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Efficacy and safety of medications for antihistamine-refractory chronic spontaneous urticaria: a systematic review and network meta-analysis

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Summary
Purpose Most medications for antihistamine-refractory chronic spontaneous urticaria (CSU) have not been compared head-to-head. This systematic review and network meta-analysis evaluates their relative efficacy and safety.
Methods Electronic databases were searched until 05 May 2022 for randomized controlled trials investigating systemic medications for antihistamine-refractory CSU. The change in the urticaria activity score over seven days (UAS7) and occurrence of adverse events were compared between treatments using random-effects network meta-analysis models.
Results In all, 32 studies with 3641 patients receiving 31 different systemic medical interventions were included. Among currently available drugs, omalizumab 300 mg injected every 4 weeks and cyclosporine 3–5 mg/kg daily per os were most effective in reducing the UAS7 with a reduction of –10.45 (95% confidence interval [CI]: –12.35, –8.55) and of –10.40 (95% CI: –19.4, –1.4) compared to placebo. Similar efficacies were shown by the nonapproved agents ligelizumab 72 mg injected every 4 weeks (–11.67, 95% CI: –16.80, –7.15) and fenebrutinib 400 mg daily per os (–9.50, 95% CI: –17.56, –1.44). The odds ratio for the occurrence of an adverse event with placebo as comparator was 1.09 for omalizumab (95% CI: 0.83, 1.42), 2.16 for cyclosporine (95% CI: 0.77, 6.07: GRADE; moderate certainty), 0.89 for ligelizumab (95% CI: 0.47, 1.69), and 2.14 for fenebrutinib (95% CI: 0.62, 7.38) in the mentioned dosages.
Conclusion Omalizumab 300 mg injected every 4 weeks and cyclosporine 3–5 mg/kg daily per os are the most effective currently available drugs for antihistamine-refractory CSU. Cyclosporine shows a relatively less favorable safety profile.

Keywords Chronic urticaria · Drug monitoring · Biostatistics · Epidemiologic methods · Treatment comparison

The authors Dr. Justin G. Schlager and Prof. Dr. Lars E. French contributed equally to the manuscript.

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Abbreviations

CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CSU	Chronic spontaneous urticaria
DLQI	Dermatology Life Quality Index
EMA	European Medicines Agency
FDA	Food and Drug Administration

IgE	Immunoglobulin E
UAS7	Urticaria activity score over seven days

Introduction

Chronic spontaneous urticaria (CSU) is characterized by the spontaneous occurrence of mast cell-driven wheals, angioedema, or both for longer than 6 weeks [1]. There is a lifetime prevalence of 0.5–1% and a serious compromise in the quality of life due to pruritus, the unpredictability of attacks, sleeping difficulties, fatigue, and esthetic impairment [2]. While several mast cell mediators may be involved, histamine binding to H_1 receptors on endothelial cells and sensory nerves is most relevant in the development of symptoms [3]. H_1 antihistamines have thus been used for decades in the treatment of CSU. The development of second-generation H_1 antihistamines helped to reduce unpleasant anticholinergic effects and sedative actions. The current first-line therapy consequently consists of nonsedating antihistamines [1]. Unfortunately, around half of patients continue to have symptoms even after a 4-fold increase of the licensed antihistamine dosage [4], which is recommended as second-line therapy [1]. Systemic medications applied for treating antihistamine-refractory CSU include immunosuppressive drugs such as cyclosporine and now also the immunomodulatory agent omalizumab, which targets immunoglobulin E (IgE) [5]. Other recently investigated immunomodulatory agents, such as ligelizumab or fenebrutinib, have not been approved for the treatment of antihistamine-refractory CSU by the European Medicines Agency (EMA) or the U.S. Food and Drug Administration (FDA) yet. Independently of the approval state, most medications for the treatment of antihistamine-refractory CSU have not been compared head-to-head. Therefore, evaluating the relative efficacy and safety is challenging.

The objective of this systematic review and network meta-analysis was to assess the relative efficacy and safety of systemic treatments for antihistamine-refractory CSU.

Materials and methods

Eligibility criteria

Population

Studies including patients with antihistamine-refractory chronic spontaneous urticaria were eligible. Studies which included patients with inducible forms of chronic urticaria, such as cholinergic or aquagenic urticaria [6], were excluded.

Interventions and comparator

Interventions of interest included systemic immunosuppressive or immunomodulatory medications as monotherapy or combination therapy. Comparators could be an active comparator, an antihistamine agent, or placebo. Antihistamine agents could also be used as background therapy.

