Current Goals of NSAID-ERD Management: Patient-Centered Approaches Involving NSAID Desensitization With and Without Biologics

Irina Bobolea, MD, PhD[a,b,*], Jan Hagemann, MD[c,d,*], Marek Sanak, PhD[e], Ludger Klimek, MD[c,†], and Joaquim Mullol, MD[b,f,†] *Catalonia and Madrid, Spain; Wiesbaden and Mainz, Germany; and Krakow, Poland*

The classic approach of nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NSAID-ERD) includes pharmaceutical and surgical treatments, as well as avoidance of cyclooxygenase 1−inhibitor NSAIDs. The introduction of biologics in the treatment of severe asthma and chronic rhinosinusitis with nasal polyps represents an alternative therapeutic approach to the classical aspirin therapy after desensitization (ATAD) in some regions, and with convincing results. However, their use is limited due to approval and/or high-cost restrictions. NSAID-ERD is a mainly type 2 and highly eosinophilic disease, and mAbs targeting IgE or IL-5, IL-4, and IL-13 have been shown to be effective for both severe asthma and severe chronic rhinosinusitis with nasal polyps. So far, dupilumab demonstrated greater efficacy in patients with NSAID-ERD than in aspirin-tolerant patients with regard to several clinical outcomes. Patients with NSAID-ERD respond very rapidly to omalizumab also, with reduction in the release of prostaglandin D_2 and cysteinyl leukotrienes. Patients favored biologic treatment over ATAD in multiple retrospective analyses, which must be acknowledged when choosing one or the other option. Although this review will summarize ATAD in general, it will more prominently focus on when ATAD should be considered, even when type 2 biologics are available. In addition, there are conflicting studies as to whether patients on a type 2 biologic become desensitized to NSAIDs, because omalizumab proved to restore tolerance to aspirin in only two-third of patients. This goal of NSAID tolerance should be considered as part of disease control future approaches, representing one of many aspects in a patient-centered care approach. **(J Allergy Clin Immunol Pract 2024;12:2934-44)**

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NONSTEROIDAL ANTI-INFLAMMATORY DRUG−EXACERBATED RESPIRATORY DISEASE

Nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NSAID-ERD) is a distinct syndrome characterized by asthma, chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP), and lower and upper airway reactions precipitated by exposure to nonsteroidal anti-inflammatory drugs (NSAIDs), either oral, parenteral, or even topical. The disease is currently referred to internationally as NSAID-ERD (synonym: aspirin-exacerbated respiratory disease [AERD]; Samter's triad). Previously, the following names were mainly used for this disease: Widal's syndrome, Samter's syndrome, Samter's triad, ASA-triad, or aspirin intolerance.[1-3] The fundamental underlying mechanism is a nonallergic hypersensitivity to all NSAIDs that inhibit cyclooxygenase (COX)-1.[1]

The prevalence of NSAID-ERD in the general population is reported to be between 0.5% and 5.7%.[4] Women are affected

[a]Severe Asthma Unit, Allergy Department, Hospital Clinic Barcelona, FRCB-IDIBAPS, Barcelona, Catalonia, Spain
[b]CIBER of Respiratory Diseases (CIBERES), Madrid, Spain
[c]Center for Rhinology and Allergology, Wiesbaden, Germany
[d]Department of Otolaryngoloy, Head and Neck Surgery, Universitätsmedizin Mainz, Mainz, Germany
[e]Department of Internal Medicine, Jagiellonian University Medical College, Krakow, Poland
[f]Rhinology Unit & Smell Clinic Unit, ENT Department, Hospital Clinic Barcelona, FRCB-IDIBAPS, Universitat de Barcelona, Barcelona, Catalonia, Spain
*These authors are sharing first authorship.
†These authors are sharing senior authorship.
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Corresponding author: Irina Bobolea, MD, PhD, Allergy Department, Hospital Clínic Barcelona, Villarroel 170, 08036 Barcelona, Catalonia, Spain. E-mail: bobolea@clinic.cat; Or: Jan Hagemann, MD, Center for Rhinology and Allergology, An den Quellen 10, 65183 Wiesbaden, Germany. E-mail: jan.hagemann@allergiezentrum.org.
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Abbreviations used

