



## Editorial

## A graduated approach to management of chronic rhinosinusitis in aspirin-exacerbated respiratory disease in the era of precision medicine



Personalized management of a disease based on patient-specific pathophysiology is 1 of the pillars of precision medicine. The management of aspirin-exacerbated respiratory disease (AERD), a disease defined in part by chronic rhinosinusitis with nasal polyps (CRSwNP) and asthma, is a unique opportunity to implement precision medicine. Driven by dysregulated arachidonic acid metabolism, AERD is characterized by overproduction of pro-inflammatory cysteinyl leukotrienes over anti-inflammatory prostaglandins, leading to eosinophilic and type 2 T-helper (Th2) inflammatory response in the airway mucosa.<sup>1</sup>

Modern-day aspirin desensitization was developed as a treatment for AERD based on clinical observations that after an aspirin challenge, AERD patients experienced a refractory period with no response to aspirin and improved symptoms lasting up to 72 hours.<sup>1</sup> Although the mechanisms of aspirin desensitization remain unclear, it is associated with immunologic changes that include sinonasal down-regulation of inflammatory mediators such as cysteinyl leukotrienes and interleukin (IL)-4, as well as their cognate receptors in some cases.<sup>1</sup> More recently, biologics targeting Th2-mediated inflammation have been approved for patients with asthma and CRSwNP, including AERD patients.<sup>2,3</sup> In this issue of the *Annals of Allergy, Asthma, and Immunology*, Steinke discusses evidence for the efficacy of aspirin desensitization and biologics to reduce sinonasal and pulmonary symptomatology, reduce polyp size, and improve pulmonary function.<sup>4</sup> The treatment of CRSwNP in the setting of AERD by using aspirin desensitization and biologics to specifically target the underlying disease mechanisms exemplifies personalized precision medicine. Given the efficacy of aspirin desensitization and biologics in the treatment of AERD, the natural next question to ask is which of these specific pathophysiology-targeting treatments should be used, as discussed by Steinke.<sup>4</sup>

Although exponentially increasing knowledge of the different underlying pathophysiologic mechanisms of CRSwNP is unlocking the possibilities of providing treatment in a patient-specific manner, we are also faced with the subtleties and considerations of implementing precision medicine. Even with the availability of novel therapeutics targeting specific pathophysiologic mechanisms and with the caveat that

comorbid asthma may influence treatment decisions, we must be mindful that management of CRSwNP should be implemented through a graduated approach.<sup>5</sup> A graduated approach begins with treatments having the lowest risks of side effects and adverse events, with escalation to treatments with higher risk to address uncontrolled disease. With ever-increasing health care expenses and the associated cost burden to society, the costs of treatments also must be weighed in the decision to use them.

Aspirin desensitization, although effective in reducing sinonasal symptoms and polyp size in AERD patients, is not an entirely benign treatment. In AERD patients treated with aspirin desensitization, adverse events including gastrointestinal side effects or bleeding occur in up to 25% of patients.<sup>6</sup> Although biologics have been shown to be largely safe, the costs for these medications are approximately \$30,000 USD per year. Finally, because neither aspirin desensitization nor biologics have yet been shown to provide durable improvement of CRSwNP disease burden or cure (ie, sinonasal symptoms and polyps return with cessation of treatment), these treatments do not provide a unique benefit with respect to treating CRSwNP compared with more commonly used treatments of sinus disease.

High-volume low-pressure saline irrigations and intranasal corticosteroids have been found by multiple randomized control trials (RCT) to be effective in the treatment of CRSwNP with minimal side effects.<sup>5</sup> As a result, these medications are recommended as the first line of treatment for all subtypes of chronic rhinosinusitis by clinical consensus guidelines.<sup>5</sup> Although most studies of saline irrigation and intranasal corticosteroids for CRSwNP have not sub-stratified results based on AERD, several studies have demonstrated that these medications are specifically beneficial for improving sinonasal symptoms and reducing polyp size in AERD patients. One RCT in AERD patients who underwent endoscopic sinus surgery (ESS) found that patients using just saline irrigation maintained large and significant postoperative reductions in both sinonasal symptoms and polyp size at 6 and 12 months.<sup>7</sup> Intranasal corticosteroids have also been studied for treatment of CRSwNP in the setting of AERD, with at least 1 double-blind RCT showing that intranasal corticosteroids significantly reduce sinonasal symptoms compared with placebo.<sup>8</sup> Moreover, although high-quality evidence is lacking, leukotriene inhibitors may be an option as well for reducing sinonasal symptomatology associated with AERD.<sup>5</sup> A subset of AERD patients will maintain control of sinonasal

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symptoms using these treatments without the addition of aspirin desensitization or biologics.

Finally, with a major complication rate close to 0.1%, the incorporation of ESS into the treatment algorithm for AERD should also be considered.<sup>5</sup> Endoscopic sinus surgery in AERD patients by itself decreases inflammatory load and improves clinical reaction to aspirin at 2 to 4 weeks after surgery (although an anti-inflammatory effect of ESS is clearly not expected to be sustained without proper postoperative medical management).<sup>9</sup> A previous study has shown that the incremental cost-effectiveness ratio (ICER) for ESS over continued medical management in patients with medically recalcitrant CRSwNP is \$5687 per quality-adjusted life year (QALY),<sup>10</sup> which is comparable to the \$6768/QALY ICER reported for aspirin desensitization<sup>4</sup> and suggests that ESS is also a cost-effective treatment for medically recalcitrant CRSwNP in AERD.

In many ways, the future of CRSwNP treatment is already here as it pertains to treatment of CRSwNP associated with AERD. With the existing knowledge of the pathophysiology of AERD, disease-specific treatments—aspirin desensitization and biologics—are available and effective and allow us to practice precision medicine for the treatment of CRSwNP in these patients. However, the implementation of any treatment, regardless of its novelty or therapeutic potential, requires careful consideration of risks to patients as well as costs to optimally position those treatments in the context of already existing treatments—for example, intranasal saline irrigations and intranasal corticosteroids in the case of CRSwNP in AERD. Therefore, while asking “aspirin desensitization vs biologics?” is appropriate in this era of precision medicine, it behooves us to also continue to ask “if, when, and in whom?”

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