

Review

How safe are the biologicals in treating asthma and rhinitis?

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Abstract

A number of biological agents are available or being investigated for the treatment of asthma and rhinitis. The safety profiles of these biologic agents, which may modify allergic and immunological diseases, are still being elucidated. Subcutaneous allergen immunotherapy, the oldest biologic agent in current use, has the highest of frequency of the most serious and life-threatening reaction, anaphylaxis. It is also one of the only disease modifying interventions for allergic rhinitis and asthma. Efforts to seek safer and more effective allergen immunotherapy treatment have led to investigations of alternate routes of delivery and modified immunotherapy formulations. Sublingual immunotherapy appears to be associated with a lower, but not zero, risk of anaphylaxis. No fatalities have been reported to date with sublingual immunotherapy. Immunotherapy with modified formulations containing Th1 adjuvants, DNA sequences containing a CpG motif (CpG) and 3-deacylated monophospholipid A, appears to provide the benefits of subcutaneous immunotherapy with a single course of 4 to 6 preseasonal injections. There were no serious treatment-related adverse events or anaphylaxis in the clinical trials of these two immunotherapy adjuvants. Omalizumab, a monoclonal antibody against IgE, has been associated with a small risk of anaphylaxis, affecting 0.09% to 0.2% of patients. It may also be associated with a higher risk of geohelminth infection in patients at high risk for parasitic infections but it does not appear to affect the response to treatment or severity of the infection.

Clinical trials with other biologic agents that have targeted IL-4/IL-13, or IL-5, have not demonstrated any definite serious treatment-related adverse events. However, these clinical trials were generally done in small populations of asthma patients, which may be too small for uncommon side effects to be identified. There is conflicting information about the safety TNF-alpha blocking agents, which have been primarily used in the treatment of rheumatoid arthritis, with serious infections, cardiovascular disease and malignancies being the most frequent serious adverse events. An unfavorable risk-benefit profile led to early discontinuation of a TNF-blocking agent in a double-blind placebo controlled of severe asthmatics.

In summary, the risk of anaphylaxis and other treatment-related serious events with of all of the biological agents in this review were relatively small. However, most of the clinical trials were done in relatively small patient populations and were of relatively short duration. Long term studies in large patient populations may help clarify the risk-benefit profile of these biologic agents in the treatment of asthma.

Introduction

A number of therapeutic agents are available to treat the symptoms and inflammation associated with allergic rhinitis and asthma. Despite the proven efficacy of these medications, there continues to be some patients whose asthma [1] or rhinitis [2] is not well controlled. In addition, medications currently available for allergic rhinitis and asthma treatment appear to be are only effective while taken and do not appear to provide a sustained benefit after discontinuation [3]. Limitations of current medications and a greater understanding of the pathogenesis of allergic disease, has lead to the development of number of a novel therapeutic approaches as well as renewed interest in an old therapeutic approach, specific allergen immunotherapy. Novel therapeutic approaches that have been used in the treatment of allergic rhinitis and asthma include: omalizumab, alternate immunotherapy routes such as sublingual, modified allergen immunotherapy

vaccines, anti-interleukin 5 (mepolizumab), interleukin-4 variant (pitrakinra) and tumor necrosis factor (TNF- α) blocking agents. The intent of this paper is to review the safety of these novel therapeutic approaches (see table 1 for summary of biological agents reviewed). Although the focus of the review is safety, there will be some discussion of the efficacy of these biological agents.

Definition and incidence of anaphylaxis

One of the difficulties in evaluating the safety of biologics is that some of the suspected adverse events may be related to the disease itself. For example, an increased risk of malignancy has been reported with TNF-alpha blockers, which are used primarily in the treatment of rheumatoid arthritis (RA). A systematic review and meta-analysis of 9 clinical trials that included 3493 RA patients treated with the anti-TNF-alpha antibodies, inflixumab or adalimumab, found a dose-related increase in malignancies

Table 1: Summary of biological agents used in the treatment of asthma and allergic rhinitis

Biological agent	Disease studied	Target	Mechanisms	Safety	Efficacy
SCIT	AR & asthma	Specific aeroallergens or venom	Several immune changes including \uparrow IL-10 & TGF- β . isotype switch to IgG	Surveys suggest; fatality rate of 1 in 2.5 million injections ³⁴⁻³⁶ & near fatal reaction rate of 5.4 per 1 million injections ³⁷	Appears to depend on dose
SLIT	AR & asthma	Specific aeroallergens	Probably similar to SCIT	Most common AEs oral-mucosal symptoms AE less common than SCIT but cases of anaphylaxis have been reported	A consistent relationship with dose and efficacy has not been established ³⁹
MPL	AR	TRL4	Shift toward Th1 response	SRs reported in 1.6% of the 1736 patients in postmarketing surveillance survey ⁵⁰	Clinical efficacy seen in first treat season after 4 injection treatment course
CpG	AR	TRL9	Shift toward Th1 response	No serious treatment-related effects ⁴⁶	Clinical efficacy seen in 1 st & 2 nd treatment season after one 4 injection course ⁴⁶
Omalizumab	Asthma & AR	IgE	Prevents binding of IgE to mast cells and basophils, downregulation of IgE receptor on these cells	Anaphylaxis in 0.09 to 0.2% of patients ^{19,20}	Efficacy in medication reduction & exacerbation in asthma, clinical improvement in AR
Mepolizumab	Asthma	IL-5	Blocks binding of IL-5 to α receptor on eosinophils	One episode of hypotension after infusion in EE study ⁵⁷	No significant improvement in asthma ⁵⁵
Pintrakinra ⁵⁸	Asthma	IL-4R α receptor	Competes with IL-4 and IL-13 for binding to the receptor	Non-neutralizing IgG anti-pintrakinra antibodies in ~30% of pts	Increased PD ₂₀ in methacholine challenge & asthma AE & beta-agonist use
Etanercept	Asthma	TNF-alpha	soluble TNF-alpha receptor	No significant treatment-related AE is asthma ⁵⁹ but increased risk of serious & opportunistic infection in rheumatologic disease	Increased markers of TNF-alpha activity & improved clinical outcomes in refractory asthma ⁵⁹

