

Accepted Manuscript

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PII: S0091-6749(18)31591-4

DOI: <https://doi.org/10.1016/j.jaci.2018.11.002>

Reference: YMAI 13721

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 28 August 2018

Revised Date: 24 October 2018

Accepted Date: 2 November 2018

Please cite this article as: Chung KF, Shedding light on corticosteroid-resistant Type-2 high severe asthma, *Journal of Allergy and Clinical Immunology* (2018), doi: <https://doi.org/10.1016/j.jaci.2018.11.002>.

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*Editorial***Shedding light on corticosteroid-resistant Type-2 high severe asthma**

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Conflict of Interest:

K. F. Chung has been remunerated for participation on Advisory Boards of GSK, MSD, AstraZeneca, Novartis, TEVA, Boehringer Ingelheim and Johnson & Johnson to discuss asthma and COPD treatments. He has received grant support from GSK, MRC, EU Innovative Medicines Initiative and National Institutes of Health.

Key words:

Asthma, Type 2 inflammation, corticosteroid resistance, eosinophils.

Abbreviations:

FeNO: Level of nitric oxide in exhaled breath

ICS: Inhaled corticosteroid

IgE: Immunoglobulin E

PCR: Polymerase chain reaction

T2: Type 2

Th2: T-helper cell type 2

Asthma is increasingly recognised as a heterogeneous condition not only with regards to its clinical features or severity or response to corticosteroid therapy, but also in terms of its inflammatory and driving immune and inflammatory processes. Eosinophilic asthma defines a phenotype characterised by more frequent exacerbations and usually with a good therapeutic response to corticosteroid therapy. Its molecular basis was determined from an analysis of genes representative of T-helper Type (Th2) or Type 2 (T2) inflammation that are overexpressed in airway epithelial cells exposed to the Th2 cytokine, IL-13, in airway epithelial brushings obtained from patients with mild asthma, not taking inhaled corticosteroids (ICS). 50% of these patients fell into 'Th2-high' or 'T2-high', and were characterised by high blood or lung eosinophilia, increased serum IgE levels, bronchial hyperresponsiveness and a larger improvement in FEV₁ to inhaled corticosteroid therapy, and with a high expression of IL-5 and IL-13 protein in biopsies when compared to the 'T2-low' group (1). However, the level of expression of Th2 or T2 inflammation in those with severe asthma has been remained unknown so far.

In this issue of *Journal of Allergy and Clinical Immunology*, Peters and colleagues (2) used quantitative PCR to measure the expression of the T2 cytokines, IL-4, IL5 and IL-13, in induced sputum cells. This approach to assessing T2-expression obviates the need for performing a fiberoptic bronchoscopic procedure to obtain airway epithelial brushings. Using patients suffering from asthma receiving high dose ICS therapy enrolled in the Severe Asthma Research Program (SARP), they measured T2-status using a mean expression of these 3 cytokines before and after 2 weeks of a triamcinolone injection. T2-high was defined as those with values above the 50th centile value measured in these asthmatics and was found in 50% of patients. Furthermore, triamcinolone had virtually no effect on the

expression of these 3 cytokines, and the 2 groups were defined as steroid-resistant T2-high, and as steroid-treated T2-low.

The steroid-resistant T2-high asthma group were older (with higher T2 expression in older compared to younger asthmatics), had more severe airflow obstruction and more exacerbations, and higher blood eosinophil counts, and sputum eosinophil counts, raised levels of NO in exhaled breath (FeNO) and serum IgE, and a higher percentage was on high dose ICS, compared to the steroid-treated T2-low. There was a greater but non-significant higher number of asthmatics on oral corticosteroid therapy (15% versus 10%). They also showed a greater bronchodilator response and a relatively greater FEV₁ response to triamcinolone. Thus, the characteristics of 'T2-high' as assayed in sputum cells in severe asthma on ICS therapy bear some similarities to the 'T2-high' (assayed in epithelial cells) in mild asthma not on ICS, notably with eosinophilic inflammation in blood and sputum and higher serum IgE levels. However, a clear difference is the response to corticosteroid therapy that is blunted in the T2-high severe asthma.

