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**Use of Omalizumab for Management of Idiopathic Anaphylaxis: A Systematic Review and
Retrospective Case Series**

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Abbreviations: DBPC, double-blind, placebo-controlled; GI, gastrointestinal; IA: idiopathic anaphylaxis; Ig: immunoglobulin; LTRA, leukotriene receptor antagonist.

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Abstract

Background: Patients with idiopathic anaphylaxis (IA) may fail to respond to a combination of high dose H1- and H2-antihistamines and mast cell stabilizers. Treatment options for these patients are currently limited.

Objective: To describe the clinical experience of omalizumab use for the treatment of patients with IA but no evidence of underlying clonal mast cell disorders.

Methods: We performed a retrospective review at two separate institutions of medical records of patients with a diagnosis of IA without evidence of mast cell clonality who had received treatment with omalizumab. We searched PubMed for studies describing omalizumab use in similar patients. Information about symptoms and omalizumab therapy were compiled and response pattern of anaphylaxis was determined.

Results: Thirty-five patients with IA and no evidence of mast cell clonality who received omalizumab were identified. The median age was 36 years of age at the start of omalizumab (range 11-54 years, N = 29). The frequency of anaphylaxis episodes prior to omalizumab treatment varied from 2 total episodes to several episodes per month. The most often used initial omalizumab dose was 300mg every 4 weeks (N = 16). Most patients ultimately achieved clinical response after starting omalizumab: complete response (63%, N = 22), partial response (28.5%, N = 10), with three nonresponders.

Conclusion: Omalizumab may be an effective treatment option for patients with IA who do not have evidence of mast cell clonality and fail to respond to antihistamines and mast cell stabilizers.

Introduction

Anaphylaxis, a potentially life-threatening systemic reaction, is most commonly caused by stinging insects and medications in adults and by foods in children and adolescents.¹ However, in about 13-18% of patients, no triggers are identified and these patients are diagnosed with idiopathic anaphylaxis (IA).² IA can be a manifestation of clonal mast cell disorders such as systemic mastocytosis and monoclonal mast cell activation syndrome;² however, evidence of mast cell clonality is absent in the majority of these patients.³ Treatment approach to these patients with IA and no evidence of mast cell clonality is not well-established.² In addition to providing these patients with an epinephrine autoinjector for treatment of acute episodes, prevention of anaphylaxis may be achieved with a combination of high-dose non-sedating H1-antihistamines, H2-antihistamines, leukotriene receptor antagonists (LTRAs), and/or cromolyn.² Some patients remain symptomatic despite these medications and require prednisone to reduce the frequency of IA, but the use of oral corticosteroids may result in undesirable side effects. A clinical response to omalizumab, a humanized monoclonal immunoglobulin (Ig)G antibody against IgE that inhibits IgE binding to the high-affinity IgE receptor, FcεR1, on mast cells and basophils, was reported in patients with clonal mast cell disorders including systemic mastocytosis;^{4,5} however, the experience of using omalizumab for treating IA patients without evidence of mast cell clonality is not well-studied and is underreported. Omalizumab is currently approved in the United States for treatment of asthma, chronic idiopathic urticaria, and nasal polyps. Herein, we sought to compile reported outcomes on omalizumab use in the treatment of IA in patients without underlying mast cell clonality using both a systematic literature review and by reporting the experience at two academic centers.

Methods

Study Protocol

We conducted a retrospective study of patients receiving omalizumab for treatment of IA at either of two centers (Penn State Health, Hershey, PA and University of Washington/Northwest Allergy and Asthma Center, Seattle, WA). Patients with a physician diagnosis of IA and anaphylactic manifestations involving at least 2 organ systems simultaneously were included in our study. Exclusion criteria were: 1) documented evidence for clonal mast cell disorders such as CD25⁺ expressing- and/or *KIT* mutant mast cells, and 2) REMA score⁶ ≥ 2 and no further evaluation for clonal mast cell disorders.⁷ The Human Subjects Protection Office at Penn State College of Medicine determined that a formal review by the Institutional Review Board is not required for this study.

