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IgE blockade with omalizumab reduces pruritus related to immune checkpoint inhibitors and anti-HER2 therapies

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Abstract

Background: Immunoglobulin E (IgE) blockade with omalizumab has demonstrated clinical benefit in pruritus-associated dermatoses (e.g. atopic dermatitis, bullous pemphigoid, urticaria). In oncology, pruritus-associated cutaneous adverse events (paCAEs) are frequent with immune checkpoint inhibitors (CPIs) and targeted anti-human epidermal growth factor receptor 2 (HER2) therapies. Thus, we sought to evaluate the efficacy and safety of IgE blockade with omalizumab in cancer patients with refractory paCAEs related to CPIs and anti-HER2 agents.

Patients and methods: Patients included in this multicenter retrospective analysis received monthly subcutaneous injections of omalizumab for CPI or anti-HER2 therapy-related grade 2/3 pruritus that was refractory to topical corticosteroids plus at least one additional systemic

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intervention. To assess clinical response to omalizumab, we used the Common Terminology Criteria for Adverse Events version 5.0. The primary endpoint was defined as reduction in the severity of paCAEs to grade 1/0.

Results: A total of 34 patients (50% female, median age 67.5 years) received omalizumab for cancer therapy-related paCAEs (71% CPIs; 29% anti-HER2). All had solid tumors (29% breast, 29% genitourinary, 15% lung, 26% other), and most ($n = 18$, 64%) presented with an urticarial phenotype. In total, 28 of 34 (82%) patients responded to omalizumab. The proportion of patients receiving oral corticosteroids as supportive treatment for management of paCAEs decreased with IgE blockade, from 50% to 9% ($P < 0.001$). Ten of 32 (31%) patients had interruption of oncologic therapy due to skin toxicity; four of six (67%) were successfully rechallenged following omalizumab. There were no reports of anaphylaxis or hypersensitivity reactions related to omalizumab.

Conclusions: IgE blockade with omalizumab demonstrated clinical efficacy and was well tolerated in cancer patients with pruritus related to CPIs and anti-HER2 therapies.

Keywords

bullous pemphigoid; cutaneous adverse event; eczema; IgE; pruritus; urticaria

INTRODUCTION

Immune checkpoint inhibitor (CPI) and anti-human epidermal growth factor receptor 2 (anti-HER2) targeted therapies have improved the survival of patients with various malignancies.^{1,2} However, these agents [e.g. anti-programmed cell death protein 1/ligand 1 (PD-1/PD-L1), anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), anti-HER2] are frequently associated with skin toxicity and represent a substantial burden on quality of life in cancer patients.^{3,4} Dermatologic reactions of CPIs and anti-HER2 monoclonal antibodies (mAbs) include pruritus and pruritus-associated cutaneous adverse events (paCAEs), such as urticaria, eczema, and bullous pemphigoid (BP) rash.⁵ The percentage of pruritus reported ranges from 14% to 47% among patients receiving CPIs and from 10% to 18% in those treated with anti-HER2 agents.⁶⁻⁸

Hitherto, therapeutic recommendations for paCAEs were based on anecdotal reports and expert opinion,⁹⁻¹³ with upto 25% of patients not responding to standard-of-care anti-pruritus measures, such as topical corticosteroids (TCS), oral antihistamines (OAHs), and gamma-aminobutyric acid analogs [GABAlogs (e.g. gabapentin, pregabalin)].⁵ Because higher total serum immunoglobulin E (IgE) levels have been reported in higher-grade immune-related cutaneous adverse events (AEs),⁵ we hypothesized that IgE blockade represents an actionable therapeutic target to block immune mediators of pruritus. Omalizumab, an anti-IgE mAb approved for chronic idiopathic urticaria (CIU) refractory to OAHs,^{14,15} is cited in the National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines in Oncology for consideration in the management of refractory cases of CPI-related dermatologic AEs in which anti-IgE therapy has demonstrated therapeutic benefit (e.g. pruritus, urticaria). However, its efficacy for this indication has not been

investigated yet. Here, we summarize the characteristics and outcomes of oncology patients treated with omalizumab for paCAEs that remained refractory to prior treatments.

METHODS

Patients

Cancer patients from two institutions [Memorial Sloan Kettering Cancer Center (MSK) in New York, NY ($n = 32$); MD Anderson Cancer Center (MDA) in Houston, TX ($n = 2$)] who were referred to the oncodermatology clinic between 23 April 2018 and 6 September 2019 for grade 2 pruritus related to CPI or anti-HER2 treatment refractory to TCS plus at least one additional systemic intervention [e.g. OAH, oral GABAlog, oral corticosteroid (OCS)] and who were subsequently managed with monthly subcutaneous injections of omalizumab were included in the analysis. Patients were identified and their electronic medical record (EMR) was retrospectively reviewed using an institutional health information and data management system. This study was conducted under institutional review board approval protocols for each participating institution (MSK Protocol #16–458 and MDA Protocol #PA-15–0959).

Study outcomes

Our primary aim was to assess the rate of clinical response to treatment with omalizumab. The primary endpoint (reduction in severity of paCAEs from grade 3/2 to grade 0/1) was evaluated either in person at patients' follow-up visits (which occurred approximately every 30 days) or via telephone calls made to patients by either dermatology or oncology clinicians following each administration of omalizumab (also approximately every 30 days). Response outcome data were retrospectively evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 toxicity grading scale¹⁶ and defined a priori. Positive clinical responses to IgE blockade with omalizumab were further subclassified as either complete (reduction from grade 3/2 to grade 0) or partial (reduction from grade 3/2 to grade 1). Patients were considered non-responders if the severity of their paCAEs changed from grade 3/2 to grade 2.

