

Original article

Modeling the effects of omalizumab over 5 years among patients with moderate-to-severe persistent allergic asthma

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Abstract**Objective:**

Omalizumab is a monoclonal antibody indicated for adults and adolescents with moderate-to-severe persistent allergic asthma whose symptoms are inadequately controlled with inhaled corticosteroids. Omalizumab has been demonstrated to improve health outcomes of asthmatic patients as compared to placebo. However, to date, the trials conducted have been relatively short (less than 1 year) and have been restricted to a limited set of patients who met the clinical study criteria. This study examined the expected effects of omalizumab over 5 years on a representative sample of all patients eligible for omalizumab in the US.

Methods:

The Archimedes Asthma Model was used to simulate the following treatment scenarios for US patients age 12 and older with moderate-to-severe persistent allergic asthma: (1) Current asthma treatment (CAT) (treatment according to National Heart, Lung, and Blood Institute (NHLBI) guidelines, without use of omalizumab, and with adherence levels as observed in the National Asthma Survey); (2) Guideline asthma treatment (GAT) without omalizumab (NHLBI guidelines without use of omalizumab, assuming perfect adherence); (3) GAT plus omalizumab; and (4) GAT plus omalizumab with steroid reduction. The simulation was run for 5 years.

Main outcome measures:

Symptom days, asthma exacerbations, emergency room/urgent care (ER/UC) visits, hospitalizations, and medication use.

Results:

For the full simulated population of omalizumab-eligible patients, the simulation forecasted that omalizumab would decrease cumulative exacerbations by 30%, ER/UC visits by 37%, and hospitalizations by 38% over 5 years. Among responders to omalizumab, assuming that 60.5% of patients respond, the results suggest that omalizumab would decrease cumulative exacerbations by 50%, ER/UC visits by 62%, and hospitalizations by 63% over 5 years.

In addition, the simulation predicted that omalizumab would allow 45% of patients who are taking more than the minimum steroid dose to reduce their steroid dose, while maintaining similar asthma control as achieved in the GAT plus omalizumab arm (no steroid dose reduction) and better asthma control than following treatment protocols that do not include omalizumab.

Conclusion:

Based on the results of this simulation, omalizumab is effective for those who respond, reducing serious events by more than 50% among the responder group, while also allowing many patients to reduce their steroid dose.

Introduction

Omalizumab is an anti-immunoglobulin E (IgE) monoclonal antibody indicated for adults and adolescents (12 years of age and above) with moderate-to-severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids (ICS)¹. National Heart, Lung, and Blood Institute (NHLBI) guidelines for the treatment of asthma recommend that omalizumab be considered as part of steps 5 and 6 of the stepwise treatment for asthma for patients who are not well-controlled with the combination of ICS and long-acting beta agonists (LABA)².

Omalizumab has been demonstrated in clinical trials to reduce the rate of exacerbations, rate of emergency room/urgent care (ER/UC) visits, rate of hospitalizations, use of rescue medications, and symptom scores, among other outcomes, as compared with placebo^{3–13}. In addition, omalizumab has been shown to have a modest steroid-sparing effect^{3–6,13}. However, the clinical trials conducted to date have not extended beyond 1 year, and the clinical trial data are restricted to patients who met the study inclusion and exclusion criteria. Therefore, there are unanswered questions as to how omalizumab may affect a wide range of asthmatics who are indicated for the medication, as well as the magnitude of the effect for those who respond to it. Also, it is not known how the long-term use of omalizumab may impact patient outcomes. To investigate these issues, the Archimedes Asthma Model¹⁴, a mathematical tool designed to help decision makers explore the implications of population-scale intervention programs or changes in guidelines for an asthmatic population, was used.

Mathematical models can play an important role in healthcare by helping decision makers integrate evidence from a variety of clinical trials and epidemiological datasets and explore, via simulation, a range of scenarios where actual trials are unfeasible because of limitations in time, resources, ethical constraints, or other factors. Such models can be used to make policy decisions and to guide medical treatment. As an example, the US Preventive Services Task Force used mathematical models to develop its guidelines for breast cancer and colorectal cancer screening^{15,16}. Kaiser Permanente, a large integrated managed-care organization in the US, used forecasts from the Archimedes Model as the impetus to launch an initiative to provide a bundle of medications to high-risk members, resulting in a more than 60% reduction in myocardial infarctions and strokes over a 2-year period¹⁷. In the asthma treatment space, the Asthma Policy Model has been used to evaluate the clinical impact and cost effectiveness of ICS therapy in adult patients with mild-to-moderate asthma¹⁸.

The Archimedes Model includes asthma, coronary artery disease, stroke, congestive heart failure,

hypertension, dyslipidemia, diabetes and its complications, obesity, metabolic syndrome, breast cancer, colorectal cancer, and lung cancer. There have been a number of studies published using different components of the Archimedes Model, a sample of which are provided in the references^{19–22}.

In this study, the Archimedes Asthma Model was used to forecast how omalizumab would affect a representative sample of all omalizumab-eligible patients in the US over 5 years. To do this, a simulation was conducted of a 5-year clinical trial of omalizumab for a representative sample of patients aged 12 years and older with moderate-to-severe allergic asthma in the US.

Methods

Model description

This study used the Archimedes Asthma Model, a mathematical, stochastic model of asthmatic patients' lung-function progression, symptoms, behavior, and response to treatment¹⁴. The model is continuous in time, allowing for outcomes to be examined at both short time scales (weeks) and long time scales (years). It was built and validated using data from the National Asthma Survey (NAS)²² and National Hospital Discharge Survey (NHDS)²⁴ from the Centers for Disease Control and Prevention (CDC), together with data from the literature^{25–33}.

The model comprises the following components:

- (1) A core asthma intensity model, which is calibrated individually for each person to reflect his/her physiology. This core model accounts for each person's sensitivity to stimuli, the time scale over which an asthma exacerbation takes place, and age-related changes in lung function. This is the framework upon which the effects of medications and other interventions are modeled.
- (2) Stimulus events, which trigger surges in an individual's asthma intensity as a function of his/her sensitivity. Stimulus events are modeled as a Poisson process.
- (3) Perception and behavior models, which determine if and when each patient experiences symptoms and exacerbations, uses medications, and seeks care.
- (4) Medication models, which specify how each medication affects the parameters of the asthma intensity model.
- (5) Hospitalization parameters, which determine the probability of hospitalization given an ER/UC visit, as well as the duration of hospitalization once a person has been admitted.

