EDITORIALS

Escalating Inhaled Glucocorticoids to Prevent Asthma Exacerbations

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Inhaled glucocorticoids are pivotal to achieve asthma control and disease stability in both children and adults; despite their use, with or without other treatments, many patients with asthma have ongoing episodic disease exacerbations.[1] Often, these are linked to provocative factors such as viral or bacterial infections, nonadherence to treatment, allergen exposure, and environmental air pollution.[2] Although the clinical presentation varies widely, exacerbations are frequently heralded by slowly declining lung function and increasing asthma symptoms. These acute flares of asthma are detrimental because they adversely affect quality of life, lung function, and health care costs and have the potential to end in death. Everyone agrees that preventing exacerbations is a priority in asthma care.[3]

Two important trials[4,5] now reported in the *Journal* examine a key question: can substantial escalation of regularly used inhaled glucocorticoid treatments prevent exacerbations if initiated at the first signs of such a setback, when asthma control has deteriorated somewhat but a full-blown exacerbation has not yet occurred? Asthma specialists have long thought that this condition, termed the "yellow zone," provides the perfect timing for initiating more aggressive care.[6] It is an important topic because even though glucocorticoids may control asthma, they can have serious side effects, and preclinical studies show that they may enhance virus replication.[7] The two trials address the same fundamental question but differ in experimental design and patient populations, and the results are different.

In the first, Jackson and coworkers studied 254 children 5 to 11 years of age with mild-to-moderate persistent asthma.[4] All the patients had had at least one exacerbation in the previous year and were receiving treatment with maintenance low-dose inhaled glucocorticoids. At early signs of loss of asthma control, when patients entered the yellow zone, they were randomly assigned to continue the same dose (low-dose group) or use a quintupled dose (high-dose group). If a full-blown exacerbation ensued, it was treated with oral glucocorticoids; the rate of these events was the primary outcome. Results indicated that quintupling the dose of inhaled glucocorticoids was not effective in reducing exacerbations, symptoms, or beta-agonist use or in lengthening the time to a first flare. Total glucocorticoid exposure was 16% higher in the high-dose group than in the low-dose group, with a notable trend toward a lower growth rate (by 0.23 cm per year) among those children.

Does this trial provide conclusive evidence that a strategy to increase inhaled glucocorticoids fails to prevent exacerbations in children? The trial design was robust; treatment was randomized and double-blind, the sample size was adequate, clinically relevant outcomes were used, and, taken together, the findings provide clinical evidence that is compelling. There are a number of caveats: conclusions pertain only to 5- to 11-year-old patients with mild-to-moderate asthma and to persons receiving maintenance treatment with inhaled glucocorticoids. Overall, this commendable trial indicates that escalating the dose of inhaled glucocorticoids is a failed strategy to prevent exacerbations in children with early symptoms of asthma instability.

The second trial, by McKeever and coworkers, involved adults and adolescents with asthma; it is more complex and is arguably more controversial.[5] This trial used a pragmatic, randomized design, and self-management plans were used to

study patients who had deteriorating asthma control (in the Asthma UK guidelines,[8] this is termed "zone 2" rather than the yellow zone). Patients were randomly assigned, in an open-label fashion, to use a quadrupled dose of inhaled glucocorticoids (quadrupling group) or to continue their usual dose (non-quadrupling group); all the patients were instructed to use symptomatic bronchodilator medication. The time to a first severe exacerbation was the primary outcome. The findings indicated that 45% of the quadrupling group had a severe exacerbation in the year after randomization versus 52% in the non-quadrupling group, with an adjusted hazard ratio of 0.81. Adverse upper-airway effects were more frequent in the quadrupling group.

The pragmatic trial design was both a strength and weakness. Inclusion criteria were broad, ensuring wide-ranging applicability, and the primary outcome was relevant to everyday practice. However, open-label treatment may have biased the primary outcome, and the real-world design meant that data on peak flow and quality of life were available for less than half of the participants. The degree of benefit is debatable. The authors had postulated that a 30% reduction in the incidence of exacerbations would represent a worthwhile effect, but the trial showed only a 19% reduction. Combination asthma treatments of inhaled glucocorticoids and long-acting beta-agonists were permitted in the trial and were used as a maintenance treatment by approximately 70% of the participants; this may have reduced the reporting of exacerbations. Finally, given the adrenal suppression caused by quadrupling the dose of inhaled glucocorticoids (equivalent to a regular course of prednisolone), it will be difficult to convince clinicians that an exacerbation-prevention strategy involving high doses of inhaled glucocorticoids is merited. Overall, these reservations preclude definitive risk–benefit analyses; future controlled studies involving adults and adolescents with asthma are needed to obtain additional evidence.

