

Management of Respiratory Symptoms Induced by Non-Steroidal Anti-Inflammatory Drugs

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Opinion Statement

Non-steroidal anti-inflammatory drugs (NSAIDs)-exacerbated respiratory disease (NERD) is defined by the combination of chronic rhinosinusitis, nasal polyps, bronchial asthma, and hypersensitivity reactions involving upper and/or lower airways after the exposure to acetylsalicylic acid (ASA) and other NSAIDs. However, airway inflammation occurs even in the absence of exposure to these drugs, leading to disease progression with aggressive polyp formation and non-optimal controlled asthma and rhinosinusitis. In this review, we discuss current and potential management strategies of NERD. This management should be multidisciplinary and comprise medical and surgical treatment of the underlying diseases. In order to prevent reactions due to NSAIDs, avoidance of COX-1 inhibitors with provision of safe therapeutic alternatives should be indicated. However, avoidance of NSAIDs does not ensure disappearance of the airway inflammation and this progresses and persists for life. ASA desensitization followed by daily ASA therapy remains the gold standard of NERD treatment. It is indicated in patients with uncontrolled bronchial and nasal symptoms as well as in patients who require NSAID treatment for specific diseases, such as rheumatic or cardiovascular conditions. ASA desensitization improves upper and lower respiratory symptoms, reduces the need for new nasal surgeries and increases quality of life. Different ASA desensitization protocols have been reported, although the addition of intranasal ketorolac and lysine aspirin prior to an oral ASA schedule has made ASA

desensitization safer and more efficient. New therapeutic strategies are being investigated and may provide an alternative treatment for those patients in which ASA desensitization are contraindicated or continuous ASA therapy is discontinued because of adverse effects. Among them, biologic agents are an important treatment option, useful for controlling symptoms of the upper and lower airways. More investigation studies into the mechanisms involved in NERD are needed in order to identify additional therapeutic targets.

Introduction

NSAID-exacerbated respiratory disease (NERD) is characterized by the combination of chronic rhinosinusitis, nasal polyposis, bronchial asthma, and hypersensitivity reactions involving upper and/or lower airways (nasal reaction and/or bronchoconstriction) within minutes to hours of therapeutic or diagnostic exposure to acetylsalicylic acid (ASA) along with other nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase (COX)-1 [1, 2, 3••].

Chronic rhinosinusitis and/or asthma often precede the onset of NSAID hypersensitivity [4]; however, NSAID hypersensitivity reaction can occur at any time in the evolution of the disease and even occasionally is the precipitator of the first asthma exacerbation [5].

NERD is considered an acquired disease typically presenting in the third or fourth decade of life. It affects 0.3–0.9% of the general population and in about 7% of all asthmatics [6•], increasing the prevalence up to 30–40% among asthmatics with nasal polyposis [7]. These patients typically experience a more severe course of their asthma and chronic rhinosinusitis complicated by recurrent nasal polyp formation [8].

Regarding the pathophysiology of NERD, dysregulation of the arachidonic acid pathways leads to overproduction of pro-inflammatory cysteinyl leukotrienes (LTs) with simultaneous underproduction of anti-inflammatory prostaglandin E2 [9]. Prostaglandin E2 is believed to slow the production of cysteinyl leukotrienes acting as a brake on the 5-lipoxygenase pathway and also acts as a mast cell stabilizer [10]. While the imbalance between cysteinyl leukotrienes and prostaglandin E2 is a constitutive feature of NERD, ingestion of COX-1 inhibitors further exacerbates this imbalance. COX-1 inhibition diverts arachidonic acid toward the lipoxygenase pathway, which causes further depletion of PGE2 regulation. This subsequently results in adverse upper and lower respiratory symptoms mediated through various cell types, including mast cells, eosinophils, and even platelets [11]. Strong COX-1 inhibitors

are considered to be “cross-reactive” and have a greater risk of inducing respiratory reactions in susceptible patients. On the other hand, weak COX-1 inhibitors or selective COX-2 inhibitors are generally well-tolerated [12]. Local and/or systemic immune responses to staphylococcal enterotoxins have been also suggested as a factor in the pathogenesis of chronic rhinosinusitis with nasal polyps in NERD patients, and being responsible for eosinophilic activation in the nasal polyp tissues of these patients [13, 14].

