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Editorial

The time to PREPARE is over; the time to improve diversity in asthma studies is now

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The benefits of inhaled corticosteroids (ICSs) in treating asthma were first described by Gelfand in 1951,[1] and their utility in preventing the severest of asthma complications is well substantiated.[2] However, when a disease characterized by waxing and waning symptoms (ie, asthma) is combined with a treatment that successfully addresses inflammation but provides little immediate symptomatic relief (ie, glucocorticoids) and then mixes in high treatment costs, multiple prescribed doses per day, and a unique means of administration (ie, inhalation), it is not surprising that the result is often poor treatment adherence. Research from our group and others suggests that less than half of prescribed ICS medication is actually taken.[3] Moreover, interventions focused on improving asthma medication adherence have been largely unsuccessful despite the considerable time and resources invested.[4]

Nevertheless, recent approaches to increase ICS use demonstrate the effectiveness of simplifying regimens to better accord with patterns of use. In 2020, single maintenance and reliever therapy (SMART) was added to the US asthma management guidelines for treatment of moderate-to-severe persistent asthma in individuals aged 4 years and older.[5] Unlike earlier approaches using separate inhaled medications for asthma control and symptom relief, SMART involves a single combination inhaler containing formoterol, a quick-onset long-acting β-agonist, and an ICS medication for both maintenance and rescue use. Clinical trials have found that SMART consistently reduces the occurrence of severe asthma exacerbations when compared with combined regular ICS dosing and as-needed short-acting β-agonist use.[5]

In the recently published Person-Empowered Asthma Relief (PREPARE) trial, Israel et al provide another elegantly simple intervention to increase ICS use.[6] Their approach uses a patient-activated, reliever-triggered inhaled glucocorticoid strategy (PARTICS). PARTICS allows individuals to continue their usual maintenance controller therapy, but rescue medication use is a prompt to take additional ICS doses of beclomethasone dipropionate (80 μg per metered dose). Specifically, patients in the intervention arm were instructed to take additional ICS doses at a 1:1 ratio with rescue inhaler use or at a 5:1 ratio with rescue nebulizer use (ie, 5 inhalations of ICS per nebulization). A total of 1201 adults (603 Black and 598 Latinx patients) with moderate-to-severe asthma were randomized to either PARTICS (n = 600) or usual care (n = 601); participants were followed for 15 months. The primary outcome, severe asthma exacerbations, was 15% lower in the intervention group than in the usual care group (hazard ratio = 0.85; 95% CI = 0.72-0.99; P = .048). Intervention group participants also reported significantly greater improvements in both patient-reported asthma control (a 0.9-point difference in composite Asthma Control Test score [95% CI = 0.5-1.2]) and asthma-related quality of life (a 0.4-point difference in Asthma Symptom Utility Index score [95% CI = 0.02-0.05]), as well as fewer days missed from work, school, or usual activities (13.4 vs 16.8 annualized days missed among the intervention and usual care group participants, respectively).

Potential benefits of PARTICS over SMART were the continuance of existing maintenance therapy, the ability to administer additional ICS therapy without concern for added β-agonist exposure, and its validation in populations of color. Regarding the last point, the unfortunate truth is that the PREPARE trial is one of the rare exceptions of racial and ethnic diversity in asthma clinical trials. Nearly one-third of US citizens identify as Black and/or Latinx, yet most clinical studies do not meet this mark of inclusiveness. Moreover, even if these percentages are achieved in a given study, the numbers are often too small for sufficiently powered subgroup analyses. Even with the laudable diversity of PREPARE, the trial still may have been underpowered to identify significant effects within the 2 population groups studied (particularly among Latino patients).[6] Among these census-defined groups, we also know that there is substantial heterogeneity. For example, Puerto Rican and Mexican individuals have very different prevalence rates for asthma (with the rate being much higher in the former), as well as observed differences in asthma treatment response.[7]

PREPARE was designed as a pragmatic clinical trial. Its permissive inclusion criteria (eg, inclusion of active smokers), limited exclusion criteria, and a hands-off approach with respect to patient interaction and monitoring were intended to more closely measure real-world effectiveness. Nevertheless, the study patients had an established record of care in their respective health systems and received monthly study surveys; the intervention group patients also received free add-on ICS medication. Hence, the study results may not reflect actual real-world effectiveness because barriers, such as poor access to care, ineffective physician-patient communication, clinical inertia, high out-of-pocket medication costs, and quantity limits on refills, could adversely affect faithful adherence to PARTICS.

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SMART has been estimated to reduce overall corticosteroid exposure versus that with usual care, whereas individuals in the PARTICS arm of PREPARE reported increased dispensing of ICS inhalers versus in usual care (8.9 vs 7.8 reported ICS inhalers received, respectively).[6] However, these differences in ICS exposure between approaches must be interpreted cautiously. Patient-reported measures of ICS use may be a poor proxy for actual use and exposure, even among participants enrolled in clinical trials.[8]

By increasing ICS use in concert with rescue medication, both PARTICS and SMART provide a tailored approach to care that appears to be both simple and effective. In an ideal world, patients would escalate ICS use in advance of requiring reliever medication; however, apart from rescue medication use and history, clinically practical biomarkers of impending exacerbations do not exist. Perhaps "omics" (eg, genomics, transcriptomics, metabolomics, proteomics) will identify better predictors of asthma severity and treatment responsiveness that can be used to guide both timely and appropriate dosing of controller medication. Genetic risk scores for other conditions have already been shown to predict disease susceptibility not identified through traditional risk factors,[9] and these scores may identify patients who can benefit from early prevention. However, these tools rely on data from existing genome-wide association studies, and this is where the conversation again pivots toward diversity and inclusiveness. Populations of color are vastly underrepresented in extant genomic studies, and genetic risk scores developed in one population group often do not predict well in other groups.[10] Therefore, even if scientific advances in predictive genomics come to fruition in terms of clinical implementation, Black and Latino patients will be among the last to benefit unless research inclusiveness radically departs from its current trajectory to fill the existing void.

Given the heightened interest in precision medicine, it is also necessary that we learn the important lesson imparted by both PARTICS and SMART, namely, that effective medicine must support the *individual* goals of the patient. As clinicians, we should strive to find treatment regimens complementing the routines of our patients, rather than drastically imposing new routines and expecting that they will be followed. Arguably, the approaches implemented by PARTICS and SMART transcend usually defined patient-centered care. The key insight was not only to address patient-desired outcomes but also to synchronize controller treatment to pattern the manner in which patients naturally take their asthma medication. Lastly, as we have repeatedly observed, findings within one group or setting often do not generalize to another. Therefore, if an ultimate goal of medicine is tailored treatment, we first need studies reflecting the diversity of the patients whom we serve. This means pressing grant funding agencies and the pharmaceutical industry to prioritize diversity and design studies that are sufficient powered to analyze outcomes both across and within population groups. The time is long overdue to close the knowledge gap that has resulted from a lack of diversity in research; kudos to trials such as PREPARE that remind us of its importance.

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