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Different doses and courses of omalizumab for patients with chronic spontaneous urticaria: A systematic review with meta-analysis and trial sequential analysis

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ABSTRACT

Background: The stability, efficacy, and safety of omalizumab at different doses and regimens for chronic spontaneous urticaria (CSU) are yet to be studied.

Objective: A systematic review (SR) with meta-analysis (MA) and trial sequential analysis (TSA) was performed to assess the efficacy and safety of omalizumab in CSU.

Methods: Randomised controlled trials (RCTs) of administering omalizumab versus placebo for CSU were searched. Random-effects MAs were performed using planned subgroup analyses. TSA was performed to control for the risk of random errors and assess the stability of our MA results. Publication bias was visually assessed using a contour-enhanced funnel plot and the trim-and-fill method. The quality of RCTs was assessed using the Cochrane Risk of Bias Tool 2.

Results: Twelve studies met the inclusion criteria. Omalizumab had remarkable effects on the patient percentage of the weekly urticaria activity score is zero (UAS = 0) [RR 4.64, 95% CI (3.38, 6.37)], percentage of no angioedema-burdened days [MD 3.15, 95% CI (0.10, 6.19], patient percentage of UAS $\leq$6 [RR 3.05, 95% CI (2.46, 3.78)], and patient percentage of the weekly itch severity score minimally important difference (ISS7 MID) [RR 1.50, 95% CI (1.36, 1.66)]. Omalizumab was well tolerated across studies [RR 0.98, 95% CI (0.90, 1.08)]. TSA confirmed the above results, except for "the percentage of no angioedema-burdened day".

Conclusion: Among the different doses and courses assessed, omalizumab (300 mg, 12 weeks) can be recommended as an effective treatment for patients with CSU. However, whether omalizumab improves angioedema requires further investigation. The clinical management of angioedema accompanying CSU requires further attention.

Keywords: Chronic spontaneous urticaria, Omalizumab, Trial sequential analysis, Efficacy, Stability

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INTRODUCTION

Urticaria is characterized by wheals, angioedema, or both,[1] a condition typified in chronic spontaneous urticaria (CSU). The estimated point prevalence of CSU worldwide is 1%.[2] Approximately 20–50% of patients have had the disease for over 5 years.[3] CSU significantly affects the patients' quality of life, sleep, and work performance, and causes psychological problems,[4,5] which burden the healthcare system and society.[6] Second-generation H1-antihistamines are recommended as first-line therapy for CSU.[1,7] Nevertheless, some patients still suffer from evident urticaria symptoms regardless of the use of standard or high-dose H1-antihistamines.[8]

Treatment options for CSU have increased in recent years. Since 2014, omalizumab has been approved for treatment of CSU in a few countries, and evidence of its efficacy and safety has accumulated in recent years;[9] Omalizumab is the only biologic currently approved for use in CSU worldwide. Omalizumab blocks the binding of immunoglobulin E (IgE) to the IgE high-affinity receptor (FcεRI), thereby attenuating mast cell degranulation and relieving hives.[10] In addition, evidence supports that omalizumab is particularly effective in patients with antihistamine-resistant urticaria.[11] Previous findings have revealed a close relation between angioedema and antihistamine resistance.[12] However, whether omalizumab improves angioedema in patients with urticaria remains unknown.[13]

Current randomised controlled trials (RCTs) have different doses, regimens, and treatment observation times, resulting in mixed-quality evidence for the clinical management of omalizumab in patients with CSU. The stability of the evidence for the appropriate dosage and course of omalizumab treatment needs to be more conclusive. Trial sequential analysis (TSA) assessed the impact of sample size on the results of a meta-analysis (MA) to further analyse the stability and efficacy of omalizumab for urticaria, including dose, duration, patient condition, and other factors. Therefore, a rigorous evidence-based approach was used to measure the reliability of the efficacy of omalizumab at different doses and regimens in patients with CSU through a systematic review (SR) and MA with TSA.

MATERIALS AND METHODS

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Supplemental Table S1).[14]

Search strategy

We searched Cochrane, OVID MEDLINE, Embase, and Web of Science for data spanning 1900 to January 2023 using the search terms "omalizumab" and "chronic spontaneous urticaria (CSU)/chronic idiopathic urticaria (CIU)" (Supplemental Appendix S1). Additionally, a clinical trial database (ClinicalTrials.gov) was searched. Literature only in English was included.

Eligibility criteria and outcomes

Inclusion criteria: (1) patients: CSU/CIU; (2) intervention: omalizumab treatment; (3) comparator: placebo treatment; (4) outcomes should include at least 1 of the following: the percentage of the weekly urticaria activity score is zero (UAS7 = 0), UAS7 $\leq$ 6, and the weekly itch severity score minimally important difference (ISS7 MID) responders, percentage of no angioedema-burdened days, and adverse events (AEs); (5) study design: RCT. We excluded literature reviews, SRs, MAs, articles with incomplete data, and articles with endpoints unrelated to our study targets.

Study selection

Two researchers independently screened all identified titles and abstracts, and assessed the full texts of the relevant articles. The reasons for excluding any study were compared and discussed. Disagreements during the review process were resolved through discussions with a third reviewer.

Data extraction

Two assessors independently extracted the data using a data extraction form. We extracted the following items: (1) trial characteristics (author, year of publication, and study design); (2) participant

characteristics (number of patients, sex, and age); (3) intervention characteristics (dose and course of the intervention); (4) outcome data.

Risk of bias assessment

We assessed the risk of bias according to the Cochrane Risk of Bias Tool 2 (RoB2).[15]

Certainty of evidence

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[16] approach to assess the strength of evidence for each outcome, which classified them as high, moderate, low, or very low certainty. Any disagreements were resolved by a third reviewer through consensus.