While the diagnosis may be suspected based on characteristic clinical features, definitive diagnosis requires NSAID challenge with objective and/or subjective evidence of an airways reaction. Four ways of challenge may be used: oral, bronchial inhalation, nasal inhalation, and intravenous routes [15, 16]. The nasal challenge test is safest and helpful in identifying NERD [14], although the sensitivity is lower compared to the other three tests [14, 16]. In addition to provocation tests, imaging studies as well as other diagnostic methods, such as rhinoscopy and nasal endoscopy, may be helpful to evaluate chronic rhinosinusitis and nasal polyps [14].

Management of NERD patients is difficult, and comprises treatment of the underlying diseases, basically bronchial asthma and sinus disease, and the prevention of exacerbations due to NSAIDs administration. It should be multidisciplinary and include a guideline-based medical and surgical approach [17, 18]. Corticosteroids, leukotriene-modifying agents, antibiotics and immunotherapy are recommended as treatment modalities for management of asthma, chronic rhinosinusitis, and nasal polyposis. Avoidance of COX-1 inhibitors prevents exacerbations, although airway inflammation will progress [2, 19•, 20, 21••]. ASA desensitization followed by daily ASA therapy remains the gold standard of NERD treatment [22]. Biologic therapies, such as omalizumab and mepolizumab, may be helpful but have not been sufficiently studied [23] (Fig. 1).

