

## Editorial

## AERD: Quo Vadis?

It was forty years ago when researchers working at Scripps Clinic began to notice that the initial two patients they had desensitized to aspirin were having better clinical outcomes than those who were simply avoiding aspirin.<sup>1</sup> That sentinel observation led to numerous studies of cytokines and other mediators which have resulted in a better understanding of the immune dysregulation which accompanies the clinical manifestations experienced by Aspirin-Exacerbated Respiratory Disease (AERD) patients. Thirty years ago, I was fortunate to be a young fellow who was involved with some of the early research on aspirin therapy after aspirin desensitization. AERD was previously referred to as Samter's triad, Aspirin Sensitive Rhinosinusitis-Asthma, Aspirin triad and Aspirin Idiosyncrasy among others. It was long thought of as a rare disease that had no other treatments except systemic corticosteroids and, prior to the age of endoscopic sinus surgery, extremely invasive surgeries like Caldwell-Luc, external ethmoidectomy and frontal sinus obliteration with osteoplastic flaps.

There has been a recent surge in the interest in AERD research. In this issue, Buchheit et al.<sup>2</sup> emphasize the importance of earlier diagnosis of AERD. Fragmentation of care and lack of awareness can lead to diagnostic delays of up to 10 years in some cases. Patient safety with regard to proper avoidance of COX-1 inhibitors, tailoring of disease specific therapy and proper treatment of pain syndromes are among the important reasons for proper and prompt diagnosis. They review a clear approach emphasizing appropriate history taking and the role of aspirin challenges which should improve early detection.

Olfaction is the strongest contributor to quality of life for AERD patients. Improvement in olfaction correlates well with global sinonasal symptoms. In this issue of the journal, Spielman et al.<sup>3</sup> reviewed olfactory outcomes with various modalities of AERD treatment. There is considerable

evidence that each of the reviewed therapies [Endoscopic Sinus Surgery (ESS), ASA desensitization(AD), and monoclonal antibodies] improves olfaction in patients with AERD, with multimodality therapy (ESS + AD) showing benefits that appear to be superior to surgery alone.

Locke<sup>4</sup> and colleagues retrospectively analyzed the psychological burden of a large cohort of AERD patients who underwent ESS plus AD. Utilizing the results of serial SNOT 22 psychological domains, they were able to demonstrate a clear improvement in the overall psychosocial burden with a significant improvement in perceived productivity and concentration in patients receiving this multi-modality therapeutic approach.

Ryan et al.<sup>5</sup> have performed a systematic review of the literature and analyzed data from six studies of patients who underwent both ESS and AD. Their review confirms that ESS results in improved symptom scores and quality of life which is sustained by AD and worsened when aspirin therapy is interrupted. Polyp recurrence was also noted in patients who stopped aspirin therapy.

Biological therapies are showing promise for the treatment of refractory AERD patients. Their extremely high price tags are certainly a concern. Workman and Bleier<sup>6</sup> reviewed the data on the efficacy and cost for these cytokine blocking therapies vs. standard surgical management for AERD. They point out that no double blind or placebo-controlled studies have been performed looking specifically at the efficacy of biologics in the AERD population. One study extrapolated data from the DBPC Dupilumab nasal polyps study demonstrated multiple improvements in subjective and objective outcomes in patients with self-reported AERD; no challenges were performed. All of the other studies were either uncontrolled, retrospective or a case series. The authors also analyzed the cost of these new therapies with respect to their results compared with established therapy such as ESS and AD. Their analysis suggests that at this time these very expensive agents should be reserved for the minority of patients who fail to respond to established multimodality surgical and medical therapy.

The appropriate extent of sinus surgery for AERD has not been well standardized. Kuan et al.<sup>7</sup> reviewed the

Peer review under responsibility of Chinese Medical Association.



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<https://doi.org/10.1016/j.wjorl.2020.05.011>

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Please cite this article as: Bosso JV, AERD: Quo Vadis?, World Journal of Otorhinolaryngology-Head and Neck Surgery, <https://doi.org/10.1016/j.wjorl.2020.05.011>

literature regarding more extensive sinus surgery procedures, focusing on the benefits and the role of frontal sinus surgery and the Draf III (Modified Lothrop) procedure. They highlight the numerous studies that suggest that early intervention with Draf III frontal sinusotomy may be advantageous to AERD patients for the purposes of improved neostial patency and proper distribution of topical therapies.

White<sup>8</sup> and colleagues provide a thorough up to date review of all of the available medical forms of therapy for AERD, including topical corticosteroids, anti-mediator therapies (Leukotriene modifiers), Aspirin therapy after desensitization (ATAD) and biological therapies. They review cost considerations, treatment approaches and discuss various clinical scenarios which provide a very practical framework.

Naples et al.<sup>9</sup> reported on otologic symptoms that can often accompany AERD and are often overlooked. They analyzed the otologic domain of the SNOT 22 questionnaire in a large cohort of patients that underwent endoscopic sinus surgery (ESS) followed shortly thereafter with aspirin therapy after aspirin desensitization (ATAD). They demonstrated that especially with regard to ear pain and fullness, there was a significant post-operative improvement which was sustained for the 12 month follow up period with aspirin treatment. No significant improvement was seen with regard to dizziness. Clinicians need to be aware that AERD patients may be at risk for hearing related complications and should consider audiology evaluation for these patients with any active ear symptoms.

A new pathway which links the type 2 cannabinoid receptor (CB2) and prostaglandin dysregulation has been described by Levy<sup>10</sup> in this issue. He presents data describing the CB2 receptor in AERD patients; its stimulation may serve as a potential counter mechanism to the prostaglandin-leukotriene balance which is abnormal in AERD. Future study of this potential therapeutic pathway is warranted.

The future looks brighter for patients with AERD. Earlier diagnosis and a recent surge in AERD research all bode well for the coming years. While aspirin therapy after aspirin desensitization, with four decades of data to support its efficacy, remains the mainstay of medical therapy for most patients, we now have advanced, refined and minimally invasive endoscopic sinus surgical techniques, enhanced delivery systems for topical steroids and cytokine blocking biologicals available to be used in various combinations to reduce the reliance on systemic corticosteroids. The placement of newer biological therapies into the treatment paradigm will be challenging given their steep costs; but their availability in the AERD toolbox will increase the number of patients who will be able to be treated especially those who have failed standard time-tested therapies.

AERD-Quo Vadis? Where do we go from here? Correcting the underlying immune dysfunction in AERD could be within the bounds of technology in the next decade. The etiology of AERD needs to be better elucidated in order to develop

preventive strategies for reducing its development in the general population. While we have come a long way from the days of having virtually all patients being steroid dependent, we await future studies that will pave the way for more permanent solutions to this aggressive inflammatory sino-pulmonary disorder.

## Declaration of competing interest

I have served on the advisory board of Sanofi/Regeneron, Novartis, Astra-Zeneca, Optinose and Glaxo Smith-Kline.

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22 May 2020