The following medications are included in the model: ICS, oral corticosteroids (OCS), LABA, short-acting beta

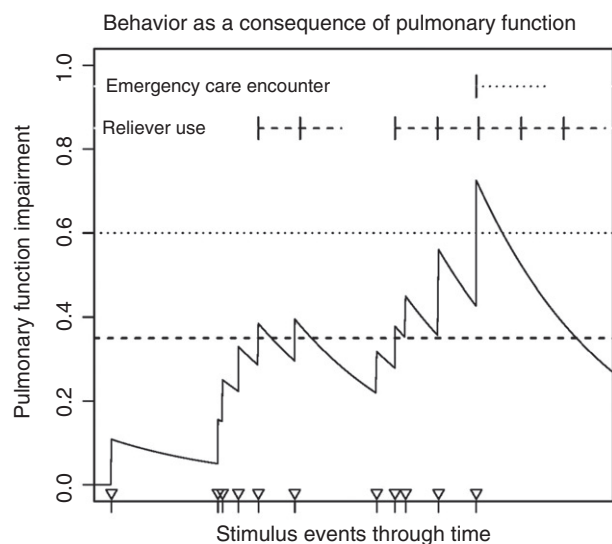


Figure 1. Illustration of the Archimedes Asthma Model. Stimulus events, shown on the horizontal axis, trigger surges in an individual's pulmonary function impairment. After each stimulus, the person's impairment decreases toward zero at a characteristic rate. If there are a number of closely spaced stimuli, the person's impairment may continue to increase, without having time to return to zero. As the impairment crosses each behavioral threshold, the individual will engage in the behavior corresponding to that threshold. In this figure, the individual has one emergency care encounter (higher threshold) and uses his/her reliever seven times (lower threshold). Other behaviors determined by thresholds (not shown in the figure) include symptom perception, the initiation of controller medications, and seeking unscheduled care from a physician.

agonists (SABA), and omalizumab. For ICS, low, moderate, and high doses are modeled, corresponding to the dose ranges given in Powell *et al.*³⁴. The ICS doses were based on the Powell *et al.* ranges due to similarities between those doses and the dosage data available to build the model³². However, had the ICS doses been modeled based on the ranges in the NHLBI guidelines, the results would be unlikely to change much.

Figure 1 demonstrates the modeling process. Stimulus events cause surges in an individual's pulmonary function impairment. The magnitude of these surges depends on that individual's sensitivity to stimuli. After each surge, the person's pulmonary function returns toward a normal state at a characteristic rate. If there are a number of closely spaced stimulus events, the individual's airway obstruction will continue to rise, without having time to return to a tolerable level. In such cases, as the person's pulmonary function impairment exceeds a series of behavioral thresholds, the individual will engage in symptomatically driven behaviors. The behavioral thresholds are uniquely calibrated for each individual so that the rates of simulated behaviors for that individual match those of the actual person, from NAS, to which he/she corresponds. Medications and other treatments act over a finite duration by modifying sensitivity to stimuli, current

pulmonary function, and rate of return toward a normal state.

Simulated population

The simulated population was a representative sample of the US population, aged 12 years and older, with moderate-to-severe persistent allergic asthma, who were eligible for omalizumab. The total simulated population size was 15 000 people. This number was chosen as a balance between a large population size to reduce statistical error and reasonable computation time. Analyses were performed based on this population and the subpopulation of responders to omalizumab.

To create the simulated population, a base population was constructed using data for moderate-to-severe persistent asthmatics from NAS²⁴ (337 unique people). A person was defined as having moderate-to-severe persistent asthma if he/she was on combination therapy (ICS and LABA, as well as possibly OCS) and was using SABA an average of at least once per day. NAS includes information about symptoms, ER/UC visits, and ICS, OCS, LABA, and SABA use, but does not have information about lung-function variability, dose of medication used, or medication response.

Individual-level data from the Busse *et al.*³ and Soler *et al.*⁵ trials (1071 people*) was then used to fill in the missing information in the base population. To do this, similar people from the base population and the trial data were matched up, based on the variables of age, gender, and SABA use, and the variables of peak expiratory flow (PEF) mean and variability over time, ICS dosage, and SABA usage patterns and response were imputed using data from the run-in period of the trials.

While the population pool consisted of a general population of moderate-to-severe persistent asthmatics from NAS who were not specifically allergic, the imputation used allergic asthmatics in the omalizumab trials^{3,5}. The patients in these trials met the following criteria: positive skin-prick test to at least one of the allergens *Dermatophagoides farinae*, *D. pteronyssinus*, dog, cat, or cockroach (whole body) and serum total IgE level between 30 and 700 IU/mL. Consequently, the population that was modeled reflected the lung-function characteristics, medication dosage, and medication response of allergic asthmatics. Moreover, the other characteristics of the population, including symptoms, ER/UC visits, and medication use, should approximate that of an allergic population, since the vast majority of severe asthmatics (93.5%) are allergic according to data from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study³⁵.

*Of the 1071 people in these trials, the imputation only used the people who matched the NAS people most closely, which turned out to be 484 people.

Table 1. Trial arms in simulation.

Arm	Treatment	Omalizumab	Steroid reduction	Adherence
Current asthma treatment (CAT)	NHLBI guidelines	No	No	Adherence levels as observed in NAS ²⁴
Guideline asthma treatment (GAT) without omalizumab	NHLBI guidelines	No	No	Perfect adherence
GAT plus omalizumab	NHLBI guidelines	Yes	No	Perfect adherence
GAT plus omalizumab with steroid reduction	NHLBI guidelines	Yes	Yes	Perfect adherence

Study protocol

The population was simulated four times, with the treatment strategies given in Table 1. These trial arms were based on NHLBI guidelines² and varied according to the inclusion of omalizumab, whether steroid reduction was done, and adherence to treatment.

The simulation included a 30-day run-in period. This time period was found to be sufficient for people to reach steady state under the treatment they were receiving in each arm. The simulated trial was begun after this run-in period and was run for 5 years.

For the steroid-reduction protocol, the following variables were defined after the 30-day stabilization period: (a) worst lung-function baseline: the worst lung-function value seen in the first exacerbation-free week of the simulation; (b) best lung-function baseline: the best lung-function value seen in the first two exacerbation-free weeks of the simulation; and (c) SABA-use baseline: the mean number of SABA uses during the first exacerbation-free week of the simulation. An exacerbation was defined as a worsening of asthma that does not resolve with the use of trial medications, including SABA, and therefore requires additional medical therapy, such as OCS³⁻⁶. Patients experiencing exacerbations in the simulation received treatment via an unscheduled doctor's office visit, ER/UC visit, and/or hospitalization.

After the first 16 weeks of the simulation and every 12 weeks thereafter, each patient was evaluated for a steroid dose reduction. At each evaluation, it was determined if the patient met any of the following criteria:

- The patient had experienced an exacerbation in the previous 12 weeks.
- The patient, on 2 consecutive days in the previous 2 weeks, had experienced a morning lung-function value of less than 80% of the worst lung-function baseline.
- The patient, on 2 consecutive days in the previous 2 weeks, had experienced a morning lung-function value of less than 50% of the best lung-function baseline.
- The patient, on 2 consecutive days in the previous 2 weeks, had used his/her reliever at least 50% more than the reliever-use baseline.
- The patient, on 2 consecutive days in the previous 2 weeks, had initiated relief therapy at night.

