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Perspective

Aspirin desensitization or biologics for AERD?

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Aspirin-exacerbated respiratory disease (AERD) is a syndrome characterized by asthma that is often severe, with progressive airway remodeling, the presence of eosinophilic chronic sinusitis with nasal polyp (CRSwNP) formation, and intolerance to aspirin and other nonselective cyclooxygenase 1 (COX-1) inhibitors.[1] The prevalence of AERD in the general population is 1%, which increases to 7% amongst those with asthma. In the most severe cases, ingestion of aspirin can trigger systemic reactions and even death. The disease has high morbidity if not properly managed, often involving multiple surgeries to decrease nasal polyp (NP) burden, because untreated NPs can regrow rapidly. Current treatment of AERD that fails conventional therapy uses aspirin desensitization followed by daily high-dose aspirin therapy; however, with the approval of biological therapies, new approaches need to be considered. How both of these will be used in the future and the benefits and drawbacks of each are the focus of this perspective.

Although aspirin can trigger acute respiratory symptoms through the release of inflammatory mediators, aspirin desensitization followed by daily high-dose aspirin therapy leads to improved long-term symptoms in AERD subjects, as shown in a double-blind placebo-controlled crossover study.[2] Many variations of the desensitization protocol exist; however, the general theme is to start with small doses of aspirin and gradually increase the amount, ultimately achieving doses of 650 to 1300 mg daily, although the use of lower dosing regimens is being investigated. The approach is analogous to traditional allergy desensitization, which addresses immunoglobulin E (IgE)-mediated reactions; however, the pathophysiology is distinct. The most significant improvements observed with aspirin desensitization relate to upper airway symptoms, including restoration of smell and decreased polyp formation, along with decreased use of steroids and fewer hospitalizations related to the underlying asthma.[3] In comparison with biologic therapy, the cost of the aspirin desensitization procedure and maintenance drug is inexpensive. As the severity of CRSwNP and inflammatory asthma associated with AERD increases, desensitization becomes increasingly cost-effective ($6768 per quality-adjusted life year saved in 2008).[4] Despite the beneficial aspects of daily high-dose aspirin therapy, there are some drawbacks. Continued aspirin therapy can lead to gastrointestinal issues and bleeding problems in some subjects, leading to discontinuation of treatment. If the need to have surgery arises, the patient will have to stop aspirin treatment until after surgery and will require subsequent desensitization again. Likewise, if the person misses 2 consecutive days of taking aspirin, the desensitization procedure will have to be repeated. Many physicians may not feel comfortable performing the desensitization procedure if they are not equipped to deal with systemic reactions that may occur during the dose-escalation phase.

Mediators identified in AERD pathophysiology include interleukin (IL)-5, IL-4, and IL-13. Multiple monoclonal antibodies targeting these immune pathways have been approved for asthma and are in trials for CRSwNP. Dupilumab is an IL-4 alpha receptor antagonist that blocks both IL-4 and IL-13 signaling. This is the first biologic drug that has been approved to treat CRSwNP, and the subjects with AERD demonstrated the greatest benefit.[5] Based on the demonstrated role of IL-4 in AERD, this represents a potentially promising new therapy for aspirin-sensitive patients with asthma. Three biologics (mepolizumab, benralizumab, and reslizumab) that are approved for asthma and target the IL-5 pathway are being investigated in phase 3 clinical trials of chronic rhinosinusitis with nasal polyps, a subgroup of which have AERD. Nasal polyps of AERD subjects have the highest eosinophil levels, so preventing them from entering the tissue should have the most benefit in this form of sinus disease. Targeting a different pathway, the anti-IgE monoclonal antibody omalizumab has proven efficacy in allergic asthma, and positive outcomes have been reported in the phase 3 trials for the treatment of CRSwNP. Although IgE has not been shown to be a prominent feature in AERD pathogenesis, multiple case reports discuss omalizumab benefiting AERD patients, indicating that further studies are warranted. In addition to the

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biologics already in clinical use, targeting novel pathways such as IL-33 or TSLP signaling will likely be explored in AERD as a treatment option. An advantage of the biologics is that although aspirin needs to be taken daily, the biologic will only need to be administered every 2 to 4 weeks depending on the drug. A missed dose or short-term stoppage of treatment for the biologics will not require going through the desensitization procedure and risk of systemic reactions as with aspirin. Side benefits of the biological therapies include improvement in comorbid conditions such as asthma and allergic rhinitis. The biggest downside to any of the biological treatments will be cost of the drug (>$25,000/yr). Because many of the biologics are recent approvals, there is a lack of long-term health data for the drugs with the exception of omalizumab.

Our experience with aspirin desensitization has been that the best results occur if we perform the procedure after surgery, similar to other reports.[6] This removes the bulk of the tissue that serves as a factory producing the mediators that drive disease in the sinuses and systemically. Patients report rapid improvement in their sense of smell, and revision surgery is either not needed or greatly delayed as polyp regrowth is inhibited. The sinus studies with biologics demonstrate reduced polyp score, improved sense of smell, and decreased computed tomography scores, with the biggest improvements observed in patients with AERD. The time in delay to surgery has only been examined in a few trials. Although approval will be made based on reduced polyp score, it will be of interest to see whether strategies of incorporating biologics after surgery will be used in AERD, as is currently done with aspirin desensitization. It will be informative for a cost comparison study of biologics vs aspirin desensitization to be performed in terms of length of time to surgery and long-term cost for each treatment to see whether one approach is superior to the other.

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