ASA- acetylsalicylic acid
ATAD- aspirin therapy after desensitization
COX- cyclooxygenase
CRS- chronic rhinosinusitis
CRSwNP- chronic rhinosinusitis with nasal polyps
Cys-LT- cysteinyl leukotriene
ESS- endoscopic sinus surgery
IV- intravenous
LTE_4- leukotriene E_4
Lys-ASA- lysine-ASA
NSAID-ERD- nonsteroidal anti-inflammatory drug—exacerbated respiratory disease
NSAID- nonsteroidal anti-inflammatory drug
PGD_2- prostaglandin D_2
T2- type 2
TSLP- thymic stromal lymphopoietin

more frequently (60%-70%) than men, and the disease could have a genetic predisposition.[5,6] In addition, the number of unreported cases of NSAID-ERD appears to be high: in a study by the *European Network of Aspirin-induced* Asthma[4] with 500 patients with asthma, a previously unknown analgesic intolerance of 15% was detected by provocation tests. In the presence of CRS, NSAID-ERD was detected in 34% of patients.[4] This association between CRSwNP and asthma is very common overall. NSAID-ERD affects about 12% to 40% of cases of severe asthma[7,8] and up to 39% of cases of severe CRSwNP.[9,10] In addition, a separate cutaneous form of analgesic intolerance in patients with chronic urticaria exists, which is also referred to as NSAID-exacerbated cutaneous disease or, in the case of urticaria/angioedema in patients without cutaneous chronic disease, as NSAID-induced urticaria-angioedema.[5,11]

The pathophysiology of NSAID-ERD is elucidated in another article of this special issue. To understand the therapeutical options discussed here, we summarize that NSAID-ERD is mainly characterized by pronounced blood and tissue eosinophilia,[12] as well as by an imbalance of the eicosanoids (cysteinyl leukotriene [Cys-LT] E_4) and prostaglandins (prostaglandin D2 [PGD_2] and prostaglandin E2), produced via arachidonic acid metabolism. Although clinically observed and known since the early 20th century, the nonallergic pathomechanism of respiratory reactions after ingestion of NSAIDs was first described by Szczeklik et al[13,14] in the 1970s by demonstrating the inhibition of PG synthesis. An imbalance between COX isoforms 1 and 2, which worsens on COX-1—inhibiting medication, has been suspected for a long time.[15,16] This leads to reduced prostaglandin E2 synthesis and an overproduction of LTC_4 and PGD_2.[17] Subsequently, in the context of chronic inflammation, alarmins such as IL-33 and thymic stromal lymphopoietin (TSLP) are released in airway mucosa. These cytokines activate T_H2 lymphocytes and type 2 innate lymphoid cells to release cytokines such as IL-4, IL-5, and IL-13, with the process currently known as the "T2 inflammation phenotype."[12] More recently, mast cell—derived PGD_2 has been demonstrated to be a major effector of type 2 (T2) immune response driven by TSLP in patients with NSAID-ERD. The dysregulation of this innate system contributes significantly to the pathophysiology of NSAID-ERD.[18] Because the T2 phenotype appears to be predominant in approximately 80% of the patients with CRSwNP in the Western civilization, and particularly in patients with NSAID-ERD,[19-22] biologics targeting IL-4, IL-5, IL-13, TSLP, and IgE are of high clinical interest in patients with severe disease.[2,23,24]

DIAGNOSIS OF NSAID-ERD

Anamnesis and provocation tests are pivotal in the diagnosis of NSAID-ERD.[4,25] Controlled challenges in respiratory patients include nasal, bronchial, or oral tests, whereas in aspirin-sensitive urticaria, only oral provocations are useful.[5] These tests must always be performed by experienced personnel, in specialized centers provided with intensive care facilities and with staff capable of handling severe reactions. According to the American Academy of Asthma, Allergy & Immunology work group report, it most likely is safe to perform both aspirin therapy after desensitization (ATAD) and provocation testing in an outpatient fashion for most individuals.[10]

