Asthma exacerbations during the pandemic: Time to rethink clinical markers

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Background: Reductions in asthma exacerbations during the coronavirus disease 2019 (COVID-19) pandemic may have an impact on clinical trial enrollment and outcomes. Objective: Our aim was 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 end point. We also reviewed recent clinical reports evaluating asthma exacerbations during the COVID-19 pandemic.

Results: We showed that studies requiring at least 2 exacerbations in the prior year resulted in a higher number of exacerbations on study in the placebo arm, and conversely, those studies in which exacerbations were not required for entering the study failed to meet the primary end point. This result confirmed that history of prior exacerbations is a good marker to predict future exacerbations. In addition, a review of the literature confirmed a reduction of asthma exacerbations during the COVID-19 pandemic. The data presented are descriptive; no formal statistics were used.

Conclusion: Because of the COVID-19 pandemic, historical exacerbations may no longer be the best predictor for exacerbations in a clinical trial or clinical practice. Other clinical markers associated with exacerbations, such as blood eosinophil count and fractional exhaled nitric oxide level, should be considered for enrollment in clinical studies assessing asthma exacerbations. (J Allergy Clin Immunol Global 2023;2:97-100.)

Key words: COVID-19, asthma exacerbations, exacerbation rate, clinical trials, viral-induced exacerbations, public health measures

INTRODUCTION

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

It is well established that the best predictor for asthma exacerbations is a 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). In the case of a history of exacerbations, this clinical marker has been used to enrich for patients at risk for exacerbations in many trials with biologics. To increase the probability of success in clinical studies, a careful collection of the patient’s clinical history is of critical importance. However, relying on a history of exacerbations as a sensitive marker in the peripandemic era is challenging, as the rate of exacerbations has been drastically reduced over the past 2 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 end point have required at least 2 exacerbations in the previous year.

RESULTS AND DISCUSSION

We tabulated asthma studies conducted for more than a decade with biologic therapies (Fig 1). Here, we show that studies requiring at least 2 exacerbations in the prior year resulted in a higher number of exacerbations on study in the placebo arm, and conversely, those studies in which exacerbations were not required for entering the study failed to meet the primary end point (eg, the LAVOLTA studies). Regardless of the asthma exacerbation entry criteria, the rate of exacerbations in the placebo arm has always resulted in a rate that is lower than the historical asthma exacerbation rate, reinforcing the importance of...
enrolling a population of frequent exacerbators. **Fig 1** also illustrates that over time, the baseline rate of exacerbations has declined, ranging from a high of 5.5 exacerbations per year in the proof-of-concept mepolizumab trial conducted by Haldar et al 9 to a low of a little over 1 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 mAbs.

Recent reports have demonstrated that the rate of asthma exacerbations was reduced when compared with the rates in prior (pre-pandemic) years. Salciccioli et al reported that asthma exacerbations in the PREPARE study decreased by more than 40% coincident with onset of the COVID-19 pandemic. 16 The decrease over time is likely due to the availability of new and effective therapies such as mAbs.

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**FIG 1.** Exacerbation end point 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 denotes the rate observed in the placebo arm. The 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. Study names are linked to the actual type of product (mAb): LAVOLTA (lebrikizumab); LIBERTY (dupilumab); DREAM, MENSA, and MUSCA (mepolizumab); SIROCCO and CALIMA (benralizumab); STRATOS (tralokinumab); NAVIGATOR (tezepelumab); P2 (Phase 2). **DUPI**, Dupilumab; **MEPO**, mepolizumab.

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, when comparing events in 2020 to the years 2016 to 2019, Sheehan et al reported the absence of pediatric asthma–related hospitalizations and emergency department visits during the typical fall seasonal spike. 17 More recently, a large retrospective cohort study in more than 500,000 patients with asthma 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 was approximately 18 months after the start of the first lockdown of the pandemic. Consistent with prior observations, exacerbation rates during the pandemic were reduced by 40% to 58% when compared with the rate during the years 2016-2019. Despite the last lockdown occurring in late December 2020 to early January 2021, the rate of asthma exacerbations has remained suppressed. This persistence of decreased asthma exacerbations is likely due to lower exposure to respiratory viruses, which are an important trigger of exacerbations. Although the epidemiologic 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. Although 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. 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 wearing a face mask or avoiding public gatherings should have a direct impact on reducing triggers for asthma exacerbations, specifically viruses.

Treatment goals in asthma include controlling symptoms 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. Therefore, it is critical to ensure that patients are adherent to their therapy, regardless of clinical trial participation. Notably, in many cases, more than 1 factor is involved when compliance issues are present. Barriers to 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 an asthma specialist.

Because of the reduction in asthma exacerbation rates during the pandemic, relying on a history of exacerbations may no longer be a sensitive marker of future exacerbations in the peripandemic era. This is evidenced by a trial with timapiprant, an oral DP2 antagonist, that was conducted from August 2019 to October 2020 (during the pandemic). The study required 2 exacerbations in the prior year for entry into the study. The mean historical exacerbation rate in enrolled patients was 2 in the prior year. The mean rate observed in the placebo group was 0.43 exacerbations per year, which is lower than expected when compared with the rate of exacerbation in the placebo arm in prior studies (Fig 1).

This highlights the potential impact of the pandemic when exploring exacerbations as an end point in clinical trials. Therefore, there is need to start thinking about other strategies that could enrich a population seeking an exacerbation signal, because 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 eosinophil count and fractional exhaled nitric oxide (FENO) level, can provide convincing support to identify patients prone to exacerbation. In a post hoc analysis, Busse et al. reported that they identified the independent prognostic value of FENO level, in addition to and in combination with baseline blood eosinophil count and a history of exacerbation, to predict risks for an asthma exacerbation. Both FENO level and blood eosinophil count provide different and complementary mechanistic information. Recently Couillard et al from the University of Oxford proposed a prototype risk scale that centers on these 2 biomarkers. Their data showed a striking difference when these 2 biomarkers are used together. As the values for FENO level and blood eosinophil count 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 a FENO level of at least 25 ppb and a blood eosinophil count of at least 150 cells/μL. These thresholds are a reasonable starting point to enrich a patient population in a clinical trial evaluating asthma attacks or exacerbations, even in the absence of a history of exacerbation 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 patients in clinical studies, such those with as history of frequent bronchial infections and a possible increase in sputum polymorphonuclear cells. 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 with specific phenotypes or endotypes, including the use of transcriptomic signatures. As the world evolves to a more “normal” life with fewer public health restrictions to prevent COVID-19 infection, it is likely that the number of exacerbations will start to manifest at a frequency similar to or even higher than in 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.

**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 eosinophil count and FENO level should be considered.

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