EXPERT OPINION

Tralokinumab for uncontrolled asthma

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Introduction: Asthma is a chronic inflammatory disease of the airways mainly related to allergen exposure, in which various cytokine-specific pathways interact among themselves to promote IgE hyperproduction, bronchial hyper-responsiveness, eosinophil local recruitment and airways remodeling. IL-13 is known for its prominent pathogenic role in this disease and therapeutic blocking approaches are underway.

Areas covered: Anti-IL-13 antibodies are currently investigated in clinical studies in uncontrolled asthma. Tralokinumab is a human IgG4 anti IL-13 antibody which was recently evaluated in a Phase II study demonstrating the maximal efficacy in a subset of asthma patients characterized by the highest sputum IL-13 levels. The results of this study are discussed in this paper.

Expert opinion: The IL-13 blockade with various therapeutic approaches such as tralokinumab has the potential to improve the asthma control in patients subsets in whom the blocked cytokine is demonstrated to be overexpressed.

Keywords: asthma, IL-13, monoclonal antibody, tralokinumab

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1. Introduction

Asthma is a chronic disease of the airways related mainly to allergen exposure in which the resulting inflammation produces bronchial hyperreactivity to various stimuli including allergens themselves. Clinically, it manifests by bronchospasm attacks characterized by episodic dyspnea, cough or chest constriction.

The airways inflammation in asthma is the result of complex interactions among the Th2-related cytokines such as IL-4, IL-5 or IL-13 and various cell populations such as eosinophils and mast cells.

IL-13 in particular was demonstrated to promote IgE production, eosinophil recruitment in the airways and airways fibrogenesis (remodeling) acting via common IL-4Rα/IL-13Rα1-dependent activating pathway or via IL-4Rα-independent mechanisms [1].

The airways inflammation in asthma is currently treated with inhaled corticosteroids or with leukotriene modifiers and in most cases such therapies are able to control the disease when given alone or in combination [2]. For more severe atopic asthma subjects, specific anti-inflammatory therapies such as omalizumab are indicated in an attempt to obtain a better diseases control [2]. However, there are subjects with therapeutic refractoriness in whom this can be caused by abnormally upregulated inflammation which is driven by a specific cytokine and which cannot be controlled by the mentioned therapies. In such situations, cytokine-specific inhibition of this inflammation added to the non-specific similar effect produced with conventional anti-inflammatory agents used in asthma can have the potential to control the disease.

One such approach can be represented by the inhibition of the inflammation with various methods including monoclonal antibodies [3-5]. Such an approach was found to be appropriate with omalizumab (anti-IgE antibody) or with mepolizumab

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Article highlights.

- In asthma, chronic inflammation of the airways is caused by a complex interaction among various cytokine pathways including IL-13 pathway.
- Asthma-related airways inflammation is usually treated with inhaled corticosteroids, but in some patients this therapy is not effective.
- In such patients, specific blockade of the involved cytokines including IL-13 can contribute to a better disease control.
- IL-13 blockade with monoclonal antibodies such as tralokinumab or lebrikizumab can reduce airways inflammation.
- These therapies can exert their maximal therapeutic benefit in patients in whom IL-13 is overexpressed.
- IL-13 pathway upregulation in the airways can be detected directly with sputum cytokine levels or indirectly with biomarkers of upregulation such as periostin.
- Tralokinumab can improve lung function and reduce airways inflammation when added to inhaled corticosteroids.

This box summarizes key points contained in the article.

(anti-IL-5 antibody). In the case of IL-13 pathway [6,7], antibodies such as lebrikizumab, tralokinumab or GSK679586 are currently investigated in clinical studies in patients with uncontrolled asthma.

Tralokinumab (CAT-354) is a human IgG4 monoclonal antibody which was evaluated in preclinical studies for its therapeutic effects and then advanced in the clinical studies in allergic diseases such as asthma [8,9].

This paper evaluates a clinical Phase II study on tralokinumab in patients with asthma.

