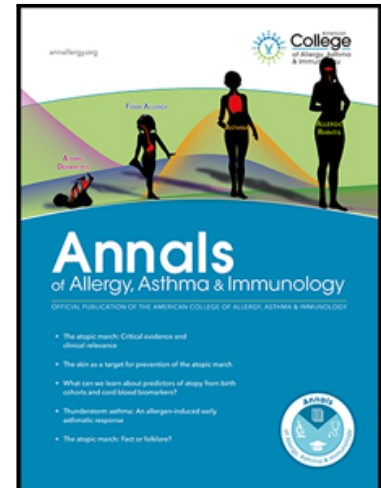


Journal Pre-proof

Tezepelumab normalizes serum interleukin-5 and -13 levels in patients with severe, uncontrolled asthma

Tuyet-Hang Pham MT, MS , Claudia Chen MS, MPH ,
Gene Colice MD , Jane R Parnes MD , Janet M Griffiths PhD ,
Bill Cook PhD

PII: S1081-1206(21)00566-4
DOI: <https://doi.org/10.1016/j.anai.2021.08.008>
Reference: ANAI 3686



To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 9 May 2021
Revised date: 8 July 2021
Accepted date: 9 August 2021

Please cite this article as: Tuyet-Hang Pham MT, MS , Claudia Chen MS, MPH , Gene Colice MD , Jane R Parnes MD , Janet M Griffiths PhD , Bill Cook PhD , Tezepelumab normalizes serum interleukin-5 and -13 levels in patients with severe, uncontrolled asthma, *Annals of Allergy, Asthma Immunology* (2021), doi: <https://doi.org/10.1016/j.anai.2021.08.008>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc.

Tezepelumab normalizes serum interleukin-5 and -13 levels in patients with severe, uncontrolled asthma

Tuyet-Hang Pham, MT, MS;^{*} Claudia Chen, MS, MPH;[†] Gene Colice, MD;[‡] Jane R Parnes, MD;[§] Janet M Griffiths, PhD;^{*,a} Bill Cook, PhD^{¶,a}

^{*}Translational Science and Experimental Medicine, Research and Early Development, Respiratory and Immunology, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, Maryland

[†]Biometrics, Late-stage Development, Respiratory and Immunology, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, Maryland

[‡]Late-stage Development, Respiratory and Immunology, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, Maryland

[§]Translational Medicine, Amgen, Thousand Oaks, California

[¶]Respiratory and Immunology, BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, Maryland

Correspondence to:

Tuyet-Hang Pham

AstraZeneca

1 Medimmune Way, Gaithersburg, MD 20878, USA

Phone: 1-301-398-6408

tuyet-hang.pham@astrazeneca.com

^aThese authors contributed equally to this work

Conflicts of interest

Tuyet-Hang Pham, Claudia Chen, Gene Colice, Janet M Griffiths, and Bill Cook are employees of AstraZeneca and may own stock or stock options in AstraZeneca. Jane R Parnes is an employee of Amgen Inc and owns stock and stock options in Amgen Inc.

Funding source

This study was funded by AstraZeneca and Amgen Inc.

Author contributions

Tuyet-Hang Pham, Claudia Chen, Gene Colice, Jane R Parnes, Janet M Griffiths and Bill Cook contributed to the conception and design of the study and interpretation of data. Claudia Chen also performed the statistical analyses. All authors contributed to drafting the manuscript, reviewing it critically for important intellectual content, gave final approval of the version to be published, and agree to be accountable for all aspects of the work related to its accuracy or integrity.

Clinical trial registration

<https://clinicaltrials.gov/>; identifier: NCT03688074

Keywords (max. 12)

Asthma, biomarkers, cytokines, inflammation, IL-5, IL-13, interleukin-5, interleukin-13, reference values, tezepelumab, thymic stromal lymphopoietin, TSLP

Abbreviations/acronyms

FeNO, fractional exhaled nitric oxide; IL, interleukin; ILC2, type 2 innate lymphoid cell; Q4W, every 4 weeks; Th2, type 2 T helper; TSLP, thymic stromal lymphopoietin