SCIT = subcutaneous immunotherapy, SLIT = sublingual immunotherapy, AR = allergic rhinitis, MPL = -deacylated monophospholipid A, CpG = immunostimulatory oligonucleotide sequence of DNA containing a CpG motif, TNF-alpha = tumor necrosis factor alpha, AE = adverse event, SAE = serious adverse event, EE = eosinophilic esophagitis, PD₂₀ = Provocative Dose, which produces a decrease in FEV1 by 20% from the initial value or baseline value

compared with the control groups with a pooled odds ratio of 3.3 (95% confidence interval [CI], 1.2-9.1) [4]. This increased rate of malignancy was not seen in another study that compared the incidence of malignancy and cardiovascular disease in two large RA observational databases: BIOBADSER, a registry for safety of biologics, which included 4459 RA patients on TNF-alpha blocking agents in 100 centers who were followed from 2001 to 2006 and EMECAR, an external RA cohort (n = 789) established to define the characteristics of the disease and to assess comorbidity [5]. In the EMECAR registry, during the period of 1999 to 2005, a TNF-alpha blocking agent was given to 1.4%, 10.6% and 16.8% of the patients in 2000, 2003 and 2005, respectively. A higher incidence of malignancies was found in the EMECAR database patients, which included a minority receiving TNF-alpha blocking agents, compared with the BIOBADSER registry, in which all received a TNF-alpha blocking agents there was a higher incidence of malignancy in EMECAR vs. BIOBADSER (Relative Risk (RR) 2.9) and a lower BIOBADSER by EMECAR cancer-related mortality ratio, 0.36 (0.10-1.30).

Likewise, atopy and asthma have been identified as risk factors for anaphylaxis, the most severe and potentially life-threatening reaction associated with the biologics discussed in this review [6]. The incidence of anaphylaxis appears to be greater in the asthmatic population and this may be dependent on the severity of asthma. A review of a large patient database in the United Kingdom was performed to determine the incidence of anaphylaxis in the asthmatic and general population [7]. Specific Read codes were used to identify potential cases of anaphylaxis. All patients (10-79 years), who had at least one year of enrollment with a general practitioner and one health contact in the previous year during the period of 1996-2005 were included. Two cohorts were identified: asthmatic patients (791,225 person-yrs of follow-up) and the general population (884,745 person-years of follow-up). Within the asthmatic cohort, a subset of severe asthmatics, were identified based on meeting any of the following 4 criteria: '

1. ≥ 1 asthma hospitalization
2. ≥ 12 canisters of inhaled beta-agonists a year
3. ≥ 3 prescriptions of oral corticosteroids a year,
4. ≥ 3 classes of asthma medication a year

There were a total of 224 cases of anaphylaxis: 170 in the asthma population and 54 in the general population. The anaphylaxis incidence rate (cases/100,000 person-years) was highest in the severe asthmatic group: 43.1 in severe asthma patients, 15.4 in non-severe asthma patients and

6.1 in the general population. Compared to the general population, the age-gender adjusted RR for anaphylaxis was greater in both the severe asthmatic patients (RR 7.2, 95% confidence interval (CI), 5.0--10.3) and non-severe asthmatic patients (RR 2.5, 95% CI, 1.8--3.5). The authors concluded that there may be an increased risk of anaphylaxis in asthmatic patients that may be dependent on the severity of asthma.

Another variable and difficulty in interpreting the safety of biologics in research and postmarketing surveillance is that there is no universal agreement on the definition of anaphylaxis or the criteria for its diagnosis. In an attempt to resolve this problem, the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network convened a meeting, which included representatives from multiple organizations and 3 continents, with the intent of developing a universally accepted definition of anaphylaxis and establishing clinical criteria that would accurately identify cases of anaphylaxis [8]. The working group developed three sets of criteria for the diagnosis of anaphylaxis (table 2). These criteria are used in some of the studies reviewed in this paper. However, in many studies and reviews, particularly ones involving allergen immunotherapy, the criteria for diagnosing anaphylaxis is not clear. Recognizing that adverse reactions to biological agents may be distinctly different from side-effects from chemicals and drugs, a classification system for adverse reactions to these agents has been proposed (table 3) [9]. This classification distinguishes five different categories:

Type α reactions due to high cytokine levels, type β reactions due to a hypersensitivity reaction against the biological agent, type γ reactions due to immune or cytokine imbalance syndromes, type δ reactions due to cross-reactivity between the biological agent's target and cells that express similar or identical antigens and type ϵ reactions, which do not directly affect the immune system.

Omalizumab

One of the most studied biologics for the treatment of asthma and rhinitis is omalizumab. Omalizumab is a 95% humanized monoclonal antibody (mAb) that binds to the Fc portion of the circulating immunoglobulin E (IgE) molecule preventing it from attaching to the high affinity IgE receptor, Fc ϵ R1. Omalizumab produces significant and rapid reductions in free serum IgE (up to 99%) [10]. One study demonstrated a 96% reduction in mean serum IgE level three days after omalizumab administration [11]. With continued treatment there is subsequent downregulation of the Fc ϵ R1 expression on several cell types that occurs over the next 4 to 6 months [12,13]. Omalizumab has been shown to be effective in the treatment of allergic asthma and seasonal and perennial rhinitis [14-17]. It is currently approved by the United States

Table 2: Clinical criteria for diagnosing anaphylaxis⁸

<p>Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:</p> <p>AND AT LEAST ONE OF THE FOLLOWING</p> <p>2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):</p> <p>3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):</p>	<p>I. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)</p> <p>a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)</p> <p>b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)</p> <p>a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)</p> <p>b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)</p> <p>c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)</p> <p>d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)</p> <p>a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*</p> <p>b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline</p>
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PEF = Peak expiratory flow; BP = blood pressure.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg / [2 times age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, 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*, 2006:391-7.

(US) Food and Drug Administration (FDA) for the treatment of moderate-to-severe persistent allergic asthma in adults and children 12 years and older. Omalizumab is also suggested as a treatment consideration for allergic asthmatics who are not well controlled with the combination of a medium-dose inhaled corticosteroid and a long-acting beta-agonist in the recently published expert panel guidelines on diagnosis and management of asthma [18]. These guidelines note that omalizumab is the only adjuvant therapy to demonstrate added efficacy to the combined regimen of a high-dose inhaled corticosteroid and a long-acting beta agonist [19].

The most common adverse reaction from omalizumab is injection-site pain and bruising but the package insert contains warnings regarding malignancies, geohelminth infections and a "black box" warning about anaphylaxis.

