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Omalizumab in patients with chronic spontaneous urticaria: a systematic review and GRADE assessment.

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Conflicts of interest

A.C. Knulst is member of the national and international Novartis omalizumab advisory council, and has received speakers fees and sponsoring for scientific studies from Novartis. M.T. van den Elzen has received speakers fees from Novartis.

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What is already known about this topic:

- Despite available treatment options many patients with chronic spontaneous urticaria remain symptomatic
- Recently published EAACI/GA²LEN/EDF/WAO guideline recommends omalizumab as 'add-on' therapy to second generation H₁-antihistamines as third line treatment

What does this study add:

- A detailed GRADE assessment indicated high quality evidence for the effectiveness and safety of omalizumab 300 mg per month for up to six months

Summary

Chronic spontaneous urticaria (CSU) is characterized by the occurrence of hives, angioedema or both for a period of at least six weeks. Many patients remain symptomatic despite treatment with H₁-antihistamines, even at higher doses. This systematic review assessed the quality of the evidence for the effects of omalizumab as treatment in patients with CSU. We searched PubMed, the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials up to 7 August 2014. Three review authors independently carried out study selection, risk of bias assessment and data extraction. Two review authors analysed the data. Five randomised controlled trials (RCTs) which included 1116 participants were evaluated. All of the RCTs were judged as low risk of bias. There was a statistically significant improvement in measures of disease activity and quality of life following treatment with omalizumab when compared to placebo (mean difference (MD) -11.58, 95% CI -13.39 to -9.77 and MD -13.12, 95% CI -16.30 to -9.95 respectively). Complete response and partial response was more frequent after treatment with omalizumab (risk ratio (RR) 6.44, 95% CI 3.95 to 10.49 and RR 4.08, 95% CI 2.98 to 5.60 respectively). There was no difference in the proportion of participants reporting adverse events between the omalizumab and placebo treatment groups (RR 1.05, 95% CI 0.96 to 1.16). There was high quality evidence to support the effectiveness and safety of omalizumab 300 mg per month for the treatment of CSU for up to six months.

Introduction

Chronic spontaneous urticaria (CSU) is characterized by recurrent itchy wheals (hives), angioedema or both, that occur for at least six weeks and have no external trigger.¹ Similar

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symptoms may also be induced by a demonstrable stimulus including, but not limited to, cold, heat, vibration or exercise which is classified as chronic inducible urticaria. CSU, formerly known as chronic idiopathic urticaria, may lead to a severe impairment in the quality of life of an individual.² One in five people will experience at least one episode of urticaria during their lifetime, with a point prevalence of up to 0.6%. Women are affected nearly twice as often as men with a peak incidence of between 20 to 40 years of age. Although CSU can resolve within months to a year, a considerable number of people suffer more than five years (10- 50%).³

Mast cells, basophils and immunoglobulin E (IgE) have been implicated in the pathophysiology of chronic urticaria.⁴ A recently updated guideline (EAACI/GA²LEN/EDF/WAO) recommended modern second generation antihistamines followed by an increase in dosage if symptoms persist, as the first two steps in the treatment algorithm for CSU.¹ Treatment options for patients where there is a lack of response to H₁-antihistamines include cyclosporine, leukotriene-receptor antagonists, and short term use of systemic corticosteroids. However, many patients remain symptomatic or suffer from side-effects, more especially with cyclosporine treatment. Omalizumab, a recombinant humanized monoclonal antibody, which selectively binds to human immunoglobulin E (IgE) was initially licensed for the treatment of allergic asthma, and has recently received approval from the European Medicines Agency and the US Food and Drug Administration (FDA) for the treatment of CSU.⁵ Omalizumab may have a beneficial role in the treatment of CSU by reducing mast cell and basophil activation mediated by IgE and its high-affinity receptor (FcεRI) on the surface of target cells, thereby reducing the levels of free IgE and the FcεRI-receptor.^{6,7}

The EAACI/GA²LEN/EDF/WAO guideline on urticaria recommends omalizumab as add-on therapy to modern second generation H₁-antihistamines as third line in the treatment algorithm of urticaria. This guideline was revised and updated using a 'modified version of GRADE'. However, for the corresponding Dutch guideline, which is currently under preparation, we have more comprehensively followed the GRADE approach to assess the quality of the evidence for the effectiveness and safety of omalizumab. Our results are summarized in this systematic review.

