

Effects of Omalizumab on Rhinovirus Infections, Illnesses, and Exacerbations of Asthma

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Abstract

Rationale: Allergic inflammation has been linked to increased susceptibility to viral illnesses, but it is unclear whether this association is causal.

Objectives: To test whether omalizumab treatment to reduce IgE would shorten the frequency and duration of rhinovirus (RV) illnesses in children with allergic asthma.

Methods: In the PROSE (Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations) study, we examined children with allergic asthma (aged 6–17 yr; n = 478) from low-income census tracts in eight U.S. cities, and we analyzed virology for the groups randomized to treatment with guidelines-based asthma care (n = 89) or add-on omalizumab (n = 259). Weekly nasal mucus samples were analyzed for RVs, and respiratory symptoms and asthma exacerbations were recorded over a 90-day period during the fall seasons of 2012 or 2013. Adjusted illness rates (illnesses per sample) by treatment arm were calculated using Poisson regression.

Measurements and Main Results: RVs were detected in 97 (57%) of 171 exacerbation samples and 2,150 (36%) of 5,959 nonexacerbation samples (OR, 2.32; $P < 0.001$). Exacerbations were significantly associated with detection of rhinovirus C (OR, 2.85; $P < 0.001$) and rhinovirus A (OR, 2.92; $P < 0.001$), as well as, to a lesser extent, rhinovirus B (OR, 1.98; $P = 0.019$). Omalizumab decreased the duration of RV infection (11.2 d vs. 12.4 d; $P = 0.03$) and reduced peak RV shedding by 0.4 log units (95% confidence interval, -0.77 to -0.02 ; $P = 0.04$). Finally, omalizumab decreased the frequency of RV illnesses (risk ratio, 0.64; 95% confidence interval, 0.49–0.84).

Conclusions: In children with allergic asthma, treatment with omalizumab decreased the duration of RV infections, viral shedding, and the risk of RV illnesses. These findings provide direct evidence that blocking IgE decreases susceptibility to RV infections and illness.

Clinical trial registered with www.clinicaltrials.gov (NCT01430403).

Keywords: rhinovirus; IgE; omalizumab; asthma

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At a Glance Commentary

Scientific Knowledge on the

Subject: Results derived from observational clinical studies demonstrate that allergic sensitization is associated with greater susceptibility to viral respiratory illnesses, especially those caused by rhinoviruses. Whether this association is causal had not yet been determined.

What This Study Adds to the

Field: The present interventional study of omalizumab use in urban children with allergic asthma included extensive sampling for diagnostic virology and allowed the investigators to test whether inhibition of IgE had effects on the frequency and duration of rhinovirus infections and illnesses. The results show that inhibition of IgE reduced morbidity caused by naturally acquired rhinovirus infections and that these effects include reductions in viral illnesses, viral asthma exacerbations, and the duration and peak of viral shedding. This interventional study is the first to provide direct evidence that IgE-mediated mechanisms can impair rhinovirus clearance and enhance susceptibility to rhinovirus illnesses.

Rhinovirus (RV) infections are important contributors to asthma exacerbations, particularly in the fall, when children return to school. However, even during the peak risk seasons, RV infections do not always cause exacerbations (1), suggesting that there are additional factors contributing to this interaction. There are three RV species (A, B, and C), and most case-control studies of acute asthma exacerbations demonstrate that infections with RV-C, and less so RV-A, are associated with acute severe wheezing, whereas RV-B is seldom associated with exacerbation (2–7). Allergic sensitization increases the risk and severity of virus-induced wheeze (8–13), and fall exacerbations are most closely associated with sensitization to perennial allergens (14). The ICATA (Inner-City Anti-IgE Therapy for Asthma) study investigators found that treatment of exacerbation-prone children with omalizumab, a therapy that specifically targets IgE-mediated inflammation, prevented the fall increase in exacerbations, including those

associated with RV infections (15). In addition, treatment with omalizumab reduces the severity of RV-induced exacerbations (16).

