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Systematic Review

Omalizumab for the treatment of chronic spontaneous urticaria: a systematic review

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ABSTRACT

Chronic spontaneous urticaria (CSU) is a mast cell-driven skin disease characterized by the recurrence of transient wheals, angioedema or both lasting for more than 6 weeks duration. Omalizumab is a newer humanized anti IgE immunoglobulin along with many new antibody treatments has shown beneficial effect in treatment of chronic spontaneous urticaria. Although many randomized clinical trials have been conducted, as of now, the effectiveness of omalizumab in the real world management of CSU is largely unknown. A systematic review of all studies should be done. The objective was to study the efficacy and safety of different doses of omalizumab in the treatment of chronic spontaneous urticaria which was refractory to treatment with H1 antihistamines. Suitable studies were recognized after searching Wiley online library, PubMed, Google scholar, NEJM/NEJ dermatology, JAAD, JACI, clinicaltrials.gov. Only randomized, double-blind, placebo-controlled clinical trials with omalizumab versus antihistamine or leukotriene antagonists as placebo were involved in this study. 10 randomized, placebo-controlled studies were involved with 1692 patients with CSU. Patients treated with omalizumab (75-600 mg every 4 weeks) had reduced UAS7 score, improved QoL (quality of life), reduced WISS, when compared to the placebo group. The effects of omalizumab were found to be dose dependent, with maximum reduction in UAS7 at a dose of 300 mg when given at an interval of 4 weeks' duration. The incidences of adverse events were almost similar in both control and placebo groups and across various dose ranges. The best effect in reduction of clinical symptoms and QoL in CSU patients was found at a dose of 300 mg subcutaneous injection once a month of omalizumab for 12 to 24 weeks. Omalizumab was found to reduce the clinical symptoms and signs in patients with CSU who were symptomatic despite treatment with upscaling dose of H1 antihistamines.

Keywords: Omalizumab, Chronic spontaneous urticaria, Efficacy, Safety, H1-antihistaminic

INTRODUCTION

Urticaria is a cutaneous reaction characterized by the development of wheals (which are variable sized swelling surrounded by reflex erythema accompanied by itching or burning, lasting for not more than 24 hours) and angioedema (sudden skin coloured swelling in lower dermis lasting for more than 72 hours) as per the EAACI/GA2LEN/EDF/WAO guidelines. Classification of urticaria is based on its episodic nature, acute or chronic along with further identifiable eliciting factors or stimuli.[1]

Chronic idiopathic/spontaneous urticaria (CIU/CSU) is characterized by itching, burning or painful evanescent wheals (hives) and/or angioedema, symptoms that present suddenly and are present most days of the week for at least 6 weeks. CU can be divided into CSU and chronic

inducible urticaria (CINDU).[1,2] It is an important cause of morbidity and even though it has a very low risk of endangering life, it has a high impact on QoL.[3] This disease affects at least 0.5-1.0% of the population and 40% may present urticarial lesions up to 10 years later.[4-7] Currently, more than 50 million people suffer from CSU, especially its negative effects on QoL and sleep, school and work performance as well as daily life activities and social relationships.[8]

Omalizumab, a humanized monoclonal anti-IgE antibody, is an effective and well-tolerated treatment for patients with CSU. Defining and better characterizing the response to omalizumab as well as predictors and markers of response to omalizumab will improve the management of patients with CSU.[8]

Objectives

The objectives were to conduct a systematic review and to assess the effect of omalizumab in improving symptoms of chronic urticaria unresponsive to conventional therapy.

Relevant literature

According to a report published in the annals of dermatology in January 2020 by Sabin et al omalizumab was currently the mainstay of treatment of antihistamine-resistant chronic spontaneous urticaria. The use of omalizumab in chronic inducible urticaria, up-dosing in chronic spontaneous urticaria and treatment of children younger than 12 years, currently off-label, were supported by evidence and further studies should be performed. Ligelizumab and UB-221 were novel anti-IgE monoclonal antibodies with a 40 to 50-fold and 8-fold greater affinity to IgE, respectively, compared with omalizumab and were currently being studied in clinical trials of CSU. Other drugs for the treatment of CSU were promising including interleukin (IL) 5-targeted monoclonal antibodies (mAbs), a chemoattractant receptor-homologous molecule expressed on TH2 cell antagonist, a mAb to Siglec-8, Bruton tyrosine kinase inhibitors, a spleen tyrosine kinase inhibitor and dupilumab, an anti-IL-4/13 mAb.[9]