TREATMENT OF NSAID-ERD

The therapeutic options for NSAID-ERD must address each determining clinical entity: asthma, CRSwNP, and NSAID intolerance. The treatment of bronchial asthma is based on the current asthma guidelines[26] and is usually structured as an incremental staircase-like scheme, with inhaled corticosteroids being the cornerstone. Systemic corticosteroids are limited as rescue medication for severe exacerbations; however, the systemic use is likely to provoke long-term side effects, and should be limited as much as possible. In a similar fashion, topical corticosteroids are the standard-of-care baseline therapy for the nasal inflammation present in NSAID-ERD.[9,27] Chronic inflammation of the upper airway in NSAID-ERD is typically presenting as CRSwNP, causing obstruction to the undrained sinonasal areas.

A special feature is the usually good response of asthma to leukotriene antagonists. Because of the overproduction of Cys-LTs in NSAID-ERD, zileuton, a 5-lipooxygenase inhibitor, is often used internationally, but is not available in Europe. Zileuton has a strong effect on leukotriene E_4 (LTE_4) because, in contrast to the Cys-LT_1 receptor antagonists montelukast, zafirlukast, and pranlukast, it partially blocks the formation of all Cys-LTs. The additional benefit of these drugs is the attenuation of severe airway reactions after accidental ingestion of NSAIDs.[28] The risk of severe, sometimes life-threatening asthma attacks after taking NSAIDs is significant for analgesic intolerance and constitutes a decisive difference to other forms of asthma. This makes it all the more important to inform the patient about the different potential of COX-1 inhibition in the various NSAIDs and to issue a corresponding medication card, and alternative analgesics.

Nonetheless, in patients with NSAID-ERD, avoiding neither NSAIDs nor topical corticosteroids or leukotriene antagonists does not change the course of the disease: asthma often remains uncontrolled even on optimum treatment, and CRSwNP frequently recurs or exacerbates, in spite of intranasal and oral corticosteroids and/or multiple endoscopic sinus surgeries (ESSs).[29] Surgical intervention is the standard non-pharmacological therapy in CRSwNP, although it benefits the distribution of future long-term topical nasal spray application. The extent of surgery is usually extensive in CRSwNP, with the need to drain and remove polyp tissue in all sinuses. Multimodal therapy including surgery seems to be more effective for a limited time.[30] However, the recurrence rate after ESS is very high in

patients with NSAID-ERD than in NSAID-tolerant patients.[31] Second or multiple surgeries over time are a frequent phenomenon in patients with NSAID-ERD.

There is evidence for beneficial effects in the lower airways when addressing the upper airway. Endoscopic sinus surgery significantly benefits patients with asthma, according to a meta-analysis with a 26.4-month follow-up.[32] Improvements included better overall asthma control (76.1% of patients), fewer asthma attacks (84.8%), and reduced hospitalizations (64.4%). Usage of oral corticosteroids decreased in 72.8% of patients, with declines in inhaled corticosteroids (28.5%) and bronchodilators (36.3%). Notably, this effect was observed in cases with severe asthma.

There are 2 main pharmacological treatment options available for severe, uncontrolled, and/or corticosteroid-dependent patients, aimed to achieve control as well as to modify the natural history of the disease: *aspirin* desensitization (internationally known as ATAD) and biologics.

These treatments are often presented as alternatives, and the question is raised as to why ATAD is still needed at all in times when biologics are available (in most areas) and have been evaluated with the highest level of evidence. This review provides an overview of the possibilities and limitations of ATAD and the use of approved biologics in NSAID-ERD patients with CRSwNP and/or asthma, and aims to answer these questions as best as possible. Patient characteristics, safety, efficacy, health care costs, but also patient preferences are factors to be considered when choosing between biologics and ATAD.

