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Original article

Immunogenicity and safety of omalizumab in pre-filled syringes in patients with allergic (IgE-mediated) asthma

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Abstract

Background:

Omalizumab, a humanised anti-immunoglobulin E monoclonal antibody for treatment of uncontrolled moderate-to-severe or severe persistent allergic asthma, was developed as a lyophilised powder for reconstitution. A liquid formulation in pre-filled syringes has now been developed. The purpose of this study was to assess the immunogenicity and safety of this liquid formulation.

Methods:

In this multinational, open-label, single-arm study, patients (≥ 12 years) with moderate-to-severe allergic asthma were treated for 24 weeks with the liquid formulation of omalizumab (75 or 150 mg in a pre-filled syringe) at 2 or 4 week intervals. Immunogenicity was assessed by measurement of human anti-therapeutic antibody (ATA) levels. Safety was assessed by monitoring adverse events (AEs), haematology, blood chemistry, urine analysis and vital signs.

Results:

A total of 155 patients were enrolled in the study. No patient had a confirmed positive ATA test result. Most frequent individual AEs were asthma (17.4%), sinusitis (17.4%) and upper respiratory tract infection (11.6%). Fourteen patients (9.0%) had serious AEs and there was one death (not treatment related). There were no cases of anaphylaxis according to Sampson criteria. Most patients remained within normal ranges for haematology and biochemistry laboratory variables.

Conclusions:

Omalizumab in pre-filled syringes was not associated with immunogenicity. This novel formulation, which does not require reconstitution, had a safety profile consistent with the lyophilised formulation. A limitation of this study is that efficacy of omalizumab in the treatment of asthma was not specifically addressed herein.

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Introduction

Omalizumab is a humanised anti-immunoglobulin E (IgE) monoclonal antibody approved in the European Union (EU) as an add-on therapy for adults, adolescents and children (≥ 6 years) with inadequately controlled IgE-mediated severe allergic asthma, and in the US for adults and adolescents (≥ 12 years) with moderate-to-severe allergic asthma^{1,2}. Omalizumab was originally developed and marketed as a highly stable, sterile, white, preservative-free, lyophilised powder contained in a single-use vial that is reconstituted with sterile water

for injection². In clinical trials, this lyophilised formulation of omalizumab has been shown to have an acceptable efficacy and safety profile in children, adolescents and adults with inadequately controlled moderate-to-severe allergic (IgE-mediated) asthma and is associated with a low risk of immunogenicity^{3–5}. The safety of the lyophilised formulation of omalizumab has also been characterised in ‘real world’ studies^{6–9}.

A liquid formulation of omalizumab has been developed and is approved in the EU. In this novel formulation, omalizumab is contained in a pre-filled safety syringe and does not require reconstitution prior to use, thus allowing direct subcutaneous administration. Compared with lyophilised omalizumab, the liquid formulation is less viscous, more concentrated, and provides a reduced injection volume. The liquid preparation allows a smaller 1 mL injection for a 150 mg dose (0.5 mL for a 75 mg dose). The dose of omalizumab administered and the dosing tables used to determine the dose are identical to those for the lyophilised formulation.

The immunogenic potential and safety of the drug in the liquid formulation is not expected to differ from that of the lyophilised formulation, since the active component (i.e. omalizumab) is the same. However, whether changes to the liquid formulation occur over time, potentially affecting the immunogenicity, safety and tolerability of the drug, is not known. In this 6 month study, we assessed the potential for immunogenicity and evaluated the safety of the aged liquid formulation of omalizumab in pre-filled syringes.

