Reviewer’s report

Title: Nerve ablation after bronchial thermoplasty and sustained improvement in severe asthma

Version: 0 Date: 06 Jul 2017

Reviewer: Brendan Canning

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Facciolongo and colleagues have studied the effects of bronchial thermoplasty on nerve staining in the airways of patients with severe asthma and related by inference the changes in nerve staining to clinical outcomes. They observed a marked decrease in the number of nerve fibers stained in bronchial biopsies in these patients at 12 months after intervention. In parallel with these anatomical changes, the authors summarized clinical benefits in these patients that seemed to far exceed those reported in several previous studies of bronchial thermoplasty in asthmatics. From these results the authors speculate that ablation of nerves and not ablation of smooth muscle may be the primary therapeutic action of bronchial thermoplasty in asthmatics.

Comments.

1. This is a well written manuscript with a clearly stated objective and with results that are both interesting and consistent with the author's discussion.

2. I would dispute the author's assertion that PGP staining is equivalent to identification of C-fiber endings in the airways submucosa. "C-fiber" is a functional definition that is not attainable in a histochemical study, with "C" referring to the slow wave of a conducted compound action potential. Even if the terminal appearance of the nerve endings are consistent with an unmyelinated nerve branch, this could simply reflect a terminal afferent axon that loses its myelination near its target structures. In fact, there is no clear way of differentiating afferent from efferent nerves in thin sections without additional phenotyping. Within the submucosa there may be arterioles receiving sympathetic adrenergic innervation, or parasympathetic cholinergic or noncholinergic innervation. The stained structures may also be portions of postganglionic axons projecting to structures (e.g. glands) that are not contained in the biopsies. The data as presented are consistent with the author's assertions. But the authors might want to acknowledge that they have not fully phenotyped the stained structures in their biopsies.

3. Implicit in the narrative of the discussion is that the authors believe that actions on smooth muscle are likely unrelated to any clinical benefits realized in patients receiving bronchial thermoplasty. One scenario mentioned is an effect on neurogenic inflammation. I would question the relevance of inflammation to any of the clinical benefits observed. Neurogenic inflammation is prominent in the airways of rats and guinea pigs but there is scant evidence that anything comparable occurs in human airways. Neurokinins are largely absent from the structures stained by PGP 9.5 in human airways while the account for upwards of 80% of the PGP-IR nerve terminals in the
mucosa of mice or guinea pigs. It is also unclear that inflammation in any form leads directly to asthma. Nonasthmatic seasonal allergic rhinitis patients have profound inflammation of their airways in season, and yet, do not have asthma, do not have an increase in reversible airways obstruction and do not develop airways hyperresponsiveness. So if the effects of thermoplasty are not due to effects on inflammation, what could be the explanation? It would be worthwhile discussing further the actions of reflex effects resulting from C-fiber activation. As the authors note, anticholinergics provide significant benefit in asthmatics and this is almost certainly attributable to their actions on smooth muscle regulation, either basal tone or reflex-induced increases in tone. Many irritant stimuli evoke bronchospasm in asthmatics primarily through parasympathetic reflexes. Preventing excessive reflex bronchospasm following C-fiber activation and not an effect on inflammation is a far more likely mechanism for bronchial thermoplasty in severe asthma.

4. The authors provide clear evidence that lung function was not improved following thermoplasty. What about airways reactivity or responsiveness to bronchodilator anticholinergics?

5. The concept of nerve ablation for obstructive lung diseases is currently being evaluated. The authors should review and cite the following publication: Slebos DJ, Klooster K, Koegelenberg CF, Theron J, Styen D, Valipour A, Mayse M, Bolliger CT. Targeted lung denervation for moderate to severe COPD: a pilot study. Thorax. 2015 May;70(5):411-9.

6. The clinical benefits observed in this small patient sample seems to exceed that reported previously in several studies of thermoplasty. Would the authors comment on what specifically about their trial or their patients rendered this treatment so effective?

7. The authors report clinical benefits 12 months after intervention and relate those benefits to a loss of airway innervation. A more complete "denervation" is achieved during lung transplant, and yet, while patients acutely lose their cough reflex following lung transplant and there is an accompanying decrease in airway innervation, by 12 months cough responsiveness is restored and at 33 months (earlier time points were not analyzed) nerve fibers in the mucosa are again present (Duarte et al., Chest. 2008; 134(2):310-316). Do the authors anticipate the need for additional thermoplasty as nerve fibers re-innervate the distal airways?

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes
Are the conclusions drawn adequately supported by the data shown?
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I am on the scientific advisory board for the company Nuvaira, formerly Holaira. Nuvaira is developing technology comparable to that used in bronchial thermoplasty that targets airway nerves for the treatment of asthma and COPD. I am compensated on an hourly basis for my role on the advisory board. I hold no ownership stake in the company.
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