As a secondary aim, we examined outcomes of clinical safety, including AEs reported by patients and documented by clinicians during treatment with omalizumab. When specified in the EMR, attribution categories of unrelated, unlikely related, possibly related, probably related, or definitely related were assigned to each AE. Demographics, clinicopathologic characteristics, and laboratory measures were described and compared across response groups.

Statistical methods

Data were summarized using descriptive statistics with Excel (Microsoft, Redmond, WA) and SPSS Statistics version 25 (IBM, Armonk, NY). Categorical data are reported as counts (percentages). Unless otherwise specified, all continuous variables are reported as median and range (minimum-maximum) values. We utilized Fisher's exact and paired *t*-tests to determine differences in categorical variables and normally distributed ordinal data, respectively; and Wilcoxon Mann-Whitney *U* and median tests for analysis of

nonparametric independent continuous samples. To detect change in related categorical and ordinal variables, McNemar's and Wilcoxon signed rank tests were carried out. All analyses were two-tailed tests based on $\alpha = 0.05$, with results reaching statistical significance if $P < 0.05$.

RESULTS

Demographics and oncologic history

A total of 34 patients [median age 67.5 years (37–84), 50% female] with solid tumors undergoing treatment with CPIs ($n = 24$, 71%) and anti-HER2 therapies ($n = 10$, 29%) were included (Table 1). All received omalizumab for paCAEs that remained refractory to other anti-pruritic or rash management strategies. Nearly half of paCAEs ($n = 16$, 47%) were attributed to anti-PD-1 agents, namely pembrolizumab ($n = 8$, 24%) or nivolumab ($n = 8$, 24%). Other CPI regimens associated with paCAEs included combination anti-CTLA-4/anti-PD-1 treatment with ipilimumab plus nivolumab ($n = 5$, 15%) and the single-agent PD-L1 blockers atezolizumab ($n = 2$, 6%) or durvalumab ($n = 1$, 3%).

Clinicopathologic characteristics

In total, 22 (64%) patients were diagnosed with urticaria (Figure 1A and B), 9 (26%) with BP (Figure 1C and D) using direct immunofluorescence and/or an enzyme-linked immunosorbent assay to detect and measure BP 180 and BP 230 serum antibodies (Supplementary Table S1, available at <https://doi.org/10.1016/j.annonc.2021.02.016>), and 3 (9%) with eczema (Figure 1E and F). paCAEs were of moderate-severe clinical severity: 25 (74%) were classified as CTCAE grade 2 and 9 (26%) as grade 3. From the onset of paCAEs to the first dose of omalizumab, the median duration of pruritic skin disease was 93 days (4–820 days) in 32 patients (Figure 2). Of 17 patients with a cutaneous biopsy carried out before receiving anti-IgE therapy, 16 (94%) had eosinophils identified on hematoxyline—eosin (H&E) histologic evaluation. Twelve of 16 patients (75%) with eosinophils on skin biopsy were responders: 6 (50%) partial, 6 (50%) complete. Four were non-responders. The patient without eosinophils identified on H&E was a partial responder. Ten of 13 patients (77%), all of whom were receiving CPI treatment, had abundance of eosinophils (>10 per 5 consecutive high-power fields).

Clinical response to omalizumab

Twenty-eight of 34 patients (82%) responded to omalizumab. Among the 28 responders, 16 (57%) had partial response (reduction of CTCAE grade 2/3 to grade 1 paCAEs) and 12 (43%) had complete response (reduction to grade 0). A relatively younger age was characteristic of omalizumab responders in comparison to non-responders (65 versus 71 years), and the proportion of females in the responder group significantly outweighed that found in the non-responder group ($n = 17$, 61% versus 0, 100%, $P = 0.018$). All non-responders ($n = 6$, 100%) were male, and most of them ($n = 4$, 67%) had genitourinary neoplasms (2 renal, 2 urothelial) that were being treated with CPIs. Anti-PD-1 agents ($n = 5$, 83%) predominated in the non-responder group. All 10 patients with paCAEs related to anti-HER2 therapies and 18 of 24 (75%) with paCAEs related to CPIs responded to omalizumab (Table 2).

The majority of patients with urticaria (18/22; 82%) (Figure 1A) and BP (7/9, 78%) (Figure 1C) derived clinical benefit from omalizumab (Figure 3A and B). IgE blockade was also effective in patients with eczema ($n = 3$, 100%; Figure 1E). Four of 22 (28%) patients with urticaria and 2 of 9 (22%) with BP did not respond to omalizumab.

The median duration of treatment with IgE blockade was 62 days (0–440 days), and the median time to response was 28 days (0–77 days): 25 days (0–65 days) in partial responders ($n = 16$) versus 53 days (5–77 days) in complete responders ($n = 12$) (Figure 2). The average number of doses of omalizumab that patients received before report of maximum clinical response was greater in complete responders than in partial responders (1.5 versus 1.0, $P = 0.007$).

