Research Article

iMedPub Journals
www.imedpub.com

Journal of Lung

2021
Vol.2 No.3:6931

The Role of Thymic Stromal Lymphopoietin in the Pathogenesis and Treatment of Severe Uncontrolled Asthma

Nightingale Syabbalo*

Department of Physiology and Medicine, Nabanji Medical Centre, Lusaka, Zambia

***Corresponding author**: Nightingale Syabbalo, Department of Physiology and Medicine, Nabanji Medical Centre, Lusaka, Zambia, Tel No: +260 966 486117; E-mail: nightsyab@gmail.com

Received date: December 19, 2020; **Accepted date:** August 16, 2021**; Published date:** August 26, 2021

Citation: Nightingale S (2021) The Role of Thymic Stromal Lymphopoietin in the Pathogenesis and Treatment of Severe Uncontrolled Asthma. J Lung Vol: 2 No: 3.

Abstract

Asthma is a highly prevalent chronic airway disease, affecting more than 358 million individuals globally [1], and it is the most common chronic inflammatory respiratory disease in children [2]. Asthma has been classified cytological depending on the predominant leucocyte count in induced sputum, and biomarkers of airway inflammation into eosinophilia, neutrophil, mixed granulocytic, and paucigranulocytic phenotypes [3, 4].

Approximately 40-60% of patients with severe asthma have eosinophilic phenotype [5-9], which is uncontrolled on high-dose inhaled corticosteroids (ICS), and long-acting β2-agonists (LABA), and leukotriene receptor antagonists (LTRA) [10,11].

Key words: Severe asthma, Interleukin, Thymic stromal lympopoietin, Tezepelumab.

Introduction

A proportion of patients with eosinophilia asthma respond favorably to monoclonal antibody (mAb), targeted at T helper lymphocytes (Th2) cytokines, such as interleukin-4 (IL-4), IL-5, IL-13, IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). Th2 cytokines play a pivotal role in the pathogenesis of eosinophilia asthma. Pharmacological blockade of IgE, IL-4, Il-5, TSLP, and their receptors has led to the development of very efficacious biologics for the treatment of eosinophilic asthma. The approved biologics for the treatment of eosinophilic asthma include omalizumab (anti-IgE) [12,13], mepolizumab and reslizumab (anti-IL-5) [14], benralizumab (anti-IL-5R) [15], dupilumab (anti-IL-4R), which block the actions of IL-4 and IL-13 [16]. Eosinophilic biologics have been demonstrated to significantly reduce exacerbation rates, emergency medical visits, improve asthma control, quality of life, and lung functions [12-17].

Several clinical trials have shown that eosinophilic targeted biologics only reduce exacerbation rates in about 48-59% of the patients [12-17]. Furthermore, some patients with eosinophilic asthma do not achieve significant symptoms control, and improvement in lung functions [18-20]. Additionally, some of the biologics may be inadequate to control sputum eosinophilia, and airway eosinophilic inflammation. Therefore, they may not have corticosteroid-sparing effects, particularly in patients with severe oral steroid-dependent asthma [12,21].

Currently, there are no biologics which have been approved for the treatment of patients with neutrophilic, paucigranulocytic, and other phenotypes of asthma [22]. There is unmet need to develop novel biologists which target different Th2 cytokine-driven pathways of asthma [23]. Epithelial "alarmin" cytokines, IL-25, IL-33, and TSLP seem attractive to inhibit, because they are upstream, and initiator cytokines [24].

TSLP plays a central role in the pathophysiology of eosinonophilic asthma, and participates in orchestrating neutrophil asthma, and airway remodeling [25]. Targeting TSLP seems to be an attractive approach for the development of novel biotherapeutics for the treatment of alarming-driven severe uncontrolled asthma [26].

Thyme stromal lymphopoietin is an epithelial derived cytokine that belongs to type 1 cytokine group, which is part of the interleukin-2 cytokine family, comprising of IL-2, IL-4, IL-5. IL-7, IL-9, IL-13, and IL-21 [27]. TSLP is released from airway epithelial cells, following environmental insults, such as allergen proteases, respiratory viral and bacterial infections, chemical irritants, pollutants, and trauma [28-34].