More recently, the PROSE (Preventative Omalizumab or Step-up Therapy for Fall Exacerbations) study was conducted to determine whether preseasonal treatment with omalizumab or inhaled corticosteroids would prevent fall exacerbations compared with standard guidelines-based therapy (15). The exacerbation rate was significantly lower in the omalizumab versus placebo group (11.3% vs. 21.0%; odds ratio [OR], 0.48; 95% confidence interval [CI], 0.25–0.92), whereas no difference was seen between the fluticasone boost and placebo arms. Additionally, treatment with omalizumab led to improved *ex vivo* RV-induced IFN- α responses of blood mononuclear cells, which have previously been shown to be suppressed when IgE is cross-linked by allergen (17, 18). Within the PROSE omalizumab group, participants with the greatest *ex vivo* increase in IFN- α experienced fewer virus-induced exacerbations of asthma (15). These findings support the overall concept that IgE-mediated mechanisms can suppress antiviral responses and that treatment with anti-IgE might reduce the severity of viral illnesses and thus lower the risk of virus-induced exacerbations of asthma.

The PROSE study was designed to include weekly sampling for virology during the fall season, thereby providing a unique opportunity to test whether blocking IgE with omalizumab would reduce the severity of RV illnesses. We formulated three hypotheses. First, we hypothesized that RV-C would be the species most strongly associated with exacerbations. Second, we proposed that treatment with omalizumab would reduce the number of symptomatic RV illnesses compared with standard therapy. Finally, because antiviral responses (e.g., type I IFN) limit rather than prevent viral infection, we hypothesized that omalizumab would reduce symptomatic RV illnesses without affecting the number of RV infections (defined as detection of RV regardless of the presence or absence of symptoms).

Methods

Study Design

The PROSE study included 478 children with respiratory allergy and asthma who were aged 6–17 years and from low-income

census tracts in eight cities for a randomized trial of guidelines-based asthma care versus add-on fluticasone boost versus add-on omalizumab (15). For the purposes of the present study, we specifically tested for effects of omalizumab on viral infection and illness; we did not include fluticasone treatment in the present analysis, because it did not reduce virus-induced exacerbations in the main study (15). Either omalizumab or placebo was administered every 2 or 4 weeks by subcutaneous injection, with dosing based on weight and serum IgE levels. Nasal mucus samples were collected weekly, either at home or during clinic visits, over a 90-day period during the fall seasons of 2012 or 2013 as previously described (15). Respiratory symptom scoring sheets were collected weekly over the 90-day treatment period (*see* Figure E1 in the online supplement).

Participants

Children aged 6–17 years were eligible to participate, provided that they had an asthma diagnosis or symptoms for longer than 1 year, one or more asthma exacerbations (requiring systemic corticosteroids) or hospitalization within the prior 19 months, and allergic sensitization with a positive skin test response to one or more perennial allergens. Subjects had to have body weight and total serum IgE levels suitable for dosing of omalizumab, and these were based on the Inner-City Anti-IgE Therapy for Asthma Study, a prior study by the Inner City Asthma Consortium (19). Additionally, school attendance beginning in August or September, residence in a low-income census tract in predefined inner-city areas, and insurance covering standard medications were also required for participation.

Definitions

Respiratory symptoms were evaluated with the respiratory symptom assessment tool (*see* Figure E1 in the online supplement), which was filled out by the child if at least 12 years of age or by the parent if the child was younger than 12 years of age. Runny nose, stuffy nose, sore throat, sneezing, and cough were scored 0–3 (absent, mild, moderate, or severe, respectively) on the basis of the Jackson cold scale (20); this was performed once weekly to reflect symptoms over the past 7 days. A composite cold score was calculated by taking the sum of these symptom scores. All definitions were

decided upon and recorded in the statistical analysis plan prior to analysis initiation. Illnesses were identified as an increase in the symptom score of at least 4 points compared with baseline, which was defined as the minimum weekly report of symptoms. For children with chronic upper respiratory symptoms (minimum score, ≥ 3), illness was defined as an increase in the total symptom score of at least 3 points. RV infection was defined as detection of virus, and detection of the same virus in consecutive samples was counted as a single infection. Duration of infection was determined by considering the number of consecutive samples (obtained every 7 d) with a positive test result for the same virus type; for example, three consecutive weekly samples with a positive test result for the same virus would represent a single infection of 21 days' duration. Viral illness was defined as RV detection at any time during the illness period. An acute asthma exacerbation was defined as a need for systemic (intravenous, intramuscular, or by mouth) steroids for asthma symptoms, as determined by the medical provider caring for the child (15). A viral exacerbation was defined as RV detection within ± 7 days of an acute asthma exacerbation.

