RESEARCH ARTICLE

Population-Based Pharmacodynamic Modeling of Omalizumab in Pediatric Patients with Moderate to Severe Persistent Inadequately Controlled Allergic Asthma

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Abstract

Omalizumab is the first approved anti-immunoglobulin E (IgE) agent for the treatment of moderate to severe persistent inadequately controlled allergic asthma in adults and adolescents ($\geq$ 12 years old). In 2016, it was approved in pediatric patients (6–11 years old). The objective of this study was to quantitatively characterize the relationship between serum free IgE and pulmonary function (as measured by forced expiratory volume in 1 s [FEV1]) in *pediatrics* using a population-based pharmacodynamic model. Data collected during the steroid-stable period (first 24 weeks) of an omalizumab trial with pediatric asthma patients (Study IA05) were used to build the pediatric IgE–FEV1 model. The previously developed population IgE–FEV1 model in adults/adolescents was adapted to characterize the FEV1 and IgE relationship in pediatrics with different magnitude and onset of response. The pediatric IgE–FEV1 model adequately characterized the IgE–FEV1 relationship in pediatrics, particularly at the extremes of the observed body weights (i.e., $\leq$ 30 kg) and IgE values at screening (i.e., > 700 IU/mL). The estimated sigmoidal free IgE–FEV1 curves were similar in shape and maximum effect, but the estimated free IgE concentration leading to 50% maximum effect (IC50) in pediatric patients (39.4, 95% confidence interval [CI] 24.3–63.9 ng/mL) was higher than estimated in adults (19.8, 95% CI 15.1–24.5 ng/mL). The model further confirmed that the current omalizumab dosing rationale based on the mean target free IgE level of 25 ng/ml was appropriate. The pediatric model can be used to predict population FEV1 response for omalizumab when combined with an omalizumab pharmacokinetic–IgE model.

Keywords allergic asthma · omalizumab · pediatric · pharmacodynamic model

Introduction

Omalizumab, a recombinant, humanized, monoclonal antibody against human immunoglobulin E (IgE), is used to treat moderate to severe persistent allergic asthma in patients 6 years of age or older whose asthma symptoms are not controlled by inhaled corticosteroids. It is derived from a murine monoclonal antibody and targets the high-affinity receptor binding site on human IgE (1). This leads to a decrease of the free IgE available to bind to mast cells and basophils,

and subsequently reduces the clinical signs and symptoms of atopic allergic asthma (2).

The relationship between serum free IgE and pulmonary function, as measured by forced expiratory volume in 1 s (FEV1), was previously characterized using a population pharmacodynamic (PD) model (3). The model was developed using data collected from EXTRA, a post market clinical study to evaluate the efficacy and safety of omalizumab in adult and adolescent patients with severe asthma. Each individual's measured serum IgE concentrations were used to describe the dynamics of their FEV1 (% predicted) response. The inhibitory effect of IgE on FEV1 at a particular time was described by a sigmoidal function. The model adequately described both the omalizumab and placebo responses. Results from the analysis confirmed the mean target free IgE level of 25 ng/ml as the current omalizumab asthma dosing rationale (4). However, the adult/adolescent IgE–FEV1 model cannot be used in FEV1 simulations for

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pediatric patients due to multiple differences between these two populations. For example, baseline FEV1 (% predicted) in pediatrics is generally much higher than in adults/adolescents, and the asthma dosing table in pediatrics has extended baseline IgE level and body weight ranges compared to adults/adolescents in the omalizumab US packet insert. Therefore, to enhance a better understanding of IgE–FEV1 relationship in pediatrics and enable future simulations of FEV1 response in pediatric asthma patients taking omalizumab, a standalone pediatric population IgE–FEV1 model was developed via adaptation of the existing adult/adolescent IgE–FEV1 model.

The overall objective of this analysis was to characterize the relationships between free IgE and pulmonary function (as measured by FEV1) in response to treatment with omalizumab in pediatric patients with moderate to severe asthma. Specific aims included (1) adapting the previously developed mathematical model of the IgE–FEV1 relationship in adult/adolescent asthma patients to characterize a pediatric population with moderate to severe asthma with a potentially different response in magnitude and onset and (2) examining the ability of the pediatric model to characterize the FEV1 response in subjects at extremes of body weight ($\leq$ 30 kg) and IgE levels (> 700 IU/mL) at screening.