Changes in supportive management of paCAEs

Before intervention with IgE blockade, the majority of patients ($n = 27$, 80%) failed three or more different types of treatments, and nearly 25% failed four or more ($n = 8$, 24%). All 34 (100%) patients failed TCS (e.g. clobetasol, fluocinonide, triamcinolone) and also at least one additional intervention of a different therapeutic class. Other failed supportive treatment categories included GABAlogs ($n = 26$, 77%) such as pregabalin, OAHs ($n = 21$, 62%) such as hydroxyzine, OCS ($n = 17$, 50%) such as prednisone, immunomodulators (IMs) ($n = 10$, 29%) such as aprepitant, and biologic agents ($n = 4$, 12%) such as dupilumab. After the introduction of anti-IgE therapy with omalizumab, patients used an average of 1.6 supportive treatments, which was significantly lower than 2.3, the average number before omalizumab ($P = 0.005$). Fewer patients continued to use

TCS concurrently with omalizumab ($n = 23$, 68% versus 34, 100%, $P = 0.001$) (Figure 4). The greatest reduction rates were observed with OCS (50% to 9%, $P < 0.001$), followed by GABAlogs (77% to 41%, $P < 0.001$), OAHs (62% to 32%, $P = 0.006$), and IMs (29% to 0%, $P = 0.002$). Of note, two (6%) patients did not require additional supportive medications concurrently with omalizumab.

Impact of omalizumab on interruption of cancer therapy

Ten of 32 (31%) patients had interruption of cancer therapy as a result of paCAEs, which were related exclusively to CPIs. Oncologic treatments were stopped within a median of 140 days (1–500 days) before receiving omalizumab. Six of these 10 (60%) patients responded to IgE blockade and were rechallenged with their respective regimen; four (67%) of the six were able to resume oncologic therapy without recurrence or worsening of skin toxicity. Among the two (33%) responders whose cancer therapy was discontinued, both had developed grade 3 BP during treatment with PD-1 inhibitors (one with pembrolizumab, the other with nivolumab). One of the two patients had progression of his lung malignancy; the other, whose baseline total serum IgE was recorded at 20 380 kU/l, died; he had renal cancer.

Safety of omalizumab

Overall ($n = 34$), the median total number of omalizumab injections administered was 3 (1–14), which was the same in responders and non-responders. An initial 300-mg injection

was administered subcutaneously once per month in most ($n = 30$, 88%) cases. Four (12%) patients had one 150-mg monthly injection as their first dose, three of whom went on to receive the standard 300-mg monthly injections thereafter. There were no reports of AEs related to omalizumab. All AEs reported by oncologists and dermatologists during treatment with omalizumab are published as supplementary material (Supplementary Table S2, available at <https://doi.org/10.1016/j.annonc.2021.02.016>).

Changes in total serum IgE

Among 18 patients with blood drawn within 30 days pre-omalizumab, the median total serum IgE was 150 kU/l (7.9–20 380.0 kU/l). Seven (39%) of those 18 patients had levels >213 kU/l [median 390 kU/l (229–20 380 kU/l)], which is the upper limit of normal (ULN). Median values at baseline were 263 kU/l in complete responders ($n = 5$), 79.5 kU/l in partial responders ($n = 9$), and 208 kU/l in non-responders ($n = 4$). In 15 patients with both pre- and post-omalizumab IgE measured within a median of 71 days (12–501 days) following their first dose, the median total serum IgE at first follow-up was 213 kU/l (10–1156 kU/l) (Figure 5). The ratio of total serum baseline IgE/follow-up IgE was 0.5 in these 15 patients (0.4 in 12 responders versus 0.9 in 3 non-responders).

Characteristics of patients with abnormally elevated total serum IgE pre-omalizumab

Pre-omalizumab (baseline), there were 11 (34%) of 32 patients with total serum IgE above the ULN, 8 (73%) of whom had a positive response to IgE blockade [5 (62.5%) with partial response; 3 (37.5%) with complete response]. Three patients with IgE above the ULN did not respond to omalizumab. Among the 11 patients with abnormally high total serum IgE, the median was higher in omalizumab responders (629 kU/l, $n = 8$) compared to non-responders (300 kU/l, $n = 3$), $P = 0.048$. Genitourinary malignancy ($n = 5$, 45%) and BP ($n = 4$, 36%) were more prevalent in these patients. Most ($n = 10$, 91%) were on CPIs; one (9%) was on anti-HER2 treatment (Supplementary Table S3, available at <https://doi.org/10.1016/j.annonc.2021.02.016>).

Changes in blood eosinophils

Among 34 patients with blood eosinophils (absolute count, abs eos) measured pre-omalizumab, the median was 200 cells/ μ l (0–3800 cells/ μ l); 6 (18%) patients had 700 cells/ μ l with a median of 950 cells/ μ l (800–3800 cells/ μ l) (Supplementary Table S4, available at <https://doi.org/10.1016/j.annonc.2021.02.016>). Median values at baseline were 200 in complete responders ($n = 12$), 250 in partial responders ($n = 16$), and 100 in non-responders ($n = 6$). Post-omalizumab ($n = 30$), the overall median was 300 cells/ μ l (0–9300 cells/ μ l), with an increase of 100 cells/ μ l (–1400 to +5500 cells/ μ l) pre- to post-IgE blockade. Overall, the ratio of baseline abs eos/follow-up abs eos was equivalent (0.5) to that observed with total serum IgE (Figure 5).

