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Revision of omalizumab dosing table for dosing every 4 instead of 2 weeks for specific ranges of bodyweight and baseline IgE

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ABSTRACT

The dosing level and frequency of omalizumab are guided by a dosing table based on total serum immunoglobulin E (IgE) and bodyweight. Using a validated, mathematical simulation model (based on concentration data from 8 studies), we evaluated the impact of a revised omalizumab dosing table (every 4 weeks dosing regimen) on the pharmacokinetic and pharmacodynamic profiles of free and total IgE. Safety analysis, in patients with high levels of exposure to omalizumab, was done using data from the clinical and post-marketing databases. The model accurately predicted observed omalizumab, free and total IgE concentrations. After reaching steady-state, the average increase in exposure was 10%, even for patients with the highest concentrations at the upper 97.5th percentile. Free IgE suppression slightly increased in the initial phase, and slightly reduced at the trough of the dosing cycle, but average suppression remained similar for both regimens. The safety profile of omalizumab was similar for patients receiving higher or lower doses. Thus, doubling the dose of omalizumab, in a subset of patients receiving 225–300 mg of omalizumab (every 2 weeks dosing regimen) can efficiently suppress free IgE without compromising safety or efficacy.

1. Introduction

Omalizumab is a humanized anti-immunoglobulin E (IgE) monoclonal antibody licensed in the European Union (EU) as an add-on therapy for adults, adolescents and children (age ⩾6 years) with inadequately-controlled severe allergic (IgE-mediated) asthma, and in the United States for adults and adolescents (age ⩾12 years) with moderate-to-severe allergic asthma (EMA Xolair® Summary of product information, 2013; US FDA Xolair® prescribing Information, 2013; Chipps et al., 2012). Omalizumab is administered by subcutaneous (sc) injection every 2 weeks (q2w) or 4 weeks (q4w), with the exact dose being individualized on the basis of baseline serum IgE measurements and bodyweight (Fig. 1). The aim of the omalizumab dosing table is to prescribe regimens to achieve an average serum free IgE of 25 ng/mL (with 95% patients below 50 ng/mL), a level associated with clinical improvement (EMA Xolair® Summary of product information, 2013; US FDA Xolair® prescribing Information, 2013; Hochhaus et al., 2003). In addition, the dosing table also acts as a reference supporting the rational prescribing of omalizumab, avoiding overdosing smaller or underdosing larger bodyweight patients, whilst administering a dose in proportion to the amount of baseline total serum IgE, in the body to be bound and hence neutralized, in the body.

Omalizumab must be administered under medical supervision and is usually given in a hospital or a physician's office. This requirement can be inconvenient for working patients, those in school, or long distance travelers. Observing that 600 mg doses had been recently approved in EU (2013), physicians in Israel asked whether it would be possible to revise the dosing table, increasing the time interval from every 2 weeks to every 4 weeks for some cells, increasing the dose from 225 or 300 mg to 450 or 600 mg, respectively, at each visit (Fig. 1). We investigated whether such a dosing table revision (DTR) would be possible without compromising safety or tolerability or losing efficacy by using a pharmacokinetic and pharmacodynamic (PK–PD) modeling and simulation approach. The logic steps were thus: (i) describe and characterize omalizumab, free and total IgE concentration-time profiles for a population of patients with asthma using a mathematical model; (ii) check that, when simulating from this PK–PD model

Abbreviations: DTR, dosing table revision; ICS, inhaled corticosteroids; K_D^{app}, apparent equilibrium binding constant; PK–PD, pharmacokinetic and pharmacodynamic; q2w, every 2 weeks; q4w, every 4 weeks; sc, subcutaneous.

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(as opposed to fitting data), it had the ability to predict PK and free IgE responses; (iii) develop and visualize a relationship between the omalizumab-induced suppression of free IgE and the signs and symptoms of asthma; (iv) if the model could be shown to be predictive, then using simulations, show the consequences of changing the administration from every 2 weeks to every 4 weeks; and, finally, for safety, (v) check that the increased peak omalizumab concentrations, that patients would experience by administering 600 mg doses, would not lead to an increase in adverse reactions by surveying the extensive safety database, concentrating especially on patients who had experienced high levels of peak exposure to omalizumab.

2. Methods

2.1. Data

PK–PD models generally start from relatively small datasets and then evolve over the years as clinical development progresses; additional data is then included and more is learned about the compound. For the omalizumab–IgE model, it started with single-dose data in atopic but otherwise healthy volunteers (Meno-Tetang and Lowe, 2005) through the addition of two Japanese and three Caucasian studies (Hayashi et al., 2007), then further intermediate incarnations (Lowe et al., 2009; Slavin et al., 2009) to the form used for the expansion of the EU dosing table in January 2010 (EMA Xolair® Summary of product information, 2013). For the DTR, the PK–PD model referenced data from 9 studies (Busse et al., 2001; Holgate et al., 2004; Humbert et al., 2005; Kornmann et al., 2014; Lanier et al., 2009; Milgrom et al., 2001; Riviere et al., 2011; Soler et al., 2001; Zielen et al., 2013).

Four phase III studies in adults contribute most of the data: two 7-month, randomized, double-blind, parallel-group, placebo-controlled, multicenter studies with 5-month blinded extension periods in adolescents and adults with moderate-to-severe allergic asthma requiring daily treatment with inhaled corticosteroids (ICS) (Busse et al., 2001; Soler et al., 2001); a 32-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter pilot trial to assess corticosteroid reduction in adolescents and adults with severe allergic asthma requiring daily treatment with high-dose ICS, with or without oral corticosteroids (Holgate et al., 2004); and INNOVATE, a 28-week treatment, 16-week follow-up, randomized, double-blind, placebo controlled study in patients with inadequately-controlled severe persistent allergic asthma (Humbert et al., 2005).

Data from two pediatric (6–12 years) pivotal phase III studies also contributed to the model: a 7-month double-blind, randomized, placebo-controlled trial that assessed the safety and efficacy of omalizumab in children with allergic asthma requiring daily treatment with ICS (Milgrom et al., 2001), and a 1-year study with moderate-to-severe, persistent, inadequately-controlled allergic asthma (Lanier et al., 2009).

In addition, two clinical pharmacology studies used the expanded dosing regimen (for patients with baseline IgE levels >100 and ⩽1500 IU/mL, requiring omalizumab by sc injection q2w). These were: (i) a randomized, double-blind, placebo-controlled study demonstrating the protective effects of omalizumab against allergen-induced bronchoconstriction in patients (aged 18–65 years) with allergic asthma and baseline IgE up to 2000 IU/mL (Zielen et al., 2013); and (ii) a multicenter, open-label, parallel-group study evaluating omalizumab at high doses in patients (aged 18–55 years) with IgE/bodyweight combinations outside the initially approved dosing regimen (Kornmann et al., 2014) . Finally, a single-dose parallel-group bioequivalence study investigated the use of omalizumab (150 and 300 mg sc) in atopic (total IgE above normal levels [30–300 IU/mL]) but otherwise healthy volunteers (Riviere et al., 2011).