EFFICACY OF ATAD

To date, ATAD has classically been performed with the approach of causal therapy in patients with severe recurrent CRSwNP and NSAID-ERD.[4,9,33-38] The aim of this therapy is to achieve disease control, and also tolerance to analgesics—namely, COX-1 inhibitors—through repetitive application of acetylsalicylic acid (ASA).[36,39,40]

These therapeutic approaches have their origins in the observations of Zeiss and Lockey, in which a refractory phase occurred in patients with NSAID-ERD after oral administration of aspirin. There is a period after aspirin intake during which taking it again does not lead to adverse reactions. This refractory period can last between 24 hours and several days,[41] and can be prolonged indefinitely by daily aspirin intake. Furthermore, the clinical condition of patients with NSAID intolerance improves during this refractory period: Stevenson et al,[35] who were the first to study ATAD, observed an increase in FEV_1, a reduction in the need for oral corticosteroids, and a reduction in inflammatory damage to the nasal mucosa after 6 months of daily aspirin intake. In addition, the daily intake of aspirin caused the nasal symptoms to disappear,[35] but there was no scoring of nasal polyp size. To further investigate the phenomenon of the refractory phase, several open and controlled studies were conducted as short-term and long-term studies. In this way, ATAD was introduced as a potential treatment option for NSAID-ERD.

The ATAD appears to function primarily via shifts in the ratio of PGD_2/Cys-LTE_4.[10,42,43] PGD_2 initially increases significantly during ATAD.[10] If the increase is exaggerated though, it predicts further reactions during the desensitization process, which might not be achieved in these cases. Otherwise, the subsequent decrease in PGD_2 during the maintenance phase with daily aspirin intake leads to reduced expression of Cys-LT receptors, inflammatory cell infiltrates, and decreased levels of type 2 cytokines such as IL-4, IL-5, and IL-13 released by T_H2 lymphocytes.[44] In addition, ATAD leads to reduced expression of urinary LTE_4.[45]

Studies on various application routes have been published in the last 20 years.[33,35,46] At present, oral application is established as the standard procedure.[34] Several other application protocols have been developed, for both systemic and topical administration[47] including intravenous (IV) administration of ASA. The IV dosing regimen achieves a cumulative dose of 900 mg IV in 5 days of therapy. One advantage of IV administration appears to be the possibility of immediately interrupting the supply of the substance in the event of an incipient reaction, which cannot be realized after oral administration.[48]

The bronchial application of ASA, which arose from the idea that the refractory phase can also be achieved by inhalation provocation,[33] has taken a back seat to the nasal and oral methods. Nasal application was primarily effective in the treatment of NSAID-ERD associated with CRSwNP. In a prospective study over 5 years, it was demonstrated in 43 patients with NSAID-ERD that the endonasal application of lysine-ASA (Lys-ASA) in ascending doses (dose increase: weekly 20, 200, 2000 mg, then weekly maintenance dose: 2000 mg) significantly reduced the recurrence rate of nasal polyposis compared with placebo.

A small, blinded cross-over study with 16 mg Lys-ASA did not lead to an improvement in symptoms, but showed a reduction in leukotriene receptors in the nasal mucosa. Open studies indicate the effectiveness of this form of application.[49,50] Pendolino et al[51] were able to show an improvement in nasal breathing and olfaction. Patients who received intranasal Lys-ASA showed a lower rate of revision surgery of the paranasal sinuses.

In the first randomized, double-blind, placebo-controlled study on oral desactivation by Stevensson et al,[35] the patients received daily doses of between 325 mg and 1300 mg. Despite the short study duration of only 3 months, a significant improvement in the symptom medication score and an improvement in bronchial asthma was shown in half the cases.

In a prospective study of 65 patients with NSAID-ERD performed between 1988 and 1994, the maintenance dose of 1300 mg daily was initiated after oral ASA provocation tests and inpatient desensitization.[34] There was a significant improvement in both asthma symptoms and nasal symptoms. In addition, there was a significantly lower incidence of recurrent polyps, such that the frequency of operations was reduced from 1 operation every 3 years to 1 operation every 9 years. However, gastric complaints were found to a considerable extent during long-term treatment.[34,36,52]

