

Anti-interleukin 13 for asthma: stick or twist?

The results of the STRATOS trials¹ of the anti-interleukin 13 monoclonal antibody tralokinumab for severe asthma might at first sight seem disappointing. The trials showed variable effects of tralokinumab on asthma exacerbations and FEV₁ in patients with raised fractional exhaled nitric oxide (FENO), whereas Asthma Control Questionnaire-6 scores were significantly reduced by tralokinumab treatment in both studies, albeit less than the minimal important difference. Perhaps we should think outside of the box and take clues from other therapeutic areas.

Benralizumab effectively blocks interleukin 5 for the treatment of severe eosinophilic asthma; however, some individuals have only a partial response and still have a persistent disease burden,^{2,3} perhaps inferring that also blocking the unopposed effects of interleukin 13 might have a potential benefit. In this regard, as shown by the MESOS study,⁴ tralokinumab decreases FENO and IgE—but not blood eosinophils—in patients with moderate-to-severe asthma. We therefore propose that a combined approach, blocking interleukin 5 with benralizumab and interleukin 13 with tralokinumab, might be required to comprehensively suppress type 2 inflammation and achieve better outcomes (figure 1). This combined regimen could perhaps be considered akin to using cotrimoxazole for infection, or valsartan and sacubitril for heart failure.

The patients who would benefit most from this combined treatment would be those with high eosinophils and FENO, although individual biomarker thresholds might be lower; for example, a combination of FENO >25 ppb and >150 eosinophils per μ l, which occurs in approximately 40% of patients, might identify optimal responders to benralizumab and tralokinumab, as was previously

seen with dupilumab.⁵ We believe that studies comparing combined benralizumab and tralokinumab with benralizumab alone are warranted to assess whether this strategy (albeit expensive) translates into improved outcomes in terms of control in severe eosinophilic asthma.

It is perhaps surprising that the MESOS study⁴ showed no significant effect on bronchial and sputum eosinophil counts after neutralisation

of interleukin 13 with tralokinumab, given that interleukin 13 is involved in the migration of eosinophils from blood vessels into tissues, regulated by interleukin 5 and eotaxin.⁶ Indeed, a putative trafficking effect of interleukin 13 would be consistent with the 17% increase ($p=0.055$) in blood eosinophils observed with tralokinumab.⁴ We postulate that blockade of interleukin 13 alone, in the presence of unopposed interleukin 4



Published Online
August 2, 2018
[http://dx.doi.org/10.1016/S2213-2600\(18\)30275-3](http://dx.doi.org/10.1016/S2213-2600(18)30275-3)

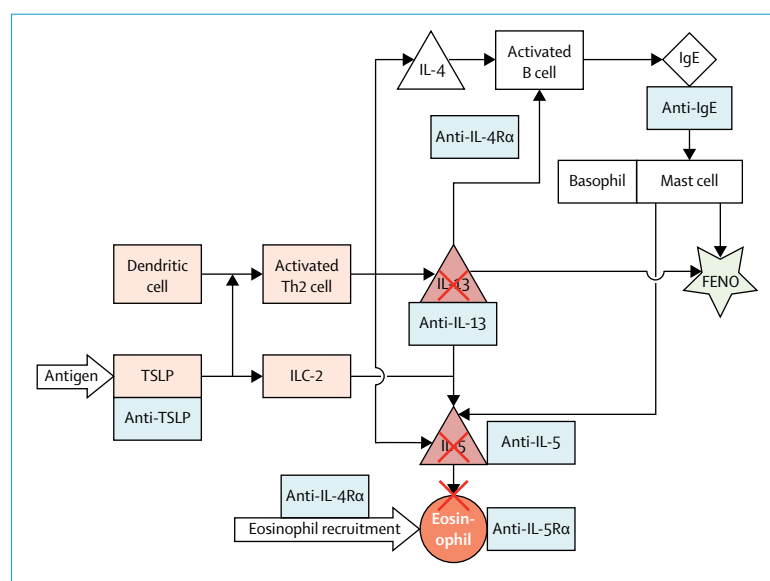


Figure 1: Diagram of biologics and biomarkers in relation to the type 2 inflammatory pathway in asthma Biologics (shown in light blue) include anti-IL-4R α (dupilumab), anti-IL-5R α (benralizumab), anti-IL-5 (mepolizumab or reslizumab), anti-IL-13 (tralokinumab or lebrikizumab), anti-IgE (omalizumab), and anti-TSLP (tezepelumab). Biomarkers include FENO, IgE, and eosinophils. IL-4=interleukin 4. IgE=immunoglobulin E. IL-4R α =interleukin 4 receptor α . Th2=T-helper-2. IL-13=interleukin 13. FENO=fractional exhaled nitric oxide. TSLP=thymic stromal lymphopoietin. ILC-2=type 2 innate lymphoid cells. IL-5=interleukin 5. IL-5R α =interleukin 5 receptor α .