Systematic Literature Review

We performed a systematic search of the PubMed database in May 2021 using the following terms: (“Idiopathic anaphylaxis” OR “Mast cell activation syndrome” OR “MCAS”) AND (“Omalizumab” OR “Xolair” OR “anti-immunoglobulin E”) and filtered to include only human studies with full text available online. No time or field restrictions were applied. Prospective studies, retrospective studies, and case studies involving the use of omalizumab for treating IA without evidence of clonal mast cell disorders were included in our review. Non-original reports, such as review articles, were excluded. Further, we manually reviewed abstracts presented at the American College of Allergy, Asthma and Immunology or the American Academy of Allergy, Asthma and Immunology scientific meetings over five years through 2020

that included the keyword “omalizumab.” Studies were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.⁸

Data extraction

Clinical variables of interest were extracted if identified including demographic variables, clinical characteristics of the anaphylactic episodes, monthly frequency of IA, atopic comorbidities, baseline and event-related tryptase, previous treatments attempted, omalizumab therapy (dose, frequency, and duration) and reported response to omalizumab.

Outcomes

The primary outcome was response pattern to omalizumab defined as complete (if provider/author indicated complete resolution or remission of IA episodes), partial (reduced frequency of IA episodes), or no response (no improvement in IA episodes). Secondary outcome was major adverse events to omalizumab.

Statistical Analysis

Descriptive statistics were used to determine the median and range for continuous variables and the number and frequency for categorical variables.

Results

Study Patients

Our retrospective study identified 14 patients with a physician diagnosis of IA and no documented evidence of mast cell clonality (**Table 1**). Based on chart review, 13 of 14 patients met the World Allergy Organization diagnostic criteria for anaphylaxis with one patient having cutaneous symptoms of urticaria, angioedema, and flushing with gastrointestinal (GI) symptoms occurring simultaneously. Thirteen of fourteen patients were female. The median age at start of omalizumab therapy was 36 years (range 15-51 years). The frequency of IA varied prior to omalizumab from 2 total lifetime episodes to once per week (**Table 1**). Anaphylaxis-related symptoms included angioedema (79%, N = 11), urticaria (93%, N = 13), flushing (36%, N = 5), dyspnea or wheezing (71%, N = 10), GI manifestations (50%, N = 7), pre-syncope or syncope (50%, N = 7), and hypotension (43%, N = 6) (**Table 1**). Eleven of fourteen patients had atopic comorbidities including allergic rhinitis (64%, N = 9), asthma (43%, N = 6), atopic dermatitis (14%, N = 2), and IgE-mediated food allergy (29%, N = 4) (**Table 1**). REMA score ranged from -4 to +1. Baseline tryptase level was <6ng/mL for all reported values (range <2 to 5.8, N = 12). All patients failed various combinations of high-dose non-sedating H1-antihistamines (100%, N = 14), H2-antihistamines (100%, N = 14), LTRAs (93%, N = 13) and/or cromolyn (29%, N = 4) based on consideration by the managing providers (**Table 1**). Additionally, oral corticosteroids were prescribed for 7 (50%) of these patients. As IA is not a current indication for omalizumab, 13 patients (93%) received omalizumab under a diagnosis of chronic idiopathic urticaria and one patient (7%) received omalizumab under an asthma diagnosis. Omalizumab at a dose of 300mg subcutaneously every 4 weeks was used as a starting dose in 13 (93%) of the patients (**Table 1**). After starting omalizumab, 13 (93%) patients had a decrease in the frequency of IA episodes.

Eight patients (57%) achieved a complete response without further IA episodes on the starting dose of omalizumab. An additional patient achieved a complete response from a partial response after omalizumab dosing was adjusted to increase the frequency from 300mg every 4 weeks to every 3 weeks after 8 months on omalizumab (**Table 1**). Another patient had the omalizumab dose adjusted after approximately 11 months from 150mg every 4 weeks to 300mg every 4 weeks to account for weight change. Approximately 5.5 years from this dose adjustment, the patient had two episodes of anaphylaxis requiring epinephrine in a short timeframe of a few weeks, so dosing was adjusted to 300mg every 2 weeks. This patient has had a partial response to omalizumab since with 1 to 2 anaphylaxis episodes per year. The median duration of therapy documented at follow-up was 1.9 years (range 0.08-12 years) and the adverse events reported were cough, chest tightness, and a sensation of feeling hot.

