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Effect of Anti-IL-13 Treatment on Airway Dimensions in Severe Asthma

To the Editor:

Asthma is an inflammatory airway disease in which IL-13, a pleiotropic cytokine, is a central mediator of the key pathological features (1). Tralokinumab (CAT-354), an investigational human monoclonal antibody that specifically binds to IL-13 to prevent its interaction with the IL-13 receptor, has shown activity in moderate-to-severe asthma (1–3). In a phase 2b trial (CP1049), tralokinumab was associated with improvements in lung function in patients with uncontrolled severe asthma (3). A key feature of severe asthma is airway remodelling (4, 5). As IL-13 is a profibrotic cytokine and modulates airway smooth muscle tone, we hypothesized its blockade with tralokinumab might affect airway morphology. Advances in the standardization of acquisition and analysis of quantitative computed tomography (QCT) have provided a noninvasive tool to assess airway morphology and informed our understanding of asthma heterogeneity and response to therapy (6–9). We sought to investigate the effects of tralokinumab on segmental and subsegmental airway morphology using QCT in adults with severe asthma. Our findings were presented as conference proceedings at the European Respiratory Society scientific meeting 2015 (10).

We undertook *post hoc* analysis of data from a subset of subjects taking part in a 52-week phase 2b randomized, double-blind study comparing two subcutaneous (SC) dosing regimens of tralokinumab with placebo in adults with severe asthma (NCT01402986) (3). Subjects were randomized (2:1) to tralokinumab 300 mg SC or placebo SC every 2 weeks (Q2W), or

tralokinumab 300 mg SC or placebo SC Q2W for 12 weeks followed by every 4 weeks (Q4W). Subjects had documented asthma for at least 12 months and had received an asthma controller regimen consistent with that described at step 4 or 5 of the Global Initiative for Asthma guidelines and the American Thoracic Society/European Respiratory Society severe asthma guidelines (5) for at least 6 of the 12 months prior to visit 1 and had received high-dose inhaled corticosteroids for at least 1 month prior to visit 1. Subjects received standardized high-dose inhaled corticosteroids and long-acting bronchodilators during run-in and continued these controller medications during the treatment period (3).

QCT of the upper part of the lung was performed using a standardized scanning protocol in a subset of subjects at baseline and at the end of treatment (Week 52). In brief, the upper part of the lung was scanned using a spiral acquisition protocol at full inspiration, using CT scanners from Siemens (Buffalo Grove, IL), Philips (Andover, MA), and GE Healthcare (Aurora, OH). Tube voltage was standardized to 120 kVp and effective exposure to 50 mAs, with no dose modulation used. Images were reconstructed using reconstruction kernels B30f (Siemens), B (Philips), and Standard (GE) to generate overlapping slices with thickness ≤ 1 mm. Fifty-two subjects underwent CT scanning. Twenty-six had assessable CT scans before and after intervention (Siemens [$n = 7$], Philips [$n = 9$], and GE [$n = 10$]), 14 subjects discontinued the study and did not have the end of treatment scan, and 12 had technical errors in either or both of the CT scans. Because of the low number of subjects (26 subjects at 12 study sites), Q2W and Q4W groups were combined in the placebo ($n = 11$) and tralokinumab ($n = 15$) groups. For those subjects who received tralokinumab, six were in the Q2W and nine in the Q4W groups. CT scans were analyzed by a single observer blinded to baseline clinical characteristics and treatment allocation. Five segmental (generation 3: RB1, RB2, RB3, LB1+2, and LB3) and 14 subsegmental/sub-subsegmental (generation 4–5: RB1a, RB1b, RB2a, RB2b, RB3a, RB3b, LB1, LB1a, LB1b, LB2, LB2a, LB2b, LB3a, and LB3b) airways were measured using the VIDA Apollo software (VIDA Diagnostics, Inc., Coralville, IA). The same airway segment was measured at baseline and end of treatment, and the relative change in dimension was computed. Changes in cross-sectional lumen area, wall area, and wall area percentage (wall area/[wall area + lumen area] $\times 100$) were estimated. Changes in airway parameters were calculated for each airway segment separately and

