

Clinical response to omalizumab in patients with hereditary α -tryptasemia



Hereditary α -tryptasemia (H α T) is a genetic trait that results from increased *TPSAB1* copy number encoding α -tryptase and is characterized by elevated basal serum tryptase (BST) levels of 8 ng/mL or higher with variably expressed clinical symptoms.¹ In addition to multisystem issues that involve gastrointestinal, connective tissue, and neurologic systems, many individuals with H α T report symptoms associated with mast cell activation, such as chronic spontaneous urticaria and, less commonly, allergic asthma. Increasing α -tryptase gene dosage at *TPSAB1* is associated with greater symptom severity² and increasing amounts of $\alpha\beta$ -tryptase heterotetramers, which have unique enzymatic properties that may contribute to these symptoms.³ Multiple individuals in our cohorts with H α T have uncontrolled chronic spontaneous urticaria or asthma symptoms, which led to an on-label indication for treatment with the monoclonal anti-IgE antibody omalizumab, which binds to free IgE and reduces the expression of Fc ϵ RI on mast cells and basophils.^{4,5} Despite the strong effect observed on symptoms of mast cell mediator release among patients with chronic spontaneous urticaria and systemic mastocytosis, a recent open-label cohort study found only modest benefit in patients identified as having idiopathic mast cell activation syndrome, with 6 of 14 having minimal to no response to omalizumab and 7 of 14 having no durable response.⁶ Given that many of the symptoms associated with H α T are often attributed to mast cell activation, we examined which of the symptoms commonly reported in these patients respond to this specific mast cell–targeted therapy and by inference suggest which symptoms may be more directly related to mast cells bearing heterotetrameric tryptase in these patients.

Comprehensive retrospective medical record review was performed, and complete medical histories were obtained from 13 individuals. Twelve individuals with H α T (6 individuals from the University of Florida [IRB-approved protocols IRB201702274 or IRB201601800], 1 individual from the University of Washington, and 5 individuals from the National Institutes of Health Clinical Center [all 6 were enrolled in National Institute of Allergy and Infectious Diseases IRB–approved protocols NCT01164241 and/or NCT00852943]) previously or concurrently treated with omalizumab were identified; 1 additional individual in New Zealand who prospectively underwent unblinded therapy with omalizumab in which H α T was the primary indication (state-funded under special authority) was also included. Individuals' weights, basal serum tryptase levels, tryptase genotypes (from *TPSAB1* and *TPSB2* loci), total serum IgE levels, and symptoms before, during, and after omalizumab therapy were queried, and dose and duration of omalizumab treatment were recorded.

The median patient weight was 63 kg (range, 35–122 kg), median total serum IgE level was 93 IU/mL (range, 11–2646 IU/mL), and

median BST level was 18 ng/mL (range, 11–33 ng/mL). Nine individuals had 1 additional *TPSAB1* copy, and 4 had 2 additional copies. The dosage of omalizumab that most individuals received was 300 mg subcutaneously every 4 weeks (Table 1). Sixteen symptoms that were documented as present or absent before omalizumab therapy in all 13 patients were queried after treatment (eTable 1). The median number of symptoms reported as present before treatment was 9 per individual (range, 3–13).

Although individual responses were variable, 12 of 13 individuals reported some improvement in at least 1 symptom (Table 2); 6 individuals reported improvement in more than half of their symptoms, with 3 to 8 symptoms being allayed per individual (Table 1). As a cohort, approximately half of reported symptoms ($n = 49$ of 105) from the 16 symptoms queried improved with omalizumab. The improvement was reported as early as 2 weeks after initiation of treatment, with the median time for response in those who reported improvement being 8 weeks. All individuals with urticaria reported improvement ($n = 10$ of 10). Most of those reporting nausea ($n = 6$ of 7), flushing ($n = 8$ of 11), fatigue ($n = 6$ of 9), and abdominal pain ($n = 6$ of 9) also described improvement with omalizumab. Although 6 of 9 individuals reported improvement in baseline fatigue, 2 additional individuals (patients 10 and 11) reported developing fatigue immediately after omalizumab injections; 1 of these individuals also reported no benefit, and the injections were stopped after 2 months. Other responses included improvement in pruritus ($n = 2$ of 4), asthma symptoms ($n = 2$ of 5), food intolerance ($n = 2$ of 5), musculoskeletal pain ($n = 3$ of 8), constipation ($n = 2$ of 6), sleep disturbance ($n = 1$ of 5), and headaches ($n = 1$ of 6). None of the individuals reported improvement in symptoms of autonomic dysfunction ($n = 5$), palpitations ($n = 4$), diarrhea ($n = 5$), or joint hypermobility ($n = 6$).