Data synthesis and analysis

MA was performed using R 4.1.3 "meta" package 6.1.0. RR and MD calculated the count and continuity data, respectively, with 95% CI. Owing to the heterogeneity of treatment protocols across studies, the random-effects model was chosen to integrate RRs or MDs for greater generalisability of the results. Heterogeneity among trials was evaluated by Cochrane's Q statistic with the I^2 test. When $P < 0.1$, $I^2 > 0\%$, it suggested heterogeneity ($0\% < I^2 < 30\%$: minimal heterogeneity; $30\% \leq I^2 < 50\%$: moderate heterogeneity; $50\% \leq I^2 < 75\%$: significant heterogeneity; $I^2 \geq 75\%$: considerable heterogeneity). A contour-enhanced funnel plot, obtained using the trim-and-fill method, was used to test for publication bias.

Subgroup analysis

Subgroup analysis was performed for 5 outcomes based on the following effect modifiers: (1) the adjudication of risk of bias; (2) the dose of omalizumab [75 mg vs. 150 mg vs. 300 mg vs. 600 mg]; and (3) the duration of intervention [4 weeks vs. 12 weeks vs. 16 weeks vs. 20 weeks vs. 24 weeks vs. 28 weeks vs. 40 weeks vs. 48 weeks].

Trial sequential analysis

We conducted TSA using TSA 0.9.5.10 Beta (https://www.ctu.dk/tsa/) to control for type I[17] and type II[18] errors in clinical trials[19,20] and test the credibility of the results. Considering the heterogeneity of the sample size in the included trials, we used the Bigger Staff-Tweedie random effects model (BT). The BT model can appropriately attribute greater weight to RCTs with larger sample sizes. TSA integrates cumulative MA with the calculation of the required information size (RIS) to determine the minimal sample size necessary for validity. It also estimates the cumulative pooled effect, as depicted by the Z-curve, for each successive trial. The upper and lower red lines represent the sequential trial monitoring boundaries. The horizontal green lines represent the traditional boundaries for statistical significance, whereas the triangular red dotted lines mark the futility boundary. (1) When the Z-curve crosses the traditional boundary without intersecting the TSA monitoring boundary and RIS, it indicates a potential false-positive conclusion, which necessitates additional trials to substantiate efficacy and suggests that the current results are uncertain. (2) When the Z-curve crosses both the traditional and TSA boundaries, it indicates that although the cumulative data did not satisfy the RIS, a positive conclusion was reached in advance, diminishing the need for further trials. This suggests that the obtained results are beneficial. (3) When the Z-curve intersects neither the traditional nor the TSA boundary and the RIS, it suggests that there is no significant difference between the groups, necessitating additional studies. This suggests that the current results may be invalid. (4) When the Z-curve crosses the futility boundary and RIS, it suggests that reliable evidence exists of no statistical difference between the 2 groups, which indicates that the current results are invalid. Based on the mean control event rate which was calculated from the control group of the included trials, we calculated the RIS, allowing for type I and II errors of 0.01 (two-sided) and 0.05 (95% power), respectively, which provided more conservative results in the estimated treatment effects.

RESULTS

Study characteristics

We identified 12 eligible studies on the use of omalizumab for CSU (n = 2166).[9,21–31] Fig. 1 illustrates the search results and reasons for excluding the other studies. RCTs were conducted in more than 15 countries between 2011 and 2022, and 91.67% were multicentre trials. The average age of the total population

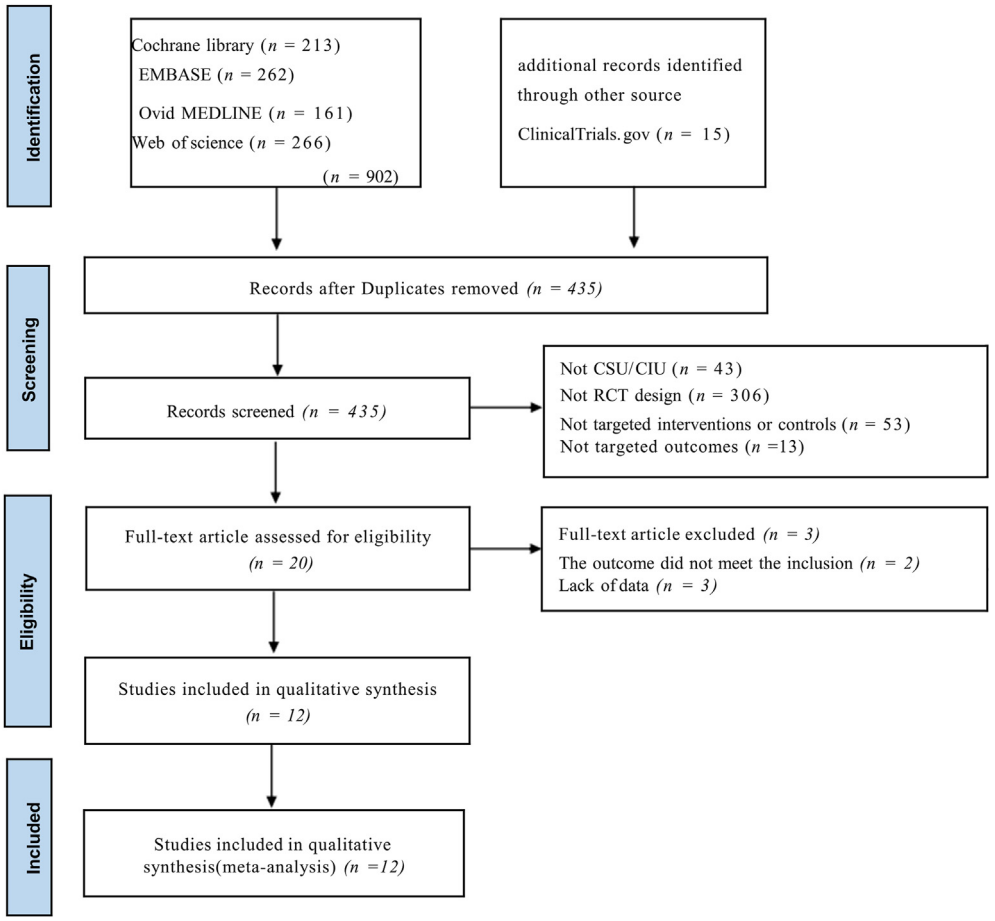

Fig. 1 Study flowchart. Subscript: PRISMA diagram of the literature search.

was 40.39 years, and 70.36% were women. Eight RCTs[9,21,23,25-27,30,31] reported the incidence of angioedema, with 38.86% of the patients reported with angioedema. The total patient loss rates were 10.9% in the omalizumab group and 17.8% in the placebo group. The baseline characteristics are presented in Table 1.