Novel and better treatments for CU were very much needed. Some agents were in clinical trials already (e.g. ligelizumab) and additional ones should be developed, making use of the many promising targets recently identified and characterized.[9] Compared to omalizumab, treatment with ligelizumab provided greater and longer suppression of free IgE, basophil FcεRI and basophil surface IgE. It also showed 6 to 9-fold greater suppression of skin prick test responses to allergen. These data suggested that ligelizumab may be more potent than omalizumab in the treatment of CSU.[10]

In an article published by Saini et al in the journal of allergy asthma and immunology in 2019, there were many other newly developed and introduced drugs which were still under trials or few of them have completed trials. Anti-sialic acid-binding immunoglobulin-like lectin-8 sialic acid-binding immunoglobulin-like lectins (siglecs) was one of those new drugs, which were a family of glycan-binding inhibitory receptors and among them Siglec-8 was selectively expressed on human eosinophils, basophils and mast cells. AK002 was a humanized non-fucosylated IgG1 monoclonal antibody directed against Siglec-8.

METHODS

Search mechanism

The following electronic databases were searched, PubMed, Embase, Medline and the following clinical trials, registers-controlledtrials.com; clinicaltrials.gov; Australian New Zealand clinical trials.gov, Cochrane central register of controlled trials; WHO international clinical trials registry platform. A search in the Wiley online library, NEJM, JACI, BJD, JAAD international journals and Chinese search platform Baidu for Chinese and foreign language databases, both was conducted thoroughly.

Search strategy

This search strategy included the terms related to the intervention “omalizumab” or “human monoclonal antibody” and “chronic spontaneous urticaria” and “other treatments of urticaria” (as a MeSH terms and in all fields). All the published interventional studies were identified, and data from January 2010 to January 2020 was searched. Reference list of each report was also searched to identify additional omalizumab studies related to CIU.

Inclusion criteria

Inclusion criteria for current study were individuals older than 12 years of age diagnosed with chronic spontaneous urticarial. The patients were both males and females of all races. The patients were given a diagnosis of CSU and treated with omalizumab. Researches done in any geographic location; in high or low-income countries was included. Also, studies published in English language only was included in this review paper.

Exclusion criteria

Exclusion criteria for current study were studies with patient not followed up to the duration of at least 6 weeks. Also, studies with missing data were excluded.

Procedure

Information sources were searched, assessed and identified for inclusion of studies, facilitated by grading each eligibility criterion as eligible/not eligible/might be

eligible. The full text of each study was reviewed and the data was checked for consistency and clarity. Selected articles were obtained through a data collection format after qualifying the inclusion, exclusion criteria's, year of publication, authors, study design, study duration, number of participants in the intervention/placebo group, drug doses, days of treatment, route of administration, adverse effects, studies including the outcome measures.

Using an excel data sheet, the various characteristics of the included studies was tabulated and was described later.

Analysis

Statistical analysis

To perform this systematic review, the following data were extracted from the studies which were summarized using Microsoft excel software. The data were then summarized using Revman 5.3 software (developed by Cochrane collaboration). For dichotomous data, the relative risk (RR, the proportion of events in the treatment group about the proportion of events in the control group) and the respective confidence interval (CI) of 95% (95% CI) were calculated. For the analysis of continuous variables, the means difference with 95% CI was calculated.

To assess the heterogeneity of the studies included in this review paper, the Chi square test ($p<0.1$ indicated heterogeneity) and the I2 test (>50% represented heterogeneity). Possible causes of heterogeneity were differences in the size of the populations, interventions and evaluations of outcomes. The whole analysis was then represented in the forest plot.

To check for the existence of publication bias, the Begg funnel plot, a graph designed to check for the existence of publication bias was used to evaluate the publication bias in this study. The largest studies were plotted near the average and smaller studies were spread evenly on both sides of the average, creating a roughly funnel-shaped distribution. Deviation from this shape can indicate publication bias.

