

ORIGINAL ARTICLE

Safety and tolerability of omalizumab

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Summary

Background Omalizumab (Xolair[®]) is a recombinant humanized monoclonal anti-IgE antibody with proven efficacy in patients with moderate-to-severe and severe persistent allergic (IgE-mediated) asthma.

Objective To review clinical study data to assess the safety profile of omalizumab.

Methods We analysed the safety of omalizumab using data from completed clinical studies (up to 1 year) involving more than 7500 patients with asthma, rhinitis or related conditions and up to 4 years in one study of patients with severe allergic asthma, as well as post-marketing safety data. Analysis focuses on the risk of immune-system effects, hypersensitivity reactions, malignant neoplasia, parasitic infections and thrombocytopenia.

Results Omalizumab exhibited a good safety and tolerability profile that was maintained up to 4 years in one study. The incidence of anaphylaxis was 0.14% in omalizumab-treated patients and 0.07% in control patients. No omalizumab-treated patient developed measurable anti-omalizumab antibodies. Post-marketing, based on estimated exposure of 57 300 patients (June 2003–December 2006), the frequency of anaphylaxis attributed to omalizumab use was estimated to be at least 0.2% of patients. Current clinical trial data do not support an increased risk of malignant neoplasia or thrombocytopenia with omalizumab.

Conclusion Data indicate that the proven efficacy of add-on omalizumab in patients with moderate-to-severe or severe allergic asthma is accompanied by a favourable safety and tolerability profile.

Keywords anti-IgE, omalizumab, safety, tolerability

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Introduction

Omalizumab (Xolair[®]) is the first monoclonal anti-IgE antibody [1] licensed for the treatment of allergic (IgE-mediated) asthma. The efficacy of omalizumab added to current asthma therapy has been proven in moderate-to-severe and severe asthma [2–13], and also in allergic rhinitis [14–17].

The use of a monoclonal antibody represents a novel approach in the treatment of asthma and, perhaps even more than conventional therapeutic interventions, evaluation of the risk of adverse effects associated with these agents is of great importance to prescribers. As it targets an immune system molecule, omalizumab might be associated with specific hypothetical safety concerns. It may have the potential to increase the risk of infection or neoplasm as a result of long-term immunosuppression [18]. In addition, monoclonal antibodies of murine origin

have been associated with a risk of anaphylactic reactions [19]. Although residues of murine origin constitute <5% of the omalizumab molecule, which reduces the potential for an immune response [20], there have been spontaneous reports of anaphylaxis occurring in association with omalizumab therapy in the post-marketing setting [21].

Patients undergoing clinical trials of omalizumab provide a large population, in which safety and tolerability can be evaluated. We evaluated the clinical safety of omalizumab in a pooled analysis of data from completed phase I, II and III studies involving more than 7500 patients with asthma, rhinitis or related conditions.

Additionally, several studies examining specific safety concerns that might be associated with omalizumab (immune system effects, hypersensitivity reactions, malignant neoplasia and parasitic infections) have been conducted, and are reviewed in this article, along with issues that have been identified during pre-clinical

investigation (thrombocytopenia) and post-marketing surveillance (anaphylaxis and Churg–Strauss syndrome). The potential for interaction with other medications, and incidences and outcomes of pregnancy occurring during clinical studies are also discussed.

Studies and patients

Analyses of adverse events (AEs) were performed on three large datasets derived from study populations who had received at least one dose of study medication and provided

some post-randomization data in the omalizumab development programme ('safety analysable population'): 2342 patients with predominantly severe, persistent allergic asthma enrolled in six placebo-controlled, phase IIB/III studies in adults and adolescents (≥ 12 years) with asthma; 2004 patients with predominantly severe, persistent allergic asthma enrolled in two large, open-label, standard-therapy studies in adults and adolescents (≥ 12 years); and 6130 patients enrolled in all-controlled studies in all indications, including children, adults and adolescents with allergic asthma as well as other indications (Table 1).

Table 1. Summary of studies included in the safety analysis

Study	Patient population	Age range (years)	Number of patients (randomized)		Number of patients (safety analysable)		Duration (weeks)
			Omalizumab	Control	Omalizumab	Control	
Placebo-controlled allergic asthma studies							
2306 [9]	Allergic asthma	12–75	245	237	245	237	28
2304 [12]	Allergic asthma and rhinitis	12–74	209	196	209	196	28
008C [6]	Allergic asthma	12–74	268	257	268	257	28
008 extension [10]	Allergic asthma		245	215	245	215	24
009C [11]	Allergic asthma	12–76	274	272	274	272	28
009 extension [4]	Allergic asthma		254	229	254	229	24
011C [8]	Allergic asthma	12–75	176	165	174	165	32
0112 [1]	Allergic asthma	18–50	22	23	22	23	16
No. of patients					1192	1150	
Total patient-years*					886.0	800.8	
Mean patient exposure (years) [†]					0.73	0.70	
Standard-therapy-controlled allergic asthma studies (adults and adolescents)							
IA04 [2]	Allergic asthma	12–75	206	106	202	89	52
ALTO [22]	Allergic asthma	12–75 [‡]	1169	591	1136	577	24
No. of patients					1338	666	
Total patient-years*					698.5	349.6	
Mean patient exposure (years) [†]					0.52	0.52	
All controlled studies							
010C [13]	Allergic asthma	5–12	225	109	225	109	28
D01 [17]	Seasonal allergic rhinitis	6–17	116	109	114	108	24
006 [15]	Seasonal allergic rhinitis	12–75	400	136	400	136	12
007 [14]	Seasonal allergic rhinitis	17–66	165	86	164	86	8
0113 [23]	Atopic dermatitis	6–16	16	9	16	9	24
0114 [16]	Perennial allergic rhinitis	12–75	144	145	144	145	16
ALTO [22]	Allergic asthma	6–11 [‡]	93	46	85	43	24
No. of patients					1148	636	
No. of patients (all controlled studies [§])					3678	2452	
Total patient-years*					1934.5	1363.7	
Mean patient exposure (years) [†]					0.53	0.56	

*Patient-years is the sum of each patient's exposure within a particular analysis population or treatment group.