Materials and methods

We conducted a systematic review of randomised controlled trials (RCTs) evaluating the evidence for the effectiveness and safety of omalizumab for chronic spontaneous urticaria.

Search strategies

We searched PubMed, the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials up to 7 August 2014 (see Table 1). International guidelines were examined for further potentially eligible RCTs.^{1,8} Two review authors (MU, MvdE) assessed the titles and abstracts identified from the searches and independently evaluated each study to determine whether predefined selection criteria were met.

Inclusion criteria

RCTs assessing the efficacy and safety of omalizumab in patients with CSU. Other study designs and those investigating participants with inducible urticaria were excluded.

Outcome measures

We rated the clinical importance of each outcome on a nine-point scale according to the recommendations in the GRADE Handbook.⁹ Our pre-specified outcomes were: 1) Mean change in disease activity from baseline; 2) Mean change in quality of life from baseline; 3) Proportion of patients with adverse events. These were considered critical outcomes for decision making; 4) Proportion of patients with a complete response; 5) Proportion of patients with a partial response; 6) Proportion of angioedema free days. These were considered to be important outcomes for decision making; and 7) Proportion of participants that experienced remission within one month, was considered of limited importance.

Data extraction and synthesis

Three authors (MU, MvdE, EvZ) independently assessed the risk of bias in the included studies following the criteria described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions.¹⁰

Three authors (MU, MvdE, EvZ) extracted data using a previously developed data extraction form. Two authors (MU, EvZ) entered data into Review Manager 2011 (RevMan).¹¹ We

contacted Novartis Pharma to retrieve missing trial details and data. All evaluations were compared and disagreements between authors were discussed and resolved. Continuous outcomes were presented as mean differences (MD) and dichotomous outcomes as risk ratios (RR). All outcomes were reported with their associated 95% CI and were analysed in RevMan according to a random effects model using the Inverse Variance method for continuous outcomes and Mantel-Haenszel test for dichotomous outcomes, unless stated otherwise.¹⁰ Heterogeneity between studies was assessed using the I^2 statistic, where $I^2 > 60\%$ was considered moderate to substantial.

We entered data into meta-analysis from studies evaluating omalizumab 300mg and also data from one study covering a dose range of 75-375 mg in which the doses were calculated based on body weight and total serum IgE levels, according to the optimised dosing strategies used in the treatment of allergic asthma.¹²

GRADE profiler (GRADEpro) was used to rate the quality of evidence and to create a 'Summary of findings' table.⁹

Results

Our searches retrieved 180 references to studies (see Fig 1).

Description of included studies

Five RCTs, comprising 1116 participants met our inclusion criteria (see Table 2).^{13–17} Out of these, only data for 749 participants receiving omalizumab 300 mg or 75 mg – 375 mg were entered into the meta-analyses. We identified one small study (20 participants) which was an abstract to conference proceedings, provided limited data, and therefore was not included in our review.¹⁸

Characteristics of the trial settings and methods

Three phase III studies (ASTERIA I, ASTERIA II and GLACIAL) and two phase II studies (MYSTIQUE and X-QUISITE) were included. All studies were double-blind, placebo controlled, multicentre trials, and had been conducted in recent years.

Characteristics of the participants

The number of participants ranged between 49 and 335 per study. All had been diagnosed with CSU and only those with moderate to severe disease activity, despite receiving treatment, participated in the studies. In the X-QUISITE study only participants with CSU and IgE autoantibodies against thyroid peroxidase (TPO) were included.¹³

Characteristics of the interventions

Four RCTs evaluated omalizumab 300 mg,^{14–17} three of which also evaluated other doses of omalizumab. One study evaluated omalizumab with a dose range of 75 mg – 375 mg versus placebo.¹³ Omalizumab was used as add-on treatment (mainly to H₁-antihistamines) in three studies.^{14,15,17} Rescue medication as either diphenhydramine, loratadine or clemastine was permitted in most studies.

Characteristics of the outcome measures

Patient-reported outcomes were assessed in daily diaries in all studies. The disease-specific urticaria activity score (UAS) was used in all of the studies.¹⁹ The UAS7, which is used to make daily assessments for one week, combines daily wheal numbers and pruritus intensity and has a total score of 42 points. Most studies used the Itch Severity Scale (ISS), which forms part of the UAS7 and has a total score of 21 points. Our other critical outcome, quality of life was assessed in four studies with the disease-specific Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL).²⁰ The CU-Q2oL consists of 23 items divided into six domains (pruritus, swelling, impact on life activities, sleep problems, limits and looks) and has a maximum score of 115 points. Four studies used generic questionnaires to assess quality of life, i.e. the Dermatology Quality Life Index (DLQI).^{13–15,17} The proportion of patients who reported adverse events were reported in all studies.