A total of 10 experimental study designs were qualified to be included in the study, related to the safety and efficacy of omalizumab in CSU patients despite treatment with H1-antihistamines. The table below represented the characteristics of the studies in terms of the methods like study design, whether the study was randomized or not; participants like relevant details of health status of participants, age, country; intervention like drug interventions including details of drug name, dose, frequency, mode of administration, duration of intervention; outcomes like a clear list of either outcomes and time-points from the study that are considered in the review or outcomes and time-points measured (or reported) in the study.

The ten studies which qualified the inclusion, exclusion criteria were all reviewed in detail and the above-mentioned characteristics were extracted and tabulated as below (Table 1).

The study design of all the included studies was that of randomized, double-blind and placebo controlled. Most of the included studies were either in phase 3 or phase 2 with one study in phase 4. The minimum number of participants involved were 30 and the maximum number of participants were 336. All the participants classified under the treatment group were diagnosed clinically as having chronic idiopathic urticaria not responding to previous treatment with antihistamines. The studies were conducted across various regions of the globe like United States of America, Denmark, Germany, Italy, Switzerland, Japan, Korea and Australia.

Each study also recorded the duration of intervention, time line of follow up, which ranged from 12 weeks to 48 weeks with follow up done mostly at 4th week. The route of administration being subcutaneous.

Outcome measures were classified as primary outcome measures and secondary outcome measures. Primary outcome measure recorded by most of the studies was a change in UAS7 or change in ISS from baseline; one study recorded change in CuQ2oL, while two of them recorded a change in FceRI receptor density. Secondary outcome measure was mainly change in UAS7, ISS, CuQ2oL, DLQI.

Biases

A bias was a systematic error or deviation from the truth, in results or inferences. Different biases can cause underestimation or overestimation of the true intervention effect. The Cochrane collaboration recommended a specific tool for assessing risk of bias in each included study. This comprised a judgement and a support for the judgement for each entry in a risk of bias table, where each entry addressed a specific feature of the study. The judgement for each entry involved assessing the risk of bias as low risk, as high risk, or as unclear risk, with the last category indicating either lack of information or uncertainty over the potential for bias. In clinical trials, biases can be broadly categorized as selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases that do not fit into these categories. The features of interest in a standard risk of bias table of a Cochrane review were sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias.[19]

Table 1: Summary of ten studies included in this paper.

Study	Methods	Participants	Intervention	Outcomes
XTEND-CIU (Xolair treatment efficacy of longer duration in CSU), United states. 2015 ID: NCT02392624[11]	Phase IV, multicentre, randomized, double-blind, placebo controlled study	206 participants with diagnosis of CIU refractory to H1antihistamines at baseline; omalizumab; n=152, placebo=53; age 12-75 years, CIU >6 months, UAS7 >16	48weeks; 6 SC inj of 300 mg; omalizumab for both experimental and control group 4weekly for 24 weeks; further 4 weekly 300 mg omalizumab in experimental group and placebo for control group for next 24 weeks	Primary outcome measures: UAS7 >12 for 2 weeks from week 24-48; secondary outcome measures: number of weeks from the first double-blind treatment to the first two-week interval with UAS7 ≥12 for both weeks
Study of efficacy and safety of omalizumab in refractory CSU patients; Japan, Korea, 2016, POLARIS study ID: NCT02329223[12]	Phase III, multicentre, randomized, double-blind, placebo controlled study	218 participants with diagnosis of CIU refractory to H1antihistamines at baseline; omalizumab 300/150 mg; n=72/68, placebo=68; ages 12-75 years, CIU >6 months	12 weeks; follow up 4 weeks. SC inj of 150 mg versus 300 mg omalizumab in experimental and placebo in control group for 12 week period	Primary outcome measures; change from baseline in the WISS at week 12; secondary outcome measures: UAS7 at week 12, % of participants with a UAS7 score ≤6 at week 12
Genentech inc. Response duration safety of Xolair in refractory CSU; 2013 Denmark, France Germany, Italy, ASTERIA II ID: NCT01292473[13]	Phase III, multicentre, randomized, double-blind, dose-ranging placebo controlled study	323 participants with diagnosis of CIU refractory to H1antihistamines at baseline; omalizumab 300/150/75 mg; n=67/74/75, placebo=74; age 12-75 years.	12 weeks; SC inj of 75, 150, 300 mg omalizumab in 3 experimental groups versus placebo in control	Primary outcome measures; change in weekly hives score at week 12; secondary outcome measures: UAS7 at week 12, DLQI at week 12
Genentech inc. response duration, safety of Xolair in refractory CSU, US, 2013 ASTERIA I ID: NCT01287117[14]	Phase III, multicentre, randomized, double-blind, dose-ranging placebo controlled study	319 participants with refractory CSU to antihistamines; omalizumab 300/150/75 mg; n=69/64/64, placebo=65; age 12-75 years.	12 weeks; SC inj of 75, 150, 300 mg omalizumab in experimental versus placebo in control	Primary outcome measures; change in WISS at week 12; secondary outcome measures: UAS7, % of complete responders, DLQI at week 12
Genentech inc. Safety study of xolair in refractory CSU, US, UK, Australia, Switzerland, 2013, GLACIAL ID: NCT01264939[1]	Phase III, multicentre, randomized, double-blind, placebo controlled study	336 participants; omalizumab 300 mg; n=252, placebo=83; age 12-75 years.	40 weeks; follow up 16 weeks; SC inj of 300 mg omalizumab in experimental versus placebo, H1 antihistamine, LTRA in control group	Primary outcome measures; % of participants with adverse events at end of 40 weeks; secondary outcome measures: UAS7, WISS at week 12, % of participants with UAS7 <6 at week 12
G study: efficacy and safety of omalizumab in adults,	Phase II, multicentre,	49 participants; omalizumab 75-	24 weeks; SC inj of omalizumab 75-375	Primary outcome measures:

Continued.

Study	Methods	Participants	Intervention	Outcomes
2011, Germany ID: NCT00481676[15]	randomized, double-blind, placebo controlled study	375 mg; n=27; placebo=22; age 18-75 years	mg based on bodyweight and baseline IgE versus loratadine, cetirizine in control group	UAS7 at week 24; econdary outcome measures: DLQI, CUQ2oL at week 24
Mystique study: dose ranging study of xolair in refractory CIU, 2011, Germany, US; ID: 10.1016.jaci.2011.06.010[16]	Phase II, randomized, double-blind, placebo controlled, dose ranging study	90 participants; omalizumab 75, 300, 600 mg; n=23/25/21; placebo=21; age 12-75 years.	16 weeks; follow up 12 weeks, SC inj of omalizumab 75, 300, 600 mg randomised on body weight versus placebo control; diphenhydramine as rescue medication in all groups	Primary outcome measures; UAS7 at week 4; secondary outcome measures: WISS, weekly hives score
X-ACT: NCT:01723072, Germny,2015, Impact of omalizumab on quality-of-life measures on refractory CSU patients[17]	Phase III, multicentre, randomized, double-blind, placebo controlled study	91 participants omalizumab 75, 300, 600 mg; n=23/25/21; placebo=21; age 12-75 years	28 weeks, follow up 8 weeks, SC inj of omalizumab in 3 experimental versus placebo in control	Primary outcome measures; CuQ2oL; secondary outcome measures: AeQ2oL, UAS7
M study, Mode of action study of omalizumab in patients with chronic idiopathic urticaria (CIU), NCT01599637[18]	Phase II, multicentre, randomized, double-blind, placebo controlled study	30 participants omalizumab 300 mg	12 weeks, follow up every 4 weeks up to 8 weeks after treatment, SC inj of omalizumab 300 mg versus placebo	Primary outcome measures; change in FceRI positive skin cells from baseline; secondary outcome measures; change in UAS7, change in IgE%

Table 2: Summary of bias assessment of each involved study as per the Cochrane's guidelines tool for bias assessment.

Study	Assessment of bias	Support for judgement	Remarks
XTEND-CIU, US, 2015 ID: NCT02392624[11]	Selection bias Performance bias Detection bias Attrition bias Reporting bias	Allocation by investigator (HR) Blinding of participants (LR) Distribution to groups judged by allocator (HR) No missing outcome data (LR) Detailed study protocol (LR)	Moderate risk
POLARIS omalizumab in refractory CSU Japan 2016 ID: NCT02329223[12]	Selection bias Performance bias Detection bias Attrition bias Reporting bias	Randomized allocation (LR) Quadruple Masking (participant, care provider investigator, outcome assessor) (LR) No missing outcome data (LR) Detailed study protocol (LR)	Low risk
ASTERIA II Genentech inc. Response duration safety of xolair in refractory CSU; 2013, Denmark ID: NCT01292473[13]	Selection bias Performance bias Detection bias Attrition bias Reporting bias	Randomized allocation (LR) Double masking (participant, investigator) (LR) No blinding of outcome assessors (HR)? No missing outcome data (LR) Detailed study protocol (LR)	Low risk
ASTERIA I Genentech inc. Response duration safety of xolair in refractory CSU, US, 2013 ID:	Selection bias Performance bias Detection bias Attrition bias Reporting bias	Randomized allocation (LR) Masking-triple (participant, investigator, outcome assessor) No missing outcome data (LR) Detailed study protocol (LR)	Low risk

Continued.

