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ORIGINAL RESEARCH

Does Comorbid Food Allergy Affect Response to Omalizumab in Patients with Asthma?

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Video Abstract

Point your SmartPhone at the code above. If you have a QR code reader the video abstract will appear. Or use: https://youtu.be/AgTlkVJtnHQ

Background: The intrinsic link between food allergy and asthma is well-established, and comorbidity can exacerbate both conditions. Omalizumab, an anti-immunoglobulin E (IgE) antibody, has the biological plausibility to manage both conditions, but only a few small studies have assessed omalizumab in patients with comorbid asthma and food allergy.

Patients and Methods: We conducted a post hoc analysis of placebo-controlled, randomized clinical trials (IA05 in children and 008/009 in adolescents/adults) and real-world observational studies (EXCELS and PROSPERO). For each study, patients with asthma were stratified by whether they had physician-reported food allergy, as per baseline characteristics data.

Results: For patients with comorbid food allergy, there was evidence for increased atopy at baseline (numerically higher total IgE levels and atopic comorbidities). The collective body of evidence found that omalizumab consistently improved general and asthma-specific patient-centered outcomes (food allergy-specific outcomes were not available). For patients with asthma, omalizumab improved healthcare resource use (emergency room visits, hospitalizations, unscheduled doctor visits), quality of life (asthma-specific Asthma Quality of Life Questionnaire), productivity (missed work/school days and the Work Productivity and Activity Impairment: Asthma), and asthma outcomes (asthma exacerbations and Asthma Control Test score) regardless of comorbid food allergy.

Conclusion: There was no loss of omalizumab efficacy even though patients with both asthma and food allergy appeared to be generally more atopic. Omalizumab may be a viable management option for patients with these comorbidities.

Clinical trial registration: NCT00079937; NCT01922037; NCT00252135.

Plain Language Summary: Food allergy and asthma are linked and if you have both conditions then you can feel worse. There is a treatment available, called omalizumab, that helps people with asthma and helps people with food allergy, but it's not clear if it can help people with both conditions. Here, we look at whether omalizumab can help people with bad to very bad asthma (also called moderate to severe asthma) who also have food allergy. We found that omalizumab improved many aspects of a person's life, including whether they visited the emergency room, were admitted to hospital, their quality of life, whether they missed school or work, and whether their asthma improved. These improvements occurred in all people with moderate to severe asthma, whether they had food allergy or did not have food allergy. This suggests that omalizumab can help people with both conditions.

Keywords: asthma, food allergy, food hypersensitivity, healthcare resource use, omalizumab, productivity, quality of life

Introduction

The intrinsic link between food allergy and asthma is well established,[1,2] and comorbidity can exacerbate both conditions. People with both food allergy and asthma have worse quality of life (versus no food hypersensitivity),[3]

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potential for worse prognosis for their food allergies (versus no asthma),[4] a higher likelihood of fatal allergic reactions to food (almost all patients had asthma),[5] and worse asthma control with increased asthma complications (versus no food allergy).[2,6–9] Given that the pathophysiology of both food allergy[10] and asthma[11] involves immunoglobulin E (IgE), the anti-IgE antibody omalizumab has biological plausibility for managing both conditions.

Although omalizumab is well-established as a treatment for asthma and recently approved in the United States for patients with IgE-mediated food allergy,[12] only a few studies (with small sample sizes) have assessed omalizumab in patients with comorbid asthma and food allergy. In adults, omalizumab improved asthma outcomes in patients with allergic comorbidities, including food allergies.[13,14] In a case series of 15 children, Fiocchi et al found that omalizumab improves quality of life, asthma outcomes, and food allergen threshold and reactions to accidental exposure in patients with severe asthma and documented food allergy.[15] In a small case series of seven children with severe asthma, high total IgE levels, and documented food allergies, Dinardo et al found that after 2 years omalizumab had reduced asthma exacerbations and patients were desensitized to their food allergen.[16] However, there are gaps in our knowledge regarding the interaction of asthma, food allergy, and treatment with omalizumab.

The objective of this analysis was two-fold: 1) to assess the effect of comorbid food allergy on the baseline characteristics of patients with asthma, and 2) to assess whether omalizumab could improve healthcare resource use, quality of life, and productivity for patients with food allergy and asthma. We conducted a post hoc analysis of placebo-controlled, randomized clinical trials and real-world observational studies to collect a body of evidence.

Methods

Study Design

The following studies of omalizumab for patients with allergic asthma were included in this post hoc analysis: the randomized clinical trials IA05 for children (ClinicalTrials.gov identifier: NCT00079937; ages 6 to <12 years) and 008/009 for adolescents/adults (conducted preregistration requirements, no NCT number available; ages 12–76 years) and the real-world observational studies PROSPERO (NCT01922037; ages ≥12 years), and EXCELS (NCT00252135; ages ≥12 years), all of which were approved by respective institutional review boards.[17–22] Study designs, including patient inclusion and exclusion criteria, have been published previously and are summarized in Figure 1.[17–21] Not all pivotal studies for omalizumab in allergic asthma[23] were included in this analysis as the number of participants with comorbid food allergy was small (<50 participants) and findings would be limited.