Asthma is a chronic, heterogeneous disease of the airways that involves a multitude of inflammatory processes triggered by various airborne stimuli. Thymic stromal lymphopoietin (TSLP) – an epithelial cell-derived cytokine produced in response to triggers such as allergens, viruses, or pollutants – has a central role in activating and maintaining downstream inflammatory processes in asthma.¹ Tezepelumab is an anti-TSLP human monoclonal antibody. In the PATHWAY phase 2b (NCT02054130) and NAVIGATOR phase 3 (NCT03347279) studies, tezepelumab significantly reduced exacerbation rates versus placebo in patients with severe, uncontrolled asthma.^{2,3}

Important downstream drivers of the asthma inflammatory response include the type 2 cytokines interleukin (IL)-5 and IL-13. The major cellular sources of IL-5 are type 2 T helper (Th2) cells and type 2 innate lymphoid cells (ILC2s). IL-5 acts as an amplifier of eosinophilic inflammation by enhancing eosinophil maturation, proliferation, and survival,⁴ which may result in airway remodeling.⁵ IL-13, produced largely by Th2 cells, ILC2s, mast cells, and basophils, contributes to immunoglobulin E synthesis and may lead to elevated fractional exhaled nitric oxide (FeNO) levels, airway hyperresponsiveness, and mucus hypersecretion.⁶ Biomarkers of IL-5 and IL-13 activity – blood eosinophil counts and FeNO levels – were substantially reduced after TSLP blockade with tezepelumab in PATHWAY.² This *post hoc* analysis aimed to evaluate serum IL-5 and IL-13 levels before and after treatment with tezepelumab in PATHWAY participants relative to levels observed in a separate cohort of healthy individuals.

PATHWAY was a multicenter, randomized, double-blind, placebo-controlled study conducted at 108 sites across 12 countries. The full study design and inclusion criteria have been described previously.² Eligible patients were current non-smokers, aged 18–75 years, with severe asthma that was inadequately controlled with medium- or high-dose inhaled corticosteroids (fluticasone dry powder or equivalent, 250–500 µg/day or >500 µg/day,

respectively) plus a long-acting β_2 -agonist. Participants (N=550) were randomized 1:1:1:1 to receive subcutaneous doses of tezepelumab 70 mg every 4 weeks (Q4W) (n=138), 210 mg Q4W (n=137), 280 mg every 2 weeks (n=137), or placebo every 2 weeks (n=138), for 52 weeks. Serum samples from healthy volunteers (n=50) who had not been clinically diagnosed with any disorders, were not taking any prescription medications, and were age-matched with the PATHWAY population, were obtained from a vendor (Bioreclamation, Westbury, NY, USA) and processed similarly to the PATHWAY samples. Simoa ultra-sensitive immunoassays (Quanterix, Lexington, MA, USA) were used to determine serum IL-5 and IL-13 levels in PATHWAY participants at baseline and week 52, as well as in healthy individuals. The lowest limit of detection and lowest limit of quantitation were 0.004 pg/mL and 0.033 pg/mL, respectively, for IL-5 and 0.002 pg/mL and 0.008 pg/mL, respectively, for IL-13. Tezepelumab data presentation focuses on the 210 mg Q4W dose group, the regimen being used in phase 3 studies.

At baseline, serum IL-5 and IL-13 levels were nominally significantly higher in PATHWAY participants than in healthy individuals (Fig 1A, B). Median (range) IL-5 levels at baseline were 0.68 (0.04–80.16) pg/mL and 0.66 (0.03–15.00) pg/mL in the tezepelumab 210 mg Q4W and placebo groups, respectively, compared with 0.34 (0.07–1.50) pg/mL in the healthy cohort (Fig 1A). Median (range) IL-13 levels at baseline were 0.03 (0.01–0.63) pg/mL and 0.04 (0.01–0.63) pg/mL in the tezepelumab 210 mg Q4W and placebo groups, respectively, versus 0.01 (0.01–0.10) pg/mL in the healthy cohort (Fig 1B). At week 52, serum IL-5 and IL-13 levels in the placebo cohort (IL-5, median [range] 0.70 [0.03–6.10] pg/mL; IL-13, 0.03 [0.01–0.85] pg/mL) were similar to levels observed at baseline in both the placebo and tezepelumab 210 mg Q4W groups (Fig 1A, B). After 52 weeks of tezepelumab treatment, serum IL-5 and IL-13 levels were nominally significantly reduced (IL-5, median [range] 0.25

[0.03–5.07]; IL-13, 0.02 [0.01–0.90]) and approached the levels observed in healthy individuals (Fig 1A, B).

