

EDITORIAL



Inhibiting Interleukin-4 and Interleukin-13 in Difficult-to-Control Asthma

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One of the most challenging aspects of the clinical management of asthma is determining how to treat patients whose condition is poorly controlled despite the use of inhaled glucocorticoids and long-acting beta-agonists (LABAs). Although most patients have a response to these treatments, it is estimated that asthma remains poorly controlled in as many as 20% of patients who use combination therapy.¹ Mainstays of the management of difficult-to-control asthma include increased adherence to treatment, avoidance of allergens and other exacerbating factors, and control of common coexisting conditions such as gastrointestinal reflux, postnasal drip, and sinusitis. Other adjuvant therapies currently available include leukotriene modifiers, theophylline, anti-IgE antibody, bronchial thermoplasty, systemic glucocorticoids, and tiotropium (which is not approved by the U.S. Food and Drug Administration for the treatment of asthma). However, response to these therapies is variable and unpredictable. In the past several years, there have been some successes reported in studies of new asthma treatments that target the cytokines thought to underlie the primary pathogenesis of asthma, including anti-interleukin-5 and anti-interleukin-13 (Table 1).^{5-9,16}

Wenzel and colleagues now report in the *Journal* the results of a randomized, masked, controlled trial examining another new asthma therapy, dupilumab, a subcutaneously administered antibody to the alpha subunit of the interleukin-4 receptor; this treatment inhibits signaling by both interleukin-4 and interleukin-13.⁴ At first glance, the response to dupilumab therapy is outstanding, with an 87% reduction in the pro-

portion of patients with an asthma exacerbation (one of the most important outcomes for clinicians and patients) and significant improvement in lung function, all while allowing for the withdrawal of inhaled glucocorticoids and LABAs. As compared with the results of previous studies of asthma therapies, these results appear superior, because dupilumab treatment almost completely prevented loss of asthma control despite discontinuation of inhaled glucocorticoids and LABAs. So is this the magic bullet for difficult-to-control asthma?

As compelling as these data seem, upon closer examination, this proof-of-principle study shows efficacy only in a limited subpopulation of patients with asthma. Only 21% of those screened for the study met the inclusion criteria, probably because of the requirement for persistent symptoms and eosinophilia in the presence of treatment with inhaled glucocorticoids. We do not know whether dupilumab will be effective in other patient populations, such as the much larger population of patients who use inhaled glucocorticoids and LABAs and do not have eosinophilia.

Furthermore, although this therapy appeared to be effective in reducing exacerbations as LABAs and inhaled glucocorticoids were withdrawn, in clinical practice, physicians do not withdraw therapy to induce exacerbations. Thus, the apparent reduction in deleterious asthma outcomes as therapies were withdrawn only serves to tell us that this biologic therapy appears to work, as a proof of concept, but may not be advantageous in a “real world” situation, and thus the finding offers little direction for clinical practitioners.

Table 1. New and Emerging Therapies Being Evaluated for Asthma.*

Therapy	Target	Reference or ClinicalTrials.gov Number
Anticholinergic agents	Acetylcholine receptor	Kerstjens ²
Chemokine-receptor antagonists	CXCR2, CCR3	Nair, ³ NCT01160224
	CCR3 (antisense)	NCT00822861
Cytokine mediators	Interleukin-4 receptor α	Wenzel, ⁴ NCT00801853
	Interleukin-5	Pavord, ⁵ Nair, ⁶ Halder, ⁷ Castro, ⁸ NCT01691508, NCT01285323
	Interleukin-5 receptor	NCT00659659
	Interleukin-13	Corren, ⁹ Piper, ¹⁰ NCT01545440, NCT01402986
Leukotriene inhibitors	5-Lipoxygenase activating protein	NCT01471665
	Leukotriene A ₄ hydrolase	NCT01241422
Mast-cell inhibitors	Tyrosine kinase	Humbert, ¹¹ NCT01449162, NCT01097694
Once-daily beta-agonists and inhaled glucocorticoids	B ₂ -adrenergic receptor and multiple targets	Busse, ¹² NCT01686633, NCT00556673
Prostaglandin D ₂ receptors antagonists	CRTH2	Busse, ¹³ Barnes, ¹⁴ NCT01545726, NCT01561690, NCT01197794
Toll-like receptor agonists	Toll-like receptor 9	Beeh, ¹⁵ NCT01673672

* This list is not exhaustive but represents a sample of therapies being investigated for asthma. CCR3 denotes chemokine (C-C motif) receptor 3, CRTH2 chemoattractant receptor expressed on type 2 helper T cells, and CXCR2 chemokine (C-X-C motif) receptor 2.

Indeed, in the first phase of the trial, while all patients were using inhaled glucocorticoids and LABAs, there was no significant difference in exacerbations between the dupilumab group and the placebo group and only a slight improvement in lung function and some inflammatory biomarkers in the dupilumab group. Moreover, the study definition of an exacerbation was weighted toward changes in peak flow, and this too may not reflect real-world exacerbations.

Hence, although one of the biggest unmet needs is for add-on therapy to inhaled glucocorticoids and LABAs, this study, using a withdrawal design, was not designed to show a beneficial adjuvant effect of dupilumab. Rather, it shows that dupilumab is able to substitute inhaled glucocorticoids and LABAs in a specific subgroup of patients with asthma, but whether or not this drug has added value over treatment with inhaled glucocorticoids and LABAs in patients with moderate-to-severe asthma remains to be established. This is both clinically and biologically important, because inhaled glucocorticoids and LABAs target type 2 helper T cell (Th2) pathways, so we may need to look elsewhere to find the needed treatments for difficult-to-treat asthma.

More work needs to be done. Longer studies comparing dupilumab with placebo as add-on therapy to inhaled glucocorticoids and LABAs, without withdrawal, are necessary to show the clinical usefulness and durability of potential benefits of this drug. Identification of patients who are most likely to respond to this versus other new therapies is also important. Given the appearance of increased eosinophilia in four patients in the dupilumab group, more safety data are also required. Although it is too early to tell whether this therapy will be of clinical value, I think we are on the right path. For our patients' sake, I hope that this, and other approaches targeting Th2 cytokines, will bring the additional relief needed to asthma patients in real-world settings.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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