Six RCTs[9,21,23,25,27,30] were judged to contain "low risk" of bias, with other studies rated as "some concerns" in at least 1 domain of potential bias (Supplemental Figure S1). High-certainty evidence revealed that omalizumab substantially improved the percentage of UAS7 = 0 responders; for other outcomes, these studies provided only moderate-certainty evidence (Supplemental Table S2).

Percentage of UAS7 = 0 responders

Nine studies (n = 2036)[9,21-23,25-27,30,31] were included with data available for UAS7 = 0. The results revealed a statistically significant difference in outcomes for patients treated with omalizumab compared with those treated with placebo [RR 4.64, 95% CI (3.38, 6.37), I^2 = 14%] (Table 2). The contour-enhanced funnel plot provided evidence of a reporting bias (Fig. 2A).

In the subgroup analysis of low vs. high risk of bias, the omalizumab group was superior to the placebo group, which is consistent with the overall pooled estimate (Supplemental Figure S2A; Table 2; test of subgroup difference, P = 0.45). Subgroup analysis of different doses of omalizumab revealed that the intervention effect increased in the omalizumab group with increasing dose (test of subgroup difference, P = 0.02) (Fig. 3, Table 2), suggesting a significant difference in effect of omalizumab at different doses. The difference in treatment effects across sessions was not significant (Supplemental Figure S2B; Table 2; test of subgroup difference, P = 0.72).

Author year	Site of study	Type of RCTs	Sample (n)		Female n (%)		Age(y) mean (SD)		OMA (mg)	Time (week)		Outcomes
			T	C	T	C	T	C		Treatment	Measurement	
Yuan, W a 2022[23]	China	Double-blind, placebo-controlled, parallel-group phase III RCT	168	83	115 (68.5)	53 (63.9)	40.4 (12.29)	42.8 (12.32)	300 4wk	12	12	①③④⑤
Yuan, W b 2022[23]	China	Double-blind, placebo-controlled, parallel-group RCT	167	83	108 (64.7)	53 (63.9)	38.8 (12.18)	42.8 (12.32)	150 4wk	12	12	①③④⑤
Janocha, R 2019[21]	Germany	Double-blind, active-controlled and placebo-controlled phase 2b RCT	85	43	66 (78)	31 (72)	41.8 (13.1)	45.4 (11.2)	300 4wk	20	12	①⑤
Casale,T.B 2018[24]	American	Double-blind, placebo-controlled, phase IV RCT	81	53	60 (74.1)	40 (75.5)	43.1 (14.7)	48.5 (13.2)	300 4wk	48	60	⑤
Staubach, P 2018[31]	Germany	Double-blind, placebo-controlled, phase III RCT	44	47	30 (68.2)	33 (70.2)	44.9 (13.7)	41.1 (10.6)	300 4wk	28	28	①⑤
Hausmann, O 2018[26]	Switzerland	Double-blind, placebo-controlled RCT	20	10	8 (40)	8 (80)	41.8 (15.2)	42.4 (13.3)	300 4wk	16	16	①③
Hide, M a 2018[25]	Japanese/ Korean	Double-blind, placebo-controlled, parallel-group Phase III RCT	73	74	40 (54.8)	48 (64.9)	44.6 (14.9)	42.5 (14.3)	300 4wk	12	12	①③④⑤
Hide, M b 2018[25]	Japanese/ Korean	Double-blind, placebo-controlled, parallel-group Phase III RCT	71	74	43 (60.6)	48 (64.9)	43.6 (12.2)	42.5 (14.3)	150 4wk	12	12	①③④⑤

(continued)

Author year	Site of study	Type of RCTs	Sample (n)		Female n (%)		Age(y) mean (SD)		OMA (mg)	Time (week)		Outcomes
			T	C	T	C	T	C		Treatment	Measurement	
Metz, M 2017[29]	Germany	Double-blind, parallel-group, placebo-controlled Phase II RCT	20	10	18 (90)	8 (80)	37.5 (11.0)	41.1 (8.0)	300 4wk	12	12	②⑤
Saini, Sarbjit S a 2015[30]	American/ Germany	Double-blind, parallel-group, placebo-controlled ASTERIA I RCT	78	80	55 (71.4)	52 (65.0)	40.7 (15.2)	40.4 (15.6)	75 4wk	24	12	①②③④⑤
Saini, Sarbjit S b 2015[30]	American/ Germany	Double-blind, parallel-group, placebo-controlled ASTERIA I RCT	80	80	64 (80.0)	52 (65.0)	41.1 (14.0)	40.4 (15.6)	150 4wk	24	12	①②③④⑤
Saini, Sarbjit S c 2015[30]	American/ Germany	Double-blind, parallel-group, placebo-controlled ASTERIA I RCT	81	80	60 (74.1)	52 (65.0)	42.4 (13.2)	40.4 (15.6)	300 4wk	24	12	①②③④⑤
Maurer, Marcus a 2013[9]	Germany	Double-blind, placebo-controlled RCT	82	79	61 (74)	55 (70)	39.7 (15.0)	43.1 (12.5)	75 4wk	12	12	①②③④⑤
Maurer, Marcus b 2013[9]	Germany	Double-blind, placebo-controlled RCT	83	79	65 (79)	55 (70)	43.0 (13.2)	43.1 (12.5)	150 4wk	12	12	①②③④⑤
Maurer, Marcus c 2013[9]	Germany	Double-blind, placebo-controlled RCT	79	79	63 (80)	55 (70)	44.3 (13.7)	43.1 (12.5)	300 4wk	12	12	①②③④⑤
Kaplan, A 2013[27]	American	Double-blind, placebo-controlled, parallel-group RCT GLACIAL	252	84	186 (73.8)	55 (66.3)	42.7 (13.9)	44.3 (14.7)	300 4wk	24	12	①②③④⑤
Saini, S a 2011[22]	American/ Germany	Double-blind, placebo-controlled, parallel-group RCT	23	21	15 (65.2)	17 (81.0)	38.8 (15.5)	41.2 (16.2)	75 4wk	4	4	①⑤

