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Andrea J. Apter, MD, MSc, MA



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The Tralokinumab Story: Nothing is ever simple

Andrea J. Apter, MD, MSc, MA

Division of Pulmonary, Allergy, & Critical Care medicine, Perelman School of Medicine,
University of Pennsylvania, Philadelphia, PA 19104, USA

Correspondence:

Andrea J. Apter, MD, MSc, MA

829 Gates Building

Hospital of the University of Pennsylvania

3600 Spruce Street

Philadelphia, PA 19104

Telephone: 215

apter@pennmedicine.upenn.edu

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Recently, we have been inundated with new biologics, monoclonal antibodies, that block specific pathologic inflammatory pathways, many for asthma addressing type 2 pathways. Among them are monoclonal antibodies directed at IL-13. They have included lebrikizumab which is no longer in development because of lack of efficacy,¹ dupilimab (which targets the receptor shared by IL-13 and IL-4 and inhibits both IL-4 and IL-13),² and tralokinumab. Recently, Phase 2 (MESOS) and Phase 3 studies (STRATOS 1, STRATOS 2) of tralokinumab were published in *The Lancet Respiratory Medicine*.^{3,4} These tralokinumab studies provide an interesting twist to the monoclonal antibody story of therapeutics: nothing is ever simple.

Tralokinumab is a human IgG4 antibody that prevents the interaction of IL-13 with its receptor. IL-13 is produced by Th2, ILC2, mast cells, eosinophils, and NKT cells. Neutralizing IL-13 has the theoretical potential of reducing eosinophilic inflammation and inhibiting IgE production, macrophage and dendritic cell activation, mucus production, as well as airway smooth muscle and fibroblast remodeling. IL-13 is thought to mediate eosinophil trafficking from blood to tissue and, through upregulation of P-selectin, to increase adhesion of eosinophils to endothelium.⁵ Interestingly IL-13 neutralization is associated with an increase in peripheral blood eosinophil count (unlike anti-IL-5 monoclonal antibodies), possibly by inhibiting eosinophil-endothelial adhesion.⁶ As noted below, this theory is explored in the MESOS Study, as it examines the effect of eosinophilic infiltration in airways and sputum.⁴ In an earlier Phase 2b trial, tralokinumab given every 2 weeks improved pre-bronchodilator FEV1, but it did not reduce asthma exacerbation rates in subjects with uncontrolled asthma.⁷ Thus, IL-13 potentially plays a role in the inflammatory pathogenesis of asthma and, if so, an IL-13 antibody has a potential therapeutic role. A clinical outcome like exacerbations is the most important marker of therapeutic relevance. The recent Phase 3 studies (STRATOS 1 and 2) address this question.

In the Phase 2 study (MESOS), Russell et al. examined whether tralokinumab could affect airway eosinophilic infiltration, blood and sputum eosinophil concentration, eosinophil activation, and airway remodeling. In a double-blind, randomized, placebo-controlled trial, adults were randomized to tralokinumab or placebo SQ (Table 1). At enrollment subjects were required to be exacerbation-free for at least 6 weeks before enrollment, and to have had no more than 3 exacerbations requiring oral corticosteroids in the preceding 12 months. Enrolled subjects then entered a run-in period during which they demonstrated post-bronchodilator reversibility of at least 12% and at least 200 ml and an Asthma Control Questionnaire (ACQ)-6 score greater than or equal to 1.5 (in the uncontrolled range).

Of 274 enrolled subjects in MESOS, only 79 were randomized (52 did not participate in the run-in, 88 did not meet eligibility criteria, 5 withdrew). There was no difference between the tralokinumab-treated and the placebo groups in the primary outcome: change from baseline to week 12 in eosinophil count of a bronchial biopsy. There was no difference between tralokinumab and placebo groups in blood, or sputum eosinophil counts. FENO and total IgE concentration in blood were reduced but these are biomarkers and not direct clinical events. Importantly, only one exacerbation of asthma was reported and it was in the placebo group. Thus, the MESOS findings did not support the efficacy of tralokinumab or the hypothesis that IL-13 inhibits eosinophil-endothelial adhesion in which one would have expected an increase in blood eosinophilia and decrease in eosinophils in tissue (sputum and bronchial submucosa). FENO and total IgE concentrations, out of a series of potential biomarkers tested, were reduced in the MESOS tralokinumab-exposed group. Investigators wondered if tralokinumab would be efficacious in a subgroup of those with high baseline FENO concentration. STRATOS 1 examined the annual asthma exacerbation rate in all subjects and STRATOS 2 in those in a subgroup with high baseline FENO defined in STRATOS 1.

STRATOS 1 and STRATOS 2 were 52-week randomized double-blind, parallel-group, placebo-controlled clinical trials (Table 1). Subjects in STRATOS 1 were randomized 2:1 to receive tralokinumab 300 mg SQ or placebo every 2 weeks or every 4 weeks. In STRATOS 2 participants were randomized 1:1 to 300 mg tralokinumab or placebo SC every 2 weeks. Both studies had a run-in similar to MESOS. In both trials asthma exacerbations, the main outcome, were defined as worsening of asthma that led to use of systemic corticosteroids for at least 3 days, an ED visit due to asthma that required systemic corticosteroid, or a hospital admission for asthma.

In STRATOS 1 tralokinumab did not show any effect on the annual asthma exacerbation rate, the primary outcome, over placebo. FENO concentrations and total blood IgE were reduced in the tralokinumab –treated group. However, the subgroup with high FENO did not show a difference in eosinophilic inflammation compared to placebo.

In STRATOS 2 neither the entire group nor those with baseline elevated FENO had a significant reduction in annual asthma exacerbation rate compared with placebo. Development of tralokinumab has since ceased.