Study	Assessment of bias	Support for judgement	Remarks
NCT01287117[20]			
GLACIAL Genentech inc. Safety study of xolair in refractory CSU, US, UK, Australia, Switzerland, 2013 ID: NCT01264939[21]	Selection bias Performance bias Detection bias Attrition bias Reporting bias	Randomized allocation (LR) Masking: Triple (Participant, Investigator, Outcomes Assessor) (LR) No missing outcome data (LR) Detailed study protocol (LR)	Low risk
G STUDY Efficacy and safety of omalizumab in adults, 2011, Germany ID: NCT00481676[22]	Selection bias Performance bias Detection bias Attrition bias Reporting bias	Randomized allocation (LR) Quadruple Masking (participant, care provider investigator, outcome assessor) (LR) No missing outcome data (LR) Detailed study protocol (LR)	Low risk
MYSTIQUE NCT:00866788 Dose ranging study of xolair in refractory CIU, 2011, Germany, US; ID:10.1016. jaci.2011.06.010[16]	Selection bias Performance bias Detection bias Attrition bias Reporting bias	Randomized allocation (LR) Quadruple Masking (participant, care provider investigator, outcome assessor) No missing outcome data (LR) Detailed study protocol (LR)	Low risk
M STUDY NCT01599637 Mode of action study of omalizumab in patients with chronic idiopathic urticaria (CIU)[22]	Selection bias Performance bias Detection bias Attrition bias Reporting bias	Randomized allocation (LR) Double blind treatment (LR) No missing outcome data (LR) Detailed study protocol (LR)	Low risk
S STUDY Double-blind placebo-controlled trial of the effect of omalizumab on basophils in chronic urticaria patients[23]	Selection bias Performance bias Detection bias Attrition bias Reporting bias	Randomized allocation (LR) Double blind treatment (LR) No missing outcome data (LR) Detailed study protocol (LR)	Low risk
X ACT study NCT01723072 Impact of omalizumab on quality-of-life measures in refractory CSU patients[24]	Selection bias Performance bias Detection bias Attrition bias Reporting bias	Randomized allocation (LR) Double blind treatment (LR) No missing outcome data (LR) Detailed study protocol (LR)	Low risk

After reviewing each study carefully, the data of the bias involved in each study was collected and carefully evaluated. By using the Cochrane collaboration tool, risk of bias assessment was done for all the 10 studies included in this analysis (Table 2). All of them used random sequence generation and allocation concealment. There was double blinding and quadruple blinding in some studies, with blinding of the participants, care provider, investigator and outcome assessor. The outcome measures in all of the included studies were similar and had no missing data. All of the included studies had a detailed study protocol. Therefore, all the studies included in this study were of a low risk.

RESULTS

The numerical data of all the studies was tabulated separately in an excel sheet and is as below (Table 3). The data in terms of the drug dose, sample size, age (was recorded in terms of mean±SD), the outcome measures and the adverse events. Outcome measures were almost the same with very slight variations amongst studies. Most of the included studies recorded the baseline values as well as the result after intervention. Most commonly used outcome measures events were of the change in UAS7, change in ISS, change in DLQI, change in CuQ2oL, presence of angioedema. Very few studies have recorded the serum IgE values, presence of angioedema free days. The adverse events were recorded by all the included studies and the adverse events were classified into 3 categories, at least one adverse event, adverse events during follow up and serious adverse events. The numerical data were mostly recorded in terms of mean and standard deviation. Adverse events were all recorded in terms of percentage.

Table 3: Numerical characteristics of various variables recorded in the included studies.

