



Contents lists available at ScienceDirect



Perspective

Aspirin desensitization vs biologics for patients with aspirin-exacerbated respiratory disease

Tanya M. Laidlaw, MD

Division of Allergy and Clinical Immunology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

ARTICLE INFO

Article history:

Received for publication June 30, 2020.

Received in revised form July 28, 2020.

Accepted for publication August 3, 2020.

As the director of one of the largest evaluation and treatment centers for patients with aspirin-exacerbated respiratory disease (AERD) in the world, I am often asked on how we should approach the use of aspirin desensitization followed by high-dose aspirin therapy for our patients with AERD in the current age of newly available biologics. I feel strongly that, at least for now, there is a place for both treatment modalities, sometimes even both in the same patient at the same time. In the end, it is always a set of decisions that need to be made on an individual patient basis, and I consider the following 4 general domains when approaching the decision and my recommendation: efficacy, safety, cost, and patient preference.

The efficacy of biologics, either for the treatment of uncontrolled asthma or for the treatment of nasal polyposis, is relatively well established, in part because to be awarded an approval from the Food and Drug Administration, rigorous prospective studies with clear end points were required. The mean expected improvement in the forced expiratory volume in 1 second or the likely decrease in the need for long-term oral steroids for asthma control has been published for the use of omalizumab, mepolizumab, benralizumab, reslizumab, and dupilumab. Similarly, the mean reduction in nasal polyp burden or the increase in the sense of smell is known for dupilumab, with detailed results expected soon from phase 3 nasal polyp trials with omalizumab and mepolizumab, because earlier phase 2 studies with these agents indicated promise. In contrast, there have been no international multisite, industry-sponsored randomized controlled trials for aspirin desensitization, followed

by initiation of high-dose aspirin treatment. Several groups have published careful clinical studies of the efficacy of high-dose aspirin in AERD, but the total daily aspirin dose has differed, as has the length of treatment and the prespecified end points of each study. There have only ever been 4 randomized, placebo-controlled trials of high-dose daily aspirin in AERD¹ (totaling only 163 patients studied), and even with the addition of several other studies that included low-dose daily aspirin in lieu of a true placebo, the data are difficult to summarize in aggregate. Those of us who have offered aspirin desensitizations to our patients with AERD for many years will confirm with dozens of anecdotes to say that “when it works, it works magically.” Each of us have long lists of contented patients who had suffered through the regrowth of polyps despite multiple repeat surgeries and appropriate standard postoperative care, and after initiating high-dose aspirin, their polyps have not returned, their asthma control has been more consistent, and their steroid requirements are at an all-time low. However, if we are to be honest, each of us can also dig up anecdotes of patients whose desensitizations were particularly difficult, or whose gastrointestinal tracts simply could not put up with the higher doses of aspirin, or whose sinuses and asthma refused to respond, and their polyp regrowth sprang back unabated. Without careful, prospective, well-designed, multicenter trials of high-dose aspirin therapy, our data on efficacy for the treatment of respiratory disease in AERD will remain lacking. However, in addition to the utility of high-dose aspirin for the prevention of nasal polyp regrowth, aspirin desensitization also provides the opportunity for patients to use aspirin or nonsteroidal anti-inflammatory drugs for other indications, including for non-opioid pain control, cardioprotection, and as anti-inflammatory agents for a myriad of inflammatory disorders. To the best of our knowledge, none of the available biologics will completely prevent all nonsteroidal anti-inflammatory drugs–induced reactions in patients with AERD; therefore, this end point is one that is unique to aspirin desensitization.

As for the efficacy, our understanding of the safety of daily high-dose aspirin in AERD is hampered by small trial size and few

Reprints: Tanya M. Laidlaw, MD, Division of Allergy and Clinical Immunology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 60 Fenwood Road, Building of Transformative Medicine, Rm 5002M, Boston, MA 02115; E-mail: tlaidlaw@bwh.harvard.edu.