In another study, a daily maintenance dose of only 100 mg ASA was chosen to minimize possible side effects such as gastritis. Over a period of 3 years, a clear therapeutic effect was also found with this significantly lower dose, with a reduced recurrence rate of nasal polyposis, reduced severity of intrinsic asthma, and an improvement in olfaction. No significant difference in the nasal polyp score between the ASA group and the placebo group was demonstrated though with 100 mg ASA. Interestingly, ATAD also improves alcohol intolerance in patients with NSAID-ERD.[53]

Fruth et al[54] investigated 70 NSAID-ERD patients with CRSwNP in a randomized, double-blind, placebo-controlled study. Because of the high dropout rate, only 31 patients could

be analyzed. After 36 months, nasal polyps occurred less frequently in the treatment group (primary end point) ($P = .0785$) and the nasal polyp score was lower ($P = .0702$). Quality of life improved ($P = .0324$) and clinical symptoms decreased significantly ($P = .0083$), and no severe aspirin-related side effects were observed. Even though the primary end point was therefore not met with statistical significance, ATAD with a maintenance dose of 100 mg led to an improvement in clinical symptoms and quality of life in this study.[54]

However, it must be pointed out that since the first introduction of ATAD by Stevenson et al,[35] only 5 double-blind, placebo-controlled studies have been conducted to evaluate the efficacy and safety of ATAD, involving a total of only 163 patients. The low number of double-blind, placebo-controlled studies can be explained by the high regulatory hurdles of clinical drug trials and a low interest of the manufacturers of ASA preparations, in addition to difficulties blinding patients, given aspirin-related common side effects.

In cross-over studies from the early 1980s, 67% of the patients experienced an improvement in nasal symptoms, whereas only half the patients experienced an improvement in their asthma. In general, most patients reported improvement in overall disease control. ATAD addresses the 3 aspects of the triad—improves CRSwNP and asthma control, and allows patients to safely take any other NSAID because they are cross-desensitized. The American Academy of Asthma, Allergy & Immunology considers ATAD to be a valuable treatment option for patients with NSAID-ERD, including a position paper focusing on ATAD.[10]

BIOLOGIC THERAPY OF CRSWNP AND ASTHMA IN THE CONTEXT OF NSAID-ERD

CRS is mainly divided into 2 phenotypes, with (CRSwNP) or without (CRSsNP) nasal polyps.[55] CRSwNP with NSAID-ERD is considered a subphenotype, whereas in asthma NSAID-ERD is acknowledged as a separate asthma endotype. General recommendations on the diagnosis and treatment of CRSwNP are available,[56] as well as practice-oriented criteria for the use of currently approved biologics dupilumab (anti−IL-4Rα), omalizumab (anti-IgE), and mepolizumab (anti−IL-5).[57,58] Biologics have been established for some time in the treatment of bronchial asthma.[59−64]

The biologics omalizumab, mepolizumab, and dupilumab are approved for use in patients with severe, uncontrolled CRSwNP, as add-on therapy to intranasal corticosteroids,[56,65] and lead to a significant reduction in nasal polyp size, large enough to potentially explain a significant reduction in symptom burden, including loss of smell, also for patients with NSAID-ERD.[23,66] Although benralizumab (anti−IL-5Rα) is not yet approved for CRSwNP, in a phase III study, both coprimary end points were met with a good safety profile.[67] Tezepelumab (anti-TSLP) is approved for the add-on treatment of severe asthma and is also investigated in a phase III clinical study for use in CRSwNP.[68]

In the previous studies with biologics in patients with CRSwNP, the proportion of patients with NSAID-ERD was 27% in the mepolizumab studies, 28% in the dupilumab studies, 30% in the benralizumab studies, and between 17% and 39% for the 2 studies with omalizumab.[69−73] However, it should be noted that the diagnosis of NSAID-ERD in all these studies was made on the basis of medical history alone, whereas provocation tests are actually required to make a reliable diagnosis of NSAID-ERD.[1] Nonetheless, *post hoc* analyses of the pivotal studies show that patients with NSAID-ERD benefited equally well from the biologic treatment in terms of a reduction in polyp size compared with the NSAID-tolerant subgroup.[74] In addition, patients with NSAID-ERD responded equally well to dupilumab treatment in terms of improvement in olfaction and to benralizumab treatment in terms of nasal obstruction. Dupilumab is the only biologic that showed a difference between NSAID-tolerant and NSAID-intolerant patients with CRSwNP: patients with NSAID-ERD reported a significantly greater improvement in nasal obstruction and sino-nasal outcome test-22.[75] Biomarkers connected to T2 disease in general and to NSAID-ERD in particular were observed to improve under dupilumab treatment as well.[76]

