Biological therapy in severe asthma: A gem or a jam

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Severe asthma remain a great challenge for physicians. Several therapies are suggested. The only one proved to be effective in severe allergic asthma is Omalizumab. Other biological agents are in different phases in research, yet, only few of them proved some effectiveness in clinical trial. Recently Mepolizumab (a monoclonal antibody against interleukin-IL-5)was approved by the food and drug administration in United States of America (FDA) as an effective drug in severe esinophilic asthma. Other agents include anti IL 13, anti IL 4, and anti IL 17. In this editorial some of the biological therapies are reviewed.

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Severe asthma

The control of severe asthma may represent the most challenging issue in those subset of patients [1]. Patients with severe asthma are usually forced to resort to several bursts of systemic steroids in an attempt to achieve some control of their symptoms. Albeit steroids usually do not disappoint those patients, it leads to risk for one or more of a long list of adverse effects, some of which may add more impediment to their quality of life [2].

A greater understanding of the fundamental details of the pathophysiology of severe asthma has led to the identification of several targets (key mediators). The alteration of those targets is expected to add more control in patients with severe asthma and allow more limitations in systemic steroid use.

The first of such targeted therapy was the use of humanized monoclonal antibodies against IgE, which was investigated as early as 1999 [3]. Results showed a significant reductions or even discontinuation of oral steroids, improvement in asthma-related quality of life, and increase in peak expiratory flow. Numerous studies were conducted on such treatment strategy with reproducible results [4]. Accordingly, anti-IgE therapy was confidently included in the Global Initiative for Asthma (GINA) guidelines since 2005 in the treatment of severe disease (GINA stage 4) [5].

Interleukin-5 (IL-5) is pivotal in almost all functional, maturational, and survival processes of eosinophils [6]. Targeting IL-5 is expected to be beneficial in the treatment of severe asthma [7]. Humanized monoclonal antibodies against IL-5 was investigated as early as 2000 [8]; however, unexpectedly, clinical results were disappointing despite a significant decrease in blood and sputum eosinophilia. Those results were reproducible in several trials [9,10]. Nevertheless, improvement in exacerbations was achieved after selecting a subset of patients with uncontrolled asthma and high blood and sputum eosinophilia [11]. However, secondary clinical endpoints were still unsatisfactory. A more recent trial proved that mepolizumab (humanized monoclonal antibodies against IL-5) significantly reduced asthma exacerbations and improved markers of asthma control. Nevertheless, results were variable and mild in a substantial percentage of patients [12]. Currently, we are awaiting the results of a multicenter trial on mepolizumab in which the primary endpoints are clinical and functional parameters in severe asthmatic patients of eosinophilic phenotype (http://www.clinicaltrials.gov). Strong positive results will render mepolizumab a real new gem, in addition to anti-IgE therapy (omalizumab), in the treatment of severe asthma. However, if the results were a borderline positive one, as in various previous investigations, it will leave the investigators in a jam concerning the real usefulness of mepolizumab in severe asthma. Recently, the Food and Drug Administration in United States of America (FDA) approved mepolizumab as effective in improving patients with severe esinophilic asthma as compared to placebo paving the way for the drug to a real life clinical test.

Reslizumab is another monoclonal antibody against IL-5. Trials in severe eosinophilc asthmatic patients also resulted in marginal improvement in lung function parameters and asthma control questionnaire [13]. Likewise, benralizumab

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(anti-IL-5α receptor monoclonal antibody) therapy rendered weak and variable positive results in a similar set of participants [14].

IL-13 is another potential key mediator target in severe asthma. IL-13 is central in the pathophysiology of chronic asthmatic inflammation, hyper-responsiveness, and, notably, remodeling [15]. Tralokinumab [16,17], anrukinzumab [18], and librikizumab [17,19,20] are several monoclonal antibodies against IL-13, and, in severe asthma, the result of therapy was again either negative, or just yielded marginal and variable improvement. The closely related IL-4 was also a proposed target in severe asthma. Dupilumab [21] and AMG-317 [22] are IL-4 antagonists; both trials retrieved some positive results, but not enough to reach target clinical goals. Pitrakinara [23] is a recombinant human IL-4 variant, which competitively inhibits IL-4Rα receptor complex, and thus interferes with the actions of both IL-4 and IL-13. Altrakincept [24] is a soluble recombinant human IL-4 receptor that inactivates naturally occurring IL-4. Both agents were investigated earlier and yielded barely significant improvements in lung functions in asthma.

