J Bras Pneumol. 2023;49(3):e20230220
https://dx.doi.org/10.36416/1806-3756/e20230220

Anti-alarmin asthma therapies: where do we go from here?

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Asthma is a chronic airway inflammatory disorder that is characterized by reversible airway obstruction, inflammation, and hyperresponsiveness. Stable control of asthma symptoms is achievable by using combinations of inhaled corticosteroids and β_2 agonists; however, severe asthma patients do not respond well to these combinations.[1] Improved understanding of the inflammatory pathways in the airways of asthma patients has led to tremendous progress in the development of effective biologics blocking the actions of type-2 (T2) cytokines (IL-4, IL-5, and IL-13). While these biologics reduce asthma exacerbation rates by approximately 50%, they are not as effective in uncontrolled asthma, especially in those with non-eosinophilic and non-allergic phenotypes.[2] Interventions targeting mediators further upstream in the inflammatory cascade have been under evaluation (Table 1).

Alarmins are a diverse group of endogenous danger signals and multifunctional host-defense peptides (or proteins) released by epithelial cells into the extracellular microenvironment upon exposure to pathogens and environmental insults, and they play a critical role in innate immunity, antigen presentation, and adaptive immune response.[3] Among the numerous constitutively expressed alarmins, thymic stromal lymphopoietin (TSLP), IL-33, and IL-25 are pivotal to the initiation of T2 inflammatory responses in the airways and have been implicated in the pathobiology of chronic inflammatory conditions such as asthma.[4] Targeting the alarmins may help address the unmet medical need of T2-low (and non-T2) inflammation, which constitutes approximately 50% of the asthma population.[2]

Developing an effective anti-alarmin for asthma therapy requires consideration of several factors including the downstream inflammatory pathways, the target molecule (cytokine versus receptor), and the route of administration.

TSLP is present in two different isoforms, signaling through a heterodimer receptor consisting of TSLPR and IL-7R-alpha. The comparative efficacy of targeting TSLP long versus short isoform, or TSLP versus TSLPR, is unknown. To date, blockade of the TSLP pathway with a human monoclonal antibody (mAb) that binds to TSLP (tezepelumab, also known as AMG 157) has been approved in several countries for the treatment of severe asthma. Despite the potentially redundant actions of TSLP, IL-33, and IL-25 in driving T2 immune responses, tezepelumab added to inhaled corticosteroid treatment successfully improved FEV_1, reduced asthma exacerbation rates by nearly 70%, and decreased airway inflammation in severe asthma patients, with efficacy demonstrated in both T2-high and T2-low asthma.[5] Numerous other anti-TSLP and anti-TSLPR drugs are being tested for safety and efficacy in asthma patients (Table 1). Although head-to-head comparisons of anti-TSLP mAbs have not been conducted, two proof-of-concept studies using identical methodology examined the effect of systemically administered tezepelumab mAb (700 mg, i.v.) and inhaled CSJ 117 mAb-fragment (4 mg once daily), compared to placebo, on allergen-induced early and late asthma responses, as well as on markers of airway and systemic inflammation.[6,7] Tezepelumab and CSJ 117 both inhibited allergen-induced late asthma responses, sputum eosinophils, and fractional exhaled nitric oxide at 12 weeks post-dosing; however, only tezepelumab inhibited all allergen-induced outcomes at 7 weeks post-dosing and consistently inhibited the early asthma response and circulating eosinophil levels. The faster onset of action by i.v. administration may occur via systemic suppression of cells involved in the allergic cascade.