Systematic review

A flow diagram summarizing the systematic literature review process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines is shown in **Figure 1**.⁹ PubMed and scientific abstract search identified 76 articles, of which, 12 studies met our inclusion criteria. Ten studies met the inclusion criteria: nine case reports (N= 9; GRADE, very low quality evidence),¹⁰⁻¹⁸ one abstract (N=1; GRADE, very low quality evidence)¹⁹, one prospective study (N=5; GRADE, moderate quality evidence),⁴ and one double-blind, placebo-controlled (DBPC) trial (GRADE, high quality evidence).²⁰ From the DBPC trial, 6 patients treated with omalizumab who remained on omalizumab throughout the 6-month study period were included in our analysis.²⁰ Another patient from the DBPC trial had dosing discontinued due to unclear possible adverse effect and an additional patient had dosing

discontinued due to unrelated hospitalization.²⁰ A total of 21 patients with reported IA and no evidence of mast cell clonality treated with omalizumab were reviewed (**Table 2**). Age at start of omalizumab was available from 15 (71%) of the reports: median age was 42 years (range 11-54 years) at the start of omalizumab. Sex was identified for 16 (76%) of the patients with 8 (50%) females and 8 (50%) males (**Table 2**). The frequency of IA episodes prior to omalizumab was variable from multiple per year to multiple per month (**Table 2**). Information on baseline serum tryptase levels were available from 12 patients and reported as elevated in two patients. Information on previous treatments were available from 15 patients (71%) (**Table 2**). Patients failed a various combination of antihistamines (100%, N = 15), LTRAs (33%, N = 5), and/or cromolyn (20%, N = 3) with one of those patients having an intolerance to cromolyn (**Table 2**). Omalizumab was started at variable dosing and frequency (range 150mg every 4 weeks to 375mg every 2 weeks) (**Table 2**). Omalizumab therapy resulted in complete response in 13 (62%) patients, partial response in 6 (28.5%) patients, and no response in 2 (9.5%) patients (**Table 2**). Omalizumab doses were adjusted in 4 patients. One patient with complete response had omalizumab dose decreased from 375mg every 2 weeks to 150mg every 4 weeks due to fatigue and continued without IA episodes.¹² Another dose adjustment was an increase in frequency of omalizumab dosing from 300mg every 4 weeks to 300mg every 3 weeks due to mild breakthrough symptoms, not IA episodes, and this patient continued with complete response.¹⁵ The third dose adjustment included a patient who received 300mg omalizumab every 4 weeks for 4 doses and did not have any episodes of IA while on omalizumab or for 9 months after the final dose of omalizumab.¹⁸ This patient then had one IA episode and restarted omalizumab without additional IA episodes.¹⁸ The fourth dose adjustment was a decrease in omalizumab from 375mg every 2 weeks after 6 months to 375mg every 4 weeks, but the patient

had moderate urticaria and hoarsening and omalizumab dosing was adjusted back to every 2 weeks.¹⁰ The duration of follow-up on omalizumab was identified for 15 (71%) patients. The median duration of follow-up on therapy was 0.5 years (range 0.42 - 2 years) (**Table 2**).

Compiled Descriptive Analysis

From the systematic review and our retrospective case series, a total of 35 patients with IA and no evidence of mast cell clonality who were treated with omalizumab were identified. For those with sex and age identified, median age was 36 years at the start of omalizumab (range 11-54 years, N = 29) and 70% were female (N = 21/30), 30% male (N = 9/30). The frequency of IA episodes prior to omalizumab treatment was variable (**Table 1** and **Table 2**). The most often used starting dose and frequency of omalizumab was 300mg every 4 weeks (N = 16) (**Figure 2A**). Most patients achieved a clinical response on omalizumab: complete response (63%, N = 22) or partial response (28.5%, N = 10) with three (8.5%) patients categorized as having no response as there was no improvement in frequency of anaphylaxis episodes (**Figure 2B**). Response was observed in both adults and children. A starting dose of 300mg every 4 weeks was used in 16 patients and resulted in a complete response in 75% (N = 12) of patients and partial response in 19% (N = 3) of patients with one (6%) patient not having any improvement in the frequency of IA. The median duration of follow-up after start of omalizumab therapy was 1 year (range 0.08-12 years, N = 29). The adverse events reported included fatigue, cough, chest tightness, lip edema, flushing, and feeling hot with additional symptoms of edema of the larynx, dyspnea, fever, headache, malaise, nausea, abdominal pain, bleeding, pruritus, local rash, and sweating reported in the literature,^{4, 12, 20} but it was unclear if these symptoms occurred specifically in these patients included in our systematic review.