For each study, patients were stratified by the presence or absence of physician-reported food allergy, as per the patient baseline characteristics data. Food allergy diagnostic results (for example, skin prick tests, specific IgE, oral food challenge, reaction history, food allergens) were not available for these clinical trials and observational studies.

Outcomes

Each study collected different endpoints and at different timepoints; where possible, similar endpoints are presented across the individual studies.

Healthcare resource use was assessed by emergency room visits, hospital visits, and unscheduled doctor visits. Quality of life was assessed using the Asthma Quality of Life Questionnaire (AQLQ).[24] Productivity was assessed through missed work/school days and the Work Productivity and Activity Impairment (WPAI): Asthma.[25] Asthma outcomes were assessed through clinically significant and protocol-defined asthma exacerbations (for the clinical trials) and the Asthma Control Test (ACT; observational studies).[26]

For baseline characteristics, comorbidities were reported based on physician-reported information at screening.

Food allergy-specific outcomes, for example food allergy-specific healthcare resource use and patient reported outcomes such as the Food Allergy Quality of Life Questionnaire, were not assessed in these studies.

Statistical Analysis

For each study, outcomes were compared between “with food allergy” and “without food allergy” groups.

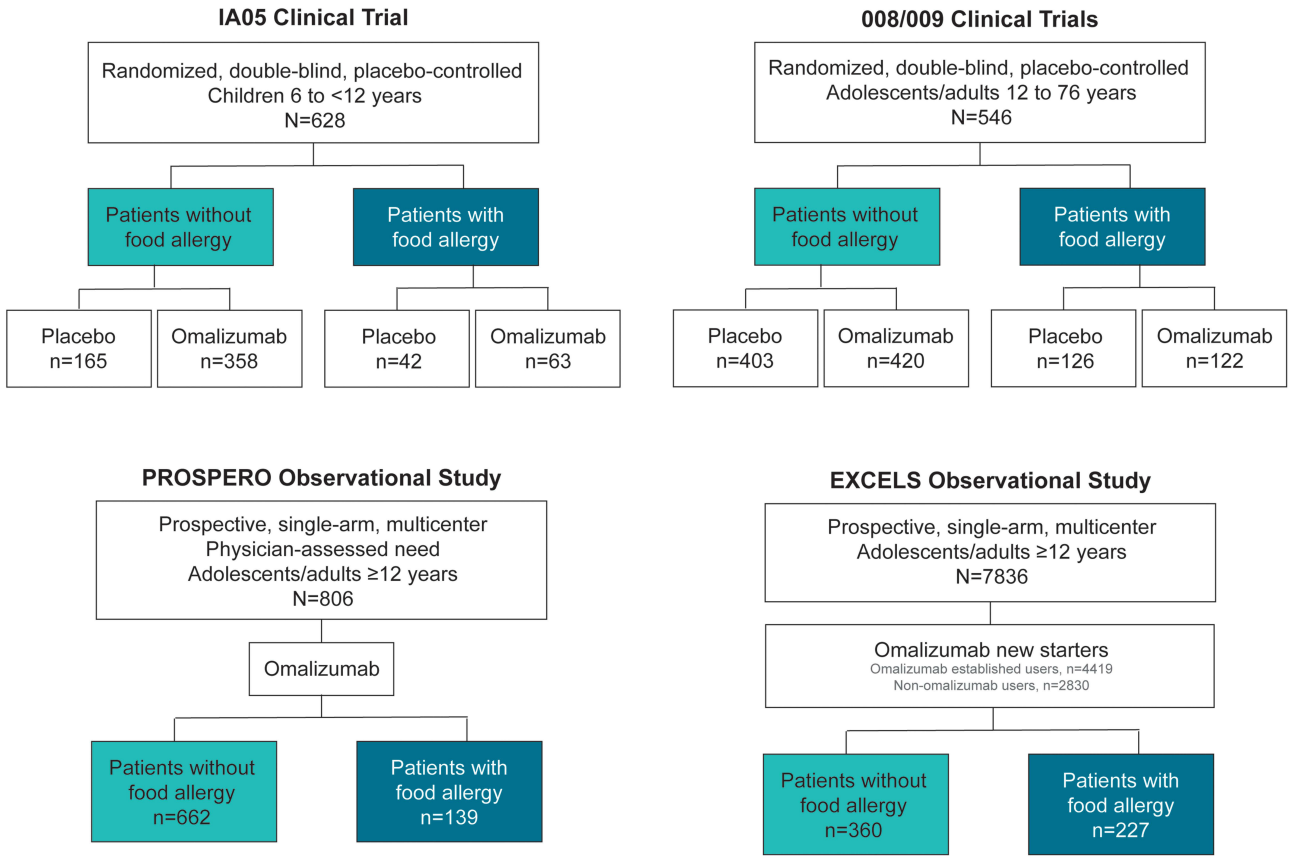

Figure 1 Summary of study design and participants for studies included in this analysis. Patient numbers included in this analysis are presented in the bottom row of each flow chart. Study designs, including patient inclusion and exclusion criteria, have been published previously. Data from these studies.[17–21]

For the IA05 study, Poisson regression analysis was used to examine the rates of asthma exacerbations and healthcare resource use. To remain consistent with the methods used in the primary study, all analyses were adjusted by dosing schedule, treatment, and baseline asthma exacerbation count. To assess the potential for differential treatment effects by food allergy status, an additional main effect for food allergy status and a treatment-by-food allergy status interaction were added to the Poisson regression models and interaction P values were extracted. Outcomes at 12 months are reported.