2. Study overview

This was a Phase IIa proof-of-concept 24-week study evaluating the efficacy and safety of tralokinumab in patients with moderate-to-severe uncontrolled asthma over a 12-week dosing period (ClinicalTrials.gov identifier: NCT00873860). Three doses of tralokinumab 150, 300 or 600 mg given subcutaneously every 2 weeks were compared with placebo. Enrolled patients received during the study the previous maintenance therapy, that is, inhaled corticosteroids associated with inhaled long-acting β2 agonists or with cysteinyl leukotriene antagonists [5]. Among the inclusion criteria considered were reversible airflow obstruction, Asthma Control Questionnaire (ACQ-6) score ≥ 1.5 at randomization and at least one asthma exacerbation requiring healthcare professional attention during the previous year. Patients with a history of smoking ≥ 10 pack-years, with recent history of infections or undergoing immunosuppressive medications were excluded.

The primary end point was the change from baseline in the ACQ-6 at the week 13 of study, and secondary end points included time to asthma control, time to the first exacerbation, asthma exacerbation rate, use of rescue medication, lung function and health-related quality of life (HRQoL). Adverse events were recorded throughout the study period. Additional end points included sputum IL-13 content and tralokinumab pharmacokinetics. *Post hoc* analyses were performed on 12-week change in FEV1 and in ACQ-6 scores in various populations defined according to the presence of atopic status or baseline dose of inhaled corticosteroids, or baseline sputum IL-13 content. Intention-to-treat population included 194 patients, most of them (60%) being women, 52% of the enrolled subjects were atopic, the mean baseline FEV1 percent predicted (%pred) was 61%, the mean baseline ACQ-6 was 2.66 and the median dose of inhaled corticosteroids was 1000 µg/day.

Although tralokinumab was associated with a greater improvement in baseline ACQ-6 as compared with placebo, this was not statistically significant. A higher percentage of subjects receiving tralokinumab clinically exhibited meaningful improvements in ACQ-6 (i.e., ≥ 0.5 units) as compared with placebo (58.3 vs 52.2%). The maximum effect was obtained in patients with sputum IL-13 levels ≥ 10 pg/ml (sputum-'positive') subjects (-0.97 compared with -0.62 in sputum-negative tralokinumab group and -0.43 in placebo group).

Overall, at week 13, tralokinumab improved the baseline pre-bronchodilator FEV1 as compared with placebo, this effect being dose-dependent (0.16 l with 150 mg to 0.26 l with 600 mg). The therapeutic effect became obvious after the first dose and persisted over an interval of 24 weeks. An effect similar to that on the ACQ-6 was found for the FEV1 in populations stratified according to the sputum IL-13 level (0.37 l in sputum-positive subjects compared with 0.10 l in sputum-negative subjects treated with tralokinumab and 0.12 l in placebo group). Compared with placebo, tralokinumab reduced significantly the use of rescue medication after 12 weeks, and this effect persisted after 12 weeks of therapy discontinuation. No significant effects were reported for asthma exacerbations rate and for HRQoL scores. The incidence of treatment-emergent adverse events was reported to be higher in subjects receiving tralokinumab, asthma control loss, headache and nasopharyngitis being the most commonly reported events. A dose-dependent increase in drug exposure was reported for tralokinumab up to 10 weeks of dosing when the steady state was reached, and no immunogenicity was detected over the dosing period.

3. Discussion

This proof-of-concept study demonstrates that the addition of an anti-IL-13 antibody to the regular maintenance therapy in patients with moderate to severe uncontrolled asthma can produce beneficial effects on lung function and secondarily on the overall disease control. Such effects seem to be dose-dependent and more prominent in subjects with upregulated IL-13 pathway, that is, with higher IL-13 sputum levels. Thus, such effects are supportive enough to prompt the further clinical

evaluation of tralokinumab in other studies with populations predefined based on the results of the current study.

As regards the study methodology, its duration was appropriate for evaluating the lung function, the asthma disease control and the use of rescue medications, such as short-acting inhaled bronchodilators. Surprisingly, the weekly variability of peak expiratory flow (PEF) was not analyzed, although this variable was measured both at home and during hospital visits. PEF variability is also an indirect measure of the therapeutic control of the chronic inflammation in the airways. Another marker (biomarker) of airways inflammation commonly used in asthma trials is the fraction of the exhaled nitric oxide (FeNO), which was not considered as an end point. One could argue that given the early stage of clinical evaluation of this therapy this variable could be avoided. However, given the very appropriate consideration of the sputum baseline IL-13 level as a stratifier of efficacy in the *post hoc* analysis, the FeNO behavior in the related population subsets would have further informed on the magnitude and dynamics of airways inflammation under tralokinumab therapy. HRB should also be considered in the next studies.

