

Asthma: developments in targeted therapy

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Despite advances in long-term management, asthma remains a health problem in industrialized countries. Even if the updated guidelines continues to emphasize that the most effective medications for long-term asthma therapy are inhaled corticosteroids, the actual pharmacological therapies are unable to modify the natural course of ‘asthma history’, so there is an urgent need for targeted, disease-modifying asthma treatments [1]. The definition of the pathogenic mechanisms of asthma has opened the way to new therapeutic strategies. In the present article, we briefly discuss the past, present and particularly the future perspectives of targeted asthma therapies. However, it is now accepted that there are distinct asthma phenotypes, and that available therapeutic approaches may only interfere with some aspects of the disease process [2].

Past

Several years ago, asthma was considered to be a disease of bronchoconstriction and treated by bronchodilators. The definition of asthma as an inflammatory disease has been followed by the acceptance of the key role of inhaled corticosteroids in the treatment. However, steroids are not target-specific in their actions and different clinical response of asthmatics to the therapy is common. A subsequent step in asthma therapy was the role of long-acting β_2 agonists in association with inhaled corticosteroids for long-term control of asthma. The only new class of drugs developed in the last decades has been the leukotriene receptor antagonists, such as montelukast, that displayed a good performance, particularly in childhood asthmatics, in exercise- and aspirin-induced asthma. Recently, leukotriene receptor antagonists

have been shown to be equivalent to beclomethasone as a first-line controller therapy and to a long-acting β_2 agonist as add-on therapy for chronic asthma in the community [3]. A limitation of this therapeutic approach is that both responders and nonresponders exist, related to the genetically determined levels of leukotrienes. At the end of the 1990s, anti-IgE therapy was proposed and a clinical trial with the monoclonal antibody (mAb) omalizumab started and confirmed the efficacy of this first target strategy [4].

Present

As mentioned above, the only other specific target therapy available and recognized as an add-on therapy in severe persistent asthmatics with inadequately controlled symptoms is the humanized anti-IgE mAb omalizumab. The basis of clinical efficacy is complex and, in addition to the reduction of free IgE and blocking of mast cells/basophils activation, is also related to the inhibition of function of APCs in the ongoing response to allergens [4]. However, it is recognized that only approximately a third of patients treated with omalizumab experience substantial efficacy, and a third show only some clinical benefit. To date, there is no understanding of what determines a responder from a nonresponder.

Cytokines actively participate to the pathology of asthma, thus representing specific targets in developing asthma treatment. Among them, TNF- α contributes to airway remodeling and to steroid resistance, and thus represents a recognized target of therapy. Infliximab, a chimeric anti-TNF- α mAb, shows significant improvements in lung function and exacerbation rate, particularly in patients with

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severe steroid-resistant asthma [5]. By contrast, clinical trials with golimumab, the fully human anti-TNF- α mAb and etanercept, a soluble TNF- α receptor linked to the human Fc of IgG1, reported conflicting results [6,7]. This may be largely dependent on the selection of patients. It is probable that the inhibition of TNF- α may represent a useful strategy in 'TNF- α -high' asthmatic patients. The inhibition of eosinophil accumulation in asthma represents a well-known potential therapeutic strategy. Blocking the effects of IL-5 using specific mAbs, such as mepolizumab, suppresses eosinophilic inflammation. However, clinical outcomes are disappointing as there are no significant effects on airway hyper-responsiveness or the late asthmatic reaction [8]. In addition, in this case, the different clinical findings could be explained by different phenotypes of asthma of the subjects included in the studies. Furthermore, cytokines other than IL-5, such as IL-3, GM-CSF and IL-9, may sustain the eosinophilic airway inflammation. Mepolizumab may be potentially useful for treatment of patients with Churg–Strauss Syndrome, a well-known asthma-associated condition in which eosinophils are largely expanded. Eotaxin represents a key chemokine that promotes selective recruitment of eosinophils into inflammatory tissues via CCR3. Specific antagonists have been tested in mouse models but their effectiveness in asthma is unknown [9]. With regards to other cytokines, IL-4 is also an established clinical target. It is a key factor in airway inflammation and IgE synthesis by B cells, but despite initially promising findings with biologics able to block its functions (pitakinra, pascolizumab), subsequent trials have not been as successful [10].

Future

Novel T-cell subsets (Th9 and Th17) involved in the effector mechanisms of bronchial asthma, as well as novel cytokines driving Th2 differentiation (IL-25, TSLP and IL-33) have been recently described and identified as attractive emerging therapeutic targets. As chronic airway inflammation in asthma is driven by T cells, some strategies have been oriented toward this target. Different biological agents, such as mAbs or fusion proteins, directed towards T-cell membrane or costimulatory molecules (daclizumab, xelizimab, mogamalizumab and abatacept), are in advance phases of study in asthmatic subjects [11].

These strategies may be helpful in the treatment of severe steroid-resistant asthma. Among novel asthma therapies, human IL-13-neutralizing antibodies have been developed, but further studies are awaited [12].

Despite the variable efficacy observed with omalizumab, there remains considerable interest in improving the efficacy of anti-IgE approaches by producing new mAbs towards IgE or blocking high- and low-affinity IgE receptors (RG7449; lumilixumab) [13]. These strategies could be relevant for a subgroup of patients since IgE seems to play a pivotal immunomodulatory role in not only allergic, but also in intrinsic asthma.

The majority of biologics have proven to be partially adequate or inadequate in the clinical setting of asthma. As previously outlined, the conflicting results of the trials with biological agents may be due to the selection of asthmatic subjects, taking into account that asthma is not a 'unique' disease but rather a 'syndrome', including different biological and clinical phenotypes. Indeed, the development of specific biomarkers, the definition of particular clinical features as well as genetic profiles, will be useful to identify patients with different asthma phenotypes susceptible to selected target therapies. As concerns the potential side effects of biologics, they are associated with immunogenicity and with the interference with mechanisms of both innate and acquired immunity [14]. However, it is relevant to remember that in severe steroid-resistant asthma the requirement for high doses of oral glucocorticoids and immunosuppressors (e.g., cyclosporine A) are also associated with similar side effects. Therapy tailored to each patient and a combination of several drugs, biological and pharmaceutical compounds would be a desirable solution and could have several approaches.

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