Methods

Study Design and Patient Population

Study IA05 was a randomized, double-blind, placebo-controlled, multicenter evaluation of efficacy, safety, pharmacokinetic (PK), and PD of omalizumab in children (6–11 years) with moderate-to-severe, persistent, inadequately controlled allergic asthma. Study design and patient population for Study IA05 have been previously published (5). In summary, a total of 627 patients (421 omalizumab and 206 placebo patients) were randomized in the study. Omalizumab 75 to 375 mg (or placebo) was administered subcutaneously (SC) every 2 or 4 weeks over a period of 52 weeks (24-week steroid-stable phase followed by a 28-week steroid-adjustable phase). The dose and dosing frequency of omalizumab were determined based on body weight and serum IgE level at screening (details in omalizumab US package insert), which was designed to achieve individualized dosing for optimal clinical efficacy (4).

Study IA05 was conducted according to US FDA regulations, the International Conference on Harmonisation E6 Guidelines for Good Clinical Practice, and other national requirements. All sites obtained institutional review board approval to conduct this study and obtained signed informed consent from study participants before enrollment.

Data Used in the Population Pediatric IgE–FEV1 Model

Data collected during the steroid-stable period (first 24 weeks) of Study IA05 were used to develop the pediatric IgE–FEV1 model to control for the confounding effect of steroid use on FEV1. During this period, serum free IgE (i.e., IgE not bound to omalizumab) and total IgE (i.e., free IgE and IgE bound to omalizumab) were sampled at week 0 (randomization), week 1, and week 24, before the administration of omalizumab or placebo. Given omalizumab's mechanism of action, it binds to IgE and lowers free IgE levels. So, before omalizumab treatment, free IgE is the same as total IgE. Free and total IgE assays were measured using enzyme-linked immunosorbent assays described previously (6, 7). FEV1 was sampled at weeks 0, 12, and 24, prior to omalizumab or placebo administration. The measured FEV1 (in milliliters [mL]) was expressed as a percentage of predicted FEV1 (mL) (FEV1 % predicted = FEV1 / predicted FEV1 × 100%) as is conventionally done in FEV1 data analysis (8), where the predicted FEV1 (FEV1pred, mL) was calculated for each patient based on their most recently measured height instead of the baseline height and was calculated using the Polgar formula (9).

Model Development and Covariate Analysis

The previously developed population IgE–FEV1 model with data from adults/adolescents (3) (referred as adult/adolescent model) was used as the starting point for these updated analyses. The adult/adolescent model was then adjusted and refined as necessary to characterize FEV1 and IgE in a pediatric population (e.g., alternative structural models, random-effect structures, and covariate models were tested). The adult/adolescent model described the relationship between free IgE and FEV1 (% predicted) in both omalizumab and placebo groups as:

$$\frac{d\text{FEV1}_i}{dt} = \text{Kdet}_i \times \text{FEV1max}_i \times \left(1 - \frac{\text{Imax}_i \times C^{\gamma}_{IgE,i}(t)}{\text{IC50}^{\gamma}_i \times C^{\gamma}_{IgE,i}(t)} \right) - \text{Kdet}_i \times \text{FEV1}_i\,(t)$$

where for the ith subject, FEV1_i is FEV1 (% predicted). Kdet_i is the rate constant reflecting FEV1 (% predicted) improvement and deterioration. FEV1max_i is the theoretical maximum steady-state FEV1 (% predicted) that can be achieved given a free IgE concentration of 0. Imax_i is the maximum IgE inhibitory effect. IC50_i is the serum free IgE concentration causing 50% of the maximum inhibitory effect. The γ is the Hill coefficient reflecting the steepness of the sigmoidal curve for the IgE-FEV1 relationship. $C_{\text{IgE},i}(t)$ is the free IgE serum concentration in the ith individual, at time t. Population and individual model parameters were estimated using the first-order conditional estimation with interaction (FOCEI) method. The population IgE-FEV1 analyses were conducted via mixed-effect modeling with a qualified installation of the nonlinear mixed-effect modeling (NONMEM) software, Version 7.4 or above (ICON Development Solutions, Hanover, MD) [10]. Same as the adult/adolescent model [3], this model is not an indirect response (IDR) model [11], and this model is used to describe both the omalizumab and placebo responses. In contrast to a typical IDR model, FEV1 is not assumed to be in equilibrium before and after treatment. Moreover, this single model can describe each individual's FEV1 response in both the omalizumab and placebo groups that can show an increase, decrease, or no change in FEV1.

The IgE–FEV1 model used the serum IgE concentrations as model input to describe the dynamics of FEV1. Similar to the adult/adolescent model [3], for patients in the placebo group, the model input was the average total IgE level over the steroid-stable period of the trial, as it was considered more representative of the subject's IgE in the absence of a drug effect [3]. For patients receiving omalizumab, total IgE measurements at baseline and free IgE measurements post-treatment were used. Omalizumab was expected to rapidly and extensively suppress free IgE within 1 day of a SC dosing [6, 12], but the first post-treatment IgE observation occurred weeks after treatment. To appropriately capture the early and rapid IgE suppression effect, IgE was imputed at 0.1 week by back-extrapolating from the first post-treatment free IgE value. Moreover, FEV1 (i.e., the dependent variable in the model) was measured more frequently than IgE, so the free IgE was derived, at each FEV1 observation time point, using interpolations (both linear and log-linear interpolations were tested). A similar approach (linear interpolation) was used when developing the adult/adolescent model [3].

Assessment of model adequacy and decisions about increasing or decreasing model complexity were driven by the data and guided by goodness-of-fit criteria, including visual inspection of diagnostic scatter plots (observed vs. predicted concentration, residual/weighted residual vs. predicted concentration or time, and histograms of individual random effects), successful convergence of the minimization routine with at least 2 significant digits in parameter estimates, plausibility of parameter estimates, precision of parameter estimates, and the Akaike information criterion (AIC), given the minimum objective function value and number of estimated parameters [10].

Exploratory investigation of covariate-parameter relationships were undertaken as part of the population PD modeling. Based on scientific interest, the covariates considered for evaluation included age, body weight, baseline FEV1, and baseline IgE. Given the different response pattern (in both magnitude and onset) observed in pediatrics and the collinearity between covariates (e.g., high correlation between age and body weight in pediatric subjects), only the age effect was examined during the pediatric model development and was modeled using a power model (covariate normalized by reference value). An attempt was made to characterize the impact of age on Imax, IC50, and FEV1max. Exploratory assessments of any remaining trends were conducted by graphical inspection of all covariate effects.

Model Evaluation

The adequacy of the final model and parameter estimates was assessed with a visual predictive check (VPC) method. The basic premise is that a model and parameters derived from an observed dataset should produce simulated data that are similar to the original observed data. Using the final model, 500 Monte Carlo simulations with the original model building dataset from Study IA05 were generated by stochastic simulation to include inter-individual variability (IIV) in the simulated data, which was then summarized to find the median, 10th, and 90th percentiles, along with their 90% CI. Observed FEV1 data at each nominal time and the median, 10th, and 90th percentiles were overlaid with the simulated data for comparison. VPCs were also stratified by IgE value at screening ($\leq$ 700 IU/mL or > 700 IU/mL) or body weight ($\leq$ 30 kg or > 30 kg) to examine the model robustness in describing the data at extreme body weight and IgE values.