For the 008/009 studies, Poisson regression or simple linear regression was used to analyze missed work/school days, AQLQ score, and asthma exacerbations. To assess the potential for differential treatment effects by food allergy status, an additional main effect for food allergy status and a treatment-by-food allergy status interaction were added to the Poisson regression models and interaction P values were extracted. Outcomes at 4 months are reported.

For PROSPERO, changes from baseline in AQLQ and WPAI: Asthma scores were calculated for each group using analysis of covariance, and least squares mean (LSM) differences were reported. The model included baseline values with and without food allergy. Outcomes at 12 months are reported.

For EXCELS, WPAI-Asthma Overall score, rate of visits, and percentage of patients with ACT score >20 were calculated and summarized descriptively. Outcomes at 12 months are reported for the omalizumab new starters group only. Omalizumab new starters had similar outcomes at 12 months as omalizumab established users (data not shown). Statistical analyses were not conducted as this was an observational study only: the study was not designed to compare between groups and therefore interpretation would be limited.

Safety

Safety data were not assessed specifically for this analysis. Safety data from each study have been published.[17–19,21,27,28]

Results

Patient Characteristics

In general, baseline characteristics were similar between patients with and without food allergy (Table 1). However, in all studies except the clinical trial 008/009, serum total IgE levels appeared to be higher in patients with food allergy versus without food allergy (Table 2). In addition, in the observational studies there appeared to be a higher incidence of allergic comorbidities, including allergic rhinitis, atopic dermatitis, and urticaria, in patients with food allergy (Table 3). There also appeared to be a higher incidence of positive skin prick test to mold in the clinical trial IA05 (patients without food allergy – placebo 45.5%, omalizumab 52.2%; patients with food allergy – placebo 66.7%, omalizumab 61.9%) and in the EXCELS observational study (patients without food allergy – 60.6%; patients with food allergy – 67.8%).

Healthcare Resource Use

Improvements in healthcare resource use for patients with asthma treated with omalizumab were similar regardless of the presence of food allergy, consistent across clinical trials and observational studies.

Table 1 Baseline Patient Characteristics

Clinical Trials			Age, Years Mean (SD)	Male	White	FEV_1, L Mean (SD)
IA05	Patients without FA	PBO	8.3 (1.7)	66.1%	53.9%	1.6 (0.4)
		OMA	8.7 (1.7)	67.0%	49.7%	1.6 (0.4)
	Patients with FA	PBO	8.7 (1.6)	69.0%	57.1%	1.7 (0.6)
		OMA	8.6 (1.8)	74.6%	53.1%	1.6 (0.5)
008/009	Patients without FA	PBO	39.0 (14.2)	46.9%	88.8%	2.4 (0.8)
		OMA	40.2 (14.2)	47.9%	90.5%	2.4 (0.7)
	Patients with FA	PBO	39.3 (12.3)	38.9%	89.7%	2.4 (0.7)
		OMA	37.9 (12.4)	36.1%	93.4%	2.5 (0.7)
Observational Studies						
PROSPERO	Patients without FA	OMA	47.9 (17.1)	35.8%	69.5%	2.2 (0.8)
	Patients with FA	OMA	43.8 (18.3)	40.3%	77.0%	2.5 (0.8)
EXCELS	Patients without FA	OMA new starters	45.1 (16.7)	37.2%	78.6%	3.0 (0.7)
	Patients with FA	OMA new starters	43.2 (15.2)	33.9%	76.7%	3.0 (0.7)

Abbreviations: FA, food allergy; FEV_1, forced expiratory volume in 1 second; OMA, omalizumab; PBO, placebo; SD, standard deviation.

Table 2 Serum Total IgE (IU/mL) at Baseline

Clinical Trials			Mean (SD)	Median (Q1, Q3)
IA05	Patients without FA	PBO	432.6 (338.0)	355 (159, 580)
		OMA	468.0 (340.5)	382 (189, 701)
	Patients with FA	PBO	552.4 (312.6)	557 (291, 843)
		OMA	521.8 (331.4)	449 (262, 765)
008/009	Patients without FA	PBO	192.4 (147.9)	155 (77, 261)
		OMA	200.7 (161.2)	155 (81, 281)
	Patients with FA	PBO	208.6 (165.2)	161 (81, 297)
		OMA	189.1 (145.7)	153 (76, 248)
Observational Studies				
PROSPERO	Patients without FA	OMA	464.2 (1060.0)	171 (71, 448)
	Patients with FA	OMA	1119.9 (5880.8)	264 (102, 613)
EXCELS	Patients without FA	OMA new starters	354.0 (551.9)	168 (77, 420)
	Patients with FA	OMA new starters	560.3 (1221.4)	213 (83, 531)

Abbreviations: FA, food allergy; IgE, immunoglobulin E; OMA, omalizumab; PBO, placebo; Q, quartile; SD, standard deviation.