Table 1. Baseline Clinical Characteristics

Characteristic	Placebo ($n = 11$)	Tralokinumab ($n = 15$)
Sex, female/male, n	6/5	10/5
Age, yr	48 (11)	50 (11)
Duration of asthma, yr	17 (13)	23 (13)
FEV ₁ , L	1.84 (0.4)	1.94 (0.61)
FEV ₁ , % predicted	67.2 (10.0)	69.2 (22.2)
FVC, L	2.79 (0.59)	3.081 (0.70)
Bronchodilator reversibility, %	11.88 (11.37)	7.14 (7.78)
ACQ-6	2.32 (0.97)	2.36 (1.26)
Wall area, % segmental	63.47 (3.18)	63.91 (2.46)
Wall area, % subsegmental	65.65 (1.19)	67.11 (1.77)

Definition of abbreviation: ACQ = Asthma Control Questionnaire. Data are mean (SD) unless otherwise stated.

Author Contributions: All authors contributed to concept and design, analysis and interpretation, and drafting the manuscript.

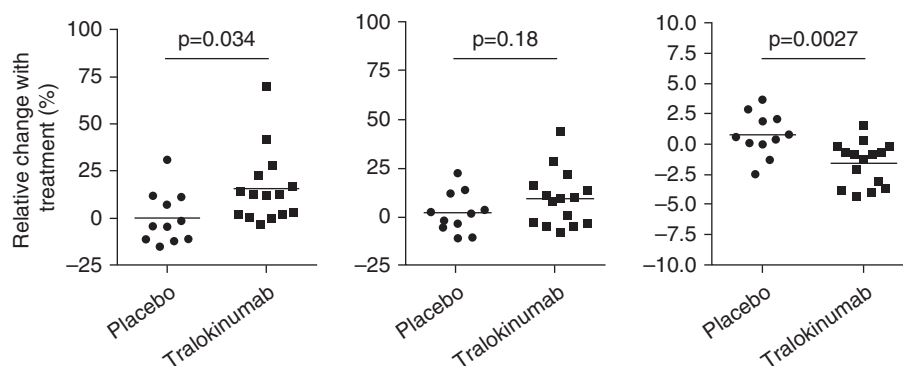


Figure 1. Relative change in subsegmental airway parameters between baseline and end of treatment. (Left) Lumen area; (middle) wall area; (right) percentage wall area. Horizontal bars indicate means.

then averaged over segmental and subsegmental airways in each patient. Between-group differences were assessed using *t* tests, and correlations between baseline characteristics and changes in response to therapy were assessed by Spearman rank correlation coefficient with a significance level of 0.05.

The baseline clinical characteristics for the subjects that were in the tralokinumab and placebo groups are shown in Table 1 and were similar to the characteristics observed in the whole study population (3). Subsegmental lumen area increased significantly more with tralokinumab compared with placebo (Figure 1), with a mean difference of 15.4% ($P = 0.034$). A significant reduction in wall area percentage with tralokinumab versus placebo was also observed (Figure 1), with a mean difference of -2.4% ($P = 0.0027$). There was no significant difference in wall area between groups (Figure 1). Because of small differences in sex between the tralokinumab and placebo groups, we reanalyzed these data using analysis of covariance corrected for sex and found that the differences observed in subsegmental lumen area and wall area percentage remained statistically significant. Similar trends, although nonsignificant, were observed for segmental airways. Among subjects receiving tralokinumab, improvement in FEV_1 was significantly correlated with baseline subsegmental wall area percentage (Spearman correlation $r = 0.53$; $P = 0.045$) but not baseline lumen area. Baseline blood periostin and di-peptidyl-peptidase-4 (3) were not correlated with change in subsegmental lumen area or wall area percentage in those subjects receiving tralokinumab.

CT imaging detected significant improvements in subsegmental airway lumen parameters in patients with severe asthma receiving tralokinumab for 1 year compared with placebo, added to standard high-dose inhaled corticosteroid/long-acting β -agonist therapy. Similar trends were observed in the segmental airways, and whether our failure to demonstrate statistical differences between the groups that received placebo versus tralokinumab in these larger airways is a consequence of our small sample size is uncertain. Within the tralokinumab group, higher wall area percentage at baseline was associated with lung function improvement. These findings support the view that tralokinumab may modify airway morphology either by attenuating airway remodeling or promoting bronchodilatation via reduction in airway smooth muscle tone. CT imaging has the potential to provide further mechanistic insights into the effects of IL-13 blockade, and its application will be used to investigate the effect of tralokinumab

on airway structure and function in a new mechanistic study (NCT02449473). ■

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Transbronchial Needle Aspiration for Peripheral Lung Lesions: The Dark Horse Winner of the AQuIRE Registry, or Is It?

To the Editor:

We read with great interest the report by Ost and colleagues of the results of the AQuIRE (ACCP Quality Improvement Registry, Evaluation, and Education) registry, a highly anticipated real-world analysis of factors associated with the yield of bronchoscopy for the diagnosis of peripheral lung lesions (1). As bronchoscopists who routinely resort to conventional transbronchial needle aspiration (TBNA) for sampling thoracic lymphadenopathy and parenchymal lung lesions in appropriate cases, we were buoyed by the authors' finding that the performance of TBNA was associated with greater than twofold increased odds of a diagnostic peripheral bronchoscopy and that TBNA was positive in nearly 10% of the cases in which transbronchial biopsy was nondiagnostic. The authors understandably concluded that this underused technique represents a potential area for performance improvement for the interventional community. It was therefore surprising to find no mention of the TBNA results in the accompanying editorial by Ferguson and Sonetti (2). Such an apparent discrepancy compelled us to reexamine the TBNA results and wonder whether AQuIRE may have over- or understated the technique's clinical utility. Our perspective on this particular component of AQuIRE can be summarized as follows.

AQuIRE builds on established data indicating that TBNA is an underused but effective tool for the bronchoscopic sampling of peripheral lung lesions, unique in its ability to provide access beyond

the airway wall (3, 4). When it comes to lung neoplasms, this is likely to be of particular value in adenocarcinoma, the most common histology of small-sized peripheral lung cancer, given its propensity for abutting the airway lumen (i.e., Tsuboi type III relationship) rather than occupying it or invading its mucosa (5). Because, as the editorialists note, the overall prevalence of cancer in this study was relatively low, the utility of TBNA may have been underestimated, as malignancy is particularly amenable to cytological diagnosis by fine-needle aspiration. More specifically, the percentage of squamous histology was surprisingly high for a study of peripheral lung lesions, so a sample enriched with cases of adenocarcinoma in particular would have likely further accentuated the value of TBNA. It would have been instructive to see a comparison of TBNA performance in adenocarcinoma versus other cell types and the extent to which positive samples were adequate for mutational analysis.

Playing devil's advocate, conclusions about TBNA are being drawn on the basis of only 16% of all registry cases (95 patients), and the ability of the proceduralist to choose the sampling technique in a given case leaves room for bias, inasmuch as TBNA could have been employed selectively in more favorable scenarios. On a related note, although it is granted that a strict definition of a "peripheral" lung lesion may be lacking, the fact that more than 40% of the targets in AQuIRE were located in the central two-thirds of the lung field on computed tomography casts doubt on whether many of these lesions should be truly considered "peripheral" (6). According to Ost and colleagues' Table E10 in the online supplement, only about half of the TBNA procedures actually took place in the lung "periphery," which is arguably the zone of most interest in the pursuit of nodule sampling.

The AQuIRE investigators should be commended for their thought-provoking contribution. The role of peripheral TBNA in the era of modern bronchoscopic guidance would be best clarified by a randomized controlled trial. ■

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