Saini, S b 2011[22]	American/ Germany	Double-blind, placebo-controlled, parallel-group RCT	25	21	17 (68.0)	17 (81.0)	42.9 (15.7)	41.2 (16.2)	300 4wk	4	4	①⑤
Saini, S c 2011[22]	American/ Germany	Double-blind, placebo-controlled, parallel-group RCT	21	21	12 (57.1)	17 (81.0)	40.0 (11.1)	41.2 (16.2)	600 4wk	4	4	①⑤
Maurer, Marcus 2011[28]	Germany	Double-blind, placebo-controlled, parallel-group RCT	27	22	19 (70.4)	19 (86.4)	39.1 (9.0)	42.3 (15.0)	75-375 4wk	24	24	⑤

Table 1. (Continued) Characteristics of the included trials *T: treatment group; C: control group; OMA: Omalizumab; wk: week. ① The percentage of UAS7 = 0 responders; ② The percentage of no angioedema-burdened days; ③ The percentage of UAS7 ≤ 6 responders; ④ The percentage of ISS7 MID responders; ⑤ Adverse events.*

TSA results indicated that the Z-curve of UAS7 = 0 (low risk of bias, 300 mg, and 12 weeks) crossed both the traditional and TSA boundaries and reached the RIS (Fig. 4A, Supplemental figures S3, S4, and S5, Table 2), suggesting that the results are significant and beneficial.

Percentage of no angioedema-burdened days

Three trials[9,27,30] of "lower risk" and 1 trial[29] of "some concerns" evaluated the outcome in 885 patients. Omalizumab significantly improved angioedema compared with placebo [MD 3.15, 95% CI (0.10, 6.19), I^2 = 46%] (Table 2). Subgroup analysis stratified by risk of bias and dose indicated no significant differences between the omalizumab and placebo groups, which was inconsistent with the preliminary analysis (Supplemental Figure S6, Table 2). The TSA revealed that the Z-curve reached the RIS and crossed the futility area (Fig. 4B–Table 2), suggesting that the result is no significant difference and futile. The contour-enhanced funnel plot indicated no obvious publication bias (Fig. 2B).

Percentage of UAS7 ≤ 6 responders

Six trials (n = 1634)[9,23,25-27,30] had outcome data. The pooled RR was 3.05 [95% CI (2.46, 3.78), I^2 = 30%]. No indications of an increased intervention effect in the low-risk group were found in the subgroup analysis according to the risk of bias (Supplemental Figure S7A, Table 2, test of subgroup difference: P = 1). Subgroup analysis was performed according to different dosages, which revealed that the results were influenced by dosage (Supplemental Figure S7B, Table 2, test of subgroup difference: P = 0.01). In the dose range of 75 mg–300 mg/4 weeks, the higher the dose of omalizumab, the better the intervention effect. TSA provided reliable evidence that omalizumab was superior to placebo with an existing cumulative sample size (n = 866) (Supplemental Figure S8A, Table 2), suggesting that the result is benefit. The contour-enhanced funnel plot indicated that the asymmetry may have arisen through heterogeneity (Fig. 2C).

Percentage of ISS7 MID responders

Five trials[23,25,27,30,32] randomized 1609 patients and evaluated the percentage of ISS7 MID responders. A statistically significant beneficial

Items	Number of trials	Number of participants	RR/MD	95% CI	Heterogeneity			Optimum sample size(n)	TSA Result	Test of subgroup difference
					p	τ^2	I^2(%)			
The percentage of complete responders (UAS7 = 0)										
Primary analysis	9	2036	4.64	3.38–6.37	0.28	0.107	14	749	benefit	NA
Subgroup analyses										
Risk of bias										0.45
low risk	6	1740	4.40	3.00–6.37	0.09	0	38	832	benefit	
non-low risk	3	296	5.83	3.11–10.93	0.92	0	0	745	benefit	
Dose of omalizumab										0.02
75 mg	3	363	2.00	0.93–4.72	0.48	0.058	0	781	futile	
150 mg	4	716	3.38	1.92–5.94	0.35	0.062	8	766	benefit	
300 mg	9	1435	6.39	4.49–9.10	0.92	0	0	775	benefit	
600 mg	1	41	13.63	0.82–226.94	NA	NA	NA	NA	NA	
Duration of intervention										0.72
4w	1	89	9.18	1.72–49.00	0.67	0.107	0	642	futile	
12w	7	1856	4.54	3.19–6.48	0.14	0.145	29	745	benefit	
28w	1	91	4.70	1.95–11.33	NA	NA	NA	NA	NA	
The percentage of no angioedema-burdened days										
Primary analysis	4	885	3.05	0.10–6.19	0.07	7.648	46	517	futile	NA
Subgroup analyses										
Risk of bias										0.13
low risk	3	860	2.85	−0.20–5.90	0.10	7.397	44	NA	NA	
non-low risk	1	25	20.40	−2.13–42.93	NA	NA	NA	NA	NA	
Dose of omalizumab										0.74