Study design

Placebo-controlled and head-to-head randomized controlled trials investigating the efficacy and/or safety of at least one systemic therapy for the treatment of antihistamine-refractory CSU were included. Studies with a nonrandomized design, studies with a run-in period with a systemic immunosuppressive of immunomodulatory therapy, animal studies, meeting abstracts, trials with trial registration entry but early termination, and comments were excluded.

Outcomes

The primary efficacy outcomes included the urticaria activity score over 7 days (UAS7) [7] and complete response, as defined in the included studies. The primary safety outcomes were occurrence of at least one adverse event during the trial, occurrence of at least one serious adverse event, and withdrawal due to an adverse event. The weekly itch severity score, weekly number of hives score [7], and Dermatology Life Quality Index (DLQI) [8] were secondary efficacy outcomes.

Search strategy, screening of references, data extraction, and data availability

Details can be found in Online Appendix A. In short, eligible trials were searched in MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) until 05 May 2022. Screening of references and data extraction was performed in duplicate. Data is available upon request.

Data analysis

Effect size estimation for pairwise treatment comparisons within studies

For continuous outcomes, the difference in the mean change from baseline between treatments with standard error was calculated as effect size. If the median change from baseline was available instead of the mean change from baseline, the median was used as substitute for the mean since we assumed symmetrical distribution [9, 10]. Because we further assumed normal distribution, the interquartile range was expected to represent 1.35 standard deviations and the range 4 standard deviations [9, 11]. If the change from baseline was not available, it was calculated using the baseline and follow-up values.

For dichotomous outcomes, the odds ratio was calculated as effect size using information on sample size and affected patients.

Network meta-analysis

To enable head-to-head comparisons for all treatments, a frequentist random-effects network meta-

analysis model was created for each outcome. The reference group was placebo. A network graph was generated to visualize the overall structure of the network. A forest plot was created to display the effect size of each treatment relative to placebo. All head-to-head comparisons were summarized in a league table. Moreover, the treatments were ranked according to *P*-scores [12]. These should be interpreted in the light of the effect sizes.

Subgroup and sensitivity analysis

Subgroup analyses for adolescents, adults, and patients on long-term treatment (>16 weeks) were planned. Corresponding to the network meta-analysis of Drucker et al. on systemic immunomodulatory treatments for atopic dermatitis [13], a treatment duration of more than 16 weeks was defined as long-term treatment. In addition, a sensitivity analyses with the exclusion of studies with high risk of bias was conducted.

Quality of evidence

Cochran's Q statistic was used to test for heterogeneity in the network (within designs). Net splitting was applied to evaluate inconsistency (between designs).

The risk of bias in individual studies was evaluated for each outcome by two reviewers (B.K. and J.F.) using the revised Cochrane Risk of Bias Tool 2 for randomized trials [14]. A third reviewer (J.S.) was consulted if discrepancies between the two reviewers could not be solved by discussion.

The risk of publication bias across studies was assessed for each outcome using Egger's regression test in a comparison-adjusted funnel plot.

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group approach was used to rate the certainty in all treatment effect estimates relative to placebo [15].

Software

The code for the statistical analysis was written in R language, version 4.0.3, by one reviewer (B.K.). Functions of the meta, netmeta, robvis, and ggplot2 R packages were included in the code. An alpha (α) level of 0.05 was set for reaching statistical significance, which corresponds to a 95% confidence interval of the difference in means without inclusion of zero.

Protocol

The protocol for this systematic review and meta-analysis was published in PROSPERO (CRD4202021 3897). Changes to the protocol are summarized in Online Appendix B. All changes were made before data analysis.

Results

Included studies and patients

The search strategy revealed 1176 references. After title, abstract, and full text review, 32 eligible studies with 3641 randomized patients were included [16–47]. The screening process including reasons for exclusion is summarized in Fig. 1. Included studies differed in terms of clinical research phase, primary and secondary endpoints, and inclusion of adults only or both adults and adolescents. The main characteristics of all 32 included studies are listed in Table 1. Details of each study can be found in Appendix C.