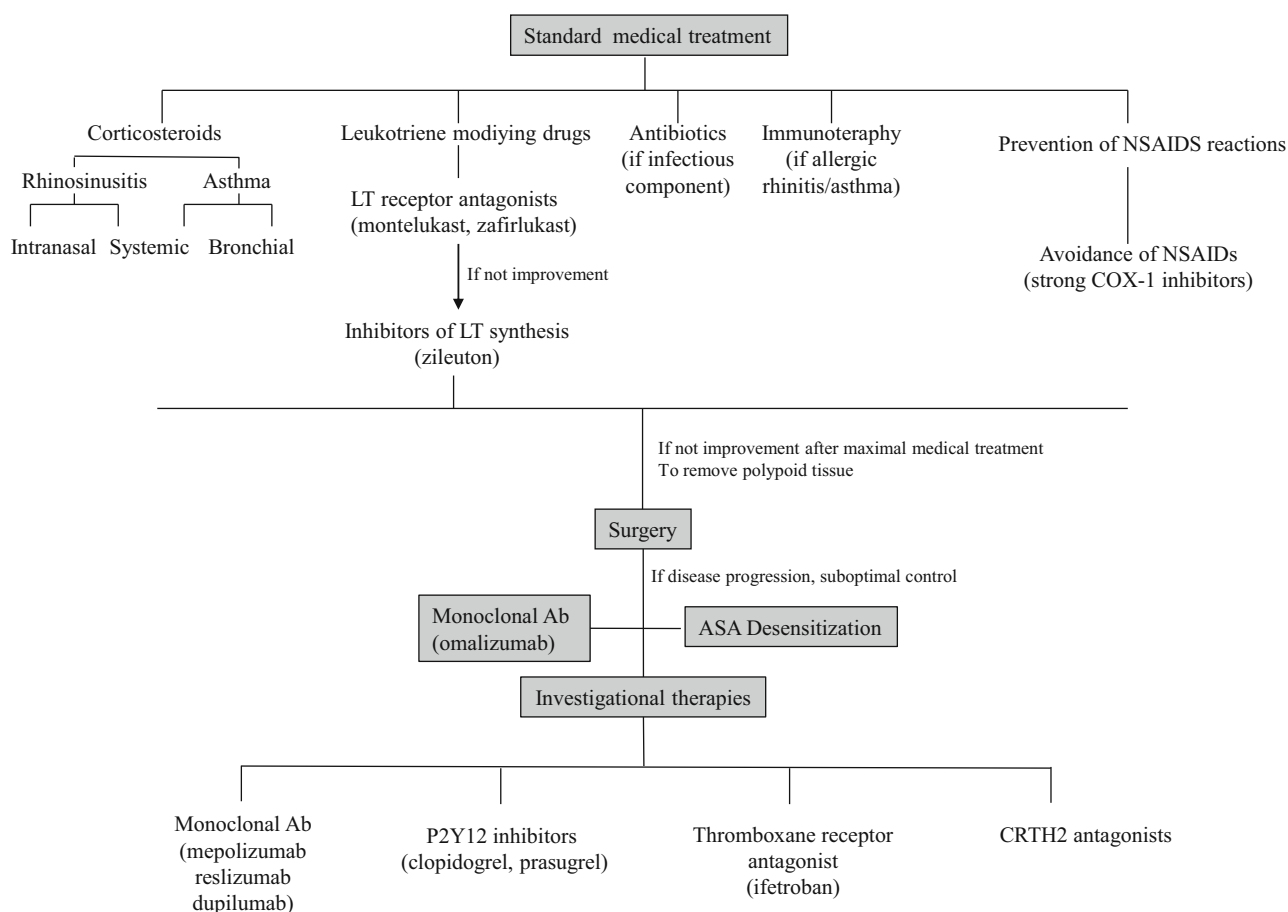


Fig. 1. Algorithm for management of respiratory symptoms induced by non-steroidal anti-inflammatory drugs.

Treatment

Avoidance of NSAIDs

The initial recommendation among NERD patients is to avoid NSAIDs that inhibit COX-1 strongly [19•, 20, 21••] leading to the prevention of reactions due to ingestion of NSAIDs. On the contrary, weak COX-1 inhibitors such as paracetamol, preferentially COX-2inhibitors such as meloxicam as well as highly selective COX-2 inhibitors such as etoricoxib and celecoxib, are generally well tolerated and can be provided as a safe alternative for these patients [24, 25]. Nonetheless, it is suggested that the first full dose of a weak COX-1 inhibitors and preferentially and highly selective COX-2 inhibitors should be given in a physician's office due to the slight chance that the patient could develop an adverse reaction to the drugs.

Avoidance of NSAIDs has no disease modifying effect. It does not ensure disappearance of the airway inflammation and therefore, does not lead to resolution of asthma or chronic rhinosinusitis. Chronic airways inflammation usually continues to progress and most patients with NERD will experience worsening asthma and sinus disease along their lives [2].

Corticosteroids

For management of asthma and rhinosinusitis, standard therapies in accordance with established guidelines should be prescribed. Inhaled corticosteroids in conjunction or not with a long-acting beta2-agonist, and an as-needed short acting beta 2-agonist are the best drugs for controlling asthmatic inflammation in NERD patients [17, 18]. For chronic rhinosinusitis, intranasal corticosteroids have been demonstrated to reduce the eosinophilic mucosal inflammation, improve control of rhinitis symptoms, nasal congestion, nasal airflow and peak nasal inspiratory flow and the size of the nasal polyps [21••]. They reduce polyp regrowth and are indicated after nasal polypectomy [26]. They also decrease reactivity to nasal challenge with lysine aspirin [27]. For rhinosinusitis and nasal polyps control, nasal drops are likely to be more effective than sprays because of their distribution within the sinus cavities, specifically postoperatively [28]. Long-term inhaled corticosteroids treatment is well tolerated and adverse events are minor, being the most frequent epistaxis and nasal irritation when they are administered intranasally and throat irritation and oral candidiasis when administered in the bronchia [27].

In certain patients, oral corticosteroids might be essential to control bronchial inflammation [17]. They have also demonstrated effects on nasal polyp size and nasal symptoms [29]. In rhinosinusitis and nasal polyps there is a lack of evidence of systemic corticosteroids showing efficacy as monotherapy [30]. The chance of significant side effects increases with the dose and duration of treatment. Therefore, side effects must be considered and long-term high-dose treatment is discouraged [31, 32].