DISCUSSION

Omalizumab as a therapeutic option for paCAEs related to CPIs and anti-HER2 therapies

Our assessment of cancer patients receiving omalizumab for pruritus associated with urticaria, BP, and eczema related to CPIs and anti-HER2 therapies resulted in positive

outcomes of clinical efficacy. In concordance with the high response rates reported in randomized clinical trials and case series that have evaluated omalizumab for CIU,¹⁵ BP,¹⁷ and pediatric atopic dermatitis,¹⁸ our study demonstrated a response rate of 82%, which is clinically highly impactful.

In our study, whereas a significantly greater proportion of females were found in the responder group, males exclusively populated the non-responder group. This difference may be explained by the types of cancer and treatments that predominated in each group. Compared to CPIs, anti-HER2 mAbs were more frequently observed among responders, which were utilized exclusively by females for breast cancer. Thus, differences in degree of clinical response to omalizumab may be dependent on the target of mAbs and CPIs.

All BP and eczema lesions appeared under CPIs. While maculopapular rash remains one of the most common AEs observed in patients treated with CPIs,¹⁹ there is also increasing evidence to suggest that BP eruptions occur frequently among those receiving PD-1/PD-L1 inhibitors^{20,21} and that treatment is challenging. Although we observed a high degree of response among BP patients, additional controlled clinical studies with large samples are warranted to characterize the mechanisms responsible for recalcitrant pruritus in this population.

Reduction in the proportion of patients requiring additional supportive management during treatment with omalizumab

Both the average number of supportive treatments and the proportion of patients requiring their use concurrently with omalizumab decreased significantly. Before IgE blockade, >40% of our patients were prescribed supportive OCS and/or other IM measures to manage pruritus related to CPIs and anti-HER2 mAbs. However, the utilization of OCS and IMs decreased by 82% and 100%, respectively, which has clinical implications in the prevention of serious infections in those who are already immunocompromised.

While management of most paCAEs with TCS and/or oral antipruritics such as GABAlog and OAHs is successful, there are patients who fail to demonstrate sustained clinical improvement, ultimately requiring OCS, IMs, or biologics. Pregabalin is often considered in patients with recalcitrant pruritus; however, its utilization is limited by sedation, dizziness and drowsiness, drug interactions, withdrawal seizures, and need for renal dosing.^{22–24} It is also not universally effective, as anecdotally many patients fail to improve. As refractory cases of paCAEs emerge, with up to 25% of patients not responding to symptom-directed dermatologic interventions,⁵ many will lead to anticancer therapy dosing interruptions and/or discontinuation.

Reduction of cancer therapy interruption with omalizumab

A substantial proportion (31%) of patients had interruption of oncologic therapy due to severe pruritus exclusively related to CPIs. Thus, as both CPI and anti-HER2-related dermatologic toxicities may result in dosing alterations and permanent discontinuation of cancer treatment,^{11,25} successful control of paCAEs related to these life-saving therapeutic mechanisms remains a priority. More than half of the patients who resumed oncologic treatment after receiving omalizumab did not have recurrence or worsening of skin toxicity,

which further highlights the potentially beneficial therapeutic role of IgE blockade in cancer care.

Omalizumab as a safe treatment option for paCAEs related to CPIs and anti-HER2 therapies

The omalizumab dosing strategies and safety profile herein were similar to those in the CIU study,¹⁵ with the majority of patients receiving 300-mg monthly injections and a low reported incidence of AEs related to the anti-IgE agent. However, whereas the rate of serious AEs in the pivotal trial ranged between 1% and 6% across the intervention groups,¹⁵ there were zero cases in our study attributed to omalizumab, potentially due to uncontrolled AE reporting and a smaller study sample size.

Predictors of clinical response to omalizumab

Consistent with previous data, our study findings suggest that a lower ratio of total serum baseline IgE/follow-up IgE is a good predictor of response to omalizumab,²⁶ with a lower total serum baseline IgE/follow-up IgE ratio resulting from a slower elimination rate of omalizumab-IgE complexes (compared to free IgE).²⁴ Additionally, we observed better response outcomes in patients with greater abnormally high pre-omalizumab total serum IgE levels, which clinical studies on omalizumab for CIU have also reported.^{26,27} However, as evidenced in this study and in the previous CIU literature, the majority of patients with normal baseline IgE levels responded to omalizumab. Thus, our data would not justify a particular threshold of total serum IgE before the administration of omalizumab for its use in oncology patients.

Limitations

Conclusions drawn from this investigation are limited primarily by its retrospective design, moderate sample size, and lack of matched placebo-treated controls. Hence, all statistical inferences have been taken with these concerns into account. While omalizumab appeared to be beneficial in this moderately sized cohort of cancer patients with grade 2/3 paCAEs resistant to TCS plus at least one additional systemic treatment, this group may not be representative, and thus not generalizable to all oncology patients with toxicities of similar phenotype and severity related to CPI and anti-HER2 agents.