75 mg	2	276	2.06	−3.63–7.75	0.24	5.162	29	NA	NA	
150 mg	2	280	1.96	−2.5–6.42	0.83	0	0	NA	NA	
300 mg	4	601	4.97	−1.65–11.59	0.01	28.987	72	NA	NA	
The percentage of participants with UAS7 ≤ 6										
Primary analysis	**6**	1634	3.05	2.46–3.78	0.15	0.047	30	813	benefit	NA
Subgroup analyses										
Risk of bias										1
low risk	5	1609	3.05	2.44–3.81	0.15	0.047	30	NA	NA	
non-low risk	1	25	3.06	0.90–10.45	NA	NA	NA	NA	NA	
Dose of omalizumab										0.01
75 mg	2	318	1.72	2.46–3.78	0.30	0.009	8	NA	NA	
150 mg	4	715	2.85	2.07–3.92	0.31	0.17	17	NA	NA	
300 mg	6	1076	3.77	2.94–4.82	0.88	0	0	NA	NA	
The percentage of ISS7 MID responders										
Primary analysis	5	1609	1.50	1.36–1.66	0.13	0.01	33	1196	benefit	NA
Subgroup analyses										
Dose of omalizumab										0.40
75 mg	2	318	1.32	1.01–1.73	0.24	0.01	28	NA	NA	
150 mg	4	715	1.43	1.24–1.66	0.38	0.003	3	NA	NA	
300 mg	5	1051	1.60	1.37–1.88	0.09	0.016	51	NA	NA	

Table 2. Subgroup analysis and trial sequential analysis of the effect of omalizumab compared to placebo on outcomes in CSU patients. *RR: relative ratio; MD: mean difference; TSA: trial sequential analysis; Benefit: Z-curve crosses both the traditional and TSA boundary, or Z-curve crosses the traditional and TSA boundary, and RIS; Futile: Z-curve crosses neither the traditional nor the TSA boundary, and RIS, or Z-curve crosses futility boundary and RIS.*

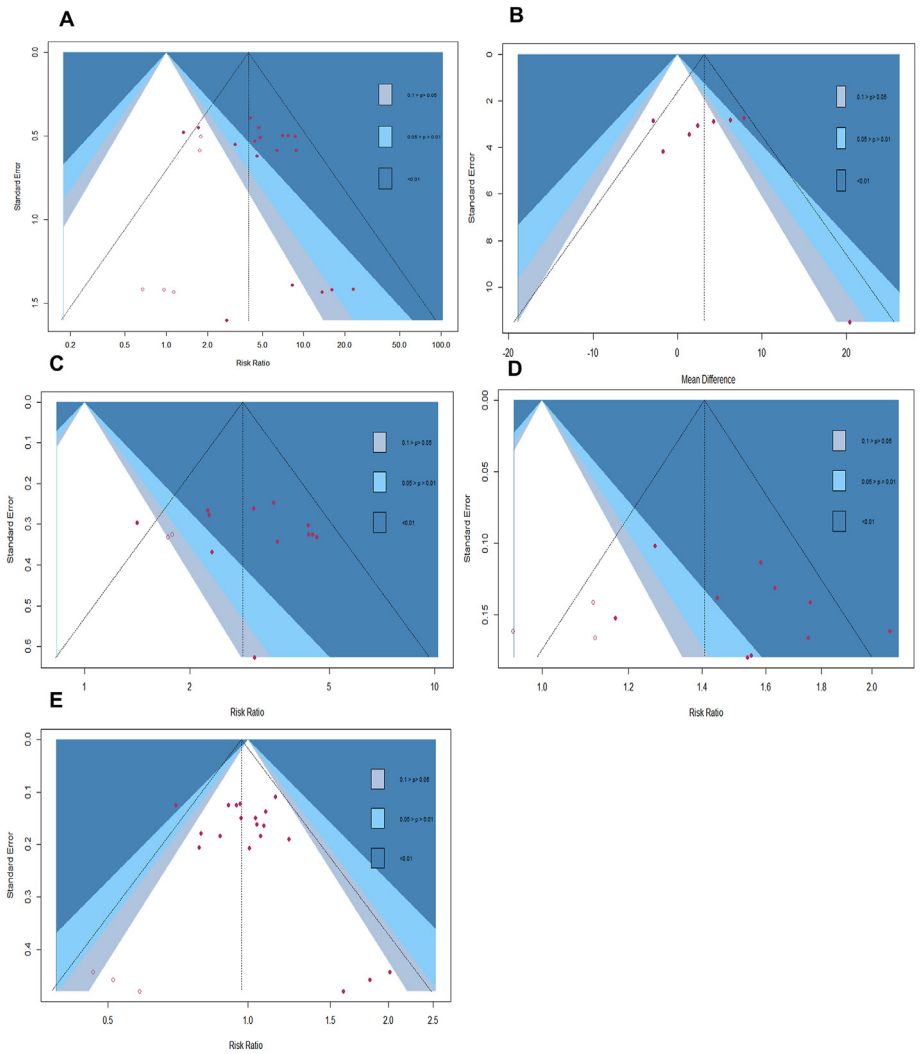

Fig. 2 Contour-enhanced funnel plots [The percentage of UAS7 = 0 responders (A); The percentage of no angioedema-burdened days (B); The percentage of UAS7 ≤ 6 responders (C); The percentage of ISS7 MID responders (D); Adverse events (E)]. Subscript: The solid scatters in the figure represent the existing studies, while the hollow scatters represent the additional studies needed to correct the asymmetry obtained by the shear and complement methods. The steel blue region, light sky blue region, light steel blue region, and blank region, respectively, represent regions with different significance levels, which are, $P < 0.01$, $0.01 < P < 0.05$, $0.05 < P < 0.1$, and $P > 0.1$. The first 3 regions are collectively referred to as statistically significant regions, and the last region is referred to as a statistically significant region.

effect was found from omalizumab group [RR 1.50, 95% CI (1.36, 1.66), I^2 = 33%]. Although no subgroup differences were present for different doses of omalizumab, a dose-dependent pattern was revealed, with 300 mg of omalizumab being the most effective (Supplemental Figure S9, Table 2, test of subgroup difference: P = 0.40). TSA results revealed that the Z-curve crossed both the conventional and TSA boundaries and reached the RIS (Supplemental Figure S8B, Table 2), suggesting that the result is significant and beneficial. The contour-enhanced funnel plot indicated that the asymmetry may have arisen through publication bias (Fig. 2D).