Methods

Patients

The study enrolled adults and adolescents (≥ 12 years) with moderate-to-severe persistent allergic asthma who had not received omalizumab in the past. Patients had to have a bodyweight of ≥ 30 to ≤ 150 kg, a serum total IgE level of ≥ 30 to ≤ 700 IU/mL and demonstrated evidence of inadequately-controlled, moderate-to-severe persistent allergic asthma, despite therapy with inhaled corticosteroids, according to the classification (Step 3/4) of the Expert Panel Report of the National Heart, Lung, and Blood Institute (NHLBI) National Asthma Education and Prevention Program (<http://www.nhlbi.nih.gov/>). Patients also had to have a positive skin prick test to at least one perennial allergen for at least 1 year. Patients were also required to have been free of clinically significant asthma exacerbations requiring systemic corticosteroids during the 4 weeks prior to the screening visit and during the screening period.

Permitted concomitant therapy during the study included rescue medication and systemic corticosteroids

for asthma maintenance therapy. Immunotherapy was only permitted if received as a stable dose for ≥ 3 months prior to screening and had to be maintained at the same dose throughout the trial. Antihistamines were also allowed, but to avoid interference with allergen testing, washout periods were required prior to skin-prick testing.

Patients were not enrolled if they had previous exposure to other humanised proteins or monoclonal antibodies, were receiving investigational drugs, were using systemic corticosteroids for reasons other than asthma maintenance therapy or were receiving methotrexate, gold salts or cyclosporine. Patients were also excluded if they had a history of hypersensitivity to any of the study drugs (or to drugs with similar chemical structures), had clinically significant laboratory or electrocardiogram (ECG) abnormalities, were pregnant or nursing, had a history of drug or alcohol abuse, had clinically significant uncontrolled disease or a history of such disease, had active lung disease other than allergic asthma, had elevated IgE levels for reasons other than allergy or were diagnosed with, being investigated for, or had a history of cancer. Women of child-bearing potential were required to use a reliable contraceptive method during the study.

Study design and treatments

This was a Phase III, multinational, multicentre, open-label, single-arm study conducted between July 2007 (first patient/first visit) and September 2008 (last patient/last visit) in 37 sites in the United States of America, Germany, and Spain. Eligibility for enrolment was assessed at a screening visit, during which the patient's medical history, standard biochemistry and haematology values, bodyweight and total serum IgE level were obtained; bodyweight and serum IgE were used to determine omalizumab dose and dosing schedule. Patients who met the enrolment criteria entered a 24-week treatment phase during which they received omalizumab as add-on therapy at 2 or 4 week intervals. The treatment phase was followed by a 16-week follow-up period, during which omalizumab was not administered.

Omalizumab was supplied in a pre-filled safety syringe containing either 75 mg (0.5 mL) or 150 mg (1.0 mL) of the drug. It was administered as a subcutaneous injection every 2 or 4 weeks at a dose determined using a dosing table (Table 1) based on the patient's bodyweight and baseline total serum IgE level. The stability of omalizumab in pre-filled syringes was evaluated by using omalizumab that had undergone forced aging (exposure to an accelerated temperature of 25°C) or natural aging (exposure to a temperature of 5°C). The force-aged and naturally-aged omalizumab were assessed as being of the same nominal age at the time of administration to the patient; this was determined by analysing age-related degradation products

Table 1. Omalizumab doses (mg) administered every 2 or 4 weeks.

Pre-treatment serum IgE (IU/mL)	Bodyweight (kg)			
	30–60	>60–70	>70–90	>90–150
≥30–100	150	150	150	300
>100–200	300	300	300	225
>200–300	300	225	225	300
>300–400	225	225	300	
>400–500	300	300	375	
>500–600	300	375	Do not dose	
>600–700	375			

■ Every 4 weeks; ■ Every 2 weeks.

Dosing table used at the time of the study. The dosing table was expanded in 2010 in the EU, increasing the maximum dose of omalizumab from 375 mg to 600 mg every 2 weeks, based on bodyweight (max. 150 kg) and baseline, pre-treatment serum IgE, which was increased from a maximum of 700 IU/mL to 1500 IU/mL¹⁰. The table was further revised in 2012, to allow certain patients receiving 225 mg–300 mg every 2 weeks to move to 4 weekly dosing, whilst doubling the dose².