Despite the clinically meaningful response rate observed in our study, important questions remain to be addressed regarding the efficacy and safety of omalizumab for paCAEs related to CPIs and anti-HER2 targeted therapies. Firstly, characterization of additional blood markers, such as free serum IgE, autoantibodies to IgE, thyroid hormone, tryptase, and estrogen/progesterone, in women treated with anti-HER2 therapies for breast cancer would add to our understanding of the mechanism through which omalizumab improves pruritus related to anti-HER2 mAbs compared to CPIs. Secondly, the question of optimal dosing and when, if ever, therapy with omalizumab should be stopped while patients continue to undergo anticancer treatment with CPIs and anti-HER2 agents remains unanswered. As stipulated by Navarro-Triviño and colleagues,²⁸ it may be possible that in certain patients with cancer, such as the ones we encountered with CPI-related BP and a lack of response to

omalizumab, the use of higher doses (>300 mg/month) or even a shorter therapeutic interval (300 mg every 2 or 3 weeks) may be necessary to optimize the full effect of IgE blockade.

Conclusions

The results of our study suggest that blockade of IgE may represent a novel intervention for patients with pruritus related to CPIs and anti-HER2 therapies. Importantly, omalizumab appears to reduce the need for additional supportive medications, including OCS. Omalizumab has the potential to safely and effectively improve severity of paCAEs, as well as provide the opportunity for successful rechallenge and continuation of anticancer treatment. However, these observations require further evaluation and characterization in a prospective clinical trial. Also, given this initial signal of potential efficacy in pruritus related to CPIs and anti-HER2 agents, the investigation of anti-IgE therapy among a broader class of pruritus-inducing targeted anticancer therapies is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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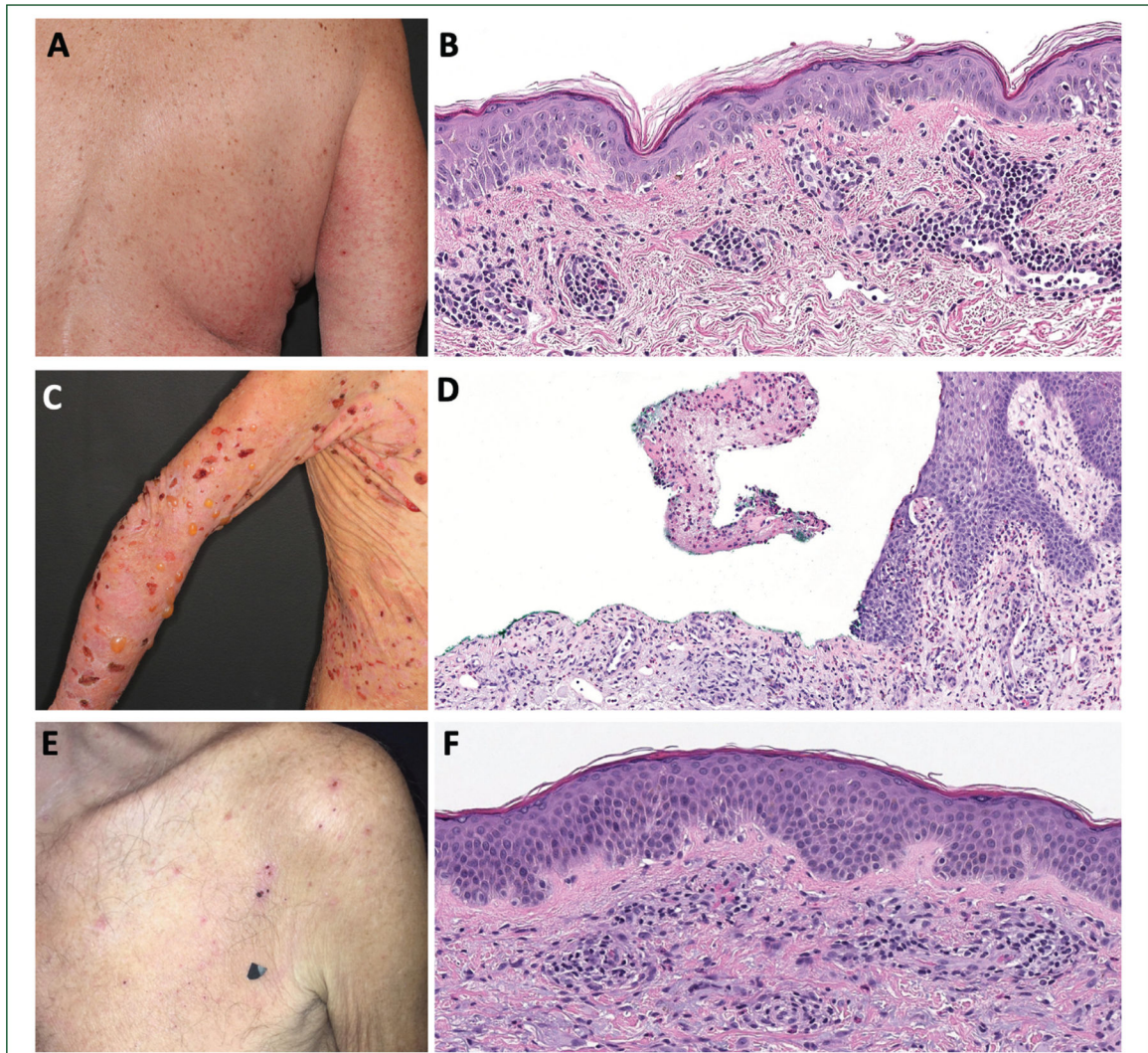


Figure 1. Clinico-pathologic features of patients receiving IgE blockade with omalizumab for pruritus related to immune checkpoint inhibitors and anti-HER2 therapies.

