

Letter to the Editor

Severe winter asthma exacerbations can be prevented by omalizumab, but there is no carryover effect

To the Editor:

Recurrent severe asthma exacerbations are associated with decreased lung growth or accelerated loss of lung function and add substantially to both the cost and morbidity associated with asthma. Risk factors for acute exacerbations include previous acute exacerbation, young age, poorly controlled asthma, and, in particular, viral respiratory tract infections. Exacerbations in school-aged children have been associated with sensitization to aeroallergens, particularly severe exacerbations requiring hospitalization, in which up to 90% of the affected group is atopic and has a viral infection.¹ This apparent comorbidity is the subject of ongoing controversy, but recent studies have provided a plausible and testable hypothesis that might explain how atopy contributes to the exacerbation process.¹ Notably, cross-linking of high-affinity IgE receptors (FcεRI) on plasmacytoid dendritic cells² and myeloid dendritic cells³ of atopic subjects at airway mucosal infection sites, leading to attenuation of type 1 interferon production and enhancement of proinflammatory T_H2 cytokine production, respectively, markedly amplifies local inflammation.¹⁻³ This amplification process is IgE dependent, and hence blocking of available IgE during winter periods, which are at high risk for viral infection, might protect against these events.¹

Several recent studies support this general concept. First, the addition of omalizumab, a humanized IgG₁ anti-IgE mAb, to regular inhaled steroids given to children with inadequately controlled atopic asthma reduced their exacerbations by 43% compared with placebo.⁴ Second, in the Inner-City Asthma Study the addition of omalizumab to guidelines-based therapy reduced the number of days with asthma symptoms and reduced the proportion of study participants having 1 or more exacerbations from 48.8% to 30.3% across the 1-year treatment period. The strongest effect was on exacerbations occurring during the fall virus season.⁵ Third,

short-term preseasonal treatment with omalizumab blunted the ensuing fall asthma “epidemic” in atopic schoolchildren.⁶

An important question arising from these observations is whether reducing virus-associated exacerbations in a single season is a sufficient “circuit breaker” to decelerate progression of asthma toward chronicity. To test this, we conducted a double-blind, randomized, controlled 2-year pilot study of 27 children (58 screened; age, 6–15 years [mean, 11.45 ± 2.99 years]; 14 male subjects) with a history of a severe asthma exacerbation in the previous winter (clinical trial registration ACTRN12611001106921). Details of the study protocol and methods are shown in the [Methods](#) section in this article’s Online Repository at www.jacionline.org. All children were sensitized to aeroallergens and had asthma for a mean of 7.7 years (SD, 4.5 years). Demographic and clinical characteristics are shown in [Table I](#), with no important differences between groups. Children received omalizumab (n = 14) or placebo (n = 13) injections every 2 (n = 15) to 4 (n = 12) weeks based on their baseline total IgE level, per the manufacturer’s recommendations (see [Table E1](#) in this article’s Online Repository at www.jacionline.org), for 5 months to cover the winter viral season in Australia. Severe and moderate asthma exacerbations were defined according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus statement on asthma control.⁷ Children were assessed at the time of each injection at the end of the treatment period and then followed without treatment through the following year (follow-up period). The study schedule and procedures are shown in the [Methods](#) section in this article’s Online Repository (also see [Table E2](#) in this article’s Online Repository at www.jacionline.org). Primary comparisons between groups were made by using negative binomial regression.

Twenty-five children completed the treatment, and 22 completed the follow-up. Despite the small number, significantly fewer severe asthma exacerbations were seen in children treated with omalizumab (n = 1) than placebo (n = 6), with an incident rate in the placebo group 10.8 times greater than that in the omalizumab group ($P = .024$). The time to first severe exacerbation was longer in those receiving omalizumab (mean, 240.5 days [SD, 87.9 days] vs 107.0 days [SD, 115.9 days]; $P = .08$; [Fig 1](#)).

