Eosinophilia and Response to Bronchial Thermoplasty

To the Editor:

Goorsenberg and colleagues reported, in their 35 patients with severe asthma who underwent bronchial thermoplasty (BT), that higher baseline blood eosinophil count was associated with greater improvement in Asthma-related Quality of Life Questionnaire (AQLQ) ($\rho = 0.48$, $P = 0.004$) and Asthma Control Questionnaire (ACQ) scores ($\rho = -0.46$, $P = 0.006$) following BT treatment (1). Our clinical experience has been just the opposite (2, 3). In an analysis of 14 patients who underwent BT, we had previously reported a greater improvement in AQLQ score (mean ± SD, 2.2 ± 1.2 vs. 0.8 ± 0.9, $P = 0.04$), ACQ score (−2.3 ± 1.3 vs. −0.5 ± 1.1, $P = 0.02$), and airway hyperresponsiveness quantified by the provocative concentration of methacholine that results in a 20% drop in FEV_1 (PC_{20}) (3.9 ± 1.2 vs. 0.6 ± 0.8 doubling-doses, $P = 0.008$) in those whose sputum cell counts were normalized before BT compared with those who were treated based on standard clinical optimization (3). The improvement in ACQ and AQLQ scores reported by patients with asthma in whom airway inflammation was absent or controlled prior to BT was >4 times the minimum clinically important difference, being the largest improvement when compared with published trials (4–6) and approximately 3 times that reported by Goorsenberg and colleagues. In contrast to their observations, lower baseline blood eosinophil count was associated with greater improvement in AQLQ score ($\rho = -0.62$, $P = 0.02$) but not ACQ score ($\rho = 0.44$, $P = 0.11$). Additionally, PC_{20} improved by 3.9 ± 1.2 doubling-doses ($P = 0.06$) in patients with asthma in whom airway inflammation was absent or controlled prior to BT. This observation is in agreement with the mechanism of action of BT, at least in part, being a reduction in airway smooth muscle mass confirmed in this report by Goorsenberg and colleagues (1).

We are not quite sure why the results are contradictory. Both studies are limited by small sample sizes and could therefore be underpowered for responder analyses to draw definite conclusions. It should also be emphasized that the reported P value cutoff after Bonferroni correction for multiple comparisons in Goorsenberg's responder analysis is $P < 0.006$. Using this corrected cutoff, the associations of higher baseline blood eosinophil count with greater improvement in AQLQ and ACQ scores reported by Goorsenberg are rendered statistically insignificant. It is also conceivable that in Goorsenberg's analysis, the predictive benefits attributed to baseline eosinophilia (unclear when this was assessed), which is a marker of steroid responsiveness, may have been confounded by the 150 mg prednisone (over 3 d) administered before each session of BT.

In conclusion, there is considerable variability in patient outcomes following BT in clinical practice. Therefore, we share the enthusiasm of the authors to identify baseline characteristics of optimal candidates for BT treatment. However, we caution overinterpretation of the BT responder analysis reported by Goorsenberg and colleagues. In agreement with the authors, the current literature has shaped a debatable BT responder profile, necessitating a large multicenter cohort study that is sufficiently powered for BT responder analysis. ■

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Reply to Svenningsen *et al.*

From the Authors:

With interest we read the letter by Svenningsen and colleagues, regarding airway inflammation and bronchial thermoplasty (BT) response in

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patients with asthma. In their recent study, they show in two groups of seven patients with asthma that those with normalized sputum cell counts (eosinophils <3%; neutrophils <64%) had more improvement in Asthma Control Questionnaire (ACQ) and Asthma-related Quality of Life Questionnaire (AQLQ) scores after BT compared with patients with sputum cell counts that were unknown (1). They mention that their findings contradict results of the prospective TASMA (Unravelling Targets of Therapy in Bronchial Thermoplasty in Severe Asthma) trial, in which we reported in 35 patients with severe asthma that higher blood eosinophils at baseline is associated with more improvement in ACQ and AQLQ scores 6 months after BT (2).

Svenningsen and colleagues suggested small sample sizes and bias caused by prednisolone around the BT procedures as potential causes for the discrepancy.

We agree that both patient cohorts have limitations to draw definite conclusions in terms of a responder profile. Svenningsen and colleagues report a large improvement in ACQ, AQLQ, and bronchial hyperresponsiveness in the inflammation-optimized group, although it should be noted that the findings are prone to bias because of the retrospective design, as reflected in baseline discrepancies between both patient groups. The inflammation-optimized group ($n = 7$) had worse AQLQ scores (mean ± SD, 3.42 ± 1.32 vs. 5.18 ± 1.34) and trend toward worse asthma control measured with ACQ-5 (3.31 ± 1.47 vs. 1.86 ± 1.06) compared with the guideline-based care group. Interestingly, Langton and colleagues recently investigated predictors for BT response in 77 patients and showed that higher ACQ at baseline was significantly associated with more improvement after BT (3, 4). Furthermore, in the Svenningsen report, sputum cell counts were not available in the guideline-based care group, hampering interpretation.

Although sputum was not collected in all TASMA patients because of technical and safety issues, sputum cell counts were measured in 14 (out of 35) patients before randomization; 8 patients had high amounts of sputum inflammatory cells: eosinophils >3% in 3 patients, neutrophils >64% in 4 patients, and both high eosinophils and neutrophils in 1 patient. Interestingly, by comparing the inflammatory group with the noninflammatory group, the results were opposite to Svenningsen's observations; ACQ/AQLQ scores significantly improved in the inflammation group (ACQ-6 improved from 2.8 ± 0.4 to 1.7 ± 1.2 [$P = 0.04$] and AQLQ improved from 4.0 ± 5.0 to 5.3 ± 1.0 [$P = 0.03$]), whereas in the noninflammatory group, no significant improvements after BT were found (ACQ-6, 2.6 ± 0.7 to 2.0 ± 0.9 [$P = 0.19$] and AQLQ, 4.5 ± 1.3 to 4.9 ± 1.7 [$P = 0.69$]).

Related to the above, it is interesting that baseline characteristics of the inflammation-optimized group in their report are to some extent similar to the TASMA patients in terms of AQLQ, ACQ scores, baseline blood eosinophils, and add-on asthma medication use. Therefore, their patients, categorized as inflammation-optimized, intrinsically might have an inflammation-driven asthma profile, which is in line with the TASMA results.

In our opinion, it is unlikely that prednisolone given around the BT procedures is driving the association between baseline blood eosinophils and BT response. First, BT response is measured 6 months after BT, by which the potential effect of 3 days prednisolone should be minimized. Second, the above-reported sputum results in a subgroup of 14 patients from the TASMA study showed that not only patients with high eosinophil count but also those with high neutrophil count had favorable BT response.

In conclusion, we agree with Svenningsen and colleagues that interpretation of responder analyses in smaller sample size patient cohorts should be addressed carefully. In our opinion, the prospective multicenter TASMA data contributes to understanding BT treatment and response. Whether BT impacts airway inflammation (5, 6) and how inflammation interacts with BT response needs further research. Next to well-characterized BT patient cohorts to further define a BT responder profile, the concept to optimize inflammation before BT to improve BT response is interesting and deserves further trials. ■

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Risk-Stratifying Pulmonary Nodules

To the Editor:

I congratulate Dr. Massion and colleagues on their Lung Cancer Prediction Convolutional Neural model for differentiation of

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