In all studies, omalizumab was administered by sc injection q2w or q4w according to patients' pre-treatment bodyweight and baseline IgE levels using either the earlier US dosing table or

Baseline IgE IU/mL	Body weight									
	20–25	>25–30	>30–40	>40–50	>50–60	>60–70	>70–80	>80–90	>90–125	>125–150
≥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	450	525
>400–500	225	300	225	225	300	300	375	375	525	600
>500–600	300	300	225	300	300	375	375	450	600	
>600–700	300	225	225	300	375	450	525	525		
>700–800	225	225	300	375	450	450	525	600		
>800–900	225	225	300	375	450	525	600			
>900–1000	225	300	375	450	525	600				
>1000–1100	300	300	375	450	600					
>1100–1200	300	300	450	525	600					
>1200–1300	300	375	450	525						
>1300–1500	300	375	525	600						

Do not administer

treatment every 4 weeks
could be switched to q4wk
mg/kg dose too high to switch
Too many injections to switch

Fig. 1. Omalizumab dosing table with cells which were updated.

the later and more individualized EU dosing table (Fig. 1). All studies were approved by Institutional Review Boards and all patients gave informed written consent. The studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

2.2. Model used for simulation

The nonlinear mixed-effects model, which specifies omalizumab binding and capture of IgE to form complexes and thereby suppression of free unbound IgE, has been described previously (Lowe and Renard, 2011). This PK–PD model included parameters for the clearances of omalizumab and IgE, volumes of distribution for omalizumab, IgE and the IgG–IgE complexes, rates for IgE synthesis (daily production) and drug absorption and, finally, an *in vivo* apparent equilibrium binding constant, K_D^{app}, the omalizumab concentration for 50% binding of IgE under idealized conditions when IgE levels are very low (the equivalent of K_M for enzyme reactions). The binding equations in the model use K_D^{app} together with the input and output rates of omalizumab and IgE to calculate target capture (occupancy) for all IgE levels at all time-points.

The only changes to the parameters from the dosing table expansion variation (EMA Xolair® Summary of product information, 2013) were to update the population mean and inter-individual variances for drug absorption and the volume of the omalizumab–IgE complexes, based on improved estimation methods, which could be used with richly sampled PK and IgE data in the first days post-dose in two bioequivalence studies; these values were reported by Lowe and Renard (2011).

2.3. Predictive ability of the model

The model was checked for its predictive ability, focusing on maximum and pre-dose trough omalizumab concentrations and trough concentrations of free IgE. This was achieved by creating simulations and overlaying data from clinical studies for:

a) Omalizumab and free IgE concentrations after single administrations for atopic healthy individuals enrolled in the bioequivalence study (Riviere et al., 2011).
b) Omalizumab and free IgE concentrations in patients with allergic asthma after multiple administrations q2w and q4w.

To be considered valid for subsequent predictions, the model had to be able to accurately simulate the median (50th percentile) and the degree of random variation between patients' data, as represented by the upper 97.5th and lower 2.5th percentile responses.

An alternative weighted residuals method was also used to assess and confirm predictivity (Boeckmann et al., 2011). In this, deviations of observations from predictions were examined over time and from low to high concentrations of omalizumab, free and total IgE. This diagnostic method to assess the "quality of fit" takes account of fixed patient factors (covariates) and has the ability to provide simple plots even when patients receive different doses and have samples taken at different times. To take account of random variation between patients, the deviations were normalized by the variance estimates to a standard deviation scale; 95% of the data should then be within ±2 standard deviations of the prediction.

2.4. Simulations for the revised dosing regimen

Following validation of its predictive ability, the model was used to simulate the proposed every 4 weeks dosing regimens for the areas of the dosing table to be revised. This revision would apply to patients currently on doses of 225 and 300 mg q2w. Simulations for concentration–time profiles of omalizumab and free IgE were performed using the Berkeley Madonna™ software

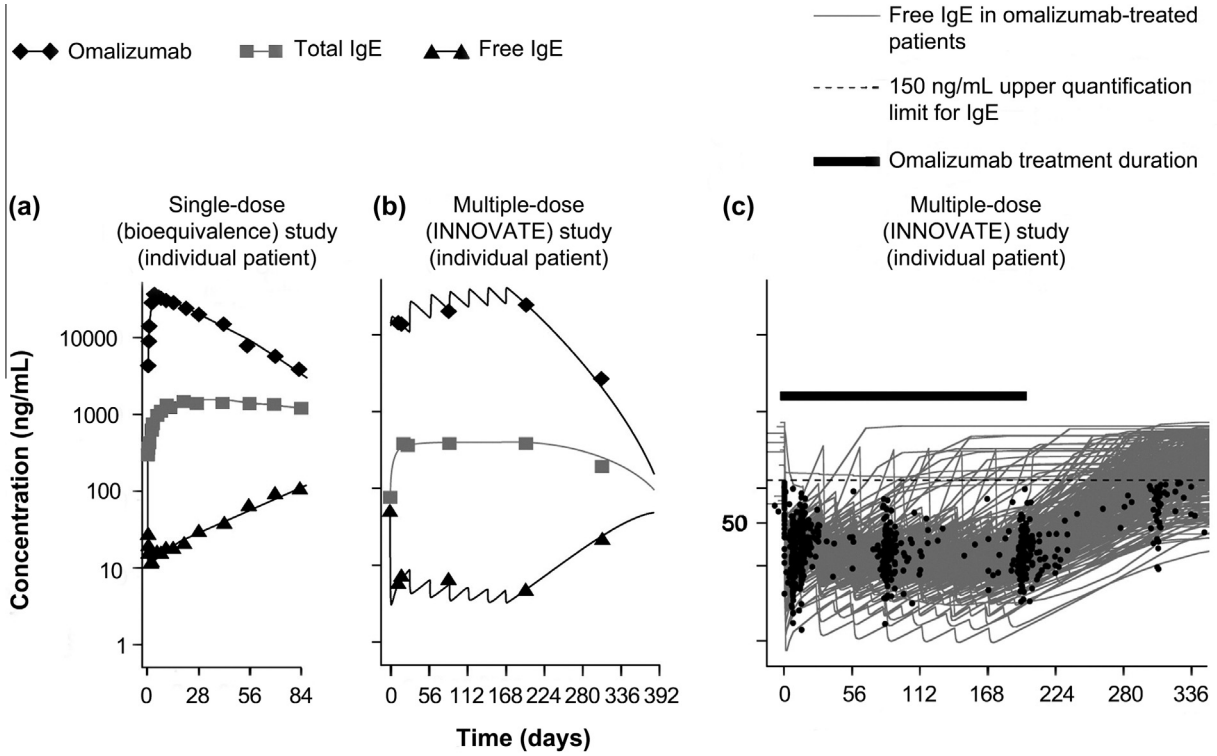

Fig. 2. Illustration of omalizumab total and free IgE data from one phase III study. Example fits of the model for a single 300 mg dose (a) and multiple 150 mg doses given every 4 weeks (b) to samples collected from 2 individual patients showing model fits for each patient's plasma omalizumab, total IgE, and free IgE. Individual patient predictions for free IgE in all omalizumab-treated patients from the INNOVATE study (c) Omalizumab concentrations present a similar (mirrored) image. Reproduced with permission from (Slavin et al., 2009).

