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REVIEW

The safety of monoclonal antibodies in asthma

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ABSTRACT

Introduction: In the last two decades the knowledge of the mechanisms of the inflammatory processes underlying asthma rapidly evolved, several key mediators (cytokines and receptors) were identified, and the laboratory techniques have allowed us to synthesize monoclonal antibodies highly specific for those target molecules. Nowadays, many biological agents are investigated in asthma (with anti IgE being the only commercially available). The clinical efficacy of some biologics was demonstrated in many cases, however, the safety issue has progressively emerged and has been recognized as a crucial aspect.

Areas covered: We summarized the currently available knowledge on the safety and side effects of biologics in asthma, as derived by reviews, meta analyses and clinical trials. PubMed was searched with the terms *anti IL-x [AND] safety [OR] side effects*, within the categories "clinical trial", meta-analysis" and "review". Case reports were excluded. The authors collegially selected the relevant entries to be included.

Expert opinion: Overall, the safety of most of the investigated agents seems to be satisfactory, a certain risk of side effects remains present, and is variable for the different molecules. Thus caution must be paid in evaluating the risk to benefit ratio. Specific biomarkers to predict the response to each biological are urgently needed to improve the safety profile.

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1. Introduction

Asthma, which remains a high-prevalence disease worldwide, [1,2] is currently recognized as a 'heterogeneous disease',[3] and this definition profoundly differs from what stated only few years ago in Guidelines, when asthma was considered as a single and uniform disease. This is the result of the more detailed knowledge that we have gained on clinical presentation, biological/immunological aspects, functional behavior, and treatment approaches. Consequently, there have been many attempts to identify distinct phenotypes of asthma, according to clinical and biological criteria.[4] So far, a quite clear distinction can be made only between the T-helper 2 (TH2) and low-TH2 phenotypes.[5] Within these large and partially overlapping groups, allergic asthma (AA) remains the paradigm of TH2-driven asthma, whereas other forms, such as adult-onset or smoke-related or obesity-related asthma, well represent some of the usual low-TH2 presentations.

Starting from the well-known IgE-mediated mechanisms underlying allergic asthma, the pathophysiology of the disease was progressively and rapidly elucidated in the past two decades, and also applied to other forms of asthma. Cytokines, receptors, cell function, and chemokines were progressively identified and dissected. The evolving knowledge, in addition to the evolving biotechnology, allowed to identify precise molecular targets to be addressed by specifically constructed molecules to be applied in asthma, especially in the more severe forms.[6,7] This is the era of 'precision medicine',[8,9] where each single molecular target can be inhibited by biological agents (BA), monoclonal antibodies (MAbs) in particular. In less than 15 years, many MAbs targeted to single components of the immune-mediated inflammation of asthma were synthesized, tested, and proposed for clinical use.[10] In parallel to clinical use and large-population trials, the problem of the safety and tolerability of these approaches rapidly emerged: as any other drug, MAbs are not totally devoid of side effects.[11,12]

The clinical efficacy, in the view of the personalized medicine, remains the primary goal of MAb-based therapy but, due to the costs and affordability problems, the safety assumes a comparable importance. Here, we reviewed the available data on the tolerability and safety profile of the MAbs currently used or under evaluation for the treatment of asthma (listed in Table 1). We searched PubMed for each of them using the terms *name of the molecule [AND] safety [OR] side effects*, within the categories 'clinical trial', 'meta-analysis' and 'review'. Case reports were excluded. The authors collegially selected the relevant entries to be included and discussed.

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Article highlights

- Asthma is a heterogeneous disease. Despite the clinical and functional aspects are common, different phenotypes/endotypes can be recognized. Allergic asthma is the most studied model.
- Several cytokines, cells and receptors are currently recognized as pivotal elements in asthma-related inflammation (IgE, IL-4, IL-5, IL13, IL-17)
- Monoclonal antibodies specific to relevant targets of inflammations are now available, and many of them are undergoing clinical trials.
- For anti IgE (in use since >10 years), there is a large amount of evidence. Efficacy and safety data are available for many of the biological agents from the published clinical trials.
- Biologicals (in particular Monoclonal Antibodies) may exert both favourable and undesired side effects with various mechanisms.
- Non-specific adverse events (headache, local reactions, diarrhea etc.) invariably resulted to be more frequent in active than in placebo groups.
- Overall, the biological agents tested in asthma displayed an overall efficacy to safety favourable profile, but this is not applicable at the same extent to each single agent.
- A 'precision medicine' approach, including the search for biomarkers, would be necessary to appropriately prescribe biological agents, maintaining an optimal safety profile.