Results

Study Data

The analysis dataset included data collected during the first 24 weeks (steroid-stable phase) of Study IA05 with pediatric asthma patients. The dataset was comprised of 535 patients and 1515 observations: 184 patients (555 observations) received placebo treatment and 351 patients (960 observations) received omalizumab. Key baseline variables/covariates used in this study are summarized in Table I. Overall, age ranged from 6 to 11 years with a median of 9 years old, body weight ranged from 19.3 to 81.3 kg with a median of 31 kg, and height ranged from 104 to 168 cm with a

Table I Summary of Covariates in the Pediatric IgE–FEV1 Model

Variables	N	Mean	Median	SD	Range
Age (year)	535	8.6	9.0	1.69	6.0–11.0
Body weight (kg)	535	33.8	31.0	11.3	19.3–81.3
Height (cm)	535	134	134	11.4	104–168
Baseline serum IgE (ng/mL)	535	950	737	810	36.0–4500
Baseline FEV1 (mL)	535	1640	1590	445	430–3850
Baseline FEV1 (% predicted)	535	87	87	18	25–148

N number of records summarized, *SD* standard deviation, *range* minimum to maximum, *FEV1* forced expiratory volume in 1 s, *IgE* immunoglobulin E

median of 134 cm. As expected for pediatric patients, age was positively correlated with both height and body weight with correlation coefficients of 0.80 and 0.55, respectively. The mean (range) baseline FEV1 (% predicted) was 87% (25 to 148%), which is much higher than that in adult/adolescent patients from the EXTRA study (66% [26 to 119%] (3). The mean (range) serum IgE observed at baseline was 950 (36–4500) ng/mL in pediatric patients, which was generally much higher and with a wider range than that observed in EXTRA (425 [36–1680] ng/mL) (3).

Observed individual and mean FEV1 and IgE time profiles for placebo and omalizumab groups in study IA05 are illustrated in Fig. 1. In the placebo group, the mean average serum IgE was 957 ng/mL, and the mean FEV1 (% predicted) showed minimal change from 87% at baseline to 87% at week 12 to 86% at week 24. In the omalizumab group, the mean serum IgE dropped from 961 ng/mL at baseline to 21.5 ng/mL at week 0.1 (extrapolated) and 16.4 ng/mL at week 24, and mean FEV1 (% predicted) increased from

86% at baseline to 88% at week 12 and 88% at week 24. The variability across individual profiles was relatively large in both the placebo and treatment groups.

Model Development and Covariate Analysis

The final IgE–FEV1 model structure was generally consistent with the previously developed population IgE–FEV1 model (3). The pediatric dataset was smaller in size and included more sparse data than the original adult/adolescent dataset (e.g., an average of three FEV1 measurements per patient in Study IA05 versus 12 measurements in Study EXTRA). Therefore, the original adult/adolescent model was simplified as follows: (1) observed baseline FEV1 was used rather than an estimated value for each individual; (2) the IIV of model parameters was reduced to a common parameter, i.e., the same IIV magnitude was estimated on Imax and FEV1max; and (3) the Hill coefficient, γ, was fixed to 9 after a sensitivity analysis investigated values from 1 to 9. The final model parameter estimates are summarized in Table II.

During model development, the individual baseline values were estimated by applying the residual variability to the observed baselines (13), but this resulted in almost identical parameter estimates. Therefore, the observed baseline FEV1 (% predicted) from each individual was used instead. The potential effects of age on Imax, IC50, and FEV1max were also tested. These models either did not converge or appeared to reach local minimums during estimation, indicating that the data did not support identification of covariate effects in the current model. Furthermore, visual inspection of the IIV versus baseline covariates (including baseline FEV1, IgE, age, and body weight) did not reveal any clear trends (Supplementary Figure S1).