If none of these criteria were met, the person's steroid dose was reduced down one level among the levels that were modeled, which included low dose ICS, medium dose ICS, high dose ICS, and high dose ICS plus OCS. Therefore, for patients on maintenance therapy with both ICS and OCS, the first step in the reduction was to remove OCS. After that, the person's ICS was reduced to a lower level, down to a minimum of the lowest ICS dose; no one was reduced to zero ICS use. If exactly one of these criteria was met, the person's steroid dose and his/her eligibility for future reductions were maintained. If two or more of these criteria were met or the patient had two or more exacerbations, the person's steroid dose was increased up to a maximum of his/her original dose, and the reduction protocol was terminated. The criteria for this protocol mimic that described by Milgrom *et al.*⁴, while the timing and decision windows mimic those used by Hawkins *et al.*³⁶. This protocol is consistent with NHLBI's guidelines for a step-down reduction in pharmacologic therapy for well-controlled patients².

This protocol was followed for 1 year, as 1 year was deemed sufficient for patients to reach their optimal steroid dose. For the remaining 4 years of the simulation, patients were maintained at their optimal dose.

Outcomes reported

The simulation reported the following outcomes: symptom days, exacerbations, ER/UC visits, hospitalizations, and medication use, including omalizumab, ICS, LABA, SABA, and OCS. Symptom days were difficult to define, in that patients in the data sources appeared to have many different interpretations of what constituted a symptomatic day. There were some patients in NAS who reported high rates of SABA use but a low fraction of symptomatic days, while others reported frequent symptom days but rarely used their SABA inhaler. A high degree of correlation would be expected between these two outcomes and, given this inconsistency, it was questionable to tie the symptom-days outcome directly to the self-reported symptom-rate outcomes in NAS. Instead, a symptom threshold was defined for each patient, tied to that patient's SABA-use threshold, such that patients in the simulation would experience symptoms virtually every day, in line with

Table 2. Ratio of exacerbation rate for omalizumab versus placebo in stable steroid phase of trials.

Source	Annualized number of exacerbations per patient in stable steroid phase		Ratio of omalizumab to placebo	Weighted average ratio, using weights from Walker <i>et al.</i> ¹³
	Omalizumab	Placebo		
Busse 2001 ³	0.91	1.76	0.52	0.59
Milgrom 2001 ⁴	0.98	1.30	0.75	
Soler 2001 ⁵	0.91	2.15	0.42	
Holgate 2004 ⁶	0.49	0.75	0.65	

expectations for moderate-to-severe persistent asthmatics². While the authors believe this approach is reasonable, there is a significant degree of uncertainty in the symptom days outcome.

Responders to omalizumab

Rather than model all patients as responding equally to omalizumab, some patients were modeled as responders and some as non-responders, consistent with observations from clinical trials^{37–39}. The responder rate was taken from the INNOVATE trial^{39,40}, where a person was considered to be a responder if the physician global evaluation of treatment effectiveness (GETE) was either excellent (19.5%) or good (41%). Based on this definition, 60.5% of patients were responders. Therefore, in the simulation, 60.5% of the population were treated as responding to omalizumab, and the non-responding patients were removed from omalizumab therapy after 16 weeks.

A sensitivity analysis was also performed, in which an estimate was made of how many of the responders to omalizumab in the trials were actually responding to omalizumab, versus only experiencing a placebo effect, and this placebo-corrected response rate was used in the model. This is discussed in more detail in the Sensitivity analysis section.

The response to omalizumab was assumed to be random, rather than being correlated with any other asthmatic characteristics. This is consistent with the analysis by Bousquet *et al.*⁴⁰, which found that the effect of omalizumab on asthma exacerbations is not correlated with patient age, gender, baseline serum IgE, or dosing schedule. However, other evidence suggests that response to omalizumab may be correlated with severity of asthma as determined by history of emergency asthma treatment, high ICS dose, or low FEV₁³⁸. Such correlations were not captured in the model.

Model of omalizumab

The medication models in the Archimedes Asthma Model specify how different medications affect the parameters of the asthma intensity model. To calibrate a model for omalizumab, an iterative process was used. First, an assumption

was made about the percentage of patients who respond to omalizumab, as discussed in the previous section. Then, based on this assumption, each person was assigned a response between 0 and 1, where a response greater than 0.5 indicated someone was a responder. The response for each person was chosen from a sigmoidal distribution, where the shape of the sigmoid was defined in order to get the appropriate percentage of responders in the population.

Next, it was assumed that omalizumab would have a given effect on the parameters of the asthma intensity model. Each person would experience that effect multiplied by his/her assigned response (so those with a response of 1 would experience the full effect, while those with a response of 0 would experience no effect). Patients from the Busse *et al.*³ and Soler *et al.*⁵ trials were then simulated, and omalizumab's effect on exacerbations for the overall population was observed. Because the Busse *et al.*³ and Soler *et al.*⁵ trials did not include LABA treatment, patients were simulated on ICS alone, in trial arms defined by the addition of placebo or omalizumab treatment, in order to match the trial conditions. The simulated effects of omalizumab on exacerbations were compared to the actual effects reported in Walker *et al.*¹³, and to the extent that these were different, the magnitude of the omalizumab effect in the model was adjusted. This process was repeated until the simulated effects of omalizumab on exacerbations matched the actual effects observed in the trials.

The focus was on tuning the model of omalizumab to match the ratio of exacerbations with omalizumab to exacerbations without omalizumab (0.59, as shown in Table 2). However, the match for other outcome ratios calculated from Walker *et al.*¹³, including people with at least one exacerbation (ratio of 0.60) and rescue medication puffs per day (ratio of 0.80), was also evaluated. It was found that by calibrating the model of omalizumab to match exacerbations, the model also matched these other outcome ratios within their uncertainty, indicating that the model of omalizumab was working well. For a sensitivity analysis, the model was calibrated to match the smallest and largest reductions in exacerbations found among the trials. This is discussed in the Sensitivity analysis section.

It should be noted that the calibration for omalizumab differed depending on the responder assumption. If it was assumed that there were fewer responders, each responder would need to experience a larger effect in order to match the total population effect observed in the trials. The efficacy of omalizumab, as modeled in the simulation, was assumed to be constant over time, although the actual effect on individuals varied over time as people aged and their lung function decreased.

While the effect of omalizumab was calibrated using patients from the Busse *et al.*³ and Soler *et al.*⁵ trials, the full simulation was run using a representative sample of omalizumab-eligible patients in the US who were taking ICS, LABA, and possibly OCS. The effects of omalizumab may be different for this population, which includes more severe asthmatics as well as LABA usage. One of the purposes of this study was to forecast the effects of omalizumab on this full population of patients who are eligible for omalizumab based on NHLBI guidelines².

Statistical analysis

The analysis was focused on cumulative event rates per person over 5 years. A two-tailed Z-test was used to test for significant differences between arms*. A Z-test was appropriate because the simulation was large (15 000 people), so even though some outcomes were not continuous, the central limit theorem applied.