In summary, this analysis found that baseline IL-5 and IL-13 levels were nominally significantly higher in patients with severe, uncontrolled asthma participating in the PATHWAY study than in a separate cohort of age-matched healthy individuals. After 52 weeks' treatment, tezepelumab reduced IL-5 and IL-13 levels in patients with severe, uncontrolled asthma to levels approaching those observed in the healthy cohort. These findings suggest that TSLP inhibition may function to normalize levels of proinflammatory mediators in patients with severe, uncontrolled asthma. Importantly, these tezepelumab-mediated reductions in serum cytokines may be associated with reduced asthma exacerbations, improved lung function, and improved health-related quality of life.^{2,3}

The group comparisons presented here provide benchmark healthy ranges that researchers may reference to determine whether patients exhibit normal or abnormal levels of IL-5 and IL-13. The levels of IL-5 we observed in patients with severe asthma were similar to those seen in studies of benralizumab (median at baseline, 0.4–2.5 pg/mL).⁷ IL-13 levels in the present study were considerably lower than those reported in previous studies;^{8,9} this may be because of differences in assay sensitivity used to quantify IL-13, in patient disease severity, or in the use of background medications such as corticosteroids that may suppress type 2 cytokine production.¹⁰

The mechanism by which TSLP inhibition reduces serum IL-5 and IL-13 levels in patients with severe asthma has not yet been fully elucidated, but likely results from a dampening of the TSLP-driven inflammatory cascade triggered by insults to the airway epithelium and release of TSLP by other airway cell types, leading to reduced activity of type 2 cytokine-producing inflammatory cells. In particular, TSLP upregulates dendritic cell activity, thereby accelerating the differentiation of naïve T cells to Th2 cells, and also activates ILC2s.¹

Therefore, blocking TSLP activity would be expected to reduce levels of type 2 cytokines such as IL-5 and IL-13.

There were some limitations to this analysis. First, the healthy cohort was matched with the PATHWAY cohorts based on age, but not for other demographics or baseline characteristics. Second, the healthy cohort contained a smaller number of participants than the PATHWAY cohorts. Nevertheless, the findings of this analysis further support the potential benefits of tezepelumab in patients with severe, uncontrolled asthma.

References

1. Gauvreau GM, Sehmi R, Ambrose CS, Griffiths JM. Thymic stromal lymphopoietin: its role and potential as a therapeutic target in asthma. *Expert Opin Ther Targets*. 2020;24:1–16.
2. Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med*. 2017;377:936–946.
3. Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med*. 2021;384:1800–1809.
4. Adachi T, Alam R. The mechanism of IL-5 signal transduction. *Am J Physiol*. 1998;275:C623–633.
5. Pelaia C, Paoletti G, Puggioni F, et al. Interleukin-5 in the pathophysiology of severe asthma. *Front Physiol*. 2019;10:1514.
6. Corren J. Role of interleukin-13 in asthma. *Curr Allergy Asthma Rep*. 2013;13:415–420.
7. Pham TH, Damera G, Newbold P, Ranade K. Reductions in eosinophil biomarkers by benralizumab in patients with asthma. *Respir Med*. 2016;111:21–29.
8. Arima K, Umeshita-Suyama R, Sakata Y, et al. Upregulation of IL-13 concentration in vivo by the IL13 variant associated with bronchial asthma. *J Allergy Clin Immunol*. 2002;109:980–987.
9. Shehata IH, Mostafa MM, Ziada KW, Saeed AM. Role of IL-13 in the pathogenesis of bronchial asthma. *Egypt J Immunol*. 2007;14:19–27.

10. Kaur M, Reynolds S, Smyth LJ, Simpson K, Hall S, Singh D. The effects of corticosteroids on cytokine production from asthma lung lymphocytes. *Int Immunopharmacol.* 2014;23:581–584.

Figure 1. Serum IL-5 (A) and IL-13 (B) levels in healthy individuals and in patients with severe, uncontrolled asthma at baseline and after asthma patients had received placebo or tezepelumab 210 mg Q4W for 52 weeks. Box plots show median, interquartile range, and range. Filled diamonds indicate mean values. Group comparisons performed using Mann–Whitney nonparametric tests (healthy vs all asthma) or paired t-tests (all others). All statistical tests were exploratory, with no adjustment for multiple comparisons.