A "black box warning is the highest level of 5 possible warning categories found in pharmaceutical package inserts [20]. It is recommended, in the informed consent process, that patients be specifically informed that a medication has a "black box" warning and the reason for the "black box" warning be provided [20]. The "black box" warning on anaphylaxis (type β effect) was recently added

Table 3: Proposed classification of adverse side effects of biological agents⁹

Classification	Mechanism (s)	Clinical features
Type α	High cytokine & cytokine release syndrome	Symptoms will depend on the cytokine or cytokine being targeted e.g., high levels of INF-α may cause 'flu-like symptoms and anti- CD3 (muromunab) may induce cytokine release syndrome, which may include the following symptoms: flushing, arthralgias, capillary leak syndrome with pulmonary edema, encephalopathy, and severe gastrointestinal symptoms
Type β	Hypersensitivity	Immediate (IgE) Delayed (IgG or T cell)
Type γ	Immune or cytokine imbalance syndrome	Autoimmunity Allergic/atopic disorders Impaired function (immunodeficiency)
Type δ	Cross-reactivity	Will depend on the function of the cross-reacting antigen; e.g., Acneiform eruptions are commonly seen with cetuximab, an anti- epidermal growth factor receptor (EGFR) mAb possibly due to cross-reactivity between skin ERFr.
Type ε	Non-immunologic side-effects	Varies with the function of the biological agent; Interferon-α frequently associated with neuropsychiatric adverse effects

to Xolair® (omalizumab) package insert at the direction of the FDA in response to the spontaneous postmarketing adverse event-reports. A review of spontaneous postmarketing adverse events submitted to the FDA and Genentech/Novartis suggested that at least 0.2% of patients who received Xolair® (omalizumab) experienced anaphylaxis between June 2003 and December 2006 [21]. The review also noted that many of the cases were delayed in onset and characterized by a protracted progression. An Omalizumab Joint Task Force of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology (OJTF) also reviewed the postmarketing surveillance data from the same time period [22]. Using the definition of anaphylaxis proposed at a 2005 multidisciplinary symposia [8], the OJTF concluded that 35 patients had 41 episodes of anaphylaxis associated with omalizumab administration. During this time period 39,510 patients received omalizumab, thus the anaphylaxis-reporting rate was 0.09% of patients. Of those 36 events, for which the time of reaction was known, 22 (61%) reactions occurred in the first 2 hours after one of the first 3 doses and within 30 minutes in 5 (14%) of the events that occurred after the fourth or later doses.

The OJTF report recommends an observation period of 2 hours for the first 3 injections and 30 minutes for subsequent injections because 75% of the anaphylactic reactions occurred within these time periods. The OJTF report also provided recommendations on patient education regarding anaphylaxis.

Omalizumab and malignancies

In the initial Xolair® (omalizumab) clinical trials, a higher incidence of malignancies was observed in the group that received Xolair® (omalizumab): 20/4127 (0.5%) Xolair® (omalizumab)-treated patients compared with 5/2236 (0.2%) patients in the control group [23]. The observed malignancies in the Xolair® (omalizumab)-treated patients were heterogeneous in tumor type and organ. There were no new cases of lymphoproliferative disease and no cases were considered drug-related by a panel of blinded independent oncologists. The majority of cases (60%) were diagnosed within 6 months of treatment [24]. Overall, the clinical data did not suggest a causal relationship between Xolair® (omalizumab) and malignancy. However, the Xolair® (omalizumab) package insert does note that "the impact of longer exposure to Xolair or use in patients at higher risk for malignancy (e.g., elderly, current smokers) is not known" [24]. A multicenter, prospective, observational cohort study titled Evaluating the Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma (EXCELS) that includes approximately 5000 Xolair® (omalizumab) -treated and 2500 with moderate to severe asthma not receiving

Xolair® (omalizumab), designed to evaluate the long term safety of Xolair® (omalizumab) is currently in progress [25].

Cardiovascular and Cerebrovascular disease

On July 16, 2009, the FDA issued a statement indicating that review of the EXCELS study's interim safety data showed an excess of cardiovascular and cerebrovascular events in the patients on Xolair® (omalizumab) compared with the asthma control group [26]. The interim data submitted by the manufacturer, Genentech, suggests a disproportionate increase in ischemic heart disease, arrhythmias, cardiomyopathy and cardiac failure, pulmonary hypertension, cerebrovascular disorders, and embolic, thrombotic and thrombophlebotic events in patients treated with on Xolair® (omalizumab) compared with the group that did not receive this medication.

Being an observational study, many factors need to be evaluated before determining the relationship between Xolair® (omalizumab) and these adverse events. Considering that Xolair® (omalizumab) is indicated for moderate-to-severe asthma and the prescribing/administration process can involve a fair amount of physician and staff time, as well as, patient time and expense, it is likely there were considerable differences between the Xolair® (omalizumab)-treated group and the asthma control group in terms of asthma severity and co-morbidities. These differences may include oral corticosteroid use, underlying cardiovascular disease or hypertension and may account for the differences in adverse events. The FDA did not recommend any changes to the prescribing information (i.e., package insert) on Xolair® (omalizumab) but did recommend that patients and physicians be aware that the new information from the EXCELS study may suggest a risk of cardiovascular and cerebrovascular events.

Omalizumab and geohelminth infection

Considering that IgE may have a protective role in the immunity against parasitic infections, there are concerns that anti-IgE antibodies might impair this protective effect and increase susceptibility to parasite infection (type γ effect). The Xolair® (omalizumab) package insert recommends that patients at high risk for geohelminth infections be monitored for such infections while on treatment citing a 1-year study of patients at high-risk for geohelminth infections, in which the odds ratio for infection in the Xolair® (omalizumab)-treated group was 1.96 with a 95% CI (0.88-4.36) compared with the placebo control. Similar results were seen in a 1-year double-blind, placebo-controlled (DBPC) trial of 137 subjects (12-30 years) at high risk of geohelminth infection, who were randomized to receive 52 weeks of treatment with Xolair® (omalizumab) or placebo [27]. After adjusting for baseline infection status, gender, age and study visit, there was

a significant difference in the incidence of intestinal geohelminth infection between the 2 groups (adjusted OR 2.2 95% CI; 0.94-5.15, $p = 0.035$.) However, there was no increased morbidity in terms of laboratory or clinical adverse events in the Xolair® (omalizumab)-treated patients compared with the placebo group. The response to anti-geohelminth treatment was no different from the placebo group in both studies. These studies suggest that individuals at high-risk for geohelminth infections may be a greater risk for infection during Xolair® (omalizumab) treatment but the infection severity and response to treatment is similar to placebo-treated patients.