Virology

Each sample of nasal secretions was tested for RVs by reverse transcription–polymerase chain reaction (21). Samples with a positive test result were then quantitated by quantitative polymerase chain reaction and partially sequenced to determine the type and species (21). Peak viral shedding was determined as the highest value for RV RNA detected in nasal mucus specimens associated with each infection (mean specimens per infection, 5.3 [5.5 placebo, 5.1 omalizumab]; range, 0.9–13.4).

Statistical Analysis

Participants' baseline demographic and clinical variables were assessed using Wilcoxon rank-sum tests for continuous variables; chi-square tests were used for comparing proportions. Frequency variables were analyzed using a Poisson regression model with overdispersion correction while controlling for the set of predefined covariates, including site, dosing frequency group (every 2 wk, every 4 wk), and asthma treatment step level. Dichotomous variables were analyzed using

logistic regression, again controlling for site, dosing frequency, and asthma treatment step level. For variables measured longitudinally, we extended these models to a generalized linear mixed model using random intercepts for each participant. Data analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC). The level of significance was set at an α -value of 0.05.

Results

Study Population

Prior to the fall seasons of 2012 and 2013, a total of 727 participants were enrolled in the run-in phase; 1–2 months before the start of school, 513 participants were randomized to one of the three treatment arms. The most common reason for not getting randomized was achieving asthma control with intermittent or low-dose (fluticasone 50 μ g inhaled twice daily) controller therapy (15). A total of 478 subjects were

included in the modified intention-to-treat population (i.e., participants who were randomized, began study treatment, and had at least one study contact during the 90-day outcome period), including 259 in the omalizumab group and 89 in the placebo group. From these 348 children, 4,447 weekly nasal samples were analyzed over a 90-day treatment period, including 3,293 specimens in the omalizumab group and 1,154 specimens in the placebo group (Figure 1). Overall, 78.2% of expected specimens were collected, and the median number of samples collected was 14 for both of the groups (*see* Figure E2 in the online supplement). There were no significant demographic differences between the omalizumab and placebo treatment groups (Table 1).

RV Species and Exacerbations

We previously reported in the PROSE study that RVs were detected within 1 week in 57% (97 of 171) of exacerbation samples,

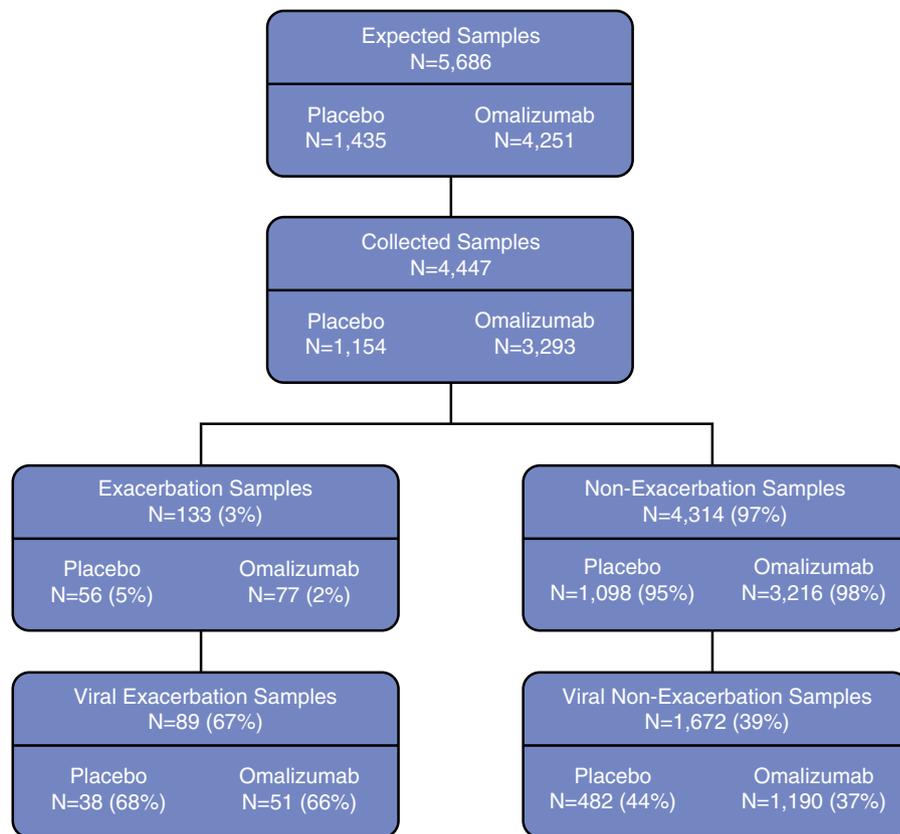


Figure 1. The PROSE (Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations) study nasal samples Consolidated Standards of Reporting Trials diagram for the intention-to-treat population ($n = 348$).

