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Review

Efficacy of biologic therapy on airway hyperresponsiveness in asthma

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Key Messages

- Airway hyperresponsiveness (AHR) is a complex process, with contributions from airway inflammation, intrinsic and extrinsic airway smooth muscle factors, and bronchial remodeling.
- Systemic biologic therapy has shown efficacy in reducing clinically significant exacerbations, improving lung function, and improving asthma quality of life and disease control.
- Recently, tezepelumab and benralizumab have shown significant attenuation of mannitol AHR in severe asthma.
- More studies looking at AHR with dupilumab, omalizumab, benralizumab, and tezepelumab are urgently required, possibly also using direct challenge agents such as methacholine.
- The small airways are more sensitive to bronchoconstriction in persistent asthma, and in this regard, biologic studies using oscillometry AHR should be considered in the future.

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ABSTRACT

Airway hyperresponsiveness refers to an exaggerated bronchial constrictor response to a given exogenous inhaled agent and is governed by airway smooth muscle along with mucosal inflammation in asthma. In recent years, the advent of biologics and antialarmins has transformed severe asthma treatment in terms of reducing oral-corticosteroid–requiring exacerbations and improving disease control, asthma quality of life, and spirometry-measured lung function. In contrast, there have been comparatively fewer studies investigating the efficacy of biologics in airway hyperresponsiveness. In this focused review, we summarize the existing evidence base in this area regarding omalizumab, mepolizumab, benralizumab, and tezepelumab.

Introduction

Airway hyperresponsiveness (AHR) refers to an exaggerated bronchial constrictor response to a given exogenous inhaled agent and is governed by airway smooth muscle along with mucosal inflammation in asthma.[1] This bronchial response is typically captured by measuring a decrease in forced expiratory volume in 1 second, with the latter being associated with a more pronounced and steeper decrease at a smaller dose of constrictor agonist in patients with severe asthma than in those with mild or no asthma.[2]

Direct airway challenges using methacholine or histamine, which act directly on bronchial smooth muscle, can be used to assess AHR and are generally more sensitive than indirect challenge agents in diagnosing asthma.[3] In this regard, methacholine has been preferentially used as histamine also acts on the bronchial sensory nerves and is less well tolerated by most patients.[4] Mannitol and adenosine

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monophosphate (AMP) are examples of indirect challenge agents that elicit endogenous AHR through the release of inflammatory mediators, including prostaglandins, histamine, and leukotrienes, and are more specific to asthma.[5] Other indirectly acting stimuli include exercise, eucapnic voluntary hyperpnoea, and hypertonic saline. Moreover, sensitization to aeroallergens is linked to increased AHR in asthma.[6]

Airway inflammation drives AHR in asthma, and this concept has previously been indicated by dose-related improvements in indirect AHR after inhaled corticosteroid therapy in persistent asthma.[7] Airway hyperresponsiveness also constitutes a key mechanistic treatable trait that occurs irrespective of type 2 high or low inflammation in the push toward personalized precision medicine in asthma.[8] A retrospective cohort study previously associated greater fractional exhaled nitric oxide levels and number of positive specific immunoglobulin (Ig) E to common aeroallergens with AHR.[9] Furthermore, there are accompanying reductions in airway remodeling and exacerbations when inhaled corticosteroid (ICS) is titrated against AHR.[10,11] Stabilization of airway smooth muscle by long-acting β-agonist results in a 0.8 doubling difference (DD) improvement in AHR compared with placebo in patients on ICS therapy.[12] To put this into perspective, allergen exposure in patients with asthma is thought to result in a worsening AHR shift amounting to 1 to 2 DD.[13] These changes are likely clinically relevant in the presence of an already accentuated baseline AHR in patients with asthma compared with in healthy volunteers.