TABLE I. Baseline demographic and clinical characteristics of randomized subjects

	Active (n = 14)	Placebo (n = 13)	P value*
Age (y), mean ± SD	11.51 ± 2.94	11.40 ± 3.15	.92
Male sex (%)	54	46	.84
Total IgE (kU/L), mean ± SD	474.57 ± 248.76	372.80 ± 287.21	.31
Lung function†			
FVC Z score, mean ± SD	−0.13 ± 0.86	−0.15 ± 1.02	.85
FEV ₁ Z score, mean ± SD	−1.06 ± 1.25	−1.17 ± 1.00	.89
FEV ₁ /FVC Z score, mean ± SD	−1.38 ± 1.36	−1.55 ± 1.31	.70
Asthma Control Test score, mean ± SD	16 ± 5.8	17 ± 4.2	.85
Inhaled corticosteroid dose (μg of BDP equivalent), mean ± SD	705.56 ± 531.89	1088.46 ± 666.51	.08
Length of asthma (y), mean ± SD	7.9 ± 5.18	7.5 ± 3.75	.78
Asthma exacerbations in previous 12 mo, median (25% to 75%)	2.5 (1.75-3.00)	2.0 (1.50-3.00)	.83
Family history of asthma	11	10	.99
Failed to complete study			
Lost to follow-up	2	2	
Withdrew consent	0	1	
Withdrew because of AEs	1	0	

AEs, Adverse events; BDP, beclomethasone dipropionate.

*The Wilcoxon rank sum test was used for continuous variables, and the χ^2 test was used for categorical variables.

†Z scores were calculated by using the GLI calculator.

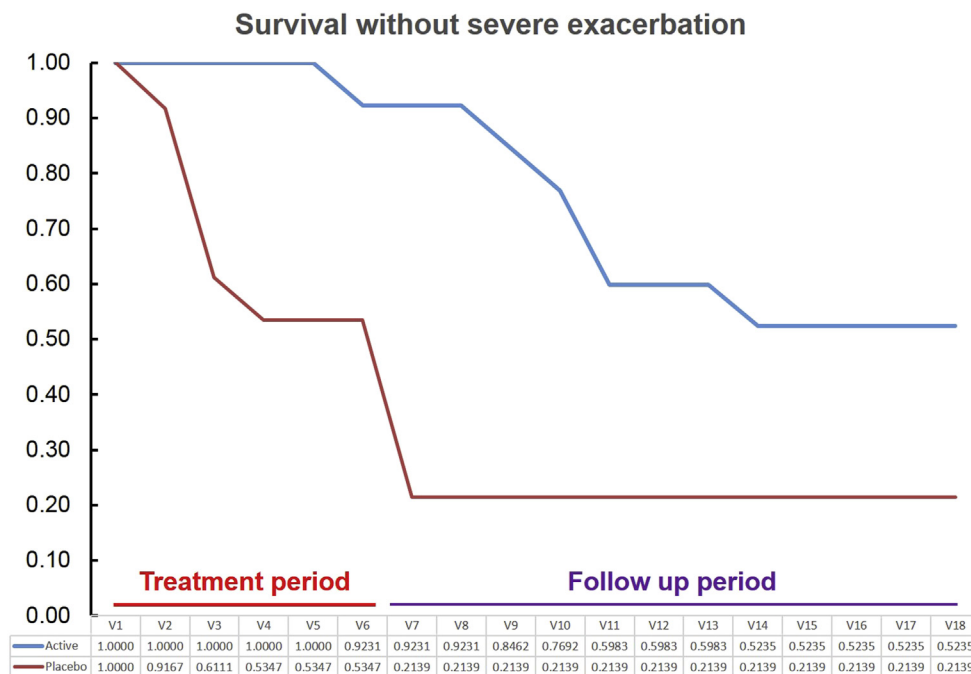


FIG 1. Time to first severe exacerbation. The proportion of the active ($n = 14$) and placebo ($n = 13$) groups “surviving” without an acute severe exacerbation is shown at each visit.

There were no differences in the number of moderate exacerbations (incident rate, 1.24; $P = .58$), time to first moderate exacerbation (177.3 days [140.6 days] vs 87.3 days [89.6 days], $P = .91$), or rate of lower respiratory tract illnesses (incident rate, 1.52; $P = .11$) between the study groups. The reduction in severe exacerbations was not seen during the follow-up period (incident rate, 0.45; $P = .45$). No statistically significant or clinically important changes were seen in lung function. We attempted to perform methacholine challenges at baseline, after treatment, and after follow-up, but many of the children were not able to perform the test because of low baseline lung function. In those able to participate ($n = 15$), there were no differences in PD_{20} values between the groups at any time point or any trend for reduction in methacholine responsiveness in either group.

