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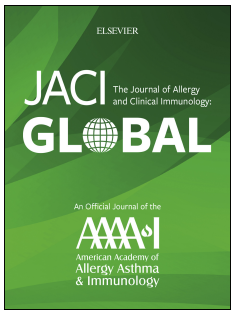

Asthma Exacerbations During the Pandemic: Time to Rethink Clinical Markers

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Brief Report

Asthma Exacerbations During the Pandemic: Time to Rethink Clinical Markers

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Abstract:

Background: Reductions in asthma exacerbations during the COVID-19 pandemic may have an impact on clinical trial enrollment and outcomes.

Objective: To review clinical studies and reports evaluating asthma exacerbations before and during the COVID-19 pandemic.

Methods: We reviewed clinical studies conducted with biologics over the past decade that evaluated asthma exacerbations as the primary endpoint. We also reviewed recent clinical reports evaluating asthma exacerbations during the COVID-19 pandemic.

Results: We showed that studies which required at least two exacerbations in the prior year resulted in a higher number of exacerbations on study in the placebo arm, and conversely those studies where exacerbations were not required for entering the study failed to meet the primary endpoint. This result confirmed that history of prior exacerbations is a good maker to predict future exacerbations. In addition, a review of the literature confirmed a reduction of asthma exacerbations during the COVID-19 pandemic. Data presented are descriptive; no formal statistics were employed.

Conclusion: Historical exacerbations may no longer be the best predictor for exacerbations in a clinical trial/clinical practice due to the COVID-19 pandemic. Other clinical markers associated with exacerbations such as blood eosinophils and exhaled nitric oxide should be considered for enrolment in clinical studies assessing asthma exacerbations.

Key Messages:

- The reduction in asthma exacerbations during the COVID-19 pandemic may have an impact on clinical trial enrollment and outcomes.
- Historical exacerbations may no longer be the best predictor for exacerbations in clinical trials.
- Other clinical markers associated with exacerbations such as blood eosinophils and FeNO should be considered.

Capsule Summary: A history of prior exacerbations may no longer be the best predictor for exacerbations in clinical trials due to the COVID-19 pandemic. Other

clinical markers such as blood eosinophils and exhaled nitric oxide should be contemplated.

INTRODUCTION

Asthma is a complex multifactorial disorder, that is influenced by interactions between genetic susceptibility, host factors (e.g., allergic sensitization, obesity), and environmental and occupational exposures (e.g., viruses, air pollution, weather, cigarette smoke, pollens, mold and other indoor and outdoor allergens, sensitizing agents, or irritants in the workplace). (1) Notably, in early 2020, wearing a face mask, social distancing, restricted contact in public gatherings, quarantines, and school closures that where enacted to reduce coronavirus disease 2019 (COVID-19) (2) also reduced exacerbations of chronic respiratory diseases including asthma.

It is well established that the best predictor for asthma exacerbations is a prior history of exacerbations. However, there are other factors that could help predict exacerbations including excessive use of rescue medication, lack of adherence to asthma medications, poor asthma control, obesity, ethnicity, asthma disease activity score and risk prediction score (seasonal dependent). (3-6) In the case of prior history of exacerbations, this clinical marker has been used to enrich for patients at risk for exacerbations in many trials with biologics. (7) To increase the probability of success in clinical studies a careful collection of patient's clinical history is of critical importance. However, relying on a prior history of exacerbations as a sensitive marker in the peri-pandemic era is challenging, as the rate of exacerbations has been drastically reduced over the past two years. The aim of this study was to review clinical studies and reports evaluating asthma exacerbations before and during the COVID-19 pandemic. This provided the basis to offer recommendations for the use of other makers associated with exacerbation risk to overcome the limitation of having a robust history of exacerbations during the pandemic. Most of the studies investigating asthma exacerbations as the primary endpoint have required at least two exacerbations in the previous year. (8-11)

RESULTS AND DISCUSSION

We tabulated asthma studies conducted for more than a decade with biologic therapies (8-15) (Figure 1). Here we show that studies which required at least two exacerbations in the prior year resulted in a higher number of exacerbations on study in the placebo arm, and conversely those studies where exacerbations were not required for entering the study failed to meet the primary endpoint, e.g., LAVOLTA studies. (13) Regardless of the asthma exacerbation entry criteria, the rate of exacerbations in the placebo arm has always resulted in a rate that is less than the historical asthma exacerbation rate, reinforcing the importance of enrolling a population of frequent exacerbators. The figure also illustrates that overtime the baseline rate of exacerbations has declined, ranging from a high of 5.5 exacerbations per year in the Haldar et al. mepolizumab proof of concept trial (9) to a low of a little over one per year in the LAVOLTA pivotal trials.(13) The decrease over time is likely due to the availability of new and effective therapies such as monoclonal antibodies.