Leukotriene modifying drugs (LTMDs)

LTMDs have proven to be of benefit in patients with NERD because the underlying pathophysiology is related to overproduction of pro-inflammatory LTs. The benefit of LTMDs has been observed with LT receptor antagonists such as montelukast and zafirlukast [33–36], as well as with inhibitors of LT synthesis such as zileuton [37, 38]. Although zileuton has been found to be more effective in NERD than LT receptor antagonists, most physicians choose for the initial therapy LT receptor antagonists, since is cheaper and better tolerated; and if patients do not improve after using the LT receptor antagonists for 4–6 days, then zileuton might be added or used as a replacement therapy [39].

The benefit of LT inhibitors is greater for asthma than for nasal and sinus inflammation. Use of LTMDs is also associated with less severe reactions when exposed to NSAIDs, such as during challenge and desensitization [40, 41]. However, LTMDs are not more efficient among ASA-tolerant patients [42].

Antibiotics

Short-term broad-spectrum antibiotic treatment should be used whenever an infectious component is apparent [43]. Long-term macrolide treatment can have additional anti-inflammatory effects. It has been found that they have the ability to block the production of proinflammatory cytokines, such as interleukin 8 and tumor necrosis factor- α , combined with effects on neutrophil migration and adhesion [44]. However, only two randomized controlled trials have been performed showing contradictory results [45, 46]. It has been reported that doxycycline has a significant effect on the size of nasal polyps, nasal

symptoms, and mucosal and systemic markers of inflammation, reducing levels of myeloperoxidase, ECP, and matrix metalloproteinase in nasal secretions [29].

Immunotherapy

Prevalence of sensitization to inhalants allergens in NERD patients is higher for the general population [47], therefore, an important group of these patients have co-morbid seasonal or perennial allergic respiratory symptoms and allergen immunotherapy should be considered [48].

Surgery

Surgical methods (polypectomy, functional endoscopic sinus surgical procedures, or ethmoidectomy) are often required to relieve signs and symptoms of chronic rhinosinusitis at certain stages of the disease, and also to remove polypoid tissue from sinuses [49]. It should be considered in patients whose symptoms do not improve after maximal medical treatment [21••].

Endoscopic sinus surgery (ESS) is the standard procedure for chronic sinus disease in order to reduce polyp size and restore sinus ventilation. It is associated with decreased morbidity compared with previous more invasive procedures and with improvements in nasal symptoms and quality of life [50, 51]. However, NERD patients respond less well to surgical intervention than patients with chronic rhinosinusitis and tolerance to NSAIDs [52] and recurrence of the disease is frequent despite parallel anti-inflammatory treatment [21••].

Desensitization

Despite NSAIDs avoidance in conjunction with standard therapies, most patients experience disease progression [2]. Suboptimal disease control should prompt for consideration of ASA desensitization.

Desensitization is defined as a temporary induction of drug tolerance. By the administration of incremental doses of a drug over time, the response of the patient to a drug is temporarily altered allowing patients to take the drug they are allergic to without developing a hypersensitivity reaction. It is indicated when there is a diagnosis of drug hypersensitivity and the medication is necessary [53]. Moreover, ASA desensitization followed by daily ASA administration has been demonstrated to be beneficial in some patients with NERD [54, 55] and is considered a valuable treatment strategy in the management of these patients [20, 56, 57].

Concerning chronic rhinosinusitis, ASA desensitization has shown to induce reduction of nasal symptoms. Nasal congestion is the symptom that has shown a higher improvement, ranging the percentage of patients reporting improvement from 33% to 90% [58–64]. It also has been reported as a significant improvement in the sense of smell [61, 65], a reduction of concomitant medications (intranasal corticosteroids) [54, 59, 63, 66], a reduction of the number of sinus infections [54, 55, 58, 59, 66] and a significant improvement in quality of life [61, 67]. It is particularly effective in reduction of polyp size [60, 62] and in inhibition of regrowth of nasal polyps after surgery, decreasing the recurrence rate [54, 55, 58, 59, 62, 65, 66, 68] when patients are desensitized within 1 month following surgery [67]. Clinical benefit has been observed as early as 1 month after initiation of treatment [54, 61] and could be maintained

as long as the treatment lasts [58, 62, 66].