Table 1. Study Population*

	Overall (n = 348)	Placebo (n = 89)	Omalizumab (n = 259)	P Value
Race or ethnic group, n (%)				0.43
African American	199 (57.2%)	54 (60.7%)	145 (56.0%)	
Hispanic	118 (33.9%)	30 (33.7%)	88 (34.0%)	
White, mixed, or other	31 (8.91%)	5 (5.62%)	26 (10.0%)	
Caregiver completed high school, n (%)	243 (70.0%)	55 (61.8%)	188 (72.9%)	0.07
Annual household income <\$15,000, n (%)	196 (57.1%)	51 (58.6%)	145 (56.6%)	0.84
Age, yr	10.0 (8.00–12.0)	9.00 (8.00–12.0)	10.0 (8.00–12.0)	0.48
Male sex, n (%)	233 (67.0%)	59 (66.3%)	174 (67.2%)	0.98
Duration of asthma, yr	7.5 (4.9–10.0)	6.7 (4.9–9.5)	7.67 (4.9–10.1)	0.15
C-ACT score in the previous month, aged 4–11 yr [†] , n = 358	21.3 (3.65)	21.3 (3.52)	21.3 (3.70)	0.91
ACT score in the previous month, aged ≥12 yr [†] , n = 119	21.3 (3.25)	21.2 (3.87)	21.4 (3.05)	0.84
Asthma-related symptoms, d in prior 2 wk [‡]	2.0 (0.0–4.0)	2.0 (0.0–4.0)	2.0 (0.0–3.0)	0.55
Baseline cold symptoms score	2.0 (0.0–3.0)	2.0 (0.0–3.0)	2.0 (0.0–3.0)	0.87
FEV ₁ , % of predicted value	88.8 (78.0–99.1)	89.6 (77.4–102)	88.7 (78.9–98.9)	0.81
FEV ₁ /FVC × 100	77.6 (71.0–84.5)	78.2 (70.0–84.8)	77.3 (71.1–84.4)	0.97
Medications [§] , n (%)				0.89
Step levels 2–4	164 (47.1%)	43 (48.3%)	121 (46.7%)	
Step level 5	184 (52.9%)	46 (51.7%)	138 (53.3%)	
Asthma exacerbation during run-in	141 (40.5%)	35 (39.3%)	106 (40.9%)	0.89

Definition of abbreviations: ACT = Asthma Control Test; C-ACT = Childhood Asthma Control Test.

*Values are counts (percentages), means (SDs), or medians (interquartile ranges).

[†]Scores on the C-ACT and the ACT were measured on scales of 0–27 and 5–25, respectively. A score of 19 or less on either test indicates that asthma is not well controlled. The minimally important difference for ACT equals 3 points; for the C-ACT, a 3-point increase suggests a clinically relevant improvement in asthma control, whereas a 2-point decrease suggests a clinically relevant worsening.

[‡]The number of days with symptoms was calculated as the largest of the following variables during the previous 2 weeks: number of days with wheezing, chest tightness, or cough; number of nights of sleep disturbance; and number of days when activities were affected. This symptom scale ranges from 0 to 14 days per 2-week period.

[§]Six treatment steps were established, which is consistent with report 3 of the National Asthma Education and Prevention (41). At step 0, the recommendation is for no asthma control medication or albuterol as needed; at step 1, the recommendation is for 50 µg of fluticasone twice daily; at step 2, the recommendation is for 100 µg of fluticasone twice daily; at step 3, the recommendation is for 250 µg of fluticasone twice daily; at step 4, the recommendation is for 250 µg of fluticasone and 50 µg of salmeterol twice daily (Advair; GlaxoSmithKline, Warren, NJ); and at step 5, the recommendation is for 500 µg of fluticasone and 50 µg of salmeterol twice daily (Advair).

compared with 36% (2,150 of 5,959) of nonexacerbation samples (OR, 2.32; $P < 0.001$) (15). We have now sequenced the RVs detected in the placebo and omalizumab group samples and tested whether RV type and species affected the risk for exacerbations (Figure 2). Compared with periods with no virus detected for RV-A (2.92 [1.66–5.14]; $P < 0.001$) and RV-C (2.85 [1.58–5.15]; $P < 0.001$), infections were most strongly associated with exacerbation, and this was true to a lesser extent for RV-B infections (1.98 [1.12–3.50]; $P = 0.019$). Detection of multiple types of RV in the same specimen was less common (2%) but was strongly associated with exacerbation (5.16 [2.14–12.45]; $P < 0.001$).