Study	Intervention (mg)	Sample size	Age (mean±SD)	IgE (IU/Ml) (mean, SD)
XTEND CIU	Omalizumab 300	81	43.1 (14.68)	-
	Placebo	53	48.5 (13.22)	-
POLARIS	Omalizumab 150 mg/300	71/73	43.6 (12.24)/44.6 (14.86)	-
	Placebo	74	42.5 (14.26)	-
ASTERIA I	Omalizumab 75/150/300	77/80/81	40.7 (15.2)/41.1 (14.0)/42.4 (13.2)	-
	Placebo	80	40.4 (15.6)	-
ASTERIA II	Omalizumab 75/150/300	82/82/79	39.7 (15.0)/43.0 (13.2)/44.3 (13.7)	-
	Placebo	79	43.1 (12.5)	-
GLACIAL	Omalizumab 300	252	42.7 (13.9)	79.0 (1-3050)
	Placebo	83	44.3 (14.7)	71.0 (1-1230)
X ACT	Omalizumab 300	44	56.2 (18.69)	-
	Placebo	47	59.9 (19.24)	-
S study	Omalizumab 300	20	41.8 (15.2)	-
	Placebo	10	42.4 (13.3)	-
M study	Omalizumab 300	20	37.5 (11.02)	-
	Placebo	10	41.1 (7.96)	-
MYSTIQUE study	Omalizumab 75/300/600	23/25/21	-	-
	Placebo	21	-	-
G study	Omalizumab 75-375	27	39.1 (9.0)	-
	placebo	22	42.3 (15.0)	-

Table 4: Numerical characteristics of various variables recorded in the included studies (UAS7 baseline).

Study	Intervention (mg)	UAS7 baseline (mean, SD)	Change in UAS7 (mean, SD) or SE	ISS baseline (mean, SD)
XTEND CIU	Omalizumab 300	32.4 (7.2)	0.6 (1.4)	15.7 (3.6)
	Placebo	32.9 (7.0)	0.9 (1.6)	16.0 (3.5)
POLARIS	Omalizumab 150 mg/300	29.6 (7.4)/31.8 (7.1)	-18.79 (1.29)/-22.44 (1.24)	13.2 (4.0)/14.6 (3.7)
	Placebo	30.1 (6.5)	-13.90 (1.27)	13.7 (3.3)
ASTERIA I	Omalizumab 75/150/300	31.7 (6.7)/30.3 (7.3)/31.3 (5.8)	-13.82 (13.26)/-14.44 (12.95)/-20.75 (12.17)	14.5 (3.6)/14.1 (3.8)/14.2 (3.3)
	Placebo	31.1 (6.7)	-8.01 (11.47)	14.4 (3.5)
ASTERIA II	Omalizumab 75/150/300	-	(-13.08) (12.67)/(-17.89) (13.23)/(-21.74) (12.78)	-
	Placebo	-	(-10.36) (11.61)	-
GLACIAL	Omalizumab 300	31.2 (6.6)	-19.01 (13.15)	14.0 (3.6)
	Placebo	30.2 (6.7)	-8.50 (11.71)	13.8 (3.6)
X ACT	Omalizumab 300	26.5 (8.2)	-	-
	Placebo	27.9 (8.7)	-	-
S study	Omalizumab 300	11	-	8
	Placebo	18.5	-	8
M study	Omalizumab 300	-	(-23.1) (12.94)	-
	Placebo	-	(-8.1) (14.45)	-
MYSTIQUE study	Omalizumab 75/300/600	-	(-9.79) (11.75)/(-19.93) (12.38)/(-14.56) (10.17)	-
	Placebo	-	(-6.91) (9.84)	-
G study	Omalizumab 75-375	-	(-17.8) (10.52)	-
	Placebo	-	(-5.8) (11.52)	-

Table 5: Numerical characteristics of various variables recorded in the included studies (presence of angioedema).