IgE, immunoglobulin E.

using chromatography techniques prior to the omalizumab being released for use in this clinical study.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was reviewed and approved by an Independent Ethics Committee or Institutional Review Board at each centre. All patients gave written informed consent before enrolling in the study.

Study assessments

The immunogenic potential of omalizumab in the pre-filled syringe was assessed by the measurement of human anti-therapeutic antibody (ATA) levels at baseline and at the end of the follow-up period, using serum samples from enrolled patients. For all analytical procedures, chemicals and reagents of the highest available quality were used, and ultra-purified water was used for the preparation of solutions and buffers. ATA levels in serum samples were assessed using two parameters (anti-Fab and anti-Fc antibody) with the antibody titres being determined by enzyme-linked immunosorbent assay (ELISA) as described in Casale *et al.* (1997)¹¹. Serum samples were tested in duplicates and the ATA titres were derived from a daily performed calibration curve using calibrators with known titres prepared from a positive control cynomolgus monkey serum. A patient was considered potentially ATA positive if either anti-Fab or anti-Fc antibodies had a titre of ≥ 2.0 , which represents the fixed cutoff point determined during assay validation. All values with a titre ≥ 2.0 were re-assayed for confirmation in an immunodepletion ELISA assay where 25 µg/mL of omalizumab was added to the sample. Samples were considered reactive for ATAs if the addition of omalizumab to the sample resulted in a titre decrease of more than 0.145 titre units in the anti-Fab

antibody assay and more than 0.154 titre units in the anti-Fc antibody assay.

Safety assessments consisted of the recording of all adverse events (AEs) and serious AEs along with information on severity and relationship to study drug. Samples were collected for haematology, blood chemistry and urine analysis at screening, 1 month, 6 months, and after the follow-up period, with an additional blood draw at 4 months for haematology analysis. All blood samples were analysed at a central laboratory. Vital signs were monitored at regular intervals, while physical condition was assessed at screening and Week 25. Bodyweight was determined at screening. Special attention was paid to AEs of special interest, especially anaphylaxis or events considered possible components of an anaphylactic reaction (including asthma, cough, dyspnoea, pruritus, urticaria, rash, cardiac arrest, chest discomfort, eye swelling, generalised pruritus and wheezing). Patients with possible anaphylaxis or its components were identified using a broad Standard MedDRA Query (SMQ) search of patient data and an algorithmic approach, such that any potential cases of interest would be captured. The broad SMQ search included both the Anaphylactic Reaction SMQ and additional search terms that were signs and symptoms (or components) possibly indicative of an anaphylactic reaction. These search terms were placed into four categories, A–D. Category A was defined as the core anaphylactic reaction terms; Category B, as upper airway/respiratory terms; Category C, as angioedema/urticaria/pruritus/flush terms and Category D as cardiovascular/hypotension terms. The algorithmic approach determined the possible incidence of anaphylaxis by identifying patients with at least one of the following combinations of signs and symptoms considered indicative of anaphylaxis, based on the four categories of terms (A–D): Category A or Category (B and C) or Category D and (B or C). Since the search criteria used contained a broad range of events possibly indicative of anaphylaxis, the cases identified by the algorithm were finally adjudicated manually against Sampson criteria¹² to identify genuine cases of anaphylaxis.

Hypersensitivity reactions were defined in two ways: 1) all AEs characteristic of potential hypersensitivity except anaphylaxis, skin rash, urticaria and injection-site reaction; and 2) all AEs characteristic of potential hypersensitivity, including anaphylaxis, skin rash, urticaria and injection-site reaction.