(version 8.0.1). For each of the affected cells of the dosing table highlighted in Fig. 1, simulations were performed for 1000 virtual patients with uniform distributions of bodyweight and baseline IgE within the dimensions of each cell. Simulations of omalizumab and free IgE geometric mean, lower (2.5th) and upper (97.5th) percentiles of the 95% range were compared for both the original and the revised dosing regimens.

2.5. Safety

The safety of high doses of omalizumab was assessed based on pooled data from studies in which patients had received at least one daily dose of ⩾600 mg of omalizumab at any time. Five studies were identified (Kornmann et al., 2014; Milgrom et al., 2001; Saini et al., 1999, 2011; Zielen et al., 2013), and their data pooled to confirm the safety profile of high dose omalizumab, especially in terms of adverse events (AEs). Additionally, a cumulative search with a cut-off date of 30 June 2011 was conducted in the global postmarketing safety database to identify patients who had received ⩾900 mg/month of omalizumab.

3. Results

3.1. Predictive ability of the model

The omalizumab–IgE binding model has been shown to have the ability to fit patient data for serum concentrations of the drug and for free and total IgE (Fig. 2). This model applies to single and multiple doses, for frequently or sparsely sampled individuals. Previous reports have shown that the model can predict the time course of data not used for its creation (Hayashi et al., 2007) and can predict both the median distribution of free IgE at steady-state troughs (Lowe et al., 2009). However, to revise the dosing table by doubling the dose and halving the administration frequency, peak concentrations of omalizumab became a point of focus. To provide assurance that the omalizumab–IgE model was accurately predictive for the omalizumab maximum concentration (C_{max}) as well as trough concentrations for the many different doses, regimens, baseline IgE and bodyweight combinations, prediction-corrected visual prediction checks were created (Fig. 3). In these it can be seen that there were no notable deviations between observed data and the model predictions for omalizumab C_{max}, or the trough concentrations 14 or 28 days post-dose. The model was also predictive for maximum and trough free IgE concentrations, and the random distribution of responses, given that the observed and predicted 2.5th and 97.5th percentiles matched well. Random variation in the single dose data was somewhat overestimated; however, these data were atopic but otherwise healthy volunteers, not asthma patients, so could be expected to be more homogeneous. The alternative method of assessing predictivity using weighted residuals showed that the distribution of errors between observations and predictions was centered on zero deviation (Fig. 4). This was true for C_{max} between 2 and 13 days, for the trough samples at around 14 days for every 2 weeks dosing regimen and 28 days for every 4 weeks dosing regimen, and for both omalizumab and free IgE.

3.2. Simulations for revised dosing regimen

Given that the prediction verification suggested the omalizumab–IgE model to be predictive of maximum change and

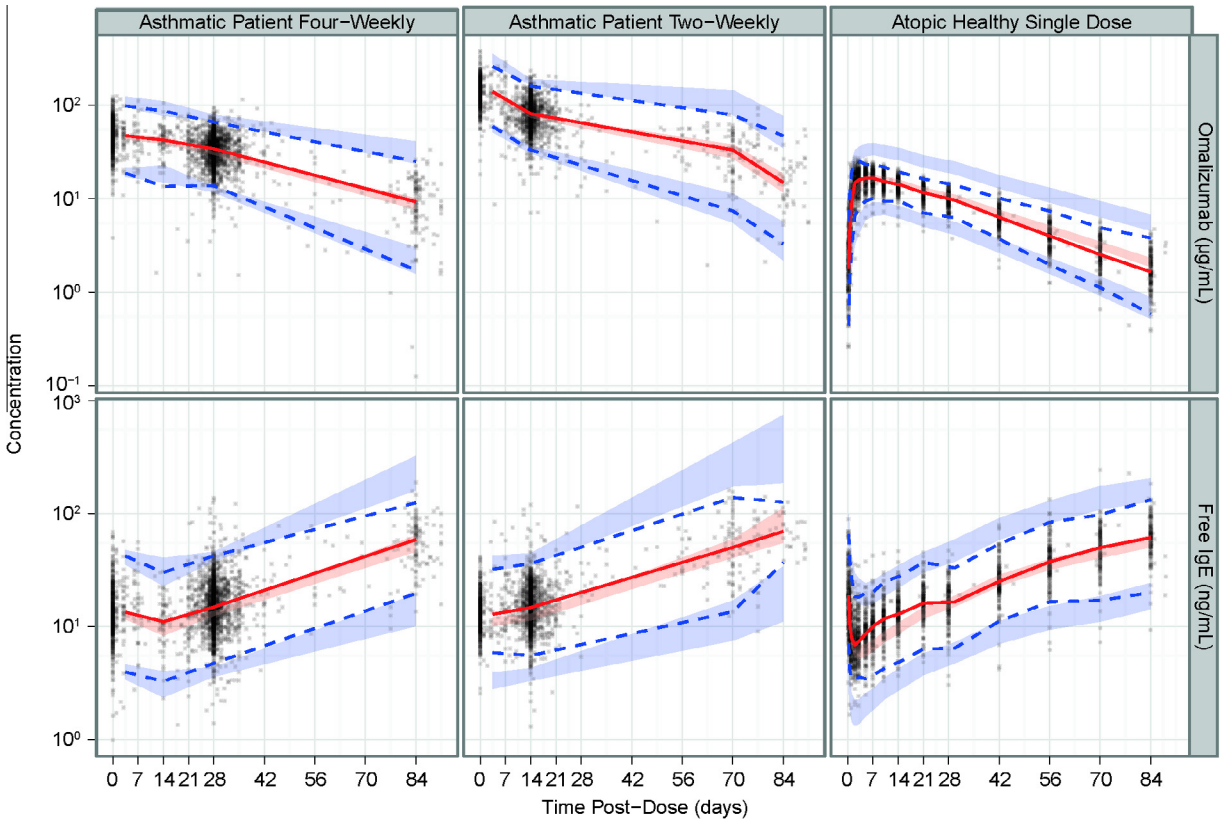

Fig. 3. Prediction-corrected visual prediction checks for omalizumab and free IgE. The data and simulations are plotted as time post-dose, being steady-state for the asthma patients, i.e. >92 days from the start of treatment (Bergstrand et al., 2011). The symbols represent the data; the lines the 2.5th, 50th (median, red line) and 97.5th percentiles of the data; the bands are the 95% prediction intervals for the specified percentiles from model simulations. The simulations and data were 'prediction corrected', i.e. important patient factors, such as bodyweight and baseline IgE and other factors, such as the dose, had been taken into account.

trough concentrations of drug and free IgE across a range of patient bodyweights and baseline IgE values, the implications of changes in dose and regimen, defined by the term posology, could be explored through simulation from the model. Fig. 5 shows the results for omalizumab, Fig. 6 for free IgE. To illustrate the result, a single cell is taken – that with the highest concentrations. In the cell for 40–50 kg bodyweight and 500–600 IU/mL baseline IgE, the original dose was 300 mg q2w, revised to 600 mg q4w. The geometric mean maximum omalizumab concentration at steady-state was about 165 μg/mL for the q2w regimen and ≈195 μg/mL for the corresponding q4w. The upper 97.5th percentile, corresponding to only 2.5% of patients, was at just over 310 μg/mL for q2w, 360 μg/mL for q4w, an increase of only 15%. Across all revised cells, the upper 97.5th percentile C_{max} increased by, on average, 10% (minimum 4%, maximum 20%).

