.1-point average reduction in UAS7 scores and a 6.1- to 10.3-point average reduction in DLQI scores. In the present meta-analysis of real-world studies of omalizumab in CIU, there was a 25.6-point reduction in UAS7 scores, and a 13.9-point reduction in DLQI scores on average. Of particular note, the average changes observed in urticaria activity and quality of life in following omalizumab treatment were numerically greater than the results of prior trials and were also above thresholds of minimally important difference in these outcomes. Thus, in the treatment of CIU, results may be better in real-world practice than in reports of clinical trials. Change in UAS7 assessed from daily vs twice-daily methods are similar enough that only the less burdensome UAS7 should be used in future research.[94,95]

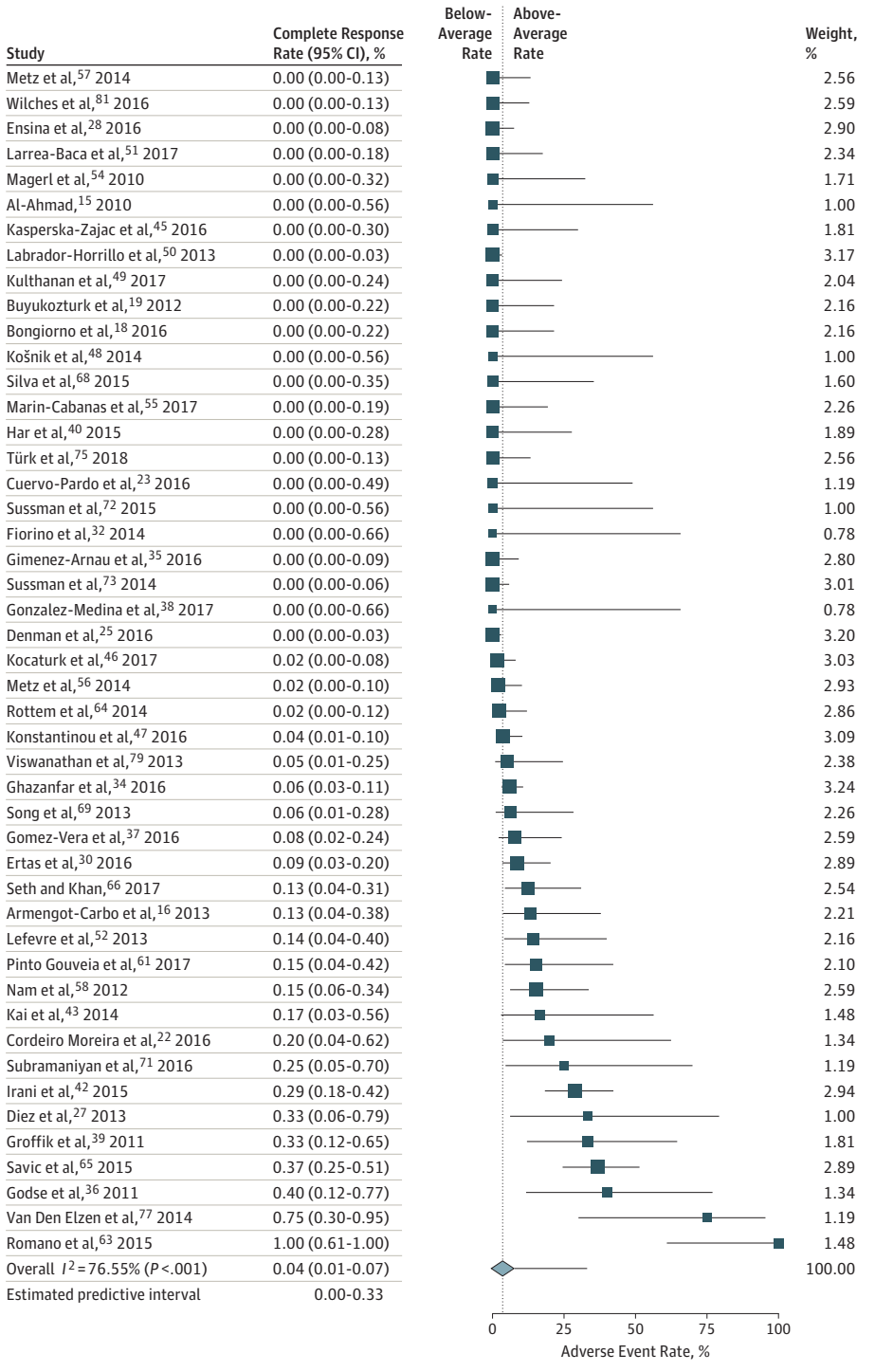
Clinical response has been operationalized in several ways in the CIU literature. Studies included in this meta-analysis most commonly defined complete response as symptom disappearance that could be followed by antihistamine discontinuation, and partial response as incomplete symptom improvement or symptom improvement followed by worsening when discontinuing antihistamines. The complete response rate in our analysis ranged from 70% to 82%, and the partial response rate ranged from 10% to 22%. Likely most informative to practice and policy are our results that the average complete response rate was 72.2% with a partial response rate of 17.8% when modeled together as opposed to considering these outcomes independently. Specifically, these results reflect what might be observed in clinical practice when looking for both complete and partial responses.