In recent years, the advent of biologics[14] and antialarmins[15] has transformed severe asthma treatment in terms of reducing oral-corticosteroid–requiring exacerbations and improving disease control, asthma quality of life, and spirometry-measured lung function. In contrast, there have been comparatively fewer studies investigating the efficacy of biologics in AHR, and in this focused review, our objective is to succinctly summarize the existing evidence base in this area. We have opted to exclude clinical trials in which AHR was evaluated after allergen response because this introduces an additional potentially confounding variable that is not reflective of real-life clinical practice. However, we have chosen to include trials in which patients had mild asthma because we feel the results are still worth exploring, although we duly appreciate that these studies are less clinically relevant. Earlier studies may have chosen to enroll patients with milder asthma as a proof of concept in the context of potential safety concerns with airway challenges. Furthermore, because the following data are heterogenous in terms of biologic choice, asthma severity, and challenge agent, this article will serve as a narrative review and possibly a starting point for readers who may wish to conduct future biologic studies involving AHR.

Omalizumab (Anti–Immunoglobulin E)

Effector mast cells are more abundant in the bronchial smooth muscle of patients with asthma than in those with eosinophilic bronchitis and normal controls, and are associated with greater AHR to methacholine.[16] Immunoglobulin E is responsible for activating mast cells and plays an important role in allergic asthma.[17] Given that AHR is closely linked to allergen sensitization, there might appear, on first principle, a cogent role for anti-IgE.[18]

Previous studies have investigated the effect of the anti-IgE monoclonal antibody omalizumab on AHR in patients with asthma. A randomized controlled trial (RCT)[19] (n = 35) found significant improvements in the provocative dose of acetylcholine required to decrease forced expiratory volume in 1 second by 20% (PC_{20}). This amounted to a 0.42 mean DD compared with placebo after 16 weeks of omalizumab in moderate-to-severe allergic asthma. Histamine release from basophils was significantly attenuated in the treatment group, but interestingly, serum interleukin (IL) 13 levels and blood eosinophils were also significantly reduced with omalizumab.

However, in another RCT[20] (n = 45) in patients with mild-to-moderate asthma, near-depletion of airway mucosal IgE and eosinophils on bronchial biopsy specimens was not accompanied by improvements in methacholine PC_{20} after 16 weeks of omalizumab. Only 1 RCT[21] in mild-to-moderate asthma used AHR as the primary outcome (n = 34), but omalizumab did not improve methacholine or AMP PC_{20} compared with placebo after 12 weeks. Notably, the distinct difference of using methacholine instead of acetylcholine is the relative resistance to degradation by cholinesterase,[22] which, in addition to disparities in asthma severity, may perhaps go toward explaining the difference in these results.

Mepolizumab and Benralizumab (Anti–Interleukin 5(Rα))

Bronchoalveolar lavage eosinophil concentrations are greater in patients with asthma with methacholine AHR,[23] and therefore, one might postulate that airway eosinophil suppression with the anti–IL-5 monoclonal antibody mepolizumab[24] would contribute to AHR attenuation. In patients with refractory asthma, 1 RCT[25] (n = 61) did not detect any improvements in methacholine AHR after 52 weeks of high-dose intravenous 750 mg mepolizumab every 4 weeks. In another RCT[26] (n = 24) looking at patients with mild asthma, the same dose of mepolizumab did not improve AHR measured by histamine PC_{20} after 20 weeks. In that study, although blood and bronchoalveolar lavage eosinophils were mostly suppressed, it is worth noting that 50% of airway tissue and bone marrow eosinophils remained. This reservoir of eosinophils with ongoing degranulation, as evidenced by persistence of major basic protein, could point toward a reason for the lack of efficacy in this study. Pointedly, the current licensed formulation for severe asthma is subcutaneous mepolizumab 100 mg every 4 weeks, and both studies did not use AHR as a primary outcome.