Table 3 Incidence of Allergic Comorbidities at Baseline

			Allergic Rhinitis[a]	Chronic Rhinosinusitis	Atopic Dermatitis	Urticaria
PROSPERO	Patients without FA	OMA	81.4%	25.7%	10.9%	7.4%
	Patients with FA	OMA	90.6%	33.8%	30.2%	19.4%
EXCELS	Patients without FA	OMA new starters	93.3%	–	16.4%	40.3%
	Patients with FA	OMA new starters	96.9%	–	36.1%	68.7%

Note: [a]Or allergic rhinoconjunctivitis.
Abbreviations: FA, food allergy; OMA, omalizumab.

In the pediatric IA05 trial, all-cause emergency room visits at 12 months were improved (numerically decreased) with omalizumab treatment compared with placebo (at 12 months, rate of visits 0.43 omalizumab vs 0.53 placebo, P= 0.179); this response was similar in patients with and without food allergies (Figure 2A; interaction P = 0.37). Asthma-related resource use – hospitalizations, unscheduled doctor visits, emergency room visits– followed a similar pattern (for overall population at

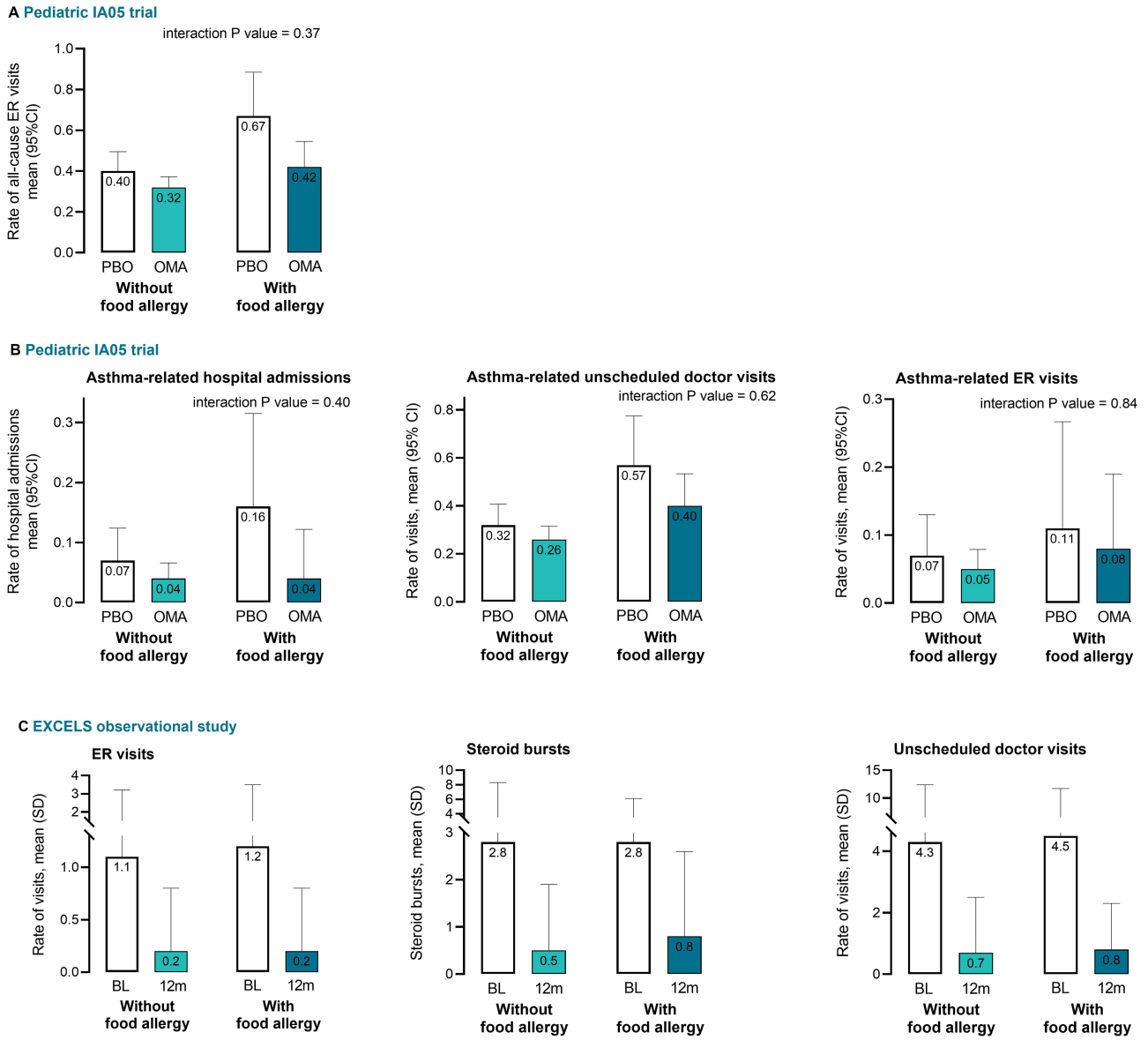

Figure 2 Healthcare resource use following omalizumab for patients with asthma by food allergy status. (**A**) Pediatric IA05 trial, rate of all-cause emergency room visits at 12 months. (**B**) Pediatric IA05 trial, rate of asthma-related hospitalizations, emergency room visits, unscheduled doctor visits at 12 months. (**C**) EXCELS observational study, rate asthma-related emergency room visits, steroid bursts, unscheduled doctor visits at 12 months.
Abbreviations: ER, emergency room; OMA, omalizumab; PBO, placebo.