Serious adverse event rates from randomized clinical trials involving omalizumab and CIU range from 2.9% to 8% depending on the dosage.[7,93] In the present meta-analysis, there was an adverse event rate (any severity) of 4% with a confidence range of 1% to 7%. Hence, based on these real-world data, omalizumab has a safety profile that is similar to if not better than what was gleaned from prior trial results. Our results need to be interpreted with caution, however, because the monitoring and reporting of adverse events in real-world studies is not always comparable to how safety is evaluated in trials.

Even when protocols identify a complete body of research, meta-analysis results may represent a wide range of the population of interest, concomitant medications, and study characteristics, as well as true variation in treatment effects (ie, heterogeneity).[96] Hence, results of this meta-analysis are more variable than trial results, as evidenced by significant heterogeneity statistics and high I^2 values. Our observations of heterogeneity, however, do not impair our principal findings that across real-world settings treatment of CIU with omalizumab is associated with significant clinical improvement in several outcomes as well as clinical response. But, our findings also indicate that treatment effectiveness should be expected to vary in clinical practice. Hence, we also have included prediction intervals in our results such that clinicians can have a full understanding of the precision of our results as well as the full range of what might be expected in similar studies and in practice (ie, prediction interval).

There are several remaining questions about the real-world effectiveness of omalizumab in CIU. Dosing and duration of omalizumab was highly variable within studies (eTable 1 in the

Figure 4. Adverse Event Rate in Response to Omalizumab in Urticaria



This forest plot represents the mean (95% CI) adverse event rate (squares [horizontal lines]) found within individual studies. The size of each square represents the weight, by random effects analysis, of the contribution of each study; exact percentage weights are listed in the Weight column. The overall meta-analytic summary mean (95% CI) is represented by the vertical line (diamond), and the estimated predictive interval, by the solid horizontal lines extending from this diamond.

Supplement); as more evidence accumulates, the effect of study-level treatment variation on outcomes can be explored. Because other medications were not reported consistently across studies,[12] the influence of concomitant medications on real-world outcomes remains unknown. Studies in this meta-analysis included patients with and without angioedema[12]; we are hopeful to gain more insight into the effectiveness of omalizumab for angioedema with uptake of the new definition of CIU that includes angioedema,[2] and as more studies report angioedema activity. Finally, few studies in this meta-analysis included patients with CIU and inducible urticarias, but not in a way that could be synthesized to understand omalizumab effectiveness under both conditions.

Strengths and Limitations

There are several strengths and limitations of this meta-analysis that must be considered. First, despite our focus on real-world data, our results may not be generalizable to all patient and clinician experiences with omalizumab in the treatment of CIU. Second, real-world study designs, data, and rigor vary considerably. Hence, despite our overall conclusions that omalizumab may be more effective in the real world than what is seen in randomized clinical trials, real-world practice results should be expected to vary, with many patients having complete response but some having less benefit. Third, 2 issues that often surface when examining meta-analyses are the influence of publication and small-sample bias. Regarding our synthesis of response rate, as a representative example, there was no evidence of publication bias when performing common trim and fill procedures,[97] and any bias from small studies[98] was nonsignificant (eFigure 8 in the Supplement). Finally, our goal was to quantitatively synthesize what is known about the benefits and harms of omalizumab as used in real-world clinical management of CIU. We acknowledge, however, potential publication bias favoring effective and safe treatment and the fact that few real-world studies included all outcomes of interest. Hence, the present analysis was based on what data were available, and not necessarily what would be most desirable analytically.

Conclusions

The benefits of omalizumab reported in the real-world treatment of CIU exceed those reported in clinical trials, and the real-world safety profile is similar or superior to that found in trials. These real-world data on the use of omalizumab in CIU may help inform clinical practice treatment expectations as well as policy decision making.

ARTICLE INFORMATION

Accepted for Publication: August 14, 2018.