Allergen immunotherapy

Although this form of therapy is nearly 100 years old, it remains one of the only disease-modifying treatments for allergic asthma and rhinitis [28-30]. Subcutaneous immunotherapy (SCIT) with unmodified allergen extracts is currently the most widely used modality worldwide. However, sublingual immunotherapy (SLIT) has been prescribed with increasing frequency in the past 25 years, particularly in certain parts of Europe. SCIT efficacy appears to be dose dependent and the immunological mechanisms responsible for the clinical efficacy of immunotherapy are still being elucidated. Immunological changes associated with SCIT include induction of T regulatory cells, increase in allergen-specific IgG4, increase in IL-10 and TGF- β production and down-regulation of the TH-2 response [31]. Allergen immunotherapy has been shown to decrease the recruitment of mast cells, basophils and eosinophils in the skin, nose, eye and bronchial mucosa, following provocation or natural exposure to allergens blocking both the immediate and late-phase allergic response [32]. Adverse reactions from SCIT include common local injection site reactions to rare life-threatening anaphylaxis and death. The frequency of systemic reactions with SCIT appears to be related to the schedule and dose. In one review of 38 SCIT studies the systemic reaction (SR) rate with conventional build-up schedules (single dose increase per visit) ranged between 0.05% to 3.2% of injections and 0.8% to 46.7% of patients (mean, 12.92%) [33]. In a 1-year prospective study of a multi-physician practice, there were 98 SRs in 96/4578 (2%) patients [34]. There was a significant difference in per injection SR rate between the maintenance (1 per 1831 visits) and build-up phase (1 per 1063 visits, $p = 0.01$).

Accelerated immunotherapy build-up schedules for inhaled allergens may be associated with greater risk, although this has not been consistently demonstrated with cluster schedules (2 to 3 injections per visit on non-consecutive days). A recent review of accelerated immunotherapy schedules found the SR rate for rush immunotherapy (multiple injections given over 1 to 3 days)

ranged from 15% to 100% of patients without premedication and 14.7% to 38% of patients with premedication [35]. A similar range was seen with cluster schedules, although one study specifically designed to compare the safety of a cluster schedule with a conventional schedule found no significant difference in the SR rate between the groups and the clinical and objective parameters improved 6 weeks sooner in the cluster group [36].

Severe reactions from SCIT are relatively rare but fatal reactions (FR) have been reported at a rate of 1 in 2 to 2.5 million injections or an average of 3.4 deaths per year in surveys of AAAAI membership that span the time period from 1945 to 2001 [37-39]. Symptomatic or poorly controlled asthma has been identified as a risk factor for a FR from SCIT. The most recent survey also assessed the frequency of SCIT near-fatal reactions (NFR) defined as severe respiratory compromise and/or fall in blood pressure requiring emergency treatment with epinephrine [40]. The incidence of unconfirmed NFRs was 23 per year or 5.4 events per one million injections. Important contributing factors for NFR included administration during peak of the allergy season (46% of respondents) and dosing errors (25% of respondents) Fifty-eight percent of the NFR received injections from the maintenance concentrate.

Sublingual immunotherapy

One of the purported advantages of SLIT over SCIT is greater safety. Like SCIT, the mechanisms of SLIT are still being elucidated but studies have suggested similar immunological changes with SLIT [41]. A number of studies have demonstrated the efficacy of SLIT in the treatment of allergic rhinitis and asthma, but the determinants of SLIT efficacy have not been clearly established. There did not appear to be a consistent relationship between dose and SLIT efficacy in a comprehensive review of 104 articles on SLIT [42]. In this review, there were 66 studies that provided some information on SLIT safety. In these 66 studies, there were approximately 1,181,000 doses given to 4378 patients. There were no fatalities or events described as anaphylaxis, although there were 14 probable serious adverse events (7 were asthma reactions). Oral-mucosal reactions, considered a SLIT local reaction, were relatively common, affecting up to 75% of patients, and seen most frequently in the build-up phase. In the studies that specified the type of reaction, 169 of 314,959 (0.056% of doses administered) were classified as SRs. There were 244 moderate adverse events (AE) requiring dose adjustment or causing withdrawal from the study in 2939 patients treated for 4586 treatment years with 810,693 doses of SLIT (50 studies). The majority of these reactions were gastrointestinal symptoms, rhinoconjunctivitis, urticaria or some combination of these symptoms. There were no identified risk factors for SLIT adverse reac-

tions in this review. There did not appear to be a consistent relationship between adverse reactions and SLIT dose or induction schedule and the majority of studies were done in rhinitis/rhinoconjunctivitis patient with or without mild-to-moderate asthma. There were no studies in high risk patients (e.g., moderate to severe asthmatics).

Subsequent to this review, there have been several case reports of SLIT-associated anaphylaxis:

- One occurred on the 3rd day of build-up with a multi-allergen SLIT [43]
- One occurred on maintenance at the height of season [44]
- One occurred on the 4th day of a latex rush protocol [45].
- One occurred after a 3 week gap in maintenance treatment after taking a dose 6 times higher than prescribed. This reaction resulted in loss of consciousness and admission to the intensive care unit [46].

Four cases of SRs with SLIT have been reported in individuals who had to discontinue SCIT due to a SR [47,48]. Two cases occurred after the first dose of a grass tablet [48]. The other two cases occurred with the maintenance dose of SLIT administered as drops shortly after completing an ultrarush protocol [47].

Some of the factors in the above cases are risk factors that have been identified with SCIT: height of season, history of prior SRs, dose and schedule. Further studies are needed to identify and characterize SLIT risk factors.

Modified allergen vaccines and adjuvants

Efforts to develop safer and more effective allergen immunotherapy vaccines have resulted in several modifications to the allergen extracts. Allergoids are modified allergen extracts that have been processed in a way that reduces the extract's allergenicity while preserving its immunogenicity. Adjuvants have also been used to enhance the effectiveness of allergen immunotherapy primarily by shifting the immune response toward Th1 production. The two adjuvants that have been most extensively studied in the treatment of allergic rhinitis, are an immunostimulatory oligonucleotide sequence of DNA containing a CpG motif (CpG) and 3-deacylated monophospholipid A (MPL), both of which target toll-like receptors (TLR). Toll-like receptors play a key role in activating antigen-presenting cells and when stimulated can influence the Th1/Th2 cytokine balance. The receptor for CpG DNA is TLR9, which is primarily expressed on plasmacytoid dendritic cells [49]. Activation can lead production of IL-10, IgG

isotype switching and other inhibition of other immune responses mediated by Th2 cells. TOLAMBA, a TLR9 agonist, is a CpG adjuvant that is covalently linked to the major ragweed allergen Amb a 1. A randomized DBPC, phase 2 trial of 25 adults with ragweed-induced allergic rhinitis randomized to receive 6 increasing doses of TOLAMBA (0.06, 0.3, 1.2, 3.0, 6.0 and 12 mcg) or placebo before the ragweed season and followed through 2 ragweed seasons found no "pattern of vaccine-associated systemic reactions or clinically significant laboratory abnormalities" [50]. Although, there was no difference in the primary outcome, which was albumin level in nasal-lavage fluid after nasal allergen provocation, there was a significant reduction in total nasal symptom scores during the peak season in the TOLAMBA group compared with the placebo-treated patients in both the first and second ragweed season. A subsequent placebo-controlled trial of 738 subjects with ragweed-induced allergic rhinitis who were randomized to either a high dose regimen (TOLAMBA 3,9,30,30,30, 30 mcg), a low dose regimen (TOLAMBA 1,2,3,6,15,21, 30 mcg) or placebo reported that treatment "was well tolerated in all groups" and that there were no TOLAMBA-related serious adverse events [51]. On January 8, 2007 Dynavax Technologies Corporation announced that the analysis of interim one-year data from this two-year study (DARTT trial) indicated that there was "no measurable disease during the ragweed season in any of the study groups making it impossible to measure the therapeutic effect of TOLAMBA treatment and the study" [52]. Based on these results, Dynavax Technologies decided to discontinue development of TOLAMBA.