Examination of the free IgE responses demonstrated that the algorithm that forms the basis for the dosing table, ⩾0.016 mg/kg bodyweight per IU/mL of baseline IgE per month, enabled all patients to achieve similar free IgE suppression irrespective of their bodyweight or baseline IgE (Fig. 6). For the revised posology, a slight increase in free IgE suppression was anticipated in the first part of the dosing cycle, with correspondingly lower suppression at trough. However, the average suppression remained the same for both regimens, with trough concentrations predicted to remain below the target of 50 ng/mL, for 95% of the population.

Given that free IgE correlates with changes in the total symptom score, peak expiratory flow and rescue medication use (Lowe et al., 2009), one should be assured that all ranges of baseline IgE and bodyweight should respond to omalizumab. Regarding the question of whether the change in regimen from q2w to q4w is likely to change the clinical response due to the more pulsatile nature of the free IgE time profile, this is considered unlikely. The clinical response to omalizumab develops slowly over the course of several months (Slavin et al., 2009), perhaps even after a year of treatment (Dal Negro et al., 2011). This would correlate well with the long lifetime of IgE secreting plasma cells, which "will take several weeks or several months (some say more than 1 year) to die off" (Lanier et al., 2009). The slow turnover of biosystem components such as mast or plasma cells would act to smooth out fluctuations from the original dosing. To illustrate this, three simulations

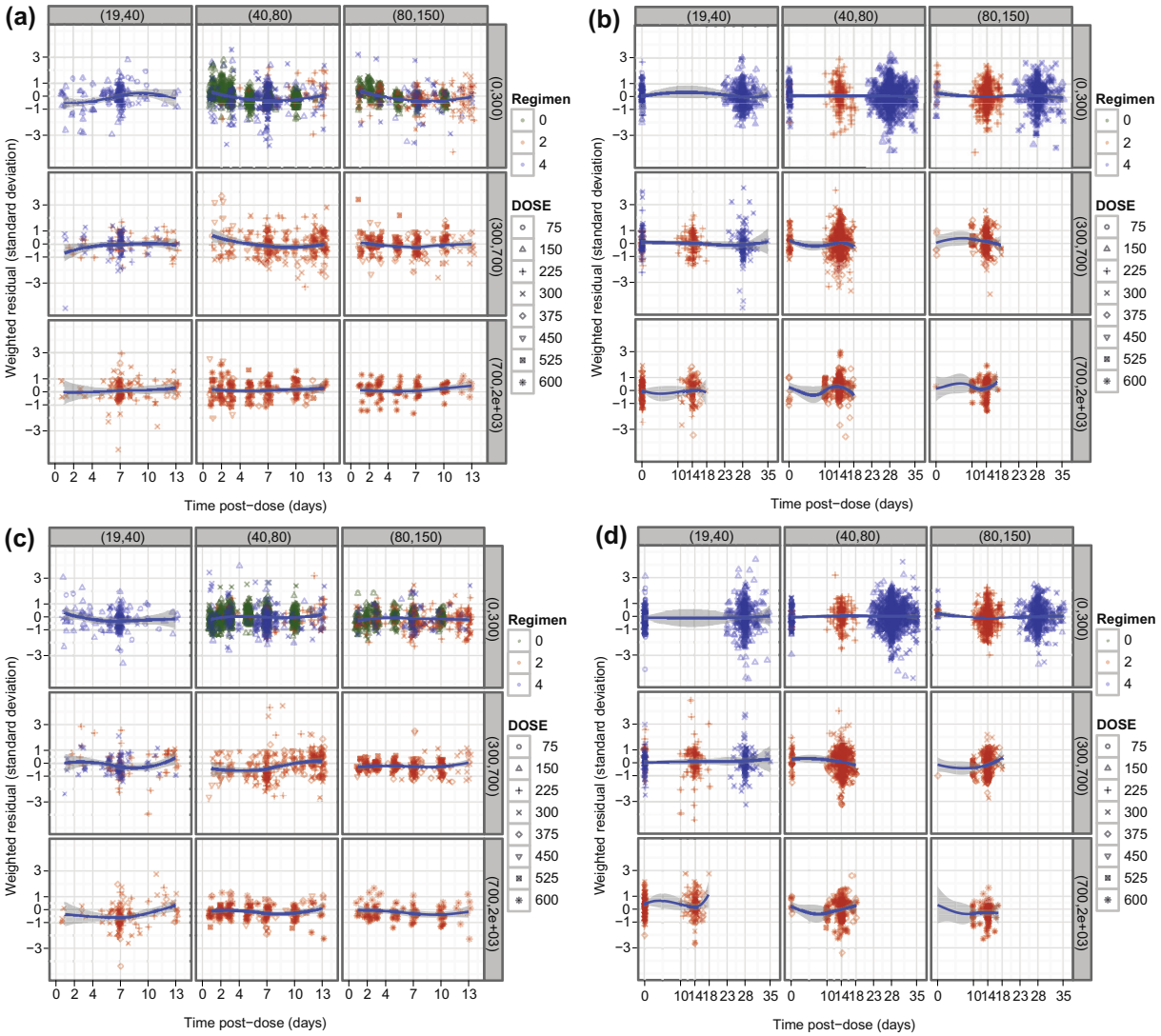

Fig. 4. Predictivity for omalizumab assessed by weighted residuals. The weighted residuals are plotted versus time for bodyweight (horizontal) and baseline IgE categories (vertical). The regimen designations are 0 for single dose (green), 2 for q2w (red) and 4 for q4w (blue). The line is a locally weighted smoothing regression. (a) omalizumab maximum concentration (C_{max}) between 1 and 13 days (b) omalizumab minimum concentration (C_{min}) or trough pre-dose or 22–35 days post-last dose for q4w, 10–18 days q2w (c) free IgE C_{min} between 1 and 13 days (d) free IgE C_{max} or trough pre-dose or 22–35 days post-last dose for q4w, 10–18 days q2w.