Complete response to treatment was assessed in all studies, with most using the UAS7 where a score of 0 indicated a complete response. One study assessed complete resolution of urticaria symptoms using an investigator global assessment of symptoms. Three studies assessed partial response which was represented by a UAS7 score of 6 or less.^{14,15,17} One study quantified partial response as the proportion of patients with 75% improvement of symptoms compared to baseline.¹⁶ Angioedema free days were assessed in three studies

while remission within one month was not addressed at all.

Risk of bias of included studies

We assessed the studies for risk of bias (see Fig 2). All five studies were categorized as at 'low risk of bias' i.e. plausible bias unlikely to seriously alter the results.

In all five studies the methods used to generate the allocation sequence were described in sufficient detail to enable a clear judgement. Sequence generation was carried out in four of the studies using an interactive voice and web response system. In the X-QUISITE study randomisation was performed using a validated system. Central allocation was used in all studies. The methods used to achieve blinding of both participants and investigators were adequately described and reported. Blinding was achieved through the use of similar packaging and we were confident that adequate measures had been taken to blind participants and key study personnel. All prespecified outcomes mentioned in the methods section were fully addressed in the results. In all phase III studies, efficacy analyses were undertaken using data from a modified intention-to-treat population (randomised patients who received at least one dose of the study drug). Although in each of these three studies one participant was not entered into the analysis we judged this as at a low risk of bias. The drop-out rates in the studies were moderate to low (10% to 16.9%). All dropout rates were balanced and therefore judged as low risk of bias, except for one study which we judged as unclear risk of bias.³. There was no baseline imbalance in urticaria severity between the study groups. As there was no selection, performance, detection nor reporting bias, we did not consider industry sponsoring to pose an additional risk.

Effects of interventions

Summary of the key results (see Table 3). The quality of the body of evidence was rated high for all critical and important outcomes.

Mean change of disease activity from baseline

Pooled data from 749 participants demonstrated that the mean difference in UAS7 was 11.58 points lower after treatment with omalizumab compared to placebo (95% CI -13.39 to -9.77; $P < 0.00001$). This improvement in measures of disease activity is clinically relevant

because the minimal important difference (MID) of the UAS7 is estimated to be between 9.5 and 10.5 (see Fig 3).²¹

Mean change of quality of life from baseline

Quality of life, assessed using the CU-Q2oL, improved by 13.12 on a scale of 0 to 115 points (95% CI -16.3 to 9.95; $P < 0.00001$).^{13-15,17} The MID of the CU-Q2oL has not been established and therefore the clinical relevance of these data cannot be ascertained (see Fig 4).

Proportion of patients with adverse events

Adverse events occurred in 73.7% (342/464) of the patients treated with omalizumab and in 64.2% (183/285) of the controls with no significant difference between the groups (risk ratio (RR) 1.05, 95% CI 0.96 to 1.16) (see Fig 5). Adverse events with an incidence of more than 1% and 2% higher than placebo during treatment in the phase III studies included headache, sinusitis, arthralgia and upper respiratory tract infections.²² Injection-site reactions such as pain, swelling, erythema and pruritus were also reported (2.7% omalizumab 300 mg vs 0.8% placebo).²²

Proportion of patients with a complete response

Complete control of symptoms was achieved in 38.1% of the patients treated with omalizumab compared to 5.6% of the patients treated with placebo. This difference was statistically significant (RR 6.44, 95% CI 3.93 to 10.43; $P < 0.00001$).

Proportion of patients with a partial response

Partial response was achieved in 55.1% in the active treatment group compared with 13.7% of the patients in the placebo group, this difference was statistically significant (RR 4.08, 95% CI 2.98 to 5.6; $P < 0.00001$).^{13-15,17}

Proportion of angioedema free days

The proportion of angioedema free days (range: 0-100%) was assessed in 576 patients.^{14,15,17} The mean proportion of angioedema free days was 5.66% higher after treatment with omalizumab when compared to placebo (MD 5.66, 95% CI 2.55 to 8.76; $P = 0.0004$). The proportion of angioedema free days was also high in the placebo group (88.1%-89.2%).

Proportion of participants that experienced remission within one month.

This outcome was not assessed in any of the studies.

Discussion

The overall quality of evidence as assessed using the GRADE approach for the effectiveness and safety of omalizumab for chronic urticaria was high. All of our critical outcomes were assessed in all the included studies with the exception of quality of life which was reported in four out of the five studies.

In the GLACIAL study the primary objective was to assess the safety of omalizumab, whereas the other studies focused mainly on the effectiveness of omalizumab. Pooling of data was feasible for all of our outcomes, with the exception of the proportion of participants who achieved remission within one month, which was not assessed in any of the studies.

Three RCTs assessed the time to achieve the MID response (≥ 5 point decrease) in weekly itch severity score (range 0-21) at week 12. The median time to achieve this MID after 12 weeks of treatment ranged from 1.0 to 2.0 weeks.^{14,15,17}

The EAACI/GA²LEN/EDF/WAO guideline on chronic urticaria provides a strong recommendation to use the validated UAS7 to assess disease severity.¹ The MID of the UAS7 is estimated at 9.5-10.5 points.²¹ Pooled data from the five studies showed a statically significant and clinically relevant improvement in disease activity assessed using the UAS7. Four studies emphasized the importance of quality of life as an outcome using the internationally accepted and validated CU-Q2oL instrument.²⁰ It is expected that the MID of this questionnaire will be established in the near future and will then provide more detail on the clinical relevance of this outcome.

Complete response and partial response was achieved more frequently after treatment with omalizumab than placebo, with a difference which was statistically significant. Furthermore, the proportion of angioedema free days was higher after treatment with omalizumab compared to placebo, although the clinical relevance of this improvement (5.66%) remains unclear. However, it suggests that omalizumab may have an effect on angioedema.

A more pronounced reduction in use of rescue medication from baseline was observed in the omalizumab 300 mg group compared to the placebo group in four of the five

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studies.^{13-15,17} In one study a statistically significant reduction in number of diphenhydramine tablets per week was noted in favour of the omalizumab group (-4.2 (6.4) compared to -1 (5.2) in the placebo group; $P < 0.03$).¹⁷ However, mean differences were not provided by the investigators in the other two other studies^{13,15}, and the mean difference was not statistically significant in Kaplan et al.¹⁴

There was no statistically significant difference in the proportion of participants experiencing adverse events between the groups. Although anaphylactic shock is a serious and well known adverse event associated with omalizumab in the treatment of allergic asthma, (estimated frequency of 1 in every 1000 injections), no cases of anaphylaxis attributed to omalizumab were reported.²² It should be noted that the safety of omalizumab in the included studies has not been studied in patients undergoing treatment beyond 24 weeks. However, overall omalizumab has a well-established good safety profile in allergic asthma.

Agreements and disagreements with other reviews

In the course of preparing the Dutch guideline on chronic urticaria, we carefully assessed the recently published EAACI/GA²LEN/EDF/WAO guideline.¹ This guideline used a “modified version of GRADE” in translating the “SIGN level of evidence into a GRADE quality of evidence”, and the developers acknowledge the fact that additional quality criteria considered in GRADE were not assessed. In our review we provide a more detailed evaluation and reporting, which includes a full risk of bias assessment of individual studies as well as grading the quality of evidence for each outcome taking into account any limitations in study design or execution, inconsistencies in the results, indirectness of the evidence, imprecision and publication bias. Clinical decision making on the choice of intervention for CSU should be based on high quality evidence if available.

In the recently published systematic review of treatments for CSU with inadequate response to licensed first-line treatments, Mitchell et al. summarized evidence for treatments in patients that remain symptomatic despite treatment.²³ The scope of their review was broader which included not only omalizumab, but leukotriene receptor antagonists and additional immunomodulating therapies, evaluated in a range of study designs. We used the Cochrane domain-based risk of bias tool for assessing the included studies, whereas Mitchell

used a checklist recommended by the National Institute for Health and Clinical Excellence to assess methodological quality.²⁴ In addition, we contacted trial investigators to retrieve missing study details to enable more accurate judgements to be made regarding risk of bias assessments. Their search date was up to December 2011, and therefore did not include the three RCTs that were published after this date.^{14,15,17} Although we are in concordance with the direction of their conclusions regarding the effects of omalizumab, we have provided a more detailed GRADE assessment to rate the quality of evidence in support of those conclusions.

A further systematic review which compared omalizumab with placebo for CSU identified the identical five studies.²⁵ Although they used the Cochrane risk of bias tool, they appear to have confused allocation concealment with blinding. They did not attempt to pool data into a meta-analysis and merely presented all data separately in tables. The reviewers concluded that the 300 mg dosage was effective, but with more side effects than with the lower dosages. As with the other review no assessments of GRADE were undertaken.²⁰

A recently published critical appraisal on the study of Maurer et al.¹⁵ raised concerns about some methodological issues, the external validity and generalizability of the results.²⁶ There were additional concerns expressed about the trial protocol and history of changes, and in particular about discrepancies regarding prespecified and reported outcomes. The concerns were subsequently responded to satisfactorily by the investigators.²⁷

The results of this review may not be generalizable to all participants with CSU in daily clinical practice for several reasons. Participants in the included studies had refractory disease, despite the use of previous medication (mostly H₁-antihistamines). Only participants with moderate to severe disease activity were enrolled in the studies and thus one of the additional limitations was that the conclusions cannot be extrapolated to the most severe cases. Furthermore, participants under the age of 18 were excluded from all the studies.

Conclusion

There is high quality evidence for the effectiveness and safety of omalizumab 300 mg per month for the treatment of chronic spontaneous urticaria up to six months. Judgements

about evidence and recommendations in healthcare are complex and GRADE assessments undertaken in this review can assist in clinical decision making and help formulate more accurate recommendations.

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Figure legends

Figure 1 Study flow diagram

Figure 2 Risk of bias summary

Figure 3 Improvement in disease activity (UAS7) from baseline

Figure 4 Improvement in quality of life (CU-Q2oL) from baseline

Figure 5 Proportion of participants with an adverse event

Table 1. search strategy

PubMed. Search date: 07-08-2014	The Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials Search date: 07-08-2014
1. chronic urticaria[tiab]	1. Chronic urticaria:ti,ab
2. chronic urticaria	2. Chronic urticaria
3. "Urticaria"[Mesh]	3. "Urticaria"
4. chronic spontaneous urticaria[tiab]	4. chronic spontaneous urticaria:ti,ab
5. chronic idiopathic urticaria[tiab]	5. chronic idiopathic urticaria:ti,ab
6. #1 OR #2 OR #3 OR #4 OR #5	6. omalizumab:ti,ab
7. omalizumab[tiab]	7. omalizumab
8. "omalizumab"	8. anti-immunoglobulin E Therapy:ti,ab
[Supplementary Concept]	9. anti-IgE:ti,ab
9. anti-immunoglobulin E therapy[tiab]	10. #1 or #2 or #3 or #4 or #5
10. anti-IgE[tiab]	11. #6 or #7 or #8 or #9
11. #7 OR #8 OR #9 OR #10	12. #10 and #11
12. #6 AND #11	
Limit: Abstract available	
Results: 160	Results 20 (15 trials / 5 reviews)

Table 2: Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes
Kaplan et al. 2013¹⁴ GLACIAL	Phase III RCT double blind, placebo-controlled, multicentre trial. Study performed in Australia, Germany, New Zealand, Poland, United Kingdom, the United States, Singapore.	335 patients with chronic spontaneous urticaria despite treatment with H1-antihistamines, plus H2-antihistamines, LTRAs of both. Omalizumab n=252, Placebo n=83 - CIU/CSU for 6 months or longer; - Age: Range 12-75 years (Germany > 18 years) - UAS7 ≥16 - ISS≥8	24 weeks. Follow-up 16 weeks. - 6 subcutaneous injections at 4-week intervals of either 300mg omalizumab or placebo. - Rescue medication (diphenhydramine 25mg, up to a maximum of 3 doses per 24-hour period) was allowed. - Throughout the treatment period, participants were required to maintain stable doses of their prerandomisation combination therapy with H1-antihistamines plus H2-antihistamines, LTRAs of both.	Primary endpoints: - Adverse events at week 24 - Severe adverse events at week 24 Secondary endpoints: - Change from baseline in mean weekly ISS at week 12. - Change from baseline in mean the UAS7 at week 12. - Proportions of patients with a UAS7 <6 at week 12. - Time to achieve a minimal important difference (MID) in weekly ISS at week 12. - Proportion of patients who were hive and itch free (UAS7=0) at week 12. - Proportion of angioedema free days from week 4 to 12 - Change in health-related quality of life, as measured by using DLQI. Exploratory endpoints: - Change in health-related quality of life, as measured by using and CU-Q2oL at week 12. Exploratory endpoints were also evaluated at week 24.
Saini et al. 2014¹⁷ ASTERIA I	Phase III randomised, double-blind, placebo-controlled, multicentre trial. Study performed in the United States, Denmark, France, Germany, Poland, Italy, Spain en Turkey.	319 patients with chronic spontaneous urticaria who remained symptomatic despite treatment with approved doses of H1-antihistamines. Omalizumab 75mg (n=78), Omalizumab 150mg (n=80) Omalizumab 300mg (n=81) Placebo (n=80) - CIU/CSU for 6 months or longer and itching for more than 8 consecutive weeks - Age: Range 12-75 years - UAS7 ≥16 - ISS≥8	24 weeks. Follow-up 16 weeks - 6 subcutaneous injections at 4-week intervals of either 75mg, 150mg, 300mg omalizumab or placebo. - Rescue medication (diphenhydramine 25mg, up to a maximum of 3 doses per 24-hour period) was allowed. - For the first 12 weeks, participants were required to maintain stable doses of their prerandomisation H1-antihistamine treatment. - During weeks 13 to 24 patients were allowed to add on additional H1-antihistamines.	Primary endpoint was the change from baseline in weekly ISS at week 12. Secondary endpoints included: - Change from baseline in UAS7 - Proportion of patients with a complete response (UAS7=0) - Proportions of patients with a UAS7 <6 - Proportion of weekly ISS MID responders. - Proportion of angioedema free days during weeks 4 to 12. Exploratory endpoints included the assessment of efficacy endpoints at week 24 and change from baseline to week 12 in CU-Q2oL.
Maurer et al. 2013¹⁵ ASTERIA II	Phase III randomised, double-blind, placebo-controlled, multicentre trial.	323 participants with CIU who remained symptomatic despite the use of approved doses of H1-antihistamines. Omalizumab 75mg (n=82),	12 weeks. Follow-up 16 weeks. - 3 subcutaneous injections at 4-week intervals of either 75mg, 150mg, 300mg omalizumab or placebo. - Rescue medication (diphenhydramine	Primary endpoint was the change from baseline in weekly ISS at week 12. Secondary endpoints included: - Change from baseline in UAS7 - Proportion of patients with a complete response (UAS7=0)

	Study performed in the United States, Denmark, France, Germany, Poland, Italy, Spain en Turkey.	Omalizumab 150mg (n=82) Omalizumab 300mg (n=79) Placebo (n=79) - CIU for 6 months or longer and hive and itching for more than 8 consecutive weeks - Age: Range 12-75 years - UAS7 $\geq$ 16 - ISS $\geq$ 8	25mg, up to a maximum of 3 doses per 24-hour period) was allowed. - Throughout the treatment period, participants were required to maintain stable doses of their prerandomisation H1-antihistamines.	- Proportions of patients with a UAS7 <6 - Proportion of weekly ISS MID responders. - Proportion of angioedema free days during weeks 4 to 12. Exploratory endpoints included the assessment of efficacy endpoints at week 24 and change from baseline to week 12 in CU-Q2oL.
Maurer et al. 2011¹³ X-QUISITE	Phase II randomised, double-blind, placebo-controlled, multicentre trial. Study performed in 16 centres in Germany.	49 patients with chronic spontaneous urticaria and IgE autoantibodies against TPO with persistent symptoms despite standard antihistamine therapy. - Age: > 18 years - Diagnosis of CU with persistent symptoms for more than 6 weeks despite receiving maximal in label antihistamine therapy - Total serum IgE level between 30IU/mL or greater and 700 IU/mL or less. - Specific serum IgE-anti TPO antibody level of 5.0 IU/mL or greater within the last 3 months before enrolment. - UAS7>10	24 weeks. - Omalizumab 75-375mg (n=27) versus placebo (n=22) every 2- 4 weeks for 24 weeks. - Rescue medication (loratadine 10mg/day or clemastine 1mg/day) was allowed.	Primary endpoint was the change from baseline in mean weekly UAS after 24 weeks of treatment Secondary efficacy endpoints included: - Daily scores for wheals, pruritus, erythema and angioedema; - Use of concomitant medication; - Change in health-related quality of life, as measured by using the DLQI, Skindex-29 and the CU-Q2oL.
Saini et al. 2011¹⁶ MYSTIQUE	Phase II randomised, double-blind, placebo-controlled, multicentre trial. Study performed in the United States and Germany.	90 patients with CIU (pruritus and hives for> 3 days in a 7-day period for > 6 consecutive weeks) despite treatment with on approved dose of an H1-antihistamine. Omalizumab 75 mg (n = 23) Omalizumab 300 mg (n = 25) Omalizumab 600 mg (n = 21) Placebo (n = 21) - Age: Range 12-75 years - UAS7 $\geq$ 12	4 weeks. Follow-up 12 weeks. - A single subcutaneous injection of 75 mg, 300mg, 600mg omalizumab or placebo. - Rescue medication (diphenhydramine 25mg, up to a maximum of 3 doses per 24-hour period (In Germany max 50mg) was allowed.	Primary endpoint was the change from baseline in mean weekly UAS after 4 weeks. Secondary outcomes included the change in weekly pruritus score and weekly score for the number of hives from baseline to week 4 (severe) adverse events

Table 3: Summary of Findings table omalizumab

Question: Should omalizumab 300mg be used in chronic spontaneous urticaria?^{1,2,3}

Settings: Multicentre hospital trials

Quality assessment							No of patients		Effect		Quality	Importance	Comments
of participants (studies)	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Omalizumab 300mg	Control	Relative (95% CI)	Absolute			
Change in disease activity from baseline (treatment 4-24 weeks ⁴ ; measured with: Change in UAS7 from baseline; range of scores: 0-42; Better indicated by lower values)													
7/9 (5 studies ⁵)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	464	285	-	MD 11.58 lower (13.39 to 9.77 lower)	⊕⊕⊕⊕ HIGH	CRITICAL	The MID of UAS7 is between 9.5 and 10.5, therefore this difference of 11.58 is clinically important
Change in quality of life from baseline (treatment 12-24 weeks ⁴ ; measured with: Change in CU-Q2oL from baseline; range of scores: 0-115; Better indicated by lower values)													
703 (4 studies ⁶)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	439	264	-	MD 13.12 lower (16.3 to 9.95 lower)	⊕⊕⊕⊕ HIGH	CRITICAL	
Adverse events (treatment 4-24 weeks ⁴ ; assessed with: Any adverse events during treatment)													
9 (5 studies ⁵)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	342/464 (73.7%)	183/285 (64.2%)	RR 1.05 (0.96 to 1.16)	32 more per 1000 (from 26 fewer to 102 more)	⊕⊕⊕⊕ HIGH	CRITICAL	
								48%		24 more per 1000 (from 19 fewer to 77 more)			
								86%		43 more per 1000 (from 34 fewer to 138 more)			
Complete response (treatment 4-24 weeks ⁴ ; assessed with: UAS7=0 or complete resolution of urticarial symptoms ⁸)													
7/9 (5 studies ⁵)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	177/464 (38.1%)	16/285 (5.6%)	RR 6.44 (3.95 to 10.49)	305 more per 1000 (from 166 more to 533 more)	⊕⊕⊕⊕ HIGH	IMPORTANT	
								5%		272 more per 1000 (from 148 more to 475 more)			
Partial response (treatment 4-24 weeks ⁴ ; assessed with: UAS7<6 or proportion of patients with 75% improvement in UAS7)													
700 (4 studies ⁹)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	241/437 (55.1%)	36/263 (13.7%)	RR 4.08 (2.98 to 5.6)	422 more per 1000 (from 271 more to 630 more)	⊕⊕⊕⊕ HIGH	IMPORTANT	
								9%		277 more per 1000 (from 178 more to 414 more)			
								20%		616 more per 1000 (from 396 more to 920 more)			
Angioedema free days (treatment 12-24 weeks ⁷ ; measured with: Proportion of angioedema free days; range of scores: 0-100; Better indicated by higher values)													
6 (3 studies ¹⁰)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	372	204	-	MD 5.66 higher (2.55 to 8.76)	⊕⊕⊕⊕	NOT	

	trials	risk of bias	inconsistency	indirectness	imprecision					higher)	HIGH	IMPORTANT	
of remission within 1 month - not measured													
- (0 studies)	-	-	-	-	-	-	-	-	-	-		NOT IMPORTANT	