Beneficial effect of ASA desensitization and daily aspirin asthma has also been observed, although the overall effect on lower airways seems to be less dramatic than in chronic rhinosinusitis, and studies reported improvement in asthma symptoms in variable proportion of patients [54, 55, 58, 59, 62, 66, 69]. It has been reported that improvement of bronchial symptoms [68] and pulmonary function [62, 69], decrease the number of emergency room visits and hospitalizations [54, 55, 58, 66] and a reduction in the maintenance doses of oral and inhaled corticosteroids [54, 58, 64, 68].

Although clinically convincing, overall evidence of ASA desensitization followed by daily ASA administration from these studies is of low quality because of methodologic limitations: variability in ASA dosing and duration of treatment, and concomitant pharmacologic treatment has not been consistently reported, and only four studies were placebo controlled [70].

Prolonged repeated intranasal application of lysine aspirin has also been shown to be effective, and although not confirmed in a double-blind placebo-controlled trial, it has been demonstrated to reduce the recurrence rates for polyposis [71, 72] as well as to improve nasal peak flow, olfaction, and nasal nitric oxide levels in patients with NERD treated for 3 months. In a subgroup of patients, several asthma outcomes also improved: decrease in emergency visits, hospitalization, and oral steroid use [73].

The mechanism of ASA desensitization is not completely understood. One theory proposes that desensitization and subsequent daily ASA treatment reduces interleukin-4-caused expression of leukotrienes by inhibiting the transcription factor, signal transducer, and activator of transcription 6 (STAT-6) [74, 75]. It is of note that there are no data indicating that ASA is beneficial in the treatment of patients with asthma and nasal polyposis but without NSAIDs intolerance.

Indications for desensitization

Appropriate patients for desensitization should include those with chronic rhinosinusitis with nasal polyps refractory to standard therapies, frequent need for systemic corticosteroids, regrowth of nasal polyps after surgery and/or indication for ASA or other NSAIDs for the treatment of a comorbidities, such as cardiovascular diseases requiring the antiplatelet effects of ASA, or chronic inflammatory conditions requiring daily NSAID therapy, such as rheumatic disease [19•, 76]. In this review, we focus on desensitization as treatment for NERD.

Contraindications for desensitization

Contraindications include pregnancy, unstable asthma, FEV1 less than 60% predicted and ASA specific contraindications such as gastric ulcers and bleeding disorders. A history of a previous severe reactions to an NSAID does not exclude patients from desensitization. The severity of historical reactions does not predict reaction severity during desensitization [77].

Considerations prior to desensitization

Prior to desensitization, patients should be medically optimized to reduce the risk of a severe reaction. Specifically, patients with active sinus/bronchial

Table 1. Protocols of ASA desensitization

Time	Oral ASA Stevenson [81]	Lee [82•]	Chen [83•]	Intranasal Lee [82•]
Day 1				
8:00	30 mg	20-40 mg	40 mg (20 mg if history of serious reaction)	Ketorolac 1.26 (1 spray in one nostril)
8:30				Ketorolac 2.52 (1 spray in each nostril)
9:00			81 mg	Ketorolac 5.04 (2 sprays in each nostril)
9:30				Ketorolac 7.56 (3 sprays in each nostril)
10:00			120 mg	
10:30				Oral ASA 60 mg
11:00	45 mg	40-60 mg	162 mg	
12:00			325 mg	Oral ASA 60 mg
13:30				
14:00	60 mg	60-100 mg		
Day 2				
8:00	100 mg	100 mg		Oral ASA 150 mg
11:00	150 mg	160 mg		Oral ASA 325 mg
14:00	325 mg	325 mg		

infections, allergic rhinitis, and gastroesophageal reflux should be treated with appropriate pharmacologic and non-pharmacologic interventions prior to desensitization [22, 78].