[†]Mean patient exposure is the mean time from date of first study drug administration to last visit for patients completing the study, or date of last study drug administration for those withdrawing early.

[‡]For the purposes of the safety analysis, only patients ≥ 12 years from the ALTO study were included in the standard-therapy-controlled asthma studies grouping, based on current licensed populations; paediatric patients were included in all controlled studies.

[§]All controlled studies also included placebo-controlled and standard therapy-controlled allergic asthma studies.

C, core study.

Table 2. Asthma-related baseline history and disease characteristics in placebo-controlled and standard-therapy-controlled allergic-asthma studies

	Placebo-controlled studies		Standard-therapy-controlled studies	
	Omalizumab (<i>n</i> = 1192)	Placebo (<i>n</i> = 1150)	Omalizumab (<i>n</i> = 1338)	Control (<i>n</i> = 666)
Any prior year overnight hospitalization for asthma, <i>n</i> (%)	181 (15.2)	159 (13.8)	208 (15.1)	110 (15.8)
Any prior year ICU admission for asthma, <i>n</i> (%)	40 (3.4)	36 (3.1)	95 (6.9)	51 (7.3)
FEV ₁ (% of predicted), mean (SD)	69.6 (12–126)	70.5 (22–127)	71.3 (15–139)	69.8 (14–130)
FEV ₁ (% reversibility), mean (SD)	23.2 (–100–158)	23.0 (–100–169)	28.4 (1.6–129)	30.3 (6.6–178)
Baseline ICS in BDP equivalent (µg/day), mean (SD)	1430 (500–8000)	1412 (200–8000)	1508 (0–10 000)	1540 (88–8000)

ICU, intensive care unit; FEV₁, forced expiratory volume in 1 s; SD, standard deviation; ICS, inhaled corticosteroid; BDP, beclometasone dipropionate equivalent.

Table 3. Summary of adverse event (AE) profile in placebo-controlled and standard-therapy-controlled allergic-asthma studies and all-controlled studies

	Placebo-controlled studies		Standard-therapy-controlled studies		All-controlled studies	
	Omalizumab (<i>n</i> = 1192)	Placebo (<i>n</i> = 1150)	Omalizumab (<i>n</i> = 1338)	Control (<i>n</i> = 666)	Omalizumab (<i>n</i> = 3678)	Control (<i>n</i> = 2452)
Patients experiencing AEs, <i>n</i> (%)						
Any AE	983 (82.5)	946 (82.3)	1030 (77.0)	448 (67.3)	2752 (74.8)	1844 (75.2)
Mild or moderate	829 (69.5)	774 (67.3)	866 (64.7)	370 (55.6)	2356 (64.1)	1535 (62.6)
Severe	154 (12.9)	172 (15.0)	164 (12.3)	78 (11.7)	396 (10.8)	309 (12.6)
Drug-related AE	110 (9.2)	87 (7.6)	183 (13.7)*	NA	377 (10.3)	122 (5.0) [†]
Serious AE	50 (4.2)	41 (3.6)	85 (6.4)	39 (5.9)	153 (4.2)	92 (3.8)
AE causing discontinuation	15 (1.3)	17 (1.5)	42 (3.1)	2 (0.3)	64 (1.7)	22 (0.9)

*For these studies, drug relatedness was captured only for the omalizumab group, not the standard-therapy control, so cannot be interpreted in a comparative manner.

[†]Only placebo patients were considered.

NA, not applicable.

The baseline demographics and asthma-related disease characteristics of patients were similar between treatment groups in each study population (Table 2). The majority of patients were Caucasian (81–88%), female (56–61%) and aged 18–64 years (77–90%). Baseline mean total IgE ranged from 184.4 to 213.4 IU/mL and 179.9 to 209.6 IU/mL in the omalizumab and control groups, respectively.

Exposure to study drug. In the placebo-controlled and standard-therapy-controlled allergic asthma populations, the majority of patients were treated for at least 24 weeks in both treatment groups. Overall, 2484 patients were exposed to omalizumab for ≥24 weeks, of whom 555 were exposed for at least 52 weeks.

For all studies (except studies 006 and 007), the omalizumab dose was 150 or 300 mg every 4 weeks or 225, 300 or 375 mg every 2 weeks, based on pre-treatment serum total IgE concentration and body weight. For study 006 the omalizumab dose was 50, 150 or 300 mg every 3–4 weeks and for study 007 the omalizumab dose was 300 mg every 3–4 weeks. The majority of patients in each of the three populations were treated with omalizumab 150 or 300 mg at 4-week intervals.

Patient disposition. At least 85% of patients completed the studies in each of the three study populations. The most frequent reason for discontinuation in each population was withdrawal of patient consent (3–6%). In the placebo-controlled studies population, the incidence of discontinuations due to AEs was 9.4% in the omalizumab group and 3.9% in the placebo group. Rates of discontinuation were similar between treatment groups in the other populations.

Adverse events

The AE profiles in each study population are presented in Table 3. In the all-controlled-studies population, the number of patients reporting AEs was similar between treatment groups. The majority of AEs were of mild to moderate severity. Severe AEs were reported in 10.8% of patients receiving omalizumab and in 12.6% of patients in the control group. Serious AEs were reported by 4.2% of patients receiving omalizumab and by 3.8% of patients in the control group.