Statistics

Background and demographic variables were summarised for the safety population (all patients who received any part of a dose of study drug and had any post-baseline assessment) using median, mean, standard deviation and ranges for continuous variables and frequency tables for

discrete variables. Immunogenicity data were summarised as numbers and percentages of patients with confirmed positive ATA results. AEs and serious AEs were numbers and percentages of patients with each event. The planned sample size of 125 patients was sufficient to identify any on-study event (e.g. a positive ATA or AE) that occurred with an incidence of at least one in 33 patients with 95% probability, assuming approximately a 20% on-treatment dropout.

Results

Patient disposition and baseline characteristics

A total of 266 patients were screened and 155 were enrolled in the study. The 24-week treatment period was completed by 140 (90.3%) patients. Fifteen patients (9.7%) discontinued during the treatment period. The most frequent reasons for premature discontinuation were protocol deviation (3.2%) and AEs (2.6%). In addition to the 140 patients who completed the treatment period, eight of the fifteen patients who had discontinued during the treatment period also entered into the 16-week follow-up period: 136 of these 148 patients (91.9%) completed the follow-up period. The most frequent reason for discontinuing during the follow-up period was loss to follow-up (2.0%). The mean age of the patients was 42.7 years, with the majority (69.7%) aged 18–54 years (Table 2). The majority of patients were female (61.3%) and most were Caucasian (83.9%). The median duration of asthma was 14 years (range 1–70 years).

Immunogenicity

Samples were collected for ATA analysis from 136 patients at baseline and at the end of the follow-up period. At the baseline assessment, three patients had an initial assay result with a titre >2.0 (anti-Fc antibody [$n = 2$], anti-Fab antibody [$n = 1$]), but were all found to be ATA negative in the confirmatory analysis. The same three patients had similar findings at the follow-up assessments with initial titres >2.0, but with negative results in the confirmatory analysis. Therefore, no patient had a confirmed positive ATA test result.

Safety

AEs occurred in 80.0% of patients during the treatment period and 34.5% of patients during the follow-up period. Most AEs recorded during the treatment period were of mild or moderate severity, with severe AEs reported in 23 patients (14.8%) (Table 3). The most frequent organ system class for AEs was infections and infestations (Table 3), while the most frequent individual AEs were

Table 2. Baseline demographic and clinical characteristics.

Omalizumab ($n = 155$)	
Age, years	
Mean (SD)	42.7 (14.3)
Median (range)	44.0 (12–80)
Age group (years), n (%)	
12–17	13 (8.4)
18–54	108 (69.7)
55–64	27 (17.4)
≥ 65	7 (4.5)
Gender, n (%)	
Female	95 (61.3)
Race, n (%)	
Caucasian	130 (83.9)
Black	19 (12.3)
Asian	4 (2.6)
Pacific islander	1 (0.6)
Other	1 (0.6)
Weight, kg	
Mean (SD)	81.2 (20.7)
Median (range)	78.0 (33–142)
BMI, kg/m ²	
Mean (SD)	24.22 (5.79)
Median (range)	22.95 (11.7–44)
Height, cm	
Mean (SD)	167.1 (10.7)
Median (range)	165.0 (141–194)
Smoking history, n (%)	
Never smoked	95 (61.3)
Ex-smoker	44 (28.4)
Current smoker	16 (10.3)
Duration of allergic asthma, years	
Mean (SD)	19.1 (15.5)
Median (range)	14.0 (1–70)

BMI, body mass index; SD, standard deviation.

asthma (17.4%), sinusitis (17.4%) and upper respiratory tract infection (11.6%) (Table 4). The most common severe AEs during the treatment period were asthma (6 patients, 3.9%), sinusitis (2 patients, 1.3%) and pregnancy (2 patients, 1.3%), with all other severe AEs reported in no more than 1 patient each.

Treatment-related AEs (based on the opinion of the investigator) were reported for 22 patients (14.2%) during the treatment period and were mostly related to the study drug injection (Table 5). These treatment-related events included injection-site pruritus in 5 patients (3.2%), injection-site reaction in 4 patients (2.6%), injection-site irritation in 3 patients (1.9%) and injection-site pain in 3 patients (1.9%), with all other treatment-related events occurring in no more than 1 patient each. During the follow-up, 34.5% of patients had at least one AE (Table 6). Three patients (2.0%) had severe events. None of the AEs reported during the follow-up period were determined to be related to study drug. The most frequent system organ class was infections and infestations (19.6%), followed by respiratory, thoracic and mediastinal disorders class (14.2%).

Fourteen patients (9.0%) had serious AEs during the treatment period, the most frequent of which was asthma

Table 3. Frequency of adverse events in patients receiving omalizumab in pre-filled syringes during the treatment period (after the first treatment dose and within 28 days after the last dose) by maximum severity and system organ class.

	Patients with adverse events (n = 155)	
	n	%
Maximum severity grade		
Mild	25	16.1
Moderate	76	49.0
Severe	23	14.8
Primary system organ class affected		
Infections and infestations	77	49.7
Respiratory, thoracic and mediastinal disorders	49	31.6
General disorders and administration site conditions	24	15.5
Musculoskeletal and connective tissue disorders	23	14.8
Gastrointestinal disorders	21	13.5
Nervous system disorders	21	13.5
Skin and subcutaneous tissue disorders	18	11.6
Injury, poisoning and procedural complications	15	9.7
Investigations*	10	6.5
Eye disorders	6	3.9
Cardiac disorders	5	3.2
Renal and urinary disorders	4	2.6
Reproductive system and breast disorders	3	1.9
Vascular disorders	3	1.9
Endocrine disorders	2	1.3
Immune system disorders	2	1.3
Metabolism and nutrition disorders	2	1.3
Pregnancy, puerperium and perinatal conditions	2	1.3
Psychiatric disorders	2	1.3
Blood and lymphatic system disorders	1	0.6

*Includes abnormalities in: clinical laboratory tests (e.g. raised cholesterol, abnormal liver function tests), radiologic tests, physical examination (e.g. cardiac murmur) and physiological tests (e.g. body temperature increase).

(2.6%). One patient (a 60-year-old male) experienced a severe asthma exacerbation 26 days after completing the treatment period, did not respond to the medication and subsequently died on the same day due to cardiac arrest. Neither the asthma exacerbation nor the cardiac arrest was considered treatment related. There were no other deaths during the treatment or follow-up periods. Of the four patients discontinuing because of an AE, two (1.3%) were due to serious AEs (anaemia, dehydration), and two (1.3%) to non-serious AEs (pregnancy, injection-site pain).

Most AEs reported during the follow-up period were of mild or moderate severity, with the most frequent individual events being asthma (10.8%), sinusitis (8.1%) and upper respiratory tract infection (4.1%). Three patients had severe AEs during the follow-up period (conjunctivitis, spontaneous abortion, and asthma). None of these AEs were considered to be related to the study drug. Spontaneous abortion was reported in a patient who discovered she was 8 weeks pregnant approximately 11 weeks after the last study treatment (this was not the same patient that discontinued due to pregnancy).

Table 4. Most frequent adverse events (>1.5% of patients) in patients receiving omalizumab in pre-filled syringes during the treatment period (after the first treatment dose and within 28 days after the last dose).