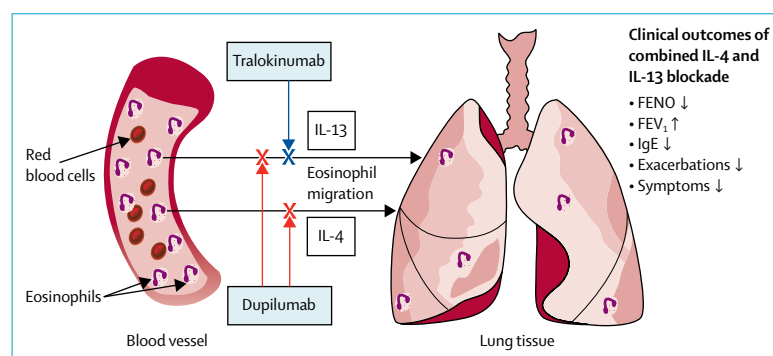


Figure 2: Blockade of IL-4 and IL-13

IL-13 and IL-4 are involved in trafficking eosinophils from blood vessels into the lungs. Blockade of IL-13 alone is insufficient to suppress tissue eosinophils in the presence of unopposed IL-4 signalling. Combined IL-4 and IL-13 blockade therefore results in putative reduction of lung eosinophils in conjunction with raised blood eosinophils. IL-13=interleukin 13. IL-4=interleukin 4. FENO=fractional exhaled nitric oxide.

signalling, is ineffective at arresting tissue eosinophil migration (figure 2). Notably, patients with eosinophilic oesophagitis showed a 92% reduction in epithelial eosinophils in response to dupilumab,⁷ which blocks signalling of both interleukin 4 and interleukin 13. We therefore await the results of the EXPEDITION study of dupilumab (NCT02573233) in patients with persistent asthma, in whom we would expect to see similar reductions in submucosal eosinophils from bronchial biopsy. In patients with severe persistent asthma, the use of dupilumab was associated with 48% fewer exacerbations despite a transient increase in blood eosinophils,⁵ in turn suggesting that airway eosinophils might have been reduced, although tissue eosinophils were not directly measured. Thus, we propose that blockade of both interleukin 4 and interleukin 13 is required to regulate eosinophil tissue trafficking in patients with asthma. Studies might therefore be indicated to directly compare the clinical efficacy of combined blockade with interleukin 4 and interleukin 13 versus interleukin 5 and interleukin 13 in

severe eosinophilic asthma. There is also the prospect of blocking thymic stromal lymphopoietin higher up the type 2 pathway with tezepelumab, which reduces FENO, IgE, and eosinophils.

BL reports grants and personal fees from AstraZeneca and Sanofi, personal fees and other from Teva, personal fees from Novartis and Genentech, grants from Roche, and other from GlaxoSmithKline in relation to the submitted work; grants and personal fees from Meda, Boehringer Ingelheim, and Chiesi, grants from Janssen, personal fees from Lupin, Cipla, and Dr. Reddy's Laboratories, and Circassia, and consulting for Sandoz and Circassia outside of the submitted work; and his son is employee of Boehringer Ingelheim. SJ reports personal fees and non-financial support from Chiesi, Pfizer, and AstraZeneca, non-financial support from Teva, Meda, and Napp, personal fees from Boehringer Ingelheim, and travel fees from Napp outside of the submitted work. CRK reports personal fees and non-financial support from Pfizer outside of the submitted work.

*Brian Lipworth, Sunny Jabbal,
Chris RuiWen Kuo

b.j.lipworth@dundee.ac.uk

Scottish Centre for Respiratory Research, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, UK

- 1 Panettieri RA Jr, Sjöbring U, Péterffy A, et al. Tralokinumab for severe, uncontrolled asthma (STRATOS 1 and STRATOS 2): two randomised, double-blind, placebo-controlled, phase 3 clinical trials. *Lancet Respir Med* 2018; **6**: 511–25.

- 2 FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016; **388**: 2128–41.
- 3 Bleecker ER, FitzGerald JM, Chaney P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIRIOCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016; **388**: 2115–27.
- 4 Russell RJ, Chachi L, FitzGerald JM, et al. Effect of tralokinumab, an interleukin-13 neutralising monoclonal antibody, on eosinophilic airway inflammation in uncontrolled moderate-to-severe asthma (MESOS): a multicentre, double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Respir Med* 2018; **6**: 499–510.
- 5 Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018; **378**: 2486–96.
- 6 Pope SM, Brandt EB, Mishra A, et al. IL-13 induces eosinophil recruitment into the lung by an IL-5- and eotaxin-dependent mechanism. *J Allergy Clin Immunol* 2001; **108**: 594–601.
- 7 Hirano I, Dellon ES, Hamilton JD, et al. Dupilumab efficacy and safety in adult patients with active eosinophilic esophagitis: a randomized double-blind placebo-controlled phase 2 trial. World Congress of Gastroenterology at ACG2017; Orlando, FL; Oct 13–18, 2017. Abstract 20.