In the treatment of asthma, the efficacy of mepolizumab, benralizumab, and dupilumab in patients with NSAID-ERD is equipotent if chosen correctly and according to latest treatment algorithms.[69] It is important to note that, in contrast to the situation with CRSwNP, the treatment of asthma can usually be tailored to phenotyping and endotyping.

Concerning the third aspect of the triad, the aspirin/NSAID intolerance, over the last decade, first isolated case reports and small case series, and then larger trials, reporting aspirin tolerance in patients treated with omalizumab or dupilumab have been published, opening a door to these otherwise limited patients, in terms of pain relief and antiplatelet therapy.[77−79] The study by Schneider et al[80] reported a heterogeneous improvement with regard to aspirin tolerance upon dupilumab therapy, thus making general assumptions and recommendations for patients with NSAID-ERD risky at this moment.

In a recent real-world evidence study in patients with severe asthma and positive oral provocation test to ASA, Sanchez et al[81] showed efficacy of omalizumab and dupilumab, but not of mepolizumab and benralizumab, with regard to the result of the oral provocation test outcome. However, this study was a small pilot study with 9 patients included for mepolizumab and benralizumab and 10 patients each for dupilumab and omalizumab. Further results from larger studies remain to be seen.[82]

SAFETY AND PREREQUISITES FOR EITHER ATAD OR BIOLOGIC THERAPY

Long-term safety data for biologics are lacking, particularly in the indication for CRSwNP.[56] In the short-term, the use of biologics appears to be relatively safe, with a discontinuation rate of less than 5% in most of the published phase 3 trials.[69] In a meta-analysis of 24 randomized controlled double-blind trials, the incidence of adverse events with the different biologics (dupilumab, omalizumab, mepolizumab, benralizumab, and reslizumab) was comparable and hardly differed from placebo.[82]

An issue frequently discussed for dupilumab treatment is the risk of temporarily elevated blood eosinophil levels in up to 10% of patients. Although this is usually transient and unharmful, some patients (<5%) required therapy to continue treatment with dupilumab for their asthma or CRSwNP.[69] Permanent discontinuation of dupilumab treatment was required in 7 patients, compared with 1 patient in the placebo group.[83] However, peripheral blood eosinophilia can also occur with high-dose ASA therapy for NSAID-ERD treatment.[10]

The safety data on high-dose ATAD are limited due to the small size of the studies and high rate of discontinuation, some

not treatment-associated.[84] In a retrospective study, the rate of serious adverse effects associated with ATAD was analyzed.[85] Most frequently, gastrointestinal bleeding (8.2%), anaphylaxis (0.92%), exacerbations of upper (0.92%) and lower respiratory tract symptoms (3.7%), and recurrent epistaxis (0.92%) led to discontinuation of treatment.

These findings are consistent with other reports that found gastritis to be the most common reason for discontinuation of maintenance treatment of ATAD.[69,86,87] Although the risk of bleeding with long-term oral ASA administration has not been specifically studied in NSAID-ERD, extrapolated data from cardiovascular use of ASA show a 50% increased risk of gastrointestinal bleeding.[10,84] The risk of ATAD in the biologic era has been highlighted by the meta-analysis of Oykhman et al,[82] showing a convincing risk difference between biologics and ATAD and thus significantly influencing the choice of treatment since then.

An alternative option is the use of topical, intranasal Lys-ASA (the only soluble form) both for nasal provocation testing to diagnose NSAID-ERD and for subsequent therapy. Intranasal ATAD, in which the used ASA doses are lower than in oral ATAD at less than 100 mg, causes fewer gastric problems[88] and is more compatible with cardiovascular prophylaxis, because oral doses above 100 mg (as commonly used with oral ATAD) are associated with poorer cardiovascular outcomes.