Published Online: November 14, 2018. doi:10.1001/jamadermatol.2018.3447

Author Affiliations: Department of Dermatology, Rush University Medical Center, Chicago, Illinois (Tharp); Division of Immunology, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio (Bernstein); US Health Economics & Outcomes Research, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey (Kavati); Respiratory Medical Unit, US Clinical Development and Medical Affairs, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey (Ortiz); Matrix45, Tucson, Arizona (MacDonald, Denhaerynck, Abraham, Lee); Department of Public Health, University of Basel, Basel, Switzerland (Denhaerynck); Associate Editor for Quantitative Methods, *JAMA Dermatology* (Abraham); Department of Pharmacy Practice and Science, College of Pharmacy, University of Arizona, Tucson, Arizona (Abraham); Department of Family and Community Medicine, College of Medicine, University of Arizona, Tucson, Arizona (Abraham); Boston College Connell School of Nursing, Chestnut Hill, Massachusetts (Lee).

Author Contributions: Drs MacDonald and Lee had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Tharp, Bernstein, Kavati, Ortiz, MacDonald, Abraham, Lee.
Acquisition, analysis, or interpretation of data: Tharp, Bernstein, MacDonald, Denhaerynck, Abraham, Lee.
Drafting of the manuscript: Bernstein, MacDonald, Abraham, Lee.
Critical revision of the manuscript for important intellectual content: Tharp, Bernstein, Kavati, Ortiz, Denhaerynck, Abraham, Lee.
Statistical analysis: MacDonald, Lee.
Obtained funding: MacDonald, Abraham.
Administrative, technical, or material support: Tharp, Kavati, MacDonald, Abraham, Lee.
Study supervision: Tharp, Abraham.

Conflict of Interest Disclosures: Dr Tharp served as a consultant to Novartis Pharmaceuticals Corporation for work on this study. Dr Bernstein served as a consultant to Novartis for work on this study; he is affiliated with Bernstein Clinical Research Center, LLC, which was under contract with Novartis as a primary investigator to conduct clinical research outside of the submitted work; he has received speaker fees from Novartis as well as consulting fees from Genentech; and he is an author on the Joint Task Force for Practice Parameters for Urticaria guideline and the GALEN international guideline for urticaria. Drs Kavati and Ortiz are employees and stockholders of Novartis. Drs MacDonald, Denhaerynck, Abraham, and Lee are affiliated with Matrix45; by company policy, they are prohibited from owning equity in client organizations (except through mutual funds or other independently administered collective investment instruments) or contracting independently with client organizations; Matrix45 provides services similar to those described in this article to other biopharmaceutical companies on a nonexclusivity basis. No other disclosures are reported.

Funding/Support: This study was supported by Novartis.

Role of the Funder/Sponsor: Novartis had a role in reviewing the manuscript, but had no role in its preparation and approval and no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and decision to submit the manuscript for publication.

Disclaimer: Dr Abraham is Associate Editor for Quantitative Methods, *JAMA Dermatology*, but he was not involved in any of the decisions regarding review of the manuscript or its acceptance.

REFERENCES

1. Greaves MW. Chronic urticaria. *N Engl J Med*. 1995;332(26):1767-1772. doi:10.1056/NEJM199506293322608

2. Zuberbier T, Aberer W, Asero R, et al; Endorsed by the following societies: AAAAI, AAD, AAIITO, ACAAI, AEDV, APAAACI, ASBAI, ASCIA, BAD, BSACI, CDA, CMICA, CSACI, DDG, DDS, DGAKI, DSA, DST, EAACI, EIAS, EDF, EMBRN, ESCD, GA^{2}LEN, IAACI, IADVL, JDA, NVvA, MSAI, ÖGDV, PSA, RAACI, SBD, SFD, SGAI, SGDV, SIAAIC, SIDeMaST, SPDV, TSD, UNBB, UNEV and WAO. The EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73(7):1393-1414. doi:10.1111/all.13397

3. Kang MJ, Kim HS, Kim HO, Park YM. The impact of chronic idiopathic urticaria on quality of life in Korean patients. *Ann Dermatol*. 2009;21(3):226-229. doi:10.5021/ad.2009.21.3.226

4. Maurer M, Weller K, Bindslev-Jensen C, et al. Unmet clinical needs in chronic spontaneous urticaria: a GA^{2}LEN task force report. *Allergy*. 2011;66(3):317-330. doi:10.1111/j.1398-9995.2010.02496.x

5. Saini S, Rosen KE, Hsieh HJ, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol*. 2011;128(3):567-73.e1. doi:10.1016/j.jaci.2011.06.010

