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Is Omalizumab a Safe and Effective Treatment for Chronic Urticaria?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not omalizumab is a safe and effective treatment for chronic urticaria.

STUDY DESIGN: Review of two randomized controlled studies and one crossover study. All three studies are published in English between 2008-2011.

DATA SOURCES: Two randomized, double blind, placebo controlled studies and one crossover study found using PubMed and EBSCOhost.

OUTCOMES MEASURED: Each trial measured the duration, size, number and/or intensity of wheals. This was done by using the urticaria activity score (UAS). Quality of life was also measured using Dermatology Life Quality Index (DLQI), Skindex-29, and Chronic Urticaria Quality of Life Questionnaire (Cu-Q2oL).

RESULTS: The first study, the Maurer et al study showed that after 24 weeks of treatment with omalizumab, there was a mean change in UAS7 from baseline of -17.8. Saini et al study showed a mean change in UAS7 from baseline of -19.9 after four weeks of omalizumab treatment. Quality of life measured in the Maurer et al study showed that those treated with omalizumab experienced as least a 50% improvement. No serious adverse events were noted in any of the three studies. Most common adverse events include diarrhea, nasopharyngitis, and headache.

CONCLUSION: Based on these three trails, omalizumab is a safe and effective treatment for chronic urticaria. Each study showed a significant improvement of symptoms without any serious side effects when using omalizumab.

KEY WORDS: Omalizumab, Xolair, Urticaria

INTRODUCTION

Urticaria is a pruritic dermatologic wheal like lesion that can be associated with angioedema. It is considered chronic, if symptoms persist for more than six weeks. In about half of patients with chronic urticaria, a cause cannot be identified making it increasingly difficult to properly treat.[1] This paper evaluates two double blind randomized controlled studies and one crossover study comparing the efficacy of omalizumab compared to a placebo for the treatment of chronic urticaria.

Chronic urticaria is relevant to the Physician Assistant profession due to its prevalence, lack of successful treatment options and costs to the patients effected. Chronic urticaria can have significant effects on patients' quality of life. Urticaria is extremely common, effecting 15-23% of the general populations.[2] Whereas the incident rate for chronic urticaria is about 0.5%.[2] The annual medical costs per patient is estimated at about $1,725 with medications costing about $1,280, outpatient visits costing $280, emergency department/hospital visits costing about $148, and laboratory studies costing about $17 per year per patient.[3] Not only do these patients spend a significant amount of money per year due to chronic urticaria but they also have many health care visit. The exact number of visits each year is unknown but a study published in January of 2008 in JAMA took 50 patients with chronic urticaria and analyzed them from December 1, 2004 to May 31, 2006. Of the 50 participants, 46 went to visit an outpatient facility and 15 went to visit the emergency department at least once within this time period.[3]

For 80% of patients with chronic urticaria, the cause is unknown making it extremely difficult to find a successful treatment. For the other 20%, chronic urticaria can involve IgG auto-antibody production against IgE or its receptor (FceRI) leading mast cell degranulation and subsequently causing symptoms.[4,5] Some patients with chronic urticaria can produce IgE

autoantibodies against thyroperoxidase (TPO).[5] As previously stated, in the majority of cases, a cause cannot be identified but exasperating factors such as stress, alcohol, extreme heat/cold, NSAIDS, and spicy foods may contribute to an outbreak.[2] Due to the unknown etiology, there is currently no curative treatment.[4]

In acute urticaria, the treatment of choice is to remove the cause. Because the cause is usually unknown in terms of chronic urticaria, symptomatic treatment has been the standard of care.[2] Usually, urticaria is treated with antihistamines. If symptoms do not resolve, you can increase the dose or add another antihistamine.[6] If antihistamines are ineffective, glucocorticoids, immunosuppressive agents, immunomodulatory agents or leukotriene modifying agents can be used.[6] Once symptoms have resolved, patients should stay on the current drug regimen as maintenance therapy.[6]

The current recommended drug regimen is many times unsuccessful. Omalizumab (Xolair) is a humanized anti-IgE monoclonal antibody.[1] It is currently being used for the treatment of IgE mediated asthma but may be of some benefit to those suffering from chronic urticaria.[1] Xolair binds to the C3 area of the IgE heavy chain. The C3 area is where IgE would essentially bind to FceRI receptor on the target cells (mast cells and basophils).[5] By occupying this site, free IgE levels in the serum will be reduced as well as a down regulation of FceRI expression leading to a decrease in the release of inflammatory mediators.[5]

OBJECTIVE

The objective of this systematic review is to determine whether or not omalizumab is a safe and effective treatment for chronic urticaria.