This box summarizes key points contained in the article.

2. An overview on the pathogenic mechanisms of asthma

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During the past two decades, a great research effort has been undertaken to clarify the complex mechanisms, which regulate airways inflammation in asthmatic patients (Figure 1). The vast majority of our knowledge about the immunological aspects of asthma derives, for historical reasons, from the allergic model. In such case, the triggering mechanism that starts the inflammatory processes is well known: the specific IgE–allergen–mast cell interaction. It has become quite clear that the reaction of inhaled allergens with IgE-specific antibodies bound to FcεRI receptors on the surface of mast cells is not sufficient to account for the persistent histological, pathophysiological, and clinical alterations that characterize the allergic asthma. The definition of phenotypic and functional activities of different T cell subsets based on their profiles of cytokine secretion has been of the primary importance. One type of T helper cells (TH1) produces interleukin (IL)-2 and IFN-g, whereas the other type (TH2) secretes IL-4, IL-5, IL-9, IL-13, and IL-10, but not IL-2 and IFN-g.[13,14] In particular, atopic subjects have a pre-existent background that interacts with external factors (allergen exposure, maternal factors, infections, intestinal microbiota), leading to an overproduction of IgE specific for ubiquitous and innocuous antigens. This abnormal production of IgE is the consequence of a relative imbalance between TH1 and TH2T cells. In fact, IL-4 and IL-13 favor IgE synthesis, whereas IL-5 increases eosinophil activation and survival.[15] IL-13, is actively involved in inducing goblet cell metaplasia and bronchial hyper-reactivity, and prime the upregulation of the adhesion molecule VCAM-1 and ICAM-1 on endothelial cells, that is a key step for eosinophils migration.[16] However, it should be remembered that T cells may play an important role also in non-atopic asthma. In fact, similarly to what observed in atopic asthmatics, the biopsies taken from intrinsic asthmatics are characterized by large numbers of eosinophils and activated T lymphocytes.[17] Non-allergic asthmatics also display increased levels of IL-2 and IL-5, but not IL-4.[18]

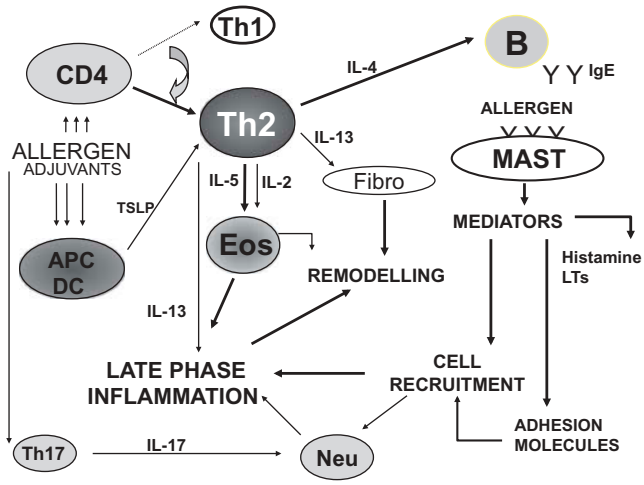

Figure 1. Schematic view of the allergic reaction. APC-DC: antigen presenting cell-dendritic cell; Eos: eosinophil: MAST: mastcell; Neu: neutrophil; TSLP: thymic stromal lymphopoietin.

Table 1. MAbs currently used or tested in asthma.