Discussion

The use of omalizumab beyond allergic asthma and chronic idiopathic urticaria has been increasingly explored²¹ and as of November 2020, has also been approved for treatment of nasal polyps. In patients with clonal mast cell disorders such as mastocytosis, omalizumab successfully ameliorated many of the vasomotor symptoms including anaphylaxis.⁵ Omalizumab was also successful for controlling symptoms in patients with hereditary alpha-tryptasemia.²² In this retrospective case series and systematic review of the published literature, omalizumab was effective in reducing the frequency of IA in most patients without evidence of mast cell clonality who were already optimized on a combination of H1-antihistamines, H2-antihistamines, LTRAs, and/or cromolyn. Although cromolyn may be beneficial in patients with prominent GI symptoms,²³ many patients were not on cromolyn. It was unclear if this low prevalence of cromolyn use was due to absence of GI symptoms in the IA episodes. One patient in our case study and another patient included in the systematic review trialed cromolyn but were unable to tolerate the medication due to GI side effects, including bloating, cramping, and diarrhea.

Although the data from this study provide evidence to support a clinical response to omalizumab in patients with IA, a recently published small scale DBPC trial of omalizumab for treating patients with IA did not find a statistically significant difference between omalizumab and placebo when comparing the number of anaphylaxis events at 6 months after starting omalizumab.²⁰ However, there was a possible benefit in reducing the incidence of anaphylaxis episodes in the omalizumab group after exclusion of anaphylactic events prior to the 60-day time-point after omalizumab start²⁰ suggesting that the benefit of omalizumab in these patients may be delayed. Our study results could differ from this DBPC trial as median duration of follow-up was 1 year in our study. Additionally, the DBPC trial found evidence of a placebo

effect,²⁰ and we cannot rule-out an impact of the placebo-effect in the patients included in our study.

The observed efficacy of omalizumab in treating IA is intriguing since omalizumab has been linked to delayed anaphylaxis, especially among those with a previous history of anaphylaxis.²⁴ While the mechanism underlying IA remains unclear, possibilities include increased proportion of activated T-cells expressing HLA-DR and excess production of the type-2 cytokines IL-4, IL-5, and IL-13 making mast cells more prone to degranulation.² Since omalizumab downregulates expression of the high-affinity IgE receptor, FcεR1, on the surface of basophils and mast cells,^{25, 26} the response of IA patients to omalizumab suggests a role for IgE in the pathogenesis of IA. Omalizumab efficacy was observed in both children and adults and the omalizumab dose was variable. Frequently, the initial dose of omalizumab prescribed was 300mg every 4 weeks due to concomitant urticaria and the approval of omalizumab by the Food and Drug Administration for chronic idiopathic urticaria at this dose. Similar to previous observations in chronic idiopathic urticaria,²⁷ escalation of omalizumab dose and/or frequency appeared to improve efficacy when the initial response was unsatisfactory. However, this observation should be interpreted with caution since the number of omalizumab dose adjustments from the starting dose for patients included in this study was limited.

The safety of omalizumab is well-established. Omalizumab is approved by the United States Food and Drug Administration for treatment of chronic idiopathic urticaria in adolescents and adults, allergic asthma in children and adults, and nasal polyps in adults. In this study, the majority of patients were maintained on omalizumab for at least six months, and treatment was well-tolerated with reported symptoms of fatigue, cough, chest tightness, feeling hot, edema of the larynx, lip edema, dyspnea, fever, headache, malaise, nausea, abdominal pain, bleeding,

pruritus, local rash, flushing, and sweating.^{4, 12, 20} A recent systematic review examined the use of omalizumab for treatment of systemic mastocytosis, and fatigue was reported in 3 patients with 6 of 69 patients having discontinued omalizumab because of adverse effects.⁵

The study has several limitations including: 1) the small sample size, 2) the inclusion of patients with a physician diagnosis of IA with most patients lacking confirmatory studies such as a rise in event-related tryptase level, 3) the literature review included studies comprised mostly of single case reports, and 4) although patients included in this retrospective case series had no documentation of mast cell clonality and their REMA score was less than 2, the possibility of clonal mast cell disorder cannot be completely ruled out. Nonetheless, REMA score has been shown to have a sensitivity of 84% and a specificity of 74% for predicting mast cell clonality.⁶ Larger studies are needed to be able to make management recommendations for use of omalizumab for IA. Additional considerations include extended duration at follow-up after omalizumab start as there may be a delay in onset of action, and possibility of dose and/or frequency increases if no response or only partial response to omalizumab is initially achieved. The current study provides preliminary results that may serve to inform physicians caring for patients with IA, especially those unresponsive to high dose non-sedating antihistamines and those who are steroid-dependent.

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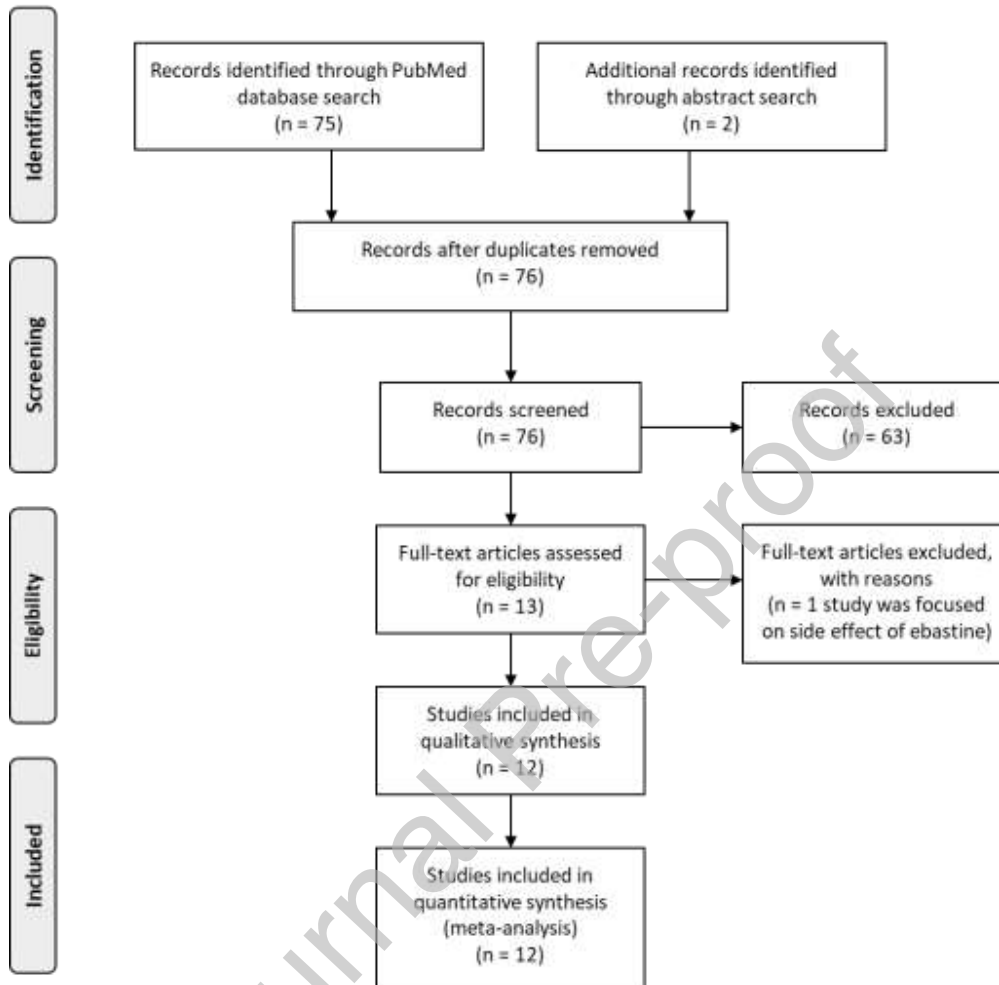
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Figure 1. Systematic literature search as recommended by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.

Figure 2. A, Known starting doses of omalizumab in patients with idiopathic anaphylaxis (N = 29). **B,** Response of patients with idiopathic anaphylaxis to omalizumab based on anaphylaxis frequency (N = 35).

**Figure 1.**

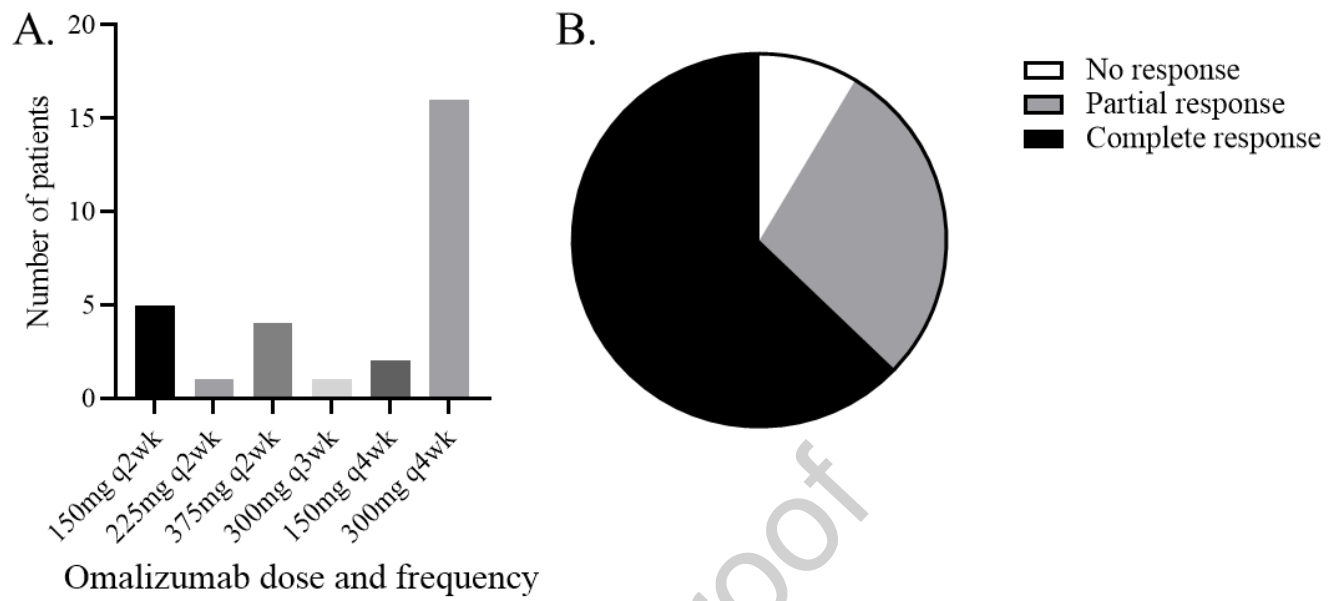


Figure 2.

Table 1. Clinical characteristics of case series patients with IA treated with omalizumab

Sou rce	Age at omaliz umab start (yrs)	S e x	Anaphyla xis symptoms	Atopi c condi tions	Treat ments prior to omaliz umab	Omaliz umab dose and freque ncy	Frequ ency of IA episod es before omaliz umab	Frequ ency of IA episod es after omaliz umab	Respon se class	Foll ow- up (yrs)
U W	37	F	Angioede ma, flushing, dyspnea/w heezing	As, AR	H1 and H2, LTRA, prn epi, OC	150mg q4wk to 300mg q4wk after ~11 months, then 300mg q2wk ~5.5	1/mont h	1- 2/year	Partial	12.0 0

						years later				
U W	44	M	Urticaria, pre- /syncope, dyspnea/w heezing, hypotensio n	AR	H1 and H2, LTRA, prn epi, OC	300mg q4wk	3/year	0	Comple te	1.25
U W	27	F	Angioede ma, urticaria, pre- /syncope, dyspnea/w heezing, hypotensio n	FA	H1 and H2, LTRA, prn epi, OC	300mg q4wk	4/year	0	Comple te	0.67
U W	17	F	Angioede ma, urticaria, dyspnea/w heezing	As, AR, FA	H1 and H2, LTRA, prn epi,	300mg q4wk	2 episod es total	1	Partial	0.08

					OC					
U W	24	F	Urticaria, flushing, pre- /syncope, GI symptoms, hypotensio n	None	H1 and H2, LTRA, prn epi, OC	300mg q4wk	3 episod es total	0	Comple te	1.33
U W	36	F	Urticaria, pre- /syncope, GI symptoms, dyspnea/w heezing	As	H1 and H2, LTRA, prn epi	300mg q4wk	1/mont h	2 within 1mont h of omaliz umab start then 0	Now complet e	1.75
U W	43	F	Angioede ma, urticaria, pre- /syncope, hypotensio	None	H1 and H2, LTRA, prn epi	300mg q3wk	"too many to count"	1/year	Partial	3.00

			n							
UW	48	F	Angioedema, urticaria, flushing, GI symptoms	As, AR	H1 and H2, LTRA, prn epi	300mg q4wk	2-3/year	0	Complete	3.00
PSH	33	F	Angioedema, urticaria, flushing, pre-syncope, GI symptoms, dyspnea/wheezing	None	H1 and H2, LTRA, cromolyn, prn epi	300mg q4wk	1/week	1/week	No response	0.33
PSH	26	F	Angioedema, urticaria, GI symptoms, dyspnea/w	AD, As, AR, FA	H1 and H2, LTRA, cromolyn, prn epi,	300mg q4wk	3/month	2/6 months	Partial	2.08

			heezing		OC					
PS H	43	F	Angioede ma, urticaria, flushing, dyspnea/w heezing	AD, As, AR, FA	H1 and H2, LTRA, cromol yn, prn epi	300mg q4wk	1- 2/mont h	0	Comple te	3.25
PS H	36	F	Angioede ma, urticaria, GI symptoms, dyspnea/w heezing, hypotensio n	AR	H1 and H2, LTRA, cromol yn, prn epi, OC	300mg q4wk	1/mont h	0	Comple te	1.33
PS H	15	F	Angioede ma, urticaria, pre- /syncope, dyspnea/w heezing	AR	H1 and H2, LTRA, prn epi	300mg q4wk increas ed to q3wk after 8 months	Unable to determ ine (3 in 2016)	1 while on q4wk dose, 0 on q3wk dose	Partial then co mplete after dose adjuste d	2.17

PS	51	F	Angioede	AR	H1 and	300mg	1 every	0	Comple	2.25
H			ma, urticaria, GI symptoms, hypotensio n		H2, prn epi	q4wk	3-4 weeks		te	

AD, atopic dermatitis; AR, allergic rhinitis; As, asthma; FA, food allergy; H1, H1-antihistamines; H2, H2-antihistamines; IA, idiopathic anaphylaxis; LTRA, leukotriene receptor antagonist; OC, oral corticosteroids; prn epi, as needed epinephrine autoinjector; PSH, Penn State Hershey; UW, University of Washington and Northwest Asthma and Allergy Center.

Table 2. Clinical characteristics of literature review patients with IA treated with omalizumab

Source	Number of patients	Age at omalizumab start (yrs)	Sex	Anaphylaxis symptoms	Treatments prior to omalizumab	Omalizumab dose and frequency	Frequency of IA episodes before omalizumab	Frequency of IA episodes after omalizumab	Response class	Follow-up (yrs)
Jones et. al.¹¹	1	48	M	Urticaria, flushing, GI symptoms, dyspnea/wheezing, hypotension	Antihistamine, prn epi, OC	375mg q2wk	6/yr	0	Complete	1.00
Demirtürk	1	46	F	Angioedema,	H1, prn epi, OC	375mg q2wk	4-5/last month,	0 by 3mont	Complete	1.00