6. Maurer M, Altrichter S, Bieber T, et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol*. 2011;128(1):202-209.e5. doi:10.1016/j.jaci.2011.04.038

7. Maurer M, Rosén K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368(10):924-935. doi:10.1056/NEJMoa1215372

8. Nordon C, Karcher H, Groenwold RH, et al; GetReal consortium. The "efficacy-effectiveness gap": historical background and current conceptualization. *Value Health*. 2016;19(1):75-81. doi:10.1016/j.jval.2015.09.2938

9. Eichler HG, Abadie E, Breckenridge A, et al. Bridging the efficacy-effectiveness gap: a regulator's perspective on addressing variability of drug response. *Nat Rev Drug Discov*. 2011;10(7):495-506. doi:10.1038/nrd3501

10. Abraham I, Alhossan A, Lee CS, Kutbi H, MacDonald K. 'Real-life' effectiveness studies of omalizumab in adult patients with severe allergic asthma: systematic review. *Allergy*. 2016;71(5):593-610. doi:10.1111/all.12815

11. Alhossan A, Lee CS, MacDonald K, Abraham I. "Real-life" effectiveness studies of omalizumab in patients with severe allergic asthma: meta-analysis. *J Allergy Clin Immunol Pract*. 2017;5(5):1362-1370.e2. doi:10.1016/j.jaip.2017.02.002

12. Bernstein JA, Kavati A, Tharp MD, et al. Effectiveness of omalizumab in adolescent and adult patients with chronic idiopathic/spontaneous urticaria: a systematic review of 'real-world' evidence. *Expert Opin Biol Ther*. 2018;18(4):425-448. doi:10.1080/14712598.2018.1438406

13. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med*. 2009;151(4):W65-94. doi:10.7326/0003-4819-151-4-200908180-00136

14. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting: Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008

15. Al-Ahmad M. Omalizumab therapy in three patients with chronic autoimmune urticaria. *Ann Saudi Med*. 2010;30(6):478-481.

16. Armengot-Carbo M, Velasco-Pastor M, Rodrigo-Nicolas B, Pont-Sanjuan V, Quecedo-Estebanez E, Gimeno-Carpio E. Omalizumab in chronic urticaria: a retrospective series of 15 cases. *Dermatol Ther*. 2013;26(3):257-259. doi:10.1111/j.1529-8019.2013.01549.x

17. Asero R, Marzano AV, Ferrucci S, Cugno M. D-dimer plasma levels parallel the clinical response to omalizumab in patients with severe chronic spontaneous urticaria. *Int Arch Allergy Immunol*. 2017;172(1):40-44. doi:10.1159/000453453

18. Bongiorno MR, Crimi N, Corrao S, et al. Omalizumab for the treatment of chronic spontaneous urticaria in clinical practice. *Ann Allergy Asthma Immunol*. 2016;117(6):703-707. doi:10.1016/j.anai.2016.08.006

19. Büyüköztürk S, Gelincik A, Demirtürk M, Kocaturk E, Colakoğlu B, Dal M. Omalizumab markedly improves urticaria activity scores and quality of life scores in chronic spontaneous urticaria patients: a real life survey. *J Dermatol*. 2012;39(5):439-442. doi:10.1111/j.1346-8138.2011.01473.x

20. Chicharro P, Rodríguez-Jiménez P, de Argila D. Eficacia y seguridad de omalizumab en un paciente con urticaria crónica espontánea e infección activa por el virus de la hepatitis B. *Actas Dermosifiliogr*. 2017;108(4):383-384. doi:10.1016/j.ad.2016.10.005

21. Clark JJ, Secrest AM, Hull CM, et al. The effect of omalizumab dosing and frequency in chronic idiopathic urticaria: retrospective chart review. *J Am Acad Dermatol*. 2016;74(6):1274-1276. doi:10.1016/j.jaad.2015.12.052

22. Cordeiro Moreira AS, Rosmaninho Lopes de Soares E Silva MI, Pereira Guilherme MA, da Silva Ferreira JA, Fonseca Moreira da Silva JP. Use of omalizumab in the treatment of chronic urticaria. *Eur Ann Allergy Clin Immunol*. 2016;48(6):242-246.

23. Cuervo-Pardo L, Barcena-Blanch M, Radojicic C. Omalizumab use during pregnancy for CIU: a tertiary care experience. *Eur Ann Allergy Clin Immunol*. 2016;48(4):145-146.