Name	Function	Structure	Phase status in asthma
Omalizumab	Anti-IgE	Humanized	Commercialized (Xolair ™)
Ligelizumab	Anti-IgE	Humanized	IIb
Benralizumab	Anti-interleukin (IL)-5 receptor	Humanized	II
Mepolizumab	Anti-IL-5	Humanized	III European Medicines Agency and US Food and Drug Administration (FDA) approved (Nucala™)
Reslizumab	Anti-Il-5	Humanized	III FDA approved
Pascolizumab	Anti-Il-4	Humanized	II
Annukizumab	Anti-Il-13	Humanized	II
Lebrikizumab	Anti-IL-13	Humanized	III
Pitrakinra	Anti-IL-4/IL-13 receptor	Humanized	IIb
Tralokinumab	Anti-IL-13	Human	IIb
Pitrakinra	IL-4/IL-13 antagonist	Mutein	IIb (withdrawn)
Dupilumab	Anti-IL-4/IL-13	Human	IIb
Infliximab	Anti-tumor necrosis factor-α (TNF-α)	Chimeric	III (withdrawn)
Golimumab	Anti-TNF-α	Human	III (withdrawn)
Etanercept	Soluble TNF-α receptor	Fusion protein	III (withdrawn)
Brodalumab	Anti-IL-17	Human	II

Eosinophils represent 1–6% of the circulating white blood cells. They are important effectors of the allergic inflammatory response, playing a primary role in the pathogenesis and severity of chronic inflammatory disorders of the airways.[19] The accumulation in the target tissues and the activation of allergen-specific TH2-like cells as well as mast cells through an IgE-dependent pathway play a central role in orchestrating the airway allergic inflammation, by the recruitment of effector cells, mainly eosinophils. In this regard, different cytokines, such as IL-3, IL-5, and GM-CSF are involved. IL-5 appears to be the most specific for eosinophils by promoting their differentiation from bone marrow precursors, enhancing their adhesion to endothelial cells, prolonging their survival in target tissues and priming them for many activities as effector cells.[20–22] The recruitment of eosinophils to airways wall is regulated by the production of chemokines, such as eotaxins 1, 2, and 3 now called CCL11, CCL24, and CCL26, respectively.[23]

In non-atopic 'intrinsic' asthma, the accumulation and activation of T cells able to produce cytokines, particularly IL-5, may be responsible for the peculiar eosinophilic airway inflammation. Eosinophils can damage the respiratory mucosa by releasing basic proteins, oxygen-free radicals, and lipid mediators, such as leukotriene C4 and platelet-activating factor, contributing to microvascular leakage, bronchoconstriction, mucus secretion, and shedding of the airway epithelium. Eosinophils has been demonstrated to be also able to elaborate cytokines, such as IL-3, TGF-β, GM-CSF, IL-1, IL-6, and IL-5.[24] Recently, a key role in eosinophilic asthma has been attributed to the so called 'type 2' innate lymphoid cells (ILC2 cells), able to produce IL-5 as well as IL-9 and IL-13.[25] ILC2 cells lack antigen-specific receptors, but like TH2 cells, they react to the epithelium-derived cytokines IL-25, IL-33, and thymic stromal lymphopoietin (TSLP).[26]

3. Pathogenic mechanisms of adverse reaction to biological agents

The safety of BA is an important field of research considering their growing clinical applications. Adverse events (AEs) should be defined as any untoward medical occurrence associated with the use of a drug, whether or not considered drug related (Table 2). The safety profile of biologicals is negatively impacted by their immunogenicity, which leads to the production of specific anti-drug antibodies (ADA).[27] Similar to other biologicals, therapeutic MAbs are structurally immunogenic. They are classified as chimeric (variable regions from murine sources and constant regions from human immunoglobulins) or humanized (containing only the complementarity-determining regions of a murine immunoglobulin with the remaining being human), and fully human (Figure 2). These latter usually elicit minor, subclinical, and transient phenomena, but, sometimes, they can induce complete cellular and humoral immune responses, which impact the efficacy. Various types of ADA were observed during biological treatments, mostly IgG, but also IgE, IgM, and IgA.[28] Patients developing high levels of ADA are more likely to show acute hypersensitivity reactions, and both IgE and non IgE-mediated mechanisms may be involved. Other adverse events, such as serum sickness-like reactions appear to be associated with the presence of ADA, related to the formation of complement-binding immune complexes, with subsequent immune complexes deposition, complement activation, and inflammatory infiltration around small vessels. In fact, at immunofluorescence, the presence of complement deposition around vessels of skin specimens can be observed.[29] In addition, data from clinical trials and from real-life clinical practice suggested that the currently used biologicals may constitute a risk factor for the reactivation of latent bacterial infections or parasitic infestations as in the case of tumor necrosis factor-α (TNF-α) blockers. In general, TH1 cells are more suitable for protection against intracellular infection agents, such as *Mycobacterium tuberculosis* whereas the optimal reaction against parasites is provided by TH2 cells and IgE antibodies and eosinophils. Among biological agents used for the treatment of severe asthma and their association with the risk of infections, anti-IL-5 MAbs have been closely followed-up. The role of T cells in the protection of *mycobacterium* is indirectly demonstrated by the effects of TNF-α blockers, also proposed for the treatment of severe forms of asthma. These biological agents are able to interfere with the *mycobacterium*-specific-induced proliferation and cytokine production by T cells, thus increasing the risk of infection or reactivation. TH1 cells produce IFN-γ, IL-2, and TNF-β, which activate the macrophages responsible for cell-mediated immunity to intracellular pathogens.[30]