It has previously been shown that indirect AHR using AMP is more closely associated with airway inflammatory parameters such as sputum and blood eosinophils and eosinophil cationic protein than is direct methacholine PC_{20}.[27] Airway eosinophilia, measured by sputum eosinophils and fractional exhaled nitric oxide, is associated with mannitol and methacholine AHR—however, it is more strongly associated with mannitol AHR.[28] In this regard, a recent phase IV clinical trial investigated the effect of anti–IL-5Rα monoclonal antibody as open label subcutaneous benralizumab 30 mg every 4 weeks in severe asthma.[29] This study revealed significant improvements in mannitol AHR in n = 21 patients as the primary end point after 12 weeks, with significant changes occurring as early as 8 weeks. Although no placebo arm was performed owing to ethical reasons, the improvements in AHR amounted to a mean (95% confidence interval [CI]) of 2.1 DD (1.0-3.3), with the lower CI exceeding biological variability of 1.0 DD. Moreover, in this study, depletion of eosinophils was accompanied by a 77% suppression of eosinophil-derived neurotoxin, whereas improvements in the Asthma Control Questionnaire and mini-Asthma Quality of Life Questionnaire both exceeded the minimal clinical important difference of 0.5 units. Interestingly, 4 months after the last dose of benralizumab, there was still significant attenuation of AHR amounting to 1.3 DD (0.4-2.3). The significant AHR attenuation with benralizumab but not mepolizumab might be explained by eosinophil depletion rather than merely suppression; differences in airway challenge agent; and the fact that the benralizumab trial was properly powered to investigate mannitol AHR as the primary outcome.

Table 1
Summary of Available Biologic Airway Hyperresponsiveness Clinical Trials in Asthma

Study	Biologic	Challenge agent	Primary outcome	n	DD (95% CI)	Asthma severity
Noga et al,[19] 2003	Omalizumab	Acetylcholine	No	35	0.42[a]	Moderate-severe
Djukanovic et al,[20] 2004	Omalizumab	Methacholine	No	45	−0.78	Mild-moderate
Prieto et al,[21] 2006	Omalizumab	AMP/Methacholine	Yes	34	0.96 (−0.19 to 2.12)	Mild-moderate
Flood-Page et al,[26] 2003	Mepolizumab	Histamine	No	24	−0.16	Mild
Haldar et al,[25] 2009	Mepolizumab	Methacholine	No	61	0.87	Severe
Diver et al,[34] 2021	Tezepelumab	Mannitol	No	48	0.84 (0.04-1.65)[a]	Moderate-severe
Sverrild et al,[33] 2022	Tezepelumab	Mannitol	Yes	40	0.9 (−0.1 to 1.9)	Any

Abbreviations: AMP, adenosine monophosphate; CI, confidence interval; DD, doubling difference.
NOTE. Where data are available, 95% CI presented.
[a]Significant vs placebo.

Dupilumab (Anti−Interleukin 4Rα)

At present, there are no published in vivo studies relating to the anti−IL-4Rα monoclonal antibody dupilumab and AHR. One might expect suppression of IL-13 inflammation would improve AHR through its effect on mucus hypersecretion and potentiation of airway narrowing.[30] Intriguingly, 1 ex vivo study elicited AHR in the small airways with IL-13 and IL-4 that was blocked by dupilumab.[31] We therefore anticipate the results of the ongoing clinical trials investigating the effect of dupilumab on mannitol (Eudract No. 2021-005593-25) and methacholine (NCT03884842) AHR in severe asthma.

Tezepelumab (Antithymic Stromal Lymphopoietin)

Along with IL-25 and IL-33, the upstream epithelial alarmin thymic stromal lymphopoietin (TSLP) exerts its effect on downstream inflammatory cytokines IL-4, IL-5, and IL-13,[15] and therefore, the results of the large genetic association study[32] showing an association between the TSLP gene variant with methacholine AHR are possibly intuitive.