24. Dawicka J, Wilkowska A, Grubska-Suchanek E, Nowicki R. Omalizumab in the treatment of chronic spontaneous urticaria—literature review and own experience. *Przegl Dermatol*. 2016;103:64-70. doi:10.5114/dr.2016.57747

25. Denman S, Ford K, Toolan J, et al. Home self-administration of omalizumab for chronic spontaneous urticaria. *Br J Dermatol*. 2016;175(6):1405-1407. doi:10.1111/bjd.15074

26. Deza G, Bertolín-Colilla M, Pujol RM, et al. Basophil FcεRI expression in chronic spontaneous urticaria: a potential immunological predictor of response to omalizumab therapy. *Acta Derm Venereol*. 2017;97(6):698-704. doi:10.2340/00015555-2654

27. Díez LS, Tamayo LM, Cardona R. Omalizumab: opción terapéutica para la urticaria crónica espontánea de difícil control con vasculitis asociada, reporte de tres casos. *Biomedica*. 2013;33(4):503-512. doi:10.7705/biomedica.v33i4.782

28. Ensina LF, Valle SO, Juliani AP, et al. Omalizumab in chronic spontaneous urticaria: A Brazilian real-life experience. *Int Arch Allergy Immunol*. 2016;169(2):121-124. doi:10.1159/000444985

29. Ertas R, Ozyurt K, Ozlu E, et al. Increased IgE levels are linked to faster relapse in patients with omalizumab-discontinued chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2017;140(6):1749-1751. doi:10.1016/j.jaci.2017.08.007

30. Ertaş R, Özyurt K, Yıldız S, Ulaş Y, Turasan A, Avcı A. Adverse reaction to omalizumab in patients with chronic urticaria: flare up or ineffectiveness? *Iran J Allergy Asthma Immunol*. 2016;15(1):82-86.

31. Ferrer M, Gamboa P, Sanz ML, et al. Omalizumab is effective in nonautoimmune urticaria. *J Allergy Clin Immunol*. 2011;127(5):1300-1302. doi:10.1016/j.jaci.2010.12.1085

32. Fiorino I, Loconte F, Rucco AS, et al. Long-term treatment of refractory severe chronic urticaria by omalizumab: analysis of two cases. *Postepy Dermatol Alergol*. 2014;31(5):332-334. doi:10.5114/pdia.2014.44023

33. Gericke J, Metz M, Ohanyan T, et al. Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2017;139(3):1059-1061.e1. doi:10.1016/j.jaci.2016.07.047

34. Ghazanfar MN, Sand C, Thomsen SF. Effectiveness and safety of omalizumab in chronic spontaneous or inducible urticaria: evaluation of 154 patients. *Br J Dermatol*. 2016;175(2):404-406. doi:10.1111/bjd.14540

35. Giménez-Arnau A, Velasco M, Armario Hita JC, Labrador-Horrillo M, Silvestre Salvador JF. Omalizumab: what benefits should we expect? *Eur J Dermatol*. 2016;26(4):340-344. doi:10.1684/ejd.2016.2809

36. Godse KV. Omalizumab in treatment-resistant chronic spontaneous urticaria. *Indian J Dermatol*. 2011;56(4):444. doi:10.4103/0019-5154.84737

37. Gómez-Vera J, Gutiérrez-Ávila SA, Acosta-Gutiérrez DN, López-Tiro JJ, Bedolla-Barajas M. Omalizumab in the treatment of antihistamine-resistant chronic urticaria in adults. *Ann Allergy Asthma Immunol*. 2016;117(2):204-206. doi:10.1016/j.anai.2016.06.010

38. González-Medina M, Curto-Barredo L, Labrador-Horrillo M, Giménez-Arnau A. Omalizumab use during pregnancy for chronic spontaneous urticaria (CSU): report of two cases. *J Eur Acad Dermatol Venereol*. 2017;31(5):e245-e246. doi:10.1111/jdv.14034

39. Groffik A, Mitzel-Kaoukhov H, Magerl M, Maurer M, Staubach P. Omalizumab—an effective and safe treatment of therapy-resistant chronic spontaneous urticaria. *Allergy*. 2011;66(2):303-305. doi:10.1111/j.1398-9995.2010.02472.x

40. Har D, Patel S, Khan DA. Outcomes of using omalizumab for more than 1 year in refractory chronic urticaria. *Ann Allergy Asthma Immunol*. 2015;115(2):126-129. doi:10.1016/j.anai.2015.05.010

41. Iemoli E, Niero F, Borgonovo L, Cossu MV, Piconi S. Successful omalizumab treatment in HIV positive patient with chronic spontaneous urticaria: a case report. *Eur Ann Allergy Clin Immunol*. 2017;49(2):88-91.