Recent reports have demonstrated that the rate of asthma exacerbations was reduced when compared to prior years (pre-pandemic). Salciccioli et al. reported that asthma exacerbations in the PREPARE study decreased by greater than 40% coincident with the onset of the COVID-19 pandemic. (16) The PREPARE study was designed to investigate changes in asthma exacerbation rates among African American and Hispanic adults enrolled at 19 centers across the United States. Patients provided monthly reports including a questionnaire designed to document the occurrence of an asthma exacerbation. The study began collecting data prior to the pandemic and continued to collect data during the pandemic. This study provides a unique window into the incidence of asthma exacerbations during the pandemic as data have been prospectively collected both before and during the pandemic. Findings from this study included reductions in exacerbations with the greatest decrease occurring in individuals who were working outside of the home and in those without type 2 inflammation. The authors suggest that this may be related to social-distancing and occupational changes and is unlikely to be related to reduced health care system avoidance during the

COVID-19 pandemic. Additional studies have provided support for the reduction of asthma exacerbations during the pandemic. For example, Sheehan et al. reported the absence of pediatric asthma-related hospitalizations and emergency department visits during the typical fall seasonal spike when comparing events in 2020 to the years 2016 to 2019.(17) More recently, a large retrospective cohort study in over 500,000 asthma patients managed by general physicians across the United Kingdom confirmed the continued suppression of asthma exacerbations into 2021. (18) It is noteworthy that this study has the longest follow-up period, as it provides data through September 2021, which is approximately 18 months since the start of the first lock down of the pandemic. Consistent with prior observations, exacerbation rates during the pandemic were reduced 40% to 58% when compared to the rate during the years of 2016-2019. Despite the last lockdown occurring in late December 2020 - early January 2021, the rate of asthma exacerbations remains suppressed. This persistence of decreased asthma exacerbations is likely due to lower exposure to respiratory viruses, which are an important trigger of exacerbations. While the epidemiological reports tracking asthma exacerbations from 2021-2022 are not fully available at the current time, it is likely that the frequency of asthma exacerbations will follow the 2020 pattern. However, recent data evidenced that easing of public health measures during the pandemic has resulted in an increase in respiratory viruses, which could lead to a return to pre-pandemic exacerbation rates. (2, 19) While it is difficult to estimate with precision the loss of power in a clinical trial, it is likely that a larger sample size will be required to study exacerbations, at least during the interim period, while the rate of exacerbation rate returns to pre-pandemic levels. Viral respiratory infections, primarily from rhinoviruses, are the dominant trigger for most patients with asthma. (20) Allergic sensitization and allergen exposure contribute directly and enhance susceptibility to respiratory viral infections. Respiratory viruses infect airway epithelium to promote underlying inflammation. Therefore, reduction in exposure via face mask or avoiding public gatherings should have a direct impact on reducing triggers for asthma exacerbations, specifically viruses.

Treatment goals in asthma include symptom control and reducing the risk of future exacerbations. However, it is estimated that more than 10% of patients with severe asthma remain with persistent symptoms or exacerbations despite maximal treatment. (21) Therefore, it is critical to ensure that patients are adherent to their therapy, regardless of clinical trial participation. Notably, in many cases more than one factor is involved when compliance issues are present. Barriers for quality asthma care include inadequate knowledge or adherence to treatment recommendations, lack of time and resources, patient and systemic financial constraints, and lack of prompt referrals to asthma specialist. (22)

Due to the reduction in asthma exacerbation rates during the pandemic, relying on prior history of exacerbations may no longer be a sensitive marker of future exacerbations in the peri-pandemic era. This is evidenced by a trial with timapiprant, an oral DP2 antagonist, which was conducted from August 2019 to October 2020 (during the pandemic). The study required two exacerbations in the prior year for entry into the study. The mean historical exacerbation rate in enrolled patients was two in the prior year. The mean rate observed in the placebo group was 0.43 exacerbations per year, (23) which is lower than expected when compared to the rate of exacerbation in the placebo arm in prior studies, see Figure 1. Of note, the studies presented in Figure 1 were conducted during the pre-pandemic era, with the exception of NAVIGATOR which was conducted from November 2017 through September 2020 and therefore overlapped with the pandemic for a short period of time. (10)