(A) Urticaria with (B) interface dermatitis and superficial perivascular lympho-eosinophilic infiltrate ($\times 200$ magnification). (C) Bullous pemphigoid with (D) subepidermal vesicle with eosinophils and lymphocytes ($\times 100$ magnification). (E) Eczema with (F) slight spongiosis with superficial perivascular lympho-eosinophilic infiltrate ($\times 200$ magnification).

Anti-HER2, anti-human epidermal growth factor receptor 2; IgE, immunoglobulin E.

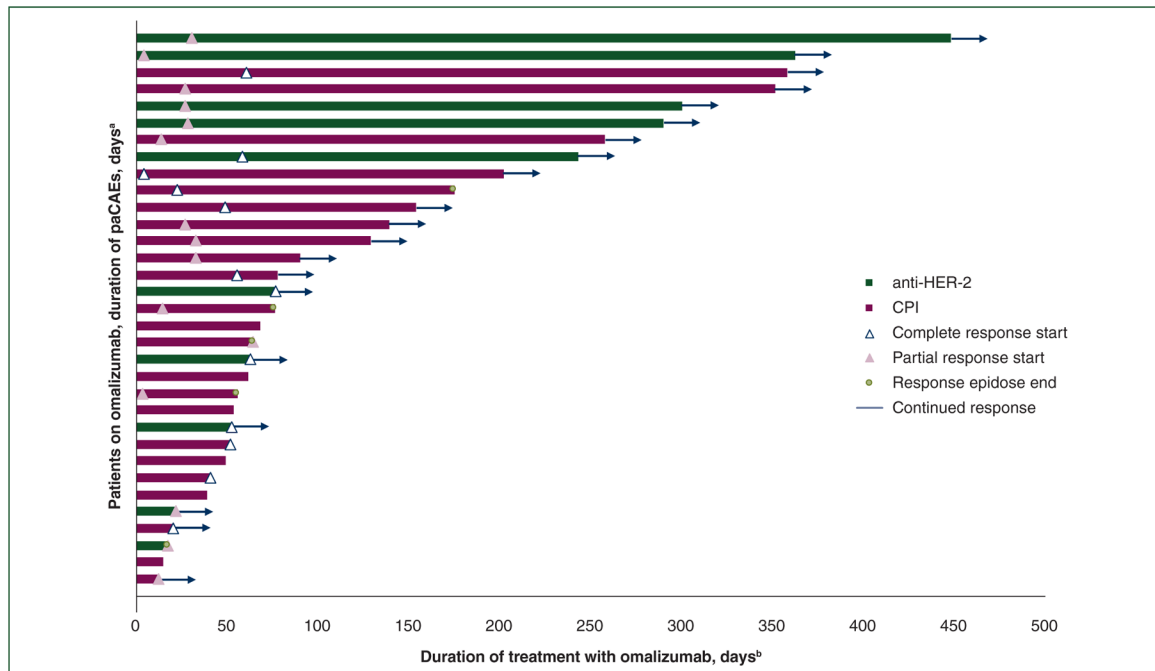


Figure 2. Time course and efficacy of IgE blockade in patients receiving omalizumab for pruritus related to CPIs and anti-HER2 therapies.

Anti-HER2, anti-human epidermal growth factor receptor 2; CPI, checkpoint inhibitor (e.g. PD-1, PD-L1, CTLA-4); CTLA-4, cytotoxic T-lymphocyte-associated protein 4; paCAEs, pruritus-associated cutaneous adverse events; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.

^a Median (min-max), 93 days (4–820 days) in 32 patients.

^b median (min-max), 62 days (0–440 days) in 34 patients.



Figure 3. Clinical manifestation of paCAEs before (left) and after (right) IgE blockade with omalizumab.

(A) Patient with metastatic breast cancer and CTCAE grade 2 dermatographic urticaria related to anti-HER2 therapy (resistant to alclometasone dipropionate, clobetasol, diphenhydramine, hydroxyzine, levocetirizine, pregabalin). Two subcutaneous 300-mg doses of omalizumab resulted in complete response with reduction of paCAE to CTCAE grade 0. (B) Patient with advanced melanoma and CTCAE grade 3 bullous pemphigoid related to anti-PD-1 + anti-CTLA-4 immune checkpoint inhibition (resistant to cetirizine, diphenhydramine, mycophenolate mofetil, rituximab, prednisone, pregabalin). One subcutaneous 300-mg injection of omalizumab resulted in partial response with reduction of paCAE to CTCAE grade 1.

Anti-HER2, anti-human epidermal growth factor receptor 2; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IgE, immunoglobulin E; paCAEs, pruritus-associated cutaneous adverse events; PD-1, programmed cell death protein 1.