TSLP signaling pathway is mediated through its complex heterodimer receptor formed by a TSLP-specific TSLPR subunit (CRLF2), and the IL-7α signaling chain [35,36]. Signal transduction of the TSLP receptor is via activation of signal transducer and activator of transcription (STAT)1, 3, 4, 5 and 6, as well as Janus Kinase (JAK)1 [37-39]. Upon binding to its receptor, TSLP activates several immune pathways leading to the production of cytokines, chemokine's, growth factors, and enzymes by immune and structural cells. The aforementioned pro-inflammatory mediators orchestrate eosinophilia airway inflammation, and participate also in airway neutrophil, hyper responsiveness (AHR), and remodeling [26].

TSLP seems attractive to target in therapeutic interventions to treat asthma because it is an upstream cytokine at epithelial barrier. It plays a central role in the pathophysiology of both severe eosinophilia and Europhilic asthma, and

paucigranulocytic asthma through its effects on AHR, and airway remodeling.

Tezepelumab is a first-in-class fully human IgGʎ2 me that bind to TSLP, and prevents it to interact with its receptor TSLPR, thus inhibiting multiple downstream immune pathways, and production of cytokines, and chemokine's [40]. Tezepelumab has been shown to attenuate both the early and late asthmatic responses, reduce exacerbation rates by 62-71% depending on the dosage [41,42], and to decrease biomarkers of Eosinophilic inflammation (blood eosinophil counts, IgE, and fractional exhaled nitric oxide, FeNO) [43]. The improvements were observed in all the phenotypes of asthma, and independent of baseline blood eosinophil counts, IgE levels, and FeNO concentration [43]. Recently, Tezepelumab has also been shown to decrease serum IL-5, and IL-13 by 30% at 1 year, FeNO by 25%, and total serum IgE by 20% [44]. Therefore, Tezepelumab may be an effective add-on biologics for the treatment of severe uncontrolled Eosinophilic asthma. Additionally, Tezepelumab may ameliorate airway remodeling in other phenotypes of asthma.

Most recently, CSJ117, a fully human neutralizing antibody antigen-binding fragment (Fab) that belongs to IgG1 isotope subclass attenuated both the early asthmatic response (EAR), and late asthmatic response (LAR) in 28 patients with mild, atopic asthma [45]. CSJ117 will probably be the first inhaler biologic for the treatment of asthma.

In summary, asthma is a prevalent chronic airway disease affecting both adults and children, and impacts a incommensurate socio-economic impact of health care systems in many countries. Add-on biologics targeting Th2 cytokines are very effective therapeutic options for the treatment of severe Eosinophilic asthma. However, they do not reduce exacerbation rates, improve asthma control, and lung functions in most patients with different phenotypes of asthma. Tezepelumab is an effective biologics which has been shown to reduce exacerbations in patients regardless of biomarkers of inflammation, and phenotypes of asthma. An inhaler topical anti-TSLP offers an advantage in the management patients with asthma, particularly when added to single maintenance and reliever therapy (SMART) with low-dose ICS-formoterol therapy.

