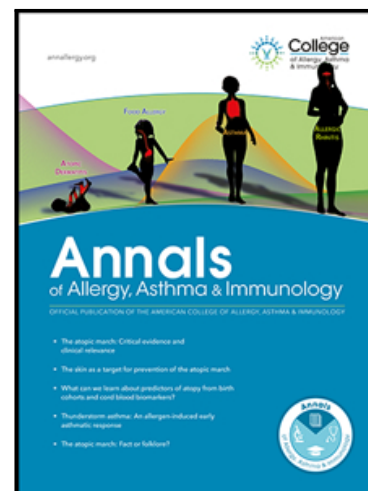


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Update: Asthma Yardstick: Practical recommendations for a sustained step-up in asthma therapy for poorly controlled asthma

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Recently Chipps and colleagues published a comprehensive update on how to conduct a sustained step up in asthma therapy for patients with not well or poorly controlled asthma – the Asthma Yardstick (1).

In this document the authors focused on the use of biologic agents, including omalizumab, mepolizumab and reslizumab. Although only published a year ago, a great deal has been learned in the world of biologic agents since.

After publication of the article by Chipps et al. the family of biologics targeting IL-5 has been supplemented with benralizumab, a molecule that in contrast to mepolizumab and reslizumab, targets the IL-5 receptor (IL-5R). In addition to behaving similarly to these agents as IL-5 antagonists, through its

ability to mediate antibody-dependent cellular cytotoxicity, benralizumab has the *theoretical* advantage of being able to opsonize and eliminate eosinophils (and perhaps also basophils) even in the absence of circulating IL-5. Meta-analyses of studies using these agents highlight that in asthmatics with an enhanced type 2 (T2) high signature there is a greater likelihood of efficacy with use of these agents. This is exemplified in an article by Fitzgerald and colleagues who performed a pooled analysis of the two pivotal benralizumab trials, CALIMA and SIRROCO, examining over 2000 subjects in which they found that annual asthma exacerbation rates were lower in those stratified to receive benralizumab every 8 weeks compared to those who received placebo (rate ratio 0.64, (95% CI = 0.55–0.75; $p < 0.0001$) (2). With regard to the T2 signature, they found that exacerbation rates were further improved in those with higher baseline eosinophil counts. Specifically, in those with eosinophil counts of 150-299 cells per μL the annual exacerbation rate absolute difference estimate vs placebo (95% CI) was -0.27 (-0.65 to 0.10), for those with eosinophil counts of 300-449 cells per μL it was -0.32 (-0.58 to -0.05) and for those with baseline eosinophil counts of >450 cells per μL the absolute difference estimate vs placebo for annual exacerbation rate was -0.59 (-0.80 to -0.37). Similar data have been seen with mepolizumab and omalizumab regarding enhanced efficacy with larger T2 signal.

Furthermore, since the publication of the asthma yardstick, a new class of biologic agent, dupilumab, directed at the IL-4 receptor α chain (IL-4R α) which results in blockade of both IL-4 and IL-13 has demonstrated efficacy in asthma and is presently undergoing evaluation by the FDA. In a recent study by Castro et al., patients with uncontrolled asthma were randomized in a 2:2:1:1 ratio to receive add-on subcutaneous dupilumab at a dose of 200 or 300 mg every 2 weeks or matched-placebos for 52 weeks (3). They found that the annualized rate of severe asthma exacerbations was 0.46 (95% confidence interval [CI], 0.39 to 0.53) among patients randomized to 200 mg of dupilumab every 2 weeks and 0.87 (95% CI, 0.72 to 1.05) among those receiving placebo, for a 47.7% lower rate with dupilumab than with placebo ($P < 0.001$), with similar results seen with the dupilumab dose of 300 mg every 2 weeks. At week

12, the FEV₁ had increased by 0.32 liters in patients receiving the lower dose of dupilumab (difference vs. matched placebo, 0.14 liters; $p < 0.001$), with similar results seen with the higher dose. Subsequently, Rabe et al. extended the work reported by Castro, investigating the efficacy of dupilumab in a cohort of oral corticosteroid-dependent severe high-risk asthmatics (4). This study involved asthmatics on oral steroids who were randomized to dupilumab (300 mg) or placebo every 2 weeks for 24 weeks. The study involved a standardized dose-adjusting regimen and the primary endpoint was the percentage of reduction in oral steroid dose. 70.1% of subjects in the dupilumab cohort achieved this primary endpoint compared to 41.9% in the placebo group ($p < 0.0001$). Even more impressively, 69% of treated patients were able to reduce their steroid dose to < 5 mg/day, including 48% who were able to completely discontinue their oral steroid use. And this was achieved with both a significantly greater reduction (59%) in exacerbation rate and an FEV₁ that was 0.22L higher than with the placebo. As with other studies utilizing this agent, the use of dupilumab was associated with increases in circulating absolute eosinophil count, however, all other adverse events occurred with equal frequency in the treatment and placebo cohorts. The higher eosinophil count is an intriguing finding that in the presence of striking clinical improvement does not appear to have clinical significance. This finding can best be ascribed to the initial persistence of IL-5 expression that is driving eosinophilopoiesis but with those eosinophils “stranded” in the circulation as a result of the ability of the dupilumab to block expression of chemokines (eotaxins) and adhesion molecules (VCAM-1) that underlie transmigration of those cells into the airway.

Lastly, research is ongoing with the hope of finding an agent with efficacy in T2 low asthmatics. A recent publication by Corren and colleagues, examined a monoclonal antibody directed against TSLP, Tezepelumab. Thymic Stromal Lymphopoietin (TSLP) is produced primarily by epithelial cells, including the bronchial epithelial cells of asthmatics, in response to numerous environmental and locally generated “danger” signals. Amongst its primary activities is the generation of a type 2 inflammatory

response through its activity on innate immune cells including dendritic cells, type 2 innate lymphoid cells, eosinophils, and mast cells as well as through direct actions on T and B cells including Th2 effector cells. In this study, tezepelumab at 3 dose levels or placebo was administered to a cohort of moderate-to-severe asthmatics for 52 weeks, with annualized rate of asthma exacerbation examined as the primary endpoint. Tezepelumab reduced exacerbation frequency by 61%, 71%, and 66% when administered at doses of 70 mg every 4 weeks, 210 mg every 4 weeks, and 280 mg every 2 weeks, respectively ($p < 0.001$) (5). And this was achieved with significantly higher lung function in all the treatment groups. However, the most remarkable outcome of this study was that similar results were observed in patients *regardless of blood eosinophil counts, FeNO, or IgE level* at enrollment. Observed reductions in eosinophil counts and IgE were consistent with predicted targeting of IL-4, IL-5, and IL-13 downstream pathways. However, the observed benefit in T2 low asthmatics is unique among all currently active biologics. This efficacy points to both the tendency of non-allergic factors such as smoke and viruses to trigger TSLP release, as well as the importance of TSLP in engaging cellular targets that are not entirely type 2-specific including mast cells, basophils, innate lymphoid cells, and neutrophils.

Presently we have a robust biologic armamentarium for the treatment of T2 high asthmatic patients, with the ability to block several key steps in their inflammatory cascade. Studies indicate that with an enhanced T2 signal, there is greater likelihood that these agents will be effective. It is hoped in the near future that similar biologic agents will be available for the treatment of asthmatic patients with a T2 low phenotype.

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Larry Borish, MD

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