Immunomodulatory treatments for aspirin exacerbated respiratory disease

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ABSTRACT

Background: Aspirin triad is a subclass of chronic sinusitis characterized by nasal polyposis, nonallergic induced asthma, and aspirin sensitivity. Also known as Samter's triad or aspirin-exacerbated respiratory disease, aspirin triad commonly affects the adult population and is seldom found in pediatric patients.

Methods: This rhinosinusitis has multiple layers of pathological process, but the ultimate predicament is caused by cysteinyl leukotrienes (cysLTs).

Results: Pharmacotherapies include oral steroid, lipoxygenase inhibitor, and cysLT receptor inhibitor drugs, which can provide some relief for these patients.

Conclusion: Immunomodulation via aspirin desensitization is considered when pharmacotherapy has failed. When aspirin triad is unmanageable with medical treatment alone, endoscopic sinus surgery with polypectomy can alleviate the patient's symptoms, allowing for a better response to postoperative medical management such as topical medication as well as delivery of topical medications.

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Aspirin-induced asthmatic dyspnea was first recognized in 1911 by Gilbert.¹ This anomaly was later described by Widal² as a triad of symptoms: nasal polyposis, nonallergic induced asthma, and aspirin sensitivity. In 1968, the triad was popularized by Samter and Beers,³ prompting the use of "Samter's triad." Aspirin-sensitivity triad or aspirin triad is also known as aspirin-intolerant asthma, aspirin-sensitive asthma (ASA-sensitive), Widal triad, Francis triad, Fernand-Widal triad, or aspirin-exacerbated respiratory disease (AERD).

NATURAL HISTORY

Clinical symptoms of aspirin-sensitive patients usually present in the third decade of life and are characterized by mucosal inflammation and rhinitis, severe asthma precipitated by aspirin ingestion, and aggressive nasal polyposis.⁴ Two large-scale studies, by Szczeklik *et al.* with 500 subjects and Berges-Gimeno *et al.* with 300 subjects, have reported the average age of onset as 30 and 34 years, respectively.^{5,6} Rhinitis is typically the first symptom to appear. The rhinitis is persistent, difficult to manage, and the rhinorrhea is thin and nonpurulent, characteristic of nonallergic rhinitis with eosinophilia syndrome. Asthma usually appears an average of 2 years after initial symptoms of rhinitis. Intolerance to aspirin follows, with co-occurrence of nasal polyps.⁵ These symptoms appear to occur in a typical pattern, but not all patients may present with or be able to account for a similar timeline.

The asthma experienced by patients with AERD is severe and can require emergent care. In a study of 145 adult patients with asthma requiring emergency ventilation, 24% were found to be aspirin sensitive.⁷

Nasal polyposis in AERD is typically aggressive in recurrence, involving bilateral paranasal sinuses. The presence of polyps has been reported in 60–70% of these patients, compared with ~4% in the general population.^{5,6} Multiple endoscopic surgeries are often necessary to manage the aggressive polyposis. The recovery of a normal sense of smell after medical and surgical treatment appears to be less likely in AERD patients compared with patients with allergic rhinitis.⁸

Recurrence of nasal polyps after medical or surgical treatment is typical in AERD patients and has been reported to be nearly three times higher than in aspirin-tolerant asthmatic patients.⁹

DIAGNOSIS

No *in vitro* diagnostic test is available to date, but the possibility has been investigated.¹⁰ Currently, diagnosis is based on a history indicative of aspirin sensitivity, which includes at least two episodes of nonsteroidal anti-inflammatory drug (NSAID) ingestion and subsequent respiratory reactions. An acute asthma attack can occur within a few minutes and up to 3 hours after ingestion.⁴

Aspirin challenge can be used to confirm a diagnosis of aspirin sensitivity in AERD. Four types of ASA challenge have been performed: oral, inhalant, nasal, and i.v.⁴ Patients with predominant nasal symptoms are recommended for a nasal challenge test. When negative nasal challenge tests occur, a strong suspicion of AERD may warrant additional bronchial or oral challenge tests.¹¹ Lysine aspirin (L-ASA), a soluble form of ASA, is used in bronchial, intranasal, and i.v. challenges. Unfortunately, L-ASA is unavailable in the United States, leaving oral administration as the only challenge option.