MPL, the other adjuvant used in allergen immunotherapy is derived from the lipopolysaccharide of *Salmonella Minnesota* R595. It contains lipid A, which is a TLR4 agonist, that has been shown to induce TH1 cytokines in human and animal studies. An allergen vaccine composed of a tyrosine-absorbed (delays absorption), glutaraldehyde-modified allergen (allergoid) containing the MPL adjuvant has been shown to provide significant improvement in clinical and immunological parameters in patients with seasonal rhinitis [53-55]. The dosing regimen was 4 doses (300,800, 2000, 2000 standardized units (SU) administered at 1-2 week intervals ending 2 to 4 weeks before the start of season. The highest dose and cumulative dose was equivalent to 24 mcg and 60 mcg of group 1 grass pollen allergen, respectively [53]. The treatment was well tolerated in the clinical trials with systemic adverse events occurring at a similar frequency in the active and placebo groups [53,56,57]. There were no serious or severe adverse events or anaphylactic reactions in these clinical trials. In a one-year postmarketing surveillance assessment of 1736 patients, who received a total of 8512 injections, systemic reactions were reported by 1.6%

of the patients [54]. Fourteen patients reported severe reactions but there were no instances of anaphylactic shock. One of the potential adverse effects of concern with Th1-inducing adjuvants is autoimmunity (type γ effect). In addition to the clinical immunotherapy trials, MPL has been used as an adjuvant in licensed vaccines for many years: Melacine® (Corixa Inc./Schering-Plough, Canada) and the human papillomavirus, Ceravarix® (Glaxo-Smith-Kline, UK). To date, there has been no evidence of increased incidence of autoimmune diseases in the populations that have been exposed to MPL.

In the past four years, there have been several clinical trials designed to study the efficacy and safety of MPL in the treatment of grass-pollen or ragweed-induced allergic rhinitis (Grass MATAMPL, RagweedMATAMPL, Allergy Therapeutics Ltd.) conducted in the US and Canada. However, the FDA placed a clinical hold on all of MPL-related vaccine studies in the US after a case of transverse myelitis was reported in the grass-pollen study.

Mepolizumab (anti-IL-5)

Mepolizumab is a high-affinity, humanized non-complement-fixing IgG₁mAb that blocks binding of IL-5 to the α chain receptor complex on eosinophils. IL-5 plays key role in eosinophilic differentiation, maturation, migration, activation and survival and it is highly expressed in bronchial alveolar lavage fluid and biopsies of asthmatics. Single dose and multiple dose (6 monthly) intravenous and subcutaneous mepolizumab toxicity studies in monkeys found no target organ toxicity or immunotoxicity with doses up to 300 mg/kg [58]. In a DBPC study of 363 asthmatics, symptomatic on inhaled corticosteroids, randomized to 3 infusions of either placebo, 250 mg or 750 mg of mepolizumab, there were no significant differences between the 3 groups in any of the clinical outcomes [59]. However there was a trend toward reduced exacerbations in the 750 mg dose group ($p = 0.065$). Side effects were similar in the three groups and there were no serious adverse events attributed to the study medication. The withdrawal rate due to adverse reactions was highest in the placebo group: placebo (5%), 250 mg (3.3%) and 750 mg (0.9%). Mepolizumab has also been used in small open-label studies of patients with eosinophilic disorders. In a study of 4 patients with hypereosinophilic syndrome, who received 3 infusions of up to 750 mcg of mepolizumab, there was a reduction in peripheral eosinophils and clinical improvement in all 4 patients [60]. The only reported medication-related AEs were fatigue and headache after the infusions. In another open label study of 4 patients with eosinophilic esophagitis treated with the same protocol, there was one episode of symptomatic hypotension 30 minutes after the 3rd infusion, which resolved with fluid replacement [61]. The investigators

questioned whether this was related to the infusion. Other symptoms reported in this trial included nausea, fatigue, headache, non-specific chest pain and cough. All patients reported improved clinical outcomes.

Essentially, there was one possible serious-adverse event (hypotension) and no evidence of cytokine imbalance syndrome (type γ effect) in the relatively small populations of patients in these mepolizumab clinical trials.

Interleukin-4 and Interleukin-13 Inhibition

Interleukin-4 (IL-4) and Interleukin-13 (IL-13) are cytokines that play a role in allergic inflammation by inducing Th2 responses. Interleukin-4R α is the signaling component of the receptor complex for both IL-4 and IL-13. Pitrakinra is a recombinant IL-4 variant that competitively binds IL-4R α receptor inhibiting the binding of both IL-4 and IL-13. Two DBPC 28 day trials of pitrakinra administered subcutaneously (SQ) or via nebulizer demonstrated some clinical efficacy [62]. There was a significant difference in post allergen challenge FEV₁ compared with the placebo group in the SQ pitrakinra study and fewer asthma-related adverse events and beta-agonist rescue use in the group that received inhaled pitrakinra. There were also no significant differences in safety outcomes between the pitrakinra and placebo groups except for an increased frequency of injection site reactions in those who received SQ pitrakinra. IgG antibodies against pitrakinra were seen 3/10 patients in the SQ study (titers of 1:40 and 1:80) and 3/15 patients in the inhalation study (titers were 1:30, 1:60, and 1:480). None of IgG antibodies against pitrakinra were able to block the binding of the drug to interleukin 4R α ; i.e., they were non-neutralizing antibodies.