More recently, 2 studies in the effect of the anti-TSLP tezepelumab on mannitol AHR have been published. In the first RCT[33] (n = 40) in patients of any asthma severity, intravenous tezepelumab 700 mg every 4 weeks improved mannitol AHR nonsignificantly (P = .06) by 0.9 DD (−0.1 to 1.9) as the primary outcome at week 12 compared with placebo. In this study, the mean blood eosinophil count was 214 cells/μl with attenuation of AHR most pronounced in patients with eosinophilic asthma. In the second RCT[34] (n = 48) investigating patients with moderate-to-severe asthma and a mean blood eosinophil count of 287 cells/μl in which AHR was an exploratory outcome, subcutaneous tezepelumab 210 mg every 4 weeks significantly improved mannitol AHR by a mean (95% CI) of 0.84 DD (0.04-1.65) after 28 weeks compared with placebo. In addition to its broad spectrum effect on type 2 biomarkers,[15] tezepelumab may mechanistically improve AHR via its inhibitory effect on mast-cell activation.[35]

Conclusion

It is important to bear in mind that AHR is a continually moving target, in that the presence and severity are dependent on choice of constrictor agonist and level of antiasthma therapy. Airway hyperresponsiveness is also the result of complex biomechanisms that may have differential effects on individual patients.[36] One health informatics study showed that 14% of methacholine responders had negative AHR to mannitol, whereas 16% of mannitol responders exhibited negative AHR to methacholine, further illustrating the heterogeneity of AHR.[37] In clinical practice, clinicians may wish to consider repeating an airway challenge test using an alternative agent if the initial test is negative and clinical suspicion remains high.

There is an urgent need for future biologic trials to include AHR as the primary outcome because this will ensure adequate statistical power for the study. Airway hyperresponsiveness is particularly clinically relevant because it is closely associated with type 2 inflammation, asthma severity, and an enhanced response to ICS therapy.[9] Furthermore, providing improvements in AHR in addition to those achieved from ICS therapy satisfies an unmet need. In this regard, attenuating AHR is associated with reductions in severe exacerbations in asthma.[11]

A summary of the available biologic clinical trials in AHR is depicted in Table 1 and Figure 1. Figure 2 portrays a simplified mechanism by which biologics attenuate AHR. Four of the 9 clinical trials in this review included patients with mild asthma, which probably would have resulted in a lower likelihood of detecting AHR attenuation because presumably there would be less room for improvement. With this review, we highlight the urgent need for more biologic studies powered on AHR as the primary outcome in severe asthma, although we duly appreciate the recent difficulties involving aerosol-generating procedures in the pandemic era. Another potential area of research interest includes the degree of contribution of the small airways (those <2 mm in internal diameter) to overall AHR because the small airways are more sensitive to bronchoconstriction in asthma.[38] In this regard, 1 study showed that patients with asthma with

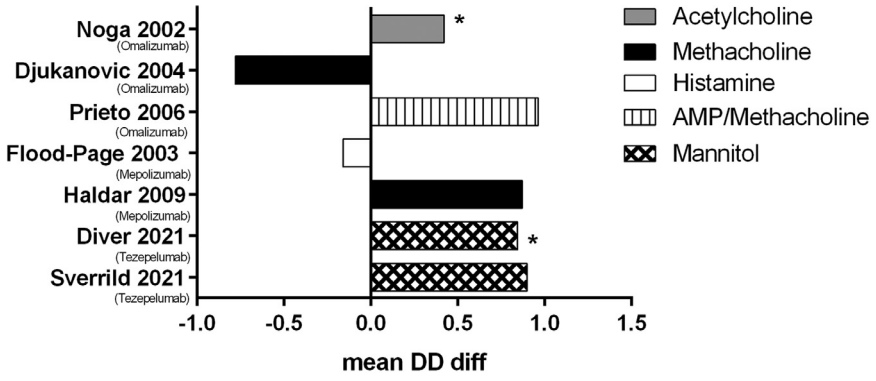

Figure 1. Mean doubling difference in airway challenge agent for various biologics in asthma. Asterisk denotes significant vs placebo.

