Expert Opinion

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Safety of omalizumab in asthma

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Introduction: Omalizumab is the first mAb to be introduced for the management of asthma. It is also the first agent designed to block the effects of IgE in initiating the allergic cascade resulting in asthma manifestations. Introduced in 2003, it is now widely used as an effective therapeutic tool in moderate-to-severe allergic asthmatics who are uncontrolled on maximal conventional therapy, including high-dose inhaled steroids and long-acting β-agonists. There is still understandable concern regarding the long-term effects of this drug.

Areas covered: The authors provide a review of safety data generated by controlled clinical trials and post-marketing surveillance as well as a brief overview of the clinical indications and efficacy of omalizumab. They also address specific issues of concern, including the risk of anaphylaxis and malignancy. The reader will gain a working knowledge of the role of omalizumab in current guidelines for the management of asthma.

Expert opinion: Omalizumab appears to be safe and well-tolerated. The possible association of malignancy with omalizumab has been of the greatest concern to patients and physicians. Analysis of clinical study data shows that this incidence is rare and the relative risk of cancer with omalizumab is not significantly different from that which is expected in the general population of people with asthma. As part of a relatively new class of agents, continued surveillance is needed as its indications expand and its use in the population continues to grow.

Keywords: anaphylaxis, asthma, IgE, omalizumab, safety

Expert Opin. Drug Saf. (2011) ***10****(3):463-471*

1. Introduction

IgE plays the major role in the allergic cascade that results in the manifestations of asthma, allergic rhinitis and other atopic disorders. In patients with asthma, allergen-specific IgE binds to the high affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. On re-exposure to the allergen, adjacent IgE molecules crosslink and trigger the degranulation and release of inflammatory mediators such as histamine and leukotrienes which induce bronchial constriction, mucus production and edema.

Omalizumab is a recombinant humanized mAb which binds to the Fc portion of the free IgE molecule (**Box 1**). Omalizumab contains 95% human and 5% murine sequences. The murine residues are grafted into a human IgG1κ framework.

A trimer is formed with two omalizumab molecules per IgE molecule. Omalizumab-bound IgE can no longer bind to the surface IgE receptors on mast cells and basophils preventing any subsequent crosslinking and release of mediators (Winchester *et al.* 2006 [1]).

There is 99% drop in free IgE levels within 2 h of the administration of omalizumab. Observations in patients receiving omalizumab for asthma

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Box 1. Drug summary.

Drug name	Omalizumab
Phase	Launched
Launched indication	Asthma
Pharmacology description	Immunoglobulin E inhibitor
Route of administration	Parenteral, subcutaneous Parenteral, intravenous
Pivotal trial(s)	[15-17]

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include: decrease in free IgE and IgE bound to FceRI [2]; reduction in eosinophil levels in the blood and tissues of patients with asthma [3]; decrease in airway eosinophils, mast cells, basophils, T and B lymphocytes [4]; decrease in IgE+, FceRI+ and IL-4+ cells in bronchial epithelium [5]; decrease in FceRI expression on basophils, mast cells, dendritic cells and monocytes [6]; and decreased circulating IL-13 [4] and decreased fractional exhaled NO [7].

Omalizumab was the first anti-IgE therapy and the first mAb introduced for treatment of allergic disease. It was approved in 2003 by the FDA for the treatment of moderate-to-severe persistent asthma in patients 12 years or older, with positive skin test or *in vitro* reactivity to a perennial aeroallergen, and with symptoms inadequately controlled by inhaled corticosteroids. Most insurance plans require an IgE level of 30 – 700 IU/ml. The dosage is individualized based on a patient's IgE level and weight and administered subcutaneously every 2 or 4 weeks.

In 2007, the National Heart, Lung and Blood Institute Guidelines for the Diagnosis and Management of Asthma (Expert Panel Report 3) added omalizumab to its stepwise approach to long-term asthma management. Omalizumab is currently recommended to be considered in steps 5 and 6 in patients with allergic asthma not controlled with high-dose inhaled steroids and long-acting β-agonists [8].

While it is currently indicated for use only in asthma, it is also being investigated for its efficacy in treating chronic urticaria, another challenging allergic problem [9]. Studies have shown benefits in allergic rhinitis [10], atopic dermatitis [11], food allergies [12] and as an adjunct to allergen immunotherapy [13].