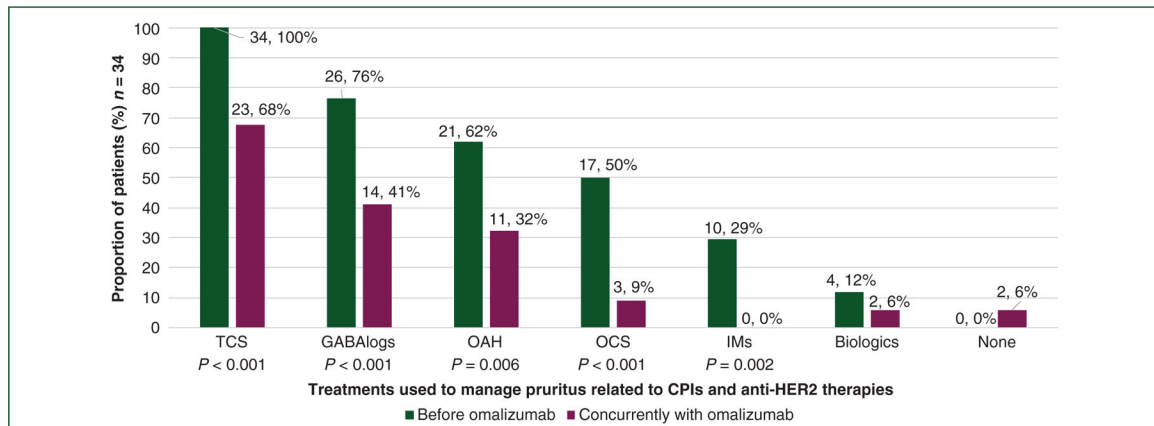


Figure 4. Pre- to post-omalizumab changes in the proportion of patients requiring supportive treatments to manage paCAEs related to immune checkpoint inhibitors and anti-HER2 therapies.

Anti-HER2, anti-human epidermal growth factor receptor 2; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; GABAlogs, gamma-aminobutyric acid analogs; IMs, immunomodulators; OAH, oral antihistamine; OCS, oral corticosteroids; paCAEs, pruritus-associated cutaneous adverse events; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; TCS, topical corticosteroids.

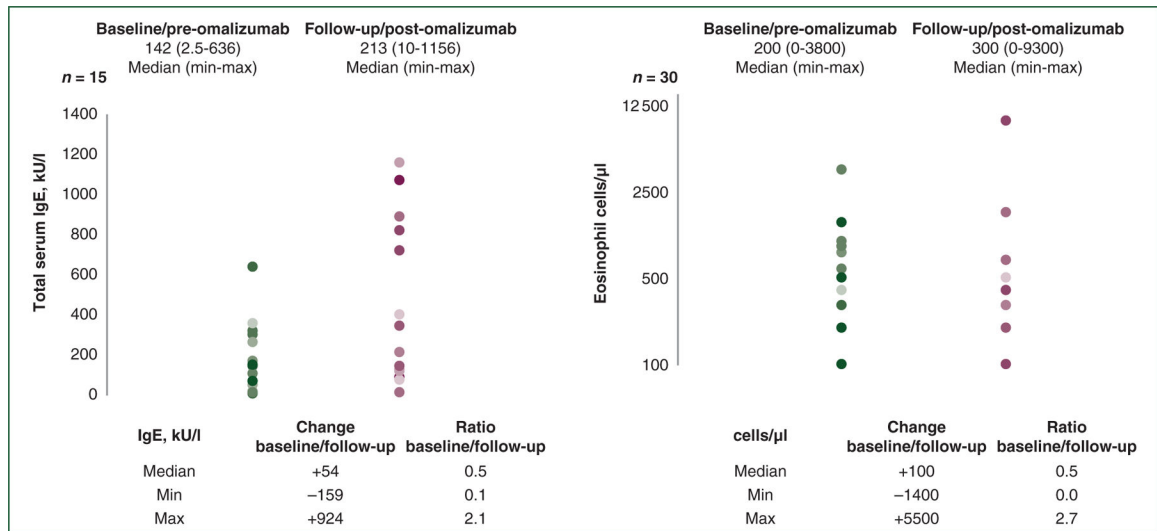


Figure 5. Pre- to post-omalizumab changes in total serum IgE and blood eosinophils of patients with paCAEs related to immune checkpoint inhibitors and anti-HER2 therapies.

Measured analytes correspond to total serum IgE and absolute count of blood eosinophils. The upper limit of normal (ULN) values were established a priori at 213 kU/l and 699 cells/μl, respectively, as per our institutional laboratory services provider (Mayo Clinic Laboratories, Rochester, MN).

Anti-HER2, anti-human epidermal growth factor receptor 2; IgE, immunoglobulin E; paCAEs, pruritus-associated cutaneous adverse events.

Characteristics of cancer patients receiving IgE blockade with omalizumab for pruritus related to immune checkpoint inhibitors and anti-HER2 therapies

Table 1.

	All patients	Omalizumab responders ^a Reduction from baseline to CTCAE grade 0/1	Omalizumab non-responders ^a No reduction from baseline to CTCAE grade 0/1	P value ^{b,c}
n (%) ^a	34 (100)	28 (82)	6 (18)	
Age, years				
Median(range)	67.5 (37–84)	65 (37–84)	71 (65–84)	0.177
50	8 (24)	8 (29)	0 (0)	0.434
51–69	11 (32)	9 (32)	2 (33)	
70	15 (44)	11 (39)	4 (67)	
Sex				
Female	17 (50)	17 (61)	0 (0)	0.018
Male	17 (50)	11 (39)	6 (100)	
Race				
White	23 (68)	19 (68)	4 (67)	0.641
Asian	4 (12)	4 (14)	0 (0)	
Other ^d	7 (21)	5 (18)	2 (33)	
Ethnicity				
Non-Hispanic	28 (82)	22 (79)	6 (100)	0.562
Hispanic	6 (18)	6 (21)	0 (0)	
Cancer diagnosis				
Breast	10 (29)	10 (36)	0 (0)	0.114
Genitourinary ^e	10 (29)	6 (21)	4 (67)	
Lung	5 (15)	4 (14)	1 (17)	
Other ^f	9 (26)	8 (29)	1 (17)	
Cancer therapy type				
Anti-PD-1	16 (47)	11 (39)	5 (83)	0.098
Anti-HER2	10 (29)	10 (36)	0 (0)	
Anti-PD-1 + CTLA-4	5 (15)	5 (18)	0 (0)	
Anti-PD-L1	3 (9)	2 (7)	1 (17)	