Omalizumab and RV Detection

We next tested whether omalizumab treatment reduced RV detection among the weekly nasal mucus samples. RV was detected in 498 (43%) of 1,154 weekly specimens in the placebo group and in

1,174 (36%) of 3,293 specimens in the omalizumab group. Compared with placebo, treatment with omalizumab significantly decreased weekly rates of RV

detection (OR, 0.74; 95% CI, 0.60–0.92) (Figure 3A).

The reduced viral detection rates in the omalizumab group could have been

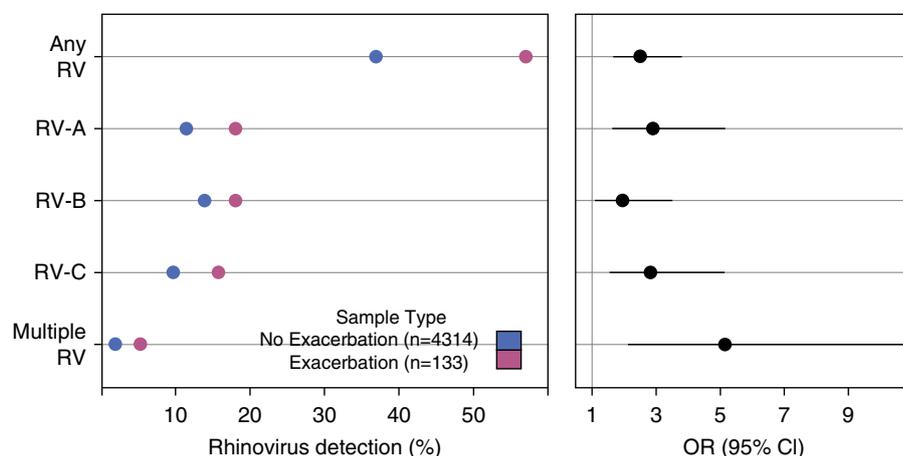


Figure 2. Comparison of rhinovirus (RV) detection in exacerbation versus nonexacerbation samples. The graphs depict (A) the prevalence of RV detection in exacerbation versus nonexacerbation samples and (B) the odds ratio (OR) (95% confidence interval [CI]) between exacerbation samples with RV detection versus no RV detected.

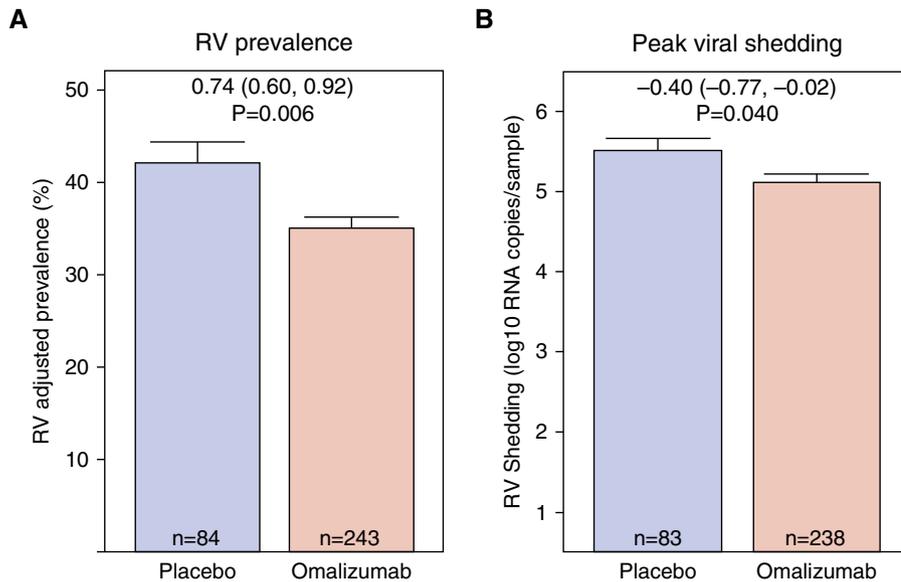


Figure 3. Omalizumab effects on viral detection. Bars represent omalizumab versus placebo effects on (A) rhinovirus (RV) prevalence (odds ratio and 95% confidence interval) and (B) peak viral shedding (log₁₀ difference and 95% confidence interval). The counts represent the number of participants with at least one virus sample detected.