12 months: rate of hospitalizations 0.07 omalizumab vs 0.13 placebo, P= 0.085; rate of unscheduled doctor visits 0.25 omalizumab vs 0.29 placebo, P= 0382; rate of emergency room visits 0.11 omalizumab vs 0.14 placebo,P= 0.665) (for food allergy subgroups: Figure 2B; interaction P = 0.40, 0.62, 0.84, respectively). Of interest, healthcare resource use at 12 months for patients in the placebo group appeared to be numerically greater for patients with food allergy versus patients without food allergy.

In the EXCELS observational study, improvements versus baseline in asthma-related resource use at 12 months for omalizumab new starters appeared to be similar for patients with and without food allergy (Figure 2C).

Quality of Life

Improvements in quality of life for patients with asthma treated with omalizumab were similar regardless of presence of food allergy, consistent across clinical trials and observational studies.

In both clinical trials and observational studies, improvement in quality of life assessed by the asthma-specific AQLQ was observed with omalizumab treatment (LS mean change from baseline, omalizumab versus placebo at 4 months, 0.94 versus 0.67, P = 0.001 and 0.88 versus 0.59, P < 0.001 for 008 and 009). In the adolescent/adult 008/009 trial, response to omalizumab versus placebo at 4 months was similar for patients with and without food allergies (Figure 3A; interaction P = 0.86). In the PROSPERO observational study, improvement in AQLQ at 12 months after initiation of omalizumab appeared to be similar for patients with and without food allergy (Figure 3B).

Productivity

Improvements in productivity for patients with asthma treated with omalizumab were similar regardless of presence of food allergy, consistent across clinical trials and observational studies.

In the adolescent/adult 008/009 clinical trial, missed work or school days at 4 months were numerically decreased by omalizumab treatment compared with placebo (mean 0.46 days omalizumab versus 0.74 days placebo, P = 0.121); this response was similar for patients with and without food allergies (Figure 4A; interaction P = 0.53).

In both observational studies, improvements from baseline in productivity and activity at 12 months, assessed by the asthma-related WPAI, appeared to be similar for patients with and without food allergy. For PROSPERO, improvements were observed in percentage of work time missed, percentage work impairment, and percentage activity impairment

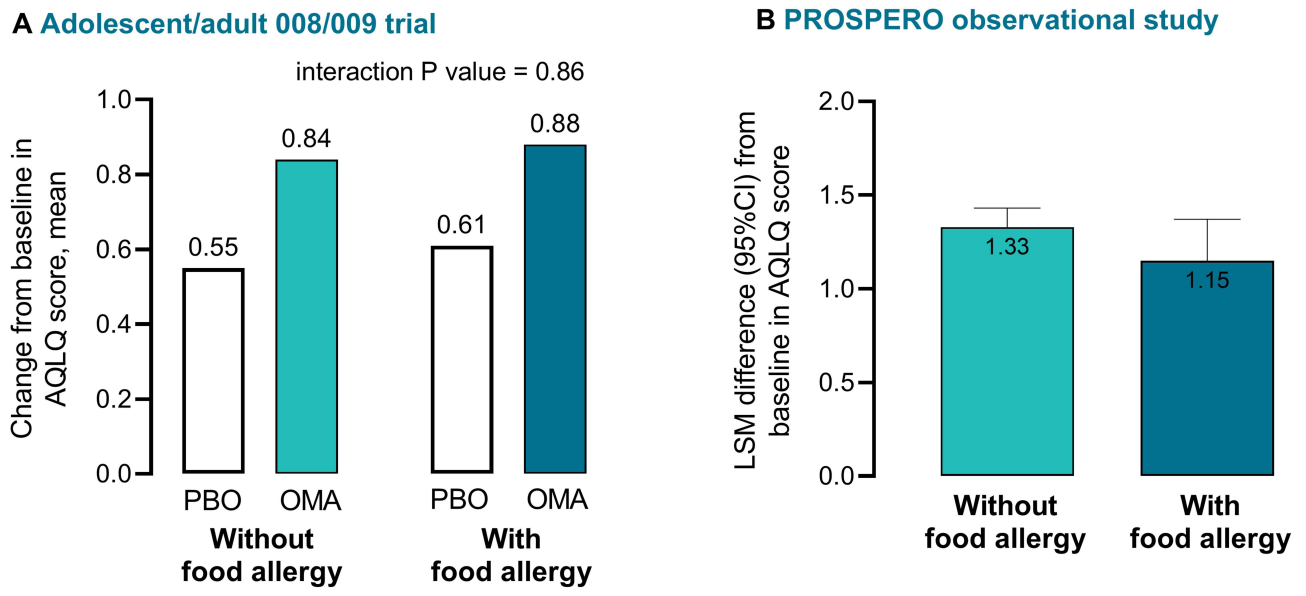

Figure 3 Quality of life following omalizumab for patients with asthma by food allergy status. (**A**) Adolescent/adult 008/009 trial, change from baseline in AQLQ at 4 months. (**B**) PROSPERO observational study, LSM difference from baseline in AQLQ at 12 months.
Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; LSM, least squares mean; OMA, omalizumab; PBO, placebo.