The small numbers of children in this study means that our results must be treated with caution because our prestudy sample size calculations suggested that we needed 42 subjects per group to have 80% power to detect a 50% reduction in severe exacerbations with omalizumab. In addition, members of the placebo group were taking higher doses of inhaled corticosteroids, raising the possibility of less-well controlled asthma. However, they had a similar number of severe exacerbations in the previous 12 months (Table I). Nevertheless, taken in conjunction with similar recent findings on omalizumab-mediated blunting of the “fall” epidemics in susceptible children,⁶ they do support the general concept of targeted disruption of atopy-associated pathways during periods of high risk as an asthma treatment strategy. Our findings of a lack of carryover of the protective effect of omalizumab treatment in a single virus season into the subsequent year leaves open the question of whether omalizumab can halt disease progression. This important question needs to be addressed in subsequent prospective studies.

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METHODS

Study

This study was a phase 3, multicenter, double-blind, randomized, placebo-controlled study testing the efficacy of winter-only treatment with omalizumab for the reduction of asthma exacerbations in children aged 6 to 15 years. Clinical sites included the Royal Children's Hospital, Brisbane, Australia (site investigator: Professor Peter Sly); Royal Children's Hospital, Melbourne, Australia (site investigator: Professor Mimi Tang); and Princess Margaret Hospital, Perth, Australia (site investigator: Professor Peter LeSouef). The study population included children aged 6 to 15 years with asthma who were prone to acute exacerbations. Ninety-six children will be randomized. Randomization occurred in blocks stratified by study site based on pre-determined block sizes.

Inclusion criteria

Participants who met all of the following criteria were eligible for enrollment:

1. children of either sex, aged 6 to 15 years, with current asthma;
2. admission to a hospital emergency department in the previous winter season for acute asthma exacerbation, as defined by the ATS/ERS statement on asthma control and exacerbations;
3. positive skin prick test responses to aeroallergens;
4. atopic family history; and
5. written informed consent form signed and dated by parent/legal guardian according to local regulations.

Exclusion criteria

Participants who met any of the following criteria were not eligible for enrollment:

1. hypersensitivity to omalizumab;
2. treatment with omalizumab within 30 days before screening;
3. use of prolonged high-dose oral steroids;
4. participation in another randomized controlled trial within the 3 months preceding inclusion in the study; and
5. a significant medical disease or condition other than asthma likely to interfere with the child's ability to complete the entire protocol.

Study design

The study was conducted as a multicenter, double-blind, randomized, placebo-controlled study testing the efficacy of omalizumab treatment during winter for the reduction of asthma exacerbations in children with exacerbation-prone asthma. Children identified from emergency department records as having an acute asthma exacerbation during the previous winter viral season and found eligible in the screening visit were randomized into 2 groups. The active group received omalizumab every 2 or 4 weeks for 5 months timed to cover the winter viral season (April/May to September/October). The control group received identical placebo. Omalizumab was administered by means of subcutaneous injection every 2 or 4 weeks based on the baseline serum total IgE level (in international units per milliliter) measured before the start of treatment and body weight (in kilograms). The dosing regimen is shown in [Table E1](#).^{E1} All children also received standard asthma therapy, as prescribed by their treating pediatrician.

Primary efficacy end point

The primary efficacy end point was the proportion of children with acute asthma exacerbations, as defined by the ATS/ERS statement on asthma control and exacerbations,^{E2} during the treatment period (ie, from visit 1 [first dosing] to visit 6 [1 month after the last dose]). Severe and moderate exacerbations were treated separately.

Secondary efficacy end points

Secondary efficacy end points were as follows:

- the proportion of viral respiratory tract infections that result in lower airway symptoms during the treatment period (ie, from visit 1 [first dosing] to visit 6 [1 month after the last dose]) and

- lung function and airway responsiveness over the follow-up period (ie, from visit 6 [1 month after the last dose] until visit 18 [12 months after the last dose]).

Safety end points

Safety end points were as follows:

- urticarial or anaphylactic reaction to omalizumab;
- treatment-related adverse events; and
- hematology and clinical chemistry.

Data Safety Monitoring Board

Safety data were presented by group in a blinded fashion to the Data Safety Monitoring Board (DSMB) at scheduled DSMB meetings during the trial. The DSMB had the authority to request unblinded data, if necessary. The DSMB had the authority to recommend that enrollment or study treatment be discontinued for the safety of participants. Although the DSMB was to examine all safety data, they were requested to pay particular attention to the number of episodes of anaphylaxis.

Study procedures

Procedures conducted as a part of the participant's routine clinical management and obtained before informed consent were allowed to be used for screening purposes or assessment of eligibility criteria. However, the procedure must have met the protocol-defined criteria and have been performed within the timelines permitted by the protocol.

Informed consent

A signed written informed consent form was obtained from the participant's parent/legal guardian before any study-specific assessments or procedures.