due to fewer infections or reduced duration of viral shedding. In fact, omalizumab treatment had no significant effect on the number of infections, although there were nonsignificant trends for fewer infections with RV-A or RV-B (Table 2). In contrast, omalizumab treatment significantly reduced the average length of infection with any RV (11.2 vs. 12.4 d; *P* = 0.03) and with RV-C (9.5 vs. 11.6 d; *P* = 0.03).

Given that omalizumab shortened the duration of shedding, we next analyzed RV RNA in nasal secretions to determine whether omalizumab also reduced peak viral shedding, which was determined for each infection. Compared with placebo, omalizumab treatment reduced peak viral shedding by 0.4 log units (95% CI, -0.77 to -0.02; *P* < 0.04) (Figure 3B).

Omalizumab and Illnesses

Among the 4,248 weekly illness assessments (1,101 placebo, 3,147 omalizumab), there were 458 symptomatic illnesses (mean, 1.3 per participant; range, 0–6), including 313 illnesses in the omalizumab group (mean, 1.2/subject; range, 0–6) and 145 illnesses in the placebo group (mean, 1.6/subject; range, 0–5). Treatment with omalizumab significantly reduced the frequency of respiratory illness (risk ratio [RR], 0.73; *P* = 0.005) (Figure 4A). This reduction was seen across asthma treatment steps; the same rate of reduction was observed in participants with moderate asthma as in those with severe persistent asthma (data not shown).

Symptoms of RV illnesses (e.g., runny nose, stuffy nose, sore throat, sneezing, and

cough) overlap with those of allergic rhinitis. Therefore, we specifically evaluated the effects of omalizumab on illnesses that were associated with RV infections. Overall, 170 (54%) of 313 illnesses in the omalizumab group and 93 (64%) of 145 illnesses in the placebo group were associated with RV infections. Compared with placebo, treatment with omalizumab significantly reduced the frequency of RV illnesses (RR, 0.64; 95% CI, 0.49–0.84) (Figure 4B). There was a marginal and nonsignificant trend for omalizumab to reduce rates of non-RV illnesses (RR, 0.88; 95% CI, 0.65–1.20), which may have included illnesses caused by infections with other pathogens or noninfectious rhinitis. Omalizumab had no effect on the duration of respiratory symptoms (Figure 4C).

Discussion

Observational studies have demonstrated close associations between allergic sensitization and the risk of acute virus-induced wheezing episodes (11, 14, 22), and there is experimental evidence that allergic inflammation can impair antiviral responses (17, 23–25). Furthermore, in children who develop allergic sensitization and viral wheezing in early childhood, allergic sensitization usually occurs first (8, 26). These findings suggest that mechanisms involving IgE are associated with wheezing illnesses and reduced antiviral responses, but they do not establish causality. In this intervention study, omalizumab, which removes IgE and consequently suppresses IgE-mediated inflammation, reduced the duration and peak level of viral shedding during RV infections, and it also decreased the frequency and severity of RV illnesses. Our findings support the hypothesis that reducing IgE limits RV replication and promotes clearance, and through these mechanisms, reduces the