METHODS

Three studies were utilized in this review. Two being randomized, double blind, placebo controlled studies and one crossover study. The population includes patients with symptomatic chronic urticaria. The intervention used was omalizumab. The dose depends on the patients' weight and serum IgE levels. The treatment group receiving omalizumab was compared to those receiving a placebo. Outcomes measured include number and size of hives, adverse events, pruritis intensity and quality of life.

Keywords used when searching for the articles used consist of omalizumab, xolair, and urticaria. The articles chosen were researched by the author and obtained through either PubMed or EBSCOhost. They were selected based on the types of studies and relevance to the clinical question. All articles chosen are published in English. Inclusion criteria for selecting these articles included randomized controlled or crossover studies which include outcomes that directly benefit the patient. Exclusion criteria included patients that experience acute urticaria, those with other skin conditions, and those successfully being managed with antihistamines, steroids, or immunosuppresants. The statistics that were utilized and reported include numbers needed to treat (NNT), numbers needed to harm (NNH), relative risk reduction (RRR), absolute risk reduction (ARR), relative benefit increase (RBI), absolute benefit increase (ABI), relative risk increase (RRI), absolute risk increase (ARI) and p-value. Table 1 displays the demographics and characteristics of the included studies.

Table 1 - Demographics and Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Maurer[5] (2011)	Double blind RCT	49	18-70	-Symptoms for ≥6 weeks despite anti-histamine use. -Body weight between 20-150 kg. -IgE level between 30-700 IU/mL. -IgE-anti-TPO antibody level ≥5 IU/mL. -Weekly UAS ≥10.	-Acute urticaria -Steroid or immuno-suppressant use within 4 weeks. -Hx of epilepsy, malignancy, or CVA. -Increased IgE levels for other reasons.	7	Subcutaneous Omalizumab (75-375 mg) q2-4 wks x 24 wks Dose based on body weight and IgE levels
Saini[1] (2011)	Double blind RCT	90	12-75	-Moderate-severe chronic urticaria despite anti-histamine use. -UAS of ≥4 (clinic), and ≥12 (pt diary)	Weight <40 kg. Omalizumab within 12 months. Other skin d/o.	19	Omalizumab Dose - 75, 300, and 600 mg
Kaplan[7] (2008)	Cross-over study	12	18-75	-Symptoms for ≥6 weeks despite anti-histamine use -IgE <700 IU/mL -(+) basophil histamine release OR autologous skin test -At least moderate pruritus (score of ≥2) -At least moderate pruritus, # of hives, and size (score of ≥4).	Physical, vasculitis, or urticaria d/t secondary reasons. Steroid or immuno-suppressant use within 4 weeks	0	Placebo for 4 weeks. Then omalizumab for 16 weeks. Given q2 or 4 weeks Dose depends on weight and IgE levels

OUTCOMES MEASURED

The outcomes measured include duration, size, number and/or intensity of wheals, pruritus, erythema, and angioedema were done so by using the urticaria activity score (UAS).[1,5,7] The UAS is based off patient diaries. Because of the day to day variations of the disease, the mean weekly UAS (UAS7) ranging from 0-42 was utilized and compared with baseline scores.[1,5,7] Quality of life was also measured using Dermatology Life Quality Index (DLQI), Skindex-29, and Chronic Urticaria Quality of Life Questionnaire (Cu-Q2oL).[5,7] DLQI is a questionnaire consisting of 10 items under 6 headings (symptoms, daily activities, leisure, work/school, personal relationships, and treatment). Each item is scored based on severity/impairment from 0-3 with higher scores meaning more severe impairment.[5,7] Skindex-29 consists of 29 items in three categories (physical symptoms, social functioning, and emotional state) with scores ranging from 0-100 combined.[5] Cu-Q2oL consists of 23 items with the following categories: limits, looks, swelling/eating, functioning, sleep, mental status, and embarrassment.[5] Each item is scored based on a five point scale.[5]