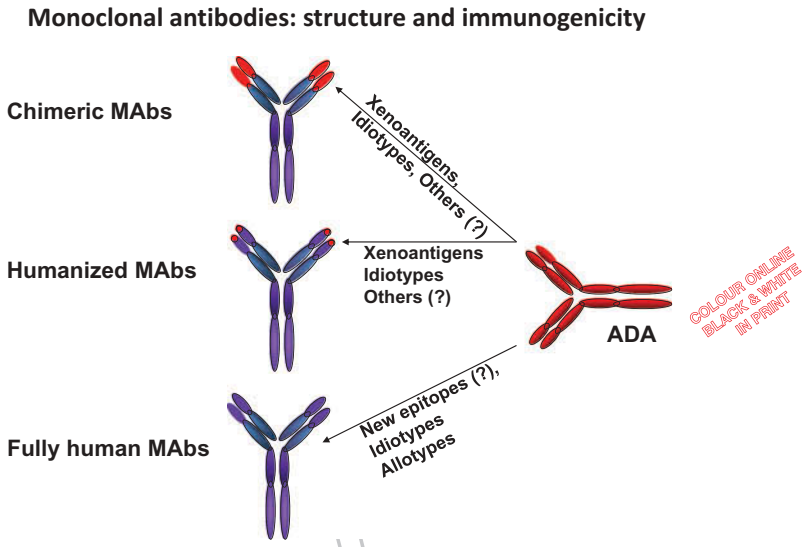

Figure 2. Schematic representation of therapeutic monoclonal antibodies and their structure-related immunogenic profile. ADA: anti-drugantibodies.

Table 2. Adverse reactions to biological agents.

Target-related events
• Infections
• Increased tumor susceptibility
• Autoimmunity (ADA, with possibly reduced efficacy of the MAb)
Drug-related events
• Infusion reactions
• Local (immediate or delayed)
• Systemic (immediate or delayed)

4. Anti-IgE (omalizumab)

For historical reasons, IgE was immediately regarded as an optimal target for a MAb-based strategy. In fact, IgEs are the primary trigger of the allergic reaction. The atopic subject produces abnormal amounts of allergen-specific IgE, which bind the high affinity receptor (FCεRI), widely distributed on tissue mast cells and circulating basophils. The rationale of the anti-IgE strategy was to synthesize a MAb capable of specifically bind the heavy chain of the circulating IgE, thus preventing them from engaging with the receptor. The MAb obtained was a humanized one (human IgG with a 5% murine fraction), named omalizumab. [31] Omalizumab underwent numerous phase II and phase III clinical trials in the past 15 years,[32] and was then approved for commercial use more than 10 years ago. Its indication is severely uncontrolled asthma due to perennial allergens with a total IgE concentration of 30–1500 kU/L and a body weight between 50 and 120 kg. Due to the long-standing clinical use, there is now a large amount of data available on its efficacy [33–35] and safety. Looking at the clinical trials so far published, the occurrence of AEs, including severe (SAEs) ones, was negligible and approximated that of placebo groups.[36,37] In particular, in the published trials the most frequently reported AEs were local (induration/irritation at the injection site) or systemic (headache, pharingytis, or rhinitis), none of them exceeding 10% of patients.