Started in 2004, the Evaluating the Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma (EXCELS) is a 5 year observational study of ~ 5000 patients receiving omalizumab and a control group of ~ 2500 patients not receiving the drug. The primary objective of the EXCELS study is to assess the long-term safety profile of omalizumab in patients followed for 5 years. Analysis of this data is ongoing and will provide much needed additional data on existing concerns such as anaphylaxis and malignancy as well as identify any new safety issues with long-term use of omalizumab [14].

2. Overview of efficacy in asthma

The FDA approval of omalizumab in moderate-to-severe asthma has been based in part on at least three large scale Phase III controlled studies with a total of 1405 subjects [15-17]. These studies have demonstrated the benefit in uncontrolled asthmatics of adding omalizumab to inhaled steroids in terms of improvement in pulmonary function, clinical symptoms and reduced use of rescue medications. Patients on omalizumab had fewer asthma exacerbations despite significant reductions in inhaled corticosteroid dose, stable symptom control despite concomitant reductions in rescue medication use and improvement in quality of life compared with placebo. Decrease in asthma-related unscheduled office visits, emergency room visits and hospitalizations has been shown in patients receiving omalizumab in controlled studies [18]. In a 52 week study, omalizumab-treated subjects has significantly fewer exacerbations which was sustained despite significant reduction of inhaled corticosteroid doses indicating long-term asthma control [19]. In moderate-to-severe asthmatics on stable therapy with concomitant persistent allergic rhinitis, omalizumab significantly decreased asthma exacerbations and improved quality of life [20].

Omalizumab has been shown to be effective in seasonal and allergic rhinitis with significantly decreased nasal symptom scores, missed school or work days, rescue antihistamine use and improved quality of life [10,21]. Addition of omalizumab to standard maintenance dose allergen immunotherapy appeared to have additive beneficial effects in decreasing seasonal allergic symptoms [22]. Omalizumab has been studied as a pretreatment to prevent allergic reactions to rush allergen immunotherapy. Pretreated patients had fewer adverse allergic events and also appeared to have greater improvement in allergic symptoms compared to non-pretreated subjects [23].

3. Safety in clinical trials

There have been at least 17 controlled clinical trials undertaken to investigate the efficacy and safety of omalizumab in pediatric and adult populations and for asthma, allergic rhinitis and other indications. These studies have provided a wealth of safety data.

The majority of clinical study subjects have been severe persistent asthmatics. Most of the important controlled trials have randomized at least 200 subjects to receive omalizumab. Busse *et al.* randomized 268 inhaled steroid-dependent subjects to receive omalizumab every 2 – 4 weeks for a total of 28 weeks [15]. Inhaled steroids were kept at a constant dose for the first 16 weeks and tapered down over another 12 weeks. Omalizumab significantly reduced exacerbations even with inhaled steroid reduction. The most common side effects were headache, upper respiratory infection and sinusitis with no adverse events more frequent than placebo. The INNOVATE (Investigation of Omalizumab in Severe Asthma Treatment) study followed 245 severe persistent

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patients inadequately controlled despite Global Initiative for Asthma (GINA) step 4 therapy treated with omalizumab over 28 weeks [24]. Omalizumab was found to be significantly effective and showed a similar adverse event profile to placebo. In another large study, Soler *et al.* studied 274 moderate-to-severe asthmatics symptomatic despite inhaled steroids who received omalizumab for 28 weeks [17]. Omalizumab was effective in improving asthma control and maintaining it despite inhaled steroid reduction. The omalizumab group did not have significant higher incidence of adverse events over placebo.

The preceding studies are included in the most current and largest analysis of safety data, published in 2009 and including at least 7500 patients who participated in completed Phase I – III studies of omalizumab [25]. In this analysis, data were obtained on three groups: 2342 patients in placebo-controlled allergic asthma studies in adolescents and adults, 2004 patients in standard-therapy controlled studies in adolescents and adults, and 6130 patients in all other controlled studies for pediatric and non-asthma indications. In all, 2484 patients received omalizumab for at least 24 weeks including 555 patients who received omalizumab for at least 52 weeks.