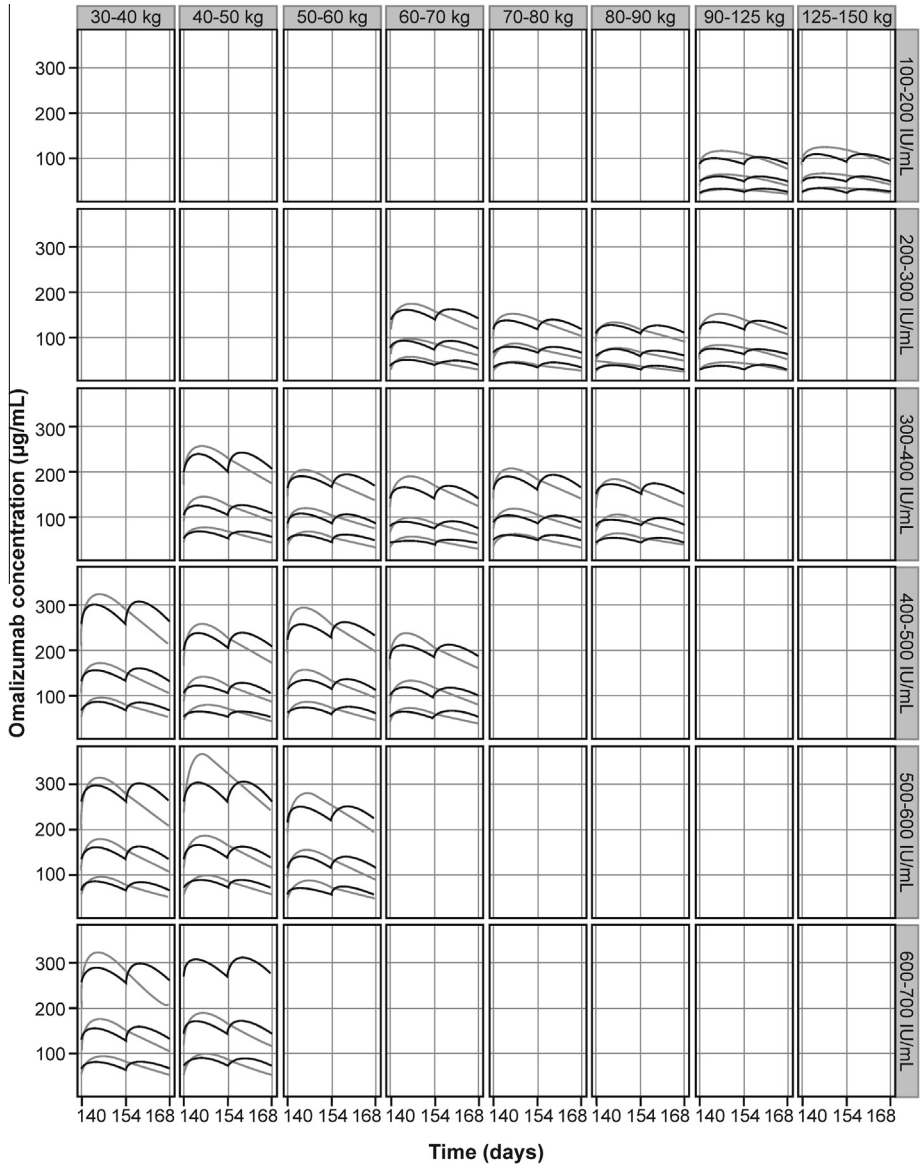

Fig. 5. Steady-state 4-week interval omalizumab simulations for revised cells of the dosing table. The pairs of lines (black lines for the q2w regimen with two dosing cycles and grey lines for the q4w regimen) represent, from the top, upper 97.5th percentiles, geometric means, and 2.5th percentiles.

were created, extending from the omalizumab–IgE model so that omalizumab, free IgE, or cellular high affinity IgE receptors (FcεRI) drives the turnover of factors responsible for the production of symptoms (Fig. 7). Comparing the same monthly dose given either every 2 or 4 weeks, one can see that, although in theory there could be very minor fluctuations in response, in practice, given random day-to-day variation, there would likely be no significant difference in the signs and symptoms of asthma. The longer it takes for a clinical response to build, the less the influence of changes in regimen.

3.3. Safety

Using the pooled data, patients receiving ⩾600 mg of omalizumab were compared with all other patients (Kornmann et al., 2014; Milgrom et al., 2001; Saini et al., 1999, 2011; Zielen et al., 2013). A total of 87 out of 404 patients from the 5 studies analyzed were identified as having received ⩾600 mg of omalizumab. Although incidences of oral herpes and urticaria were slightly higher in patients treated with higher dose of omalizumab compared to the standard dose ([oral herpes: 5/87 versus 6/317; 95% CI: −0.013, 0.090], [urticaria: 8/87 versus 10/317; 95% CI: −0.003, 0.124]), the differences were not significant based on the 95% CI for the difference between proportions. There were no cases of thrombocytopenia, arterial thrombotic events, Churg-Strauss syndrome or parasitic infections in patients receiving ⩾600 mg of omalizumab. One case of malignant melanoma was detected in a patient who received ⩾600 mg of omalizumab, but was not suspected to be related to omalizumab. A single moderate anaphylactoid reaction was also observed in a patient who received an intravenous dose of 1150 mg omalizumab. There was no evidence of unexpected adverse events; all the adverse events seen in this pooled analysis were consistent with the known safety profile of omalizumab.

Clinical data from an empirical subset of 100 patients with the highest concentrations of omalizumab (all above the upper limit predicted to occur with the revised dosing regimen) showed a similar safety profile to that of the rest of the treated population. In the omalizumab postmarketing database, 129 patients were identified who had received multiple doses of omalizumab cumulative to