Urticaria activity score over 7 days

Network meta-analysis

Sixteen studies with 2659 randomized patients qualified for the network meta-analysis on the change in the UAS7. Fig. 2 shows the structure of the network with 17 treatments and how these were compared with each other in the original studies. Placebo was used by most studies as comparator [21–24, 27, 29, 30, 32–35, 37, 40, 41, 47], several studies compared different dosages of the same agent [21, 24, 32, 33, 35, 40, 41, 44, 47], and only a three studies directly compared different systemic medications [21, 32, 39]. Fig. 3 shows the efficacy of the different medications in reducing the UAS7 in relation to placebo and the ranking of treatments according to the *P*-score. Omalizumab injected every 4 weeks in a dosage of 300 mg was ranked the most effective currently available drug for the reduction of the UAS7 with a score reduction of –10.45 (95% CI: –12.35, –8.55) compared to placebo. Cyclosporine in an oral dosage of 3–5 mg/kg daily was ranked the second most effective currently available drug with a score reduction of –10.40 (95% CI: –19.40, –1.40) compared to placebo. Ligelizumab 72 mg injected every 4 weeks (–11.67, 95% CI: –16.80, –7.15; GRADE: moderate certainty) and daily oral administration of fenebrutinib 400 mg (–9.50, 95% CI: –17.56, –1.44; GRADE: moderate certainty) showed promising efficacies in reducing the UAS7 compared to placebo; however, published data showed no significant differences in efficacy compared to omalizumab 300 mg injected every 4 weeks or cyclosporine 3 to 5 mg/kg daily per os. Estimated mean differences for the change in UAS7 for all possible treatment comparisons are listed in Online Appendix D Table D1.

Quality of evidence

Cochran's Q statistic did not show significant heterogeneity in the network (Q = 6.24; degrees of freedom (df) = 6; $p = 0.397$). Net splitting showed inconsistency in the network for the comparisons between ligelizumab in different dosages and omalizumab 300 mg every 4 weeks as well as placebo (Online Appendix D Table D2). Online Appendix D Figure D1 displays

