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Review Article

Aspirin-exacerbated respiratory disease: Update on medical management

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Abstract Aspirin-exacerbated respiratory disease (AERD) is frequently diagnosed in patients with severe type 2 airway inflammation presenting with nasal polyps and severe asthma. It has been associated with a recalcitrant course with high medical and surgical requirements. The advent of recent biological and other targeted treatments show promise in the medical management of patient with AERD. The goal of complete disease control where patients no longer require recurrent surgical procedures, systemic corticosteroid exposure and may live with a stable and relatively normal quality of life is now within reach. Further work is necessary to identify biomarkers predictive of treatment response.

Introduction

Aspirin-exacerbated respiratory disease (AERD) is a common diagnosis in patients with severe and recurrent nasal polyposis. It is diagnosed when the triad of nasal polyposis, acetyl salicylic acid/nonsteroidal anti-inflammatory drugs (ASA/NSAID) hypersensitivity and asthma are identified. AERD generally is identified in those with the most severe inflammation and is associated with higher morbidity. There have been several important advances in the management of asthma and nasal polyps which have the potential to change the treatment paradigm in the management of AERD.

Importance of AERD

AERD, while often thought of as a rare syndrome, is actually present in 15% of severe asthmatics, and 7%–8% of all asthmatics and patients with chronic rhinosinusitis.[1] Although this represents a fraction of the total population of these diseases, it is well known that AERD patients

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exhibit numerous factors associated with poor outcomes. Severe asthma is heavily enriched with AERD patients.[2] These patients are much more likely to have intubation, persistent airflow obstruction and need for systemic corticosteroids. In AERD, the sinus burden of illness is evident by much higher need for sinus surgery, much earlier polyp recurrence at 6 months, worsened sense of smell scores. The Lund—Mackay (LM) computed tomography scoring system is used to grade the intensity of sinus inflammation. Higher LM scores are strongly associated with positive aspirin challenges.[3] The burden of illness in AERD is significant. AERD subjects simultaneously experience both the asthma and sinusitis components of the disease, often with additive effects from both of these which lead to a heightened burden of illness.

Treatment options in AERD

Topical therapy

A mainstay of therapy in both asthma and nasal polyps is topical corticosteroid treatment. Multiple inhaler regimens are useful for control of the lower airways inflammation and are an early step in treatment of all patients. Unfortunately, topical therapy for nasal polyposis is less successful, particularly in AERD. Although topical mometasone is approved for nasal polyposis at 2 sprays each nostril, twice daily, it is frequently ineffective in bringing control to the upper airway disease. This is likely in part related to anatomy and limited accessibility of higher levels of inflammation unreached by typical nasal delivery sprays. This led to the use of topical budesonide in combination with nasal lavage or nebulization. This has been recommended in many different applications and has been useful in several case series, including in AERD patients, to better control nasal polyp growth.[4—6] These treatments are off-label and can sometimes be inaccessible for that reason to patients. Most recently, fluticasone in a unique delivery mechanism marketed as Chance in the United States has been approved for nasal polyps. Compared to fluticasone nasal spray, Chance provides both higher dose of fluticasone and its delivery mechanism allows for higher delivery of topical corticosteroid into areas directly impacted by nasal polyps. This involves an "exhalation delivery" system where the patient blows into the device through a mouthpiece and with the device placed to seal the nostril this closes the soft palate resulting in the greater deposition to the polyps. Although this treatment has proven effectiveness in nasal polyposis it has not been studies in AERD nor were there any specific AERD sub analyses in the published studies.

Anti-mediator therapy

AERD is strongly associated with production of cysteinyl leukotrienes which are increased at baseline when compared with aspirin tolerant asthmatics or nasal polyp sufferers. These levels increase dramatically during ASA/NSAID provoked reactions.[7] Numerous studies implicate the important role that leukotrienes have in disease pathogenesis. Despite this, there are limited data on the specific effectiveness in the long-term treatment of AERD. There are two categories of leukotriene modifiers. First are the CysLT1 receptor antagonists montelukast and zafirlukast. These block signaling through the CysLT1 receptor but do not effect signaling through CysLT2 or GPR99 (CysLT3). Montelukast and zafirlukast have a clear role in protection of the lower airway during aspirin desensitization.[8,9] The long-term benefit in asthma or nasal polyps is less clear. Although routinely added to the regimen of AERD patients, this strategy merits further study in terms of polyp recurrence rates, sinus outcomes and asthma control specifically in AERD.