The studies included in the analysis are listed in **Table 1**. The subjects were predominantly Caucasian, females with ages from 18 to 64. Baseline mean total IgE in the omalizumab treated groups was 184.4 – 213.4 IU/ml [25].

The most common adverse events (**Table 2**) observed with omalizumab in placebo-controlled studies were nasopharyngitis (23.2%), upper respiratory tract infection (17.6%), headache (19.3%), sinusitis (12.6%), influenza (9.2%), pharyngolaryngeal pain (8.2%) and back pain (8%). The frequency of these events did not differ from the placebo-treated groups. The adverse event profile was generally similar in the standard-therapy controlled studies [25].

The frequency of suspected drug-related adverse events was slightly higher in the omalizumab compared to the placebo group (9.2 vs 7.6%). There was no significant difference in the number of serious adverse events and adverse events causing discontinuation between the two groups [25].

Laboratory values obtained during clinical trials did not show significant abnormalities and were similar in the omalizumab and control groups. Mild differences between the omalizumab and control groups were seen in the incidence of lower hemoglobin after treatment (10 vs 8.3%), elevated eosinophil count (8.4 vs 14.2%) and positive leukocyte count in urinalysis (19 vs 15.9%) [25].

Another current systematic review of placebo-controlled studies of omalizumab as add-on therapy to inhaled steroids also analyzed the safety data. Eight trials involving 3429 participants were analyzed and no significant difference in the frequency of serious adverse effects was seen between omalizumab (3.8%) and placebo (5.3%). No increased risk of hypersensitivity reactions, cardiovascular effects and malignant neoplasms were found. The authors concluded that omalizumab had an acceptable safety profile [26].

4. Specific issues

4.1 Malignancy

Malignancy is understandably a major concern for patients and practitioners considering long-term use of omalizumab. Data are available on the incidence of malignancy in Phase I – III studies involving 5015 patients [25]. The analysis found malignancy reported in 0.5% (25 of 5015) of patients in the omalizumab-treated group versus 0.18% (5 of 2854) in the control group.

A total of 24 out of the 25 malignancies reported in the omalizumab group were solid tumors. There was one case of non-Hodgkin's lymphoma. The most common malignancies were skin (non-melanoma), breast and prostate. Overall, 20 of the 25 cases were diagnosed within the first year of treatment. Four cases were believed to have been present before participation in the clinical trials with documented signs or symptoms prior to enrollment. The five cases diagnosed after 1 year of treatment were parotid gland, prostate, pancreatic, colon and basal cell carcinomas [25].

The relative risk of malignancy in both the omalizumab and control groups was considered to be consistent with and not significantly higher than the relative risk in patients with asthma [27-29]. At this time, a causal relationship between omalizumab and malignancy has not been found. There is ongoing surveillance for cases as the use of omalizumab increases.

4.2 Anaphylaxis

Analysis of post-marketing adverse events spontaneously reported to the FDA and the manufacturer as well as reports published in the literature from June 2003 to December 2006 showed a 0.2% estimated frequency of anaphylaxis based on 124 cases identified out of an estimated exposure of 57,300 patients. Anaphylaxis has presented as bronchospasm, urticaria and/or angioedema of the throat or tongue, hypotension and syncope. Pulmonary involvement was reported in 89% of the cases. Hypotension or syncope was reported in 14% of cases. Fifteen percent of the reported cases resulted in hospitalization. A previous history of anaphylaxis unrelated to omalizumab was reported in 24% of the cases. 39% occurred with the first dose, 19% with the second and 10% with the third dose. Cases of anaphylaxis after 1 year of treatment were also identified. In one case, anaphylaxis occurred after a 3 month gap in treatment in a patient who had already received 39 doses over 19 months of continuous therapy. Although anaphylaxis was rare, many cases were unusual with delayed onset beyond 2 h and protracted progression of symptoms over hours. No predictive risk factors for the delayed onset or protracted progression were identified.

The time to onset of anaphylaxis in these cases was up to 30 min in 35%, > 30 and up to 60 min in 16%, > 60 and up to 90 min in 2%, > 90 and up to 120 min in 6%, > 2 h and up to 6 h in 5%, > 6 h and up to 12 h in 14%, > 12 h

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Table 1. Summary of studies in safety analysis.