Tumor Necrosis Factor Alpha Blocking Agents

TNF-alpha blocking agents have been used extensively in rheumatology primarily in the treatment of rheumatoid arthritis. One randomized DBPC, cross-over study investigated the effects of ten-weeks of treatment with etanercept, a soluble TNF-alpha receptor, administered twice weekly to 10 patients with refractory asthma [63]. Etanercept was associated with a significant increase in the methacholine provocation dose ($P = 0.05$), an improvement in the asthma-related quality of life scores (by 0.85 point; $P = 0.02$), and a 0.32-liter increase in post-bronchodilator FEV₁ ($p = 0.01$). There were no treatment-related adverse events or withdrawals. The study also measured markers of TNF-alpha activity and found that patients with refractory asthma had increased expression of membrane-bound TNF-alpha, TNF-alpha receptor 1, and TNF-alpha-converting enzyme by peripheral-blood monocytes compared with the mild-to-moderate asthma and the control groups. This study suggests that patients with refractory

asthma may have up-regulation of the TNF-alpha axis and may benefit from treatment with a TNF-alpha blocking agent.

In a double-blind placebo controlled trial 309 patients with severe, uncontrolled asthma randomized to one of 3 doses of the TNF-alpha blocking agent, golimumab administered subcutaneously (50, 100 or 200 mg) once a month or placebo, there was no significant difference in clinical efficacy between the 4 groups [64]. There was a higher frequency of severe adverse reactions, including serious and life-threatening infections in the golimumab-treated groups compared with placebo. One death and all 8 malignancies occurred in the golimumab-treated groups. The steering committee decided to discontinue the study-agent administration after reviewing the safety data at the Week-24 database lock.

The relatively small patient populations studied in these trials makes it difficult to assess the safety of TNF-alphas blocking agents in asthma. However, these agents have been extensively studied in rheumatologic diseases. In an open-label extension study of 257 patients with ankylosing spondylitis treated for up to 192 weeks with etanercept, injection site reactions, diarrhea and headaches were the most frequent complaints [65]. The rate for serious infections, which is listed in a 'black-box' labeled warning in the package insert, was 0.02 per patient-year. The safety of TNF-alpha blocking agents was evaluated in an open, prospective study of 163 patients with juvenile idiopathic arthritis: 68 received infliximab and 95 received etanercept [66]. Adverse leading to discontinuation occurred in 26 (32.1%) patients treated with Infliximab and 18 (14.2%) patients treated with etanercept. The authors noted that some AEs, "...such as thrombocytopenia, neuropsychiatric disorders, new onset of Crohn's disease, new onset or flare-up of chronic iridocyclitis, were unusual and had rarely been described before, yet proved to be significant in frequency and/or clinically noteworthy in the large population..." they followed. One review of 18 randomized trials involving 8800 patients, found no increase in the odds of death, serious adverse events, serious infection, lymphoma, non-melanoma skin cancers or the composite endpoint of non-cutaneous cancers plus melanomas with recommended doses of TNF-alpha blocking agents when evaluated using the unadjusted meta-analytic method [67]. For individuals receiving two to three the times the recommended dose of the TNF-alpha blocking agent, there was a twofold increase in serious infection.

As discussed earlier in the paper there are conflicting data on the risk of malignancies with TNF-alpha blocking agents [4,5]. In August of 2009, the FDA notified health-care professionals that it has completed its analysis of

TNF-alpha blocking agents and concluded that there is an increased risk of lymphoma and other cancers associated with the use of these drugs in children and adolescence [68]. The current prescribing information for TNF-alpha blocking agents does contain a warning for malignancies, but does not specifically mention leukemia. This new safety information is now being added to the *Boxed Warning* for these products.

Other potential safety issues with TNF-alpha blocking agents include (all type γ effects): [69-71]

- Increased susceptibility to tuberculosis (TB) and certain opportunistic infections or reactivation of latent TB--screening prior to initiation of therapy should include identifying risk for latent TB (e.g., HIV infection, drug addiction, living in a region of high TB prevalence, etc.), tuberculin skin test and chest x-ray [70]
- Serious bacterial infections: incidence of 0.07 to 0.09 per patient year compared 0.01 to 0.06 per control population year [70]
- Autoimmune- like syndromes: lupus-like reactions, demyelinating syndromes

Conclusion

There are several reasons why biologic agents may offer distinct advantages over conventional pharmacotherapy in the treatment of rhinitis and asthma. Both conditions are likely to present with active symptoms requiring some medical management for many years [72]. Biological agents that have an immunomodulatory effect such as allergen immunotherapy may produce sustained clinical improvement after discontinuation of treatment, Whereas, conventional pharmacotherapy is generally only effective during active treatment [3]. The most serious adverse reaction from biologic agents is anaphylaxis and this has been seen most frequently seen in SCIT with unmodified extracts. The delivery of these unmodified allergens via the sublingual route appears to be associated with less risk of anaphylaxis and similar efficacy.

Newer immunotherapy formulations containing Th1 adjuvants (CpG and MPL) appear to provide the benefits of SCIT with a much shorter course of treatment (4 to 6 injections) and a lower risk of adverse events. Biologic agents that target specific components of the immune system may provide clinical efficacy to patients that have failed to respond to optimal pharmacotherapy. Omalizumab is the most extensively studied and prescribed agent for the treatment of allergic asthma that targets a single molecule. Adverse reactions to omalizumab are uncommon but anaphylaxis (none fatal) has been reported at a rate of 0.09 to 0.2% of patients. Some studies have sug-

gested that patients on omalizumab, who are at high risk of geohelminth infections, may be more susceptible to parasitic infection but not more resistant to treatment. Other biologic agents targeting IL-5, and IL-4/IL-13 did not demonstrate any serious or severe treatment-related adverse events in asthma patients. There has been some conflicting information on the safety of TNF-alpha blocking agents in the treatment of asthma.

In general, these biological agents were studied in clinical trials that included relatively small patient populations and there may have not been a sufficient number of patients to identify adverse treatment-related events that occur at a low frequency. Some uncommon adverse effects, such as 1 fatality in 2.5 million SCIT injections or anaphylaxis in 0.09% of omalizumab-treated patients, may not become apparent in clinical trials or postmarketing surveillance data until a very large number of patients have been studied or the medication has been in use for several years. In general, the risk of serious reactions, such as anaphylaxis, with these biological agents is relatively small, and may be reduced by appropriate medical supervision during treatment.