Since the beginning, one of the major concerns was the risk of inducing or unmasking malignancies, since MAbs interferes with the immune system. After many years of clinical use, it can be stated that the incidence of malignancies in the omalizumab-treated patients does not differ from that expected in the general population.[38,39] Another possible safety problem is the occurrence of parasitosis, since IgE are well known to be actively involved in the natural defensive response to parasites. According to the currently available data, an increased occurrence of parasite infestation during omalizumab treatment was not observed,[40] although a slight but not significant excess in geoelminthic infestations (in at risk regions) was reported in a single study.[41] Finally, some cases of anaphylaxis, anaphylaxis-like reactions or serum sickness following omalizumab treatment have been sporadically reported.[42,43] In some case reports, cases of omalizumab-related AEs on the pathogenic mechanism were sustained by IgE antibodies directed against additives that are present in the drug formulation.[44] Indeed, according to the more recent survey conducted in the United States, the incidence of anaphylaxis or anaphylaxis-like events was about 0.09%, with 16 out of the 77 reported events occurring more than 2 h after the administration, thus leaving the diagnosis of anaphylaxis uncertain.[45] Based on these results, in the United States, an observation period of at least 2 h and the prescription of autonjectable epinephrine are recommended, whereas those recommendations are not applied in most other countries. When omalizumab was first commercialized and introduced in clinical practice, some reports of Churg–Strauss disease possibly related to the drug were published. These cases were attributed to the systemic steroid withdrawal that unmasked a pre-existing disease. Nowadays, the Churg–Strauss syndrome is suggested as a promising, although off-label, indication for omalizumab.[46]

In conclusion, looking back to more than 15 years of clinical trials and clinical use in real life, the safety profile of omalizumab is extremely satisfactory. Mild AEs (e.g. local) may occur, but systemic and/or SAEs are very rare, if not anecdotal. From a very conservative and cautious point of view, a 2-h period of observation after each injection (and the prescription of autoinjectable epinephrine) are applied in the United States, but not in the remaining countries.

5. Anti-IL-5 and IL-5Ra chain (mepolizumab, reslizumab, benralizumab)

IL-5 is secreted mainly by Th2 cells, mast cells, natural killer T cells, basophils, eosinophils, and type-2 ILCs. The IL-5R is a heterodimer composed of β-subunit, responsible for binding of IL-5 and expressed both on progenitors of mature eosinophils but also by basophils, and the alpha subunit, necessary for signaling. IL-5 induces the maturation, activation, and recruitment of eosinophils.[47] The BA interfering with IL-5 and its receptor proposed for asthma are mepolizumab and reslizumab (anti-IL-5 MAbs) and benralizumab (anti-IL-5Ra MAb).[24] Differently from the two anti-IL-5 MAbs, benralizumab targets IL-5Ra chain receptor and might thus also affect leukocytes via antibody-dependent cell-mediated cytotoxicity.[48]

To date, few clinical trials with benralizumab have been completed, showing a significant efficacy in patients with mild-to-severe asthma along with a reduction in peripheral blood and sputum eosinophils and eosinophil cationic protein. A single dose administered intravenously and subcutaneous multiple dose of benralizumab reduced eosinophil counts in airway mucosa and submucosa in sputum, and suppressed eosinophil counts in bone marrow and peripheral blood.[49–51] Only nonspecific mild AEs (headache, fatigue) were described, and local reactions occurred in about 5% receiving subcutaneous injections.

More data are available for mepolizumab, that invariably showed a significant benefit in eosinophilic asthma, characterized by the decrease in the frequency of exacerbations, increase in FEV1, improvement in quality of life, along with a significant decrease in blood and sputum eosinophilia.[52–56] This was confirmed in a recent meta-analysis.[57] The most commonly reported AEs were nasopharyngitis, headache, chest pain, facial flushing, fatigue, upper respiratory tract infection in 10–25% of actively treated patients on average, with few SAEs not related to treatment. Mepolizumab was usually given intravenously. In the case of subcutaneous administration, local side effects (induration, pain) occurred in about 10% patients (one case of anaphylaxis reported). Similar results were obtained with reslizumab in asthmatic patients with sputum eosinophil levels of 3% and more. [58,59] In this case, there was not a significant difference in common AEs between placebo and active groups, but two cases of anaphylaxis were reported with intravenous reslizumab.