This highlights the potential impact of the pandemic when exploring exacerbations as an endpoint in clinical trials. Therefore, there is need to start thinking about other strategies that could enrich a population seeking an exacerbation signal, because the “number of exacerbations in the past year” may no longer be a reliable clinical marker. Elevated levels of markers of Type 2 inflammation such as blood eosinophils and exhaled nitric oxide (FeNO) can provide convincing support to identify patients prone to exacerbate. In a post-hoc analysis reported by Busse et al. (24) they identified the independent prognostic value of FeNO, in addition to and in combination with baseline blood

eosinophil count and prior exacerbation history, to predict risks for an asthma exacerbation. Both FeNO and blood eosinophils provide different and complementary mechanistic information. Recently Couillard and collagues from the University of Oxford proposed a prototype risk scale that centers on these two biomarkers. (25) Their data showed a striking difference when these two biomarkers are used together. As the values for FeNO and blood eosinophils increase, the risk of an asthma exacerbation also increases. The tipping point to see an increased risk of an exacerbation appears to start at a threshold of at least 25 ppb of FeNO and a blood eosinophil count of at least 150 cells/μL. These thresholds are a reasonbale starting point to enrich a patient population in a clinical trial evaluating asthma attacks or exacerbations, even in the absence of exacerbation history in the prior year. However, these markers are not applicable to the low-Type 2 phenotype, and therefore other makers are required to enhance the probability of selecting the right patient in clinical studies, such as history of frequent bronchial infections, and possible increase in sputum PMNs. In addition, applicable to all phenotypes the degree of airflow limitation, increase in symptoms and asthma medication requirements, should be considered. There is a need for additional research to better understand which biomarkers are associated to specific phenotypes or endotypes, including the use of transcriptomic signatures. As the world evolves to a more “normal” life with less public health restrictions to prevent COVID-19 infection, it is likely that the number of exacerbations will start to manifest in a similar frequency or even greater than the pre-pandemic era. This will allow us to again study asthma exacerbations in a more reliable and consistent manner. But, perhaps it is time to ask whether exacerbations should continue to be the focus of asthma studies.

Figure 1. Exacerbation endpoint influenced by the number of exacerbations at study enrollment

The data illustrate the “number of exacerbations in the past year” across different clinical studies with biologics for the treatment of asthma over a period of 12 years. The blue bar denotes the historical rate of asthma exacerbations, and the orange bar the rate observed in placebo. Requirement for asthma exacerbations at the time of study enrollment ranged from 0 to 2 exacerbations in the past-year. Most of the studies required at least 2 exacerbations in the past year.

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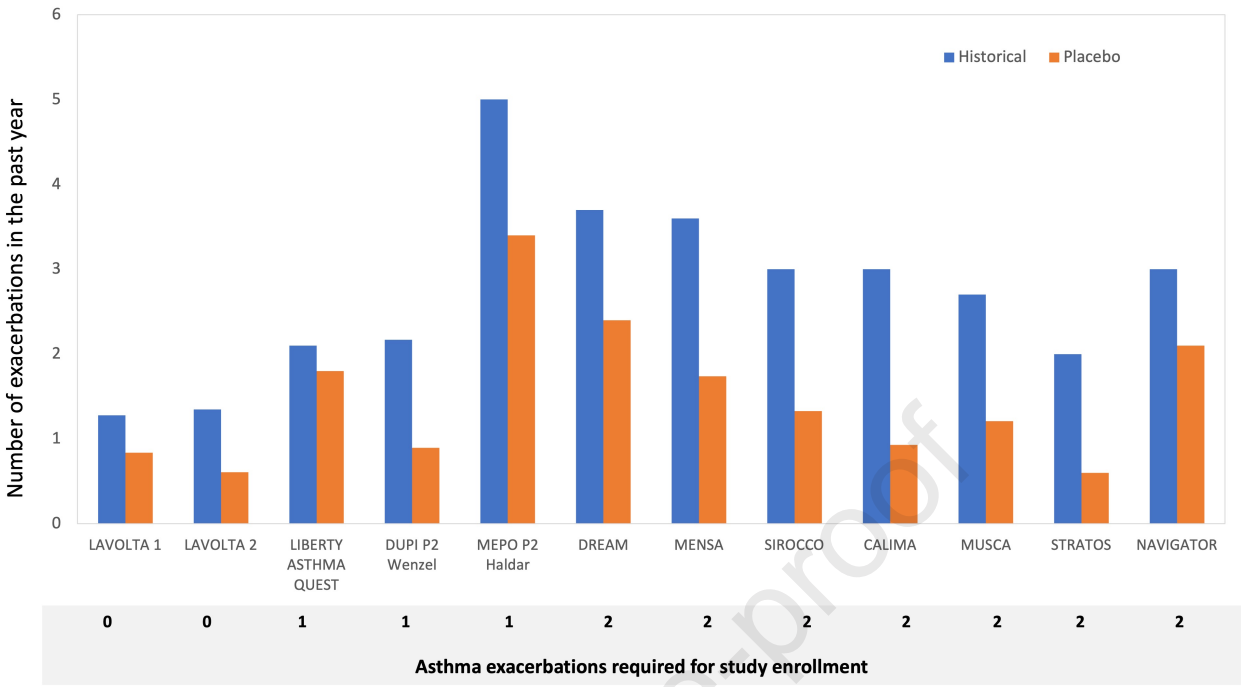

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: