



## Aspirin desensitization for aspirin-exacerbated respiratory disease in the era of biologics: Clinical perspective

Forty years ago, researchers at the Scripps Clinic desensitized 2 aspirin-exacerbated respiratory disease (AERD) patients to aspirin and noticed that the rate of regrowth of their polyps had abated with continued aspirin therapy. Subsequently, approximately 16 retrospective studies and 4 double-blind, placebo-controlled studies supported the use of aspirin therapy after aspirin desensitization (ATAD) as an efficacious, steroid-sparing treatment for AERD.<sup>1</sup>

Over 91% of the AERD patients on ATAD followed for at least 30 months after a complete endoscopic sinus surgery (ESS) did not require revision surgery.<sup>2</sup> The rate of aspirin therapy intolerance approaches 15%. Gastrointestinal (GI) intolerance is the most common reason for discontinuation.<sup>3</sup> There is also a small subset of AERD patients that produce so much prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) and leukotriene E<sub>4</sub> (LTE<sub>4</sub>) that they have a distinct pruritic urticarial-like rash.<sup>4,5</sup> These patients do not tolerate the Aspirin Desensitization procedure or ATAD without the addition of zileuton or a T2 biologic.

The dose of aspirin required to prevent polyp regrowth seems to decline after 60 years of age.<sup>6</sup> Long-term ATAD in the AERD population appears to be quite safe. Less than 2% of an ATAD cohort of 109 patients had serious adverse events, with severe GI bleeding requiring treatment occurring in <1%.<sup>7</sup>

In addition to preventing polyp regrowth, and therefore further revision surgeries, improving sense of smell, reducing nasal congestion, improving asthma control, and reducing the need for overall corticosteroid use, ATAD provides the ability for patients to use aspirin or nonsteroidal anti-inflammatory drugs for other indications and cardiovascular prophylaxis, and reduces the need for opioid analgesics.<sup>3</sup> Furthermore, ATAD has been shown to improve alcohol tolerance in AERD patients.<sup>8</sup> None of these properties have been attributed to any of the T2 biologics.

T2 biologics are effective for the treatment of eosinophilic asthma refractory to standard therapy. Recently, one agent,

dupilumab, was approved for use in chronic rhinosinusitis with nasal polyps (CRSwNP) uncontrolled with topical steroids. Extrapolated data show that approximately 30% of patients in the studies had history-defined AERD and responded equally well with reduction of polyp size and improvement in sense of smell.<sup>9</sup> Omalizumab and mepolizumab also have data that may soon result in their approval for CRSwNP.<sup>10,11</sup> T2 biologics are a welcome addition to the AERD treatment armamentarium. Patient-specific considerations, previous therapeutic interventions, comorbidities, shared decisionmaking, and costs are all very important in deciding on long-term treatment for AERD patients.<sup>12</sup> The choice is not necessarily binary, as both therapies can be used in difficult cases. Emerging data on subendotypes of AERD may aid in the process.

According to Medispan 2019, the cost of T2 biologics ranges from \$33,000 to \$49,000 per year. Further, there is the expectation that treatment will be lifelong, as there is no permanent disease-modifying effect and AERD has not been shown to remit spontaneously. Considering the average age of onset of AERD is around 30 years,<sup>1</sup> the costs to the system for 1 patient can be in the multimillion-dollar range over one's lifetime. Thus, before turning to T2 biologics, there should be due-diligence use of all the less costly established therapies administered properly. ESS can be performed multiple times before the cost approaches that of just 1 year of biologic therapy. Complete ESS offers almost immediate relief and a reduction of the polyp score to zero. The postoperative state allows for topical steroid therapy, ATAD, and other established therapies to be more effective for the majority of cases at a fraction of the cost of a T2 biologic. Further, surgery reduces the severity of reactions that occur during aspirin desensitization, making it a much safer procedure.<sup>14</sup> The cost of an aspirin desensitization procedure is approximately \$1700 to \$3000.<sup>15</sup> Aspirin itself costs about 5 cents per tablet or <\$100 per annum. Although T2 biologics appear to have a good margin of safety overall, we do not have long-term safety data for most of them to offer to our patients.