	Patients with adverse events (n = 155)	
	n	%
Asthma	27	17.4
Sinusitis	27	17.4
Upper respiratory tract infection	18	11.6
Nasopharyngitis	15	9.7
Headache	13	8.4
Cough	9	5.8
Gastroenteritis viral	8	5.2
Acute sinusitis	7	4.5
Oropharyngeal pain	7	4.5
Viral upper respiratory tract infection	7	4.5
Bronchitis	6	3.9
Diarrhoea	6	3.9
Injection-site pruritus	6	3.9
Dysphonia	5	3.2
Nasal congestion	5	3.2
Nausea	5	3.2
Back injury	4	2.6
Contact dermatitis	4	2.6
Influenza	4	2.6
Injection-site reaction	4	2.6
Pain in extremity	4	2.6
Pyrexia	4	2.6
Abdominal pain upper	3	1.9
Arthralgia	3	1.9
Arthritis	3	1.9
Dyspnoea	3	1.9
Haematuria	3	1.9
Injection-site irritation	3	1.9
Injection-site pain	3	1.9
Otitis media	3	1.9
Pharyngitis	3	1.9
Pruritus	3	1.9
Rhinitis	3	1.9
Skin laceration	3	1.9
Urticaria	3	1.9
Viral infection	3	1.9

During the treatment period, 49 patients (31.6%) had hypersensitivity reactions (all AEs characteristic of potential hypersensitivity including anaphylaxis, skin rash, urticaria and injection-site reactions).

With the exception of asthma (27 patients, 17.4%) and cough (9 patients, 5.8%) the incidence of AEs considered possible components of anaphylaxis (identified using the broad SMQ search previously described) was low (<2.0%). Since the search criteria comprised a broad range of events possibly indicative of anaphylaxis, all potential cases of anaphylaxis were manually adjudicated against Sampson criteria¹¹ to identify actual cases of anaphylaxis. Two cases contained the required number of events to partially meet Sampson criteria, however they lacked the clinical context/temporal relationship required to fully meet Sampson criteria so were, ultimately, not judged to be cases of anaphylaxis.

Table 5. Adverse events suspected (by the investigator) to be treatment related in patients receiving omalizumab in pre-filled syringes during the treatment period (after the first treatment dose and within 28 days after the last dose).

	Patients with adverse events (n = 155)	
	n	%
Injection-site pruritus	5	3.2
Injection-site reaction	4	2.6
Injection-site irritation	3	1.9
Injection-site pain	3	1.9
Anaemia	1	0.6
Cardiovascular disorder	1	0.6
Palpitations	1	0.6
Vision blurred	1	0.6
Abdominal pain	1	0.6
Nausea	1	0.6
Oral pruritus	1	0.6
Chest discomfort	1	0.6
Fatigue	1	0.6
Injection-site erythema	1	0.6
Rhinitis	1	0.6
Sinusitis	1	0.6
Body temperature increased	1	0.6
Hepatic enzyme increased	1	0.6
Bone pain	1	0.6
Myalgia	1	0.6
Dizziness	1	0.6
Headache	1	0.6
Paraesthesia	1	0.6
Asthma	1	0.6
Dermatitis atopic	1	0.6
Pruritus	1	0.6
Urticaria	1	0.6

With the exception of asthma (16 patients, 10.8%), adverse events during the follow-up period considered possible components of anaphylaxis occurred in one patient; this case did not meet Sampson criteria.

Additional hypersensitivity reactions included injection-related events (i.e. injection-site irritation, pain, erythema or swelling) and skin rash, each occurring in 7 patients (4.5%) and urticaria in 3 patients (1.9%). While 3 patients (1.9%) reported urticaria, only one of the cases of urticaria was considered to be related to study treatment. The treatment-related urticaria event was of moderate severity, occurred on Day 2, lasted for 5 days and did not result in treatment discontinuation. Hypersensitivity reactions excluding anaphylaxis, skin rash, urticaria and injection-site reaction occurred in 30 patients (19.4%) and comprised asthma (27 patient, 17.4%), chest discomfort (1 patient, 0.6%), eye pruritus (1 patient, 0.6%) and eye swelling (1 patient, 0.6%).

One suspected case of malignancy was reported in a 66-year-old male due to elevated prostate-specific antigen levels. The suspected event was not considered to be treatment-related and a subsequent biopsy was benign.

Most patients remained within the normal range for haematology and biochemistry laboratory variables

Table 6. Frequency of adverse events* during the follow-up period (16 weeks after last dose) in patients who received omalizumab in pre-filled syringes by maximum severity and system organ class.

