

Biological therapy in severe asthma: A gem or a jam

Hesham Raafat

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 eosinophilic asthma. Other agents include anti IL 13, anti IL 4, and anti IL 17. In this editorial some of the biological therapies are reviewed.

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

Egypt J Broncho 2016 10:1–4

© 2016 Egyptian Journal of Bronchology.

Egyptian Journal of Bronchology 2016 10:1–4

Keywords: biological therapy, mepolizumab, omalizumab, severe asthma

Department of Chest Diseases, Ain Shams University, Cairo, Egypt

Correspondence to Hesham Raafat, MD, Department of Chest Diseases, Ain Shams University, 31411 Cairo, Egypt

Tel: +966138200000; fax: +966138203436;

e-mails: heshamraafat@yahoo.com, hesham.raafat@med.asu.edu.eg

Received 23 November 2015 **Accepted** 29 November 2015

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 eosinophilic 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 eosinophilic asthmatic patients also resulted in marginal improvement in lung function parameters and asthma control questionnaire [13]. Likewise, benralizumab

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

(anti-IL-5 α 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-4R α 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-2R α) [25]. Daclizumab is a monoclonal antibody against IL-2R α 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 outweigh 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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

- Jarjour NN, Erzurum SC, Bleeker ER, Calhoun WJ, Castro M, Comhair SA, *et al.*, NHLBI Severe Asthma Research Program (SARP) Severe asthma: lessons learned from the National Heart, Lung, and Blood Institute Severe Asthma Research Program. *Am J Respir Crit Care Med* 2012; **185**:356–362.
- Frauman AG. An overview of the adverse reactions to adrenal corticosteroids. *Adverse Drug React Toxicol Rev* 1996; **15**:203–206.
- Migrom H, Fick RB, Su JQ, Reimann JD, Bush RK, Watrous ML, *et al.* Treatment of allergic asthma with monoclonal anti-IgE antibody. *N Engl J Med* 1999; **341**:1966–1977.
- Humbert M, Beasley R, Ayres J, Slavin R, Hébert J, Bousquet 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**:309–316.
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. *NIH Publication* 2005: 111–120. Available at: <http://www.ginasthma.com>
- Rosenberg HF, Phipps S, Foster PS. Eosinophil trafficking in allergy and asthma. *J Allergy Clin Immunol* 2007; **119**:1303–1310quiz 1311–1312.
- Kips JC, Tournoy KG, Pauwels RA. New anti-asthma therapies: suppression of the effect of interleukin (IL)-4 and IL-5. *Eur Respir J* 2001; **17**:499–506.
- Kips JC, O'Connor BJ, Langley SJ, Woodcock A, Kerstjens HAM, Postma DS, *et al.* Results of a phase I trial with SCH55700, a humanized anti-IL-5 antibody, in severe persistent asthma. *Am J Respir Crit Care Med* 2000; **161**:A505.
- Kips JC, O'Connor BJ, Langley SJ, Woodcock A, Kerstjens HA, Postma DS, *et al.* Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. *Am J Respir Crit Care Med* 2003; **167**:1655–1659.
- Flood-Page P, Swenson C, Faiferman I, Matthews J, Williams M, Brannick L, *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**:1062–1071.
- Pavord ID, Korn S, Howarth P, Bleeker ER, Buhl R, Keene ON, *et al.* Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012; **380**:651–659.
- Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, *et al.* Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; **371**:1198–1207.
- Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, *et al.* Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2011; **184**:1125–1132.
- Castro M, Wenzel SE, Bleeker ER, Pizzichini E, Kuna P, Busse WW, *et al.* Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med* 2014; **2**:879–890.
- Zhu Z, Homer RJ, Wang Z, Chen Q, Geba GP, Wang J, *et al.* Pulmonary expression of interleukin-13 causes inflammation, mucus hypersecretion, subepithelial fibrosis, physiologic abnormalities, and eotaxin production. *J Clin Invest* 1999; **103**:779–788.
- Piper E, Brightling C, Niven R, Oh C, Faggioni R, Poon K, *et al.* A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma. *Eur Respir J* 2013; **41**:330–338.
- Brightling CE, Chanez P, Leigh R, O'Byrne PM, Korn S, She D, *et al.* Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet Respir Med* 2015; **3**:692–701.
- Hua F, Ribbing J, Reinisch W, Cataldi F, Martin S. A pharmacokinetic comparison of anrukinzumab, an anti-IL-13 monoclonal antibody, among healthy volunteers, asthma and ulcerative colitis patients. *Br J Clin Pharmacol* 2015; **80**:101–109.
- Corren J, Robert F, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, *et al.* Lebrikizumab treatment in adults with asthma. *N Engl J Med* 2011; **365**:1088–1098.
- Hanania NA, Noonan M, Corren J, Korenblat P, Zheng Y, Fischer SK, *et al.* Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies. *Thorax* 2015; **70**:748–756.
- Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, *et al.* Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013; **368**:2455–2466.
- Corren J, Busse W, Meltzer EO, Mansfield L, Bensch G, Fahrenholz J, *et al.* A randomized, controlled, phase 2 study of AMG 317, an IL-4/IL-13 antagonist, in patients with asthma. *Am J Respir Crit Care Med* 2010; **181**:788–796.
- 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**:1422–1431.
- Borish LC, Nelson HS, Lanz MJ, Claussen L, Whitmore JB, Agosti JM, Garrison L Interleukin-4 receptor in moderate atopic asthma. A phase I/II randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 1999; **160**:1816–1823.
- Park CS, Lee SM, Chung SW, Uh S, Kim HT, Kim YH. Interleukin-2 and soluble interleukin-2 receptor in bronchoalveolar lavage fluid from patients with bronchial asthma. *Chest* 1994; **106**:400–406.
- Busse WW, Israel E, Nelson HS, Baker JW, Charous BL, Young DY, *et al.* Daclizumab improves asthma control in patients with moderate to severe persistent asthma: a randomized, controlled trial. *Am J Respir Crit Care Med* 2008; **178**:1002–1008.
- Kudo M, Melton AC, Chen C, Engler MB, Huang KE, Ren X, *et al.* IL-17A produced by ab T cells drives airway hyper-responsiveness in mice and enhances mouse and human airway smooth muscle contraction. *Nat Med* 2012; **18**:547–554.
- Busse WW, Holgate S, Kerwin E, Chon Y, Feng J, Lin J, Lin SL Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. *Am J Respir Crit Care Med* 2013; **188**:1294–1302.
- Obase Y, Shimoda T, Mitsuta K, Matsuo N, Matsuse H, Kohno S. Correlation between airway hyperresponsiveness and airway inflammation in a young adult population: eosinophil, ECP, and cytokine levels in induced sputum. *Ann Allergy Asthma Immunol* 2001; **86**:304–310.
- Erin EM, Leaker BR, Nicholson GC, Tan AJ, Green LM, Neighbour H, *et al.* The effects of a monoclonal antibody directed against tumor necrosis factor- α in asthma. *Am J Respir Crit Care Med* 2006; **174**:753–762.
- Howarth PH, Babu KS, Arshad HS, Lau L, Buckley M, McConnell W, *et al.* Tumour necrosis factor (TNF α) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax* 2005; **60**:1012–1018.
- Berry MA, Hargadon B, Shelley M, Parker D, Shaw DE, Green RH, *et al.* Evidence of a role of tumor necrosis factor alpha in refractory asthma. *N Engl J Med* 2006; **354**:697–708.
- Catal F, Mete E, Tayman C, Topal E, Albayrak A, Sert H. A human monoclonal anti-TNF α antibody (adalimumab) reduces airway inflammation and ameliorates lung histology in a murine model of acute asthma. *Allergol Immunopathol (Madr)* 2015; **43**:14–18.
- Wenzel SE, Barnes PJ, Bleeker ER, Bousquet J, Busse W, Dahlén SE, *et al.*, T03 Asthma Investigators A randomized, double-blind, placebo-controlled study of tumor necrosis factor- α blockade in severe persistent asthma. *Am J Respir Crit Care Med* 2009; **179**:549–558.
- Nair P, Gaga M, Zervas E, Alagha K, Hargreave FE, O'Byrne PM, *et al.* Safety and efficacy of a CXCR2 antagonist in patients with severe asthma and sputum neutrophils: a randomized, placebo-controlled clinical trial. *Clin Exp Allergy* 2012; **42**:1097–1103.
- Chapman RW, Minniccozzi M, Celly CS, Phillips JE, Kung TT, Hipkin RW, *et al.* A novel, orally active CXCR1/2 receptor antagonist, Sch527123,