Spirometry should be performed to assess asthma severity. FEV1 should be greater than or equal to 60% of predicted values [19•]. It is recommended that patients continue their current controller medications, including inhaled corticosteroids with or without a long acting beta 2-agonist, as well as intranasal and oral corticosteroids if indicated [22, 79]. A LTMD should be started at least one week prior to desensitization if patients are not already taking it [22, 79]. Evidence supports their ability to dampen the reaction and patients on LTMD premedication tend to have less severe bronchospasm during procedure [2, 36, 41, 80]. Nasal decongestants and oral antihistamines should be stopped one week prior to desensitization to allow the assessment of upper airway symptoms [79].

Desensitization slows disease progression including polyp regrowth but tends not to eliminate nasal polyps if already present. Therefore, those patients with nasal polyps should undergo sinus debulking surgery 2 to 4 weeks before desensitization to maximize the benefit [22, 79].

Premedication

Premedication with inhaled medication has decreased the severity of reactions in most cases and has essentially shifted them from the lower to the upper airway [22].

Protocols

Most desensitization procedures may be safely carried out in an appropriately equipped allergy clinic. However some patients, based on asthma severity or other comorbidities such as β -blocker use, recent myocardial infarction, any other underlying medical condition or drug treatment regimen that would make the management of severe asthma reaction difficult may undergo inpatient desensitization [19•, 22].

There are numerous ASA desensitization protocols conducted similarly with increasing doses of ASA. The historical standard protocol uses dose escalation in 3-hour intervals and requires at least 2–3 days to complete [81]. Recently, protocols for ASA desensitization stretched over 2 days have been proposed. The following sequential doses administered every 3 hours have been reported: first day, 20–40 mg (if history of an emergency department visit for asthma and/or an FEV1 of less than 80% predicted), 40–60, 60–100mg and second day, 100, 150–160, and 325 mg [81, 82•]. Others may begin with a dose of 40–60 mg [77] (Table 1). The average time between ASA dosing and reaction is 104 min; therefore, a 3 h interval between doses has been suggested to allow sufficient time to identify a reaction prior to administration of the next dose [77]. The patient should also be observed for 3 h following the last ASA dose each day [22].

An hourly dose escalation protocol has been recently published, stretching the average time to complete to 1.6 days [83•] (Table 1). It was performed in patients who reported a history of reacting to ASA within an hour of exposure or had never been exposed to it.

Over the past several years, a protocol using intranasal ketorolac and modified oral ASA administration has been used, allowing to reduce the time of completion to 1.9 days [22, 82•]. Desensitization begins on the first day with increasing doses of intranasal ketorolac at 30-minute intervals, following two consecutive doses of 60 mg of oral ASA at 90-minute intervals. On the second day, two increasing doses of oral ASA from 150 to 325 mg were administered with a 3 h interval. Both days, the patient is observed for 3 h prior to discharge. Spirometry, nasal inspiratory flow, and symptom scores are monitored before each dose of ASA and at regular intervals after the administration of the last ASA dose [82•] (Table 1).

In Europe, intranasal lysine-aspirin is used as a diagnostic and therapeutic agent for NERD. Thus, intranasal treatment with increasing doses of lysine aspirin corresponding to 20, 200, and 2000 micrograms of ASA, until a maximal dose of 2000 micrograms weekly has been proposed [71] (Table 1).

When a reaction occurs, symptoms are treated appropriately with antihistamines, bronchodilators, corticosteroids and epinephrine, if necessary. When symptoms resolve, the procedure resumes by repeating the dose that elicited the reaction if the patient reacts to oral ASA, or administering the next scheduled ketorolac dose if the patient reacts to intranasal ketorolac. This is repeated until the patients no longer react to it. At that point, the procedure continues with the next step in the protocol until patients have ingested a full 325-mg dose without developing symptoms [22].