Fig. 1 FEV1% predicted **a** and IgE **b** data over time for pediatric IA05 study stratified by treatment
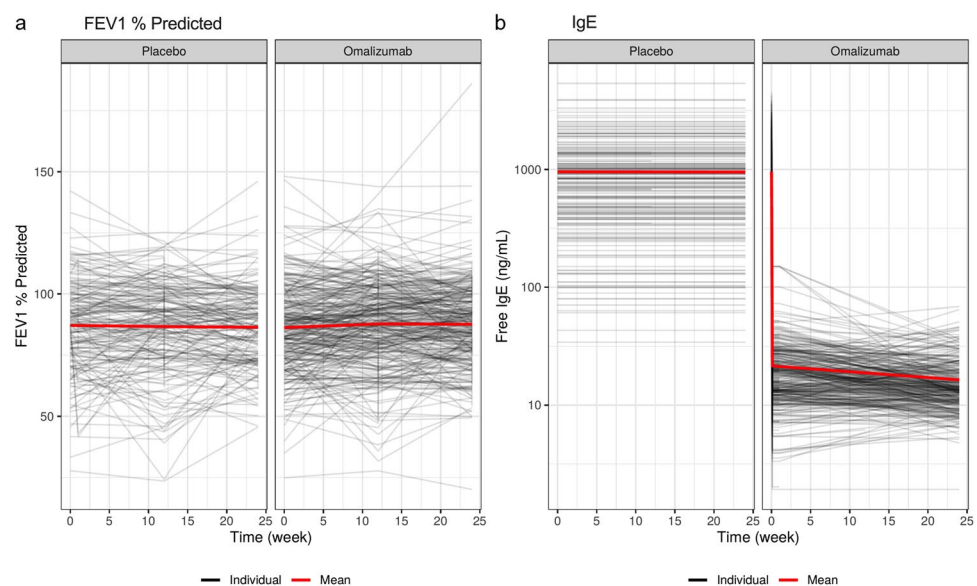
Table II Summary of Estimated Parameters in the Final Pediatric IgE–FEV1 Model

|			Estimate	95% CI	Shrinkage	%RSE (%)
Structural model parameters						
Kdet (1/week)	$\exp(\theta_1)$	Rate constant of % predicted FEV1 improvement an deterioration	0.0198	0.0163, 0.0240	NA	9.95
Imax	$\exp(\theta_2)/(1+\exp(\theta_2))$	Maximum IgE inhibitor effect	0.0717	0.0288, 0.168	NA	-
IC50 (ng/mL)	$\exp(\theta_3)$	Serum free IgE concentration leading t 50% of the maximu inhibitory effect	39.4	24.3, 63.9	NA	25.0
Γ	$\exp(\theta_4)$	Hill coefficient	9	FIXED	NA	-
FEV1$_{max}$	$\exp(\theta_5)$	Theoretical maximum % predicted FEV1 that can be achieved given a free IgE concentration of 0	0.879	0.844, 0.915	NA	2.08
Inter-individual variance parameters						
IIV–Imax	Ω (2, 2)	Variance of Imax/FEV1max	0.095 [SD = 0.309]	0.0648, 0.126	96.5 and 20.3	16.3
IIV–FEV1max	Ω (3, 3)					
Residual variance						
Additive	θ_7	Standard deviation	0.0704	0.0674, 0.0734	NA	2.18

Confidence intervals = estimate $\pm$ 1.96 $\times$ SE. %RSE of an untransformed parameter = (SE / abs (estimate)) $\times$ 100. %RSE of a log-transformed parameter = sqrt(exp(SE^2) − 1) $\times$ 100. The variance for Imax and FEV1max is given as the SD with parameters modeled using logit and log-normal transformations, respectively

%RSE relative standard error (%), *SD* standard deviation, *γ* Hill coefficient reflecting the steepness of the sigmoidal curve representing the IgE–FEV1 relationship, *CI* confidence intervals, *NA* not applicable

The pediatric IgE–FEV1 model provided a reasonable description of the data, as judged by visual inspection of model diagnostic plots (goodness-of-fit plots in Supplementary Figure S2). Fixed and random-effect parameters were estimated with reasonable precision. The condition number of the correlation matrix of the estimates was 11.8. Inter-individual random-effect distributions were modeled using an exponential variance model for FEV1max and a logit transformation for Imax to constrain it between 0 and 1. A full block covariance matrix was tested, but, given the lack of identifiability of Imax, it was ultimately simplified. An IIV of 0.0952 (standard deviation (SD) = 0.309) was estimated for both Imax and FEV1max with associated shrinkage of 96.5% and 20.3%, respectively. Residual error shrinkage was 12.0% for the additive residual error.

