EDITORIAL

High-altitude treatment in severe asthma: Effective and needed in an era of precision medicine

J.H. Kappen*, J.C.C.M. in 't Veen, G.J. Braunstahl

Department of Pulmonology, Centre of Excellence for Asthma, COPD and Respiratory Allergy, Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands,
*corresponding author: email: J.Kappen@Franciscus.nl

Asthma is a chronic often inflammatory disorder of the airways characterised by typical symptoms such as wheezing, shortness of breath and cough that vary over time.[1] About 500,000 patients in the Netherlands have asthma, varying from mild to severe. The disease is classified as severe refractory asthma if symptoms cannot be controlled despite treatment with a high dose of inhaled corticosteroids, beta2 agonists, anticholinergica and/or oral steroids. The diagnosis 'severe asthma' is confirmed when a step-wise algorithm is followed.[2] In this algorithm other causes for poor asthma control are excluded, such as treatment adherence and inhalation technique issues. In the Netherlands approximately 3.6% of asthma patients have severe refractory asthma.[3]

Not all asthma is the same: there are different endotypes or underlying inflammatory profiles such as eosinophilic asthma, neutrophilic asthma or allergic asthma, or combinations. Different phenotypes require different treatment strategies.[4,5] In severe asthma, biologicals have been applied since the introduction of anti-IgE for severe allergic asthma. More recently, several anti-IL5 treatments became available for severe eosinophilic asthma.[6] More phase 3 studies with biologicals targeting specific pathways in asthma are currently being performed.

Because of this wide range of biologicals for different phenotypes, one might think that high-altitude treatment has lost its relevance in the treatment of severe asthma. Hashimoto, Rijssenbeek-Nouwens and collegues show the opposite in this issue of the *Netherlands Journal of Medicine*.[7] High-altitude treatment is still very effective in a wide range of severe asthma patients.

A prospective cohort of 136 patients who received high-altitude treatment in the Dutch Asthma Centre in Davos is presented in the article of Hashimoto. The results show, independent of the phenotype, a significant increase in lung function (FEV1), quality of life (measured using AQLQ). Since none of the patient characteristics were correlated with these outcomes, the authors suggest that the non-specific aspects of their treatment, such as improved adherence to medication or removal from stress at home, could be responsible for this effect. However, the reduction in oral corticosteroid use that was observed was related to the severity of symptoms at baseline and younger patients with low blood eosinophil counts, as expected based on the phenotype. Importantly, the reduction in oral steroids was possible with preserved improvement in asthma control. Patients with an allergic phenotype with a high IgE showed less airway inflammation after treatment, probably caused by the minimised exposure to allergens in the high-altitude environment. The authors conclude that high-altitude treatment improves the quality of life as well as the lung function in all patients with severe asthma. Furthermore, patients' characteristics may be used to predict the beneficial effect of the treatment and might optimise selection of patients who are eligible for this treatment.

The results presented by Hashimoto, Rijssenbeek-Nouwens and colleagues are of relevance, first because there remains a group of severe asthma patients who are not eligible for or do not respond to treatment with biologicals. High altitude is often successful in this group of patients as it may act on both inflammatory as well as behavioral aspects of the disease.

Furthermore, high-altitude treatment can play a key role in precision medicine.[8] While entering the era of precision medicine the focus will be on treatable traits rather than phenotypes. Airway inflammation is just one of the treatable traits, medication adherence, infection, allergy and deconditioning are some of the traits that can be relevant in severe asthma. Therefore, high-altitude treatment remains very relevant in the future treatment of severe refractory asthma.

REFERENCES

1. Hering T. [Update of the GINA-Recommendations]. MMW Fortschr Med. 2017;159:63-4.
2. Bel EH, Sousa A, Fleming L, et al. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). Thorax. 2011;66:910-7.
3. Hekking PP, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. J Allergy Clin Immunol. 2015;135:896-902.
4. Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med. 2008;178:218-24.
5. Chung KF. Precision medicine in asthma: linking phenotypes to targeted treatments. Curr Opin Pulm Med. 2018;24:4-10.
6. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. Cochrane Database Syst Rev. 2017;9:CD010834.
7. Hashimoto S, Rijssenbeek-Nouwens LH, Fieten KB, Weersink EJ, Bel EH. Predictors of benefit from high-altitude climate therapy in adults with severe asthma. Neth J Med. 2018;5:218-25.
8. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. Eur Respir J. 2016;47:410-9.