Study	Intervention (mg)	CUQ2OL improvement (mean, SD)	Presence of angioedema baseline, N (%)	Angioedema free days (%)
XTEND CIU	Omalizumab 300	-	-	-
	Placebo	-	-	-
POLARIS	Omalizumab 150mg/300	-	12 (16.9)/12 (16.4)	-
	Placebo	-	15 (20.3)	-
ASTERIA I	Omalizumab 75/150/300	-	35 (45.5)/38 (47.5)/34 (42.0)	-
	Placebo	-	44 (55.0)	-
ASTERIA II	Omalizumab 75/150/300	-	-	93.5 (14.9)/91.6 (17.4)/95.5 (14.5)
	Placebo	-	-	89.2 (19.0)
GLACIAL	Omalizumab 300	-	137 (54.4)	91.0 (21.0)
	Placebo	-	41 (49.4)	88.1 (18.9)
X ACT	Omalizumab 300	55.4 (13.6)	19 (43.2)	-
	Placebo	56.1 (17.2)	22 (46.8)	-
S study	Omalizumab 300	-	45	-
	Placebo	-	45	-
M study	Omalizumab 300	14.51 (22.319)	-	90.9 (22.83)
	Placebo	53.53 (29.817)	-	70.5 (28.50)
MYSTIQUE	Omalizumab 75/300/600	-	-	-
	Placebo	-	-	-
G study	Omalizumab 75-375	(-21.0) (21.97)	-	-
	Placebo	(-2.3) (14.14)	-	-

Table 6: Numerical characteristics of various variables recorded in the included studies (angioedema free days).

Study	Intervention (mg)	Angioedema free days (%)	At least 1 adverse event N (%)	Adverse events during follow up	Serious adverse events, N (%)
XTEND CIU	Omalizumab 300	-	34.57	-	2.47
	Placebo	-	41.51	-	5.66
POLARIS	Omalizumab 150mg/300	-	57.7/54.8	-	4.23/4.11
	Placebo	-	55.40	-	0
ASTERIA I	Omalizumab 75/150/300	-	78.6/82.8/70.4	58.6/69/56.8	0/2.3/2.5
	Placebo	-	66.30	51.3	1.3
ASTERIA II	Omalizumab 75/150/300	93.5 (14.9)/91.6 (17.4)/95.5 (14.5)	39.47/47.73/44.30	-	1.32/1.14/6.33
	Placebo	89.2 (19.0)	44.30	-	2.53
GLACIAL	Omalizumab 300	91.0 (21.0)	56.35	-	7.14
	Placebo	88.1 (18.9)	49.40	-	6.02
X ACT	Omalizumab 300	-	68.20	-	9.1
	Placebo	-	72.30	-	4.3
S study	Omalizumab 300	-	-	-	-
	Placebo	-	-	-	-
M study	Omalizumab 300	90.9 (22.83)	85	-	-
	Placebo	70.5 (28.50)	60	-	20
MYSTIQUE	Omalizumab 75/300/600	-	39.13/44/ 38.1	39.13/48/23.8	0/4/0

Continued.

Study	Intervention (mg)	Angioedema free days (%)	At least 1 adverse event N (%)	Adverse events during follow up	Serious adverse events, N (%)
	Placebo	-	23.81	33	0
G study	Omalizumab 75-375	-	70.37	-	0
	Placebo	-	54.55	-	9.09

DISCUSSION

The objective of this study was to quantitatively summarize about the already well-known facts about the benefits and harms of omalizumab. A total of ten studies involving 1692 patients were included in this analysis. The Cochrane tool was used for the assessment of bias involved in each study and 9 out of the ten studies were considered to be of low risk and one study was of moderate risk. Thus, provided the first basis that this review was quality assured and providing an evidence in favour of omalizumab. Synthesizing the results from ten qualified studies, this study revealed, with high-quality evidence, that omalizumab was effective in the treatment of CSU in those patients who were refractory to antihistamine treatment when compared to a placebo.

Through this systemic review, it was found that omalizumab was effective in the treatment of CSU, not responding to conventional antihistamines. Although the antihistamines refractoriness and was variably defined in the different evaluated studies, the results obtained were all significant.

Clinical response to therapy with omalizumab to CSU in literature had been defined by several ways and various studies published have used different criteria to judge the efficacy. The importance of using standardized tools for assessment of real-life efficacy of the drug had been well known. The consensus recommends the use of tools like UAS7 (urticaria activity score), DLQI (dermatology life quality index), ISS (itch severity score), CuQ2oL (chronic urticaria and quality of life questionnaire), measures of sleep, adverse events recorded and lastly response rate. These tools were not only limited for use in clinical studies, but also recommended for use in clinical practice. There were also various other indices which have been used like the DSQL (dermatology specific quality of life), Skindex-16, Skindex-29, urticaria severity score, AE-QoL (angioedema quality of life). The usage of wide variety of indices and different instruments to measure the outcomes across different clinical studies make it difficult to do a comparison.