Oral aspirin challenge is not recommended for patients with unstable asthma. The technique for oral aspirin challenge is similar to oral aspirin desensitization. The notable difference is that patients would not be required to repeat provoking doses in order to tolerate a higher dose for maintenance purposes. Once the patient exhibits a positive reaction, the challenge protocol is discontinued and the patient has a confirmed sensitivity to aspirin.

For lack of another aqueous form of aspirin, other methods of confirming a diagnosis of aspirin sensitivity have been investigated. Ketorolac tromethamine, an NSAID available for use in the United States, is approved for treating moderate to severe pain in various formulations and for use as an ophthalmologic topical anti-inflammatory agent. In 2006 a study investigated whether ketorolac nasal challenge is an acceptable method for diagnosing AERD.¹² A positive reaction was defined as having nasal symptoms, tearing (epiphora), or red eyes (ocular hyperemia). A decrease in peak nasal inspiratory flow of >20% from baseline was not considered a positive reaction to the challenge unless accompanied by nasal or ocular signs and symptoms. Ketorolac nasal challenge was 78% sensitive and 64% specific. Therefore, intranasal ketorolac may be an alternative when the oral aspirin challenge is contraindicated.

PREVALENCE

The prevalence of aspirin sensitivity in the general population has been reported to be 0.6–2.5%, with a higher incidence in adult asth-

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matic patients, ranging from 4.3 to 11%.^{9,13} In a 1999 Finnish survey of 3102 subjects, the prevalence of aspirin intolerance was 5.7%, with only 1.2% experiencing aspirin-induced asthma.¹⁴ AERD is generally uncommon in the pediatric population. A history of pediatric asthma, eczema, or allergic rhinitis in AERD is also uncommon. Rather, adult-onset asthma is more characteristic of AERD.

Female predominance in AERD has been documented, as well as a more severe form of the disease in women. Szczeklik *et al.* collected data on 500 European subjects, reporting a female/male ratio of 2.3:1.⁵ Another study conducted in the United States reported that of 300 subjects, 57% were women and 43% were men.⁶ No difference in disease severity between genders was found, but the authors acknowledged that the greater willingness of women to visit their doctors may contribute to the higher predominance of women with the disease.⁶

PATHOGENESIS

The mechanism for aspirin intolerance has been partially elucidated. It is accepted that abnormal metabolism of arachidonic acid in the lipoxygenase (LO) and cyclooxygenase (COX) pathways lead to an imbalance of pro- and anti-inflammatory mediators. Aspirin and other nonspecific NSAIDs block COX prostanoid production, shunting arachidonic acid to the alternative LO metabolic pathway.¹³ This leads to a decrease in anti-inflammatory prostaglandins and overproduction of leukotrienes. Cysteinyl leukotrienes (cysLTs) promote mucus secretion, increase vascular permeability, and are potent bronchoconstrictors. Excessive production of cysLTs has been reported in AERD patients at baseline and during aspirin challenge.¹⁵

Several possible pathomechanisms have been proposed. The basic COX theory describes NSAIDs inhibiting the COX-1 enzyme, which is present in most cells in the body.¹⁶ Prostaglandin E₂ (PGE₂), an anti-inflammatory prostanoid synthesized by the COX pathway, represses the production of cysLTs by braking the 5-LO pathway and suppresses mast cell activation. Inhalation of PGE₂ before aspirin challenge has been shown to attenuate bronchial reactions, providing for its bronchoprotective effects.¹⁷ AERD patients reveal a PGE₂ deficiency when compared with aspirin-tolerant and healthy control subjects.¹⁸ NSAIDs block COX-1 activity, further decreasing the synthesis of PGE₂, releasing the production of cysLTs from its inhibitory effect.