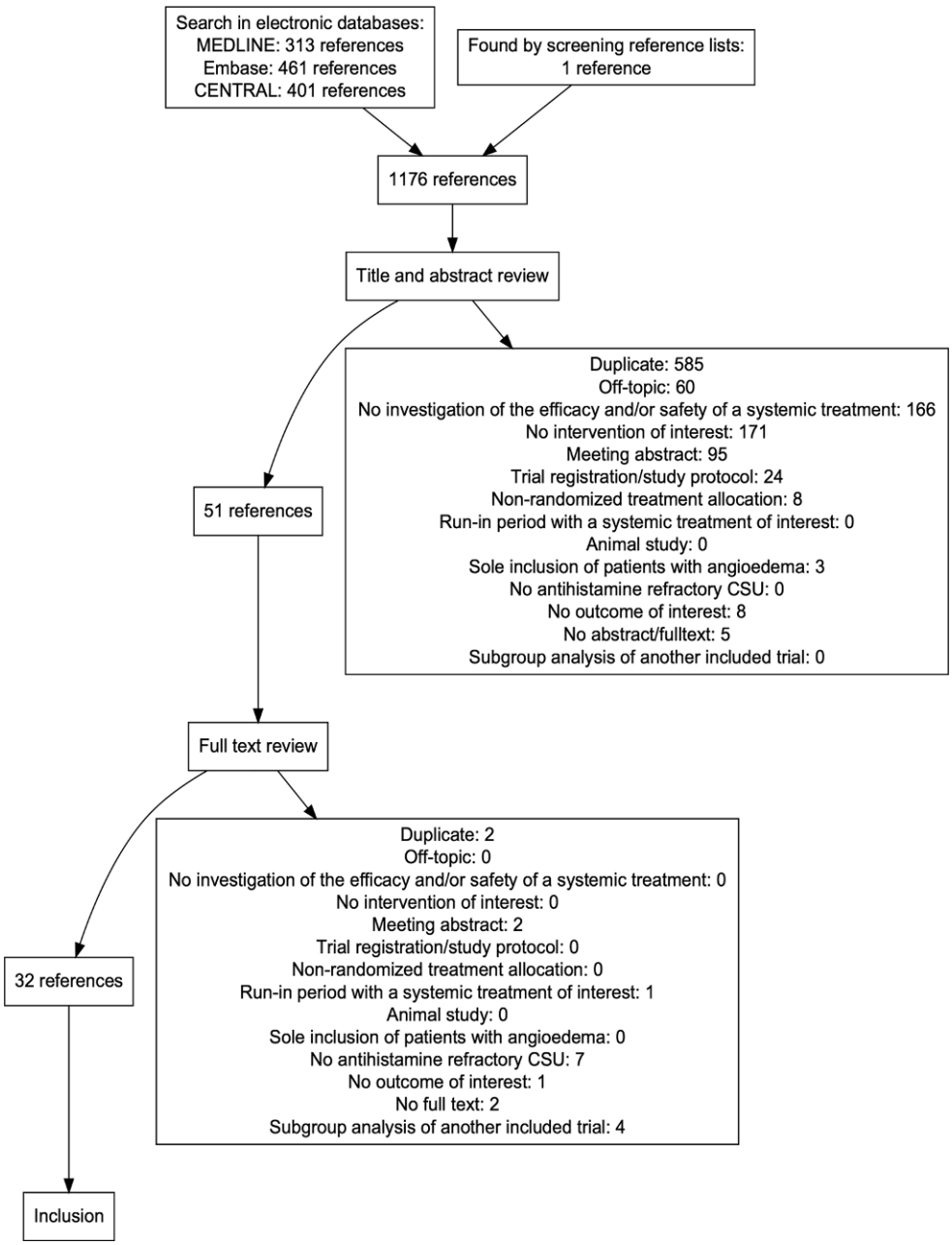

Fig. 1 Screening of references. Of 1176 studies found by the search strategy, 32 studies fulfilled the inclusion criteria and were included

the judgement on the risk of bias in original studies included in this analysis. Some concerns were found in 11 of 17 studies. Egger's regression test in a comparison-adjusted funnel plot did not show publication bias across studies ($p = 0.696$). Grading of the certainty of evidence according to the GRADE approach is included in Fig. 3. The effect estimates for ligelizumab in different dosages were downgraded from high to moderate because of inconsistency. The effect estimates for cyclosporine, fenebrutinib, azathioprine, canakinumab, quilizumab, and AZD1981 were downgraded due to imprecision.

Weekly itch severity score

Network meta-analysis

Eleven studies which randomized 2175 patients to 14 different treatments were included in the network analysis on the change in the weekly itch severity score. The structure of the network is shown in Online Appendix E Figure E1. The individual treatments' efficacies in reducing the weekly itch severity score in relation to placebo are displayed in Online Appendix E Figure E2 sorted by the *P*-score. Again, Omalizumab injected every 4 weeks in a dosage of 300 mg was ranked the most effective currently available drug with a score reduction of –4.30 (95% CI: –5.09, –3.52) compared to placebo. Data for cyclosporine was not

Table 1 Main characteristics of included studies and patients

Number of studies, *n*	32
– Multicenter, *n* (%)	19/32 (59.4)
– International, *n* (%)	10/32 (31.2)
– Inclusion of adults only, *n* (%)	21/32 (65.6)
– Inclusion of children only, *n* (%)	0/29 (0)
– Inclusion of both adults and adolescents, *n* (%)	11/32 (34.4)
Randomized patients, *n*	3641
Age, mean years (95% CI)	41.0 (40.0; 42.1)
Proportion of female patients, mean % (95% CI)	70.2 (67.8; 72.7)
UAS7 at baseline, mean (95% CI)	28.0 (26.9; 29.2)
Weekly itch severity score at baseline, mean (95% CI)	13.6 (13.2; 14.0)
Weekly number of hives score at baseline, mean (95% CI)	16.2 (15.7; 16.8)
DLQI at baseline, mean (95% CI)	11.5 (10.8; 12.3)

CI confidence interval, *UAS7* urticaria activity score over 7 days, *DLQI* Dermatology Life Quality Index

available. The currently nonapproved interventions ligelizumab 72 mg injected every 4 weeks (–5.25, 95% CI: –7.24,–3.27) and fenebrutinib 400 mg daily per os (–3.60, 95% CI: –7.16, –0.04) showed similar reductions in the weekly itch severity score without significant differences to omalizumab 300 mg every 4 weeks. Online Appendix E Table E1 lists the estimated mean differences for the change in the weekly itch severity score for all possible treatment comparisons.

Quality of evidence

Cochran's Q statistic did not reveal significant heterogeneity (Q = 4.99; df = 5; $p = 0.417$). The comparisons between ligelizumab in different dosages and omalizumab 300 mg every 4 weeks as well as placebo showed inconsistency between direct and indirect effect estimates (Online Appendix E Table E2). The assessment of the risk of bias in original studies outcome is shown in Online Appendix E Figure E3. Some concerns were found in six of eleven studies. Egger's regression test in a comparison-adjusted funnel plot did not find publication bias across studies ($p = 0.506$). The certainty of evidence was downgraded from high to moderate for the different dosages of ligelizumab because of inconsistency and for dapsone, fenebrutinib, quilizumab, and AZD1981 due to imprecision.