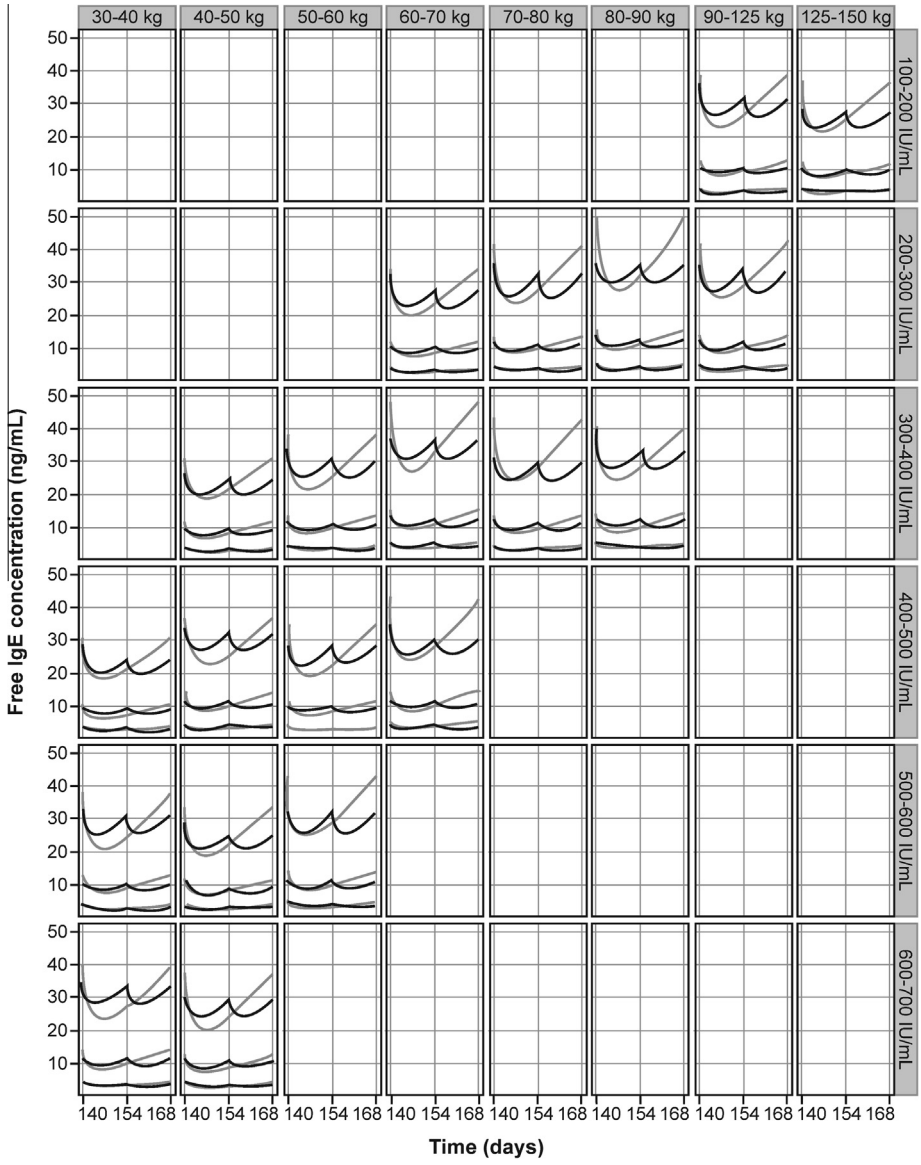

Fig. 6. Steady-state 4-week-interval free IgE simulations for revised cells. The pairs of lines (black lines for the q2w regimen with two dosing cycles and grey lines for the q4w regimen) represent, from the top, upper 97.5th percentiles, geometric means, and 2.5th percentiles.

⩾900 mg/month, with a total of 543 adverse events. Among these, 307 events (in 70 patients) were identified as serious and 236 events (in 89 patients) were classified as non-serious. The distribution of adverse events in these patients was consistent with that seen at lower omalizumab doses. No increase in the incidence of anaphylaxis was seen.

4. Discussion

Asthma is a chronic inflammatory disorder of the airways. When uncontrolled, asthma can be a cause of substantial morbidity and mortality; it is also economically burdensome (Croisant, 2014). In the case of omalizumab prescribed to patients with uncontrolled severe asthma, frequent attendance for injections interferes with their personal and work life and may be associated with indirect expenses such as extra costs for travel or income lost from work to attend an injection clinic. Reducing the frequency of administration of omalizumab to every 4 weeks, where possible, reduces patient burden and costs. This less burdensome treatment regimen for eligible patients may aid persistence with treatment, thereby improving the chance of full clinical benefit from therapy (Cochrane, 1992; Cochrane et al., 1999). Furthermore, reduced time spent with patients will decrease the burden of healthcare practitioners, with a direct impact on the expense for drug administration.

The omalizumab dosing table revision described in this report allowed the frequency of administration of omalizumab to be reduced for patients with certain combinations of bodyweight and baseline IgE level. This report also supports the notion that in some cases, when there is sufficient validation, i.e. evidence that a model is predictive of data, that simulation can be used in place of clinical studies to predict the impact of changes such as in dosage and dosage interval.

Using a model created from clinical data and simulation thereof, we predicted that, for certain patients, doubling the dose of omalizumab and dosing every 4 weeks instead of every 2 weeks would produce acceptable PK–PD biomarker profiles and would be unlikely to have a clinically significant effect on treatment efficacy or to present significant additional safety concerns.

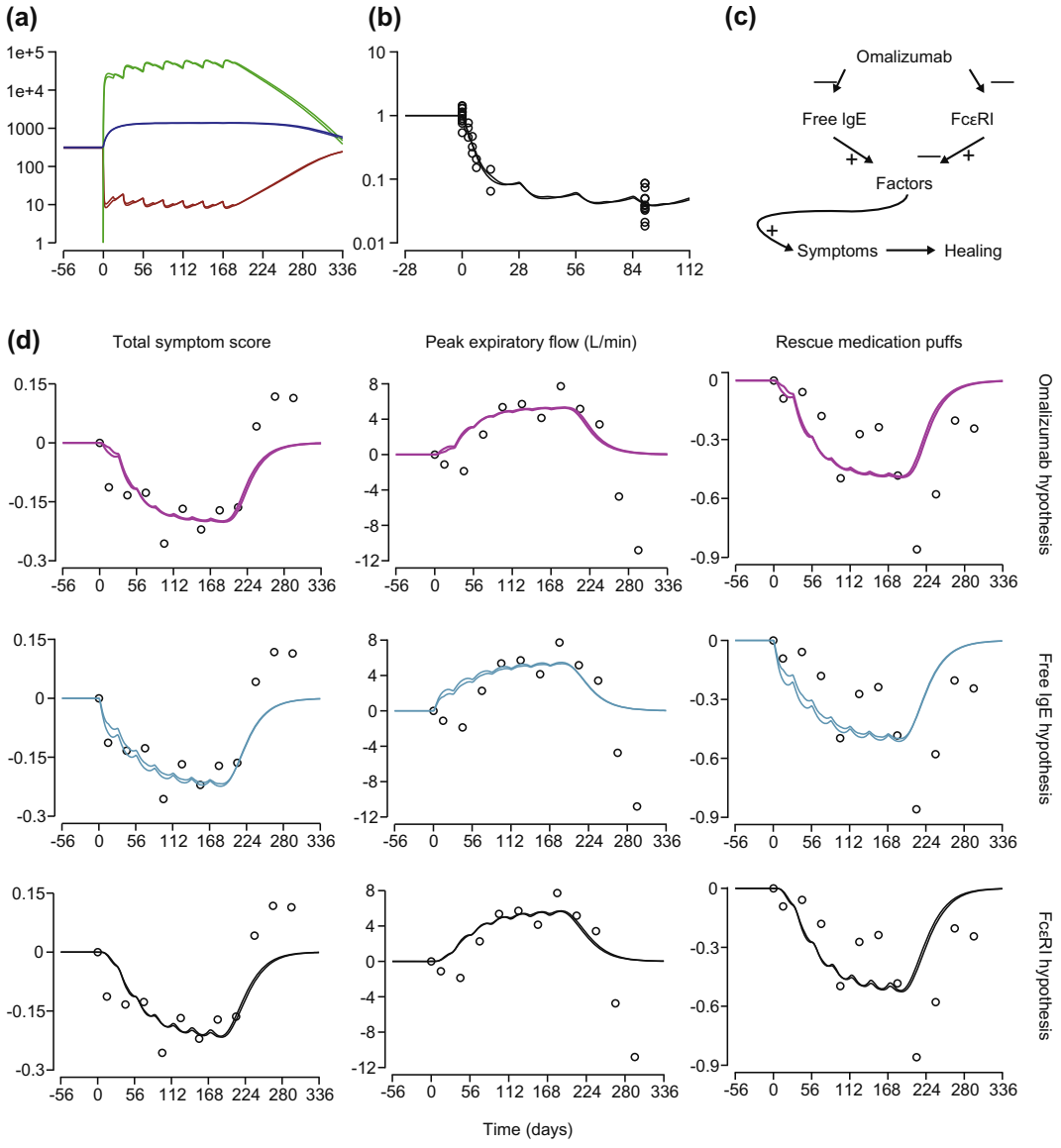

Fig. 7. Omalizumab–IgE model with basophil FcεRI and asthma symptoms. (a) simulation of the geometric mean serum concentrations of omalizumab (upper, green), total IgE (middle, blue) and free IgE (lower, red) from 1000 patients 40–150 kg bodyweight, 30–700 IU/mL baseline IgE using the omalizumab dosing table. (b) Basophil FcεRI data from MacGlashan et al. (1997) was digitized and fitted with a time-delay indirect response function driven by omalizumab concentrations. (d) Symbols are placebo-corrected changes in asthma symptoms from Slavin et al. (2009), shown together with PK–PD curves representing three causal hypotheses. All three were indirect response functions: pink had omalizumab driving symptom change, cyan free IgE, black omalizumab driving basophil FcεRI, which drove symptom change. The simulations were for either the original dosing table or the revision with doses up to 600 mg q4w. To illustrate better any possible differences, the symptom simulations were for the 6 cells covering 40–70 kg bodyweight and 300–500 IU/mL baseline IgE, originally licensed for 225 or 300 mg q2w, now revised to 450 and 600 mg q4w. Within each panel the q4w dosing is that with the slightly larger peak-to-trough variation.