The simulated population consisted of multiple copies of the people from the source data sets for the purpose of enriching the sample size. Each time the same source person was run through the simulation, a slightly different result would be obtained due to the stochastic nature of the simulation. However, the results would not be as different as those obtained by running two different source people. Therefore, the effective sample size of the simulation was larger than the number of source people, but smaller than the total number of simulated people. Given this, a random effects model^{41,42} was used to calculate the error in event rates for the individual arms.

To calculate the error for the difference in rates or ratio of rates between arms, the propagation of errors formula was used⁴³. Because the event rates in different arms were strongly correlated, due to the same set of people being simulated in each of the arms, the covariance term in the propagation of errors formula had a large effect.

*Because the simulation was perfectly controlled (the same set of people were modeled in each arm), it was not necessary to adjust for control variables in the analysis.

Table 3. Summary of baseline characteristics of simulated population.

Characteristic	Population simulated in all arms
Number of people	15 000
Mean age (years)	38.9
Female (%)	67%
Race (%)	
White	77%
Black	11%
Hispanic	5%
Asian	1%
Multiple race	3%
Other	4%
Smoking status (%)	
Current smoker	20%
Ex-smoker	26%
Never smoked	54%
Mean FEV ₁ (L)	2.21
Mean FEV ₁ (% predicted)	69.5
Controller medication usage (% of people taking each medication)	
ICS	100%
LABA	100%
Long-term OCS (more than six months of use)	10%
In year prior to simulation start:	
Mean rescue medication uses per day	1.9
Mean symptom days per year	220
Mean exacerbations per year*	3.5
Mean ER/UC visits per year	0.8
Mean hospitalizations per year	0.24

*For the purposes of this table, exacerbations were defined as the sum of unscheduled doctor's office visits and ER visits in the NAS data.

Results

Population characteristics

Table 3 shows the baseline characteristics of the simulated population. This same population set was simulated for all of the arms.

Percentage of people able to reduce steroid dose

Among the full population, 76% of people were taking more than the minimal dose of ICS and LABA therapy and were therefore eligible for steroid reduction. Of these eligible people, 45% reduced their ICS and/or OCS dose in the GAT plus omalizumab with steroid reduction arm.

Exacerbation rate over time

Figure 2 shows the cumulative exacerbations per person over time in the different arms of the simulation, for the full and responder-only populations. For the full population, patients in the GAT without omalizumab arm had about 0.9 (5%) fewer exacerbations per person over the 5-year period than patients in the CAT arm. Thus, it appears that going from partial to full adherence for the population has only a minor effect on exacerbations. Patients in the GAT plus omalizumab arm had 4.6 (30%) fewer exacerbations than patients in the GAT

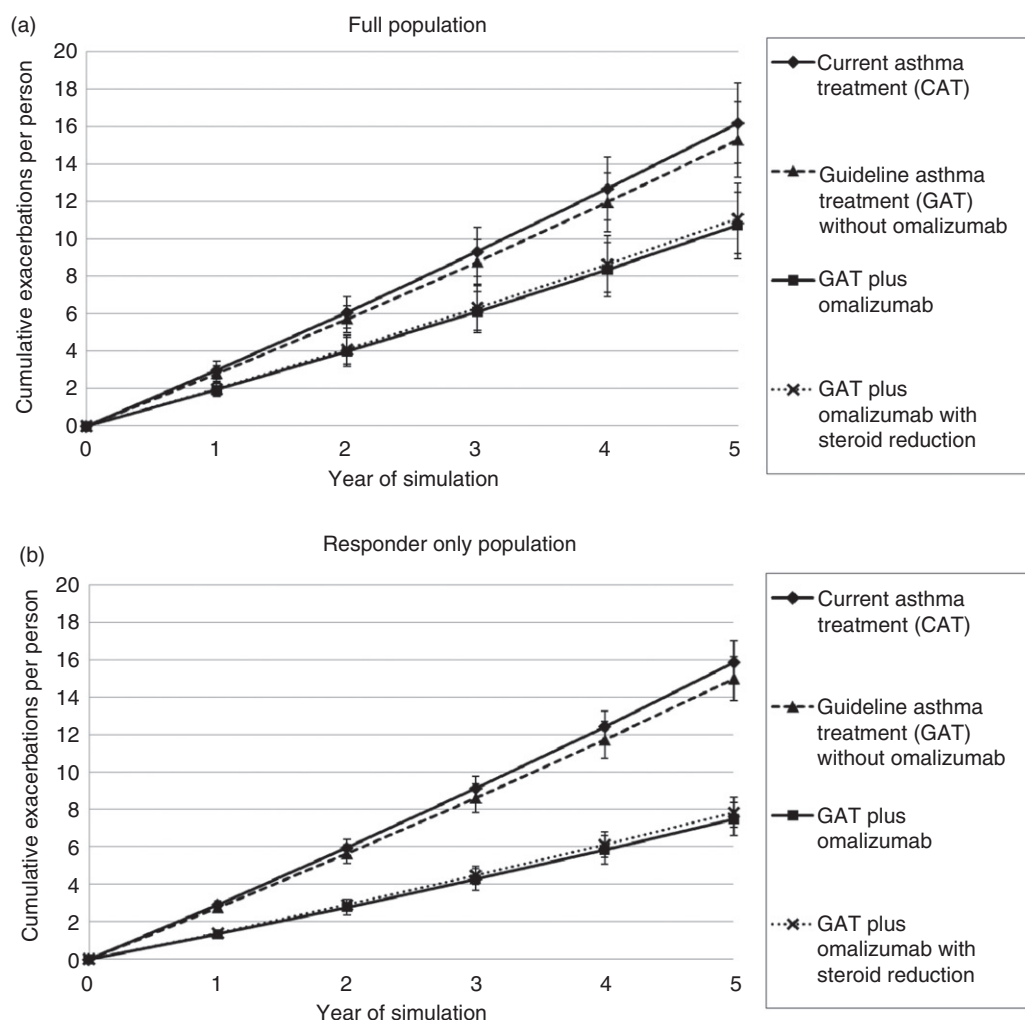


Figure 2. Cumulative exacerbations per person over time for the (a) full population and (b) responder-only population. Error bars represent 95% confidence intervals.

without omalizumab arm, and patients in the GAT plus omalizumab with steroid reduction arm had 4.2 (28%) fewer exacerbations than patients in the GAT without omalizumab arm over the 5-year period.

For the responder-only population (60.5% of the population), the reduction in exacerbations between the GAT without omalizumab arm and the CAT arm was the same as that for the full population. This is because of the assumption that responders were randomly distributed in the population. However, the reductions in exacerbations between the omalizumab arms and the GAT without omalizumab arm are much larger here because only people who have a response are considered. Responders in the GAT plus omalizumab arm had 7.5 (50%) fewer exacerbations than the same set of people in the GAT without omalizumab arm, and responders in the GAT plus omalizumab with steroid reduction arm had 7.1 (48%) fewer exacerbations than the same set of people in the GAT without omalizumab arm over the 5-year period.