RESULTS

All three articles compared the use of omalizumab with the use of a placebo for the treatment of chronic urticaria. Mauerer et al and Saini et al are double blind, randomized controlled trials whereas Kaplan et al study is a crossover study. Each article was presented as continuous data which then was converted into dichotomous data in order to asses the improvement in symptoms, adverse reactions, and quality of life.

Maurer et al study excluded those taking steroids, or immunosuppresants within the last four weeks. Also, those with increased IgE levels for reasons other than chronic urticaria were excluded as well.[5] The UAS7 scores were compared from baseline to week 24 (Table 2). The

mean change in UAS7 from baseline in the treatment group was -17.8 and the placebo group, only -7.9. There was a difference of 9.9 points between the treatment and the control group which is statistically significant (95% CI, P-value=0.0089).[5] After 24 weeks of treatment, 67% of those being treated with omalizumab were completely symptom free whereas only 4% of those receiving placebo were symptom free according to the investigator's global assessment (Table 3).[5] Therefore, the NNT was calculated as two (Table 3). This indicates that for every two patients treated with omalizumab for 24 weeks, one patient will achieve complete resolution of their symptoms.

Saini et al study excluded those who have taken omalizumab within the last 12 months and those with other skin conditions. The UAS7 scores were compared at baseline and then again at week four (Table 2). There was a statistically significant improvement with the P-value <0.001 in those treated with 300mg of omalizumab compared to those treated with the placebo. In four weeks, patients in the treatment group had a mean UAS score 19.9 points lower than they did at baseline (Table 2) and 36% achieved complete resolution of symptoms (Table 3). No single patient in the placebo group were symptom free after four weeks of treatment (Table 3). Furthermore, the NNT was calculated as three after converting continuous data into dichotomous data (Table 3). For every three patients with chronic urticaria that receive 300mg of omalizumab for four weeks, one patient will have complete resolution of symptoms.

Kaplan et al study is a crossover study where 12 patients with chronic urticaria received a placebo for four weeks and then omalizumab for 16 weeks. The mean baseline UAS7 score was 7.50 (1.78).[7] During the last 4 weeks of omalizumab treatment, the mean UAS7 score was 2.66 (3.31).[7] There was a significant mean change from baseline of -4.84 (2.86) with a P-value of 0.0002 during the last four weeks of omalizumab treatment (Table 2). Out of the 12 participants,

seven of them (58%) achieved complete resolution of symptoms.[7] This being said, NNT was calculated to be two patients (Table 3) meaning that for every two patients treated, one will achieve complete resolution of symptoms.

Table 2. Efficacy of omalizumab when compared to placebo

Study	Group	Mean (SD) change in UAS7 from baseline
Maurer[5], 2011	Omalizumab	-17.8
	Placebo	-7.9
Saini[1], 2011	Omalizumab	-19.9 (12.38)
	Placebo	-6.9 (9.84)
Kaplan[7], 2008	N/A	-4.82 (2.86)

Table 3. Efficacy of treating chronic urticaria with omalizumab

Study	Complete Resolution of Symptoms	Relative Benefit Increase (RBI)	Absolute Benefit Increase (ABI)	Number Needed to Treat (NNT)	P-Value
Maurer[5], 2011	Omalizumab - 67% Placebo - 4%	15.75	0.63	2 Patients	N/A
Saini[1], 2011	Omalizumab - 36% Placebo - 0%	N/A	0.36	3 Patients	<0.001
Kaplan[7], 2008	58%	N/A	N/A	2 Patients	<0.05

Adverse reactions were analyzed by the Maurer et al and the Saini et al study. Maurer et al study showed that 81.5% of those being treated with omalizumab and 86.4% being treated with a placebo experienced an adverse reaction with diarrhea, nasopharyngitis, and headache being some of the most common.[5] The NNH was calculated by converting continuous data into

dichotomous data at -20 (Table 4). Therefore, for every 20 patients treated with omalizumab, one fewer patient would experience an adverse effect (AE) when compared to placebo.