Weekly number of hives score

Network meta-analysis

Ten studies with 2152 patients could be included in the network analysis on the change in the weekly number of hives score. The network's structure is displayed in Online Appendix F Fig F1. Online Appendix F Figure F2 shows the efficacies of all 13 included treatments relative to placebo and their ranking according to *P*-scores. Omalizumab injected every 4 weeks in a dosage of 300 mg was ranked the most effective currently available drug with a score reduction of –5.69 (95% CI: –6.70, –4.68) relative to placebo. Data on the efficacy of cyclosporine in reducing the weekly number of hives score could not be included. Ligelizumab 240 mg every 4 weeks showed a score reduction of –6.71 (95% CI: –9.21, –4.20) and fenebrutinib 400 mg daily per os a score reduction of –6.00 (95% CI: –10.43, –1.57) compared to placebo. Both ligelizumab 240 mg every 4 weeks and fenebrutinib 400 mg daily per os showed no significant difference in efficacy compared to omalizumab 300 mg every 4 weeks. Estimates for the mean difference of the change in the weekly number of hives score for all possible treatment comparisons are provided in Online Appendix F Table F1.

Quality of evidence

There was no relevant heterogeneity according to Cochran's Q statistic (Q = 5.9; df = 5; $p = 0.316$). Net splitting revealed inconsistency for ligelizumab in different dosages vs. placebo, ligelizumab in different dosages vs. placebo, and omalizumab 75 mg vs placebo (Online Appendix F Table F2). Risk of bias was graded as low in five of ten studies. Some concerns were found in five studies (Online Appendix F Figure F3). Egger's regression test in a comparison-adjusted funnel plot revealed no significant publication bias across studies ($p = 0.202$). The certainty in the effect estimates for the different dosages of ligelizumab and omalizumab 75 mg were downgraded from high to moderate for inconsistency. The effect

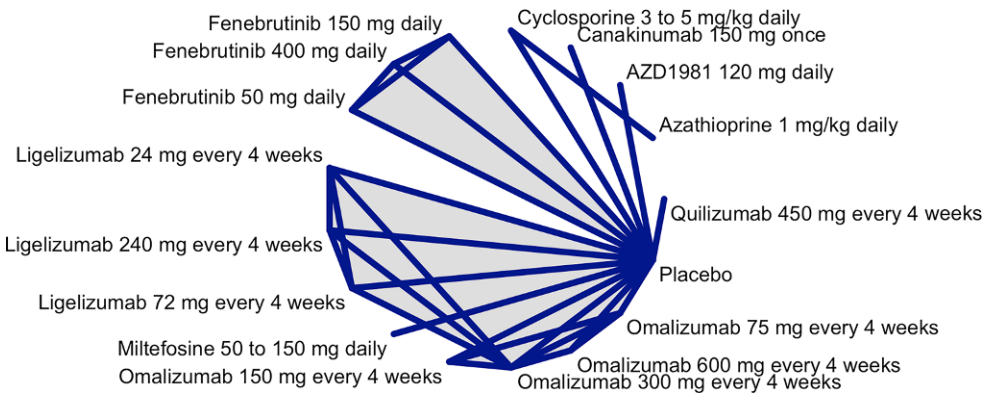

Fig. 2 Network graph of studies included in the network analysis on the change in UAS7. *Lines* represent direct comparisons. *Grey triangles* depict multiarm studies. *UAS7* urticaria activity score over 7 days