Table 2. Rhinovirus Species and Frequency and Duration of Infection

	Frequency (per 16-wk Monitoring Period)				Duration (d)			
	Placebo [Mean (SE); n]	Omalizumab [Mean (SE); n]	OR (95% CI)	P Value	Placebo [Mean (SE)]	Omalizumab [Mean (SE)]	OR (95% CI)	P Value
Any RV	3.4 (0.19); n = 84	3.3 (0.11); n = 243	0.95 (0.84–1.08)	0.47	12.4 (0.49)	11.2 (0.29)	0.90 (0.82–0.99)	0.03
RV-A	1.8 (0.12); n = 50	1.5 (0.07); n = 156	0.86 (0.73–1.01)	0.06	10.6 (0.68)	10.6 (0.39)	1.01 (0.87–1.16)	0.94
RV-B	1.7 (0.10); n = 59	1.4 (0.05); n = 154	0.87 (0.76–1.01)	0.06	12.3 (0.88)	11.9 (0.57)	0.97 (0.82–1.15)	0.70
RV-C	1.4 (0.09); n = 49	1.4 (0.05); n = 149	1.03 (0.88–1.20)	0.72	11.6 (0.94)	9.5 (0.33)	0.82 (0.68–0.98)	0.03
Multiple	2.0 (0.27); n = 16	1.9 (0.14); n = 61	0.94 (0.68–1.30)	0.70	16.1 (1.75)	13.7 (0.88)	0.85 (0.66–1.09)	0.20

Definition of abbreviations: CI = confidence interval; OR = odds ratio; RV = rhinovirus. The n values represent the number of participants with at least one of the specified viruses detected in a nasal mucus sample.

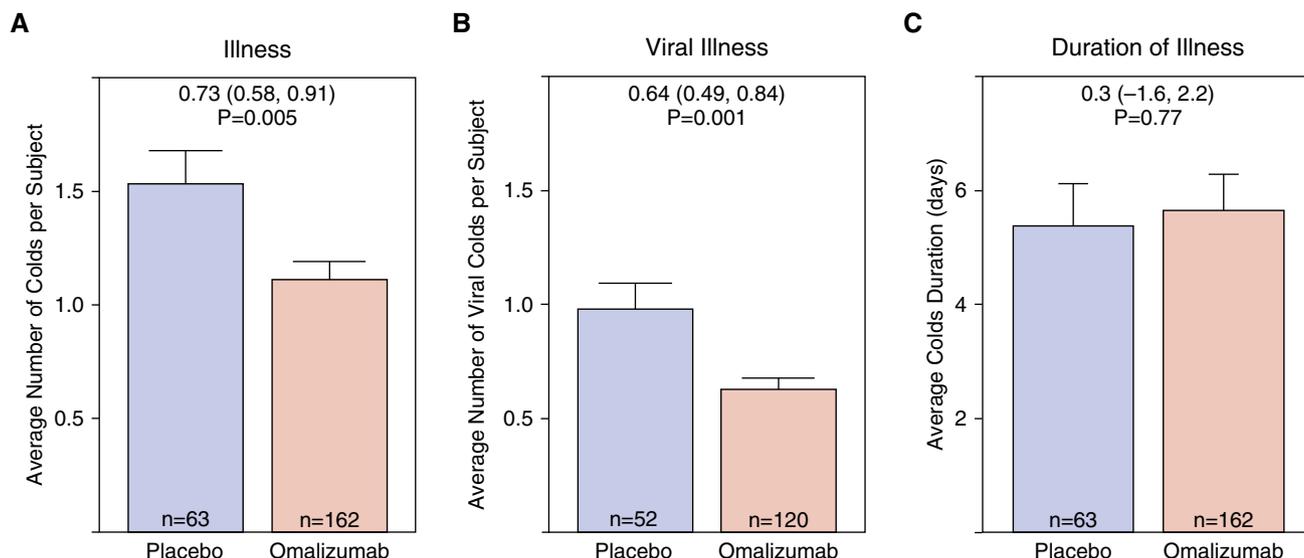


Figure 4. Omalizumab's effects on illnesses. (A) Mean numbers of illnesses per subject were calculated for the groups treated with omalizumab versus standard therapy. Data shown are the risk ratio (95% confidence interval). (B) Mean numbers of viral illnesses per subject were calculated for the group treated with omalizumab versus standard therapy. Data shown are the risk ratio (95% confidence interval). (C) Symptom duration of respiratory illnesses is depicted for children in the omalizumab and standard therapy groups. The numbers represent the number of participants with at least one (A and C) illness or (B) viral illness from randomization to the end of the 90 days.

frequency and severity of associated upper and lower respiratory illness.

Treatment with antiviral medications such as oseltamivir and pleconaril directly inhibit the replication of respiratory viruses and thereby reduce both the duration and peak of viral shedding as well as respiratory symptoms. In treatment studies, these medications decrease viral symptoms by 1 day and viral shedding by approximately 1 log unit (27–29). In our study, omalizumab reduced the duration of RV infection by about 1 day and the detection of RV-C, commonly associated with severe asthma exacerbations (3, 4), by 2 days. In addition, peak viral shedding was decreased by 0.4 log units (60%). These are modest effects, but the concurrent 40% reduction in viral respiratory illnesses indicates that these effects are clinically significant. By comparison, prophylactic use of oseltamivir has been shown to reduce the risk of symptomatic influenza by 55% (30).