There is increased activation of CD25+ T cells in the airway inflammation in asthma, with increased levels of IL-2 and soluble IL-2 receptor α chain (IL-2Rα) [25]. Daclizumab is a monoclonal antibody against IL-2Rα chain used mainly in patients with renal transplantation and investigated in moderate-to-severe persistent asthma with some clinical improvements over placebo [26].

Another subset of T cells, Th17 with its production of IL-17, is known to be involved in airway hyper-responsiveness in asthma by recruiting both eosinophils and neutrophils [27]. However, brodalumab, an IL-17 receptor A monoclonal antibody failed to show significant clinical improvement in moderate and severe asthmatic patients [28].

Tumor necrosis factor-α (TNF-α), which is upregulated in asthma [29], was also marked as a possible therapeutic target. Infliximab [30], a recombinant human monoclonal antibody against TNF-α, was investigated in asthma and found to improve exacerbation, symptoms, and spirometric data, but benefits did not overweigh the potential hazards, especially activation of tuberculosis in patients whose steroids are a cornerstone in their treatment regimens. Etanercept [31,32], adalimumab [33], and golimumab [34] are other anti-TNF-α agents. Results of trials on asthma revealed either negative outcomes or modest positive improvements that was also questioned compared with the possible risks of such therapy.

One unmet need in the management of asthma is the treatment of those patients with neutrophilic phenotype who are steroid resistant [1]. Sch 527123 is a CXCR 1/2 receptor antagonist [35,36]. Both CXCR1 and CXCR2 are expressed in human neutrophils in asthma and chronic obstructive pulmonary disease, and thus may be a target for specific therapy [37]. Sch 527123 was found to ameliorate airway inflammation in animal models [36], and trial in humans with severe asthma with sputum neutrophilia provided some positive results; we are awaiting more profound studies [35,38,39].

The inflammatory cytokines, chemokines, and growth factors, targets for therapy in severe asthma, are numerous, estimated to be over 100 [40]. More than 30 biological therapies in asthma have been developed and investigated [41]. Most of such therapies left investigators cheerful behind the bench as they grasp definite targeted results concerning markers of inflammation they are chasing. Examples are the profound decrease in sputum and blood eosinophilia in treatment with anti IL-5 (7–10) and decrease in periostin with anti IL-13 (17–22). Nevertheless, clinicians at bedside were only disappointed with the clinical results of either negative or trivial positive statistics. Neither patients nor even clinicians are interested in improving inflammatory markers. They are mostly concerned with improving lung functions, exacerbation rate, and scores of quality of life in asthmatic patients. It is expected that overcoming one mediator, even if a pivotal one, will not arrest other counterparts from function. Thus, the broader spectrum anti-inflammatory therapy, such as with corticosteroids, is more effective compared with switching off one pathway among several ones in asthma. Moreover, ameliorating the inflammatory cascade at the starting steps is expected to be more clinically relevant in controlling most of the subsequent pathways and thus achieving strong positive clinical benefits. Such concept may be the one that allowed omalizumab to be the only biological therapy to date that is clinically relevant. Moreover, meticulous selection of certain phenotypes in asthma may pave way for a better clinical outcome. With anti-IL-5 mepolizumab therapy, patients with high blood and sputum eosinophilia showed some clinical benefits and the drug may be released in practical life after some two decades in research [11,12]. Anti-IL-13 therapy showed better outcomes in lung functions in a subset of patients with high periostin levels [19]. Nevertheless, even with good selection of the targeted phenotypes, the clinical results did not assign any drug as passed for joining the real practical life. Most of the current trials of biological therapies are neither as good as to be considered a gem in asthma treatment nor have an obviously negative outcome to omit further research,

leaving investigators in a jam of digging more for segregating the patients in sophisticated phenotypes trying to grasp a better clinical response.

We are awaiting results from a large number of clinical trials and looking forward for other therapies to be applied in treating severe asthma, to overcome the adverse effects of systemic corticosteroid use.

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