References

- Bateman ED, Boushey HA, Bousquet J, et al.: **Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study.** *Am J Respir Crit Care Med* 2004, **170**:836-44.
- Naclerio R, Hadley J, Stoloff S, Nelson H: **Patient and physician perspectives on the attributes of nasal allergy medications.** *Allergy Asthma Proc* 2007, **28**:S11-S7.
- Guilbert TW, Morgan WJ, Zeiger RS, et al.: **Long-term inhaled corticosteroids in preschool children at high risk for asthma.** *N Engl J Med* 2006, **354**:1985-97.
- Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V: **Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials.** *JAMA* 2006, **295**:2275-85.
- Carmona L, Descalzo MA, Perez-Pampin E, et al.: **All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists.** *Ann Rheum Dis* 2007, **66**:880-5.
- Simons FE, Frew AJ, Ignacio JA, et al.: **Risk assessment in anaphylaxis: Current and future approaches.** *The Journal of Allergy and Clinical Immunology* 2007, **120**:S2-S24.
- Gonzalez-Perez AFC, Suissa S, Garcia Rodriguez LA: **Risk of anaphylaxis in the general population and asthma patients European Respiratory Society Annual Congress.** *Poster* 2007:3660.
- Sampson HA, Munoz-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* 2006:391-7.
- Pichler WJ: **Adverse side-effects to biological agents.** *Allergy* 2006, **61**:912-20.
- MacGlashan DW Jr, Bochner BS, Adelman DC, et al.: **Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody.** *J Immunol* 1997, **158**:1438-45.
- Lin H, Boesel KM, Griffith DT, et al.: **Omalizumab rapidly decreases nasal allergic response and FcεRI on basophils.** *The Journal of allergy and clinical immunology* 2004, **113**:297-302.
- Prussin C, Griffith DT, Boesel KM, Lin H, Foster B, Casale TB: **Omalizumab treatment downregulates dendritic cell FcεpsilonRI expression.** *J Allergy Clin Immunol* 2003, **112**:147-54.
- Lin H, Boesel KM, Griffith DT, et al.: **Omalizumab rapidly decreases nasal allergic response and FcεpsilonRI on basophils.** *J Allergy Clin Immunol* 2004, **113**:297-302.
- Nagakura T, Ogino S, Okubo K, Sato N, Takahashi M, Ishikawa T: **Omalizumab is more effective than suplatast tosilate in the treatment of Japanese cedar pollen-induced seasonal allergic rhinitis.** *Clin Exp Allergy* 2008, **38**:329-37.
- Casale TB, Condemi J, LaForce C, et al.: **Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial.** *JAMA* 2001, **286**:2956-67.
- Milgrom H, Fick RB Jr, Su JQ, et al.: **Treatment of allergic asthma with monoclonal anti-IgE antibody. rhuMAB-E Study Group.** *N Engl J Med* 1999, **341**:1966-73.
- 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.
- Expert Panel Report 3 (EPR-3): **Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007.** *J Allergy Clin Immunol* 2007, **120**:S94-138.
- 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.
- Aaronson D: **The "black box" warning and allergy drugs.** *The Journal of Allergy and Clinical Immunology* 2006, **117**:40-4.
- 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.
- Cox L, Platts-Mills TA, Finegold I, Schwartz LB, Simons FE, Wallace DV, American College of Allergy, Asthma and Immunology, American Academy of Allergy, Asthma & Immunology: : **Linda, Cox, Thomas AEP-M, Ira F, Lawrence BS, Simons FER, Dana VW. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis.** *The Journal of Allergy and Clinical Immunology* 2007, **120**:1373-7.
- Xolair® (Omalizumab) for Subcutaneous Use---Genentech, Inc. July 2008** [http://www.xolair.com/prescribing_information.html]. Accessed 12/05/2008, 2008
- Data on file, Genentech and Novartis Pharmaceuticals Corporation.** 2008.
- A Study of Xolair to Evaluate Effectiveness and Long-Term Safety in Patients With Moderate to Severe Asthma (EXCELS)** [<http://clinicaltrials.gov/ct2/show/NCT00252135?term=omalizumab&rank=56>]
- FDA: Early Communication about an Ongoing Safety Review of Omalizumab (marketed as Xolair).** 2009 [<http://www.fda.gov/DrugsSafety/PostmarketDrugSafetyInformationforPatientsandProviders/SafetyInformationforHealthcareProfessionals/ucm172218.htm>].
- 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.
- Jacobsen L, Niggemann B, Dreborg S, et al.: **Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study.** *Allergy* 2007, **62**:943-8.
- Durham SR, Walker SM, Varga EM, et al.: **Long-term clinical efficacy of grass-pollen immunotherapy.** *N Engl J Med* 1999, **341**:468-75.
- Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J: **Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. VI: Specific immunotherapy prevents the onset of new sensitizations in children.** *J Allergy Clin Immunol* 1997, **99**:450-3.
- Till SJ, Francis JN, Nouri-Aria K, Durham SR: **Mechanisms of immunotherapy.** *J Allergy Clin Immunol* 2004, **113**:1025-34. quiz 35
- Durham SR, Varney VA, Gaga M, et al.: **Grass pollen immunotherapy decreases the number of mast cells in the skin.** *Clin Exp Allergy* 1999, **29**:1490-6.
- Stewart GE 2nd, Lockey RF: **Systemic reactions from allergen immunotherapy.** *J Allergy Clin Immunol* 1992, **90**:567-78.