42. Irani C, Nahas O. Real-life experience of clinical efficacy of omalizumab use in the Middle East: Should we also be concerned about parasites? Clinical Anti-Inflammatory & Anti-Allergy Drugs [discontinued]. 2015;2(1):43-46. http://www.eurekaselect.com/openurl/content.php?genre=article&issn=2212-7038&volume=2&issue=1&spage=43. Accessed September 4, 2018.

43. Kai AC, Flohr C, Grattan CE. Improvement in quality of life impairment followed by relapse with 6-monthly periodic administration of omalizumab for severe treatment-refractory chronic urticaria and urticarial vasculitis. *Clin Exp Dermatol*. 2014;39(5):651-652. doi:10.1111/ced.12320

44. Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. *J Allergy Clin Immunol*. 2008;122(3):569-573. doi:10.1016/j.jaci.2008.07.006

45. Kasperska-Zajac A, Jarząb J, Żerdzińska A, Bąk K, Grzanka A. Effective treatment of different phenotypes of chronic urticaria with omalizumab: case reports and review of literature. *Int J Immunopathol Pharmacol*. 2016;29(2):320-328. doi:10.1177/0394632015623795

46. Kocatürk E, Can PK, Akbas PE, et al. Management of chronic inducible urticaria according to the guidelines: a prospective controlled study. *J Dermatol Sci*. 2017;87(1):60-69. doi:10.1016/j.jdermsci.2017.02.283

47. Konstantinou GN, Chioti AG, Daniilidis M. Self-reported hair loss in patients with chronic spontaneous urticaria treated with omalizumab: an under-reported, transient side effect? *Eur Ann Allergy Clin Immunol*. 2016;48(5):205-207.

48. Košnik M, Kopač P, Eržen R, et al. Omalizumab in chronic urticaria: our experience and literature review. *Acta Dermatovenerol Alp Pannonica Adriat*. 2014;23(3):57-61.

49. Kulthanan K, Tuchinda P, Chularojanamontri L, Likitwattananurak C, Ungaksornpairote C. Omalizumab therapy for treatment of recalcitrant chronic spontaneous urticaria in an Asian population. *J Dermatolog Treat*. 2017;28(2):160-165. doi:10.1080/09546634.2016.1200710

50. Labrador-Horrillo M, Valero A, Velasco M, et al. Efficacy of omalizumab in chronic spontaneous urticaria refractory to conventional therapy: analysis of 110 patients in real-life practice. *Expert Opin Biol Ther*. 2013;13(9):1225-1228. doi:10.1517/14712598.2013.822484

51. Larrea-Baca I, Gurpegui-Resano M. Mejora de la calidad de vida de los pacientes con urticaria crónica espontánea tratados con omalizumab en vida real. *Enferm Clin*. 2017;27(6):361-368. doi:10.1016/j.enfcli.2017.03.010

52. Lefévre AC, Deleuran M, Vestergaard C. A long-term case series study of the effect of omalizumab on chronic spontaneous urticaria. *Ann Dermatol*. 2013;25(2):242-245. doi:10.5021/ad.2013.25.2.242

53. Lundberg C, Martinez B, Banks TA. Expanding the spectrum: chronic urticaria and autoimmune

polyendocrinopathy-candidiasis-ectodermal dystrophy. *Ann Allergy Asthma Immunol*. 2015;114(4):353-354. doi:10.1016/j.anai.2015.01.014

54. Magerl M, Staubach P, Altrichter S, et al. Effective treatment of therapy-resistant chronic spontaneous urticaria with omalizumab. *J Allergy Clin Immunol*. 2010;126(3):665-666. doi:10.1016/j.jaci.2010.05.047

55. Marín-Cabañas I, Berbegal-de Gracia L, de León-Marrero F, Hispán P, Silvestre JF. Manejo de la urticaria crónica espontánea en la práctica clínica diaria siguiendo las indicaciones de la guía EAACI/GA(2)LEN/EDF/WAO. *Actas Dermosifiliogr*. 2017;108(4):346-353. doi:10.1016/j.ad.2016.12.012

56. Metz M, Ohanyan T, Church MK, Maurer M. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. *J Dermatol Sci*. 2014;73(1):57-62. doi:10.1016/j.jdermsci.2013.08.011

57. Metz M, Ohanyan T, Church MK, Maurer M. Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria. *JAMA Dermatol*. 2014;150(3):288-290. doi:10.1001/jamadermatol.2013.8705