The exuberance over the new T2 biologic agents is clear. We have waited many years to have these available for our refractory patients. They are a welcome addition in treating severe upper or lower airways inflammation. However, existing therapies, such as complete ESS and ATAD, when utilized in a multidisciplinary coordinated care environment, provide excellent results for the majority of patients and have not been utilized to their full potential. Therefore, this combination of treatments is still appropriate to discuss with most patients early on. There will remain a minority of patients who are either intolerant to aspirin, have an aspirin

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Conflict of interest: J.V.B. has served on the scientific advisory boards for Glaxo SmithKline, Sanofi, Regeneron, Novartis, Optinose, and Astra-Zeneca.

Received: 10 August 2020; Revised: 11 September 2020; Accepted: 13 September 2020

DOI: 10.1002/alr.22709

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contraindication, have a surgical contraindication, refuse surgery or aspirin desensitization, or do not have an excellent response to these coordinated therapies. Fortunately, for these patients, there is now another treatment option available.

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## References

- White AA, Stevenson DD. Aspirin exacerbated respiratory disease. *N Engl J Med*. 2018;379:1060-1070.
- Adappa ND, Ranasinghe VJ, Trope M, et al. Outcomes after complete endoscopic sinus surgery and aspirin desensitization in aspirin-exacerbated respiratory disease. *Int Forum Allergy Rhinol*. 2018;8:49-53.
- Berges-Gimeno MP, Simon RA, Stevenson DD. Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2003;111:180-186.
- Cahill KN, Bensko JC, Boyce JA, Laidlaw TM. Prostaglandin D2: a dominant mediator of aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2015;135:245-252.
- Laidlaw TM, Gakpo DH, Bensko JC, Buchheit K. Leukotriene-associated rash in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. 2020;8(9):3170-3171.
- Sweis A, Locke T, Kohanski, MA, Palmer JN, Bosso JV, Adappa ND. Age as a factor in the treatment of aspirin-exacerbated respiratory disease: relationship to required aspirin maintenance dose post-desensitization. *Int Forum Allergy Rhinol*. 2020;10(10):1180-1181.
- Sweis AM, Locke TB, Ig-Izevbehai KI, et al. Major complications of aspirin desensitization and maintenance therapy in aspirin-exacerbated respiratory disease. *Int Forum Allergy Rhinol*. 2020;00 1-5.
- Glicksman JT, Parasher AK, Doghramji L, et al. Alcohol-induced respiratory symptoms improve after aspirin desensitization in aspirin-exacerbated respiratory disease. *Int Forum Allergy Rhinol*. 2018;8:1093-1097.
- Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52) results from two multicenter, randomized, double-blind, placebo-controlled, parallel group phase 3 trials. *Lancet*. 2019;394:1638-1650.
- Bachert C, Sousa AR, Lund VJ, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: randomized trial. *J Allergy Clin Immunol*. 2017;140:1024-1031.e14.
- Gevaert P, Omachi TA, Corren J, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J Allergy Clin Immunol*. 2020;146:595-605.
- Laidlaw TM. Aspirin desensitization vs biologics for patients with aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. (in press).
- Thomas AJ, Smith KA, Newberry CI, et al. Operative time and cost variability for functional endoscopic sinus surgery. *Int Forum Allergy Rhinol*. 2019;9:23-29.
- Jerschow E, Edin ML, Chi Y, et al. Sinus surgery is associated with a decrease in aspirin-induced reaction severity in patients with aspirin exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. 2019;7:1580-1588.
- Shaker M, Lobb A, Jenkins P, et al. An economic analysis of aspirin desensitization in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2008;121:81-87.