

Why Current Therapy Does Not Cure Asthma. Is It Time to Move Towards a One Health Approach?

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Abstract: Asthma continues to be a disease for which there is no cure, even if it can be very well controlled with the appropriate therapies, which take into account the specific phenotype. The paradox of asthma is that asthma can heal spontaneously, albeit in a small percentage of cases. This observation is highly relevant, since understanding the mechanisms of spontaneous healing can pave the way for new strategies for treating asthma. It is likely that the lack of cure for asthma is due to the fact that current therapies target downstream mediators of the inflammatory response. Asthma can be considered a response of maladaptation of the airway epithelium to the environment, through the orientation of the innate immunity towards an inflammatory response. The important effect of the environment on asthma progress comes from interventions which help children who live in disadvantaged urban neighborhoods move to higher resourced neighborhoods. It is quite interesting that the magnitude of decrease of exacerbations associated with moving was larger than the effect of inhaled corticosteroids and similar to that observed for the effect of biologic agents. Alpine altitude climate treatment is a natural treatment that targets biological pathway, improving various outcomes such as asthma control and quality of life, exacerbation rate and hospitalizations. If as researchers we want to set ourselves the goal of achieving complete remission of asthma, without the need for ongoing maintenance treatment, we need to change the approach to finding new asthma treatment strategies. The One Health approach, an interdisciplinary strategy with focal point on human, animal, and environmental health interconnections, appears to be the right tool for researching asthma prevention and treatment.

Keywords: asthma, environment, alpine treatment, one health

Introduction

Asthma continues to be a disease for which there is no cure, but which can be very well controlled with the appropriate therapies, which take into account the specific phenotype.

Recently, clinical definitions of asthma remission and disease-modifying anti-asthmatic drugs have been proposed.¹ The criteria for asthma remission are the sustained absence of asthma symptoms and asthma exacerbations, stable lung function and no need for systemic corticosteroids for the treatment of asthma.² The proposed definition of disease-modifying anti-asthmatic drugs are any drug class that can potentially achieve the goal of asthma remission.

Today, thanks to a wide choice of effective, safe, phenotype-specific drugs, the aim of asthma treatment has changed from simple relief of symptoms to the disease modification and remission. The most recent document of Global Initiative for Asthma (GINA 2022)³ recommend treatment options targeting type 2 inflammation (anti IgE, anti-IL5, anti-IL4/IL13 monoclonal antibodies) which are highly effective in reducing asthma exacerbations and improving asthma control in patients with severe asthma. Unfortunately, equally effective drugs are not yet available for patients with non-T2 inflammation.

Why despite progress in asthma treatment is it not possible to cure asthma?

The paradox of asthma is that asthma can heal spontaneously, albeit in a small percentage of cases. The proportions of asthma remission, defined as no asthma symptoms and no asthma medications use, per age group at follow-up have been reported 33–53% in adolescence (<18 years), 6–33% in young adulthood (≥ 18 and ≤ 30 years), 11–52% in adulthood (>30 years).⁴ The majority of the studies focused on asthmatic children and their chance of going into asthma remission.

In a longitudinal study of 119 allergic asthmatic children followed-up for 30 years,⁵ a Dutch group found that clinical remission occurred in 30% and complete remission in 22% of all cases. This observation is highly relevant, since understanding the mechanisms of spontaneous healing can pave the way for new strategies for treating asthma.

On the other hand, studies determining the adult-onset asthma remission proportion, are limited, because cohorts usually include individuals with child- and adulthood-onset of asthma. A prospective study, which assessed patients with adult-onset asthma, found a remission prevalence of 16% within five years.⁶

Asthma can be considered a response of maladaptation of the airway epithelium to the environment, through the orientation of the innate immunity towards an inflammatory response.

It is likely that the lack of cure for asthma is due to the fact that current therapies target downstream mediators of the inflammatory response. However, no therapy is aimed at reprogramming the response of the airways to the environment, with the possible exception of allergen-specific immunotherapy. Some studies have shown that allergen immunotherapy may be a disease modifier, as clinical benefits last beyond the time of treatment.^{7,8}

However, more trials are needed to support this concept, especially in adults with established disease.

Innovative Approaches

An innovative approach by Taiwan researchers has shown that individual behavior and environmental exposure strongly affect asthma control.⁹ By using diary-based follow-up, these authors found that exposure to secondhand smoke, persons with influenza-like illness, and high concentrations of ozone were linked to higher chances of having asthma symptoms and exacerbations. On the other hand, keeping good diet behaviors and sleeping quality, and paying more attention to personal perception of temperature and air quality reduced the chance of asthma symptoms. The authors concluded that these behavioral changes may help improve asthma control, preventing acute onset and severe exacerbation of asthma flare-ups.

The important effect of the environment on asthma progress comes from interventions which help children who live in disadvantaged urban neighborhoods move to higher resourced neighborhoods. One such housing mobility intervention, Moving To Opportunity, resulted in reductions in long-term asthma-related hospitalizations.¹⁰ In a similar study¹¹ of children with asthma living in urban, high poverty areas, participation in a housing mobility intervention was associated with statistically significant reductions in asthma exacerbations and symptomatic days. It is quite interesting that the magnitude of decrease of exacerbations associated with moving was larger than the effect of inhaled corticosteroids (43% reduction in exacerbation rate in the Childhood Asthma Management Program),¹² and similar to that observed for the effect of biologic agents ($\geq 50\%$).^{13,14}

An EAACI position paper on alpine altitude climate treatment (AACT) for severe and uncontrolled asthma¹⁵ points to AACT as a natural treatment that targets biological pathway.

AACT may be a therapy for those asthma patients who, despite the appropriate use of all the asthma drugs, including biologics, still cannot achieve optimal control of their complex condition and therefore run the risk of falling into a downward spiral of loss of physical and mental health. AACT improves various outcomes such as asthma control and quality of life, exacerbation rate and hospitalizations, oral corticosteroid reduction, lung function parameters, upper airways symptoms, and exercise tolerance in adults and children.

The mechanisms underlying the effectiveness of the alpine stay on asthma control are not completely known. Characteristics of the alpine environment that may contribute to the improvement of asthma include a reduced aeroallergen burden regarding HDM, pollen, fungi but also air pollution and different microbial exposure.

According to the cited EAACI position paper,¹⁵ AACT can be seen as a natural treatment that targets biological pathways.

Asthma, like many chronic diseases, is the result of interaction with the environment. More precisely, the cumulative exposure that the individual has experienced (diet, exercise, environmental exposure, genetics, etc.), the so-called exposome, directs the immune system towards immune training and immune tolerance.^{16,17} The One Health approach appears to be the right tool for researching asthma prevention and treatment. One Health approach aims to optimize the health of people, animals, and ecosystems,¹⁸ as the health of humans, domestic and wild animals, plants are closely linked and interdependent.

To convince us of the importance of the one health approach, it is enough to think of the consequences of climate change. Rising temperature lead to increased ground-level ozone, changes in pollen concentrations and immunogenicity due to altered flower blooming patterns, and an increase in the emission of carbon dioxide, which all can trigger airway inflammation and damage the lung tissues.¹⁹

Conclusion

If as researchers we want to set ourselves the goal of achieving complete remission of asthma, without the need for ongoing maintenance treatment, we need to change the approach to finding new asthma treatment strategies. Behavioral changes, moving children who live in disadvantaged urban neighborhoods to higher resourced neighborhoods and One Health approach, as reported above, are examples of new approach to asthma therapy that contribute to the reprogramming of the airway response to the environment, increasing the likelihood of asthma recovery.

Disclosure

The author reports no conflicts of interest in this work.

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