Of the 2 treated individuals in whom the calculated dose of omalizumab was below the studied 0.016 mg/kg/IU (IgE/mL) cutoff, there was not a significant difference in mean symptomatic improvement compared with those who did achieve this calculated level (eFig. 1A). However, in 1 individual the dose was 0.015 mg/kg/IU and 6 of 8 symptoms improved, whereas in the other individual the dose was 0.002 mg/kg/IU and only 1 of 6 symptoms improved, potentially because of subtherapeutic dosing in the latter patient. This was not a potential explanation for treatment failure in patient 10, who was the only individual to report no symptomatic response, because the calculated dose for this individual was 0.095 mg/kg/IU on a monthly basis. A weak positive correlation was seen between calculated omalizumab dose and the number of symptoms improving (eFig. 1B), whereas individual BST levels did not appear to correlate with symptomatic responses overall (eFig. 1C). Finally, we observed a nonsignificant decrease in the mean percentage of symptoms improving (36% vs 54%) among the 4 individuals with 2 extra-allelic *TPSAB1* copy number when compared with individuals with duplications (eFig. 1D).

Although these findings are preliminary in nature, improvement of some symptoms, such as flushing, urticaria, and asthmatic symptoms, occurred as expected in response to omalizumab therapy. However, improvement of fatigue and some pain symptoms was unexpected. Furthermore, autonomic and gastrointestinal symptoms, including constipation and diarrhea, that one might have attributed to mast cell mediator effects were unchanged with omalizumab therapy. Because these symptoms failed to respond to the systemic mast cell–targeted therapy omalizumab, despite universal responsiveness of urticaria in this study, it is possible that

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Table 1
Patient Characteristics and Treatment Responses to Omalizumab in Hereditary α -Trypsinemia

Patient No.	Weight, kg	BST, ng/mL	Trypsin genotype copy number		IgE, IU/mL	No. of stated symptoms	No. of symptoms responding to omalizumab	Dosage	Time to response or failure
			α	β					
1	73	16	3	2	279	8	6	300 mg every 4 weeks	2 weeks
2	122	22	2	3	289	10	7	300 mg every 2 weeks	8 weeks
3	66	18	2	3	11	12	8	300 mg every 4 weeks	12 weeks
4	53	18	4	2	14	10	7	150 mg every 4 weeks	4 weeks
5	59	13	3	2	147	9	4	300 mg every 4 weeks	4 weeks
6	59	13	3	2	107	3	3	300 mg every 4 weeks	12 weeks
7	73	17	3	2	44	9	1	300 mg every 3 weeks	4 weeks
8	63	11	3	2	2,646	6	1	300 mg every 4 weeks	8 weeks
9	62	24	3	3	93	4	2	150 mg every 4 weeks	8 weeks
10	81	13	4	2	78	9	0	300 mg every 2 weeks	No response ^a
11	45	18	3	2	63	13	2	150 mg every 4 weeks	8 weeks ^a
12	77	33	4	2	187	4	1	300 mg every 4 weeks	2 weeks
13	35	21	3	2	74	8	7	300 mg every 4 weeks	2 weeks

^aAlso reported severe fatigue with omalizumab injections.

in this H α T cohort these symptoms are occurring as a result of as yet unknown mechanism(s) other than mast cell activation. It is unclear why some individuals reported substantial benefit, whereas others reported minimal or no benefit and in some cases were even intolerant of the drug, but this finding points to potentially distinct mechanisms that contribute to some of the phenotypes in these patients, that may be modified by H α T. Given the small sample size, as well as the unblinded and retrospective nature of these findings, one must be cautious regarding the generalizability of these results. However, given the difficulties in managing the types of symptoms frequently reported in individuals with H α T, coupled with the severity of their symptoms and their negative effect on quality of life, this report provides initial evidence of a role for omalizumab in management of selected individuals with H α T. This finding is particularly relevant given the recent in vitro data demonstrating how mast cells from patients with H α T and other cells containing $\alpha\beta$ -heterotetrameric trypsin may enhance vibration-induced urticaria via cleavage of epidermal growth factor–like module-containing mucin-like hormone receptor-like 2.³ As more mechanisms and biomarkers are established for the clinical phenotypes observed in patients with H α T and other disorders associated with nonclonal mast cell activation, future double-blind, placebo-controlled trials will be necessary to establish efficacy of mast cell–directed therapies in these patients.

Table 2
Symptoms That Were Responsive or Persistent During Omalizumab Therapy

Symptoms	No./total No. (%) of symptoms
Responsive symptoms	
Urticaria	10/10 (100)
Nausea	6/7 (86)
Flushing	8/11 (73)
Fatigue ^a	6/9 (67)
Abdominal pain	6/9 (67)
Pruritus	2/4 (50)
Persistent symptoms	
Asthma symptoms	2/5 (40)
Food intolerance	2/5 (40)
Musculoskeletal pain	3/8 (38)
Constipation	2/6 (33)
Sleep disturbance	1/5 (20)
Headaches	1/6 (17)
Autonomic dysfunction	0/5 (0)
Joint hypermobility	0/6 (0)
Palpitations	0/4 (0)
Diarrhea	0/5 (0)

^aTwo individuals who did not report baseline fatigue developed fatigue while taking omalizumab.