Study	Patient population	Age range (years)	Number of patients (randomized)		Number of patients (safety analyzable)		Duration (weeks)
			Omalizumab	Control	Omalizumab	Control	
Placebo-controlled							
2306 [24]	Allergic asthma	12 – 75	245	237	245	237	28
2304 [20]	Allergic asthma and rhinitis	12 – 74	209	196	209	196	28
008C [15]	Allergic asthma	12 – 74	268	257	268	257	28
008 Extension [19]	Allergic asthma		245	215	245	215	24
009C [17]	Allergic asthma	12 – 76	274	272	274	272	28
009 Extension [36]	Allergic asthma		254	229	254	229	24
011C [37]	Allergic asthma	12 – 75	176	165	174	165	32
0112 [3]	Allergic asthma	18 – 50	22	23	22	23	16
No. of patients					1192	1150	
Total patient-yrs*					886.0	800.8	
Mean pt. exposure (years)					0.73	0.70	
Standard-therapy controlled							
IAO4 [38]	Allergic asthma	12 – 75	206	106	202	89	52
ALTO	Allergic asthma	12 – 75	1169	591	1136	577	24
No. of patients					1338	666	
Total patient-yrs					698.5	349.6	
Mean pt. exposure (years)‡					0.52	0.52	
All controlled studies							
010C [16]	Allergic asthma	5 – 12	225	109	225	109	28
D01 [22]	Seasonal allergic rhinitis	6 – 17	116	109	114	108	24
006 [10]	Seasonal allergic rhinitis	12 – 75	400	136	400	136	12
007 [39]	Seasonal allergic rhinitis	17 – 66	165	86	164	86	8
0113	Atopic dermatitis	6 – 16	16	9	16	9	24
0114 [21]	Perennial allergic rhinitis	12 – 75	144	145	144	145	16
ALTO	Allergic asthma	6 – 11§	93	46	85	43	24
No. of patients					1148	636	
No. of patients (all controlled studies)¶					3678	2452	
Total patient-yrs					1934.5	1363.7	
Mean pt. exposure (years)					0.53	0.56	

Adapted from [25].

*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; pediatric patients were included in all controlled studies.

¶All controlled studies also included placebo-controlled and standard therapy controlled allergic asthma studies.

C: Core study.

and up to 24 h in 8%, > 24 h and up to 4 days in 5% and unknown in 9% (Limb 2007) [30]. Eighteen of twenty-three patients who experienced anaphylaxis had recurrence of symptoms of anaphylaxis when re-challenged with omlaizumab.

The mechanism of these atypical features is unclear. There is some doubt whether the reported events occurring after months or a year of treatment are true anaphylaxis episodes and continued surveillance is needed. Although the manufacturer package insert only recommends observing patients for the 'appropriate period of time', many practitioners choose to keep patients in the office for up to 2 h. Due to the unpredictability of the reported onset and appearance of

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Table 2. Most common adverse events (≥ 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 (n = 1192)	Placebo (n = 1150)	Omalizumab (n = 1338)	Control (n = 666)	Omalizumab (n = 3678)	Control (n = 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)	160 (14.6)	160 (12)	74 (11.1)	373 (10.1)	295 (12)
Influenza	110 (9.2)	114 (9.9)	43 (3.2)	19 (2.9)	184 (5)	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)
Viral infection	45 (3.8)	46 (4)	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)	234 (6.4)	147 (6)
Cough	81 (6.8)	103 (9)	56 (4.2)	13 (2)	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)	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)	25 (3.8)	570 (15.5)	383 (15.6)
Gastrointestinal disorders						
Diarrhea	59 (4.9)	53 (4.6)	41 (3.1)	5 (0.8)	124 (3.4)	73 (3)
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)	92 (8)	44 (3.3)	10 (1.5)	162 (4.4)	117 (4.8)
Arthralgia	72 (6)	56 (4.9)	41 (3.1)	4 (0.6)	138 (3.8)	73 (3)
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)	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

Adapted from [25].

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anaphylaxis, many practitioners also provide epinephrine autoinjectors for possible delayed anaphylaxis outside of the office.