Asthma control

The Childhood Asthma Control Test for children 11 years and younger and the Asthma Control Test for children 12 years and older were performed at visits 0, 6, and 18 to document asthma control.

Analysis sample

The following groups of participants will define samples for end point analysis:

- *Intention-to-treat sample*: All participants who are randomized and have evaluable data for the end point under investigation. Participants will be analyzed in the group to which they were randomized, regardless of compliance with their allocated treatment. The number of participants who have evaluable data might differ for each end point being investigated.
- *Safety sample*: All participants who take at least 1 dose of the investigational product.

Statistical analysis

The primary data on asthma exacerbations and lower respiratory tract infections were not normally distributed and did not fit with a Poisson distribution. Because the data were overdispersed (ie, the variance was greater than the mean), negative binomial regression was used for these primary analyses. Kaplan-Meier survival analyses were used to examine the time to first exacerbation, with the log-rank test used to test the difference in survival between treatment groups. Group differences in demographic data were tested by using the Wilcoxon rank sum test for continuous variables and the χ^2 test for categorical variables.

Schedule of study assessments and procedures

A schedule of study visits, procedures, and assessments is shown in [Table E2](#).

RESULTS

Asthma Control Test scores

There were no differences in Asthma Control Test scores between groups at baseline (omalizumab group: mean, 16 [SD, 5.8] vs placebo group: mean, 17 [SD, 4.2]; $P = .85$), at the end of the treatment period (mean: 20 [SD, 3.6] vs 20 [SD, 3.1], respectively; $P = .90$), or at the end of the follow-up period (mean, 20 [SD, 5.5] vs 22 [SD, 1.7], respectively; $P = .10$).

Exacerbations and lower respiratory tract infections

Treatment period:

- Severe exacerbations: incident rate, 10.83 ($P = .024$)
- Moderate exacerbations: incident rate, 1.24 ($P = .58$)
- Lower respiratory tract infections: incident rate, 1.52 ($P = .11$)

Follow-up period:

- Severe exacerbations: incident rate, 0.45 ($P = .10$)
- Moderate exacerbations: incident rate, 0.53 ($P = .53$)
- Lower respiratory tract infections: incident rate, 1.05 ($P = .86$)

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TABLE E1. Pediatric dosing schedule for omalizumab (in milligrams) per 4-week or 2-week interval

Dosing interval	Baseline IgE (IU/mL)	Body weight (kg)									
		>20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
Q4 weeks	≥30-100	75	75	75	150	150	150	150	150	300	300
	>100-200	150	150	150	300	300	300	300	300	225	300
	>200-300	150	150	225	300	300	225	225	225	300	375
	>300-400	225	225	300	225	225	225	300	300		
	>400-500	225	300	225	225	300	300	375	375		
	>500-600	300	300	225	300	300	375				
	>600-700	300	225	225	300	375		Do not administer			
Q2 weeks	>700-800	225	225	300	375						
	>800-900	225	225	300	375						
	>900-1000	225	300	375							
	>1000-1100	225	300	375							
	>1100-1200	300	300								
	>1200-1300	300	375								

TABLE E2. Schedule of assessments and procedures

Study period	Screening	Treatment						Follow-up												RTI	UV
Visit	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
Week	8 wk to 1 d	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	72		
Visit window			± 3d	± 3d	± 3d	± 3d	± 3d	± 5d	± 5d	± 7d	± 5d	± 5d	± 7d	± 5d	± 5d	± 7d	± 5d	± 5d	± 7d		
Telephone call								X	X		X	X		X	X		X	X			
Informed consent	X																				
Review eligibility criteria	X	X																			
Randomization		X																			
History	X																				
Physical examination	X	X	X	X	X	X	X			X			X			X			X		
Drug delivery		X	X	X	X	X															
Skin prick test	X																				
Nasal wash	X		X	X	X	X	X			X			X			X			X*		
Nasal swab																			X†		
Posterior palatal swab	X						X												X		
Lung function/methacholine challenge		X					X												X		
Pregnancy test	X	X	X	X	X	X	X			X			X			X			X		
Asthma Control Test	X						X												X		
Dispense diary card		X	X	X	X	X	X			X			X			X					
Diary card review			X	X	X	X	X			X			X			X			X		
Dispense rescue medication		X																			
Review rescue medication procedures			X	X	X	X															
Collect rescue medication							X														
Asthma severity score																			X*		
Blood collection	X						X												X		
Adverse event review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

RTI, Respiratory tract infections; UV, unscheduled visit.

*When presenting to A&E for acute asthma exacerbation.

†Respiratory tract infections only.