References

1. Global Initiative for Asthma. Global Strategy for Asthma management and Prevention - updated 2020. April 2020.
2. Maglione M, Poeta M, Santamaria S (2019) New drugs for pediatric asthma. Fron Pediatr
3. Simpson JL, Scott R, Boyle MJ, Gibson PG (2006) Inflammatory subtypes in asthma: assessment and identification using induced sputum. Respirology 11 : 54-61.
4. Wang F, He XY, Baines KJ, Gunawardhana LP, Simpson JL, et al. (2011) Different inflammatory phenotypes in adults and children with acute asthma. Eur Respir J 38: 567-574.
5. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE, et al. (2004) Distinguishing severe asthma phenotypes: role of onset and eosinophilic inflammation. J Allergy Clin Immunol 113: 101-108.
6. Harder P, Pavord ID, Shaw DE, Barry MA, Thomas M, et al. (2008) Cluster analysis and clinical asthma phenotypes. Am Rev Respir Crit Care Med 178: 218-224.
7. De Groot JC, Ten Brinke A, Bel EHD (2015) Management of patients with eosinophilic asthma: a new era begins. ERJ Open Res 1: 00024-2015.
8. Hekking PP, Wener RR, Amelink M (2015) The prevalence of severe refractory asthma. J Allergy Clin Immunol 135: 896-902.
9. Varsano S, Segev D, Shitrit D (2017) Severe and non-severe asthma in the community: a large electronic database analysis. Resp Med 123: 131-139.
10. National Asthma Education and Prevention Program. Guidelines for the Diagnosis and Management of Asthma. ERP-3. 2007. www.nhlbi.gov/health-topics/guidelines-for-diagnosis-management-of asthma. Date last accessed: October 28, 2019.
11. Holguin F, Cardet, Chung KF, Diver S, Ferriera DS, et al. (2020) Management of severe asthma: A European Respiratory Society/ American Thoracic Society guidelines. Eur Respir J 55: 1900588.
12. Bousquet J, Cabrera P, Berkman N, Buhl R, Holgate S, et al. (2005) Wenzel S, Fox H, Hedgecocks S, Blogg M, Ciopa GD. The effect of with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. Allergy 60: 302-308.
13. Busse W, Corren J, Lanier BQ, McAlary M, Flower-Taylor A, et al. (2001) Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol 108: 184-190.
14. Parvord ID, Korn S, Howarth P, Bleecker ER, Buhl R, et al. (2012) Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 380: 651-659.
15. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, et al. (2015) Reslizumab for inadequately controlled asthma with elevated eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 3: 355-366.
16. Bleecker ER, FitGerald JM, Chanez P, Papi A, Weinstein SF, et al. (2016) Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 388: 2115-2127.
17. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, et al. (2018) Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 378: 2486-2496.
18. Normansell R, Walker S, Milan SJ, Walters EH, Mair P (2014) Omalizumab for asthma in adults and children. Cochrane Database Syst Rev 1:CD003559. 858.pub4.
19. Farne HA, Wlson A, Powell C, Bax L, Milan SJ, et al. (2017) Anti-IL5 therapies for asthma. Cochrane Database Syst Rev 9: CD01834.
20. Zayed Y, Kheiri B, Banifadel M, Hicks M, Aburahma A, et al. (2018). Dupilumab safety and efficacy in uncontrolled asthma: a systematic review and meta-analysis of randomized clinical trials. J Asthma 56: 1110-1119.
21. Mukherjee M, Radford K, Huang C, Leigh R, Dorscheid DR, et al. (2019) Omalizumab in patients with severe asthma and persistent sputum eosinophilia. Allergy, Asthma & Clin Immunol 2019 15:21.
22. Syabbalo N (2020) Clinical features and management of neutrophilic asthma. J Pulm Med Respir Res 6:036.

23. Menzie-Gow A, Wechsler M, Brightling CE. Unmet need in severe, uncontrolled asthma: can anti-TSLP therapy with tezepelumab provide valuable new treatment option. Respir Res 2020; 21:268.

24. Mitchell PD, O'Byrne PM. Epithelial-derived cytokines in asthma. Chest 2017; 151(6):1338-1344.

25. Lin S-C, Chou H-C, Chen C-M, Chiang B-L. Anti-thymic stromal lymphopoietin antibody suppresses airway remodeling in asthma through reduction in MMP and CTGF. Pediatr Res 2018; 86:181-187.

26. Gauvreau GM, Sehmi R, Ambrose CS, Griffths JM. Thymic stromal lymphopoietin: its role and potential as a therapeutic target in asthma. Expert Opin Ther Targets 2020; 777-792.

27. Leonard WJ. TSLP: finally in the limelight. Nat Immunol 2002; 3: 605-607.

28. Allakhverdi Z, Comeau MR, Yoon PB-R, Brewer A, Charter S, et al. Thymic stromal lymphopoietin is released by human epithelial cells in response to microbes, trauma, or inflammation and potentially activates mast cells. J Exp Med 2007; 204:253-258.