4.3 Other hypersensitivity reactions

In the clinical trials, possible hypersensitivity reactions, aside from anaphylaxis, reported in clinical studies include symptoms suggesting immediate-type hypersensitivity with urticaria and other forms of rash. The incidence of urticaria was low and did not differ between the treatment and control groups. The frequency of pruritus and all kinds of rash was 6.9% in the omalizumab group and 5.3% in the control group. No measurable anti-omalizumab antibodies were found in the omalizumab treated groups [25].

Symptoms and signs suggestive of a serum sickness type reaction including fever, arthralgia and rash were not observed in the clinical studies but have been reported in post-marketing surveillance. According to the manufacturer, some patients have experienced a constellation of signs and symptoms including arthritis/arthralgia, rash (urticaria or other forms), fever and lymphadenopathy with an onset 1 – 5 days after the first or subsequent injections of omalizumab. These were considered similar to the presentation of serum sickness but circulating immune complexes or a skin biopsy consistent with a type III reaction were not seen with these cases (Novartis).

4.4 Parasitic infections

Parasitic infections are usually associated with high blood levels of eosinophils and IgE. IgE binds to helminthic parasites and induces an antibody-dependent, cell-mediated cytotoxic response against them. Eosinophils bind to the IgE and its granules degranulate and release products toxic to the parasites. A primary concern, therefore, was that anti-IgE treatment would have a potential undesirable effect of predisposing to parasitic infections.

The clinical studies have shown only rare parasitic infections with no difference between omalizumab and control groups (0.19 vs 0.16%) [25]. An exploratory, randomized, double-blind, placebo-controlled study was conducted in Brazil to determine if omalizumab therapy increased the incidence of parasitic infections. A total of 137 subjects at high risk for geohelminth infection were enrolled and received pre-study anti-helminthic treatment followed by 52 weeks of omalizumab or placebo. Results showed only a mild increase in incidence of geohelminth infection in the omalizumab group (50%) compared to the placebo group (41%) (odds ratio (OR) 1.47, 95% CI 0.74 – 2.95, one-sided p = 0.14; OR (adjusted for study visit, baseline infection status, gender and age) 2.2 (0.94 – 5.15); one-sided p = 0.035), Time to first infection (OR 1.30, 95% CI 0.79 – 2.15, one-sided p = 0.15) was similar between treatment groups. The authors concluded that omalizumab did not appear to affect morbidity due to helminth infection as assessed by clinical and laboratory adverse events, infection severity and response to anti-helminthic medications as measured by stool egg counts [31].

4.5 Cardiac

In 2009, the FDA issued an early communication that interim safety analysis of the EXCELS study data showed an increased frequency of cardiovascular and cerebrovascular adverse events in the omalizumab treatment group [32]. The interim data submitted by the manufacturer suggested a disproportionate increase in ischemic heart disease, arrhythmias, cardiomyopathy and cardiac failure, pulmonary hypertension, cerebrovascular disorders, and embolic, thrombotic and thrombophlebitic events. The FDA has not recommended any changes in the prescribing information at this time.

Cardiac and cerebrovascular events were not seen in previous analyses of clinical trial data. The specific information on the cases mentioned in the FDA early communication has not been published in the literature. The final analyses from the EXCELS investigators as well as the FDA will hopefully provide more information and guidance on this issue. In the meantime, patients receiving omalizumab should be closely monitored for cardiac and thromboembolic events.

4.6 Churg-Strauss

Churg-Strauss syndrome is a systemic vasculitis of small and medium blood vessels with manifestations in the pulmonary, gastrointestinal, neurologic, cardiac, renal and dermatologic systems. Many patients with this disorder present with symptoms of severe asthma controlled only with systemic steroids.

The reports of Churg-Strauss syndrome in patients receiving omalizumab appear to be related to unmasking of the underlying syndrome initially diagnosed as severe asthma. When oral steroids are reduced or discontinued as patients improve on omalizumab, worsening asthma, rash and eosinophilia may surface [33-35].

4.7 Thrombocytopenia

Thrombocytopenia has been observed in animal studies with cynomolgus monkeys but has not been observed in human clinical trials and post-marketing surveillance.