Disclosures: Dr Laidlaw has served on the scientific advisory boards of GlaxoSmithKline, Sanofi Genzyme, Optinose, and Regeneron Pharmaceuticals, Inc.

Funding: This work was supported by grant numbers U19AI095219 and R01HL128241 from the National Institutes of Health.

<https://doi.org/10.1016/j.anai.2020.08.008>

1081-1206/© 2020 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

long-term studies. The aspirin-induced increased risk of gastritis is something that we counsel our patients on carefully and see in around 10% of our patients. Although frank gastrointestinal bleeding is rare, it does occasionally occur. An idiosyncratic worsening in asthma control or worsening pruritic rash while on high-dose aspirin is also reported by approximately 10% of the patients with AERD, leading to a total of approximately 15% patient dropout rate owing to aspirin-induced adverse effects.^{1,2} The use of aspirin comes with decades of historical data from the cardiovascular literature that can be extrapolated to our patients. Recent clinical research suggests that daily aspirin causes a very small but measurably higher risk of major bleeding and hemorrhage^{3,4} and possibly a higher all-cause mortality in older adults,⁵ suggesting that perhaps high-dose aspirin should be contraindicated in elderly patients with AERD. In contrast, the use of biologics in allergy and rhinology is a comparatively new practice, with safety data going out for only 1 year for several of the available drugs. However, in the short term, there seems to be a relatively safe profile for the existing biologics, with less than 5% dropout rate for most of the published studies.

A discussion of the therapeutic utility of biologics must be contextualized with a consideration of the cost. The annual cost of any of the Food and Drug Administration–approved biologics for asthma or nasal polyposis ranges from approximately \$33,000 to \$49,000 (as per the Medi-Span Price Rx, Wolters Kluwer, Alphen aan den Rijn, Netherlands, 2019). Although in many states the health insurance coverage of these agents is quite good, allowing for low out-of-pocket costs for some patients, the cost to our health care system at large is still very high. The cost of an aspirin desensitization procedure is generally billed at \$1000 to \$4000, with an annual cost of over-the-counter enteric-coated aspirin of less than \$100.

Let us not ever make an elective clinical decision without including the patient in a shared decision making process. We, as specialists, must be sufficiently knowledgeable and informed to provide patients with current evidence-based information, and

then work with our patients and their families to take into account their values and preferences, and come together to an optimal treatment decision. There are patients who are terrified of undergoing an aspirin desensitization procedure, and perhaps justifiably so, considering how severe some of their previous nonsteroidal anti-inflammatory drugs–induced reactions may have been. There are also those patients for whom the notion of an injectable biologic or new antibody conjures up fears of medical experimentation, exploitation, or mistrust. Thoughtful education and a patient-centered approach are often enough to provide reassurance, but it takes time and care to get there.

In conclusion, there are some patients for whom a sinus surgery followed by aspirin desensitization and high-dose aspirin therapy is clearly the best choice—particularly younger patients whose asthma seems to temporarily disappear after sinus surgery and for whom prevention of nasal polyp regrowth is the main goal. There are also some patients for whom a biologic is the best choice—especially those with multiple comorbidities including severe asthma, recalcitrant nasal polyps, or uncontrolled allergies or atopic dermatitis. For everyone else, the answer is “it depends,” and it is our job to provide guidance where we can.

References

1. Chu DK, Lee DJ, Lee KM, Schünemann HJ, Szczeklik W, Lee JM. Benefits and harms of aspirin desensitization for aspirin-exacerbated respiratory disease: a systematic review and meta-analysis. *Int Forum Allergy Rhinol.* 2019;9(12):1409–1419.
2. 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(1):180–186.
3. McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med.* 2018;379(16):1509–1518.
4. ASCEND Study Collaborative Group, Bowman L, Mafham M, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med.* 2018;379(16):1529–1539.
5. McNeil JJ, Nelson MR, Woods RL, et al. Effect of aspirin on all-cause mortality in the healthy elderly. *N Engl J Med.* 2018;379(16):1519–1528.