<i>et. al.</i> ¹⁰				urticaria, flushing, pre-syncope, GI symptoms, dyspnea/ wheezing, hypotension		then decreased to q4wk after 6mont hs but back to q2wk after moderate urticaria and hoarsening	1-2/week while egg free, on H1	hs		
Özdemir et. al. ¹⁷	1	16	F	Angioedema, urticaria, flushing, dyspnea/ wheezing	H1, prn epi, OC	225mg q2wk	2-3/week over 1yr	0	Complete	0.50
Sanc	1	17	F	Angioede	H1 and	375mg	10/6	2/3mo	Comp	1.5

hez-Valenzuela et. al.¹²				ma, urticaria, pre- /syncope, dyspnea/ wheezing	H2, prn epi, OC	q2wk decrea sed to 150mg q4wk after 2mont hs due to fatigue	months	nths then 1/6mo nths then 0/ 12 month s	lete	8
Warriner et. al.¹³	1	12	M	Urticaria, dyspnea/ wheezing	Unkno wn	375mg q2wk	4- 5/mont h (50/yr)	0	Comp lete	NS
Chen et. al.¹⁹	1	28	F	Urticaria, pre- /syncope, GI symptoms , hypotensi on	H1 and H2, LTRA, cromol yn	300mg q4wk	1/mont h	Only one mild episod e	Comp lete	0.4 2
Kaca	1	21	M	Unknown	H1 and	300mg	1/2wee	0	Comp	2.0

r et. al.¹⁵					H2, LTRA, cromol yn, imatini b	q4wk, increas ed to 300mg every 3wk (due to mild breakt hrough sympto ms)	k to 1/2mo nths		lete	0
Lema l et. al.⁴	5	Unkno wn	Unk now n	Unknown	Unkno wn	150mg q2wk	Unkno wn	Unkno wn	4 Comp lete/1 Partial	NS
Cami nati et. al.¹⁴	1	54	F	Unknown	H1 and H2, cromol yn, prn epi	300mg q4wk	3- 4/mont h	0	Comp lete	0.5 0
Bell et.	1	11	M	Urticaria, flushing,	H1 and H2, prn	150mg q4wk	several /month	1/10m onths	Partial	0.8 3

<i>al.</i> ¹⁶				dyspnea/ wheezing	epi, OC					
Lee ¹⁸	1	Unkno wn	M	Angioede ma, urticaria, pre- /syncope, GI symptoms , dyspnea/ wheezing	Antihis tamine, prn epi, OC	300mg q4wk for 4doses	8 in 12mon ths	0/12m onths (9mon ths after stoppi ng omaliz umab) then 1 event and restart ed omaliz umab	Comp lete while on omali zuma b	1.1 7
Carte r et. al. ²⁰	1	51	M	Urticaria, flushing, dyspnea/ wheezing	Antihis tamine, LTRA, prn epi	(150m g q4wk or 150mg q2wk)	6/yr for 2yrs	2/6mo nth	Partial	0.5 0

1	44	F	Angioedema, flushing, pre-/syncope, GI symptoms	Antihistamine, LTRA, prn epi	(150mg q4wk or 150mg q2wk)	10/yr for 22yrs	6/6mo nth	No response	0.50
1	42	M	Urticaria, flushing, pre-/syncope, GI symptoms	Antihistamine, prn epi	(150mg q4wk or 150mg q2wk)	8/yr for 2yrs	2/6mo nth	Partial	0.50
1	27	F	Angioedema, urticaria, flushing, pre-/syncope, GI symptoms, dyspnea/	Antihistamine, LTRA, prn epi, OC	(150mg q4wk or 150mg q2wk)	20/yr for 5yrs	8/6mo nth	Partial	0.50

				wheezing						
	1	50	M	Angioedema, flushing, pre-/syncope, dyspnea/ wheezing	Antihistamine, prn epi	(150mg q4wk or 150mg q2wk)	6/yr for 8yrs	3/6mo nth	No response	0.50
	1	45	F	Angioedema, pre-/syncope, GI symptoms	Antihistamine, prn epi	(150mg q4wk or 150mg q2wk)	12/yr for 7yrs	3/6mo nth	Partial	0.50

H1, H1-antihistamines; H2, H2-antihistamines; IA, idiopathic anaphylaxis; LTRA, leukotriene receptor antagonist; NS, not stated; OC, oral corticosteroids; prn epi, as needed epinephrine autoinjector.