Clinical updates in aspirin-exacerbated respiratory disease

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ABSTRACT

Background: *Aspirin-exacerbated respiratory disease (AERD), a syndrome that includes asthma, recurrent nasal polyps, and pathognomonic reactions to aspirin and other nonselective cyclooxygenase inhibitors, is still not fully understood and lacks specific disease-modifying therapeutic options.*

Objective: *To review the most recent clinical updates in the evaluation and treatment of patients with AERD.*

Methods: *Recent clinical research studies relevant to patients with AERD were reviewed.*

Results: *Multiple new biologics are available for the treatment of severe asthma, several of which have been specifically studied and determined to be efficacious in the subset of patients with asthma who are also aspirin sensitive. Zileuton continues to be underprescribed for AERD and is considered to be very effective by many patients with AERD. Dietary modifications toward a diet that is high in omega-3 fatty acids and low in omega-6 fatty acids can reduce the production of the inflammatory leukotriene and prostaglandin D_2 lipids and help improve symptoms for patients with AERD.*

Conclusion: *A lack of definitive understanding of the causative mechanisms of AERD and the absence of an AERD-specific patient-reported outcome measure are obstacles that remain in this field, but much progress has been made over the past decade.*

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Aspirin-exacerbated respiratory disease (AERD) is an enigmatic syndrome that is characterized by eosinophilic asthma, chronic rhinosinusitis with nasal polyposis, and respiratory reactions to nonsteroidal anti-inflammatory drugs that inhibit cyclooxygenase 1. Many mysteries remain about AERD, but recent progress has fueled a palpable energy and enthusiasm in the field of AERD over the past few years. Multiple clinical trials are now underway that involve specific investigations into both new treatments for patients with AERD and the mechanism behind this enigmatic disease. Both the National Institutes of Health and a number of pharmaceutical companies have begun to acknowledge the unmet medical need of these patients and are providing resources for further research.

More and more centers across the United States are being trained with proficiency in AERD and aspirin challenges and/or desensitizations, which has led to increased availability of health-care teams with expertise in diagnosis and management of the disease. Physician-observed aspirin challenges are still considered the standard for confirming a diagnosis of AERD because no current laboratory or biomarker-based testing yet has high enough sensitivity and specificity. Furthermore, aspirin desensitization and initiation of high-dose aspirin therapy has appropriately become the accepted standard of care for patients with AERD, with the understanding that daily aspirin therapy will reduce or delay the regrowth of nasal polyps in >70% of patients.[1,2] This progress in the field has encouraged patient-advocacy groups to double their efforts with renewed optimism. Indeed, there is much hope on the horizon, although there are still many challenges ahead.

UPDATES IN CLINICAL CARE OPTIONS FOR PATIENTS WITH AERD

There has been a near-flurry of new biologic agents studied for asthma and nasal polyposis, with several of them recently approved by the U.S. Food and Drug Administration for the treatment of severe asthma. Although AERD-directed trials have not been formally pursued by any of their respective pharmaceutical companies; nonetheless, there have been a number of separate investigations or substudies that can help guide us toward the best biologic choices for patients with AERD. Omalizumab has been shown to decrease urinary cysteinyl leukotrienes and prostaglandin D_2 metabolites, both of which are implicated in the chronic inflammatory disease process of AERD as well as in the acute aspirin-induced reactions. Because many patients with AERD do not have clinical atopy,[3] it is not clear whether direct immunoglobulin E mediated immune hypersensitivities play a role in AERD.

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Therefore, the therapeutic benefit afforded by omalizumab treatment to patients with AERD strongly suggests that mast cell activation is a key component in the disease.[4] The availability of mepolizumab for the treatment of severe eosinophilic asthma has afforded many of our patients with AERD with a new therapeutic option, and our group conducted a retrospective study that indicated that mepolizumab is indeed quite efficacious as an adjunct treatment for AERD.[5] A substudy conducted on the 19 patients who had AERD and participated in the phase II trial of the utility of dupilumab for the treatment of nasal polyps clearly demonstrated the benefit of this drug on the upper respiratory tract of patients with AERD; treatment with dupilumab provided a 2.5-point reduction in the Total Polyp Score, a 30-point reduction in the SNOT-22 (Sino-Nasal Outcome Test-22) score, and an improvement of nearly 10 items on the UPSIT (University of Pennsylvania Smell Identification Test) smell identification test.[6]

Many patients prefer to avoid medications whenever possible, and a study from our AERD[7] Center at the Brigham and Women's Hospital on the role of dietary changes for the treatment of AERD provided insight into possible nonmedical methods to improve symptoms. Based on patient observations of patients who reported that certain dietary modifications seemed to lessen their symptoms of AERD, we aimed to determine whether a 2-week diet that was high in omega-3 fatty acids and low in omega-6 fatty acids would be efficacious for the treatment of AERD. Cysteinyl leukotrienes and prostaglandin D_2 are inflammatory lipids present in very high levels in patients with AERD and are derived from the metabolism of omega-6 fatty acids. Therefore, we hypothesized that reducing the availability of the omega-6 precursors would reduce leukotriene production and decrease inflammation. In the 10 patients with AERD who completed the dietary intervention, levels of both urinary leukotriene E4 and urinary prostaglandin D_2 metabolites decreased after 2 weeks on the diet. Furthermore, both sinus symptoms and asthma control improved significantly while on the diet. We now routinely offer a high-omega-3–low-omega-6 diet as a treatment option for our patients with AERD.[7]

Furthermore, two studies have now shown that alcohol-induced respiratory reactions are common in patients with AERD, with 63–83% of patients reporting symptoms of nasal and/or bronchial symptoms on ingestion of even small amounts of alcohol.[8,9] Although the underlying mechanism of these reactions is not yet understood, a history of respiratory reactions on alcohol ingestion in patients with asthma and nasal polyps may aid in the suspicion of AERD. Furthermore, clinicians should warn their patients about this possibility and may need to recommend discontinuing alcoholic beverages as part of a larger dietary intervention.

A clinical questionnaire study by Ta and White,[10] showed that, although zileuton was not as commonly prescribed a leukotriene-modifying drug such as montelukast, a higher proportion of patients with AERD reported that zileuton was extremely effective, which suggests that the drug may be underutilized. After this, a subanalysis study was done to look back at some of the original investigational work that led to the approval of zileuton for use in asthma in general. In the subset of patients who had reported that their asthma symptoms "were worsened with aspirin" (which, despite not being a substitute for formal aspirin challenge, nonetheless, is likely to capture a large majority of the patients who had AERD in that study), treatment with zileuton led to a dramatic increase in forced expiratory volume in the first second of expiration from baseline of nearly 20%.[11] In addition to validating the patient responses from the earlier questionnaire study,[10] these data[11] also provide a strong push to prescribers to consider the use of zileuton for the treatment of uncontrolled asthma in patients with AERD.

AREAS THAT REQUIRE FURTHER EFFORT

Those of us who evaluate and treat patients with AERD are still frustrated by the lack of awareness of this disease within the wider medical field and by the lack of integration of AERD into the teaching curriculum for residents and fellows. These frustrations are fully validated by the evidence, which demonstrates an average of a nearly 10-year gap between the onset of disease symptoms and proper diagnosis of AERD.[12] Furthermore, we found that, even of the most classic patients who describe all three symptoms of the AERD triad (adult-onset asthma, recurrent nasal polyps, and respiratory reactions to aspirin and nonsteroidal anti-inflammatory drugs), >10% of them are not given the proper diagnosis of AERD.[13] This is one of the reasons that we are so thankful for the active patient-advocacy groups who are working to increase the outreach to afflicted patients and health-care workers alike. Due entirely to campaigns put forth by several of these patient groups, AERD has gained traction and garnered much-deserved attention in the media and medical community, and September 26, 2018, marked the very first AERD Awareness Day,[14] which we hope will become an annual event.

We remain beset both by a poor understanding of the underlying causative mechanisms of AERD and by the absence of any AERD-specific patient-reported outcome measure or clinical response measure. More explicit investigations into the inciting trigger for the disease and the cause(s) of the ongoing inflammation will surely yield valuable information that could be

translated into more advanced therapeutics. Furthermore, the development of an AERD-specific outcome or clinical response measure would be a powerful tool that could be applied in future longitudinal studies of disease severity and in therapeutic response trials. Such a clinical tool would need to encompass assessments of upper and lower respiratory symptoms, along with comorbidities, including skin and/or gastrointestinal symptoms that are often seen as part of the AERD disease spectrum.[15] An infusion of information from mechanistic studies, in combination with the development of an AERD-specific patient-reported outcome measure would provide for wonderful progress in the field, and we remain hopeful that these achievements are within our near-term grasp.

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