In the placebo-controlled studies population, 1.3% of omalizumab-treated patients and 1.5% of placebo-treated patients discontinued treatment due to AEs. Serious AEs occurred infrequently (omalizumab 4.2%, placebo 3.6%). In

Table 4. Most common adverse events ($\geq 3\%$ in any group) in placebo-controlled and standard-therapy-controlled allergic-asthma studies and all-controlled studies, *n* (%)

MedDRA Organ Class Preferred term	Placebo-controlled studies		Standard-therapy-controlled studies		All-controlled studies	
	Omalizumab (<i>n</i> = 1192)	Placebo (<i>n</i> = 1150)	Omalizumab (<i>n</i> = 1338)	Control (<i>n</i> = 666)	Omalizumab (<i>n</i> = 3678)	Control (<i>n</i> = 2452)
Infections and infestations						
Nasopharyngitis	277 (23.2)	274 (23.8)	151 (11.3)	58 (8.7)	529 (14.4)	390 (15.9)
Upper respiratory tract infection	210 (17.6)	214 (18.6)	209 (15.6)	83 (12.5)	579 (15.7)	385 (15.7)
Sinusitis	150 (12.6)	168 (14.6)	160 (12.0)	74 (11.1)	373 (10.1)	295 (12.0)
Influenza	110 (9.2)	114 (9.9)	43 (3.2)	19 (2.9)	184 (5.0)	163 (6.6)
Bronchitis	77 (6.5)	86 (7.5)	96 (7.2)	45 (6.8)	190 (5.2)	137 (5.6)
Gastroenteritis	49 (4.1)	36 (3.1)	28 (2.1)	8 (1.2)	Not available	Not available
Pharyngitis	54 (4.5)	53 (4.6)	33 (2.5)	10 (1.5)	127 (3.5)	73 (3.0)
Viral infection	45 (3.8)	46 (4.0)	33 (2.5)	12 (1.8)	117 (3.2)	76 (3.1)
Lower respiratory tract infection	58 (4.9)	55 (4.8)	34 (2.5)	24 (3.6)	Not available	Not available
Respiratory, thoracic and mediastinal disorders						
Pharyngolaryngeal pain	98 (8.2)	98 (8.5)	61 (4.6)	13 (2.0)	234 (6.4)	147 (6.0)
Cough	81 (6.8)	103 (9.0)	56 (4.2)	13 (2.0)	217 (5.9)	175 (7.1)
Rhinitis	57 (4.8)	53 (4.6)	16 (1.2)	17 (2.6)	77 (2.1)	79 (3.2)
Nasal congestion	43 (3.6)	35 (3.0)	25 (1.9)	12 (1.8)	Not available	Not available
Rhinitis allergic	25 (2.1)	37 (3.2)	20 (1.5)	9 (1.4)	Not available	Not available
Nervous system disorders						
Headache	230 (19.3)	229 (19.9)	121 (9.0)	25 (3.8)	570 (15.5)	383 (15.6)
Gastrointestinal disorders						
Diarrhoea	59 (4.9)	53 (4.6)	41 (3.1)	5 (0.8)	124 (3.4)	73 (3.0)
Nausea	59 (4.9)	47 (4.1)	46 (3.4)	8 (1.2)	135 (3.7)	72 (2.9)
Dyspepsia	44 (3.7)	65 (5.7)	16 (1.2)	2 (0.30)	82 (2.2)	79 (3.2)
Musculoskeletal and connective tissue disorders						
Back pain	96 (8.0)	92 (8.0)	44 (3.3)	10 (1.5)	162 (4.4)	117 (4.8)
Arthralgia	72 (6.0)	56 (4.9)	41 (3.1)	4 (0.6)	138 (3.8)	73 (3.0)
Myalgia	52 (4.4)	48 (4.2)	22 (1.6)	3 (0.5)	Not available	Not available
Pain in extremity	40 (3.4)	27 (2.3)	18 (1.3)	3 (0.5)	Not available	Not available
General disorders and administration site conditions						
Pyrexia	43 (3.6)	39 (3.4)	13 (1.0)	4 (0.6)	114 (3.1)	76 (3.1)
Psychiatric disorders						
Insomnia	29 (2.4)	37 (3.2)	11 (0.8)	4 (0.6)	Not available	Not available
Injury, poisoning, and procedural complications						
Joint sprain	40 (3.4)	25 (2.2)	17 (1.3)	8 (1.2)	Not available	Not available

the standard-therapy-controlled studies population, more omalizumab-treated patients (3.1%) discontinued due to AEs than standard-therapy patients (0.3%), probably due to the open-label study designs. In the placebo-controlled studies population, the overall incidence of suspected-drug-related AEs was slightly higher in the omalizumab group (9.2%) than in the placebo group (7.6%).

The most frequent AEs ($\geq 3\%$ in any group) are shown in Table 4. Any differences between groups were small and not indicative of specific toxicity. In studies where the local symptoms and signs of injection-site reactions were evaluated prospectively after each dose, the overall

frequency of injection-site reactions was similar in the omalizumab group (45%) and the placebo group (43%).