Nothing is ever simple. These results are consistent with the lack of efficacy in lebrikizumab and the efficacy demonstrated in clinical trials of dupilumab, other antibodies that affect IL-13. They are not inconsistent with the findings regarding anti-IL-5 molecules. But it is disconcerting that findings that anti-IL-13 exposure reduces some but not all relevant biomarkers: FENO and IgE, but has no effect on clinical events like exacerbations immunologically-linked to these markers. One also wonders why an antibody to IL-4 would make a clinical difference (reduce exacerbations) when an antibody to IL-13 would not. Recently the route of administration was considered along with the size of the antibody

particles. Lightwood and colleagues reported the preliminary efficacy of an inhaled IL-13 mAB Fab antibody fragment in macaques using a vibrating membrane nebulizer.⁸ The macaques were sensitized to *Ascaris suum*. Inhaled anti-IL-13 abrogated the increase in pulmonary resistance and lung inflammation caused by challenge with inhaled *A. suum*. This research suggests other questions worthy of investigation. Have we identified all the relevant biomarkers that might identify a subset of patients that might respond? And, particularly for eosinophil-mediated diseases, would introducing the antibody or antibody fragments directly into relevant compartments, that is, inhalation of antibody fragments, result in an efficacious response with little toxicity?

Even if monoclonal antibodies like anti-IL-13 do not prove to be effective, studying these new biologics and their associated immunologic markers will eventually help us better understand the mechanism of inflammation and how it is affected by other antibody molecules. Ultimately what must be determined is clinical effectiveness and the duration of benefit under real-world conditions in patients who also have co-morbidities. These patients are not included in Phase 2 and 3 trials. Comparisons will have to be made about the cost effectiveness of these medications compared with the cost-effectiveness of the older medications, particularly in vulnerable populations at high risk for poor outcome.

REFERENCES

1. Hanania NA, Korenblat P, Chapman KR, Bateman ED, Kopecky P, Paggiaro P, et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir Med* 2016;4:781-96.
2. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *The New England journal of medicine* 2018;378:2486-96.
3. Panettieri RA Jr, Sjobring U, Peterffy AM, Wessman P, Bowen K, Piper E, et al. Tralokinumab for severe, uncontrolled asthma (STRATOS 1 and STRATOS 2): two randomised, double-blind, placebo-controlled, phase 3 clinical trials. *Lancet Respir Med* 2018;6:511-25.
4. Russell RJ, Chachi L, FitzGerald JM, Backer V, Olivenstein R, Titlestad IL, et al. Effect of tralokinumab, an interleukin-13 neutralising monoclonal antibody, on eosinophilic airway inflammation in uncontrolled moderate-to-severe asthma (MESOS): a multicentre, double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Respir Med* 2018;6:499-510.
5. Rosenberg HF, Phipps S, Foster PS. Eosinophil trafficking in allergy and asthma. *The Journal of allergy and clinical immunology* 2007;119:1303-10; quiz 11-2.
6. Brightling CE, Saha S, Hollins F. Interleukin-13: prospects for new treatments. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology* 2010;40:42-9.
7. 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.
8. Lightwood D, Tservistas M, Zehentleitner M, Sarkar K, Turner A, Bracher M et al. Efficacy of an Inhaled IL-13 Antibody Fragment in a Model of Chronic Asthma. *American journal of respiratory and critical care medicine* 2018;198:610-9.

9. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respiratory medicine* 2005;99:553-8.
10. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902-7.

Table 1. Summary of hypotheses, demographics, study characteristics, and results of the MENOS, STRATOS 1, and STRATOS 2 randomized placebo-controlled trials.

	MENOS	STRATOS 1	STRATOS 2
Hypothesis: tralokinumab...	...affects airway eosinophilic infiltration, blood and sputum eosinophil concentration...	...reduces AAER in all patients	... is efficacious in all patients and in those positive for certain biomarkers identified in STRATOS 1
Study Design	RDBPCT	RDBPCT	RDBPCT
Subjects			
No of subjects	79*	856	1207
Female	~53%	~65%	~67%
Age (years)	18 - 75	12 - 75	12 - 75
Mean (years)	49	~50	~50
Black/ African American	<5%	<5%	<10%
History of asthma	Diagnosed $\geq$ 12months earlier	Diagnosed $\geq$ 12months earlier	Diagnosed $\geq$ 12months earlier
Daily Inhaled corticosteroid requirement (mcg/d fluticasone equivalent)	$\geq$ 250	$\geq$ 500	$\geq$ 500
Asthma control [†]	ACQ-6 > 1.5 at baseline	ACQ-6 > 1.5 at baseline	ACQ-6 > 1.5 at baseline
Excluded comorbidities	Other clinically important pulmonary disease	Other clinically important pulmonary disease	Hx interstitial lung disease, COPD, or other clinically significant lung disease
Study characteristics			
Number of sites/countries	15/3	246/14	242/13
Tralokinumab dose	300 mg SQ q 2weeks	300 mg SQ q 2weeks or every 4 weeks	300 mg SQ q 2weeks
Randomization scheme	1:1	2:1	1:1
Primary Outcome	Change in number of eosinophils/mm ² from baseline to week 12	AAER up to week 52	AAER up to week 52
Treatment period (weeks)	12	52	52
Follow up (weeks)	14	20	30
Conclusion	Hypothesis not supported	No effect on AAER	No effect on AAER

AAER = annualized asthma exacerbation rate, RDBPCT = randomized double-blind placebo-controlled trial

*274 enrolled, 79 randomized, [†]ACQ-6 is the 6-item Asthma Control Questionnaire^{9,10}