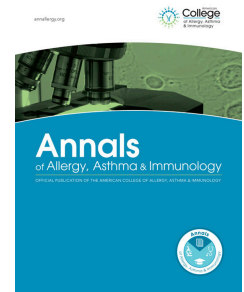


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Anti-Eosinophil Therapy is associated with Decreased Body Mass Index in Severe Asthmatics: a Preliminary Retrospective Analysis

Merin Kuruvilla, MD, Meera Patrawala, MD, Joshua M. Levy, MD, Jennifer Shih, MD, Frances E. Lee, MD



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Title: Anti-Eosinophil Therapy is associated with Decreased Body Mass Index in Severe Asthmatics: a Preliminary Retrospective Analysis**Authors:**

- **Merin Kuruvilla, MD**
Division of Pulmonary, Allergy and Critical Care
Emory University School of Medicine, Atlanta, Georgia, U.S.A.
- **Meera Patrawala, MD**
Division of Pulmonary, Allergy and Critical Care
Emory University School of Medicine, Atlanta, Georgia, U.S.A.
- **Joshua M Levy, MD**
Department of Otolaryngology-Head and Neck Surgery
Emory University School of Medicine, Atlanta, Georgia, U.S.A.
- **Jennifer Shih, MD**
Division of Pulmonary, Allergy and Critical Care
Emory University School of Medicine, Atlanta, Georgia, U.S.A.
- **Frances E Lee, MD**
Division of Pulmonary, Allergy and Critical Care
Emory University School of Medicine, Atlanta, Georgia, U.S.A.

Corresponding Author Contact Information:

Merin Elizabeth Kuruvilla, MD
Address: 1365 Clifton Rd NE, Bldg A, 3rd Flr
Atlanta, GA-30322
Email: merin.ek1@gmail.com
Phone: 972-890-3847 (Home)
404-778-3261 (Business)
Fax: 404-778-4431 29

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Asthma – Eosinophil – Obesity – Interleukin-5 – Adipose tissue

Abbreviations:

- AT: adipose tissue
- IL-5: Interleukin-5
- ILC2s: type 2 innate lymphoid cells
- BMI: body mass index

Word count: 1063

1 The type 2 high endotype of asthma with adult onset is often characterized by severe persistent,
2 steroid refractory eosinophilic inflammation. Interleukin-5 (IL-5) is a pivotal cytokine for
3 eosinophil survival. The amelioration of eosinophilic inflammation through anti-IL-5 therapies
4 (mepolizumab, reslizumab, and benralizumab) has been demonstrated to reduce exacerbations
5 and improve control, and overall well-tolerated.

6 Eosinophils have recently been implicated in adipose tissue (AT) homeostasis. A threshold
7 number of eosinophils appear critical for weight loss and glucose tolerance [1]. Wu et al first
8 reported the residence of eosinophils in AT [2] with weight gain and insulin resistance in an
9 eosinophil deficient murine model, in contrast to hypereosinophilic mice that demonstrated
10 weight loss and improved glucose tolerance.

11 An accumulating body of evidence has since supported these findings, and implicated
12 eosinophils in browning of AT, which decreases weight while enhancing insulin sensitivity [3].
13 Eosinophils induce polarization of AT macrophages into M2-like macrophages which enhances
14 catecholamine import into the local environment thereby improving glucose tolerance. Obese
15 individuals have fewer eosinophils and type 2 cytokines in their AT [4].

16 The literature suggests a critical mass of eosinophils is necessary for AT homeostasis, but
17 increasing eosinophil levels alone does not appear sufficient to confer metabolic benefits [5]. The
18 effect of depleting eosinophils on subject weight is a potentially important area of AT biology.
19 While anti-IL-5 treated asthmatics are theoretically an ideal population for evaluation, this may
20 be precluded in reality by multiple confounding factors. These include concomitant use of
21 steroids in severe asthmatics as well as the underlying association of tissue eosinophilia with
22 obesity in severe asthma. In a cohort of severe asthmatics stratified by weight, those with a

higher body mass index (BMI) had higher sputum IL-5 and eosinophils in lung tissue, but not in the lumen [6]. The redistribution of eosinophils from AT to lungs has been postulated to determine disease severity [6].

This retrospective analysis utilized a cohort of adult asthmatic patients receiving anti-IL5 therapies between January 2016 and September 2018 at a single institution. Inclusion criteria were: adult-onset asthmatics with severe persistent disease, and treatment with anti-IL-5 therapy for six consecutive months. The primary objective was to determine the long-term effect of anti-eosinophil agents in subjects with severe asthma on BMI trajectories.