As with anti-IgE, a possible safety problem is the occurrence of parasitic infestation, since eosinophils are involved in the natural defense against parasites. Indeed, experiments in

parasite-infested mice and receiving anti IL-5 antibodies showed no change in immune response,[60] but no data are available in humans. An indirect evidence of the safety of IL-5/IL-5Ra blockers is that patients lacking eosinophils, do not display any abnormality related to eosinophil reduction.[61] Concerning the risk of malignancies, it is important to note the role of eosinophils in both anti-carcinogenic and pro-carcinogenic effects depend on many factors mainly on the type of cancer. Eosinophil infiltration is considered unfavorable in Hodgkin's lymphoma, but conversely, it was associated to a favorable prognosis in solid cancers (e.g. colorectal or prostatic). A variety of cytokines and factors produced by eosinophils such as major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin have either anti-tumor effects or stimulate tumor progression.[62] Although clinical experience of IL-5 blockers in asthmatic patients is limited to clinical trials, additional information of the safety profile of these BA were obtained by the data of patients with the hypereosinophilic syndromes treated with mepolizumab for several years: these subjects did develop no AE at all.[63]

6. Anti IL-4 and IL-13

Dupilumab antagonizes the effects of both IL-4 and IL-3 by blocking the IL-4 receptor alpha chain. Wenzel and colleagues described the safety results in a clinical trial involving 104 asthmatics treated with dupilumab or placebo.[64] In this study, the overall proportion of AE in the two groups was similar (77% vs. 81%). The reported AEs were mild or moderate and only four patients had serious adverse event (three in the placebo group and one in the dupilumab group). There was no fatal event and most AEs were judged by investigators as not related to study drug. Six patients discontinued therapy: three in the placebo group (psoriasis, asthma exacerbation, and upper respiratory tract infection) and three in the dupilumab group (worsening of bipolar disorder, angioedema and increase in asthma symptoms). The most common adverse events were injection-site reactions (29%), nausea, headache, and nasopharingitis (8–13%), which occurred more frequently with dupilumab. One case of angioedema, judged as treatment-related was reported. In addition, in 4/52 patients an unexpected increase in eosinophil count, not associated with asthma worsening was described.

The safety of pitrakinra, a mutein antagonizing both IL-4 and IL-13, was described by Wenzel and colleagues in a clinical trial in asthmatic people. Two group of patients, the first treated with pitrakinra by subcutaneous injections and the second one by inhalation route, were investigated in the same trial. The most frequent symptoms recorded were about general disorders (headache, fatigue, musculoskeletal pain) and injection site reactions. Other reported adverse events were related to the nervous system (somnolence, dizziness), respiratory, and thoracic disorders (wheezing, chest discomfort, dyspnea, and nasal obstruction) and gastro-enteric symptoms (nausea, abdominal discomfort, and diarrhea). All those AEs were mild and occurred in about 10% of patients.[65] Despite the initial enthusiasm, no further trial with pitrakinra was conducted after 2007.

The use of human anti IL-13 MAb lebrikizumab in asthma was explored in few studies, with conflicting results. A pooled analysis of two phase II trials reported a significant reduction in asthma exacerbations, with a marginal effect on pulmonary function.[65] Corren et al. [66,67] showed a significant clinical efficacy of the treatment only in a subgroup of patients with high blood periostin, whereas another trial failed to demonstrate a clinical efficacy.[68] The first study involved 219 adult patients with asthma. The overall occurrence of adverse events was similar in the active and placebo group, with the exception of musculoskeletal pain, more frequent in the active group (13% vs. 5%). In the second ranging phase II (dose ranging) trial in mild asthma [68], the safety profile was good as well, with a similar proportion of AEs in placebo and active arms. Most of AEs were moderate, only one of the six SAEs in the lebrikizumab arm (Lofgren syndrome) was considered drug related. A third small study with lebrikizumab in 29 mild asthmatic patients, evidenced 61 AEs, with a greater incidence in the placebo group. Only one event (decreased platelet count) was judged as drug related. No patient was withdrawn because of AEs.[69]

Another anti IL-13 drug, tralokinumab, was evaluated in 194 asthmatic patients in a phase II study, at three different dose 150, 300, or 600 mg. The six reported SAEs were equally distributed between groups and not treatment related. The most frequent AEs in the Tralokinumab arm were asthma, headache, nasopharyngitis, and local reactions. Interestingly, urinary tract infections were reported in 4% of the active-group patients as well as an increased eosinophil count in 2–6% of patients at week 13.[70]