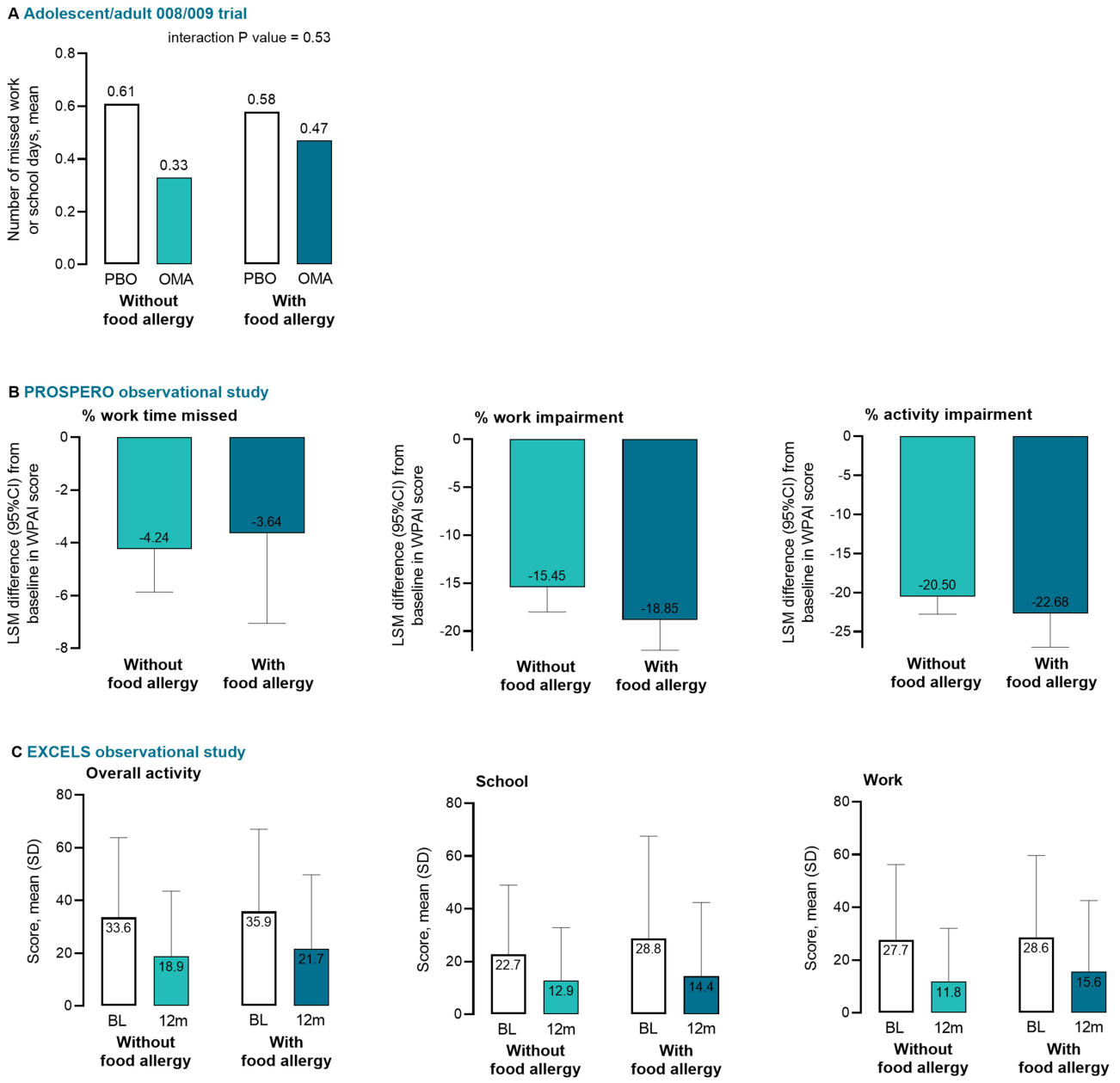

Figure 4 Productivity following omalizumab for patients with asthma by food allergy status. (**A**) Adolescent/adult 008/009 trial, number of missed days of work or school at 4 months. (**B**) PROSPERO observational study, LSM difference from baseline in WPAI-Asthma subsections at 12 months. (**C**) EXCELS observational study, WPAI-Asthma subsection scores at 12 months.

Abbreviations: LSM, least squares mean; OMA, omalizumab; PBO, placebo; WPAI, Work Productivity and Activity Impairment.

(Figure 4B). For EXCELS, improvements were observed for omalizumab new starters in overall activity score, school score, and work score (Figure 4C).