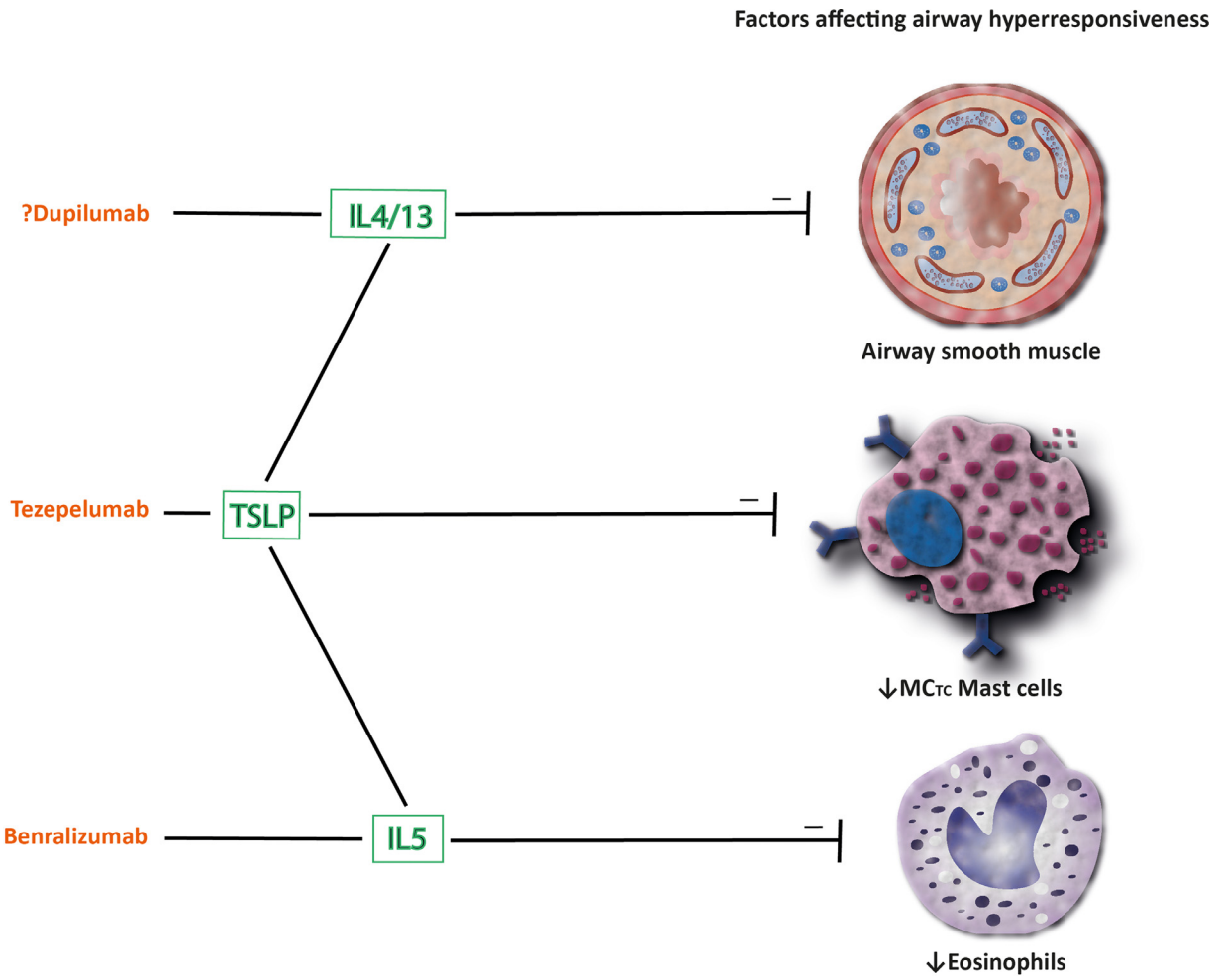

Figure 2. Tezepelumab and benralizumab have shown effectiveness in attenuating airway hyperresponsiveness in patients with persistent asthma through different pathways. Putative mechanism for dupilumab shown.

spirometry-defined small airways obstruction had significantly greater AHR to histamine.[39] Future biologic AHR trials may benefit from the enhanced sensitivity of measurements of small airways obstruction such as oscillometry.

To conclude, this focused review article has summarized the current available evidence surrounding the impact of biologic therapies on AHR in persistent asthma. There remains a paucity of data to definitively answer this important question, and therefore, future studies should include AHR as the primary outcome to ensure that results are properly powered.

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