AEs

Eleven studies (n = 2132)[9,21–30] that reported the incidence of AEs in the omalizumab and placebo groups were included. AEs were categorised as common and serious, indicating similar rates between the omalizumab and placebo groups (Supplemental Figure S10, Supplemental Table S3). In addition, the primary pooled RR of AEs for omalizumab compared with those of placebo was 0.98 [95% CI (0.90, 1.08), I^2 = 14%]. The contour-enhanced funnel plot indicated that the asymmetry may have arisen through heterogeneity and publication bias (Fig. 2E).

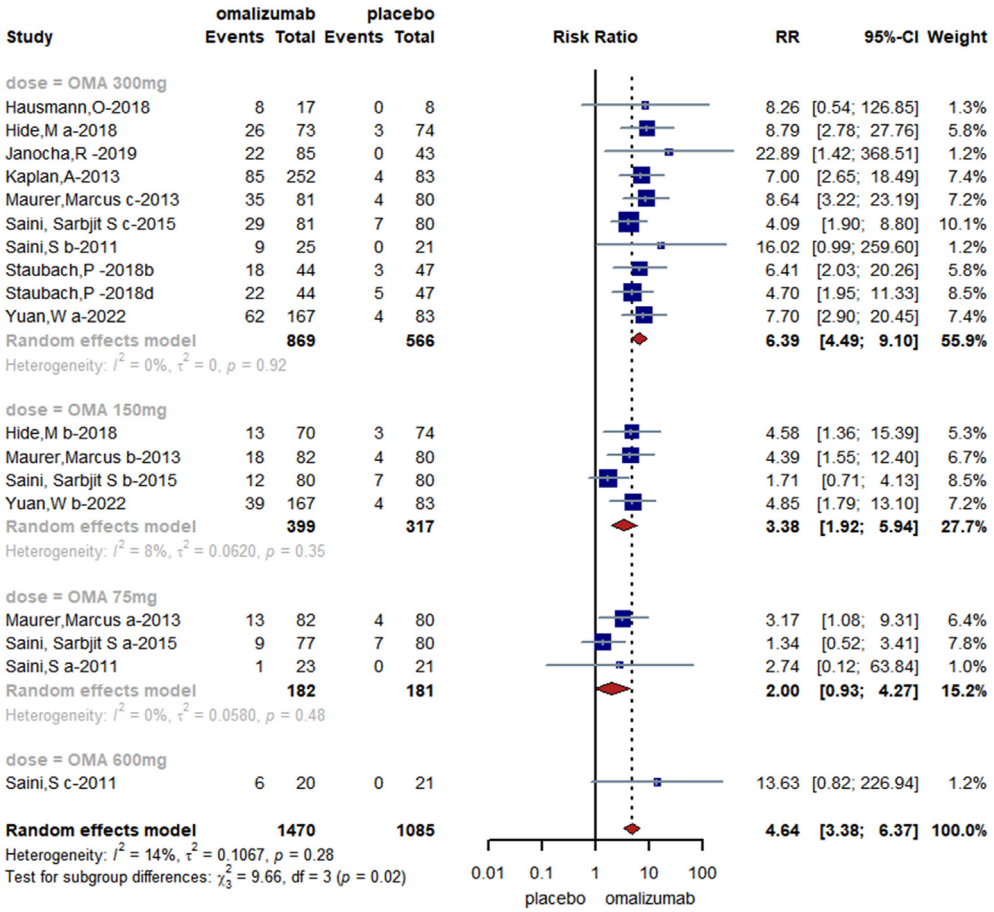

Fig. 3 The percentage of UAS7 = 0 responders: subgroup meta-analysis stratified by the dose of omalizumab. Subscript: Forest plots of the random-effects meta-analysis by subgroup analyses stratified by the dose of omalizumab. Horizontal lines represent 95% of CIs of the RR/MD estimates. The red diamond represents the meta-analysis summary effect estimate; the blue dots represent the RR/MD.

Subgroup analyses stratified by the risk of bias (Supplemental Figure S11A, Supplemental Table S3) and dose revealed no differential effects (Supplemental Figure S11B, Supplemental Table S3). Subgroup analysis based on the time point of observation revealed a differential effect (Supplemental Figure S12, Supplemental Table S3, test of subgroup difference: $P = 0.01$). The omalizumab group exhibited a significantly higher incidence of AEs than the placebo group at 16 weeks (Supplemental Table S3).

According to the TSA, the Z-curve did not reach the RIS (RIS = 2168) but reached the futility area (Supplemental Figure S8C, Supplemental Table S3), suggesting that the result is no significant difference and may be futile.

DISCUSSION

Main findings

This SR, using MA and TSA, focused on informing clinicians and researchers about omalizumab's the stability, efficacy, and safety at different doses and courses for CSU. The study results revealed that 300 mg of omalizumab was more effective and stable than placebo for 12 weeks and demonstrated a placebo-like safety profile. We found that the percentage of responders of UAS7 = 0, UAS7 $\leq$ 6, and ISS7 MID and that of no angioedema-burdened days significantly increased in the omalizumab treatment group, and omalizumab was not significantly different from placebo in tolerability. Patients treated with omalizumab exhibited greater