IL-33 is a pleiotropic cytokine that interacts with the ST2 receptor and IL-1 receptor accessory protein (IL-1RAP) to modulate its activities. From the full-length IL-33 cytokine precursor, various mature isoforms are formed with varying efficacies depending on the site of proteolytic cleavage. It is not well understood whether the pathogenic effect of IL-33 is caused by the full-length IL-33 and/or its mature isoform, making IL-33 a challenging target. The IL-33 mAb, itepekimab, positively impacted asthma control and health-related quality of life,[8] while treatment with the IL-33 mAb etokimab had no effect on blood eosinophil counts or asthma exacerbation (NCT03469934). No additional studies with anti-IL-33 mAbs have been planned, probably due to the small effect size reported in these early clinical trials. However, blocking the ST2 receptor with astegolimab has shown more promising results, reducing asthma exacerbation rates, improving FEV_1, and enhancing asthma-related quality of life.[9] Anti-ST2 mAbs may be more effective than anti-IL-33 mAbs due to the broad expression of ST2 on relevant inflammatory cells in the airways and the prevention of signaling by all forms of IL-33. However, an improved understanding of IL-33 pathway blockade for asthma treatment will require trials with larger sample sizes. Other anti-ST2 therapies under investigation for the treatment of asthma include tozorakimab (MEDI3506), a potent inhibitor of reduced and oxidized forms of IL-33, acting via ST2 and non-ST2 pathways.[10]

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Table 1. Alarmin-targeted clinical trials in asthma.

#	Clinical trial number	Trial name	Trial phase	Asthma severity	Primary outcome	Intervention (route of administration)	Age of participants, years
				Bivalent anti-TSLP/IL-13			
1.	NCT05366764		1	Mild to moderate	Incidence of AEs and TEAEs	SAR443765	18 to 60
				Anti-TSLP			
2.	NCT05329194 (Recruiting as of 2023/06/23)	PASSAGE	4	Severe asthma	Annualized AER, asthma exacerbation days & proportions	Tezepelumab (s.c.)	12 to 130
3.	NCT05280418 (Recruiting as of 2023/06/23)		3	Uncontrolled moderate-to-severe	Pre-bronchodilator 129Xe MRI ventilation defect percent	Tezepelumab (s.c.)	18 and older
4.	NCT03927157 (Active as of 2023/06/23)		3	Severe uncontrolled Asthma	Annualized AER	Tezepelumab (s.c.)	18 to 80
5.	NCT05274815 (Active as of 2023/06/23)	WAYFINDER	3	Severe uncontrolled asthma	OCS discontinuation or reduction to ≤ 5 mg/day	Tezepelumab (s.c.)	18 to 80
6.	NCT05398263 (Recruiting as of 2023/06/23)	SUNRISE	3	Severe uncontrolled asthma - OCS-dependent asthma	Reduction from baseline in the daily maintenance of OCS dose	Tezepelumab (s.c.)	18 to 80
7.	NCT04048343		3	Severe uncontrolled asthma	Adverse events	Tezepelumab (s.c.)	12 to 80
8.	NCT03406078	SOURCE	3	Severe uncontrolled asthma - OCS-dependent asthma	Categorized reduction from baseline in the daily OCS dose	Tezepelumab (s.c.)	18 to 80
9.	NCT03706079	DESTINATION	3	Severe uncontrolled asthma	Exposure adjusted AEs and severe AEs	Tezepelumab (s.c.)	13 to 81
10.	NCT05740748 (Active as of 2023/06/23)		2	Mild allergic asthma	Methacholine PD20	Tezepelumab (s.c.)	18 to 65
11.	NCT05774340 (Active as of 2023/06/23)		2	Moderate to severe	Annualized AER	CM326 (s.c.)	18 to 75
12.	NCT05593250 (Enrolling as at 2023/06/23)		2	Severe uncontrolled asthma	Annualized AER	SHR-1905 (s.c.)	18 to 75
13.	NCT02054130	PATHWAY	2	Severe uncontrolled asthma	Annualized AER	Tezepelumab aka MEDI9929 (s.c.)	18 to 75
14.	NCT04410523 (Terminated: sponsor decision)		2	Severe uncontrolled asthma	Change in baseline FEV_1	Ecleralimab aka CSJ117 (inh)	18 to 75
15.	NCT02698501	UPSTREAM	2	Uncontrolled asthma	Change in baseline mannitol PD15	Tezepelumab aka AMG 157 (i.v.)	18 to 75
16.	NCT01405963		1	Mild allergic asthma	Allergen-induced change in FEV_1	Tezepelumab aka AMG 157 (i.v.)	18 to 60

Continue...▶

Table 1. Alarmin-targeted clinical trials in asthma. (Continued...)