The model developed and described in this article and in previous studies (Lowe et al., 2009; Lowe and Renard, 2011) has been shown to be predictive for observed clinical data including C_{max} and C_{min} (i.e. C_{trough}) for omalizumab, C_{min} and C_{trough} for free IgE, irrespective of the dose, regimen and patient factors such as bodyweight and baseline IgE. The model is useful for aiding the assessment and interpretation of patient safety and efficacy. The results of simulations show that the model has high predictivity for omalizumab concentrations and free IgE levels in healthy subjects and patients with asthma, and that a reduced efficacy when using the revised dosing table versus the existing dosing table would not be expected. In theory, fluctuations in response could follow a switch from every 2 weeks to every 4 weeks dosing regimen; however, calculations suggest that this is unlikely to be observed in practice.

The revised dosing regimen will increase peak serum concentrations of omalizumab, as the dose will be doubled but be given every 4 weeks. Once steady-state is reached, however, the increase in exposure will only be, on average, 10%, even for patients exposed to the highest concentrations at the upper 97.5th percentile. The peak serum concentrations are tolerable; peak and average drug exposure for the revised cells will, in any case, be lower than in those patients already needing to receive 600 mg doses every 2 weeks due to their higher baseline IgE or larger bodyweights. Similarly, the PD effects on free IgE will be such that there will be slightly increased suppression in the first part of the dosing cycle; the average suppression will remain the same.

It might be argued that the PK–PD model presented herein only relates to free IgE; other potential mechanisms of action, such as reduction of FcεRI on relevant cells (including mast cells and

basophilic granulocytes), were not measured. Statements regarding clinical efficacy based on IgE suppression alone may not be sufficiently reliable. As a counterpoint, it is possible to explore the implications of potential mechanisms of action by representing them as PK–PD models and fitting them to symptom data. If the models can adequately describe said data, one can then, by simulation, demonstrate the clinical significance of changes in posology. Three hypotheses were investigated.

In the first, omalizumab is responsible for the improvements in the signs and symptoms of asthma. A delay between exposure to serum omalizumab and its effects on symptoms was allowed by having omalizumab working indirectly by affecting undefined (latent) processes responsible for the production of symptoms. This is the commonly described indirect response model which combines all elements of the causal chain between a drug and downstream responses into a single input–output process with some factors promoting and others removing or healing the symptoms (Derendorf and Meibohm, 1999). This model is the most straightforward and does not invoke any deeper mechanisms other than the fact that omalizumab is carried from the injection site to its site of action by the blood, which is sampled.

In the second hypothesis, an element of the mechanism of action was included by stating that omalizumab works by binding and capturing IgE to form complexes, thereby lowering free (unbound) IgE concentrations. It is the free IgE that is responsible for the production of factors responsible for the asthma symptoms; therefore suppression of this will improve symptoms.

In the third hypothesis, omalizumab works not via free IgE *per se*, but by inhibiting the expression of cellular Fcε receptors. The cellular receptors are then responsible for the production of symptoms; down-regulating these will therefore allow healing. Since no cellular FcεRI data were directly available from in-house studies, the data from MacGlashan 1997 was digitized and a model curve fitted (MacGlashan et al., 1997).

The results from the three models demonstrated that each of the three hypotheses have the ability to explain the observed changes in symptoms equally well, within the range of variation in the observed mean data over time. Both the omalizumab and free IgE hypotheses estimated a 20–22 day mean response time between exposure to omalizumab or suppression of free IgE and symptom changes. For the FcεRI hypothesis, the system response was split into two: the first a 4-day mean response time to down-regulate basophil FcεRI, then 14 days for the symptoms to respond to changes in FcεRI. The end result was the same as the other two hypotheses.

Asthma symptoms take a minimum of 12–16 weeks to stabilize following the introduction of omalizumab, i.e. 4–5 of the above described 'mean response times', just as it takes 4–5 pharmacokinetic half-lives for a drug to reach steady-state. In general, the longer it takes a biological system to respond, the less likely it is that changes in the regimen would influence that response (Slavin et al., 2009). Hence, changing the omalizumab dosing regimen from every 2 weeks to every 4 weeks will not affect its efficacy.

On average, levels of omalizumab–IgE complexes will also be unaffected by the revised dosing schedule. Omalizumab is dosed in excess of IgE; there can be no more complexes formed than there is available IgE in the body. Given that omalizumab suppresses free IgE 100-fold, the main contributor to total IgE are the omalizumab–IgE complexes. During omalizumab therapy, total IgE initially increases, and then reaches a plateau. Higher doses of omalizumab cannot further increase total IgE to any discernable extent, but will further suppress free IgE (Fig. 7a).

The clinical trials and postmarketing database showed that the adverse event profiles of patients with the highest serum concentrations of omalizumab were generally similar to those in patients receiving lower doses, suggesting that safety would not be compromised using the higher doses every 4 weeks. The analyzed dataset did not identify any specific, more frequent or serious adverse events that may be attributable to the use of high doses of omalizumab. There is no evidence that anaphylaxis is a dose- or concentration-dependent AE. Hence, the incidence of anaphylaxis is not expected to increase with the revised dosing regimen as compared with the previously reported incidence of 0.2% (Limb et al., 2007).

5. Conclusions

PK–PD modeling and simulation, together with pooled analyses of safety data, suggests that those patients currently receiving omalizumab at doses of 225 or 300 mg every 2 weeks will be able to switch to omalizumab 450 and 600 mg, respectively, every 4 weeks, without compromising safety or efficacy. Whether the sequence of actions is driven by omalizumab arriving at the effector site from the blood, or is indirect via free IgE suppression, or via inhibition of effector cells, or even combinations of these mechanisms, is immaterial to the point in question that 300 mg q2w and 600 mg q4w will translate to comparable steady-state concentrations of drug, the same steady-state concentrations of free IgE and the same steady-state downstream effector cell desensitization, and hence the same clinical response. The new dosing regimen will simplify posologies for eligible patients, may improve patient and healthcare provider convenience for the treatment and the associated direct and indirect expenses.

Conflict of interest

Philip J. Lowe is an employee of Novartis Pharma AG, Basel, Switzerland. Panayiotis Georgiou and Janice Canvin were employees of Novartis Pharmaceuticals UK Limited, Horsham, West Sussex, UK during the conduct of the study.