7. Anti-IL-17

Busse and colleagues described results about a clinical trial of phase IIa with in asthmatic patients with the anti-IL-17 MAb Brodalumab at different doses. The safety was evaluated monitoring adverse events and laboratory parameters. The occurrence of AEs was similar for all dosages, and the most common events were described in upper and lower airways (asthma, upper respiratory tract infection, nasopharyngitis, oral candidiasis, and sinusitis), local injection site reaction, and cutaneous events such as erythema. AEs were most frequent in the brodalumab group than in placebo one, including events that led to discontinuation. During the trial, seven patients showed serious adverse events, and two patients (one active and one placebo) had an asymptomatic decrease of neutrophil count.[71]

8. TNF-α antagonists

Among the TH2-low or no primarily TH2-driven asthma some phenotypes are well recognized including: adult onset and obesity associated asthma and overlapping syndromes.[72–74] In such cases, a neutrophilic or pauci-cellular, rather than eosinophilic, inflammation seems to predominate. Based on these observations, a mainly TH1-driven inflammation strategy was hypothesized. TNF-α is known as a central mediator of the Th1 inflammation, involved in the pathogenesis of many inflammatory diseases, such as Crohn disease, rheumatoid

arthritis, and various neuropathies.[75,76] In some forms of asthma, TNF-α can enhance mucus production, smooth muscle proliferation, and epithelial disruption. Thus, TNF-α antagonism was hypothesized to be an optimal therapeutic target. There were some already in use agents (TNF-α soluble receptor, etanercept, or TNF-α antagonists golimumab and infliximab) to be also tested in asthma. The earliest studies showed some beneficial effect of etanercept and infliximab in refractory asthma where increased levels of TNF-α were well ascertained.[77–79] Nonetheless, similar studies performed in COPD evidenced an excess of SAEs, such as malignancies,[80] and a randomized double-blind placebo controlled trial in asthma had to be interrupted due to the unacceptable rate of AEs.[81] However, these data must be compared with those obtained in anti-TNF-α-treated patients suffering from rheumatic diseases in which there was no evidence for an increased risk of lymphoma and solid cancers.[82–84] In addition, those diagnosed with cancer during or after anti- TNF-α treatment have not been shown to have a worse prognosis than anti-TNF-α naive patients.[85] Noticeably, the frequency of local (injection site) reactions with TNF-α antagonists is overall low (5%).[86]

Although the TNF-α antagonism remains a reasonable strategy in some forms of asthma, the available results in this kind of patients display an unfavorable benefit-to-risk rate, and this approach in asthma has been abandoned.

9. Conclusions

The knowledge on the pathogenic mechanisms of asthma has rapidly evolved in the past two decades. Although a precise phenotyping or endotyping cannot still be well defined, some biological characteristics can be reasonably attributed to some specific forms of asthma (e.g. TH-2 high or TH2-low). In this context, biological drugs (namely monoclonal antibodies) specifically constructed to antagonize relevant mediators and cytokines (e.g. IgE, IL-5, IL-4, IL-13) have been clinically tested. According to the available results, many of these approaches are clinically effective especially in the most severe forms of asthma. In parallel, the safety aspects of biological drugs became emergent. So far, the safety profile results favorable for anti-IgE and anti-IL-5 monoclonal antibodies, which are undergoing clinical trials and practical use since many years. The efficacy/safety ratio remains a matter of debate for the new biologicals (anti-IL-13, anti-IL-4, and anti-IL-17), which are more recent in development (Table 3). Some other approaches, that are justified from an immunological point of view (TNF-α antagonism), produced an unacceptable rate of severe adverse events, and were abandoned at least in asthma.

In the near future, the 'personalized' medical approach will become more and more relevant,[87] with an appropriate investigation of biomarkers. Nonetheless, it must be kept in mind that acting on immunological effectors is not totally devoid of risk,[11] and that a careful and strict surveillance is mandatory needed.

10. Expert opinion

Asthma is currently recognized as a heterogeneous disease, and different phenotypes/endotypes have been proposed in the past decade. This fact is directly linked to the more and more detailed knowledge on the mechanisms underlying the inflammatory aspects (mainly derived from the allergic model). In this framework, many sensible molecular targets have been identified, which can be selectively blocked by monoclonal antibodies (biological agents). An anti-IgE treatment is already in clinical use since more than 10 years, whereas other biological are under investigation in clinical trials, often with good clinical results. The increasing number of patients treated, both in clinical practice and trials, attracted the medical attention on the safety aspect, especially for those drugs that are expected to be commercialized soon.