Asthma Outcomes

Improvements in asthma outcomes for patients with asthma treated with omalizumab were similar regardless of presence of food allergy, consistent across clinical trials and observational studies.

In the clinical trials, asthma exacerbations were decreased with omalizumab (rate of clinically significant or protocol defined asthma exacerbations, omalizumab versus placebo, $P < 0.001$ at 12 months for IA05, $P < 0.001/P = 0.092$ at 6 months for 008/009), and this response was similar in patients with and without food allergies (Figure 5A; interaction $P = 0.21$ for

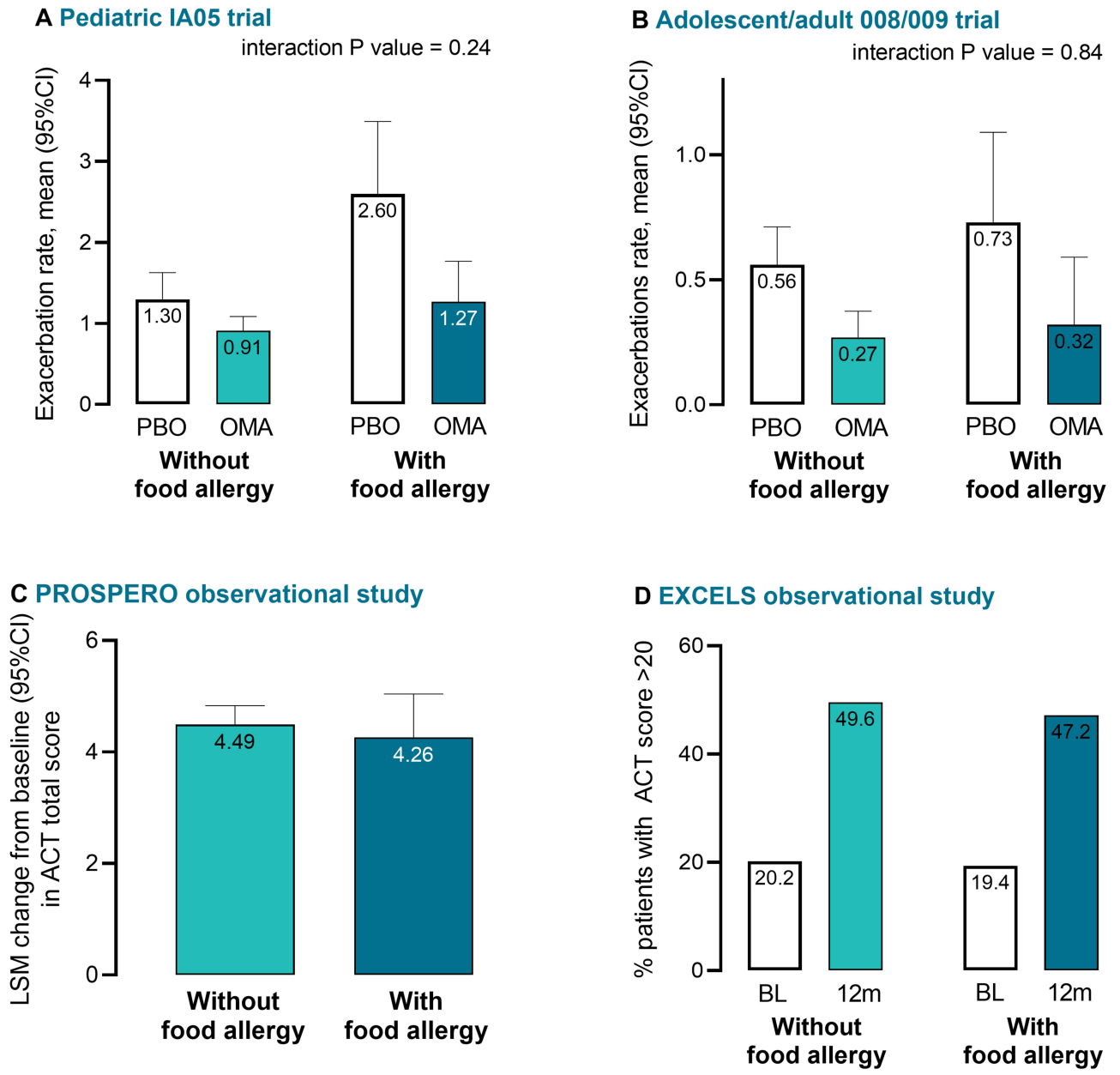

Figure 5 Asthma outcomes following omalizumab for patients with asthma by food allergy status. (**A**) Pediatric IA05 trial, asthma exacerbation rate at 12 months. (**B**) Adolescent/adult 008/009 trial, asthma exacerbation rate at 4 months. (**C**) PROSPERO observational study, change from baseline in ACT at 12 months. (**D**) EXCELS observational study, proportion of patients with ACT score >20 at 12 months.
Abbreviations: ACT, Asthma Control Test; BL, baseline; m, months; OMA, omalizumab; PBO, placebo.