paCAE phenotype	All patients	Omalizumab responders ^a Reduction from baseline to CTCAE grade 0/1	Omalizumab non-responders ^a No reduction from baseline to CTCAE grade 0/1	P value ^{b,c}
Urticaria	22 (64)	81 (64)	4 (67)	0.678
Bullous pemphigoid	9 (26)	7 (25)	2 (33)	
Eczema	3 (9)	3 (11)	0 (0)	
Baseline CTCAE v5.0 severity grade ^b				
Grade 2	25 (74)	21 (75)	4 (67)	0.644
Grade 3	9 (26)	7 (25)	2 (33)	

CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IgE, immunoglobulin E; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; paCAEs, pruritus-associated cutaneous adverse events.

^aClinical response to omalizumab was evaluated retrospectively by clinicians using the CTCAE version 5.0 toxicity grading scale.

^bFisher's exact test for categorical variables.

^cMann-Whitney *U* test for continuous variables.

^dOther races include unknown and undisclosed.

^eGenitourinary cancer diagnoses include renal cell carcinoma (*n* = 7, 21%) and urothelial tumors (*n* = 3, 9%).

^fOther malignancies include head and neck (*n* = 2, 6%), melanoma (*n* = 2, 6%), glioblastoma (*n* = 1, 3%), angiosarcoma (*n* = 1, 3%), gastric (*n* = 1, 3%), ovarian (*n* = 1, 3%), and laryngeal (*n* = 1, 3%) cancer.

Table 2. Characteristics of cancer patients responding to IgE blockade with omalizumab for pruritus related to immune checkpoint inhibitors and anti-HER2 therapies

	All responders <i>n</i> = 28		Patients with CPI-related paCAEs <i>n</i> = 18		Patients with anti-HER2-related paCAEs <i>n</i> = 10	
	<i>n</i> (%)	Partial responders ^a	Complete responders ^b	Partial responders ^a	Complete responders ^b	Complete responders ^b
<i>n</i> (%)	28 (100)	10 (56)	8 (44)	6 (60)	4 (40)	
Age, years						
Median(range)	65 (37–84)	67 (50–81)	75 (66–84)	47 (37–68)	52 (43–63)	
50	8 (29)	1 (10)	0 (0)	5 (83)	2 (50)	
51–69	9 (32)	4 (40)	2 (25)	1 (17)	2 (50)	
70	11 (39)	5 (50)	6 (75)	0 (0)	0 (0)	
Sex						
Female	17 (61)	4 (40)	3 (38)	6 (100)	4 (100)	
Male	11 (39)	6 (60)	5 (63)	0 (0)	0 (0)	
Race						
White	19 (68)	6 (60)	6 (75)	5 (83)	2 (50)	
Asian	4 (14)	0 (0)	2 (25)	1 (17)	1 (25)	
Other	5 (18)	4 (40)	0 (0)	0 (0)	1 (25)	
Ethnicity						
Non-Hispanic	22 (79)	7 (70)	7 (88)	5 (83)	3 (75)	
Hispanic	6 (21)	3 (30)	1 (13)	1 (17)	1 (25)	
Cancer diagnosis						
Breast	10 (36)	0 (0)	0 (0)	6 (100)	4 (100)	
Genitourinary	6 (21)	4 (40)	2 (25)	0 (0)	0 (0)	
Lung	4 (14)	2 (20)	2 (25)	0 (0)	0 (0)	
Other	8 (29)	4 (40)	4 (50)	0 (0)	0 (0)	
paCAE phenotype						
Urticaria	18 (64)	4 (40)	4 (51)	6 (100)	4 (100)	
Bullous pemphigoid	7 (25)	4 (40)	3 (38)	0 (0)	0 (0)	
Eczema	3 (11)	2 (20)	1 (13)	0 (0)	0 (0)	
Baseline CTCAE v5.0 severity grade						

	All responders <i>n</i> = 28		Patients with CPI-related paCAEs <i>n</i> = 18		Patients with anti-HER2-related paCAEs <i>n</i> = 10	
	Partial responders ^a	Complete responders ^b	Partial responders ^a	Complete responders ^b	Partial responders ^a	Complete responders ^b
Grade 2	21 (75)	7 (70)	7 (70)	4 (50)	6 (100)	4 (100)
Grade 3	7 (25)	3 (30)	3 (30)	4 (50)	0 (0)	0 (0)

Anti-HER2, anti-human epidermal growth factor receptor 2; CPI, immune checkpoint inhibitor; CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; IgE, immunoglobulin E; paCAE, pruritus-associated cutaneous adverse events.

^aPartial responders = reduction in severity of paCAEs from baseline CTCAE grade 2/3 to grade 1/2.

^bComplete responders = reduction in severity of paCAEs from baseline CTCAE grade 2/3 to grade 0/1.