The estimated IC50 in pediatric patients (39.4, 95% CI 24.3–63.9 ng/mL) was higher than that estimated in adults/adolescents (19.8, 95% CI 15.1–24.5 ng/mL) (1). The estimated Imax was similar in pediatric and adult/adolescent patients (median = 0.0717 vs. 0.0814). However, the high-shrinkage (96.5%) for IIV of Imax suggested a lack of sufficient information to support the individual estimate of Imax in this pediatric model. Given the sparse data in pediatric patients, the Hill coefficient parameter, γ, was fixed at 9 based on sensitivity analyses examining values between 1 and 9. There was a relatively steep free IgE–FEV1 relationship with respect to the range of free IgE in placebo and omalizumab treatment groups according to the simulations based on the final pediatric model (Fig. 2). The observed

free IgE values clustered around the maximum effect range for omalizumab-treated subjects and minimal effect range for placebo subjects, which made it challenging to precisely characterize the sigmoidal exposure–response relationship of omalizumab on IgE (Fig. 2). Of note, the estimated Hill coefficient was 15.9 (percent relative standard error [%RSE] 38.0%) in the adult/adolescent model (3). Although this
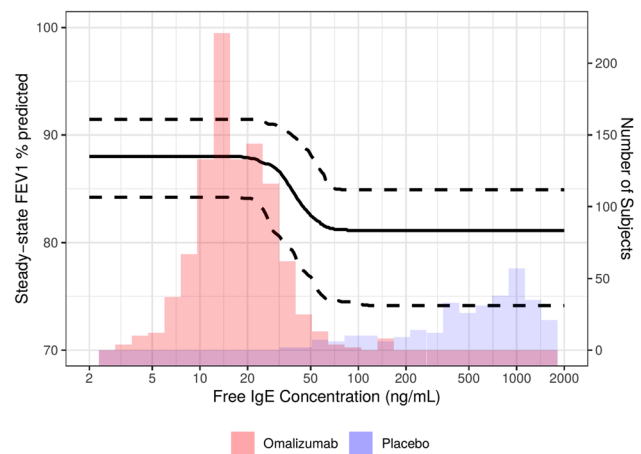
Fig. 2 Model-predicted relationship between serum free IgE level and steady-state FEV1 (% predicted). Solid line is the mean of the model estimated steady-state FEV1 (equivalent to the population predicted steady-state FEV1), and the dashed lines are the 90% CI of model estimated steady-state FEV1. The histograms show the distribution of the mean observed free IgE (post treatment) for patients receiving omalizumab (red) or placebo (blue) treatments

large value was not used in the pediatric model, a sensitivity analysis indicated that values greater than 5 gave similar fits to the pediatric data and a value of 9 was appropriate.

Figure 2 also indicates that subjects with free IgE level reduced to 50 ng/mL or below would have better FEV1 than subjects in the placebo group. At free IgE level of 25 ng/mL, the maximum response would generally be achieved. Similar to the original IgE–FEV1 model in adults/adolescents (3), the pediatric IgE–FEV1 model indicates that subjects with free IgE level reduced to 25 ng/mL would have optimal FEV1 response. Therefore, these results are generally consistent with those from the original IgE–FEV1 model and support the free IgE targets of the Xolair dosing table (4).

Model Evaluation

The VPCs demonstrated that model-predicted FEV1s were in reasonable agreement with the observed values (Fig. 3). The median and 10th/90th percentiles of the observed data were in close agreement with the

distributions summarized from 500 simulated replicates for both treatment groups (i.e., placebo and omalizumab) and also when stratified by screening IgE value (≤ 700 IU/mL or > 700 IU/mL) or body weight (≤ 30 kg or > 30 kg) (Fig. 3a, c, and d). Of note, as shown in Fig. 3b, the model also described the median responses well in spite of the large variability of the FEV1 responses.

Discussion

The previously developed population model describing the IgE–FEV1 relationship in adult/adolescent asthmatics was adapted for pediatric asthmatic patients (3). The final pediatric IgE–FEV1 model adequately described the pediatric data, as demonstrated by model diagnostics and VPCs. Also, it reasonably characterized the IgE–FEV1 relationship at the extremes of the observed body weights (i.e., ≤ 30 kg) and IgE values at screening (i.e., > 700 IU/mL).