Subgroup analyses to evaluate the effect of race on AEs compared Caucasian and non-Caucasian (the numbers of patients within individual, non-Caucasian racial groups were insufficient for meaningful analysis). Among Caucasian patients in the all-controlled-studies population, the overall frequency of AEs was identical (76%) in the 3153 omalizumab recipients and 2099 control patients. The only AE with a $> 2\%$ difference between treatment groups was sinusitis (omalizumab 10.1%, control 12.2%). For non-Caucasian patients within the all-controlled-

Table 5. Overall incidence of adverse events during the core and extension periods of a study in patients with severe allergic asthma [8, 24–26]

Event	Incidence, n (%)				
	Core study (32 weeks)		Extension 1 (96 weeks)	Extension 2 (52 weeks)	Extension 3 (104 weeks)*
	Omalizumab (n = 174)	Placebo (n = 165)	Omalizumab (n = 222)	Omalizumab (n = 178)	Omalizumab (n = 118)
Any AE	136 (78.2)	135 (81.8)	195 (87.8)	134 (75.3)	78 (66.1)
Mild or moderate	120 (69.0)	105 (63.6)	156 (70.3)	115 (64.6)	71 (60.2)
Severe	16 (9.2)	30 (18.2)	39 (17.6)	19 (10.7)	7 (5.9)
Serious AEs	11 (6.3)	11 (6.7)	27 (12.2)	8 (4.5)	5 (4.2)
Treatment-related AEs	6 (3.4)	8 (4.8)	26 (11.7)	4 (2.2)	1 (0.8)

*Extension 3 was originally designed as a 52-week extension study, but has subsequently been extended to 104 weeks following a protocol amendment. The table shows data up to the point of the protocol amendment; exposure in Extension 3 varied from 1 to 44 weeks (mean 22 weeks) depending on when a patient was enrolled relative to when the protocol amendment was implemented.

studies population, the overall frequency of AEs was 69% among the 525 omalizumab recipients and 72% in the 353 control patients. The only AE occurring with at least 2% greater frequency in the omalizumab group was pain in extremity (2.5% vs. 0.3%).

Longer-term data. The allergic-asthma studies included in this safety analysis have included data for up to 1 year's duration. However, one study, which was followed by a series of open-label extensions, collected data on the safety and tolerability of omalizumab in patients with severe allergic asthma for up to 4 years [8, 24–26].

Throughout the core study and extension periods, omalizumab exhibited a good safety and tolerability profile up to 4 years [8, 24–26]. Overall incidence of AEs was similar in the omalizumab and placebo groups during the core study (approximately 80% in both groups) (Table 5). The mean (standard deviation) total exposure (core study, Extensions 1, 2 and 3) for Extension 3 patients was 191.4 (21.3) weeks. The most frequently reported AEs ($\geq 3\%$) during Extension 3 (up to the protocol amendment) were bronchitis (4.2%), acute bronchitis (3.4%), lower respiratory tract infection (3.4%), pyrexia (3.4%) and headache (3.4%).

Laboratory values. Laboratory data were evaluated to identify possible haematological, hepatic, renal, general biochemical and immune system effects. For patients with normal haematological values at baseline in the all-controlled-studies population, the only abnormality that occurred with a $> 2\%$ difference in frequency between treatment groups was high eosinophil count, (omalizumab 8.4%, control 14.2%).

The incidence of patients with normal or high haemoglobin values at baseline who had low or noticeably low values after treatment was 10.0% in the omalizumab group and 8.3% in the control group. In both treatment groups, the majority of patients had a maximum decrease in haemoglobin of between 0% and 10% from baseline (67.9% with omalizumab, 65.1% with controls). The frequency of decrease in the haemoglobin of $\geq 20\%$ from

baseline was 0.2% in the omalizumab and 0.5% in the control group.

The number of patients with normal or high leucocytes at baseline who had low values post-treatment was similar between treatments in the all-controlled-studies population. Seven patients receiving omalizumab and two receiving controls had a shift to notably low leucocytes ($< 2.4 \times 10^9/L$) after treatment.

There were no between-treatment-group differences $\geq 2\%$ in the frequency of shifts from normal to abnormal in liver function tests or urinalysis results, with the exception of a shift to positive haemoglobin, which was slightly less frequent in the omalizumab group (11.5%) than in the control group (13.8%), and a shift to positive white blood cell count, which was more frequent in the omalizumab group (19.0%) than in the control group (15.9%).

Adverse events of special interest

Immune system effects and hypersensitivity reactions. AEs that were suggestive of hypersensitivity reactions (such as anaphylaxis, urticaria or serum sickness-like syndrome) or immune deficiency were recorded, and patient serum samples from all completed controlled studies (except ALTO [22] and IA04 [2]) were screened for anti-omalizumab antibodies at baseline and at a post-treatment follow-up visit. In the all-controlled-studies population, the frequency of skin rash (any type) including pruritus was 6.9% in the omalizumab group and 5.3% in the control group. Urticaria occurred infrequently (omalizumab 1.3%, control 1.3%). The incidence of other AEs suggestive of hypersensitivity reactions in the all-controlled-studies population was 4.2% in the omalizumab group and 4.7% in the control group. The incidence of anaphylaxis in the all-controlled-studies population (reported by investigator) was rare (omalizumab 0.14%, control 0.07%). There were no AEs reported as serum-sickness or serum-sickness-like syndrome in any treatment groups and none of the omalizumab-treated patients developed measurable anti-omalizumab antibodies.

The omalizumab post-marketing safety database has also been analysed to determine the incidence of spontaneous reports of anaphylaxis between 1 June 2003 and 31 December 2006 [21]. Spontaneous AE reports in the United States were examined using diagnostic criteria, which may be indicative of an anaphylactic event [27]. Based on an estimated exposure of 57 300 patients from 1 June 2003 to 31 December 2006, 124 cases of anaphylaxis were attributed to omalizumab (reporting proportion 0.2%) [21]. Within these 124 cases, 24% of patients had a previous history of anaphylaxis [21]; 39% of anaphylactic events occurred with the first dose, 19% with the second, 10% with the third and the remainder after subsequent doses (with some occurring after ≥ 1 year of omalizumab treatment) [21]; the reported time to onset ranged from ≤ 30 min (35%) to $> 1-4$ days (5%) [21]; 15% of the reported cases resulted in hospitalization [21].