inhibits neutrophil recruitment, mucus production, and goblet cell hyperplasia in animal models of pulmonary inflammation. *J Pharmacol Exp Ther* 2007; **322**:486–493.

- 37** Traves S, Smith SJ, Barnes PJ, Donnelly LE. Specific CXC but not CC chemokines cause elevated monocyte migration in COPD: a role for CXCR2. *J Leukoc Biol* 2004; **76**:441–450.
- 38** Gaga M, Nair PK, Hargreave F, Sadeh J, Chanez p. Sch527123, a novel treatment option for severe neutrophilic asthma. *Am J Respir Crit Care Med* 2010; **181**:A6763.
- 39** Planagumà A, Domènech T, Pont M, Calama E, García-González V, López R, *et al.* Combined anti CXC receptors 1 and 2 therapy is a promising anti-inflammatory treatment for respiratory diseases by reducing neutrophil migration and activation. *Pulm Pharmacol Ther* 2015; **34**:37–45.
- 40** Adcock IM, Caramori G, Chung KF. New targets for drug development in asthma. *Lancet* 2008; **372**:1073–1087.
- 41** Durham AL, Caramori G, Chung KF, Adcock IM. Targeted anti-inflammatory therapeutics in asthma and chronic obstructive lung disease. *Transl Res* 2016; **167**:192–203.