IA05 at 12 months and Figure 5B; interaction P = 0.84 for 008/009 at 4 months). Of note, asthma exacerbations at 12 months for patients in the placebo group appeared to be numerically greater for patients with food allergy than patients without food allergy. In the observational studies, improvements in ACT score at 12 months following omalizumab initiation appeared to be similar for patients with and without food allergy (Figure 5C and D).

Discussion

Although food allergy and asthma are intimately linked,[1,2] little is known about the response to the biologic treatment, omalizumab, when patients have these comorbidities. Our analysis of the collective body of data showed that, despite evidence for increased atopy at baseline (by numerically higher serum total IgE levels and higher rates of atopic

comorbidities), omalizumab improved asthma-specific and all-cause outcomes in patients with comorbid asthma and food allergy. The response to omalizumab in both placebo-controlled randomized clinical trials and real-world observational studies, across children, adolescents, and adults, for outcomes including healthcare resource use, quality of life, productivity, and asthma assessments, was similar in patients with asthma regardless of whether they had comorbid food allergy (see link to Video Abstract). Combined with the related pathophysiology pathway of both allergic asthma and food allergy, these findings suggest that omalizumab may be beneficial for patients with either or both conditions.

Our preliminary evidence for increased atopy in patients with asthma and food allergy is consistent with previous studies, especially in children where it likely reflects the "atopic (or allergic) march."[2] In the IA05 study in children, we found that the placebo group at 12 months trended to poorer outcomes in every measure for patients with food allergy versus those without. This trend is similar to a study by Arabkhazaeli et al of children aged 4–12 years with asthma: in this study 79% of children had at least one additional atopic condition (hay fever, eczema, food allergy; 26% had all three), which were associated with increased oral corticosteroid use, more emergency department visits, and inadequate asthma control.[6] These findings serve as a reminder to physicians that patients with concomitant food allergy and asthma should be considered for close and deliberate management.

The relationship between food allergy and asthma is complex as a recent study confirmed that food allergy in infancy is associated with asthma at 6 years of age.[29] Theoretically, this suggests that preventing or treating food allergies early may possibly have an effect on asthma. Indeed, interruption of the atopic march by biologic agents has been recently hypothesized by Spergel et al.[30] In addition, the National Institutes of Health-sponsored Preventing Asthma in High Risk Kids (PARK) study with omalizumab is currently ongoing.[31] This double-blind, placebo-controlled, randomized trial will assess whether omalizumab versus placebo (for 2 years followed by 2 years off-treatment observation) administered to children aged 2–3 years who are at high risk for development of asthma will prevent the development of asthma. Of interest, this study will also examine the incidence of food allergy and other atopic conditions (atopic dermatitis, allergic rhinitis); thus the ability of omalizumab to prevent these conditions will also be assessed.

Omalizumab has recently been approved in the United States for the treatment of food allergies in the United States (based on the OUtMATCH trial[12,32] and is highlighted by the GA^{2}LEN Food Allergy Guideline Group as the conditionally recommended biologic for treatment of patients with asthma and coexisting food allergy,[33] and is also recommended during the initial stages of oral immunotherapy for milk allergy.[34] Wood et al recently published the key primary outcomes from OUtMATCH:[35] the study found that 79 of 118 (67%) patients on omalizumab with initial reactivity to <100 mg of peanut protein could ingest >600 mg (cumulative >1044 mg) of peanut protein without dose-limiting symptoms (versus 4 of 59 [7%] patients on placebo), suggesting that omalizumab is able to increase the reaction threshold and protect against small accidental exposure. Of note, patients in OUtMATCH were highly atopic, including 79% with atopic dermatitis and 52% with asthma, providing additional evidence that omalizumab is effective in patients with asthma and food allergy. Our findings buttress these results with consistent improvements in healthcare resource use and asthma-specific quality of life and productivity with omalizumab in patients with food allergy.

Our study is limited by the post hoc exploratory nature of the analysis. In addition, most outcomes assessed were asthma-specific, which limits extrapolation to all-cause or food allergy-specific outcomes. Finally, food allergy in these studies was physician-reported and characteristics such as food allergens, food-specific IgE levels, skin prick test, and food challenge results were unavailable.

Conclusion

In our analysis the collective body of evidence from multiple studies across different patient populations with allergic asthma showed that omalizumab consistently improved key general and asthma-specific patient-centered outcomes in patients with food allergy, although food allergy-specific outcomes were unavailable. Furthermore, omalizumab improved asthma outcomes, regardless of whether patients had comorbid food allergy, suggesting that there is no loss of omalizumab efficacy even though patients with both conditions were generally more atopic. Therefore, treatment with omalizumab presents a viable management option for patients with both asthma and food allergy.

Abbreviations

ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; IgE, immunoglobulin E; WPAI, Work Productivity and Activity Impairment.

Data Sharing Statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

Ethics Approval

Review and approval of study protocols was required for this research by applicable institutional review boards or ethics committees before trial commencement. The clinical trials and observational studies reported in this study were approved by the institutional review boards or ethics committees at each site for each study. Given this manuscript reports a post hoc analysis of these studies, details of institutional review boards or ethics committees are provided in the respective primary manuscripts for each study. All patients provided informed consent.

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