The poor response to triamcinolone of the T2 gene composite score in the T2-high group was correlated with its relatively small effect on sputum eosinophils (0.2% reduction), blood eosinophils (reduced by 30%) and FeNO (2.4 ppm reduction), and lung function (3% improvement in FEV₁), that was reported previously (3). These results are surprising in terms of a rather poor response of these T2 cytokines to triamcinolone, indicating the presence of corticosteroid-resistance in severe refractory asthma. It should be noted that these results are different from those of a smaller study of triamcinolone in 22 patients with severe asthma in whom both the clinical response and the suppression of blood eosinophil counts were much greater, although the T2-status was not measured in that study (4). This different response may be due to the 3-fold higher injected dose of 120 mg of triamcinolone

used in this study compared to the 40 mg dose used in the Peters study, which supports the concept of relative corticosteroid insensitivity. The study of Peters et al therefore confirms what has been known to occur in severe asthma with previous demonstration of ex-vivo corticosteroid resistance in inflammatory and structural airway cells (5,6). Corticosteroid resistance might underlie the persistence of eosinophilic inflammation in severe asthma patients on regular ICS and often on daily oral CS therapy. Furthermore, this study provides evidence that the lack of response to CS therapy in these patients is not due to lack of adherence of the patient in taking CS therapy.

The mechanisms underlying corticosteroid resistance in severe asthma have been reviewed, and ways of reversing corticosteroid resistance remain an active field of investigation (**Table**). Daily oral CS therapy is observed in up to 50% of patients with severe refractory asthma and oral CS-dependent asthma may represent a particular phenotype of CS-resistant asthma. Interestingly, in this group of *oral steroid-dependent eosinophilic severe asthma patients*, the currently-available T2-targeted anti-IL5 and anti-IL5R α antibody treatments resulted in significant reductions in maintenance oral prednisolone dose while at the same time, reducing asthma exacerbation rates (7-8).

The other important aspect of the work of Peters and colleagues was to assess the performance of non-invasive bedside biomarkers such as blood IgE levels, blood eosinophil count, sputum eosinophil counts and FeNO values in predicting T2-high asthma as assayed in sputum cells. This is an exercise that is rarely performed but remains the only way of determining the suitability of bedside biomarkers to be used as surrogate markers of T2 status. Using Receiver Operator Characteristic (ROC) analysis, the best predictability for T2-high was sputum eosinophil counts and blood eosinophil counts (Area under curve AUC of 0.79 and 0.76, respectively), and for FeNO, it was 0.72. Further analysis showed that blood

eosinophil counts performed poorly as a biomarker of T2-high in morbidly obese patients, while serum IgE levels performed well in patients younger than 35.

The considerable overlap of T2 expression between the healthy and asthmatic groups and the modest differences in clinical parameters and other predictive markers of severity between T2-high versus T2-low group raises doubt as to whether the T2-status could be an indicator of the level of severity. In addition, a blood eosinophil count of $\geq 300/\mu\text{l}$ currently used to determine the suitability of patients with eosinophilic severe asthma to receiving anti-T2 biologic therapies has a poor sensitivity of 50.8% and a modest specificity of 78.3% for predicting T2-high asthma. Furthermore, the strong modifying effect of BMI on the relationship between blood eosinophil counts and sputum cell T2 mean gene values introduces another patient characteristic to take into consideration.

Finally, one important consideration is whether the quantitative PCR assay of IL4, IL5, IL13 in induced sputum cells is appropriate, robust, reliable and reproducible measure of T2-high for severe asthma. Other investigators have been unable to detect significant levels of these cytokine mRNA in sputum cells either by chip assay or by quantitative PCR (9,10), raising the issue as to whether IL-4, IL5 and IL13 mRNA transcripts are the best gene surrogate markers for assessing T2 in sputum samples where the main sources of these transcripts would likely be eosinophils and epithelial cells. The very wide range of expression of these 3 genes that overlaps between the healthy and the asthmatic groups bring into question the use of the arbitrary cut-off for T2-high of being above the 50th percentile value seen in asthmatic subjects. Other approaches such as determining the expression of a T2-gene signature using the gene set variation analysis should be considered (10).