The other category of leukotriene modifier drugs is 5-lipoxygenase inhibitors. Zileuton, a partial inhibitor of 5-lipoxygenase blocks the downstream formation of all leukotrienes (including LTB4) and other pro-inflammatory 5-lipoxygenase pathway products. It is the only drug in this class. Zileuton decreases levels of leukotriene C4, D4 and importantly E4 which signals through GPR99/CysLT3. Zileuton has been studied in AERD specifically and has a positive effect on asthma, sinus outcomes as well as preventing or diminishing aspirin-induced reactions.[10—12] In the United States, until recently, zileuton has been difficult to obtain due to cost and insurance issues. It is now more accessible for patients and may be a viable treatment option for some patients.

Aspirin therapy

Aspirin therapy after desensitization (ATAD) was discovered inadvertently at Scripps Clinic in the late 1970's during studies of subjects undergoing aspirin challenges.[13] It was unanticipated that daily aspirin therapy after undergoing desensitization would have the potential to have a disease modifying effect. Yet, in the last 4 decades, studies have consistently confirmed many clinical and immunologic effects of this therapy. Clinically, aspirin therapy has primary effectiveness on the upper airway, where it has shown benefit on symptom control including SNOT-22(Sino-nasal Outcome Test-22) scores and sense of smell. ATAD has the potential to significantly decrease the trajectory of polyp growth and in some situations prevent need for further surgery. Patients on aspirin therapy have needed less systemic corticosteroids and may have improvement in asthma outcomes — an effect that might be secondary to improvement in upper airway inflammation. The benefit of ASA has been primarily associated with higher doses than necessary for anti-platelet effect, with most studies identifying 325 mg twice daily up to 650 mg twice daily as necessary for optimal/maximum therapeutic effect. Other studies have shown improvement on lower doses. The mechanism explaining the improvement on aspirin therapy remains elusive and somewhat speculative. Aspirin treatment in AERD patients does reduce the production of terminal cysteinyl leukotrienes. Yet, they continue to be produced at elevated levels while on aspirin therapy. Downregulation of the CysLT1 receptor occurs which would lead to blunted responsiveness to these leukotrienes.[14] CysLT1 receptor expression is under control of STAT6/IL-4 which several studies suggest might be blunted during aspirin therapy.[15,16] Recent work demonstrates that although mast cell

activation appears to be increased during chronic aspirin therapy, clinical benefit is still present.[17] This argues for another dominant pathway blunting mediator production and inflammation. The mast cell specific prostaglandin D2 has been recently identified as a dominant mediator in a subtype of AERD characterized by excessive gastrointestinal reactivity and cutaneous symptoms. These subjects have a more resistant pharmacologic effect of COX-1 inhibition in PGD2 production in parallel with the difficulty attaining the desensitized state.[18] The finding that the PGD2/CRTH2 axis is markedly elevated in severe asthma,[19] and that PGD2 is significantly decreased after aspirin therapy in the face of obvious mast cell activation argues that this effect might be an important component of therapeutic effect of aspirin therapy after desensitization.[17]

Until recently, ATAD was considered expensive, logistically difficult and unsafe for many patients. It still is not offered to many patients either because of lack of awareness or lack of capabilities for performing aspirin desensitization.[20] Yet, it is clear over the last decade that this treatment is now becoming commonplace in many outpatient allergy clinics across the United States so that nearly every large city has several options for patients to be treated. ATAD is generally recommended for patients with disease that has not responded to conventional medical therapy who experience recurrent polyposis, recurrent need for systemic corticosteroids and diminished quality of life or who have a medical need for COX1 therapy.[21]

Approximately 85% of patients will experience some degree of benefit from ATAD. There are no diagnostic tests or predictive tools to identify responders or non-responders. Between 10% and 15% will be unable to remain on aspirin therapy due to gastrointestinal side effects or bleeding/bruising.[22] Once desensitized, subject must remain on a minimum of 325 mg aspirin once daily to maintain desensitization. However, in case a patient misses their treatment, they can resume dosing within 48 h. Beyond 48—96 h off of aspirin, most patients will gradually regain their sensitivity.[23]

Biologic therapy

Over the past 5 years, the approval of 4 new biologic therapies appropriate for patients with AERD with more in the pipeline, the landscape of therapeutic options for our patients has dramatically changed. Previously, omalizumab was approved for allergic asthma, and was often an option for AERD patients. Now with the approval of reslizumab, mepolizumab, benralizumab and dupilumab for severe type 2 asthma syndromes and dupilumab also approved for nasal polyposis, there are many more options to consider.