	Patients with adverse events (n = 148)	
	n	%
Maximum severity grade		
Mild	11	7.4
Moderate	37	25.0
Severe	3	2.0
Primary system organ class affected		
Infections and infestations	29	19.6
Respiratory, thoracic and mediastinal disorders	21	14.2
Gastrointestinal disorders	4	2.7
Musculoskeletal and connective tissue disorders	4	2.7
Nervous system disorders	4	2.7
Eye disorders	3	2.0
Renal and urinary disorders	3	2.0
General disorders and administration site conditions	2	1.4
Injury, poisoning and procedural complications	2	1.4
Psychiatric disorders	2	1.4
Skin and subcutaneous tissue disorders	2	1.4
Cardiac disorders	1	0.7
Immune system disorders	1	0.7
Metabolism and nutrition disorders	1	0.7
Pregnancy, puerperium and perinatal conditions	1	0.7
Vascular disorders	1	0.7

*Defined as adverse events that begin after 28 days post last treatment dose.

during the treatment and follow-up periods and there were few notable changes or abnormalities (Table 7). Fourteen patients (9.0%) had ≥ 1 urine protein and a normal baseline; this increase was transient in ten of these patients, with urinalysis being negative for protein at the last recorded visit. No patterns were identified in the increases with the exception of one patient who had no proteinuria at baseline but three consecutive values of +1 on each visit. One patient had a post-baseline platelet count that was $\geq 50\%$ decreased from baseline. Platelet values for this patient were within the normal range at baseline and all post-baseline study visits, and had increased again at the end of the follow-up period; no bleeding event occurred during the period the platelet count decreased.

Discussion

Regulatory agencies require that any change to the formulation of a biological product is supported by a demonstration of clinical comparability to the original formulation in terms of efficacy, safety and pharmacokinetic/pharmacodynamic parameters^{13,14}. Immunogenicity is an

Table 7. Patients receiving omalizumab in pre-filled syringes with specific changes or criteria for selected laboratory tests during the treatment or follow-up periods.

	Patients (n = 155)	
	n	%
Haemoglobin $\geq 20\%$ decrease from baseline	1	0.6
Haematocrit $\geq 20\%$ decrease from baseline	1	0.6
WBC $\leq 2.4 \times 10^9/L$ and $\geq 20\%$ decrease from baseline	0	0
SGPT (ALT) $\geq 3 \times$ upper limit of normal	1	0.6
SGOT (AST) $\geq 3 \times$ upper limit of normal	0	0
Creatinine $\geq 133 \mu\text{mol/L}$ and $\geq 20\%$ increase from baseline	1	0.6
Urine protein: ≥ 1 urine protein and normal at baseline	14*	9.0
Platelets $< 75 \times 10^9/L$ or $\geq 50\%$ decrease from baseline	1	0.6

*In 10 of these patients the proteinuria was transient and normalised at the last recorded visit.

SGOT (AST), serum glutamic oxaloacetic transaminase (aspartate aminotransferase); SGPT (ALT), serum glutamic pyruvic transaminase (alanine aminotransferase); WBC, white blood cell.

Blood samples for analysis were collected at screening, 1 month, 4 months, 6 months, and after the follow-up period. Changes from baseline are to any post-baseline value, whether during treatment or follow-up.

important part of these assessments because changes to a product formulation can result in 'altered form' species or minor contaminants that can elicit an immune response¹⁵. For example, a change to the stabiliser used in a formulation of erythropoietin- α from human serum albumin to polysorbate 80 and glycine in 1998 was implicated in an increase in the number of cases of antibody-mediated pure red cell aplasia¹⁶. Therefore, it was important to establish that the safety and immunogenicity profile of the new liquid formulation of omalizumab was similar to that of the lyophilised formulation.