4.8 Pregnancy

Omalizumab is designated as a Pregnancy Category B drug. This category indicates that animal reproduction studies have failed to demonstrate a risk to the fetus and no adequate and well-controlled studies in pregnant women or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester. The EXPECT registry is an observational pregnancy registry that is following women who have received omalizumab prior to conception or during pregnancy. It aims to assess pregnancy outcomes, incidence of spontaneous fetal loss and potential risk to newborns. Data from completed Phase I – III clinical studies

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include 27 cases of pregnancy in the omalizumab treatment groups and 2 pregnancies conceived in women whose spouses were receiving omalizumab. There was no significant difference in outcomes (including normal deliveries, elective abortions, spontaneous abortions) between the omalizumab and control groups [25].

5. Conclusion

Published safety data from controlled clinical trials and post-marketing surveillance since the introduction of omalizumab in 2003 to the present suggest that omalizumab is safe and well-tolerated. Earlier concerns about malignancy appear to be alleviated by a low incidence and lack of evidence of a causal effect. Anaphylaxis is rare but may appear after long-term treatment. The risk of cardiac and cerebrovascular events is currently being investigated as part of the long-term EXCELS safety study.

6. Expert opinion

Omalizumab has been available for asthma therapy for 7 years now and has proven to be an effective addition to the therapeutic regimen for allergic asthma. It has been included in the most current update of the National Heart, Lung and Blood Institute's Guidelines for the Diagnosis and Management of Asthma (Expert Panel Report 3). It is recommended in steps 5 and 6 of the stepwise approach to long-term asthma management. Although cost and insurance coverage issues still limit its use, it is being utilized by an increasing number of primary care and specialist physicians.

Safety data from completed clinical trials involving up to 7500 subjects and from post-marketing experience have been analyzed and published. The most common adverse events reported, including nasopharyngitis, upper respiratory infection and headache, were mild and are commonly reported in asthma clinical trials and probably reflect a predisposition to these events in atopic patients rather than a causal relation to omalizumab.

The possible association of malignancy with omalizumab has been of greatest concern to patients and physicians. Analysis of clinical study data shows that the incidence is rare and the relative risk of cancer with omalizumab is not significantly different from that expected in general population with asthma.

The incidence of anaphylaxis in post-marketing data on ~ 57,300 exposures from 2003 to 2006 was very low at 0.2%. These included patient-generated reports of anaphylaxis that did not fit the typical definition of anaphylaxis as an event of fast onset usually occurring with the first few exposures. The onset of symptoms were reported as occurring up to 4 days after injection or in patients who had been receiving treatment for at least 1 year. Eighteen of twenty-three patients who experienced anaphylaxis had recurrence of symptoms of anaphylaxis when re-challenged with omalizumab. At this time, practitioners should still be alert to possible reactions even in patients on long-term omalizumab therapy.

IgE is believed to have a protective effect against parasitic helminth infections. This has led to concern about omalizumab predisposing patients to parasitic infections by blocking IgE. However, there has been no observed increase in parasitic infections in both clinical trials and post-marketing surveillance. A 52-week study specifically designed to address this concern showed only a mild increase in infections in the omalizumab group and no increased severity or decreased response to treatment in the affected patients.

There has been no increased incidence of thrombocytopenia, serum sickness-like symptoms (fever, arthralgia, rash) or urticaria in clinical studies or post-marketing experience. The occurrence of Churg-Strauss vasculitis in patients receiving omalizumab is felt by most experts to be due to unmasking of a pre-existing vasculitis when systemic steroids are reduced or stopped.

The recent early communication from the FDA indicating that interim analysis of the EXCELS long-term safety study showed an increase in cardiac and cerebrovascular events in omalizumab treated patients compared to those on standard therapy is of concern. These types of events were not observed in the completed clinical trials. The release of more specific case information and a final analysis is forthcoming.

There is a consensus among allergy specialists that the use of omalizumab is safe and effective. The EXCELS study data and analysis will hopefully provide information that will be useful and reassuring to the practitioner who regularly prescribes omalizumab.

Ongoing controlled trials are investigating the benefits of omalizumab in chronic urticaria, atopic dermatitis and food allergies. If the FDA approves new indications, the number of omalizumab prescriptions may rise in the next decade. Increased exposure numbers will provide more data for safety analysis. As with any drug, continued vigilance by regulatory authorities and physicians is crucial to ensure that long-term use of omalizumab does not produce any harm.

Declaration of interest

J Corren participates in clinical trials for Genentech and Novartis and is also a consultant for Novartis.

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