29. Kato A, Favoreto S Jr, Avila PC, Schleimer RP. TLR3- and Th2 cytokine-dependent production of stromal lymphopoietin in human airway epithelial cells. J Immunol 2007; 179:1080-1087.

30. Lee HC, Headley M, Loo YM, Berlin A, Gale M Jr, Debley JS, et al. Thymic stromal lymphopoietin is induced by respiratory synctial virus-induced airway epithelial cells and promotes a type 2 response to infection. J Allergy Clin Immunol 2012; 130:1187-1196.e5.

31. Lee HC, Ziegler SF. Inducible expression of the proallergic cytokine thymic stromal lymphopoietin in airway epithelial cells is controlled by NFkappaB. Proc Natl Acad Sci USA 2007; 104:914-919.

32. Watson B, Gauvreau GM. Thymic stromal lymphopoietin: a central regulator of allergic asthma. Expert Opin Ther Targets 2014; 18:771-785.

33. Ojanguren I, Martin JG, Lemiere C. Thymic stromal lymphopoietin: a promising target in the treatment of asthma. Archivos De Bronconeumologia 2017; 53(10):545-546.

34. Soumelis V, Reche PA, Kanzler H, Yuan W, Edward G, Homey B, et al. Human epithelial cells trigger dendritic cell mediated inflammation by producing TSLP. Nat Immunol 2002; 3:673-680.

35. Tonozuka Y, Fujio K, Sugiyama T, Nosaka T, Hirai M, Kitamura T. Molecular cloning of a human novel type 1 cytokine receptor related to 1/TSLPR. Cytogenet Cell Genet 2001; 93:23-25.

36. Park LS, Martin U, Garka K, Glinak B, Di Santo JP, Muller W, et al. Cloning of the murine thymic stromal lymphopoietin (TSLP) receptor. Formation of a functional heterometric complex require interleukin 7 receptor. J Exp Med 2000; 192:659-670.

37. Quentmeier H, Drexler HG, Fieckenstein D, et al. Cloning of human stromal lymphopoietin (TSLP) and signaling mechanisms leading to proliferation. Leukemia 2001; 15:1286-1292.

38. Pandey AK, Ozaki K, Baumann H, Levin SD, Puel A, Far AG, Ziegler SF, et al. Cloning of a receptor subunit required for signaling by thymic stromal lymphopoietin. Nat Immunol 2000; 1:59-64.

39. Isaksen DE, Baumann H, Zhou B, et al. Uncoupling of proliferation and STAT5 activation in thymic stromal lympopoietin – mediated signal transduction. J Immunol 2002; 168:3288-3294.

40. Matera MG, Rogliani P, Calzetta L, Cazzola M. TSLP inhibitors for asthma: current status and future prospects. Drugs 2020; 80:449-459.

41. Gauvreau GM, O'Byrne PM, Boulet LP, Wang Y, Cockcroft D, Bigler J, FitzGerald JM, et al. Effect of anti-TSLP antibody on allergen-induced asthmatic responses. N Engl J Med 2014; 370(22): 2102-2110.

42. Corren J, Parnes J, Wang L, Mo M, Roseti SL, Griffiths JM, van der Merwe R. Tezepelumab in adults with uncontrolled asthma. N Engl J Med 2017; 377(10):936-946.

43. Pham TH, Ren P, Parnes JR, Griffiths JM. Tezepelumab reduces multiple key inflammatory biomarkers in patients with severe uncontrolled asthma in the Phase 2b PATHWAY study. Am J Respir Crit Care Med 2019; 119:A2679.

44. Marone G, Spadaro G, Braile M, Poto R, Criscuolo G, Pahima H, et al. Tezepelumab: a novel biological therapy for treatment of severe uncontrolled asthma. Expert Opin Investig Drugs 2019; 28(11):931-940.

45. Gauvreau GM, Hohlfeld JM, Grants S, Jain M, Cabanski M, Pertel P, Boulet L, Cockcroft DW. Efficacy and safety of an inhaled anti-TSLP fragment in adults with mild atopic asthma. Am J Respir Crit Care Med 2020; 201:A4207.