Evidently, high doses of inhaled glucocorticoids do not prevent exacerbations, or may do so in only a small subgroup of patients. What do these trials therefore imply about asthma exacerbations, their nature, and other potential preventive treatment strategies? On the basis of causative factors alone, exacerbations are highly heterogeneous, and interactions between the underlying asthma phenotype and provoking factors are not understood.[9] This is an important issue, because prevention and treatment should ideally target both aspects. One solution could be to categorize asthma exacerbations by putative cause, such as infection, nonadherence to medication, and other exposures, and thus to "phenotype" asthma exacerbations. A strategy to phenotype exacerbations of chronic obstructive pulmonary disease has been implemented,[10] and a similar approach may be merited in asthma. Recent point-of-care diagnostic developments facilitate phenotyping by rapid identification of various respiratory viruses,[11] suggesting that this strategy may be feasible in the future. Other novel methods such as the electronic "nose" may be able to identify or categorize airway pathobiologic changes during exacerbations.[12] It is conceivable that this knowledge will permit earlier intervention and appropriately matched treatments, some of which may not include glucocorticoids.

Currently, clinicians are challenged to prevent and treat asthma exacerbations and to implement self-management plans. Evidence indicates that substantial escalation of regularly used inhaled glucocorticoids, even by a factor of 4 or 5, fails to prevent most asthma exacerbations. A small subgroup of adults and adolescents with asthma may have a response to an escalation strategy; however, their baseline and exacerbation characteristics remain to be defined.

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A Shift in Thinking to Reduce Mother-to-Infant Transmission of Hepatitis B

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The morbidity and mortality that are associated with hepatitis B virus (HBV) infection have been overshadowed by the public health prominence of other infectious diseases, including human immunodeficiency virus (HIV) infection, tuberculosis, and malaria. There is a dawning realization that the disease burden from HBV infection is increasing, despite the existence of an effective vaccine.[1] The World Health Organization (WHO) estimates that chronic HBV infection results in a quarter million deaths each year in the countries that are eligible for Global Vaccine Alliance (GAVI) support or cofinancing.[2] A positive status for hepatitis B e antigen (HBeAg) and a maternal HBV DNA level of more than 200,000 IU per milliliter are associated with an increased risk of perinatal HBV infection despite vaccination.[3] Infection in the neonatal period and childhood remains the leading source of new chronic infections and is a silent precursor to progressive disease. Thus, the prevention of neonatal and childhood infection by effective prophylaxis is crucial.

Schedules of either three or four doses are used for hepatitis B immunization, depending on government policy and national prevalence. Currently, HBV vaccination is most frequently administered as a pentavalent or hexavalent vaccine as part of the Expanded Program on Immunization (EPI), typically in combination with vaccines against diphtheria, tetanus, pertussis, polio, and *Haemophilus influenzae* type B. The first dose of HBV vaccine is given at 6 weeks of age to ensure immunogenicity of the combination. Despite recommendations from the WHO, only 92 of 193 countries (48%) report administering the vaccine at birth. In sub-Saharan Africa, the vaccine is currently administered at birth in 10% of neonates, and only 11 of 47 countries in the WHO African region have introduced a regimen of vaccination at birth.[4,5] As a result, an estimated 1% of newborns annually (>365,000 newborns in one model) are infected with HBV at birth in sub-Saharan Africa; this is twice the incidence of HIV infection among infants in this region.[6]

Paradoxically, GAVI support for combination vaccines within an integrated EPI schedule has unwittingly but undesirably shifted thinking and policy away from HBV vaccination at birth. This gap in vaccine strategy is disadvantageous. Antiviral therapy for pregnant women in the third trimester is effective in reducing vaccine and immune globulin failure in children born to mothers with high levels of viremia, but the HBV DNA level cannot be ascertained in many low-income countries.[7]

In this issue of the *Journal*, Jourdain et al.[8] report the results of a multicenter, double-blind trial of tenofovir disoproxil fumarate (TDF) versus placebo that was conducted in 17 public hospitals in Thailand. TDF and placebo were administered from 28 weeks of gestation to 2 months post partum in 331 women who were positive for HBeAg and the hepatitis B surface antigen (HBsAg). The median HBV DNA level was 8.1 $\log_{10}$ IU per milliliter in the TDF group and 7.9 $\log_{10}$ IU per milliliter in the placebo group. At enrollment, 90% of the women in the TDF group and 87% of those in the placebo group had an HBV DNA level of more than 200,000 IU per milliliter. HIV-positive women were excluded. All the children were given HBV vaccine and hepatitis B immune globulin at birth. Remarkably, the median time of HBV vaccination was 1.2 hours after birth, and 4% of infants received vaccine after 4 hours. Four doses of HBV vaccine were thus administered. A total of 2% of the infants in the placebo group (3 of 147 infants) and none of the infants in the TDF group were HBsAg-positive at 6 months