It could be noted that tralokinumab demonstrated a maximal efficacy in a subset of patients with severe asthma characterized by an upregulated IL-13 expression in sputum. This approach might be supported by the existing findings demonstrating that the upregulation of IL-13 is not found in all asthma patients and might use the sputum IL-13 as a biomarker to assess the efficacy of such therapies [10]. The IL-13 'phenotype' is probably going to be the most appropriate therapeutic target for such a therapy, as in this setting the IL-13 aberrant augmentation might represent the cause of severity/refractoriness to therapy despite optimal conventional therapy.

A similar approach was used in clinical trials evaluating the efficacy of another monoclonal antibody, lebrikizumab in a comparable population of patients in terms of disease severity. In one such study, the target population was not defined by the levels of IL-13 itself, but with a biomarker of its abnormal augmentation, that is, periostin: in the population subset characterized by high serum periostin levels, the improvement in lung function was significant as compared with placebo (therapeutic difference 8.2% for prebronchodilator FEV1% pred, $p = 0.03$) [3].

4. Expert opinion and conclusions

Asthma is a complex inflammatory disease of the airways in which complex interactions among various inflammatory pathways occur. In asthma, IL-13 is known for its potent pro-inflammatory effect exerted alone or via a pathogenic cross-talk with IL-4. Its inhibition with various approaches such as antibodies, receptor antagonists or modified (variant) cytokines was demonstrated to reduce the related inflammation in various animal models of asthma. Their clinical evaluation in short-term studies yielded similar results, the efficacy end point being that the most beneficially influenced by such therapies is the lung function. Most of the existing studies demonstrated that the efficacy of cytokine-directed monoclonal antibodies was not uniform but was more significant in certain asthma population subsets. This was not found only with the IL-13 blockade but also with IL-5 blockade with mepolizumab. In the former case, the most striking effects were found in subsets with biomarkers of upregulated IL-13 pathway, that is, high cytokine level in sputum, the highest blood eosinophil count or high serum periostin level. In such subjects, the increased activity of IL-13 might explain the poor disease control despite appropriate therapy.

However, IL-13-specific blockade might be associated with a compensatory IL-4 pathway upregulation. This can be used to indirectly document the potency of the IL-13 blockade by evaluating the dynamics of sputum IL-4 throughout anti-IL-13 therapy dosing.

Given that in this study a higher incidence of side effects was found in the treated population, the long-term safety of such a therapy should also be assessed in the next phases of clinical development.

Such findings open the door for personalized medicine approach in asthma. In this disease, the optimal control is usually achieved with regular use of anti-inflammatory therapies such as inhaled corticosteroids and leukotriene modifiers. However, in a small percentage of subjects, the disease control is poor because of various factors, one of them being the partial efficacy of the conventional anti-inflammatory therapies administered. This is due to the fact that one or more pro-inflammatory pathways are marginally inhibited and still able to maintain the airways inflammation at a level which is adequate to produce symptoms flare or frequent attacks.

Therefore, in such patients it is worth attempting to characterize the inflammatory cytokine pattern in serum and in sputum in order to find out which pathogenic pathway is the most suitable for therapeutic blockade.

Such an approach is justified by various reasons: first the fact that other cytokines such as IL-4, or -5 or -9 when upregulated are able to induce pathogenic and clinical features similar to those produced by the IL-13 overexpression, second the fact that compounds aimed at blocking such cytokines are currently under development and might also be found to be efficacious only in certain population subsets and third the fact that the potentially high costs of such compounds might prevent them from being given to any subject with uncontrolled asthma.

Consequently, in the near future in patients with anti-inflammatory refractoriness phenotypes it might be justified that the Th2-related inflammatory pattern should be detected with a test battery because a targeted specific anti-inflammation can be attempted based on its results.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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