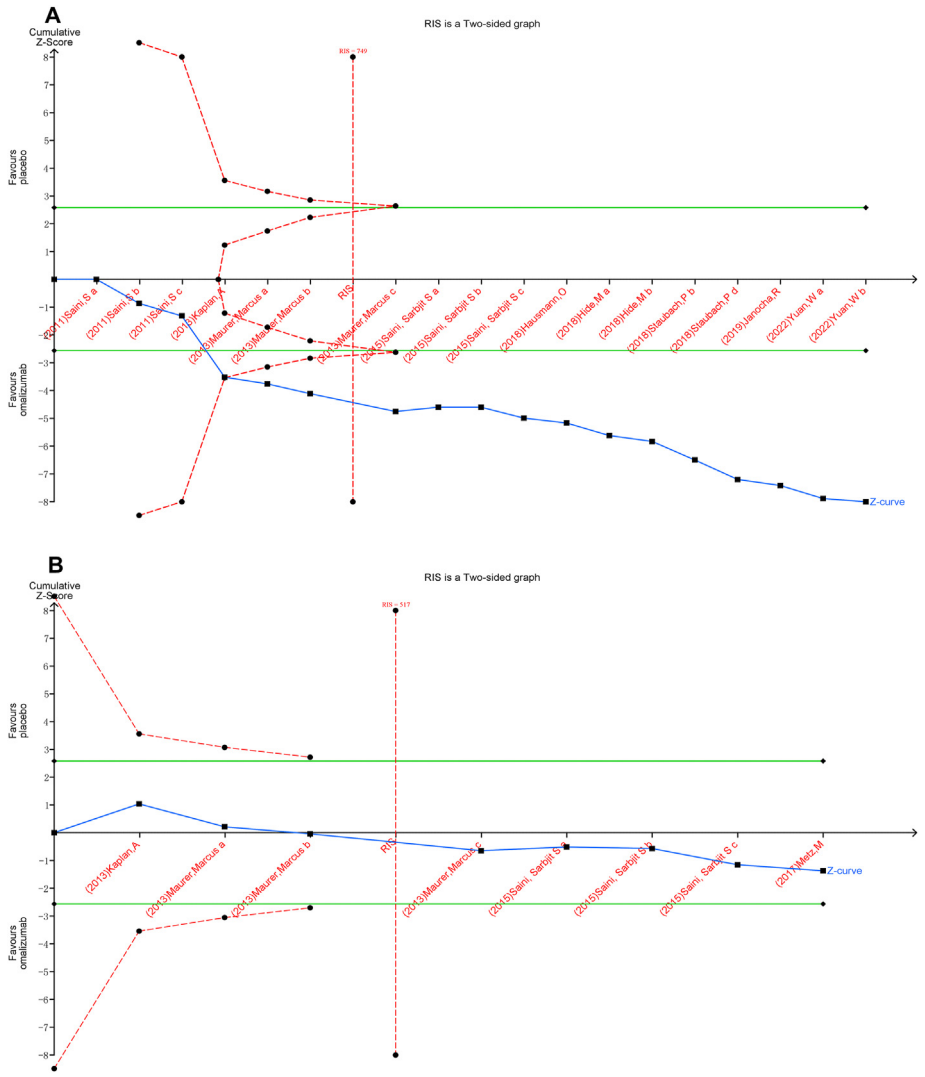

Fig. 4 Trial sequential analysis: the percentage of UAS7 = 0 responders(A); the percentage of no angioedema-burdened days (B). Subscript: The blue curve with black squares represents the Z-curve; the dashed red curves above and below represent trial sequential monitoring boundaries; the horizontal green lines represent the traditional boundaries for statistical significance; the red vertical line represents RIS; and the red dashed lines on the sides closest to the horizontal line represent the boundaries for futility. (A) The cumulative Z-curve crosses the conventional and TSA boundaries. The RIS is achieved. (B) The cumulative Z-curve crosses neither the conventional nor the TSA boundary. The RIS is achieved.

symptom relief than those treated with placebo. Meanwhile, the primary outcomes indicated that the response to omalizumab is dose-dependent.

Further subgroup analysis confirmed the beneficial effects of the majority of outcomes. First, omalizumab was dose-dependent, and exhibited an increase in efficacy with increasing dose for 3 outcomes (the patient percentage of UAS7 = 0, UAS7 $\leq$ 6, and ISS7 MID). Second, although the pooled analysis revealed positive results regarding the percentage of non-angioedema-burdened days, subgroup analyses indicated that the efficacy of omalizumab was compared to placebo, and the 300 mg subgroup showed significant heterogeneity. These findings need to be interpreted cautiously, considering the possibility of bias in the outcomes. Furthermore, no significant dose-cumulative effects of AEs were observed in the subgroup analysis. However, the AEs of omalizumab were significantly elevated when the course of treatment exceeded 16 weeks.

TSA analysis verified that these 4 results were consistent with the pooled effects, and future studies are less likely to change the results except for "the percentage of no angioedema-burdened days". Although the pooled effect was statistically

significant, all subgroups and TSA results revealed that omalizumab did not improve angioedema, suggesting the need for more RCTs. Regarding the TSA of the primary outcome subgroups (UAS7 = 0), the results indicated that the 75 mg group, 4-week treatment group, and high-risk study group did not conclude that omalizumab was significantly better than placebo. In comparison, the results of the 300 mg, 12-week treatment, and low-risk study groups all exhibited a significant and stable efficacy of omalizumab.

Comparison with other studies

Although previous MAs have also suggested that omalizumab was superior to placebo, especially in terms of 2 outcomes (the patient percentage of UAS7 = 0,[13,33–35] UAS7 $\leq$ 6[35]), they did not consider the sufficiency of sample size and reliability of the evidence. The present study builds on this body of previous work by adding a broader range of subgroup analyses and new outcomes that differ from previous studies, applying TSA with GRADE and achieving greater precision in the summary results. For the first time, we evaluated "the percentage of ISS7 MID responders", and only a few SRs assessed the change from baseline in ISS7.[33,35] First, "the percentage of ISS7 MID" may provide a more sensitive and accurate indication of pruritic changes from the patient's perspective. Relatively few studies have thoroughly assessed the robustness and limitations of MID in dermatology.[36] Assessing patient-reported outcome measures from the patient's perspective is an essential strategy for determining the effectiveness of interventions.[37] The MID measures the slightest change in an outcome, which is the improvement or deterioration that patients consider important, and can be used as a reference point for judging the magnitude of a treatment effect in clinical trials[38] and reviews.[39]