¹ Study Maurer 2011 used an 'asthma scheme' of omalizumab 75-375mg

² All patients were patients with CSU who remained symptomatic despite treatment,

³ Study Maurer 2011 comprised patients with CSU and IgE autoantibodies against TPO with persistent symptoms despite standard antihistamine therapy

⁴ Subcutaneous injections of omalizumab or placebo every 2-4 weeks

⁵ Studies Saini 2014; Saini 2011; Kaplan 2013; Maurer 2011; Maurer 2013

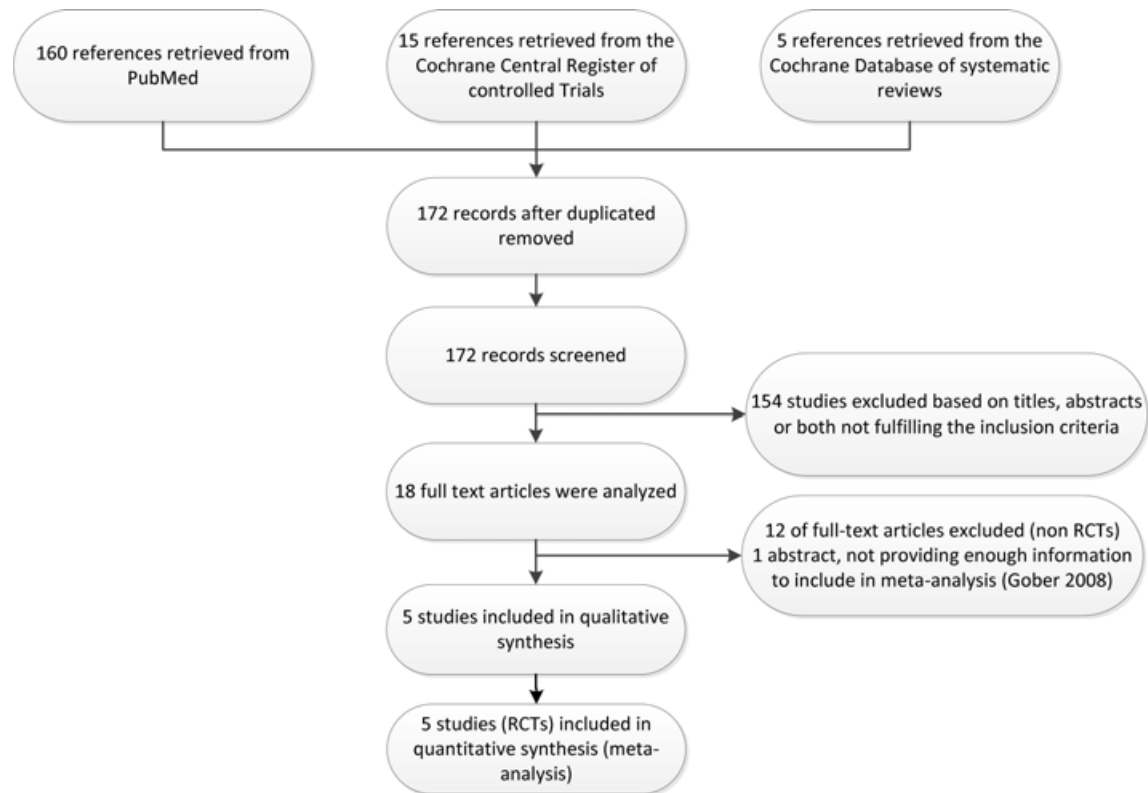
⁶ Studies Saini 2014; Maurer 2011; Maurer 2013; Kaplan 2013

⁷ Subcutaneous injections of omalizumab 300mg or placebo every 4 weeks

⁸ Study Maurer 2011 assessed complete resolution of urticarial symptoms using investigator global assessment of symptoms

⁹ Studies Saini 2014; Saini 2011; Maurer 2013; Kaplan 2013

¹⁰ Studies Kaplan 2013; Maurer 2013; Saini 2014



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Kaplan et al. 2013	+	+	+	+	+	+	+
Maurer et al. 2011	+	+	+	+	?	+	+
Maurer et al. 2013	+	+	+	+	+	+	+
Saini et al. 2011	+	+	+	+	+	+	+
Saini et al. 2014	+	+	+	+	+	+	+