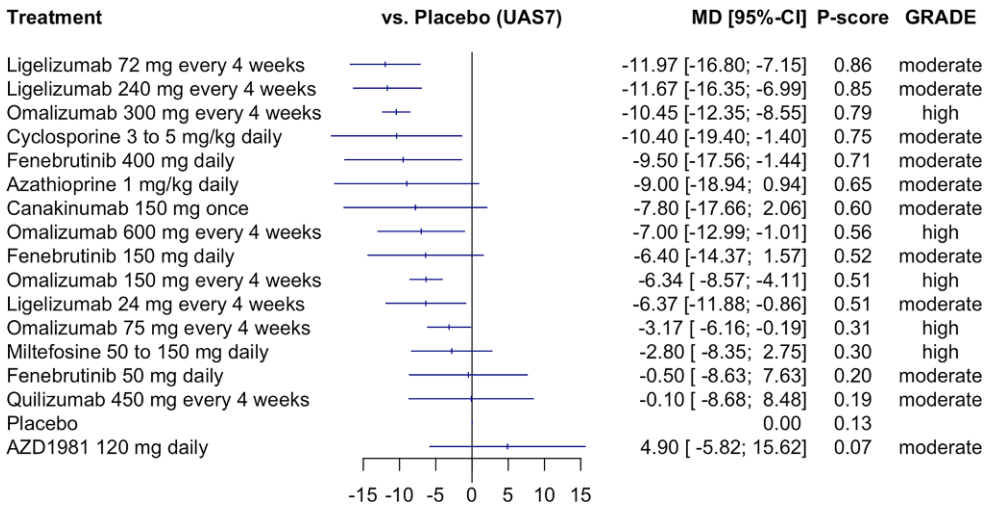

Fig. 3 Forest plot for the network analysis on the change in UAS7. The reduction in the UAS7 is shown for all treatments in relation to placebo. The treatments are ranked according to *P*-scores. The certainty of evidence is provided on the right. *UAS7* urticaria activity score over 7 days, *MD* mean difference, *CI* confidence interval

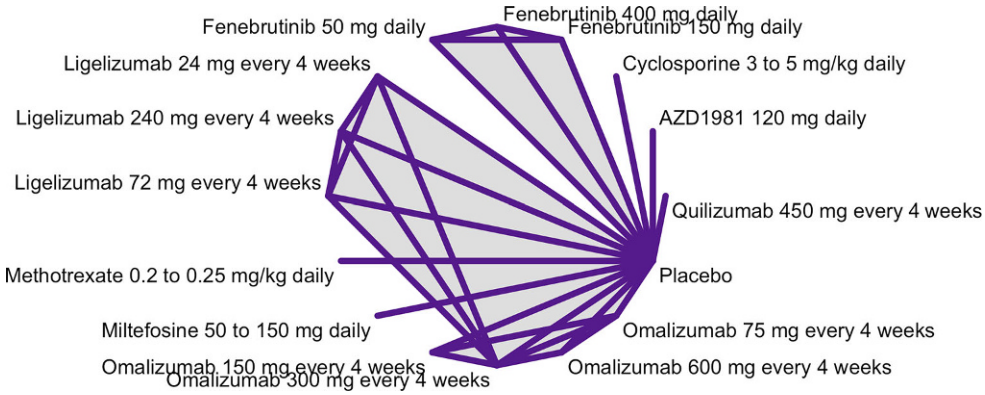

Fig. 4 Network graph of studies included in the network analysis on adverse events. *Lines* represent direct comparisons. *Grey triangles* depict multiarm studies

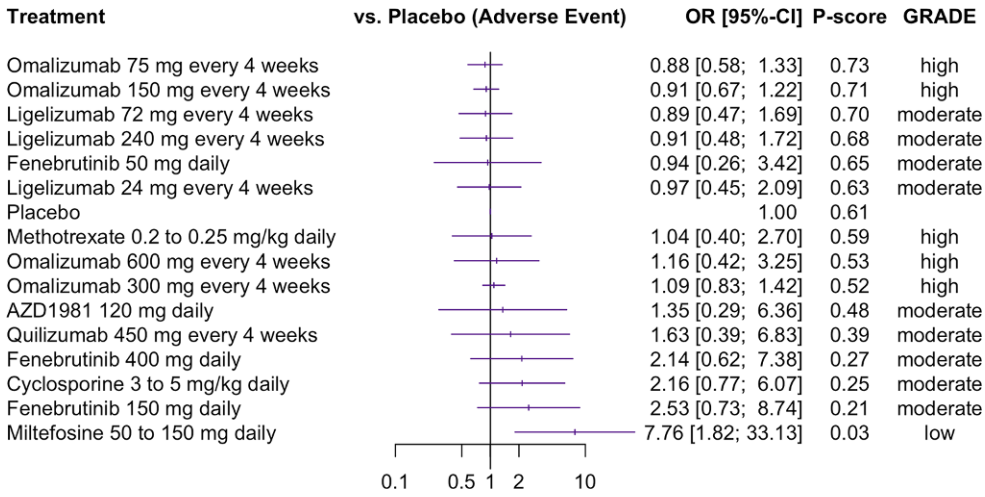

Fig. 5 Forest plot for the network analysis on adverse events. The odds ratio for experiencing an adverse event is shown for all treatments with placebo as comparator. The treatments are ranked according to *P*-scores. The certainty of evidence is provided on the right. *OR* odds ratio, *CI* confidence interval

estimates for fenebrutinib, dapsone, and quilizumab were downgraded due to imprecision.