The types and frequencies of reactions vary between different protocols. The most common reaction types with oral ASA desensitization include nasocular (90%), bronchial (43%), and gastrointestinal (23%) symptoms [22, 84, 85].

Intranasal ketorolac with modified oral ASA provokes fewer lower respiratory (32%) and extrapulmonary symptoms (18%) [82•]. On the contrary, the 1-hour dose-escalation protocol induces a higher percentage of bronchial reactions during desensitization (75%) compared to the conventional oral ASA and intranasal ketorolac protocol [83•].

Daily oral ASA therapy

Daily aspirin therapy should begin the day following completion of desensitization. Maintenance doses ranging from 81 to 1350 mg daily have been proposed [59].

Patients with NERD who take only 81 mg of ASA daily will be able to remain tolerant of that dose but may not tolerate higher doses or be cross-desensitized to other NSAIDs [22]. Moreover, ASA doses under 100 mg usually seem to be insufficient to reduce airways inflammation [19•, 62].

Tolerance of 325 mg of ASA indicates that patients will tolerate other NSAIDs and can use them as needed and 325 mg twice daily resulted in a decrease in sinus infections, sinus operations, and hospitalizations due to asthma [22].

However, some patients required an increase from 325 mg to 650 mg twice daily to achieve optimal symptoms control [2]. Once symptoms are well controlled, the daily ASA therapy generally is reduced in an attempt to find the lowest effective dose [59, 86].

Patients should be instructed in the importance of compliance with daily ASA therapy as desensitization is a temporary state and tolerance will remain as long as ASA or the equivalent of another COX-1 inhibiting NSAID is taken without an interruption of more than 48 to 72 hours [22]. For interruptions between 48 and 96 h, dosing with 325 mg of ASA should be administered under direct medical observation. For longer interruptions repeat desensitization is suggested [87].

The incidence of adverse symptoms related to ASA after desensitization has been reported in up to 34% of patients who had undergone daily ASA treatment. They are mostly gastrointestinal symptoms, with high (>650 mg/day) ASA doses and usually mild: dyspepsia, stomach pain, gastric upset or irritation [54, 59, 68]. The use of gastrointestinal prophylaxis (proton pump inhibitors or H2 blockers) in these patients prevents development of gastrointestinal symptoms, even with high doses of aspirin [88, 89]. However, gastrointestinal symptoms are the most frequent reason for ASA discontinuation [22].

Other adverse effects reported include skin symptoms (rash, urticaria) [54, 65, 68] epistaxis or ecchymosis [59, 66], and worsening of asthma [59] and nasal symptoms [54]. It has been reported that a significant decrease in urinary creatinine levels after 1 month of treatment with 650 mg in NERD desensitized patients [61], similar to effects induced by NSAIDs on renal function in patients treated with NSAIDs [90].

Emerging and investigational therapies

Monoclonal antibodies

Omalizumab and mepolizumab have both been the only two monoclonal antibodies analyzed in treating patients with NERD.

Omalizumab is an anti-IgE monoclonal approved for the treatment of severe allergic asthma. It has been described to improve asthma symptoms and quality of life as well as nasal polyp scores, sinus opacification and nasal symptoms in both allergic and non-allergic patients with chronic rhinosinusitis, nasal polyps and asthma [51, 91, 92] and respiratory symptoms during aspirin desensitization [93–95]. Thus, it is unclear whether this effect is particular to NERD. However, it seems to be the only treatment to date that has proven capable of modifying the natural course of NERD [54]. It has been hypothesized that omalizumab reduces allergic inflammation in airways, or acts through an immunomodulatory effect. Moreover, it has been reported that, in a minority of NERD patients, the combination of medications (ASA, LT receptor antagonist, oromalizumab) was more effective than one alone [39]. Therefore, omalizumab may be used additionally to the other therapies [49].