For all of the scenarios, there was little difference in the number of exacerbations between the GAT plus omalizumab arm and GAT plus omalizumab with steroid reduction arm. This suggests that with omalizumab, many patients can reduce their steroid dose while maintaining asthma control.

Improvement in different outcomes

Figure 3 shows the percent reduction in cumulative events per person over 5 years for the omalizumab arms versus the GAT without omalizumab arm, across different outcomes. Charts are shown for the full population and responders only.

Omalizumab had the largest effect on the more serious events (ER/UC visits and hospitalizations) and the smallest effect on the more common events (SABA use and symptom days). These results are consistent with observations in clinical trials^{2,5,6}.

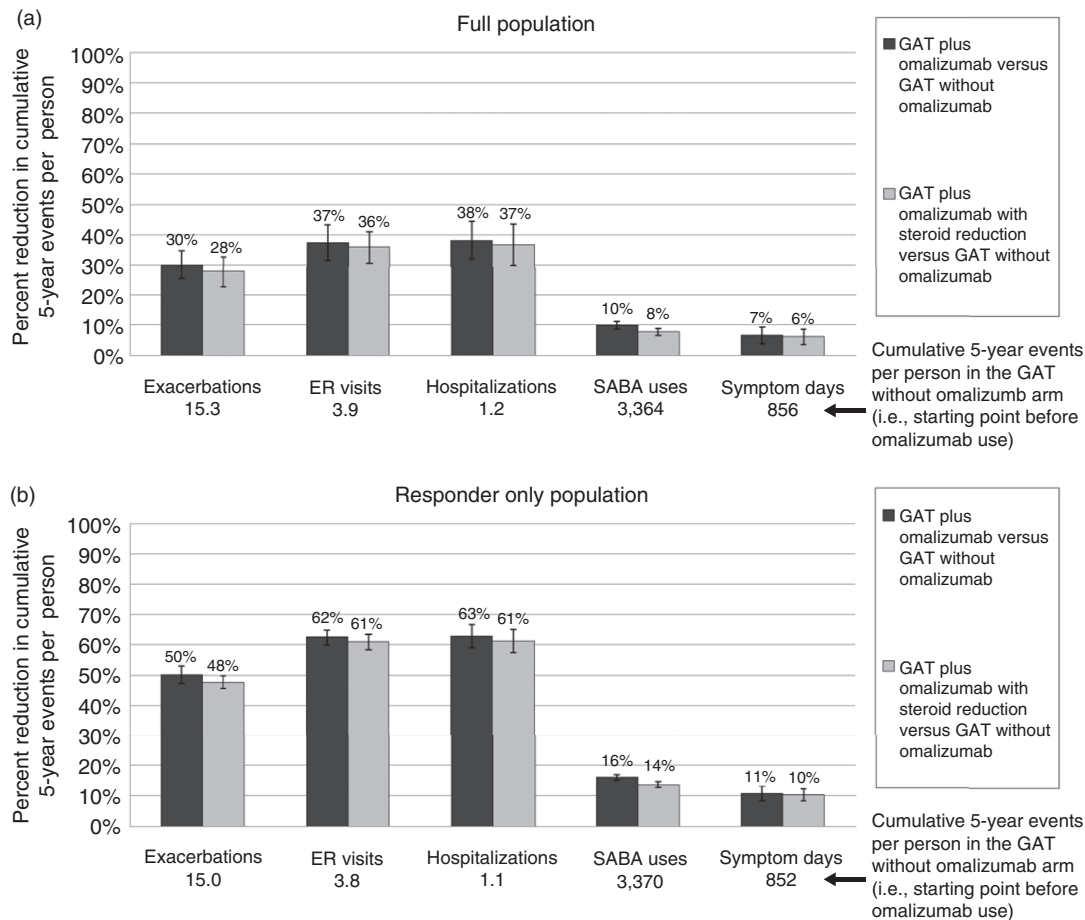


Figure 3. Percent reduction in cumulative events per person over 5 years with Guideline asthma treatment (GAT) plus omalizumab with and without steroid reduction, as compared to GAT without omalizumab. This is shown for the (a) full population and (b) responder-only population. Error bars represent 95% confidence intervals.

Table 4. Comparison of the 5-year cumulative rates of different outcomes for Guideline asthma treatment (GAT) plus omalizumab versus GAT without omalizumab.

Full population	GAT without omalizumab (N= 15 000)	GAT plus omalizumab (N= 15 000)	p-value	Ratio (95% confidence interval)
Mean exacerbations per person (SE)	15.3 (1.0)	10.7 (0.9)	<0.001*	0.70 (0.65–0.75)
Proportion of people with at least one exacerbation (SE)	0.74 (0.02)	0.62 (0.02)	<0.001*	0.84 (0.79–0.88)
Mean ER/UC visits per person (SE)	3.9 (0.2)	2.4 (0.2)	<0.001*	0.63 (0.57–0.68)
Proportion of people with at least one ER/UC visit (SE)	0.43 (0.03)	0.31 (0.03)	<0.001*	0.73 (0.65–0.82)
Mean hospitalizations per person (SE)	1.17 (0.08)	0.72 (0.06)	<0.001*	0.62 (0.56–0.68)
Proportion of people with at least one hospitalization (SE)	0.30 (0.02)	0.21 (0.02)	<0.001*	0.71 (0.59–0.83)
Mean symptom days per person (SE)	856 (24)	800 (23)	<0.001*	0.93 (0.91–0.96)
Mean SABA uses per person (SE)	3364 (99)	3035 (100)	<0.001*	0.90 (0.89–0.92)

*Statistically significant.

Statistical analysis of full set of outcomes

Tables 4 and 5 show the outcome values and standard deviations, test for statistical significance (using a two-tailed Z-test), and ratios for the cumulative 5-year rate of different outcomes in the GAT plus omalizumab arm

compared to the GAT without omalizumab arm, for the full population (Table 4) and responder-only population (Table 5). The difference in event rates between the GAT plus omalizumab arm and the GAT without omalizumab arm is statistically significant for all outcomes.

Table 5. Comparison of the 5-year cumulative rates of different outcomes for Guideline asthma treatment (GAT) plus omalizumab versus GAT without omalizumab.

Responders only	GAT without omalizumab (N= 15 000)	GAT plus omalizumab (N= 15 000)	p-value	Ratio (95% confidence interval)
Mean exacerbations per person (SE)	15.0 (0.6)	7.5 (0.5)	<0.001*	0.50 (0.47–0.53)
Proportion of people with at least one exacerbation (SE)	0.74 (0.01)	0.54 (0.03)	<0.001*	0.73 (0.66–0.80)
Mean ER/UC visits per person (SE)	3.8 (0.2)	1.4 (0.1)	<0.001*	0.38 (0.35–0.40)
Proportion of people with at least one ER/UC visit (SE)	0.43 (0.01)	0.24 (0.01)	<0.001*	0.56 (0.52–0.60)
Mean hospitalizations per person (SE)	1.14 (0.07)	0.42 (0.04)	<0.001*	0.37 (0.33–0.41)
Proportion of people with at least one hospitalization (SE)	0.30 (0.01)	0.16 (0.01)	<0.001*	0.53 (0.47–0.58)
Mean symptom days per person (SE)	852 (17)	761 (16)	<0.001*	0.89 (0.87–0.92)
Mean SABA uses per person (SE)	3370 (66)	2830 (66)	<0.001*	0.84 (0.83–0.85)

*Statistically significant.

Table 6. Cumulative reduction in the 5-year rates of different outcomes due to omalizumab treatment, based on severity of patients' asthma. Severity is defined by the 5-year rate of exacerbations in the GAT without omalizumab arm: patients are considered lower severity if they had fewer than ten exacerbations and higher severity if they had ten or more exacerbations.

Outcome	Cumulative events over 5 years in GAT without omalizumab arm		Absolute reduction in events in GAT with omalizumab arm		Percent reduction in events in GAT with omalizumab arm	
	Lower severity patients	Higher severity patients	Lower severity patients	Higher severity patients	Lower severity patients	Higher severity patients
Exacerbations	2.2	30.5	1.0	8.7	46%	29%
ER/UC visits	0.3	8.1	0.1	3.0	44%	37%
Hospitalizations	0.08	2.4	0.04	0.9	46%	38%
SABA uses	2862	3946	410	236	14%	6%
Symptom days	731	1,002	63	48	9%	5%

Effectiveness of omalizumab based on severity of asthma

The effect of omalizumab was analyzed for patients with different severities of asthma. To do this, patients were stratified by the number of exacerbations they had in the GAT without omalizumab arm over the 5-year period: a person was defined as lower severity if he/she had fewer than ten exacerbations (54% of patients) and higher severity if he/she had ten or more exacerbations (46% of patients). Because the same people were simulated in each arm, these same sets of people could be examined in the GAT with omalizumab arm. The results are shown in Table 6.

For the more serious events, including exacerbations, ER/UC visits, and hospitalizations, it was found that the higher severity patients experienced a larger absolute reduction, but lower relative reduction, in events due to omalizumab treatment. In contrast, for the less serious events, including SABA uses and symptom days, it was found that the higher severity patients experienced lower absolute and relative reductions in events due to omalizumab treatment.

Effectiveness of omalizumab over time

The effect of omalizumab over time was also analyzed. The model of omalizumab did not include a time-dependent component, so changes in the effect of omalizumab over time were dependent solely on increases in the severity of people's asthma as they aged, as represented in the model²⁷. In year 1, the population had an average of 2.8 exacerbations per person in the GAT without omalizumab arm, and this was reduced by 0.9 (31%) with omalizumab treatment. In year 5, the population had an average of 3.3 exacerbations per person in the GAT without omalizumab arm, and this was reduced by 1.0 (30%) with omalizumab treatment. Thus, as the average asthma severity of the population increased over time, omalizumab reduced exacerbations by a larger amount on an absolute basis, but a smaller amount on a relative basis. However, the differences were not statistically significant.

Sensitivity analysis

Several sensitivity analyses were conducted to explore how the forecasts would vary based on the

modeling assumptions. One important source of uncertainty was variability in the results of the omalizumab clinical trials. As shown in Table 2, different trials found ratios of exacerbation rates ranging from 0.42 (Soler *et al.*⁵) to 0.75 (Milgrom *et al.*⁴), for the omalizumab arm compared to the placebo arm. The model of omalizumab was calibrated based on the weighted average results of the clinical trials, using the weights from Walker *et al.*¹³. For a sensitivity analysis, the data from Milgrom *et al.*⁴ were used as a lower bound on the effect of omalizumab, and the data from Soler *et al.*⁵ were used as an upper bound. The model of omalizumab was then calibrated based on these different reference points.

Another source of uncertainty was the percentage of patients who respond to omalizumab. The primary assumption was that 60.5% of patients respond to omalizumab, as observed in the INNOVATE trial^{39,40}. However, this percentage includes people who may have experienced a placebo response, which was approximately 40% of patients based on the placebo arm of the trial.

To evaluate the number of omalizumab responders, excluding those who experience only a placebo effect, the GETE from the Busse *et al.*³ and Soler *et al.*⁵ trials combined was used. A person was considered a responder if either the self-reported GETE or investigator-reported GETE was good or excellent. According to this definition, 69% of patients in the omalizumab arm of these trials were responders, and 46% of patients in the placebo arm were responders. If the patients in both arms had similar characteristics, then it would be expected that 46% of patients in the omalizumab arm would have a placebo response (the same as in the placebo arm). That would leave $69 - 46 = 23\%$ of patients in the omalizumab arm who responded to omalizumab only (no placebo effect).

Next, the assumption was made that there was no correlation between the placebo response and the omalizumab response. Therefore, among the placebo responders, the same percentage would be expected to respond to omalizumab as in the population as a whole. If p_x is the percentage of the population who were omalizumab responders, then $(46\% \times p_x)$ of patients were both placebo and omalizumab responders.

Now, the percentage of omalizumab responders in the population (p_x) is equal to the percentage of people who responded to omalizumab only (23%) plus the percentage of people who responded to both omalizumab and placebo ($46\% \times p_x$):

$$p_x = 0.23 + 0.46p_x,$$

which gives $p_x = 0.43$. Therefore, based on this analysis, approximately 43% of the population were omalizumab responders. For another sensitivity analysis, the model of omalizumab was calibrated assuming a 43% responder rate.

Finally, the effects of omalizumab were examined over different time horizons ranging from 1 to 5 years.

The results of these sensitivity analyses are presented in Table 7 (full population) and Table 8 (responders only). For the full population, the reduction in exacerbations ranged from 15% to 47%, while the reduction in ER/UC visits and hospitalizations ranged from 19% to 54%. For the responder-only population, the reduction in exacerbations ranged from 23% to 78%, while the reduction in ER/UC visits and hospitalizations ranged from 29% to 90%.

Discussion

Interpretation of results

The simulation suggests that omalizumab is very effective in reducing the rate of serious events for a representative sample of omalizumab-eligible patients in the US over 5 years. If only responders are considered, assuming a response rate of 60.5%, the simulation predicts that omalizumab will decrease cumulative exacerbations by 50%, ER/UC visits by 62%, and hospitalizations by 63% over 5 years for the responder group, as compared with following treatment protocols that do not include omalizumab. Alternatively, if it is assumed that 43% of patients respond to omalizumab (the estimate for the percentage of people who respond to omalizumab, excluding people with a placebo response only), the simulation forecasts that omalizumab will decrease cumulative exacerbations by 77%, ER/UC visits by 89%, and hospitalizations by 90% over 5 years for the responder group, as compared with treatment that does not include omalizumab. When the larger (60.5%) response rate is assumed, the omalizumab response is diluted among people who appeared to respond to omalizumab in the trials, but were actually only responding to placebo. Therefore, a lower average response is found for the 60.5% responder group than for the 43% responder group, where only people estimated to have had a true omalizumab response are included.