The 5-LO pathway is up-regulated in patients with AERD, increasing the production of cysLTs.¹¹ Synthesis of leukotriene C₄ (LTC₄) is accomplished by LTC₄ synthase (LTC₄S), an enzyme that may be overexpressed in patients with AERD.¹⁹ LTE₄ is a major metabolite of LTC₄. Urinary LTE₄ (uLTE₄) levels can be useful in monitoring endogenous synthesis of cysLTs. Higashi *et al.* examined uLTE₄ levels, finding that basal levels of uLTE₄ are higher in AERD patients than aspirin-tolerant asthmatic patients (227.2 versus 90.3 pg/mg of creatinine; *p* < 0.01).²⁰ Interestingly, uLTE₄ levels were more elevated in aspirin-tolerant patients with nasal polyposis than those with normal sinuses, indicating that overproduction of cysLTs is not exclusive to AERD but is associated with asthma and nasal polyposis in general. However, aspirin-sensitive patients hyperexcrete uLTE₄. Overexpression of the cysLT receptor 1 (cysLTR1) in nasal inflammatory leukocytes has been observed, as well as a down-regulation of receptor expression after desensitization.¹⁶ IL-4 and cysLTs are interlinked because IL-4 stimulates expression of LTC₄S and up-regulates cysLTR1 expression. Other proposed pathomechanisms include a relationship between IL-10 and transforming growth factor B1²¹ and reduced lipoxin biosynthesis by 5-LO, 12-LO, and 15-LO enzymes.²²

Symptoms of AERD can present and continue in the absence of exposure to ASA. Although avoidance of ASA or other NSAIDs may help prevent the most severe episodes of symptoms, it will not prevent disease. Because avoidance of NSAIDs can be difficult, patients must be diligent to prevent severe symptoms from occurring. Educating patients on avoidance of COX-1 inhibitors is critical. Many

Table 1 Management algorithm	
1. Baseline LFT	
2. Oral or topical steroids/zileuton	
If patient fails initial medical management, continue with	
3. ESS to debulk polyps	
4. Zileuton + nasal steroid	
If symptoms persist, continue with	
5. Zileuton + steroid irrigation, or	
6. Zileuton/Singulair + steroid irrigation	
If patient fails medical and surgical management, consider	
7. Aspirin desensitization	
LFT = liver function test; ESS = endoscopic sinus surgery.	

over-the-counter drugs contain NSAIDs, such as Alka Seltzer Plus Flu that contains 500 mg of ASA.

It is essential that clinicians are aware of the potential for cross-reactivity between aspirin and other NSAIDs, paracetamol, and COX-II inhibitors. Other NSAIDs that preferentially inhibit COX-I, when taken at therapeutic doses, are considered to have 100% cross-reactivity.¹¹ Paracetamol (acetaminophen) is a poor inhibitor of COX-I, but at high doses it can induce respiratory reactions in aspirin triad patients. These asthma attacks occur at doses of paracetamol higher than 1000 mg, especially in patients sensitive to low-provoking doses of aspirin.¹³ Aspirin triad patients rarely experience respiratory reactions induced by specific COX-II inhibitors. However, case reports have indicated the rare possibility of aspirin triad patients having a severe reaction to COX-II inhibitors.^{23,24} Although the potential for reacting to specific COX-II inhibitors is small, it is recommended that the first full dose of COX-II inhibitors be given in the physician's office.²⁵

IMMUNOMODULATORY TREATMENTS

Several immunomodulatory treatments are of interest when treating patients with AERD (Table 1). After endoscopic sinus surgery, an initial trial of leukotriene modify drugs (LTMDs) with topical steroids may hinder symptom recurrence for some time. If LTMDs with nasal steroids are not sufficient to control symptoms, addition of a topical steroid irrigation is suggested. Patients that do not respond to pharmacotherapy should be considered for aspirin desensitization. The goal of these immunomodulatory treatments is long-term control of upper and lower airway inflammation.