There are several differences between pediatric and adult/adolescent asthma patients resulting in a need for the development of a standalone pediatric IgE–FEV1 model to
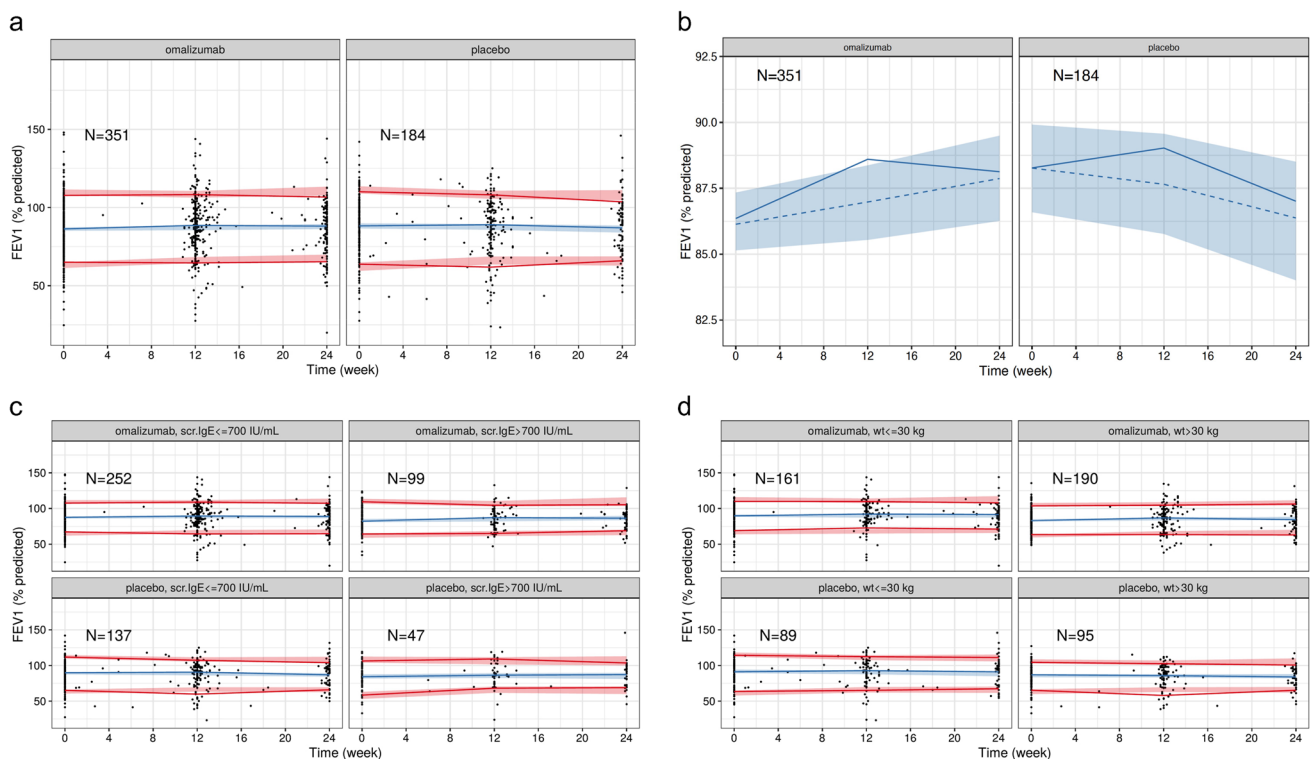
Fig. 3 Visual predictive check (VPC) of **a** FEV1 (% predicted), **b** FEV1 (% predicted) focusing on the median values, **c** FEV1 (% predicted) stratified by IgE at screening (≤ 700 IU/mL and > 700 IU/mL), and **d** FEV1 (% predicted) stratified by body weight screening (≤ 30 kg and > 30 kg), stratified by treatment group of the pediatric IgE–FEV1 model. For panels **a**, **c**, and **d**, dark blue line is the observed median; dark red lines are observed 10th and 90th percen-tiles; blue-shaded area is the 90% CI of the simulated median; red-shaded areas are 90% CI of the simulated 10th and 90th percentiles. Black dots are observed data. Scr.IgE, IgE level at screening; wt, body weight. For panel **b**, Solid blue line is the observed median; dash blue line is the simulated median; blue-shaded area is 90% CI of the simulated median

