Editorial

Sinus Surgery Effects on Diagnosis and Management of Patients with AERD

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In this issue of *JACI: In Practice*, there are 2 studies, by Jerschow et al[1] and Huang et al,[2] addressing aspirin (ASA) challenge/desensitization in patients with aspirin exacerbated respiratory disease (AERD). It is well recognized that AERD represents a group of patients with asthma with typically more severe disease that can be mitigated with ASA desensitization followed by chronic ASA use (for review, see the paper by White and Stevenson[3]). Oral challenge to ASA in an observed clinical setting is highly effective in establishing the diagnosis of AERD. When oral challenge is contraindicated, nasal or bronchial challenges are proposed as alternative approaches.[4,5]

One of the key conclusions from both studies is that the diagnostic accuracy of an ASA oral challenge is reduced after sinus surgery. This is based on the observation in both the Jerschow et al[1] and Huang et al[2] studies that patients who underwent ASA challenge before sinus surgery with the development of symptoms exhibited less frequent and less severe reactions to ASA challenge after surgery. Notably, the rates of "silent desensitization" (no symptoms from the ASA challenge) after sinus surgery, in patients previously identified with AERD, were very similar in both studies: 43% and 38% in the Jerschow et al[1] and Huang et al[2] studies, respectively. Thus, approximately 40% of patients with AERD would be misdiagnosed as ASA tolerant if a diagnostic ASA challenge were performed within a couple months after sinus surgery.

However, there is a bright side to the effect of sinus surgery. The other important conclusion from both studies, also based on the decreased reactivity to ASA after sinus surgery, is that the period after sinus surgery is the optimal time to perform an ASA desensitization. Approaches to improving safety and subsequent success of ASA desensitizations in patients with AERD have included the use of leukotriene receptor blockers and omalizumab.[6,7] Based on the results presented by Jerschow et al[1] and Huang et al,[2] the use of sinus surgery should be included as an intervention that increases the likelihood of a successful desensitization with the further benefit of optimally debulking nasal polyps. The question remains as to how long these benefits of the surgical removal of polyp tissue burden last, 3 months? 6 months? In the Jerschow et al protocol,[1] the postsurgery ASA challenge was performed after 4 weeks. The protocol used by Huang et al[2] involved sinus surgery followed by ASA challenge within 60 days, thus likely a greater time period than in the Jerschow et al[1] study, but the precise timing after the surgery was not reported. Both showed comparable benefits for patients with AERD. It is possible that the "window" to perform an ASA desensitization is dependent on the patient's individual susceptibility to the recurrence of nasal polyposis resulting from inflammatory pathways involving mast cells, eosinophils, and/or ILC2 cells.

The study by Jerschow et al[1] examined the production of several mediators before and after the ASA challenges. Of great interest would be whether any of these mediators are biomarkers that portend risk for a failed desensitization. After surgery, there were overall lower baseline levels of urinary LTE4 and PGDM and higher levels of plasma Lipoxin A4, which likely reflects the decreased nasal polyp tissue burden producing/regulating these mediators. Although baseline levels of urinary LTE4 or PGDM were not statistically different between patients reacting versus not reacting to ASA, the plasma PGD2, PGE2, and PGD2/PGE2 ratio were all significantly elevated in patients with positive aspirin challenge versus those who did not react. Thus, the measurement of plasma PGD2 and PGE2 may be used to stratify a patient's risk of reaction during an ASA desensitization. This finding warrants a prospective evaluation. There are also other biomarkers such as plasma IL-25 that are elevated at baseline in patients with AERD relative to aspirin-tolerant patients with asthma.[8] It is unknown whether sinus surgery modifies plasma IL-25 levels or whether IL-25 levels could be predictive of tolerance to an ASA challenge. Identification of any of these biomarkers may become very important in the near future and may influence the potential use of biologics such as anti-IgE (omalizumab), anti-eosinophil drugs (mepolizumab, reslizumab, and benralizumab), or anti-IL-4/13 pathway (dupilumab) in patients with AERD. Although there are data showing independent benefits in asthma (for review, see the paper by Viswanathan and Busse[9]) and nasal polyp disease (for review, see the paper by Kartush et al[10]), none of these studies specifically investigate the population of patients with AERD. Biologics may indeed be very clinically and cost effective by decreasing disease morbidity and the future need of multiple sinus surgeries and recurrent courses of systemic steroids. Furthermore, biologics could be considered within a multifaceted treatment approach that also includes interventions such as aspirin desensitization and sinus surgery in patients with severe disease. The availability of a biomarker to guide whether to pursue the intervention of

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ASA challenge and chronic ASA therapy versus use of a biologic will be ideal to ensure cost-effective patient care.

In summary, the studies by Jerschow et al[1] and Huang et al[2] demonstrate that ASA challenge in patients with AERD after sinus surgery may be falsely negative. As proposed by both groups, it is important to perform diagnostic ASA challenges in patients with asthma and nasal polyp disease before any planned sinus surgery to more reliably identify patients with AERD, and in those patients, plan to proceed with an ASA desensitization shortly after the surgery.

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