LEUKOTRIENE-MODIFYING DRUGS

Leukotriene modifiers, introduced in the 1990s, provide a therapeutic option for management of chronic and persistent asthma. There are currently two mechanisms by which LTMDs control the inflammatory effects of cysLTs: antagonism of the cysLTR and inhibition of the 5-LO enzyme. Two cysLTRs have been identified, cysLTR1 and cysLTR2. CysLTR1, which recognizes LTC₄, LTD₄, and LTE₄, is most relevant to AERD because it is found on inflammatory cells, in the lung, and in airway smooth muscle.²⁶ Medications such as montelukast and zafirlukast work by binding to the cysLTR1, blocking cysLTs from inducing downstream effects. The second mecha-

nism, inhibition of the 5-LO enzyme, prevents production of cysLTs higher upstream, and zileuton is the only approved 5-LO inhibitor available in the United States.²⁷ LTMDs have been indicated in the treatment of the underlying disease in AERD and it has been noted that these patients are more likely to benefit from LO inhibitors than cysLTR antagonists because they impact cysLTs higher upstream.²⁷

CysLTR1 Antagonists

Drugs ending in -lukast, such as montelukast and zafirlukast, are cysLTR1 antagonists. In a single-blinded, placebo-controlled, randomized crossover study, montelukast was shown to improve symptoms, rhinoscopic findings, and bronchial and nasal airflow of AERD patients.²⁸ The improvement of nasal symptoms, including nasal blockage, rhinorrhea, and sense of smell, started in the first 2 weeks of montelukast treatment. Edema, hypersecretion, and blockage assessed by rhinoscopy were significantly reduced at 6 weeks of treatment. Nasal lavage showed a decrease in cysLTs after treatment, as well as eosinophil cationic protein, albumin, substance P, and neurokinin A. Montelukast may also exhibit secondary anti-inflammatory mechanisms independent of cysLTR1 antagonism. It has been reported that montelukast inhibits the 5-LO enzyme and inhibits eosinophil adhesion and migration. The concentrations required for 5-LO inhibition are higher ($\geq 1 \mu\text{M}$) than those to block cysLTR1.²⁹

5-LO Inhibitor

Inhibition of the 5-LO enzyme is thought to intervene in the biosynthesis of cysLTs. Zileuton became available commercially in the United States in 1996 and is indicated for the prophylaxis and chronic treatment of asthma. Dahlén *et al.* investigated the effects of zileuton treatment (600 mg four times daily) in AERD patients.³⁰ Acute and chronic improvement in pulmonary function, increased sense of smell, decreased rhinorrhea, and higher nasal inspiratory flow were reported effects and were evident within 6 weeks of treatment. A randomized study by Fischer *et al.* showed that the zileuton group had a blunted cysLT response to aspirin challenge.³¹ In another study, zileuton was shown to decrease uLTE₄ excretion, block the fall in forced expiratory volume at 1 second (FEV₁), and prevent nasal, gastrointestinal (GI), and dermal symptoms.³² Recently, the possibility has been suggested that the anti-inflammatory effect of zileuton might occur through mechanisms other than just inhibiting the 5-LO enzyme. Zileuton may suppress prostanoid synthesis by interfering with the release of arachidonic acid from macrophages.³³

Treatment with zileuton requires careful monitoring of liver enzymes to assess liver toxicity.²⁷ A 12-month follow-up study assessed the liver safety profile of the drug and aimed to determine an appropriate liver biochemistry monitoring schedule for patients receiving treatment.³⁴ Injury to the hepatocytes secondary to zileuton is best measured by elevated levels of alanine aminotransferase (ALT). A total of 2458 patients taking zileuton (600 mg four times daily) had liver biochemistry checked monthly for the first 5 months of the study, and then at months 7, 10, and 12. These values were compared with the control group of 489 patients, who were treated with usual asthma care only. Of the patients receiving zileuton, 4.4% had elevated ALT levels of $\geq 3 \times$ upper limit normal (ULN), compared with five patients (1%) in the control group. Importantly, 52.5% of the patients with moderately high ALT levels (≥ 3 and $< 5 \times$ ULN) experienced spontaneous resolution of ALT levels while continuing zileuton treatment, with a mean time to resolution between 3 and 4 weeks. In patients in whom it did not resolve spontaneously, treatment was discontinued. After discontinuation, these patients were followed until resolution, with ALT levels resolving in an average of 1 month. Similar results were found in a study assessing liver toxicity in zileuton CR (1200 mg twice daily).³⁵

Of the patients in the zileuton group with elevated ALT levels, 64.2% had significant elevations within the first 3 months of treatment, and 81.7% within the first 6 months. According to this data, the

probability of ALT levels $\geq 3 \times$ ULN occurring is highest at 2.06% in the 1st month and drops to 0.35% at 3 months. There was no apparent relationship between the time of onset and magnitude of ALT elevation. This study suggests that patients treated with zileuton should be monitored monthly for the first 3 months, every few months for the remainder of the 1st year, and then periodically thereafter after a normal baseline liver function test.³⁴

CORTICOSTEROIDS

Corticosteroid therapy is common in patients with AERD. Use of systemic steroids has been reported in 51–77% of AERD patients, with chronic daily use in $\sim 22\%$.^{5,6} Widespread use of intranasal and oral corticosteroids is acknowledged in the literature. Surprisingly though, few randomized, placebo-controlled trials have been published.

Intranasal steroids can help reduce inflammation and delay recurrent polyp formation in some patients and have very few adverse side effects.¹¹ Intranasal fluticasone propionate has been shown to improve clinical rhinitis and asthma symptoms in patients with aspirin sensitivity.³⁶ The addition of budesonide inhalant suspension to nasal saline irrigations has also been shown to produce significant improvements in the sense of smell as well as objective findings on CT and nasal endoscopy, but requires further investigation in patients with AERD.³⁷

Systemic corticosteroids are used to provide rapid relief of symptoms. Use of this therapy has been shown to shrink hyperplastic tissue and restore the sense of smell in patients with nasal polyps.³⁸ A placebo-controlled study by Nizankowska *et al.* reported that 75 mg of prednisone daily for 2 days before aspirin challenge did not provide protection against adverse reaction; however, a 10-day pretreatment protocol protected against or decreased severity of bronchospasm.³⁹ The authors caution that clinicians attempting to establish aspirin sensitivity *via* challenge tests should be aware of the possibility of false negative results related to corticosteroid treatment.

Treatment with systemic corticosteroids is limited because of the undesired effects of long-term use. It has been reported that in patients with AERD, the most common side effects of systemic corticosteroids include obesity, osteoporosis, arterial hypertension, and adrenal suppression.^{5,40}

Although i.v. corticosteroids are not a first line of treatment, AERD patients do receive steroids *via* this route. Szczeklik *et al.* reported that 24% of 500 subjects had received i.v. corticosteroids within the 12 months preceding the study.⁵ Hydrocortisone therapy should be used with caution in AERD patients. Idiosyncratic reaction to hydrocortisone has been reported in patients with AERD, and hydrocortisone therapy results in a significant drop in FEV₁, naso-ocular reactions, and even bronchoconstriction. It has been recommended that steroids other than hydrocortisone be used in AERD patients.⁴¹

ASPIRIN DESENSITIZATION

The finding that AERD patients may undergo desensitization was first described by Zeiss and Lockey in 1976 when aspirin-intolerant patients yielded a 3-day refractory period after oral aspirin challenge.⁴² Based on this novel finding, various methods of desensitization have been established. A range of reactions to aspirin challenge can occur in these patients, with upper and/or lower respiratory reactions including rhinitis, conjunctivitis, laryngospasm, bronchospasm, and anaphylaxis.⁴³ Although life-threatening reactions can occur with aspirin ingestion in these patients, no deaths have been reported by any of the physicians using the oral aspirin challenge and desensitization protocols described here.

The goals of desensitization are to control rhinitis and asthma symptoms, reduce corticosteroid use, reduce growth and recurrence rate of polyps over long-term reduced rate of necessity for surgery, and, ultimately, improve the quality of life for these patients. Desensitization and daily treatment with aspirin has been shown to signif-

Table 2 Adverse reaction management

Adverse Reaction	Treatment/Instructions
Naso-ocular reactions	Oral antihistamines
Urticaria or angioedema	Oral or intravenous antihistamines
Isolated bronchoconstriction	Albuterol inhaler or nebulizer; Inhale up to 5 breaths
Laryngospasm	Racemic and/or intramuscular epinephrine
Laryngeal edema with hypotension	Intramuscular epinephrine
Anaphylaxis	Follow practice parameters, dosing recommendations, and general adverse reaction management ¹⁶

icantly improve all of the aforementioned factors.^{43,44} Various desensitization techniques and routes of administration have been established, including bronchial, intranasal, oral, and i.v. Oral challenges remain the gold standard for challenge and desensitization of AERD patients.

L-ASA has been used in bronchial and intranasal desensitization outside of the United States. Bronchial (inhalation) administration of L-ASA has been reported to have similar specificity to oral challenge, but it is not as sensitive.⁴ Patriarca *et al.* treated 28 patients with intranasal L-ASA desensitization 1 month after polypectomy and followed them for 24 months.⁴⁵ These patients had a lower rate of polyp recurrence compared with control.

Oral administration was first described by Stevenson in 1980.⁴⁶ In this study, two patients showed improvement of asthma and reduced polyp size with desensitization therapy. In 1984, the first randomized, double-blind, placebo-controlled, crossover study of oral aspirin desensitization followed 25 patients over a period of 3 months.⁴⁷ Significant improvement of rhinitis symptoms and reduced need for nasal corticosteroid use was reported. Also, about one-half of the patients experienced an improvement in asthma symptoms.

The use of i.v. administration for aspirin desensitization has been established. In a study by Pfaar *et al.*, 36³⁶ patients were treated with ascending doses of L-ASA *via* i.v.⁴⁸ This method of administration may be a useful because it poses the advantage of interrupting positive reactions by terminating L-ASA infusion. Further investigation is necessary to assess the safety and comparability with oral aspirin.

The mechanism behind aspirin desensitization is not fully understood. Decreased activity of cysLTs acting through cysLTR1 and decreased downstream intracellular signaling has been proposed.⁴⁹ Reduced cys-LTR1 expression in nasal inflammatory cells and reduced LTB₄ synthesis in peripheral monocytes may also contribute.⁵⁰ Other theories include interrupted histamine and tryptase release from mast cells and the blocking of COX enzymes in mast cells, terminating the synthesis of PGD₂.⁵⁰ The suppression of IL-4 synthesis has been shown after desensitization as well as modulation of inflammatory cell transcription factors.⁵¹ This may be important because IL-4 up-regulates LTC₄S and cysLTR1 expression. Therefore, decreasing the amount of IL-4 would decrease the amount and effect of cysLTs.

Aspirin desensitization is indicated in AERD patients whose symptoms persist despite surgical and medical intervention as described previously. Additional indications include patients requiring daily or frequent use of systemic corticosteroids to control asthma and/or rhinosinusitis symptoms, patients with aggressive nasal polyp formation requiring multiple polypectomies, and patients with other diseases or indications requiring use of aspirin or other COX-1 inhibitors. It is recommended that patients with significant polyp sinus disease undergo surgical debulking 2–4 weeks before aspirin challenge and desensitization because aspirin treatment works best in preventing new polyp formation. Patients with unstable asthma may not be eligible, and patients with a baseline FEV₁ ≤ 60% of expected are not allowed to begin oral challenge. Additional contraindications include pregnancy, gastric ulcers, or bleeding disorders.

Oral aspirin desensitization is recommended to be performed at a facility that is able to provide the following support: advanced cardiac care, ventilator support, and undivided attention from qualified per-

sonnel. Safeguards should be in place in preparation for severe reactions, including i.v. access, adequate training of support staff, and medications to treat symptoms. The supervising physician should be present at the time of the first reaction and until symptoms cease. If the first reaction is managed without physician intervention, challenges may proceed.

Inpatient desensitization should be considered in patients with severe asthma, history of NSAID reaction requiring emergent care, β-blocker use, FEV₁ ≤ 70% when not using bronchodilators, recent myocardial infarction, and underlying condition that would make management of severe symptoms or anaphylaxis difficult. Outpatient desensitization is possible. Patients with stable, well-controlled asthma and FEV₁ > 70% within 1 week before challenge can be considered for outpatient desensitization. Additional conditions that could be beneficial for outpatient desensitization is an experienced physician and medically qualified personnel who are available to monitor the patient as well as the equipment that is available for continuous respiratory and cardiovascular monitoring, pulse oximetry, spirometry, and cardiopulmonary resuscitation. Antihistamines, decongestants, short-acting inhaled β-agonists, and anticholinergics should be discontinued 48 hours before desensitization. Antihistamines and decongestants can mask positive responses used to confirm aspirin sensitivity. β-Agonists and anticholinergics can lead to false positive reactions.¹¹

The standard aspirin desensitization protocol begins with administration of a low aspirin dose, typically between 20 and 40 mg. Increasing doses are administered every 3 hours. Patients are observed for naso-ocular and bronchial reactions, but the initial dose that induces respiratory reactions is termed the provoking dose. A lower respiratory tract reaction or bronchospasm is defined as FEV₁ decrease of >15% from baseline. The average time to reaction has been reported at 102 minutes, and the 3-hour intervals are recommended over 90-minute intervals based on this finding.²⁵

A variety of aspirin maintenance doses have been reported. Side effects, such as gastric irritation, have encouraged researchers to investigate the lowest-possible controlling maintenance dose. A dose as low as 81 mg/day has been reported to maintain aspirin desensitization; however, there is no improvement of clinical disease symptoms.^{52,53} Maintenance doses of 100 mg have been explored and some reports show promising results, but other studies show conflicting data. Rozsasi *et al.* followed patients receiving 100 and 300 mg aspirin maintenance doses for 1 year to compare the doses over the long term.⁵⁴ Recurrent nasal polyps occurred in all of the patients taking 100 mg, whereas no polyp recurrence occurred in the group taking 300 mg. The classic maintenance dose of 325–650 mg twice daily should be used until lower doses have been further investigated. Long-term maintenance doses of 325–650 mg daily have been successful, indicating that lowering the maintenance dose is an option over time.

Current maintenance therapy is at least 650 mg twice daily, and it is recommended that the patient maintains this dose for at least 1 month. After 1 successful month, the maintenance dose may be dropped to 325 mg twice daily; however, a more practical assessment of desensitization can be assessed if the patient is doing well for 6 months before decreasing the maintenance dose. If maintenance

doses are missed for >48 hours, repeating the desensitization procedure is strongly recommended.²⁵ Maintenance treatment should be at least 325 mg daily, although twice daily is ideal.²⁵

There are disadvantages to aspirin desensitization. It can be time-consuming and provoke severe bronchospasm or extrapulmonary reactions. Adverse treatment to aspirin desensitization is described in Table 2. Aspirin desensitization is not recommended for all patients. Sweet *et al.* remark that ASA challenge and desensitization is not safe in patients with fixed obstructive airway diseases or those who have baseline FEV₁ values of <1.5 L.⁵⁵