Malignant neoplasia. Analyses of malignant neoplasia were performed on data from 35 phase I, II and III multiple-dose studies of omalizumab in all indications. Malignant neoplasms were reported in 25 of 5015 patients (0.50%) receiving omalizumab compared with five of 2854 patients (0.18%) receiving controls. All malignant neoplasms were solid tumours, with the exception of a case of recurrent non-Hodgkin's lymphoma in an omalizumab-treated patient, and were consistent with those expected to occur in the populations studied. The malignant neoplasms reported in more than two patients included more commonly occurring cancers [skin (non-melanoma), breast, prostate].

In four cases in the omalizumab-treated group the tumour appeared to be present before the start of the study: (1) breast cancer occurred in a patient before the study start but was not reported until the final visit; (2) prostate cancer occurred in a patient who had had elevated serum prostate-specific antigen for 4 years before entry into the study; (3) microscopic haematuria was present at screening in a patient who developed bladder cancer; and (4) a case of recurrent non-Hodgkin's lymphoma occurred in a patient who had presented to his physician with increased night sweats and generalized adenopathy before entering the study. In this last case, a computed tomography scan approximately 2 weeks after the study start showed mild splenomegaly, pelvic adenopathy and adenopathy along the iliac chain. None of the cancers was considered drug related by the investigator, with the exception of a testicular cancer in the control group where the investigator reported an inability to assess the drug relationship.

All but one of the neoplasms (basal cell carcinoma) were diagnosed in the first 2 years of drug exposure. In the majority of patients, the malignant neoplasm was reported during the first 52 weeks of treatment [20 of 25 (80%) of all cancers in omalizumab-exposed patients; five of five

(100%) in control patients]. The malignant neoplasms diagnosed after > 1 year of drug exposure in the omalizumab group included: parotid gland cancer at week 59, pancreatic cancer at week 61, sigmoid colon cancer at week 99, prostate carcinoma at week 99 and basal cell carcinoma at week 119.

The incidence of neoplasms in studies of omalizumab was compared with the NIH SEER database [28], and the expected number in omalizumab and placebo populations was calculated by applying the SEER gender- and age-specific cancer rates to the time at risk using the indirect age-standardization method [29]. The comparison excluded cancers that are not recorded in the SEER database, namely non-melanoma skin cancers (seven omalizumab patients, three control patients) and recurrent cancers (two omalizumab patients). The actual number of neoplasms in the omalizumab group ($n = 15$) was consistent with the expected value of 15.21, resulting in a standardized incidence ratio (SIR) of observed to expected number of events of 0.99 [95% confidence interval (CI) 0.55–1.63]. In contrast, the incidence of neoplasms in the control group ($n = 2$) was lower than the expected value of 6.54, resulting in a SIR of 0.31 (95% CI 0.04–1.11). The 95% CI values indicate that the differences between the observed and expected incidences of neoplasms were not statistically significant, suggesting that the results could be due to chance. The relative risk estimates (omalizumab : control) of malignant neoplasia in phase I, II and III trials ranged from 0.77 to 5.14 and are for the most part consistent with estimates in the asthmatic populations reported in the literature: 0.78–2.1 [30–35].

Parasitic infections. Parasitic helminth infection induces production of IgE, which is regarded as an important immune effector mechanism against helminth infection [36]. It is therefore theoretically possible that omalizumab could increase susceptibility to helminth infection or the associated clinical morbidity. A 52-week, randomized, double-blind, placebo-controlled study of omalizumab in adults and adolescents ($n = 137$) with asthma or rhinitis at high risk of intestinal helminth infection was conducted to investigate these risks [37].

In the all-controlled-studies population, parasitic infections were rare in both treatment groups (omalizumab 0.19%, control 0.16%) and all events were mild or moderate. In the entire omalizumab-clinical-trials programme, there was only one (0.03%) reported helminthic infection (pinworm) from 1934 patient years of omalizumab treatment in 3678 treated patients.

A 52-week, randomized, double-blind, parallel-group, placebo-controlled study in 137 patients at high risk of geohelminth infection found a slightly higher number of patients with one or more geohelminth infections during treatment in the omalizumab group (50%) than in the placebo group (41%; odds ratio 1.47, 95% CI 0.74–2.95;

one-sided $P=0.14$) [37]. Severity of infection and response to anthelmintic treatment was unaltered by omalizumab therapy [37].

Thrombocytopenia. In pre-clinical studies, reduced platelet counts were observed in juvenile cynomolgus monkeys receiving omalizumab at doses 3.7–20-fold greater than the highest dose recommended in humans. This observation was made after initiation of the phase III clinical trials and led to implementation of increased surveillance of platelet counts in all ongoing and subsequent clinical studies. There was, however, no evidence of a clinically relevant impact on platelet count during omalizumab treatment in clinical studies. Shift analyses of platelet counts showed no differences between the omalizumab and control groups. In the all-controlled-studies population, a decrease in platelet count from baseline occurred frequently in both the omalizumab and control groups (70.7% and 65.7%, respectively). The majority of patients had a decrease in platelet count of $<50 \times 10^9/L$ (55.2% with omalizumab and 52.4% with controls) or no change/increase in platelet counts (29.3% with omalizumab and 34.3% with controls). In the omalizumab group, 3.4% of patients had a decrease in platelet count of $100 \times 10^9/L$ or greater, compared with 2.3% of patients in the control group.

Churg–Strauss syndrome and hypereosinophilic syndrome. Patients with severe asthma may rarely present with systemic hypereosinophilic syndrome or Churg–Strauss syndrome (allergic granulomatous vasculitis), both of which are usually treated with systemic corticosteroids. In rare cases, patients on asthma therapies, including omalizumab, may present or develop systemic eosinophilia and vasculitis, events commonly associated with the concurrent reduction of oral corticosteroids (OCS) [38]. Published case reports relating to Churg–Strauss syndrome and omalizumab describe reduction in OCS dose before the emergence of symptoms of Churg–Strauss syndrome [39, 40] and related correspondence has supported the hypothesis that the reduction in OCS dose as improvement in asthma symptoms occurs, rather than the administration of omalizumab, is the likely reason for observed Churg–Strauss cases [40–42]. The omalizumab EU label now advises under 'special warnings and special precautions for use' that physicians should be alert to the development of marked eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications and/or neuropathy [43].

Interaction with other medications

No formal interaction studies have been performed with omalizumab. However, there is little potential for drug interactions, as cytochrome P450 enzymes, efflux pumps

and protein-binding mechanisms are not involved in its clearance. In clinical studies, omalizumab was commonly used in conjunction with inhaled corticosteroids, OCS, short-acting and long-acting β_2 -agonists and antihistamines, and no drug/drug interactions with these commonly prescribed asthma and rhinitis medications was observed.

Pregnancy

Forty-seven cases of pregnancy have been reported from all completed studies, including women whose spouse was on omalizumab treatment at the time of conception. In all cases, patients found to be pregnant were discontinued from the study and the pregnancies followed to their outcome. Of these cases, 27 were in omalizumab-treated patients, 18 were in placebo-treated, standard therapy controlled or unrandomized patients and two conceived while their spouse was receiving omalizumab. In the omalizumab-treated patients, 17 pregnancies ended in normal delivery, four ended in elective abortion and six ended in spontaneous abortion. Of those not receiving omalizumab, eight pregnancies ended in normal delivery, one ended in elective abortion, six ended in spontaneous abortion and three outcomes are unknown; both with omalizumab-treated spouses had normal deliveries. These data indicate no untoward effect of omalizumab treatment on pregnancy outcome, based on this relatively small number of events. However, as there are no adequate and well-controlled clinical studies of omalizumab in pregnant women, its use in pregnancy cannot be advised. An ongoing observational study of the use and safety of omalizumab during pregnancy (EXPECT registry) includes patients who have been exposed to omalizumab within 8 weeks of conception or during pregnancy. It will assess pregnancy outcomes, incidence of spontaneous fetal loss, and potential risk to newborns.

Discussion

The data from three large safety datasets involving more than 7500 patients with asthma or related conditions demonstrate a favourable overall safety and tolerability profile for omalizumab in clinical trials up to 1 year. Baseline demographic and clinical characteristics illustrate a high proportion of patients with severe persistent asthma in the omalizumab development programme. These patients are at greater risk of AEs than patients with less severe disease.

A favourable safety and tolerability profile, maintained up to 4 years, has also been demonstrated. The most frequent AEs occurred with similar frequency ($\leq 2\%$ difference) in the omalizumab and control groups. The majority of AEs with omalizumab were mild to moderate in severity and did not lead to treatment discontinuation.

Assessment of laboratory variables revealed no evidence of clinically relevant effects on haemoglobin, leucocytes, platelet counts, renal function or liver function tests during treatment with omalizumab. As there were no between-treatment-group differences in liver function tests or urinalysis results, it seems unlikely that omalizumab is associated with significant renal or hepatic toxicity. However, as stated in the EU label, omalizumab has not been studied in patients with pre-existing renal or hepatic impairment, and caution should be exercised when administering omalizumab in these patients [43]. Similarly, due to the lack of study in patients with autoimmune and immune complex-mediated diseases, the label also advises caution [43].

Analysis of clinical trial data revealed no evidence of an increased risk of hypersensitivity reactions in omalizumab-treated patients, and incidence of anaphylaxis was rare. However, while anaphylactic events remain relatively rare in the post-marketing setting, the reporting proportion of cases has increased. This may be partially explained as a result of the inclusion of cases where described symptoms supported a diagnosis of anaphylaxis, rather than the specific term 'anaphylaxis' appearing in an investigators report. Post-marketing data have also highlighted that anaphylaxis may occur at the first or subsequent administration of omalizumab, and after a longer period post-administration than observed in clinical trials. These findings are reflected in the recent revisions to the omalizumab EU and US labels [43, 44], and in light of post-marketing reports of anaphylaxis, the Omalizumab Joint Task Force (OJTF) of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology Executive Committees have made recommendations to prescribers of omalizumab regarding patient assessment and education, post-administration observation, and the availability of an epinephrine autoinjector [45]. The recommendations of the OJTF are summarized in Table 6. The frequency of reports of anaphylaxis associated with omalizumab remains lower than that reported for other biologicals in other indications [46–50]. Also, bearing in mind the patients in whom omalizumab is indicated, it is important to note that asthma severity [51] and atopy [23, 52] are risk factors for anaphylaxis, as is a history of anaphylaxis [52].

Clinical data do not suggest a causal relationship between omalizumab and cancer or a significantly increased risk of parasitic infection or thrombocytopenia. The incidence of malignancy in the omalizumab group was similar to the expected incidence in the general population, based on comparisons with the NIH SEER database. The relatively short time to diagnosis of malignant neoplasm seen in the clinical trials would suggest that many were probably pre-existing, as drug-induced cancers, especially solid tumours, usually occur after long exposure (cancer was not an exclusion criterion in most studies unless it had occurred

Table 6. Summary of the Omalizumab Joint Task Force (OJTF) recommendations on anaphylaxis with omalizumab [44]

Consent	Obtain informed patient consent Discuss the risks, benefits, and alternatives to omalizumab
Education	Educate the patient on the signs, symptoms, and treatment of anaphylaxis
Epinephrine autoinjector	Prescribe and educate the patient on the proper use of an epinephrine autoinjector Advise the patient to carry the epinephrine autoinjector before omalizumab administration, and for 24 h post-administration
Health assessment	Assess the patient's current health status before each injection Determine whether any recent health changes may require withholding treatment The assessment should include vital signs and some measure of lung function (e.g. PEF or FEV ₁)
Post-administration observation	Observe the patient for 2 h post-administration for the first 3 doses Observe the patient for 30 min after each subsequent dose The duration of the observation period can be modified based on the physician's clinical judgment after discussing the risks with the patient

PEF, peak expiratory flow; FEV₁, forced expiratory volume in 1 s.

within 3 months of the screening visit). Because of the very small number of malignant neoplasms reported, particularly in the control group, these data should be interpreted with caution, and it should be borne in mind that studies of a relatively short duration are not specifically designed to assess risk of malignancies. A 1-year clinical trial has shown that the risk of helminth infection was not significantly increased and responses to anthelmintic treatment did not differ in patients who received omalizumab compared with control patients [37]. Nevertheless, there is a possible risk of parasitic infection in omalizumab-treated patients who are resident in, or travel to, areas with a high prevalence of parasitic helminths. These patients should be monitored appropriately, and suspension of omalizumab should be considered if infected patients fail to respond to anthelmintic therapy. There was no evidence of a clinically relevant impact on platelets during omalizumab treatment in clinical studies or in post-marketing, and additional platelet testing is not a requirement of the EU [43] or US [44] labels for omalizumab.

Additional long-term safety data will come from EXCELS, an ongoing, 5-year, prospective, open-label, observational cohort study. Approximately, 5000 omalizumab-treated and 2500 non-omalizumab-treated patients aged ≥ 12 years with moderate-to-severe persistent asthma and a positive skin test or *in vitro* reactivity to an aeroallergen are being recruited from a variety of practice settings. The EXCELS study is currently underway in the United States [53].

In summary, several trials have provided compelling evidence of the clinical benefits of omalizumab as add-on therapy for patients with moderate-to-severe and severe, persistent allergic asthma. Safety data from these trials along with data from other studies examining specific safety concerns relating to omalizumab indicate that add-on omalizumab is an effective and well-tolerated treatment in patients with moderate-to-severe or severe allergic asthma.

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References

- 1 Djukanović R, Wilson SJ, Kraft M *et al.* Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. *Am J Respir Crit Care Med* 2004; 170:583-93.
- 2 Ayres JG, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. *Allergy* 2004; 59:701-8.
- 3 Bousquet J, Cabrera P, Berkman N *et al.* The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy* 2005; 60:302-8.
- 4 Buhl R, Soler M, Matz J *et al.* Omalizumab provides long-term control in patients with moderate-to-severe allergic asthma. *Eur Respir J* 2002; 20:73-8.
- 5 Buhl R, Hanf G, Soler M *et al.* The anti-IgE antibody omalizumab improves asthma-related quality of life in patients with allergic asthma. *Eur Respir J* 2002; 20:1088-94.
- 6 Busse W, Corren J, Lanier BQ *et al.* Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001; 108: 184-90.
- 7 Finn A, Gross G, van Bavel J *et al.* Omalizumab improves asthma-related quality of life in patients with severe allergic asthma. *J Allergy Clin Immunol* 2003; 111:278-84.
- 8 Holgate ST, Chuchalin AG, Hébert J *et al.* for the Omalizumab 011 International Study Group. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy* 2004; 34:632-8.
- 9 Humbert M, Beasley R, Ayres J *et al.* 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* 2005; 60: 309-16.
- 10 Lanier BQ, Corren J, Lumry W, Liu J, Fowler-Taylor A, Gupta N. Omalizumab is effective in the long-term control of severe allergic asthma. *Ann Allergy Asthma Immunol* 2003; 91:154-9.
- 11 Soler M, Matz J, Townley R *et al.* The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001; 18:254-61.
- 12 Vignola AM, Humbert M, Bousquet J *et al.* Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy* 2004; 59:709-17.
- 13 Milgrom H, Berger W, Nayak A *et al.* Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics* 2001; 108:E36.
- 14 Ädelroth E, Rak S, Haahtela T *et al.* Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000; 106:253-9.
- 15 Casale TB, Condemi J, LaForce C *et al.* for the Omalizumab Seasonal Allergic Rhinitis Trial Group. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. *JAMA* 2001; 286:2956-67.
- 16 Chervinsky P, Casale T, Townley R *et al.* Omalizumab, an anti-IgE antibody, in the treatment of adults and adolescents with perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2003; 91: 160-7.
- 17 Kuehr J, Brauburger J, Zielen S *et al.* Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2002; 109:274-80.