Contributions of authors statement

Philip J. Lowe and Janice Canvin contributed to the design of the project, analysis of data as well as reporting and writing the manuscript. Panayiotis Georgiou contributed to the analysis of the data in addition to reporting and writing the manuscript.

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References

Bergstrand, M., Hooker, A.C., Wallin, J.E., Karlsson, M.O., 2011. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. AAPS. J. 13, 143–151.

Boeckmann, A.J., Sheiner, L.B., Beal, S.L., 2011. NONMEM Users Guide – Part V, Introductory Guide. <http://nonmem.iconplc.com/Public/nonmem720/guides/v.pdf> (accessed 26.11.14).

Busse, W., Corren, J., Lanier, B.Q., McAlary, M., Fowler-Taylor, A., Cioppa, G.D., van, A.A., Gupta, N., 2001. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J. Allergy Clin. Immunol. 108, 184–190.

Chipps, B.E., Figliomeni, M., Spector, S., 2012. Omalizumab: an update on efficacy and safety in moderate-to-severe allergic asthma. Allergy Asthma Proc. 33, 377–385.

Cochrane, G.M., 1992. Therapeutic compliance in asthma; its magnitude and implications. Eur. Respir. J. 5, 122–124.

Cochrane, G.M., Horne, R., Chanez, P., 1999. Compliance in asthma. Respir. Med. 93, 763–769.
Croisant, S., 2014. Epidemiology of asthma: prevalence and burden of disease. Adv. Exp. Med. Biol. 795, 17–29.
Dal Negro, R.W., Guerriero, M., Micheletto, C., Tognella, S., Visconti, M., 2011. Changes in total IgE plasma concentration measured at the third month during anti-IgE treatment predict future exacerbation rates in difficult-to-treat atopic asthma: a pilot study. J. Asthma. 48, 437–441.
Derendorf, H., Meibohm, B., 1999. Modeling of pharmacokinetic/pharmacodynamic (PK/PD) relationships: concepts and perspectives. Pharm. Res. 16, 176–185.
EMA Xolair® Summary of product information. <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000606/WC500057298.pdf> (accessed 30.07.13).
Hayashi, N., Tsukamoto, Y., Sallas, W.M., Lowe, P.J., 2007. A mechanism-based binding model for the population pharmacokinetics and pharmacodynamics of omalizumab. Br. J. Clin. Pharmacol. 63, 548–561.
Hochhaus, G., Brookman, L., Fox, H., Johnson, C., Matthews, J., Ren, S., Deniz, Y., 2003. Pharmacodynamics of omalizumab: implications for optimised dosing strategies and clinical efficacy in the treatment of allergic asthma. Curr. Med. Res. Opin. 19, 491–498.
Holgate, S.T., Chuchalin, A.G., Hebert, J., Lotvall, J., Persson, G.B., Chung, K.F., Bousquet, J., Kerstjens, H.A., Fox, H., Thirlwell, J., Cioppa, G.D., 2004. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. Clin. Exp. Allergy 34, 632–638.
Humbert, M., Beasley, R., Ayres, J., Slavin, R., Hebert, J., Bousquet, J., Beeh, K.M., Ramos, S., Canonica, G.W., Hedgecock, S., Fox, H., Blogg, M., Surrey, K., 2005. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy 60, 309–316.
Kornmann, O., Watz, H., Fuhr, R., Krug, N., Erpenbeck, V.J., Kaiser, G., 2014. Omalizumab in patients with allergic (IgE-mediated) asthma and IgE/bodyweight combinations above those in the initially approved dosing table. Pulm. Pharmacol. Ther. 28, 149–153.
Lanier, B., Bridges, T., Kulus, M., Taylor, A.F., Berhane, I., Vidaurre, C.F., 2009. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. J. Allergy Clin. Immunol. 124, 1210–1216.
Limb, S.L., Starke, P.R., Lee, C.E., Chowdhury, B.A., 2007. Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. J. Allergy Clin. Immunol. 120, 1378–1381.
Lowe, P.J., Renard, D., 2011. Omalizumab decreases IgE production in patients with allergic (IgE-mediated) asthma; PKPD analysis of a biomarker, total IgE. Br. J. Clin. Pharmacol. 72, 306–320.
Lowe, P.J., Tannenbaum, S., Gautier, A., Jimenez, P., 2009. Relationship between omalizumab pharmacokinetics, IgE pharmacodynamics and symptoms in patients with severe persistent allergic (IgE-mediated) asthma. Br. J. Clin. Pharmacol. 68, 61–76.
MacGlashan Jr., D.W., Bochner, B.S., Adelman, D.C., Jardieu, P.M., Togias, A., McKenzie-White, J., Sterbinsky, S.A., Hamilton, R.G., Lichtenstein, L.M., 1997. Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. J. Immunol. 158, 1438–1445.
Meno-Tetang, G.M., Lowe, P.J., 2005. On the prediction of the human response: a recycled mechanistic pharmacokinetic/pharmacodynamic approach. Basic Clin. Pharmacol. Toxicol. 96, 182–192.
Milgrom, H., Berger, W., Nayak, A., Gupta, N., Pollard, S., McAlary, M., Taylor, A.F., Rohane, P., 2001. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). Pediatrics 108, E36.
Riviere, G.J., Yeh, C.-M., Reynolds, C.V., Brookman, L., Kaiser, G., 2011. Bioequivalence of a novel omalizumab solution for injection compared with the standard lyophilized powder formulatio. J. Bioequiv. Bioavailability 3, 144–150.
Saini, S.S., MacGlashan Jr., D.W., Sterbinsky, S.A., Togias, A., Adelman, D.C., Lichtenstein, L.M., Bochner, B.S., 1999. Down-regulation of human basophil IgE and FC epsilon RI alpha surface densities and mediator release by anti-IgE-infusions is reversible in vitro and in vivo. J. Immunol. 162, 5624–5630.
Saini, S., Rosen, K.E., Hsieh, H.J., Wong, D.A., Conner, E., Kaplan, A., Spector, S., Maurer, M., 2011. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. J. Allergy Clin. Immunol. 128, 567–573.
Slavin, R.G., Ferioli, C., Tannenbaum, S.J., Martin, C., Blogg, M., Lowe, P.J., 2009. Asthma symptom re-emergence after omalizumab withdrawal correlates well with increasing IgE and decreasing pharmacokinetic concentrations. J. Allergy Clin. Immunol. 123, 107–113.
Soler, M., Matz, J., Townley, R., Buhl, R., O'Brien, J., Fox, H., Thirlwell, J., Gupta, N., Della, C.G., 2001. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. Eur. Respir. J. 18, 254–261.
US Food and Drug Administration. Omalizumab (Xolair®) prescribing information. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103291.htm> (accessed 30.07.13).
Zielen, S., Lieb, A., De La Motte, S., Wagner, F., de, M.J., Fuhr, R., Munzu, C., Koehne-Voss, S., Riviere, G.J., Kaiser, G., Erpenbeck, V.J., 2013. Omalizumab protects against allergen-induced bronchoconstriction in allergic (immunoglobulin E-mediated) asthma. Int. Arch. Allergy Immunol. 160, 102–110.