58. Nam YH, Kim JH, Jin HJ, et al. Effects of omalizumab treatment in patients with refractory chronic urticaria. *Allergy Asthma Immunol Res*. 2012;4(6):357-361. doi:10.4168/aair.2012.4.6.357

59. Netchiporouk E, Nguyen CH, Thuraisingham T, Jafarian F, Maurer M, Ben-Shoshan M. Management of pediatric chronic spontaneous and physical urticaria patients with omalizumab: case series. *Pediatr Allergy Immunol*. 2015;26(6):585-588. doi:10.1111/pai.12407

60. Palacios T, Stillman L, Borish L, Lawrence M. Lack of basophil CD203c-upregulating activity as an immunological marker to predict response to treatment with omalizumab in patients with symptomatic chronic urticaria. *J Allergy Clin Immunol Pract*. 2016;4(3):529-530. doi:10.1016/j.jaip.2015.11.025

61. Pinto Gouveia M, Gameiro A, Pinho A, Gonçalo M. Long-term management of chronic spontaneous urticaria with omalizumab. *Clin Exp Dermatol*. 2017;42(7):735-742. doi:10.1111/ced.13173

62. Porcaro F, Di Marco A, Cutrera R. Omalizumab in patient with aspirin exacerbated respiratory disease and chronic idiopathic urticaria. *Pediatr Pulmonol*. 2017;52(5):E26-E28. doi:10.1002/ppul.23615

63. Romano C, Sellitto A, De Fanis U, et al. Omalizumab for difficult-to-treat dermatological conditions: clinical and immunological features from a retrospective real-life experience. *Clin Drug Investig*. 2015;35(3):159-168. doi:10.1007/s40261-015-0267-9

64. Rottem M, Segal R, Kivity S, et al. Omalizumab therapy for chronic spontaneous urticaria: the Israeli experience. *Isr Med Assoc J*. 2014;16(8):487-490.

65. Savic S, Marsland A, McKay D, et al. Retrospective case note review of chronic spontaneous urticaria outcomes and adverse effects in patients treated with omalizumab or ciclosporin in UK secondary care. *Allergy Asthma Clin Immunol*. 2015;11(1):21. doi:10.1186/s13223-015-0088-7

66. Seth S, Khan DA. The comparative safety of multiple alternative agents in refractory chronic urticaria patients. *J Allergy Clin Immunol Pract*. 2017;5(1):165-170.e2. doi:10.1016/j.jaip.2016.08.010

67. Shahzad H. A case of refractory chronic spontaneous urticaria treated with omalizumab. *J Pak Assoc Dermatol*. 2016;26(3):267-278.

68. Silva PM, Costa AC, Mendes A, Barbosa MP. Long-term efficacy of omalizumab in seven patients with treatment-resistant chronic spontaneous urticaria. *Allergol Immunopathol (Madr)*. 2015;43(2):168-173. doi:10.1016/j.aller.2013.11.007

69. Song CH, Stern S, Giruparajah M, Berlin N, Sussman GL. Long-term efficacy of fixed-dose omalizumab for patients with severe chronic spontaneous urticaria. *Ann Allergy Asthma Immunol*. 2013;110(2):113-117. doi:10.1016/j.anai.2012.11.022

70. Spector SL, Tan RA. Effect of omalizumab on patients with chronic urticaria. *Ann Allergy Asthma Immunol*. 2007;99(2):190-193. doi:10.1016/S1081-1206(10)60644-8

71. Subramaniyan R, Chopra A. Treatment of chronic spontaneous urticaria with a single dose of omalizumab: a study of four cases. *Indian J Dermatol*. 2016;61(4):467. doi:10.4103/0019-5154.185745

72. Sussman G, Gonçalo M, Sánchez-Borges M. Treatment dilemmas in chronic urticaria. *J Eur Acad Dermatol Venereol*. 2015;29(suppl 3):33-37. doi:10.1111/jdv.13199

73. Sussman G, Hébert J, Barron C, et al. Real-life experiences with omalizumab for the treatment of chronic urticaria. *Ann Allergy Asthma Immunol*. 2014;112(2):170-174. doi:10.1016/j.anai.2013.12.005

74. Tontini C, Marinangeli L, Cognigni M, Bilò MB, Antonicelli L. Omalizumab in chronic spontaneous urticaria: patient-tailored tapering or planned discontinuation? *Ann Allergy Asthma Immunol*. 2015;115(2):147-148. doi:10.1016/j.anai.2015.05.005