The outcomes that were used by the studies which were involved in this analysis were UAS7, WISS, DLQI, CU-Q2oL, AE-QoL and adverse events. The adverse events were recorded as incidence of at least one adverse event and serious adverse events.

Through this systematic review, it had been noted that, with growing incidence of CSU in the general population, the increase in the use of omalizumab has resulted in potential benefit. As the average duration of CSU was known to last anywhere between six months to five years and there were many patients with concomitant angioedema, the evidence that this drug had potential benefit plays a major role. There was a need for consideration of the professional, patient related personal, social and financial factors in the overall management of this condition. As with many other studies, this analysis data showed that this drug can be used as a treatment option which not only controlled the symptoms, but also helped to improve the overall quality of life for the patients with minimal adverse effects.

In this particular analysis, ten studies qualified for the inclusion and exclusion criteria's and were included in systematic review. Totally 1692 patients across ten studies were involved. The patients who were included in the treatment group were all diagnosed as having CSU who were refractory to conventional treatment with H1 antihistamines. After carefully retrieving all the data from each study, all the data was tabulated separately into word document and in excel sheet. All the data was then entered into Revman 5.3 software and a meta-analysis was done. Subgroup analysis was done wherever feasible.

The results obtained from this analysis clearly pointed to some benefit of omalizumab for CSU patients who were refractory to conventional treatment with H1 antihistamines. There was a significant reduction of the parameter of urticarial activity shown by 5 studies which measured the change in the urticarial symptoms from baseline over a 12 to 48 week period. These studies measured the reduction of the urticarial symptoms in various dosages of omalizumab. These studies were found to be of low-risk bias after using the Cochrane's tool for risk of bias assessment. The results of which was evident in the funnel plot as described in Figure 1.

Around six studies have measured the parameter of improvement in the severity of itching in CSU patients using various dosages of the drug and there was a clear-cut evidence (as was seen in the forest plot) of efficacy of omalizumab over placebo (Figure 2).

DLQI was another important parameter which was taken into account by many studies as it was a very important determinant of the impact of the disease on the life of the

patient, be it personal or social or professional life. Omalizumab again was found to be very effective in the improvement of the QoL in CSU patients treated with this drug.

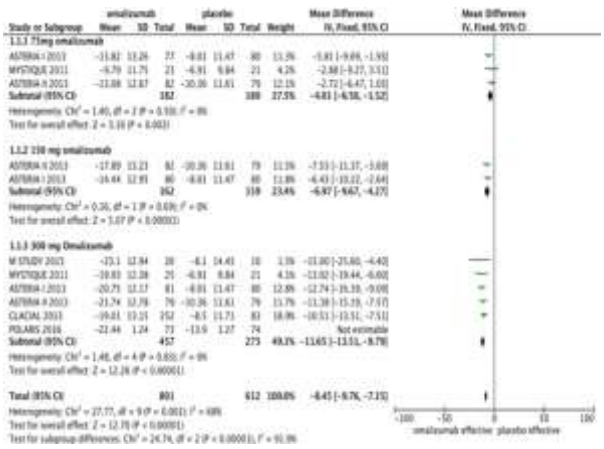

Figure 1: Funnel plot.

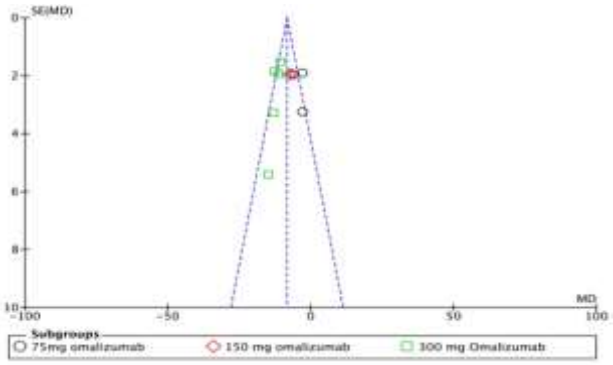

Figure 2: Efficacy of omalizumab over placebo.

Adverse events being one of the major concerns in every study, analysis didn't show any statistically significant difference in the frequency of adverse events in both the treatment and the control groups.

CONCLUSION

The results of this systematic review were found to be comparable with the other similar systematic reviews conducted in the recent past.

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