During the study period, 58 patients were initiated on anti-IL-5 agents. 51 patients (15 (29.4%) male; mean age 56.7 ± 13.4 years) met inclusion criteria and were included in analysis. 29 subjects were initiated on mepolizumab, 16 on reslizumab, and 6 on benralizumab. All three groups were broadly similar without significant difference in baseline BMI. The median age of asthma diagnosis was 38.5 years (range 18-62 years). Peak documented blood eosinophil counts ranged from 110 to 1360 cells/microliter (mean 550 cells/microliter). The large variance in eosinophils may be secondary to the fact that 19 patients were treated with maintenance oral corticosteroids (OCS), with a median maximal daily prednisone dose of 20 mg (range 5-80 mg). 23 subjects had baseline BMI >30 prior to anti-IL-5 therapy. Similar frequency of maintenance OCS was found between obese and non-obese cohorts: 11 of 20 (55%) obese subjects and 9 of 23 (39%) non-obese patients ($p=0.30$).

Table 1 stratifies weight change by baseline BMI and anti-IL-5 agent. The mean BMI change over 6 months amongst the entire cohort showed a decrease by 1 point ($p=0.03$) and was within 1 point of each other for all three agents used: -1.3 for mepolizumab, -1.1 for reslizumab, and 0.3

among benralizumab users. The largest apparent effect was among mepolizumab users, however this group also accounted for the most patients. There was also significant variability in BMI fluctuations among the mepolizumab subgroup mepolizumab (range -5.9 to 5.4, $p=0.028$), that was not observed for the other two agents (-3.0 to 1.6 for reslizumab ($p=0.34$), and -2.5 to 3.3 for benralizumab ($p=0.71$)). Obese patients with a baseline BMI of >30 had a mean BMI decrease of 1.7 across all three agents, which was significant compared to the remainder of the cohort ($p=0.04$). When analyzed within the obese category, the mean BMI change for each agent was not significantly different.

An unexpected role for eosinophils has been in AT homeostasis, potentially influencing whole-body metabolic fitness. Murine models have attempted the use of recombinant IL-5 in genetically modified mice lacking eosinophils to ameliorate obesity [7]. Conversely, eosinophil depletion may predispose to obesity. However, none of the eosinophil depletion models have been conducted in non-modified mice. Homeostatic eosinophils have different response patterns and functions depending on their localization; however, AT eosinophils depend upon IL-5 for survival. Theoretically, severe asthmatics receiving anti-IL-5 targeted therapy provide an ideal population to study the impact of eosinophil depletion. We were unable to find any data evaluating the effect of anti-IL5 mediated eosinophil depletion on BMI.

We observed a statistically significant decrease in BMI across all three anti-IL-5 therapies at six months, however, the clinical relevance is unclear in the setting of marginal change and low sample size. This effect appears to have been most pronounced in those with a baseline BMI >30 , and may have been expected based on maintenance OCS wean rates as well as decrease in acute flares requiring systemic steroids.

The major weakness of this study was the retrospective design and consequent limitations in parameters assessed. Our study is not randomized or placebo-controlled and confounded by prior and intercurrent steroid prescriptions. We did not measure other parameters such as body fat or glucose tolerance. Our lack of a more substantial association between eosinophil depletion and BMI may also have been due to relatively small sample size. Also, the effects of anti-IL5 agents on tissue eosinophils are prominent than peripheral blood, which may be explained by restricted tissue access and contribution of other mediators to eosinophil survival. There may also be a distinct resident homeostatic population of tissue eosinophils within the visceral fat, whereas bone marrow-derived eosinophils are important during inflammation.

In conclusion, anti-IL5 therapy was associated with mild but significant overall decrease in BMI for the study duration. Higher baseline BMI was associated with more pronounced weight loss. While the exact biological effects of eosinophil depletion cannot be deduced from this limited retrospective series, it does appear that any obesity promoting effect of IL-5 blockade is offset by improvement in asthma and presumable decrease in systemic steroid burden. Given the emerging paradigms associating eosinophils with AT function and the potential effects of eosinophil depleting therapies, larger future studies should clarify the true implications of eosinophil depletion. Our preliminary data will hopefully stimulate prospective trials to elucidate this relationship.

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Table 1. Stratification of BMI change by anti-IL5 agent:

Type of Medication and Obesity Category	Change in BMI (pre-treatment vs. post-treatment)			
	Mean	Standard Deviation	Median	P value
Entire cohort (n=51)	-1	3.4	-1	0.0333
• Non-obese BMI (n=28)	-0.6	2.9	-0.2	0.2988
• Obese BMI (n=23)	-1.7	3.8	-2.3	0.0471
Mepolizumab (n=29)	-1.3	3	-1.7	0.0283
• Non-obese BMI (n=14)	-1.4	2.7	-1.8	0.0558
• Obese BMI (n=15)	-1.2	3.4	-1.7	0.1759
Reslizumab (n=16)	-1.1	4.3	-0.4	0.341
• Non-obese BMI (n=9)	0.7	3.4	2.4	0.5522
• Obese BMI (n=7)	-3.3	4.4	-3.9	0.0923
Benralizumab (n=6)	0.3	2.1	0	See footnote*
• Non-obese BMI (n=5)	-0.3	1.7	-0.2	
• Obese BMI (n=1)	3.3	-	3.3	

* Due to small sample size, statistical test not conducted.