In this study, aged omalizumab in pre-filled syringes was not associated with positive ATA results in any patient, indicating that there is no evidence for an altered profile for the liquid formulation of omalizumab. Results suggestive of ATA positivity were seen at baseline and at follow-up in three patients, but were found to be negative in subsequent confirmatory analyses. The fact that ATA positivity was seen at baseline as well as at follow-up in these patients suggests that the results were not related to the liquid formulation of omalizumab used in this study. The findings in this study are consistent with the immunogenic profile of the lyophilised formulation of omalizumab, as demonstrated in a pooled analysis of data from more than 7500 patients during Phase I–III studies of omalizumab, which showed that no patient developed anti-omalizumab antibodies⁵.

Omalizumab had an acceptable overall safety and tolerability profile in the present study. The most frequently reported AEs during the treatment and follow-up periods

Table 8. Hypersensitivity reactions with omalizumab in pre-filled syringes vs lyophilised omalizumab.

	Omalizumab in pre-filled syringes	Lyophilised omalizumab*
Patients, n	155	3678
Skin rash, including pruritus (%)	4.5	6.9
Urticaria (%)	1.9	1.3
Anaphylaxis (%)†	0	0.1
Injection-site reactions (%)‡	4.5	45

*Results published by Corren *et al.* 2009⁵ involving 3678 patients who were treated with omalizumab from completed placebo-controlled and standard therapy-controlled allergic asthma studies.

†Investigator-reported cases.

‡In the present study injection-site reactions are the incidence of injection-related events (injection-site irritation, pain, erythema and swelling); in Corren *et al.* 2009⁵ the incidence relates to local symptoms and signs of injection-site reactions, not otherwise defined. This incidence was based on studies where the injection-site reactions were evaluated prospectively after each dose; however, the number of these studies and total number of patients is not stated by the authors.

were asthma and sinusitis. Most AEs were of mild-to-moderate severity, with severe events occurring in 14.8% of patients. Serious AEs were infrequent (9.0% of patients) with asthma being the only serious AE occurring in more than one patient (none of these serious asthma AEs were considered to be treatment-related). No patients discontinued due to asthma exacerbations during the treatment period. Few patients had notable changes in laboratory values during the study.

The frequency and nature of the AEs reported during the present study were similar to those observed with lyophilised omalizumab in adults and adolescents (aged ≥ 12 years) with moderate-to-severe allergic asthma⁵. In previous studies, AEs of special interest included skin rash (omalizumab 6.9%, control 5.3%), urticaria (omalizumab 1.3%, control 1.3%) and anaphylaxis (omalizumab 0.14%, control 0.07%), the incidences of which were comparable to those found in this study (Table 8). There were no reports of serum-sickness or serum-sickness-like syndrome in the clinical studies with lyophilised omalizumab⁵ and no reports of these AEs in the present study. Further in the present study there were no investigator-reported cases of anaphylaxis, nor were there any cases of anaphylaxis identified using Sampson criteria¹².

A number of limitations were associated with this study. For example, the study was open-label and there was no direct comparative group of patients on lyophilised omalizumab or placebo; therefore it is difficult to objectively assess the relationship between AEs and study drug. However, the size of the patient population ($n = 155$), was sufficient to show any potential for hypersensitivity or anaphylaxis reactions.

Overall, omalizumab in pre-filled syringes has a safety profile consistent with that seen in the published studies

of the lyophilised formulation. A prior study provided evidence that omalizumab in pre-filled syringes is bioequivalent to the currently available lyophilised formulation¹⁷, while the present study indicates that this novel formulation maintains the safety profile of omalizumab.

Conclusion

In patients with moderate-to-severe persistent allergic asthma, treatment with the liquid formulation of omalizumab in pre-filled syringes was not associated with immunogenicity, was well tolerated and had a safety profile consistent with the lyophilised formulation of omalizumab.

Transparency

Declaration of funding

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Declaration of financial/other relationships

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