Adverse events

Network meta-analysis

Data on 16 treatments extracted from 15 studies with 2751 randomized patients could be included in the network meta-analysis on adverse events. Fig. 4 illustrates the structure of the network. Most studies compared the active agent to placebo, while only few studies performed direct comparisons between different medications. Fig. 5 lists the estimated odds ratios for the occurrence of an adverse event for all medications with placebo as comparator and the treatment ranking according to calculated *P*-scores. Among all included interventions, cyclosporine 3 to 5 mg/kg daily per os was ranked third last with the third highest odds ratio for experiencing an adverse event of 2.16 (95% CI: 0.77, 6.07) compared to placebo. Miltefo-

sine 50 to 150 mg daily per os, which is primarily used to treat leishmaniasis and amoeba infections, was ranked least safe in terms of the adverse event frequency with an odds ratio of 7.76 (95% CI: 1.82, 33.13). Omalizumab 300 mg injected every 4 weeks showed an odds ratio of 1.09 (95% CI: 0.83, 1.42), ligelizumab 72 mg injected every 4 weeks an odds ratio of 0.89 (95% CI: 0.47, 1.69), and fenebrutinib 400 mg daily per os an odds ratio of 2.14 (95% CI: 0.62, 7.38) compared to placebo. Odds ratios for all possible treatment comparisons can be found in Online Appendix G Table G1.

Quality of evidence

Cochran's Q statistic showed no significant heterogeneity ($Q = 2.5$; $df = 6$; $p = 0.872$). Net splitting revealed inconsistency between direct and indirect effect estimates for the comparisons between ligelizumab in different dosages and placebo (Online Appendix G Table G2). The risk of bias assessment in individual studies is displayed in Online Appendix G Figure G1. High risk of bias was suspected in one of 15 studies, some concerns were found in six studies. Egger's regression test in a comparison-adjusted funnel plot showed no significant publication bias across studies ($p = 0.569$). The effect estimates for ligelizumab in different dosages vs. placebo were downgraded in the certainty of evidence from high to moderate for inconsistency. The effect estimates for cyclosporine vs. placebo, fenebrutinib vs. placebo, AZD1981 vs. placebo, and quilizumab vs. placebo were downgraded to moderate for imprecision. For miltefosine vs. placebo, the effect estimate was downgraded from high to low for imprecision and risk of bias.

One study, which assessed the efficacy of omalizumab, fulfilled the inclusion criteria of this review and reported information on adverse events but was not included in the network meta-analysis on adverse events. The reasoning for exclusion from the network meta-analysis and the results of this study are reported in Online Appendix H.

Other outcomes

The network analysis on complete response consisted of three separate sub-networks and was therefore omitted. Data on DLQI was published rarely and the results (Online Appendix I and Online Appendix J) should thus be interpreted with caution. The network analyses on the occurrence of serious adverse events (Online Appendix J) and withdrawal due to an adverse event (Online Appendix K) should also be interpreted with caution since many studies reported the occurrence of no or few events.

Subgroup and sensitivity analysis

Twenty-one studies included adults only, while 11 studies included both adults and adolescents. Analysis of the subset of studies including adults only showed no prominent differences to the analysis of the entire dataset (Online Appendix L). Due to unavailability of data on children only, a subgroup analysis in children could not be performed. Moreover, provision of data on long-term treatment (>16 weeks) was uncommon, which prevented a meaningful subgroup analysis with data on long-term treatment. The Cochrane Risk of Bias Tool showed high risk of bias for only one study. The sensitivity analysis with exclusion of this study showed no relevant differences to the main analysis.

Discussion

Summary of findings

Thirty-two studies, which included 3641 adults and adolescents and examined 31 different systemic medical interventions in different clinical research phases and with different primary and secondary endpoints, could be included in this systematic review and network meta-analysis on the relative efficacy and safety of systemic treatments for antihistamine-refractory CSU. Omalizumab injected every 4 weeks in a dosage of 300 mg was ranked the most effective currently available drug in reducing the UAS7, weekly itch severity score, and number of hives score with high certainty of evidence. Cyclosporine 3 to 5 mg/kg daily per os was ranked the second most effective currently available drug in reducing the UAS7 with moderate certainty of evidence. Data for the weekly itch severity score and weekly number of hives score was unavailable for cyclosporine. Ligelizumab injected every 4 weeks in a dosage of 72 mg and fenebrutinib 400 mg daily per os showed no significant differences in efficacy compared to omalizumab 300 mg injected every 4 weeks and cyclosporine 3 to 5 mg/kg daily per os. In terms of safety, the chance for an adverse event was ranked third highest for cyclosporine among all includable drugs with a moderate certainty of evidence.