- 18 Hommes DW, van Deventer SJ. Infliximab therapy in Crohn's disease: safety issues. *Neth J Med* 2003; **61**:100–4.
- 19 Choy EH, Kingsley GH, Panayi GS. Monoclonal antibody therapy in rheumatoid arthritis. *Br J Rheumatol* 1998; **37**:484–90.
- 20 Presta LG, Lahr SJ, Shields RL *et al*. Humanization of an antibody directed against IgE. *J Immunol* 1993; **151**:2623–32.
- 21 Limb SL, Starke PR, Lee CE, Chowdhury BA. Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. *J Allergy Clin Immunol* 2007; **120**:1378–81.
- 22 Genentech Inc., ALTO study. Synopsis of final report. <http://clinicalstudyresults.gene.com/q2143g.pdf>, accessed 12 February 2009.
- 23 Webb LM, Lieberman P. Anaphylaxis: a review of 601 cases. *Ann Allergy Asthma Immunol* 2006; **97**:39–43.
- 24 Bousquet J, Chung F, Tunon-de-Lara JM, Oshinyemi K, Tran G, Fox H. Retreatment with omalizumab, an anti-IgE monoclonal antibody, is well tolerated in patients with severe allergic asthma. *Allergy* 2003; **58** (Suppl): 2, A4.
- 25 Hébert J, Rolli M, Gao J, Reisner C. Omalizumab, an anti-IgE monoclonal antibody, demonstrates long-term asthma control, safety and tolerability in patients with severe allergic asthma. *J Allergy Clin Immunol* 2006; **117**:S9.
- 26 Chung KF, Holgate S, Rolli M, Gao J, Reisner C. Omalizumab demonstrates long-term asthma control, safety and tolerability in patients with severe IgE-mediated allergic asthma. *Allergy* 2007; **62** (Suppl. 83):210, abstract 574.
- 27 Sampson HA, Muñoz-Furlong A, Campbell RL *et al*. Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006; **117**:391–7.
- 28 Ries LAG, Eisner MP, Kosary CL *et al* (eds). *SEER cancer statistics review, 1973–1999*. Bethesda, MD: National Cancer Institute, 2002.
- 29 Fleiss JL. *Statistical methods for rates and proportions*. New York: John Wiley and Sons, 1981.
- 30 Eriksson NE, Holmén A, Högstedt B, Mikoczy Z, Hagmar L. A prospective study of cancer incidence in a cohort examined for allergy. *Allergy* 1995; **50**:718–22.
- 31 Källén B, Gunnarskog J, Conradson TB. Cancer risk in asthmatic subjects selected from hospital discharge registry. *Eur Respir J* 1993; **6**:694–7.
- 32 McWhorter WP. Allergy and risk of cancer: a prospective study using NHANESI follow-up data. *Cancer* 1988; **62**:451–5.
- 33 Mills PK, Beeson WL, Fraser GE, Phillips RL. Allergy and cancer: organ site-specific results from the Adventist Health Study. *Am J Epidemiol* 1992; **136**:287–95.
- 34 Reynolds P, Kaplan GA. Asthma and cancer. *Am J Epidemiol* 1987; **125**:539–40.
- 35 Vesterinen E, Pukkala E, Timonen T, Aromaa A. Cancer incidence among 78 000 asthmatic patients. *Int J Epidemiol* 1993; **22**: 976–82.
- 36 Jarrett EE, Miller HR. Production and activities of IgE in helminth infection. *Prog Allergy* 1982; **31**:178–233.
- 37 Cruz AA, Lima F, Sarinho E *et al*. Safety of anti-immunoglobulin E therapy with omalizumab in allergic patients at risk of geohelminth infection. *Clin Exp Allergy* 2007; **37**:197–207.
- 38 D'Cruz DP, Barnes NC, Lockwood CM. Difficult asthma or Churg–Strauss syndrome? Steroids may be masking undiagnosed cases of Churg–Strauss syndrome. *BMJ* 1999; **318**:475–6.
- 39 Winchester DE, Jacob A, Murphy T. Omalizumab for asthma. *N Engl J Med* 2006; **355**:1281–2.
- 40 Ruppert AM, Averous G, Stanciu D *et al*. Development of Churg–Strauss syndrome with controlled asthma during omalizumab treatment. *J Allergy Clin Immunol* 2008; **121**:253–4.
- 41 Bargagli E, Rottoli P. Omalizumab treatment associated with Churg–Strauss vasculitis. *Int Arch Allergy Immunol* 2008; **145**:268.
- 42 Giavina-Bianchi P, Agondi R, Kalil J. One year administration of anti-IgE to a patient with Churg–Strauss Syndrome. *Int Arch Allergy Immunol* 2008; **146**:176.
- 43 European Medicines Agency (EMA): Omalizumab (Xolair[®]) full prescribing information (EU), May 2007. <http://www.emea.europa.eu/humandocs/PDFs/EPAR/Xolair/H-606-PI-en.pdf>, accessed 8 April 2008.
- 44 Genentech Inc: Omalizumab (Xolair[®]) full prescribing information (US), July 2007. <http://www.gene.com/gene/products/information/immunological/xolair/insert.jsp>, accessed 8 April 2008.
- 45 Cox L, Platts-Mills TA, Finegold I, Schwartz LB, Simons FE, Wallace DV. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. *J Allergy Clin Immunol* 2007; **120**:1373–7.
- 46 Hanauer SB, Feagan BG, Lichtenstein GR *et al* for the ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**:1541–9.
- 47 EPIC investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. *N Engl J Med* 1994; **330**:956–61.
- 48 Dery JP, Braden GA, Lincoff AM *et al*. ReoPro Readministration Registry Investigators. *et al*. Final results of the ReoPro readministration registry. *Am J Cardiol* 2004; **93**:979–84.
- 49 Humira[®] (Adalimumab). *Full prescribing information*. North Chicago, IL: Abbott Laboratories, 2006.
- 50 Enbrel[®] (Etanercept). *Full prescribing information*. Thousand Oaks, CA: Immunex Corporation, 2006.
- 51 González-Pérez A, Fernández C, Suissa S, García Rodríguez LA. Risk of anaphylaxis in the general population and asthma patients. *Eur Respir J* 2007; **30** (Suppl. 51):625s.
- 52 Adkinson NF Jr, Yunginger JW, Busse WW, Bochner BS, Simons FER, (eds). *Middleton's allergy: principles and practice, Vol. II*, 2 nd Edn. Philadelphia, PA: Mosby Inc, 2003.
- 53 Miller MK, Lee JH, Forer D *et al*. Enrollment update of the epidemiologic study of Xolair: evaluating the long-term safety and clinical effectiveness in patients with moderate to severe asthma (EXCELS). *J Allergy Clin Immunol* 2006; **117**:S12.