Second, omalizumab was considered to reduce concomitant angioedema in several previous studies,[31,40] in contrast to our TSA and subgroup analyses. In adult patients with CSU, the prevalence of angioedema is high, and its presence is an essential predictor of disease course.[41] The duration and severity of CSU are associated.[42] Different studies have agreed that patients with CSU and concomitant angioedema have a prolonged course and long remission times.[43] In addition, a few studies have found that patients with CSU and angioedema have a worse prognosis.[44] Currently, although CSU accompanied by angioedema is gradually being emphasised by researchers and clinicians, and angioedema appears to be one of the best candidates to be further investigated for its validity as a predictor of efficacy and CSU disease course,[41] the efficient treatment of concomitant angioedema is still not clear. The severity of angioedema in patients with CSU is positively correlated with the incidence of refractory spontaneous urticaria. However, its correlation with the efficacy of omalizumab remains controversial and requires further investigation. Third, although very few SRs[11] found omalizumab associate with a higher frequency of adverse reactions, previous MAs have demonstrated that omalizumab had a placebo-like safety profile. Most AEs in omalizumab-treated patients were not serious. This is consistent with our findings; however, our analysis of the GRADE ratings revealed that the quality of this evidence was not considered high because of the imprecision of the results, such as the small sample size in certain studies.

Furthermore, this was the first MA to apply TSA to verify the robustness of omalizumab in CSU. Traditional MAs ignored statistical efficacy,[45] and the error in false-positive findings for traditional MAs was approximately 25%.[46] The TSA included in the present review provides essential evidence for the use of omalizumab treatment in patients with CSU to reduce unnecessary medical and research costs. In addition, this study applied GRADE to confirm the robustness of the evidence for improved complete remission rates with omalizumab.

Implications for practice and future research

The latest guidelines clearly state that the goal of CSU treatment is complete disease control (UAS7 = 0).[1] We found that 300 mg omalizumab for 12 weeks significantly and consistently increased the percentage of UAS7 = 0 responders with CSU, which is consistent with updated international guidelines.[1] However, the guidelines in a few countries only consider omalizumab as a potential new treatment for CSU, without specific dosage recommendations.[47] The differences in attitudes

towards the use of omalizumab in different guidelines suggest that a consensus is still required on the regulated use of this drug. Our study provides new evidence of the stability and efficacy of omalizumab.

In addition, our results indicated that omalizumab did not significantly alleviate angioedema. Although certain studies have suggested that omalizumab in patients with CSU and angioedema should be maintained for at least 12 months before initiating discontinuation,[8] the specific clinical value and efficacy of omalizumab in angioedema remain unclear and need to be further validated using more clinical samples. Moreover, the current clinical treatment for angioedema should be appreciated more.[48]

Although real-world data on omalizumab for CSU have been globally reported in several regions and countries, and 300 mg of omalizumab has been shown to be the optimal intervention for chronic urticaria through risk-benefit assessment,[49] additional population data are required to understand the true efficacy of omalizumab and to help better investigate potential efficacy-related predictors.[13,50] In addition, questions about the differences in the effects of omalizumab in different patients and symptoms and differences in safety at different treatment stages still need to be addressed in future high-quality studies.

Limitations

We included studies with methodological limitations and found evidence that RCTs with a low risk of bias reported significantly different effects. Second, 2 studies[22,27] used maintenance treatment with conventional antihistamines, which may have inflated the statistical validity. Third, although TSA supported certain MA results in this study, the reliability of the TSA results may have been compromised by the overall low quality of a few included RCTs. Finally, the asymmetrical funnel plots suggest that a small study bias may be present, leading to an increased risk of overestimating the effect of omalizumab.

CONCLUSIONS

Omalizumab at 300 mg for 12 weeks was safe and effective in improving the percentage of patients with UAS7 = 0. Combining results of the TSA and GRADE analyses, this evidence was reliable and stable. Regarding the percentage of days without an angioedema burden, we could not demonstrate any significant beneficial effect on angioedema. More well-performed clinical studies on whether omalizumab improves angioedema are required. These findings may aid in clinical treatment and research decisions.

Abbreviations

CSU, Chronic spontaneous urticaria; CIU, Chronic idiopathic urticaria; TSA, Trial sequential analysis; SR, Systematic review; MA, Meta-analysis; RCTs, Randomized controlled trials; UAS7 = 0, Weekly urticaria activity score is zero; UAS7 $\leq$ 6, Weekly urticaria activity score is less than or equal to 6; ISS7 MID, Weekly itch severity score minimally important difference (defined as a reduction from baseline is greater than or equal to 5 points); AEs, Adverse events; IgE, Immunoglobulin E; RoB 2, Risk of bias 2; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RR, Relative ratio; MD, Mean difference; 95% CI, 95% confidence interval; BT, Bigger Staff-Tweedie; RIS, Required information size.

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Data availability statement

The data and material used for this meta-analysis were obtained from the articles in our list of references. The datasets used in this study are available from the corresponding author upon reasonable request.

Author contributions

Yunzhou Shi and Ying Li had full access to all of the data in the study and took responsibility for the data's integrity and the data's accuracy. Concept and design: Yunzhou Shi and Ying Li. Acquisition, analysis, or interpretation of data: Huilin Liu, and Peiwen Xue. Drafting of the manuscript: Haiyan Qin, and Xianjun Xiao. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Haiyan Qin, and Di Qin. Obtained funding: Yunzhou Shi and Xianjun Xiao. Supervision: Yunzhou Shi and Ying Li.

Ethics approval
Not applicable. There were no human or animal subjects involved.

Authors' consent for publication
All authors agreed to publication of this work in World Allergy Organization Journal.

Declaration of competing interest
The authors have no conflict of interest to declare.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100898.

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