enable the FEV1 simulations in pediatric patients with omalizumab treatment. As shown in Supplementary Figure S3, the mean baseline FEV1 (% predicted) in pediatric Study IA05 (87%) is much higher than that in the adult/adolescent Study EXTRA (66%). This is because pediatric patients have had asthma for a relatively short period of time compared to adults/adolescents, and therefore, their lung function is generally less impaired. Also, in Study IA05, the predicted FEV1 is time-varying in order to capture children's height change over time, while in the adult/adolescent studies (e.g., EXTRA), predicted FEV1 is considered constant over time. In addition, the pediatric patients had higher IgE at screening (median [range] 406 [27–1370] IU/mL in Study IA05) compared to adult patients in Study EXTRA (median [range] 138 [15–693] IU/mL), leading to the extended IgE range for the omalizumab dosing table for pediatrics (30–1300 IU/mL) compared to the one for adult/adolescents (30–700 IU/mL) in the US package insert. A narrower range of absolute FEV1 (% predicted) response was also observed in the pediatric study compared to the adult/adolescent study, likely due to the higher baseline FEV1 (%predicted) in pediatric patients, which leaves less room for further improvement (Supplementary Figures S3). Given all of these reasons, the IgE–FEV1 model developed based on the adult/adolescent Study EXTRA may not accurately describe the pediatric population, so a stand-alone IgE–FEV1 model was built for pediatric Study IA05 alone, instead of pooling data from IA05 and EXTRA studies, to enable FEV1 simulations for pediatric asthmatics taking omalizumab.

Of note, the pediatric model was developed using more limited data (e.g., sparse sampling and shorter follow-up) compared to the adult/adolescent model. This led to simplifications of the adult/adolescent model when describing the pediatric population. Multiple simplifications were applied to the pediatric model, including using the observed baseline FEV1 for each individual, using a single common IIV parameter for Imax and FEV1max, and fixing the Hill coefficient, γ, to 9. Despite these simplifications, the estimated sigmoidal free IgE–FEV1 curves were similar in shape and maximum effect between the pediatric and adult/adolescent models (Supplementary Figure S4), but the IC50 in pediatric patients (39.4, 95% CI 24.3–63.9 ng/mL, %RSE 25.0%) was higher and had greater uncertainty than that estimated in adults/adolescents (19.8, 95% CI 15.1–24.5 ng/mL, %RSE 12.2%) (Table II). The difference in IC50 estimates between the adult/adolescent and pediatric models was most likely confounded with the differences in disease onset and progression (e.g., the difference in baseline FEV1 rather than the difference in the mechanism of omalizumab treatment). Given the more informative/intensively sampled data used, the adult/adolescent model is considered to be more reliable in IC50 value characterization than the pediatric model.

The key objective of developing this population IgE–FEV1 model with pediatric data is to enable the FEV1 simulations in the pediatric population taking omalizumab. Robustness of the model in serving this purpose was evaluated in multiple ways, including goodness-of-fit plots (Supplementary Figure S2), VPCs with overall FEV1 data and stratified with IgE and body weight at screening to examine the performance of the model in describing data from pediatric patients with extreme values of IgE (i.e., > 700 IU/mL) and body weight (i.e., ≤ 30 kg) (Fig. 3), and VPCs with FEV1 change from baseline to examine the model robustness in describing the FEV1 data in another commonly reported format (Supplementary Figure S5). Results from all of these evaluation approaches indicated that the pediatric model is robust enough to be used to simulate population FEV1 response in pediatric asthma patients with omalizumab treatment.

Conclusions

A population model describing the IgE–FEV1 relationship in response to omalizumab treatment was developed for pediatric patients with moderate to severe asthma, adapting a previously developed model with data in adult/adolescent asthma patients. The pediatric model reasonably characterized the IgE–FEV1 relationship at the extremes of the observed body weights (i.e., ≤ 30 kg) and IgE values at screening (i.e., > 700 IU/mL). The pediatric model could be used to predict population FEV1 response for omalizumab in pediatric asthma patients when combined with the existing omalizumab PK-IgE model (2).

Declarations

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