The work of Peters and colleagues points to the importance of obtaining a reliable and easy measure of T2-status that might bypass the use of currently-used surrogate

120 markers such as blood eosinophil counts or FeNO to indicate the suitability of patients for
121 anti-T2 treatments currently being introduced. The other message is the presence of
122 widespread corticosteroid resistance that exists in T2-high asthma through the direct
123 measurement of effects of corticosteroid therapy on T2-cytokine gene expression, which
124 reinforces the need to finding ways of reversing this resistance or of using alternative anti-
125 inflammatory treatments to corticosteroid therapies.

References:

1. Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, Koth LL, Arron JR, Fahy JV. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med*. 2009 Sep 1;180(5):388-95.
2. Peters MC, Kerr S, Dunican EM, Woodruff PG, Fajt ML, Levy BD, et al. Refractory Airway Type-2 Inflammation in a Large Subgroup of Asthmatics treated with Inhaled Corticosteroids. *J Allergy Clin Immunol*, in press.
3. Phipatanakul W, Mauger DT, Sorkness RL, Gaffin JM, Holguin F, Woodruff PG, et al. Effects of Age and Disease Severity on Systemic Corticosteroid Responses in Asthma. *Am J Respir Crit Care Med*. 2016.
4. ten Brinke A, Zwinderman AH, Sterk PJ, Rabe KF, Bel EH. "Refractory" eosinophilic airway inflammation in severe asthma: effect of parenteral corticosteroids. *Am J Respir Crit Care Med*. 2004;170(6):601-5.
5. Bhavsar P, Hew M, Khorasani N, Torrego A, Barnes PJ, Adcock I, Chung KF. Relative corticosteroid insensitivity of alveolar macrophages in severe asthma compared with non-severe asthma. *Thorax*. 2008 Sep;63(9):784-90.
6. Chang PJ, Bhavsar PK, Michaeloudes C, Khorasani N, Chung KF. Corticosteroid insensitivity of chemokine expression in airway smooth muscle of patients with severe asthma. *J Allergy Clin Immunol*. 2012 Oct;130(4):877-85.
7. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371(13):1189-97.
8. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. *N Engl J Med*. 2017;376(25):2448-58.
9. Seys SF, Scheers H, Van den Brande P, Marijsse G, Dilissen E, Van Den Bergh A, et al. Cluster analysis of sputum cytokine-high profiles reveals diversity in T(h)2-high asthma patients. *Respiratory research*. 2017;18(1):39.
10. Rossios C, Pavlidis S, Hoda U, Kuo CH, Wiegman C, Russell K, et al. Sputum transcriptomics reveal up-regulation of IL-1 receptor family members in severe asthma. *J Allergy Clin Immunol*. 2018; 141: 560-570 .

Table**Mechanisms implicated in corticosteroid insensitivity in severe asthma**

	Pathways	Molecules
1	Inflammatory pathways	Activation of p38 mitogen-activated protein kinase (MAPK) and nuclear factor- κ B (NF- κ B)
2	Th-17 cells and neutrophilic inflammation	Activation of phosphoinositol-3 kinase (PI3K) and inhibition of histone deacetylases (HDAC)
3	Cigarette smoking and oxidative stress	Imbalance of histone acetyl transferase (HAT)/HDAC activity
4	Allergen exposure and Type 2 (T2) cytokine activation	Reduction in glucocorticoid receptor (GR) ligand binding affinity, activation of MAPK and expression of the dominant negative isoform of GR α , GR β
5	Microbial factors such as viruses, bacteria, lipopolysaccharide and superantigens	Inhibition of GR nuclear translocation, and increased p38 MAPK and GR β
6	Vitamin D3 deficiency	Inhibition of regulatory T-cells with a reduction in IL-10