IL-5 has a critical role in influencing the biological activities of eosinophils, therefore the receptor of IL-5 is a clear target in the treatment of hypereosinophilic diseases [96]. Mepolizumab is an anti-IL-5 monoclonal antibody that is indicated in the treatment of severe asthma with eosinophilia and in patients with nasal polyps refractory to corticosteroid therapy [97, 98]. However, whether mepolizumab provides specific benefit in NERD remains unclear. In the only study published that includes patients reporting ASA sensitivity, this diagnosis was not confirmed by DPT [97].

Reslizumab is an anti-IL-5 that has proved to have a significant reduction of polyp score, reduction of blood eosinophil counts, as well as ECP levels, in serum. However, no significant improvement of symptoms has been reported [99].

Dupilumab is an anti-IL4 receptor α monoclonal antibody that has been shown to be beneficial in allergic asthma and atopic dermatitis [100, 101], and also induced a significant reduction of polyp with improvement of smell, symptoms and quality of life [97]. As well as reslizumab, no specific studies in NERD patients have been carried out until now.

Platelet-targeted therapies

It has been suggested the participation of platelets in airways inflammation enhancing leukocyte aggregation within the airways leading to overproduction of cysteinyl leukotrienes in NERD [102, 103]. P2Y12 is a G protein-combined receptor essential in platelet activation and aggregation. Clopidogrel and prasugrel are selective P2Y12 inhibitors recognized to decrease the introduction of platelet-leukocyte aggregates [104]. A double-blinded placebo controlled trial is underway to assess the potential efficacy of prasugrel for the treatment of NERD [48, 105].

The thromboxane receptor has been implicated in inducing bronchospasm [106, 107]. The antagonism of these receptors may provide therapeutic benefit in NERD. Therefore, there has been study of the efficacy of ifetroban, a thromboxane receptor antagonist, in the treatment of NERD in a murine model [11, 48, 105].

CRTH2 antagonists

Prostaglandin D2 acts to recruit allergic effector cells including eosinophils, basophils, TH2 lymphocytes, and type 2 innate lymphoid cells via signaling through CRTH2, a chemoattractant receptor [108–111]. Studies proving the

potential benefit of CRTH2 antagonists in patients with allergic disease are currently ongoing [48].

Conclusions

NERD is defined by the clinical tetrad of NSAIDs sensitivity, nasal polyposis, asthma, and chronic rhinosinusitis. Pathogenesis is not fully understood but is believed to involve dysregulation of the arachidonic acid metabolic pathway with overproduction of cysteinyl leukotrienes. Disease progression and airway inflammation occurs even in the absence of NSAID exposure.

Strong COX-1 inhibitors must be avoided in order to prevent hypersensitivity reactions. All patients should be treated with standard therapies according to the guidelines published for asthma and chronic rhinosinusitis including inhaled corticosteroids with or without long-acting beta-2 agonist, intranasal corticosteroids and leukotriene-modifying drugs. In patients with suboptimal control of airways with inflammation and polyp regrowth despite standard therapies, ASA desensitization followed by continuous oral ASA therapy has been highly efficacious and safe. Patients needing ASA or other NSAIDs to manage other underlying conditions would also undergo desensitization. The use of protocols including intranasal ketorolac or intranasal lysine aspirin allows to shorten the time for protocol completion, increasing safety as well as inducing fewer lower respiratory reactions. Investigational therapies include monoclonal drugs targeting allergic inflammation, antiplatelet therapies, and CRTH2 antagonists, although nowadays their efficacy in the treatment of NERD remains unproven.

Compliance with Ethical Standards

Conflict of Interest

Inmaculada Doña, María Salas, Esther Barrionuevo and Paloma Campo declare that they have no conflict of interest. The present study has been supported by the Andalusian Regional Ministry Health (grant: PI-0463-2013). Inmaculada Doña holds a "Juan Rodes" research contract (JR15/00036) supported from the Institute of Health "Carlos III" of the Ministry of Economy and Competitiveness, RETIC ARADYAL (RD16/0006/0001) (grants cofunded from the European Social Fund (ESF)).

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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