AERD is defined by a strong Type 2 inflammatory signal characterized by high levels of IL-4, Il-13, IL-5 cytokines leading to recruitment of eosinophils, lymphocytes, basophils and mast cells to the sinonasal and pulmonary mucosa.[24,25] The nasal polyps have high levels of eosinophils and often, peripheral eosinophilia is present in AERD predicting a good response to all of these new biologic therapies. Unfortunately, there are few studies specifically evaluating the AERD subgroup, and several of the registry trials did not specifically identify aspirin sensitivity as a historical characteristic that could be analyzed post hoc.

There are currently no head to head studies of the various biologics in the management of nasal polyposis or AERD specifically. The first biologic to market was omalizumab initially for atopic asthma and more recently for urticaria. It has shown benefit in a small case series of Japanese subjects with AERD where it not only led to improvement in some clinical symptoms, but also a dramatic decrease in mast cell mediators strongly associated with AERD.[26] Lang and colleagues demonstrated that omalizumab can block the clinical symptoms during aspirin challenge, although this effect was not consistently seen in a large case series including omalizumab treated patients.[27,28] Bachert has published a trial of omalizumab in CRSwNP and asthma and showed a reduction in total nasal endoscopic polyp score was seen by week 8 on therapy.[29] Recent data on the effectiveness of omalizumab for nasal polyposis increase optimism for use of omalizumab in the AERD population specifically.[30]

Mepolizumb (anti-IL-5 monoclonal antibody) has been studied in a small case series of AERD patients where benefit was seen with the intravenous dosing of 750 mg every 4 weeks. It too, was shown to improve the total polyp score.[31,32] Tuttle et al,[33] did a retrospective analysis of their patients who received mepolizumab and found that it was a useful adjunct to management of AERD. There are ongoing trials for mepolizumab in CRS with nasal polyps.

Dupilumab is an IL-4 alpha receptor antagonist that blocks both IL-4 and IL-13 signaling. This is the first biologic approved to treat nasal polyposis.[34] The nasal polyposis studies included aspirin reactivity as a specific subgroup. This group was evaluated in a post hoc analysis where the benefit of dupilumab was similar in the self-described AERD cohort when compared with the aspirin tolerant group; including a significant reduction in the total polyp score, SNOT-22 score, and improvement in the sense of smell.[35]

Additional studies looking at individual biologics in chronic rhinosinusitis with polyposis will be forthcoming which may help with the decision as to which biologic to choose for our patients.

Cost considerations: Health economics are a critical component of medical decision making. New therapies are often expensive and can be inaccessible to patients for that reason. Prior authorization, peer-to-peer discussions, dealing with insurance denials, and utilization in managed care settings all create unique challenges for a busy practice. Topical nasal corticosteroid sprays are inexpensive and in many cases available over the counter without insurance approval. This makes them a first line therapy in all situations.

Budesonide respules are generic and often can be inexpensive, but when added to nasal rinses are considered off-label and are thus sometimes not covered for use in nasal polyposis. The cost of 1 year of therapy is about $400 - $3500 depending on regional and coverage variability.

Chance™ has the clinical indication for nasal polyps. The manufacturer cooperates with commercial insurance plans to significantly decrease the out of pocket costs to patients but may not be a covered option for Medicare or other payors. The cost of a year of Chance™ is approximately $6300.

Aspirin is obviously inexpensive ($0.05 for the most expensive aspirin products) and easily accessible. The one-time cost of desensitization to allow introduction of aspirin is generally $2000-$3000. Aspirin desensitization and ongoing therapy with aspirin is inexpensive with a calculated saving of $6768 per quality-adjusted life year in 2008.[36]

Biologic therapies are much more expensive, making approval and use a bigger hurdle. The absolute cost of therapy is in the $30,000-$40,000/year with costs to payors and patients alike likely to be highly variable around the country.