The relative reduction in event rates due to omalizumab was found to be higher for the more serious events (exacerbations, ER/UC visits, and hospitalizations) than for the less serious events (SABA uses and symptom days) (Figure 3 and Table 6). Also, the relative reduction was higher for the more severe asthmatics than for the less severe asthmatics (Table 6). An interpretation is that for outcomes in which the behavioral threshold in the model is high relative to the individual's average lung function impairment (i.e., the individual does not reach the threshold often), a small improvement in lung function is enough to keep the individual below that threshold. However, for outcomes in which the behavioral threshold is low relative to the individual's average lung function impairment (i.e., the

Table 7. One-way sensitivity analysis of Guideline asthma treatment (GAT) with omalizumab versus GAT without omalizumab.

Full population	Sensitivity parameters (parameters that were changed for each scenario are marked in bold)		Ratio of cumulative 5-year event rates for GAT plus omalizumab arm versus GAT without omalizumab arm				
	Calibration	Assumed percentage of people who respond to omalizumab	Time horizon (years)	Exacerbations	ER/UC visits	Hospitalizations	SABA uses
Base case	Calibrate to weighted average of trial results	60.5%	5	0.70	0.63	0.62	0.93
Scenario 1	Calibrate to Milgrom <i>et al.</i>⁴ trial results as lower bound effectiveness	60.5%	5	0.85	0.81	0.81	0.98
Scenario 2	Calibrate to Soler <i>et al.</i>⁵ trial results as upper bound effectiveness	60.5%	5	0.53	0.46	0.46	0.83
Scenario 3	Calibrate to weighted average of trial results	43.0%	5	0.67	0.63	0.63	0.88
Scenario 4	Calibrate to weighted average of trial results	60.5%	1	0.69	0.60	0.61	0.93
Scenario 5	Calibrate to weighted average of trial results	60.5%	3	0.70	0.62	0.61	0.93

Table 8. One-way sensitivity analysis of Guideline asthma treatment (GAT) with omalizumab versus GAT without omalizumab.

Responders only	Sensitivity parameters (parameters that were changed for each scenario are marked in bold)		Ratio of cumulative 5-year event rates for GAT plus omalizumab arm versus GAT without omalizumab arm				
	Calibration	Assumed percentage of people who respond to omalizumab	Time horizon (years)	Exacerbations	ER/UC visits	Hospitalizations	SABA uses
Base case	Calibrate to weighted average of trial results	60.5%	5	0.50	0.38	0.37	0.89
Scenario 1	Calibrate to Milgrom <i>et al.</i>⁴ trial results as lower bound effectiveness	60.5%	5	0.77	0.71	0.71	0.97
Scenario 2	Calibrate to Soler <i>et al.</i> trial results as upper bound effectiveness	60.5%	5	0.22	0.10	0.10	0.71
Scenario 3	Calibrate to weighted average of trial results	43.0%	5	0.23	0.11	0.10	0.74
Scenario 4	Calibrate to weighted average of trial results	60.5%	1	0.49	0.35	0.35	0.88
Scenario 5	Calibrate to weighted average of trial results	60.5%	3	0.49	0.37	0.37	0.89

individual surpasses the threshold frequently), a small improvement in lung function is not enough to lower the individual below the threshold, and so has little impact. Therefore, when patients are treated with omalizumab, a larger relative reduction in events both for more serious events (which have higher behavioral thresholds) and for less severe asthmatics (who have lower average lung function impairment) would be expected, which is consistent with what is observed in the simulation results.

While the more severe asthmatics experienced a smaller relative reduction across all outcomes as compared with less severe asthmatics, they did exhibit a larger absolute reduction for the more serious outcomes. The absolute reduction in events is equal to the event rate in the GAT without omalizumab arm multiplied by the relative reduction in events with omalizumab treatment. For the more serious events, the event rate in the GAT without omalizumab arm was between 14 and 30 times higher for the more severe asthmatics, as compared with the less severe asthmatics (Table 6). Therefore, even though the more severe asthmatics experienced a smaller relative reduction in events with omalizumab, their baseline event rate was so much higher than that for less severe asthmatics that they experienced a larger absolute reduction in events.

In addition to the reduction in event rates, the simulation forecasted that omalizumab would allow approximately 45% of patients who are taking more than the minimum ICS dose to reduce their ICS and/or OCS dose, while maintaining better control than they were achieving without omalizumab (not shown in the figures).

One limitation to this study is that adverse events were not included, due to a lack of definitive evidence for some types of adverse events. Therefore, it was not possible to perform a balanced analysis of adverse events over all of the medications in the study. For omalizumab, the most serious adverse events are anaphylaxis (frequency of 0.1–0.2%) and malignancy (frequency of 0.3% relative to placebo)¹. For ICS, systemic adverse events include adrenal suppression, growth suppression, bone density loss and osteoporosis, cataracts and glaucoma, and skin thinning and bruising^{44,45}. For OCS, systemic adverse events include the same events as for ICS, with the addition of cardiovascular problems (MI, heart failure, and stroke), diabetes, hypertension, psychological disturbances, and non-Hodgkin's lymphoma, among others⁴⁶. Because omalizumab reduces the use of both ICS (through steroid reduction) and OCS (through steroid reduction, as well as through a reduced number of exacerbations requiring treatment with OCS), treatment with omalizumab can lessen the side-effects that would otherwise be incurred with ICS and OCS use.

Another limitation is that the NAS data set, used for constructing the simulated population, included US patients only. However, the data sets used for imputing

the lung-function characteristics, medication dosage, and medication response for the population included both international⁵ and US³ patients. Furthermore, the model for omalizumab was developed from the results of a set of clinical trials that included both international and US patients^{3–6,13}.

It was not possible to isolate allergic asthmatics in the NAS data set, so all patients with moderate-to-severe persistent asthma were utilized. However, given that most patients with severe asthma have allergy³⁶, and that lung function, medication dosage, and medication response were imputed from a population of allergic asthmatics^{3,5}, the simulated population should be a reasonable reflection of an allergic asthmatic population.

Also, while moderate-to-severe persistent asthmatics were selected from NAS based on types and frequency of medications used, NAS did not include information on medication dose. Therefore, it was not possible to ensure that all patients were on NHLBI guidelines steps 5 or 6, the steps for which NHLBI recommends that omalizumab treatment be considered². If some of the patients in the simulation were actually on steps 3 or 4, that would mean that the population that was modeled may have had less severe asthma, on average, than the population eligible for omalizumab based on NHLBI guidelines. As discussed previously, it was found that omalizumab had a larger absolute effect, but smaller relative effect on more severe asthmatics. Therefore, if the simulated population has less severe asthma than the actual eligible population, the simulation may have underestimated the absolute improvement, while overestimating the percentage improvement, of omalizumab on health outcomes.