Saini et al study found that out of the 25 patients receiving 300mg of omalizumab, 12 experienced an adverse event (Table 4).[1] Of the 21 patients receiving the placebo, 10 patients experienced an AE (Table 4).[1] After converting the continuous data into dichotomous data, the NNH is calculated to be 250 patients. Therefore, for every 250 patients treated with 300mg of omalizumab, one will then experience and adverse reaction.

Table 4. Results and Analysis of Adverse Effects

Study	% experiencing AEs	Relative Risk Increase (RRI)	Absolute Risk Increase (ARI)	Number Needed to Harm (NNH)
Maurer[5], 2011	Omalizumab - 81.5% Placebo - 86.4%	-5.7%	-4.9%	-20
Saini[1], 2011	Omalizumab - 48% Placebo - 47.6%	0.8%	0.4%	250

Quality of life was analyzed in the Maurer et al study. Table 5 shows the percentage of improvement based off of the three different questionnaires assessing quality of life (DLQI, Skindex-29, and Cu-Q2oL). Each questionnaire showed that those receiving omalizumab experienced a greater improvement in quality of life compared to those receiving the placebo. This is statistically significant for all three questionnaires with a P-value of <0.01.[5]

Table 5. Improvement in quality of life

Group	DLQI	Skindex-29	Cu-Q2oL
Omalizumab	62.4%	50%	53.2%
Placebo	15.3%	6.3%	5.9%

DISCUSSION

Omalizumab is an IgG monoclonal antibody directed against IgE and is currently only approved in the United States for the use of moderate-severe allergic asthma in those over the

age of 12.[8] Initially, several case reports and a small series showed that omalizumab may have a beneficial effect for those with chronic urticaria.[6] Because omalizumab is not currently approved for the use of chronic urticaria, cost may be a barrier preventing patients from utilizing this drug. Insurance companies reimburse on a "patient by patient basis".[6] Several contraindications and concerns need to be taken into consideration when using omalizumab. Anaphylaxis is a black box warning.[8] If anaphylaxis occurs, it usually does within the first two hours.[8] Delayed onset anaphylaxis is also possible and can even be seen over a year after the drug regimen was started.[8] Contraindications include previous hypersensitivity reaction to omalizumab, acute bronchospasm, and status asthmaticus.[8]

All three studies analyzed showed a greater improvement in chronic urticaria with the use of omalizumab compared to the use of a placebo. This review supports the use of omalizumab in the treatment of chronic urticaria but there are several limitations in the studies used. In the Kaplan et al study, the sample size was extremely small with only 12 participants. Even though the data suggests that omalizumab improves the symptoms of chronic urticaria, the small sample size may not accurately represent the total population of those effected with this disease. The larger sample sizes in Maurer et al and Saini et al studies better depict the outcome of treating chronic urticaria with omalizumab. Another limitation in the Kaplan et al study is that it is a crossover study and not a double blind randomized controlled study. P-values were not given in the Maurer et al study when discussing those who had a complete resolution of symptoms leading to questioning of statistical significance.

CONCLUSION

Based on this systematic review and the chosen studies, omalizumab is a safe an effective treatment for chronic urticaria. The data within these three studies are consistent with the

beneficial effects of omalizumab as well as its overall safety. No serious adverse effects were noted and participants' quality of life improved. Future studies should include double blind randomized controlled trials with larger sample sizes. Also, researching the use of omalizumab as a complementary drug to use along with current drug regimens may show some benefits. Continued research should include longer durations of treatment to better evaluate the benefits verses the risks of treating chronic urticaria with omalizumab.

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