Interpretation of findings

Combining the results of the outcomes, omalizumab injected in a dosage of 300 mg every 4 weeks appears to be the most effective currently available agent and a safe treatment option for antihistamine-refractory CSU. The certainty of evidence is high with no serious concerns regarding imprecision of network effect estimates, heterogeneity of network effect estimates, inconsistency between direct and indirect effect estimates, risk of bias within studies, publication bias across studies, or indirectness [15].

Cyclosporine appears to be effective for antihistamine-refractory CSU but the data suggests a less favorable safety profile compared to other treatment options including omalizumab. The certainty of evidence is moderate due to imprecision, which is the result of a low sample size for cyclosporine. However, the findings on cyclosporine can be underlined by nonrandomized trials [48, 49].

Ligelizumab injected in a dosage of 72 mg every 4 weeks shows a comparable efficacy and safety as omalizumab 300 mg every 4 weeks, both targeting IgE [5] and both being injected. Putting forward a claim of superiority to the EMA or FDA may thus be difficult. The same applies to the daily oral administration of fenebrutinib in a dosage of 400 mg when compared to cyclosporine 3 to 5 mg/kg daily per os. However, only one phase 2 trial investigating fenebrutinib in different dosages could be included in this network meta-analysis, and further studies may support superiority in efficacy or safety.

Previous research

Another network meta-analysis on pharmacologic treatments for antihistamine-refractory CSU was published previously [50]. Our systematic review and network meta-analysis includes nine additional studies, comprising a recently published study by Metz et al. on fenebrutinib [34]. Both Nochaiwong et al. and our analyses included the UAS7, weekly itch severity score, weekly number of hives score, frequency of adverse events, and frequency of serious adverse as outcomes. Besides, Nochaiwong et al. analyzed all-cause dropouts while we included withdrawals due to an adverse event and DLQI as outcomes. Nochaiwong et al. used standardized mean differences as outcome scale for continuous outcomes while we used absolute values. For categorical outcomes, odds ratios were used in both analyses. The use of different outcome scales for continuous outcomes prevents a direct comparison of the results for overlapping continuous outcomes. A comparison of the results for overlapping categorical outcomes shows similar but not identical results. Differences may be explained by the inclusion of the nine additional studies and the use of frequentist statistics in contrast to Bayesian statistics which Nochaiwong et al. applied.

Other traditional nonnetwork meta-analyses have been published. A summary of these with a comparison to our results can be found in Online Appendix M.

Limitations

First, we could not extract sufficient data to perform analyses for all planned outcomes. For example, a subgroup analysis in children could not be performed because of unavailability of data on children only. With the rising availability of data, future updates of this review and network meta-analysis might include analyses on missing planned outcomes. Second, background therapies differed among included studies. Despite finding no significant heterogeneity in any of the analyses, this might interfere with the transitivity assumption since the power in the evaluation of heterogeneity and inconsistency was limited by the fact that a minority of studies performed direct treatment comparisons instead of comparisons between an intervention and placebo. Third, some interventions were performed by one study only which resulted in imprecision and a subsequent downgrade of the certainty of evidence in several effect estimates.

Conclusion

This systematic review and network meta-analysis involving 32 studies, which included 3641 adults and adolescents and examined 31 different systemic medical interventions in different clinical research phases, suggests that omalizumab 300 mg injected every 4 weeks and cyclosporine 3 to 5 mg/kg daily per os are the most effective currently available drugs for treating antihistamine-refractory CSU with high certainty of evidence for omalizumab and moderate certainty of evidence for cyclosporine. Administration of cyclosporine shows a relatively less favorable safety profile with moderate certainty of evidence.

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Author Contribution All authors contributed to the study conception and design. Benjamin Kendziora had the idea for the study. Benjamin Kendziora, Jessica Frey, and Justin G. Schlager performed the literature search. Benjamin Kendziora performed the data analysis. The first draft of the manuscript was written by Benjamin Kendziora and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest B. Kendziora, J. Frey, M. Reinholz, F. Ruëff, E. Oppel, T. Zuberbier, D. Hartmann, J. G. Schlager, and L. E. French declare that they have no competing interests.

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