Control

What constitutes CONTROL of AERD? Control of asthma has been studied extensively.[37,38] Absence of hospitalizations and emergency visits, limited need for systemic corticosteroids, minimal symptoms and satisfactory quality of life are all markers of a controlled asthmatic. It is less clear what constitutes control of nasal polyposis. What degree of anosmia is acceptable, how many sinus infection episodes per year, what degree of polyp growth or need for future surgery is acceptable? These questions come up during every office visit with an AERD patient and the answers currently rest in the shared medical decision making between the clinician and patient to determine whether the patient feels that their disease has become controlled with the current therapy. It is the failure of control that likely guides the decision to escalate therapy, consider revision sinus surgery or add systemic corticosteroids.

Timing of treatment approaches

The authors follow a large cohort of AERD patients and review the various logistical questions and dilemmas that emerge over the course of treatment and longitudinal follow-up. Most patients with AERD benefit from the use of leukotriene modifying drugs as well as topical steroids. All patient should be offered topical corticosteroids in the most effective formulation (Chance, topical budesonide rinses, topical nasal corticosteroid sprays) and montelukast or zafirlukast.

Many patients will have already had one, if not several sinus surgeries by the time AERD is formally diagnosed.[39] Given the high likelihood of polyp recurrence in AERD, it is important that the allergist and sinus surgeon collaborate on the timing and appropriate treatment approach in all patients. The benefits of sinus surgery are the debulking of inflammatory polyp tissue and opening of natural drainage pathways allowing for deposition of topical therapy.[40]

The initial management of AERD is based on standard of care for the management of asthma and chronic rhinosinusitis with nasal polyposis. Unique to AERD, in all patients, specific counselling regarding avoidance of COX-1 inhibiting NSAIDs needs to be done. Celecoxib is a safe alternative for as needed therapy that should also be discussed with all patients in need of occasional pain relief. The use of leukotriene-modifying agents (montelukast or zafirlukast) should be utilized early in the course of the illness given the unique pathophysiology of AERD with overproduction of cysteinyl-leukotrienes.[41] The use of LTMDs may also provide added protection from severe respiratory reactions with accidental NSAID exposure.[8] Between 33% and 66% of patients with AERD are atopic and it is critical that their environmental allergies be addressed as well.[39,42]

For those patients with AERD who continue have uncontrolled asthma, recalcitrant nasal polyps, recurrent purulent sinusitis, need for repeated courses of systemic corticosteroids and or repeat sinus surgeries a step up in therapy is needed. Before consideration for ASA desensitization or starting a biologic, it would be worthwhile to do a trial of zileuton (5-lipo-oxygenase inhibitor) alone or in combination with their current LTMD. A survey study of patients with AERD found the addition of zileuton to be very effective, however it is only rarely prescribed.[43] In a clinical trial that included patients with AERD, addition of zileuton improved pulmonary function as well as decreased nasal symptoms of congestion, and impaired sense of smell in the AERD patients.[10]

Currently there are very limited data on biologics in AERD patients let alone a head to head trial with aspirin desensitization and treatment. The decision to pursue aspirin desensitization versus a biologic therapy should be based on multiple factors including whether or not there are any absolute contraindications to use of ASA: peptic ulcer disease, history of bleeding disorders, planned pregnancies etc. If ASA desensitization is not a preferred option, pursuing the use of a biologic therapy makes sense. Currently only dupilumab has an indication for nasal polyps. However, based on the underlying diagnosis of asthma, the other biologics can be considered.

Timing of surgery

In a surgically treated patient, if disease control is inadequate the decision to escalate medical management is made. If aspirin therapy is considered this has logistical considerations as many surgeons are reluctant to perform sinus surgery in a patient taking ongoing aspirin. Thus, performing aspirin desensitization about 4—6 weeks after sinus surgery is generally recommended. Additionally, available data supports the role of aspirin therapy in preventing polyp progression rather than causing polyp regression.[22] Beginning aspirin therapy in a patient with advanced polyps is far less likely to be successful and if the patient ultimately requires sinus surgery, aspirin may need to be discontinued and desensitization occur again after surgery.