A small number of cases have been reported where patients with AERD are unable to maintain a desensitized state despite undergoing standard aspirin desensitization protocol.^{49,56,57} Long-term effects of desensitization usually have a positive impact on disease management and quality of life.⁵⁵ However, in a study of 172 AERD patients, 14% discontinued aspirin therapy because of the following side effects: epigastric pain, aspirin-induced urticaria, GI bleeding, and bleeding from the nose and ear.⁴³ Sweet *et al.* conducted a retrospective study of 107 aspirin-sensitive subjects in 1990.⁵⁵ Thirty-five ASA-desensitized patients (continuing group), 30 patients who discontinued treatment after 2 years (discontinued group), and 42 patients who simply avoided ASA (control) were followed for a mean time of 3.75 years. The continuing group took maintenance doses ranging from 325 to 2600 mg (650 mg four times daily). Both the continuing and discontinued groups revealed significant reduction in number of yearly hospitalizations, ED visits, upper respiratory tract infections and use of antibiotics, and sinus surgeries and had an improved sense of smell. In the discontinued group, the most common reason that patients stopped therapy was GI intolerance (40%), followed by omitted aspirin doses for >3 days and reluctance to continue therapy (13%). The authors comment that any patient can experience GI complications, but patients with a history of gastritis, ulcer, or gastroesophageal reflux disease may be more prone. A long-term follow-up study published in 1996 followed 65 patients on a daily maintenance dose of 1300 mg of aspirin (650 mg twice daily).⁴⁴ Not only did the patients in this study show decreased growth and recurrence of polyps over time, the number of sinus surgeries decreased from one surgery every 3 years to one surgery every 9 years. Another long-term study followed 172 patients, reporting decreased yearly episodes of purulent sinusitis.⁴³ Only 9% discontinued due to GI intolerance. This may be caused by the increased use of proton pump inhibitors.

KETOROLAC (TORADOL) DESENSITIZATION

A 2010 study by Lee *et al.* investigated whether intranasal ketorolac challenge might be useful in aspirin desensitization.⁵⁸ The experimental group of patients underwent a modified desensitization that included ketorolac and aspirin, and they were compared with a control group who underwent oral aspirin challenge only. Of the 100 subjects enrolled, 82 had a positive challenge result and met the diagnostic criteria for AERD. Of these 82 subjects, 49 (60%) reacted to ketorolac but not oral aspirin, 25 (30%) experienced positive reactions to both ketorolac and oral aspirin, and 8 (10%) reacted to oral aspirin only. All positive reactions were successfully treated in an outpatient clinic, with no reactions requiring transfer to an ED or hospitalization. The duration to complete desensitization using the modified intranasal ketorolac protocol was significantly less than the control oral aspirin challenge protocol (1.9 days versus 2.6 days; $p < 0.01$). The percentage of subjects who experienced severe bronchospasm (FEV₁ $\geq$ 15%) was not statistically significant from the control group. Nine patients were not eligible for the intranasal ketorolac and aspirin challenge because of nasal obstruction for polyp because a clear nasal passage is necessary in these patients to use intranasal ketorolac desensitization. The authors recommend scheduling desensitization ~1 month after sinus and polyp surgery to allow clear sinuses and better desensitization outcomes.

COX-INDEPENDENT METHODS OF DESENSITIZATION

It has been questioned whether drugs without as much COX antagonism could be used safely as treatment for patients with AERD. Katial *et al.* reported that a specific cytokine, IL-4, may be the target of aspirin desensitization because IL-4 levels were significantly decreased in AERD patients after 6 months of daily aspirin maintenance.⁵⁶ IL-4 up-regulates cysLTR1 expression, prolongs eosinophil survival, is a cofactor for mast cell growth, induces expression of LTC₄S, and promotes differentiation of naïve T cells into TH2 cells. White *et al.* suggested that sodium salicylate may be a potential candidate for treatment of AERD patients.⁵³ Sodium salicylate has minimal effects on COX-1 but has similar anti-inflammatory effects through IL-4. In theory, sodium salicylate would improve the inflammatory disease without provoking significant reactions.

CONCLUSION

Aspirin triad is a difficult disease that causes significant burden on the patient. However, there are several medical management strategies that can assist these patients. Often, endoscopic sinus surgery with polypectomy may be needed to allow these medical management to be effective. With a stepwise approach, this challenging disease can be successfully managed.

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