Omalizumab could reduce the severity of viral illness through several pathways. For example, plasmacytoid dendritic cells, which produce large quantities of IFN- α , express high-affinity IgE receptors (Fc ϵ RI) on the cell surface. Virus-induced IFN- α responses are inversely related to expression of Fc ϵ RI and are further inhibited by receptor cross-linking (15, 17, 18). Omalizumab reduces surface

expression of Fc ϵ RI on plasmacytoid dendritic cells (and on mast cells), and by blocking IgE binding to the receptor, it also prevents receptor cross-linking by allergen (31). These effects may relate to observations that omalizumab can enhance IFN- α responses in the context of IgE receptor cross-linking (15, 17, 18). By enhancing IFN generation, omalizumab may be limiting the cell-to-cell spread of respiratory viruses and thus diminishing the severity of infection and associated level of illness.

As a downstream effect of decreasing cell-surface IgE and suppressing IgE cross-linking by allergens, omalizumab also reduces tissue eosinophilia (32, 33). Because eosinophilic inflammation is associated with increased risk for viral wheeze (13, 14, 34), it is possible that omalizumab reduces respiratory symptoms through this mechanism. Finally, omalizumab blocks mast cell activation and consequently inhibits downstream effects on type 2 inflammation (31). In our population of children with allergic asthma, baseline allergic inflammation and acute virus-induced effects are both likely to contribute to respiratory symptoms. Therefore, omalizumab's prevention of mast cell activation as well as the modification of IgE's action on antiviral

properties could contribute to suppressing the severity of respiratory illnesses.

In considering viral factors, data from several studies demonstrate that infections with RV-C and RV-A, but not RV-B, are associated with a greater risk for exacerbations (2–7). In our study, RV-A and RV-C infections were equally associated with exacerbations, and we also found a weak but significant association with RV-B infections. This finding with RV-B, which is a less virulent species (35), was likely due to the greater severity of asthma in our study population. Per study protocol (15), 52.9% of the children required inhaled fluticasone propionate/salmeterol 500 μ g/50 μ g twice daily to achieve asthma control, and 40.5% had an asthma exacerbation during the 4- to 9-month run-in period (Table 1). Compared with other RV species, RV-B causes less severe illness in infants (36) and has a slower replication rate in studies of differentiated cultures of primary airway epithelial cells (35). Thus, this less virulent RV may promote exacerbation only in children whose asthma is more severe and less stable.

Our PROSE study design has a number of strengths, including a large sample size, weekly monitoring for viral infection and illness, and an intervention that targeted

reduction of IgE. The study participants were children from eight U.S. cities; the geographic variation is important because prevalent RVs can vary by location (37). There are also limitations that should be considered in interpreting these data. The PROSE population consisted only of children living in neighborhoods with high rates of poverty, who historically have had high rates of exacerbations, raising the question of generalizability. Certainly, virus-allergen interactions have been reported in many populations (38), suggesting that these findings are broadly applicable to other groups. Second, PROSE virology was focused on RV infections; however, other respiratory viruses and airway bacteria may also contribute to respiratory illnesses and exacerbations (39, 40), and there may be other relevant covariates that were not measured. We plan

to conduct additional analyses within the PROSE study population to investigate potential interactions between viruses and the airway microbiome in relation to asthma exacerbations. Finally, the weekly frequency of nasal sampling limits the precision of measurements of the duration of infection and the peak viral shedding. However, given the regular sampling strategy, large number of specimens, and similar collection rates, there is no evidence of group-specific bias in the estimates of duration of infection or peak RV shedding.

In summary, this interventional study with omalizumab provides novel insights into interactions between IgE, RV infections, and resulting respiratory illness. For over 50 years, researchers have noted that respiratory allergies are a risk factor for increased symptoms during RV infections

(37). We provide evidence that focused treatment against IgE reduces morbidity resulting from naturally acquired RV infections and that these effects include reductions in viral illnesses, viral asthma exacerbations, and the duration and peak of viral shedding. ■

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