Indeed, the field is of primary relevance, since all those biological agents are used for severe/refractory/steroid-dependent asthma, which represent a clinical challenge and a socioeconomic burden, and where the side effects of systemic steroids are a real occurrence. The results so far available are encouraging in term of clinical efficacy, and the safety is overall satisfactory. The majority of side effects reported are nonspecific (e.g. headache, flu-like symptoms, local reactions) and mild, but treatment-emergent severe adverse events (e.g. anaphylaxis with anti-IgE) can exceptionally occur. Some events seem to be drug-specific (e.g. eosinophilia with dupilumab or anti-IL-13), but difficult to interpret from a pathogenic viewpoint. So far, no clear risk factor for severe adverse

Table 3. Brief summary of the reported adverse events in clinical trials (percentage of patients are in parentheses).

Treatment	Common AEs	Special or severe AEs
Anti-IgE (omalizumab, Xolair™)	Nasopharyngitis, headache, induration at injection site (<10%)	Anaphylaxis-like reactions (~0.09%) Churg–Strauss syndrome (exceptional case reports)
Anti IL-5 (mepolizumab, Nucala™)	Nasopharyngitis, headache, upper respiratory infection (10–25% of patients. Injection site reaction (<10% of patients)	Anti-mepolizumab *Ab* detection (5%) One case of anaphylaxis with s.c. administration
Anti IL-5 (reslizumab)	Similar occurrence in placebo and active groups	Two cases of anaphylaxis (0.05%) with i.v. administration
Anti IL-4/IL-13 (dupilumab)	Pharyngitis, headache (8–13%) Injection site reaction (30%)	One case of angioedema 4/52 (7%) hypereosinophilia in the active group
Anti IL-13 (lebrikizumab)	Injection site reactions (~10%) Similar rate of AEs in active and placebo groups, mostly mild	One case of Lofgren syndrome and 1 case of low platelet count probably treatment related
Anti IL-13 (tralokinumab)	Asthma, headache, and nasopharyngitis more frequent in active group (6–13%)	Urinary tract infection (4%) Increased eosinophils (2–6%)

events could be identified in clinical trials, but this should induce caution in view of the commercialization, since some events are quite rare and their pathogenesis can be identified only in the post-marketing phase, as happened for alpha-gal and cetuximab.[88] Based on the previous experience with anti-IgE, it is opinion of the authors that a precautional period of observation (at least 30 min) after administration) should be recommended for the newly marketed treatments. Another weak aspect of MAb-based treatment in asthma is that the effects of most cytokines are extensively overlapping, so that the blockage of a single molecule may be insufficient to achieve a meaningful effect.

Within this context, it is clear that the investigation on the role of MAbs in asthma therapy remains of primary relevance due to the fact that it covers those forms of asthma where standard therapy is not sufficient. On the other hand, this approach will not be fully effective until specific biomarkers to identify the subjects suitable for a given treatment and who will respond to that treatment are defined. Currently, very few biomarkers with respect to the number of possible targets and drugs are indeed available (e.g. IgE, bronchial/circulating eosinophils, and periostin). This is the optimal goal of which is called 'precision' or 'personalized' medicine.

The field of research with MAbs for 'difficult asthma' will certainly remain alive and progressing in the near future, also because the basic research on the mechanisms will be further refined. In addition, it is expected that the development of technology will lead to a sensible reduction in the costs of biological, that remains a main drawback. In the very near future, several anti-IL-5 compounds will be commercialized based on the good results obtained in clinical trials. This biological represents a special case, since IL-5 is specifically committed to eosinophils and has relatively few actions overlapping with other cytokines. In fact, clinical results are relevant in those patients with high eosinophil count (that represent in turn the biomarker). Another expected entry in our armamentarium would be dupilumab, since it antagonizes both IL-4 and IL-13 at the same time, and thus can partially overcome the overlapping effects of the two cytokines. The commercial use of anti-IL-4 or IL-13 alone, anti-IL-17 seems to be a more distant perspective.

It is clear that when a new drug is released for clinical use, the post-marketing data on the safety start to rapidly accumulate, and this is expected to be advantageous to identify the possible risk factor and to better define the safety to efficacy ratio.

Declaration of interests

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