75. Türk M, Yılmaz İ, Bahçecioğlu SN. Treatment and retreatment with omalizumab in chronic spontaneous urticaria: real life experience with twenty-five patients. *Allergol Int*. 2018;67(1):85-89. doi:10.1016/j.alit.2017.05.003

76. Uysal P, Eller E, Mortz CG, Bindslev-Jensen C. An algorithm for treating chronic urticaria with omalizumab: dose interval should be individualized. *J Allergy Clin Immunol*. 2014;133(3):914-5.e2. doi:10.1016/j.jaci.2013.10.015

77. Van Den Elzen MT, Rockmann H, Sanders CJG, Bruijnzeel-Koomen CAFM, Knulst AC. Treatment of chronic urticaria with omalizumab. *Ned Tijdschr Dermatol Venereol*. 2014;24(5):253-256.

78. Vestergaard C, Deleuran M. Two cases of severe refractory chronic idiopathic urticaria treated with omalizumab. *Acta Derm Venereol*. 2010;90(4):443-444. doi:10.2340/00015555-0884

79. Viswanathan RK, Moss MH, Mathur SK. Retrospective analysis of the efficacy of omalizumab in chronic refractory urticaria. *Allergy Asthma Proc*. 2013;34(5):446-452. doi:10.2500/aap.2013.34.3694

80. Wieczorek D, Kapp A, Wedi B. Omalizumab treatment of different urticaria subtypes. *Allergo J*. 2011;20(5):244-248. doi:10.1007/BF03362514

81. Wilches P, Wilches P, Calderon JC, Cherrez A, Cherrez Ojeda I. Omalizumab for chronic urticaria in Latin America. *World Allergy Organ J*. 2016;9(1):36. doi:10.1186/s40413-016-0127-y

82. Młynek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M. How to assess disease activity in patients with chronic urticaria? *Allergy*. 2008;63(6):777-780. doi:10.1111/j.1398-9995.2008.01726.x

83. Mathias SD, Crosby RD, Zazzali JL, Maurer M, Saini SS. Evaluating the minimally important difference of the urticaria activity score and other measures of disease activity in patients with chronic idiopathic urticaria. *Ann Allergy Asthma Immunol*. 2012;108(1):20-24. doi:10.1016/j.anai.2011.09.008

84. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19(3):210-216. doi:10.1111/j.1365-2230.1994.tb01167.x

85. Shikiar R, Harding G, Leahy M, Lennox RD. Minimal important difference (MID) of the Dermatology Life Quality Index (DLQI): results from patients with chronic idiopathic urticaria. *Health Qual Life Outcomes*. 2005;3:36. doi:10.1186/1477-7525-3-36

86. Baiardini I, Pasquali M, Braido F, et al. A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-QoL). *Allergy*. 2005;60(8):1073-1078. doi:10.1111/j.1398-9995.2005.00833.x

87. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, NJ: L. Erlbaum Associates; 1988:567.

88. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188. doi:10.1016/0197-2456(86)90046-2

89. IntHout J, Ioannidis JPA, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open*. 2016;6(7):e010247. doi:10.1136/bmjopen-2015-010247

90. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health*. 2014;72(1):39. doi:10.1186/2049-3258-72-39

91. Jackson D, Riley R, White IR. Multivariate meta-analysis: potential and promise. *Stat Med*. 2011;30(20):2481-2498. doi:10.1002/sim.4247

92. White IR. Multivariate random-effects meta-regression: updates to mvmeta. Stata J. 2011;11(2):255-270. https://econpapers.repec.org/article/tsjstataj/v_3a11_3ay_3a2011_3ai_3a2_3ap_3a255-270.htm. Accessed August 23, 2018.

93. Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol*. 2015;135(1):67-75. doi:10.1038/jid.2014.306

94. Hawro T, Ohanyan T, Schoepke N, et al. The urticaria activity score—validity, reliability, and responsiveness. *J Allergy Clin Immunol Pract*. 2018;6(4):1185-1190.e1. doi:10.1016/j.jaip.2017.10.001

95. Hawro T, Ohanyan T, Schoepke N, et al. Comparison and interpretability of the available urticaria activity scores. *Allergy*. 2018;73(1):251-255. doi:10.1111/all.13271

96. Gagnier JJ, Moher D, Boon H, Beyene J, Bombardier C. Investigating clinical heterogeneity in systematic reviews: a methodologic review of guidance in the literature. *BMC Med Res Methodol*. 2012;12:111. doi:10.1186/1471-2288-12-111

97. Duval S, Tweedie R. A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis. *J Am Stat Assoc*. 2000;95(449):89-98. doi:10.1080/01621459.2000.10473905

98. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629