The effect of omalizumab was calibrated by simulating patients from the Busse *et al.*³ and Soler *et al.*⁵ trials, for which baseline treatment was ICS without LABA. When the actual simulation was run, patients were simulated on both ICS and LABA, as well as possibly OCS, and the model was used to forecast the effect of omalizumab on these patients. To the extent that the model does not accurately capture the effects and interactions of the different medications, there will be uncertainty in the forecasts.

No data were available on the long-term (more than 1 year) efficacy of omalizumab, so the assumption was made that omalizumab has constant efficacy over time. The actual effect on individuals in the model did change slightly over time due to age-related changes in lung function²⁷. However, these observed changes in omalizumab's effect were not statistically significant.

The assumption was also made that responders to omalizumab are randomly distributed throughout the eligible population. However, there is some evidence that response to omalizumab may be correlated with severity of asthma³⁸. If this were the case, then the total reduction in event rates for the simulated population of

omalizumab-eligible patients in the US would be larger than that reported here. This is because the simulated population had, on average, more severe asthma than the clinical trial populations, so there would have been more responders in the simulated population, resulting in a larger total response.

In addition, while 15 000 people were simulated, there were only 821 unique individuals, each consisting of a moderate-to-severe asthmatic from NAS with additional information imputed from the omalizumab clinical trials. When the same person was run multiple times, different results were obtained due to the stochastic nature of the simulation. Therefore, the effective sample size of the simulation was between 821 and 15 000. This effective sample size was calculated to be approximately 2000, based on a random effects model^{42,43}. This effective sample size is reflected in the errors reported in the tables and figures.

Finally, this study did not include an analysis of costs. Follow-on work should be done to assess the cost-effectiveness of omalizumab.

Comparison of simulation results to clinical trial results

In the simulation, omalizumab caused a larger absolute reduction, but smaller percent reduction, in exacerbations than that found in the clinical trials on which the omalizumab model was based³⁻⁶. The weighted average ratio of exacerbations in the omalizumab arm compared to the placebo arm of the clinical trials was 0.59 (Table 2), indicating that exacerbations were reduced by 41%, or an absolute reduction of 0.62 exacerbations per person per year. In the simulation, the reduction in exacerbations was 30%, or 0.92 exacerbations per person per year, for the GAT plus omalizumab arm compared to the GAT without omalizumab arm. This difference in results is due to the higher severity asthmatics included in the simulation who would not have been present in the clinical trials. In the Busse *et al.*³ and Soler *et al.*⁵ trials, a patient was only included if his/her asthma was 'stable,' as defined by no significant change in regular asthma medication and no acute asthma exacerbation for at least 4 weeks prior to the run-in period. However, in the simulation, all omalizumab-eligible asthmatics were included, including those with recent exacerbations. For the higher severity asthmatics, the simulation forecasted that omalizumab would be more effective on an absolute basis, although less effective on a relative basis.

The results of the EXTRA trial⁴⁷ were released after the completion of the simulation. This trial enrolled a similar population to that in the simulation, namely patients at NHLBI guidelines steps 5 and 6 of asthma care². This trial, run for 48 weeks, found a 25% reduction in exacerbations for the omalizumab arm relative to the placebo arm.

This is within the confidence interval of the reduction found in the simulation for the GAT plus omalizumab arm compared to the GAT without omalizumab arm ($30 \pm 5\%$), indicating that the simulation produced reasonable results.

Extrapolation to the full US omalizumab-eligible population

The results of the simulation can be used to estimate the benefit across the US if all asthmatics eligible for omalizumab were to use it. According to NAS²⁴, there are $810\,000 \pm 160\,000$ asthmatics aged 12 years and older in the US who would qualify for omalizumab based on the severity of their asthma. Based on a study of asthmatics in the National Health and Nutrition Examination Survey (NHANES), approximately 62.1% of asthmatics have atopy, as defined by the presence of 15 specific IgEs⁴⁸. Alternatively, according to data from the TENOR study, which includes patients with severe or difficult-to-treat asthma, approximately 93.5% of severe asthmatics have atopy, as determined by a skin test³⁶.

Using the estimate from NHANES and assuming that the rate of atopy is relatively consistent across all severities of asthma, it is found that there are approximately 810 000 (asthmatics aged 12 years and up with moderate-to-severe persistent asthma) $\times$ 62.1% (percentage of asthmatics with atopy) $\approx$ 500 000 omalizumab-eligible patients aged 12 years and up in the US.

Alternatively, using the estimate from TENOR, it is found that there are approximately 810 000 (asthmatics aged 12 years and up with moderate-to-severe persistent asthma) $\times$ 93.5% (percentage of asthmatics with atopy) $\approx$ 760 000 omalizumab-eligible patients aged 12 years and up in the US.

Using these estimates, a calculation was done of the expected number of serious events which could be averted if all US patients eligible for omalizumab were to take it. Table 9 shows that more than half a million exacerbations, more than 150 000 ER/UC visits, and upwards of 50 000 hospitalizations could potentially be averted each year.

Conclusion

The simulation results suggest that omalizumab is effective in reducing the rate of serious events for omalizumab-eligible patients in the US. According to the simulation, those who respond to omalizumab would experience a reduction of 50% in exacerbations, 62% in ER/UC visits, and 63% in hospitalizations by taking the medication. These are cumulative results over 5 years, although the results are similar for shorter time horizons (Table 8).

Table 9. Annual number of serious events which could be averted in the US if all patients eligible for omalizumab were to take it.

Outcome	Mean number of events per patient per year, among omalizumab-eligible patients age 12 and up, according to NAS data ²⁴	Expected percent reduction in events, based on results of simulation	Assume population size of 500,000 omalizumab-eligible patients		Assume population size of 760,000 omalizumab-eligible patients	
			Total number of events per year	Expected number of averted events per year if all eligible patients took omalizumab	Total number of events per year	Expected number of averted events per year if all eligible patients took omalizumab
Exacerbations	3.7	30%	1 850 000	555 000	2 812 000	844 000
ER/UC visits	0.8	37%	400 000	150 000	608 000	227 000
Hospitalizations	0.24	38%	120 000	46 000	182 400	70 000

In addition to reducing event rates, the simulation suggests that omalizumab would allow almost half of patients who are taking more than the minimum ICS dose to reduce their ICS and/or OCS dose, while maintaining better control than guidelines without omalizumab. Therefore, by using omalizumab, many patients may be able to reduce the side-effects associated with ICS and OCS, while achieving better control than they experienced without omalizumab.

Transparency

Declaration of funding

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Declaration of financial/other relationships

H.L.G., A.S., and P.A. are employees of Archimedes, Inc., who were paid consultants to Novartis in connection with the development of the manuscript. E.L.S. and J.Z. are employees of Novartis Pharmaceuticals Corporation, which co-promotes Xolair* (omalizumab).

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*Xolair is a registered trade name of Genentech, Inc., USA and Novartis Pharmaceuticals Corporation, USA.

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