If a patient with AERD is desensitized to ASA prior to surgery, the dose can be decreased aspirin to 325 mg daily. ASA can then be withheld for a 48-h window around surgery and restarted without the need for repeat desensitization in that setting. Alternatively, ibuprofen which has a less potent anti-platelet effect, could be substituted for aspirin the week prior to and during surgery. This has been reported in a case series, but has not been formally studied for perioperative safety from a bleeding perspective.[44]

Ideally, aspirin should be started after sinus surgery in most situations. But the use of leukotriene modifiers and biologic therapies can be started at all time points in the continuum. In the dupilumab studies, approximately 1/3 of

patients had not undergone sinus surgery. The average reduction in polyp score was approximately 37%. Although, symptoms improved and polyp scores were reduced, it is unclear whether beginning a biologic in conjunction with surgery would have a better clinical effect.

Common clinical scenarios

Although patients present with a unique combination of variables, three common situations emerge that are reviewed below with a discussion of specific timing and treatment considerations.

Newly diagnosed patent

This patient is identified early in the course of their illness. They likely have had an evaluation for allergic rhinitis and asthma, but the full extent of their AERD has only recently been recognized. These patients should undergo imaging to gauge the extent of their disease and collaboration with a sinus surgeon should begin. Comorbid asthma should be controlled within the standard treatment guidelines, keeping in mind that lower airway control will be influenced by the upper airway disease. Aggressive nasal corticosteroid treatments should be employed with consideration for initial surgical debulking and opening of natural sinus ostia to enhance topical therapy. Early in the course of the disease, the surgeon/allergist collaboration will be able to closely follow the patient and decide when step-up therapy to zileuton, ATAD, or biologics should be considered.

The chronic surgical failure

This patient has a long history of persistent and severe chronic sinusitis with nasal polyposis. This patient has had multiple sinus surgeries, with only short-lived symptomatic improvement and early polyp recurrence. When this patient presents, it is unlikely the further surgical treatment will provide durable benefit, therefore immediate escalation in medical management needs to be considered. At this level, zileuton needs to be strongly considered. A discussion regarding the risks and benefits of ATAD or a biologic should be undertaken. Patient preference might guide treatment escalation. If the patient needs aspirin for cardiovascular disease prophylaxis or treatment with NSAID's for other indications such as pain from various etiologies, that may guide one's choice. Additionally, the need for upcoming sinus surgery will be an additional factor that should be considered in patients who are interested or good candidates for ATAD. If ATAD is planned, any sinus surgery should occur first followed 4—6 weeks later by initiation of aspirin.

Early polyp recurrence

This patient will have undergone an initial surgery and might be early in the course of their illness. They have been identified with early polyp recurrence or rapid symptom progression. At this stage, AERD might not be recognized and the purpose of the visit to the allergist might be for assessment of underlying atopic disease, immunodeficiency and AERD. Once AERD is recognized in this setting, this is an optimal time to employ ATAD. Current evidence suggests that aspirin therapy might have the best effect in patients with recent surgical debulking as prevention of polyp growth and symptoms control are the primary goals. These patients should be followed closely for the clinical benefit of aspirin, and also any progression of sinus disease. In the event of failure of other medical therapy, this is an ideal candidate for a trial of a biologic therapy.

Every patient with AERD is unique and their preferences dictate the treatment paradigm. Some patients have had sinus surgery and never want surgery again. Other patients want to do everything possible to regain sense of smell, and others are most interested in decreasing systemic corticosteroid burden. Much work is necessary to define control in sinus disease and specifically in AERD. The treatment approach, timing, and medical necessity/cost effectiveness of each of the treatments above require a detailed discussion with patients and shared medical decision making. Much work is necessary to define the role for aspirin therapy vs biologic in AERD as well as better biomarkers to predict responsiveness to these therapies. For example, might dupilumab or some future biologic allow an AERD patient to take any dose of aspirin or NSAID's without reaction? Even if not, might they prevent reactions to the escalating doses of aspirin used in desensitization? That would be the discovery of the "Holy grail" of aspirin desensitization: "silent" desensitization. This approach would drastically reduce the cost of the biologic.

In any case, at this point in time, it is encouraging that we now have numerous treatment options at our disposal in managing patients with AERD and recalcitrant disease and with more type 2 treatment options on the horizon, the landscape is now brighter for patients with AERD.

Declaration of Competing Interest

Ronald Simon, MD — none. Katharine Woessner, MD: Speakers Bureau — Glaxo SmithKline, Astra-Zeneca. Advisory Board — Regeneron. Andrew White, MD: Speakers Bureau — Astra-Zeneca, Regeneron, Optinose. Advisory Board — Optinose, Regeneron, Astra-Zeneca.

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