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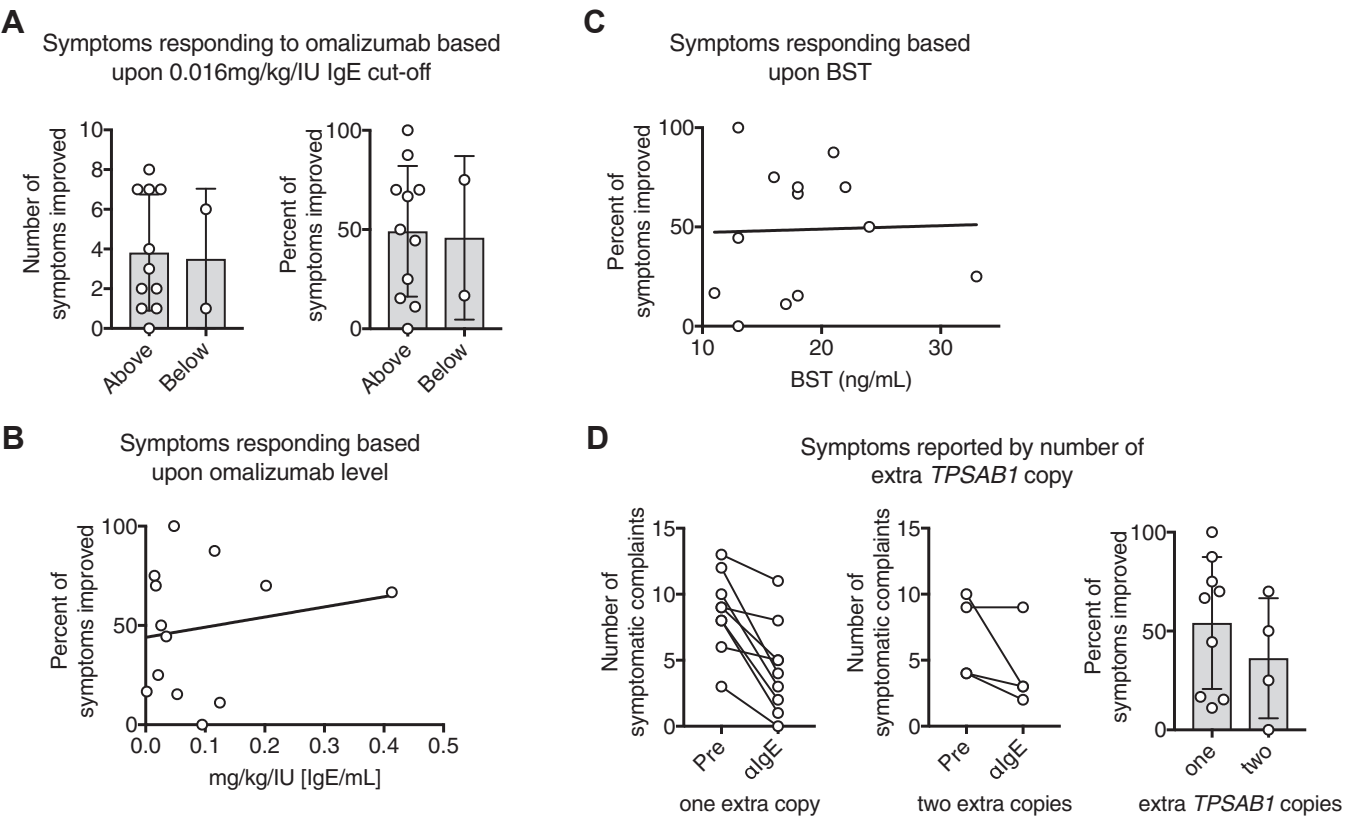
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Supplementary Data



eFigure 1. Correlation of quantitative parameters and symptomatic response to omalizumab. A, Symptom number (right) and percentage (left) with reported improvement based on whether individuals were above or below the calculated 0.016 mg/kg/IU (IgE/mL) level. Correlation between calculated omalizumab dose ($R^2 = 0.03$, $P = .60$) (B) or basal serum tryptase (BST) (C) and percentage of improvement in symptoms ($R^2 = 0.001$, $P = .90$). D, Number of symptoms (left and middle) and percentage of symptoms improving (right) with omalizumab based on number of extraallelic *TPSAB1* copies.

eTable 1
Symptoms Queried in Patients With Hereditary α -Tryptasemia Who Received Omalizumab

Urticaria
Flushing
Fatigue
Abdominal pain
Nausea
Constipation
Pruritus
Asthma symptoms
Food intolerance
Sleep disturbance
Headaches
Musculoskeletal pain
Autonomic dysfunction
Palpitations
Diarrhea
Joint hypermobility