#	Clinical trial number	Trial name	Trial phase	Asthma severity	Primary outcome	Intervention (route of administration)	Age of participants, years
17.	NCT03138811 (Terminated: met set objective without safety concern)		1	Mild allergic asthma	Allergen-induced change in FEV_1	Ecleralimab aka CSJ 117 (inh)	18 to 60
18.	NCT05110976 (Recruiting as of 2023/06/23)		1	Asthma patients on medium to high dose ICS/LABA	AEs and PK	AZD8630 (inh)	18 to 75
19.	NCT05171348		1	Healthy volunteers	Incidence of adverse events	CM326 (s.c.)	18 to 65
20.	NCT04673630	TRAILHEAD	1	Mild/moderate/severe	PK	Tezepelumab (s.c.)	05 to 11
21.	NCT02512900		1	Mild to moderate	PK	Tezepelumab aka MEDI9929 (s.c.)	12 to 17
22.	NCT04842201		1	Healthy volunteers	Number and severity of adverse events	CM326 (s.c.)	18 to 65
				Anti-TSLP receptor			
23.	NCT05448651 (Active as at 2023/06/23)		1	Mild asthma	AEs and severe AEs	UPB-101 (s.c.)	18 to 60
				Anti-IL-33			
24.	NCT03387852		2	Moderate to severe	Loss of asthma control	Itepekimab aka SAR440340 (s.c.)	18 to 70
25.	NCT03469934		2	Severe eosinophilic asthma	Safety and change in blood eosinophil count	Etokimab aka ANB020 (s.c.)	18 to 65
				Anti-ST2			
26.	NCT04570657	FRONTIER-3	2	Moderate to severe	Baseline FEV_1	Tozorakimab aka MEDI-3506	18 to 65
27.	NCT02918019		2	Severe uncontrolled asthma	Reduction in AER	Astegolimab aka MSTT1041A (s.c.)	18 to 75
28.	NCT03207243 (Terminated: high screen failure rate & low enrollment)		2	Moderate to severe	Loss of asthma control	Melrilimab aka GSK3772847 (i.v.)	18 and older
				Anti-IL-25			
29.	NCT01199289		2	Moderate to severe	Change in ACQ score from baseline	AMG 827 aka brodalumab (s.c.)	18 to 65

TSLP: tissue stromal lymphopoietin, AEs: adverse events, TEAEs: treatment-emergent adverse events, aka: also known as; PK: pharmacokinetic, AER: asthma exacerbation rate, OCS: oral corticosteroids, ICS: inhaled corticosteroids, LABA: long-acting β_2 agonist, Inh: inhaled; and ACQ: Asthma Control Questionnaire.

Despite strong evidence showing the upregulation of IL-25 and IL-17RA and B receptor subunits in asthma, as well as the role of IL-25 signaling in the development of cardinal asthma features,[2] the only clinical trial targeting this pathway using brodalumab to block IL-17RA reported no improvement on the primary outcome (FEV_1).[11] Although it is possible that the role of IL-25 in the pathobiology of human asthma may not be as crucial as that of IL-33 and TSLP, this cannot be concluded without first investigating the effects of blocking IL-17RB or IL-25 in clinical trials.

The anticipated higher efficacy of anti-alarmin therapies versus biologics targeting downstream inflammatory cytokines is based on the idea that regulation of alarmin signaling also broadly impacts multiple relevant downstream inflammatory pathways. In support, dual therapy with the anti-IL-33 mAb itepekimab plus dupilumab (inhibiting downstream IL-13) found no superior outcome from the combined therapy.[8] In contrast, however, a study of a bifunctional NANOBODY molecule (SAR443765) targeting both TSLP and IL-13 reported a greater reduction in fractional exhaled nitric oxide and T2 biomarker levels when compared with monovalent TSLP or IL-13 mAb (NCT05366764). Whether combining anti-alarmin therapy with blockade of downstream pathways such as IL-13 will be a more effective approach or not requires an improved understanding of asthma pathobiology and disease endotypes.

AUTHOR CONTRIBUTIONS

Both authors equally contributed to the drafting, writing, and reviewing of the manuscript.

CONFLICTS OF INTEREST

None declared.

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