34. Tinkelman DG, Cole WQ 3rd, Tunno J: **Immunotherapy: a one-year prospective study to evaluate risk factors of systemic reactions.** *J Allergy Clin Immunol* 1995, **95**:8-14.
35. Cox L: **Advantages and disadvantages of accelerated immunotherapy schedules.** *J Allergy Clin Immunol* 2008, **122**:432-4.
36. Tabar AI, Echechipia S, Garcia BE, et al.: **Double-blind comparative study of cluster and conventional immunotherapy schedules with Dermatophagoides pteronyssinus.** *J Allergy Clin Immunol* 2005, **116**:109-18.
37. Reid MJ, Lockey RF, Turkeltaub PC, Platts-Mills TA: **Survey of fatalities from skin testing and immunotherapy 1985-1989.** *J Allergy Clin Immunol* 1993, **92**:6-15.
38. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC: **Fatalities from immunotherapy (IT) and skin testing (ST).** *J Allergy Clin Immunol* 1987:660-77.
39. Bernstein DI, Wanner M, Borish L, Liss GM: **Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001.** *J Allergy Clin Immunol* 2004, **113**:1129-36.
40. Amin HS, Liss GM, Bernstein DI: **Evaluation of near-fatal reactions to allergen immunotherapy injections.** *J Allergy Clin Immunol* 2006, **117**:169-75.
41. Bohle B, Kinaciyan T, Gerstmayr M, Radakovic A, Jahn-Schmid B, Ebner C: **Sublingual immunotherapy induces IL-10-producing T regulatory cells, allergen-specific T-cell tolerance, and immune deviation.** *J Allergy Clin Immunol* 2007, **120**:707-13.
42. Cox LS, Linnemann DL, Nolte H, Weldon D, Finegold I, Nelson HS: **Sublingual immunotherapy: a comprehensive review.** *J Allergy Clin Immunol* 2006, **117**:1021-35.
43. Dunsky EH, Goldstein MF, Dvorin DJ, Belecanech GA: **Anaphylaxis to sublingual immunotherapy.** *Allergy* 2006, **61**:1235.
44. Eifan AO, Keles S, Bahceciler NN, Barlan IB: **Anaphylaxis to multiple pollen allergen sublingual immunotherapy.** *Allergy* 2007, **62**:567-8.
45. Antico A, Pagani M, Crema A: **Anaphylaxis by latex sublingual immunotherapy.** *Allergy* 2006, **61**:1236-7.
46. Blazowski L: **Anaphylactic shock because of sublingual immunotherapy overdose during third year of maintenance dose.** *Allergy* 2008, **63**:374.
47. Cochard MM, Eigenmann PA: **Sublingual immunotherapy is not always a safe alternative to subcutaneous immunotherapy.** *J Allergy Clin Immunol* 2009, **124**:378-9.
48. Groot H, Bijl A: **Two cases of anaphylaxis after SLIT for grass pollen in the Netherlands.** *Allergy* 2009 in press.
49. Casale TB, Stokes JR: **Immunomodulators for allergic respiratory disorders.** *The Journal of allergy and clinical immunology* 2008, **121**:288-96.
50. Creticos PS, Schroeder JT, Hamilton RG, et al.: **Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis.** *N Engl J Med* 2006, **355**:1445-55.
51. Bernstein DI, Segall N, Nayak A, Casale T, Korenblatt P, Martins E: **Safety and Efficacy of the Novel Vaccine TOLAMBA™ in Ragweed Allergic Adults, a Dose Finding Study.** *The Journal of Allergy and Clinical Immunology* 2007, **119**:S78-S9.
52. **Dynavax Reports Interim TOLAMBA™ Ragweed Allergy Results from DARTT Trial press release 2007** [<http://investors.dynavax.com/releasedetail.cfm?releaseid=231013>].
53. Drachenberg KJ, Wheeler AVW, Stuebner P, Horak F: **A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections.** *Allergy* 2001, **56**:498-505.
54. Drachenberg KJ, Proll S, Urban E, et al.: **Short-term immunotherapy using an allergy vaccine adjuvanted with monophosphoryl lipid A: a post-marketing surveillance study.** *Int Rev Allergol Clin Immunol* 2002, **8**:219-23.
55. Mothes N, Heinkill M, Drachenberg KJ, et al.: **Allergen-specific immunotherapy with a monophosphoryl lipid A-adjuvanted vaccine: reduced seasonally boosted immunoglobulin E production and inhibition of basophil histamine release by therapy-induced blocking antibodies.** *Clin Exp Allergy* 2003, **33**:1198-208.
56. Drachenberg KJ, Proll S, Urban E, Woroniecki SR: **Single-course specific immunotherapy with mixed pollen allergoids: results of a multi-centre study.** *Allergol Immunopathol (Madr)* 2003, **31**:77-82.
57. Drachenberg KJ, Heinkill M, Urban E: **Short-term immunotherapy with tree-pollen containing a novel adjuvant monophosphoryl lipid A: results from multicentre, placebo-controlled, randomized study.** *Allergologie* 2002, **25**:466-74.
58. Hart TK, Cook RM, Zia-Amirhosseini P, et al.: **Preclinical efficacy and safety of mepolizumab (SB-240563), a humanized monoclonal antibody to IL-5, in cynomolgus monkeys.** *J Allergy Clin Immunol* 2001, **108**:250-7.
59. Flood-Page P, Swenson C, Faiferman I, et al.: **A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma.** *Am J Respir Crit Care Med* 2007, **176**:1062-71.
60. Garrett JK, Jameson SC, Thomson B, et al.: **Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes.** *J Allergy Clin Immunol* 2004, **113**:115-9.
61. Stein ML, Collins MH, Villanueva JM, et al.: **Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis.** *J Allergy Clin Immunol* 2006, **118**:1312-9.
62. Wenzel S, Wilbraham D, Fuller R, Getz EB, Longphre M: **Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients: results of two phase 2a studies.** *Lancet* 2007, **370**:1422-31.
63. Berry MA, Hargadon B, Shelley M, et al.: **Evidence of a role of tumor necrosis factor alpha in refractory asthma.** *N Engl J Med* 2006, **354**:697-708.
64. Wenzel SE, Barnes PJ, Bleecker ER, et al.: **A randomized, double-blind, placebo-controlled study of tumor necrosis factor-alpha blockade in severe persistent asthma.** *Am J Respir Crit Care Med* 2009, **179**:549-58.
65. Davis JC Jr, Heijde DM van der, Braun J, et al.: **Efficacy and safety of up to 192 weeks of etanercept therapy in patients with ankylosing spondylitis.** *Ann Rheum Dis* 2008, **67**:346-52.
66. Gerloni V, Pontikaki I, Gattinara M, Fantini F: **Focus on adverse events of tumour necrosis factor alpha blockade in juvenile idiopathic arthritis in an open monocentric long-term prospective study of 163 patients.** *Ann Rheum Dis* 2008, **67**:1145-52.
67. Leombruno JP, Einarson TR, Keystone EC: **The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events.** *Ann Rheum Dis* 2009, **68**:1136-45.
68. FDA: **Follow-up to the June 4, 2008 Early Communication about the Ongoing Safety Review of Tumor Necrosis Factor (TNF) Blockers (marketed as Remicade, Enbrel, Humira, Cimzia, and Simponi).** 2009. accessed on 9/25/09
69. Botsios C: **Safety of tumour necrosis factor and interleukin-1 blocking agents in rheumatic diseases.** *Autoimmun Rev* 2005, **4**:162-70.
70. Furst D, Breedveld F, Kalden J, Smolen J, Burmester G, Sieper J, Emery P, Keystone E, Schiff M, Mease P, van Riel P, Fleischmann R, Weisman M, Weinblatt M: **Updated consensus statement on biological agents for the treatment of rheumatic diseases.** *Annals of the Rheumatic Diseases* 2007, **66**:iii2-iii22.
71. Toussiroot E, Wendling D: **The use of TNF-alpha blocking agents in rheumatoid arthritis: an update.** *Expert Opin Pharmacother* 2007, **8**:2089-107.
72. Settignano GA, Greisner WA 3rd, Settignano RJ: **Natural history of asthma: a 23-year followup of college students.** *Ann Allergy Asthma Immunol* 2000, **84**:499-503.

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