To prevent acute pulmonary impairment, further prerequisites for starting ATAD are given: it is recommended that the patient should have stable/controlled bronchial asthma, with an acceptable pulmonary function ($FEV_1 > 70\%$) before starting therapy,[69,87] which is in some cases difficult or impossible to achieve; thus, biologics are the only logical, effective, and safe option in this subgroup.

Although in severe asthma there are clear recommendations and experts' consensus on biologics' indications and efficacy evaluation,[89,90] the regulatory authorities have not yet finally defined any criteria in this regard for CRSwNP. Clinical criteria, some or all of which should be met before starting biologic therapy, include a diagnosis of bilateral CRSwNP, traceability/evidence of T2 inflammation, previous need for systemic corticosteroids or previous sinus surgery, impaired quality of life, failure of treatment with nasal corticosteroids, significant loss of olfaction, and comorbid asthma.[57,91] The indication should be supported using a standardized, validated checklist. In patients with NSAID-ERD though, asthma is not always present from the outset and may not be present at the time of diagnosis of NSAID-ERD. Furthermore, not all patients with NSAID-ERD eventually benefit from ATAD,[38] and so biologics remain an option here.

FACTORS INFLUENCING THE CHOICE OF PHARMACOLOGICAL TREATMENT

Biologic agents for NSAID-ERD–dependent airway inflammation are currently available in the European Union, the United States, Canada, Japan, and Australia. Next to difficulties providing specialty care to all patients with NSAID-ERD who exist, and reservations with regard to prescribing costly medication for some health care providers, these regulatory limits are most decisive for the choice of treatment from an international standpoint, and we must educate and provide high-quality data that support novel treatment options that benefit patient care. Meanwhile, there are currently no definite biomarkers that can predict a patient's response to aspirin desensitization or biologic therapy.[28] Add-on therapy with biologics has been the *standard of care* in Europe for severe, inadequately controlled asthma since 2005, and for CRSwNP since 2022. ATAD, however, is designed for patients with suspected impaired arachidonic metabolism in the context of NSAID-ERD only, and therefore is limited to this endotype.[84]

Comorbidities such as cardiovascular or rheumatic disease may favor a decision for ATAD. The patient with NSAID-ERD may then take the prophylactic ASA as an antiplatelet agent, or the daily NSAIDs as analgesics to relieve the pain associated with a rheumatic disease,[47] and benefit from an ATAD at the same time; however, low-dose administration of ASA may not improve CRSwNP and asthma control.

However, ATAD is not the preferred option if there are absolute or relative contraindications to ASA, such as a history of peptic ulcer disease, eosinophilic esophagitis (which may also be associated with NSAID-ERD), renal insufficiency, anticoagulant use, or a history of coagulopathy.[28,86,87] These patients have an increased risk of ASA-related side effects, because long-term use of ASA reduces the synthesis of gastric prostaglandin (prostacyclin or PGI_2) and causes insufficient regeneration of gastric mucosal cells, which can lead to stomach pain or ulceration. Bleeding may also occur because aspirin inhibits platelet function by acetylating COX.[92] Between 10% and 15% of patients with NSAID-ERD cannot continue long-term ATAD due to gastrointestinal side effects or bleeding.[28] The risks and comorbidities of oral ASA administration are also becoming increasingly important in older patients with NSAID-ERD. Although the overall risk of bleeding and hemorrhage is very low, it is significantly higher than in younger patients, and may result in higher overall mortality.[10,84] Conversely, there is a lack of specific data for biologics in the elderly.[56]

In pregnant patients with NSAID-ERD, taking aspirin doses higher than 81 mg daily may contribute to premature closure of the ductus arteriosus and increase the risk of maternal and fetal bleeding. Therefore, oral administration of ASA should not be started or continued during pregnancy.[87] However, these contraindications for the oral administration of ASA in the context of ATAD (pregnancy, planned operations such as sinus surgery) are only temporary, and therapy can be carried out afterward after undergoing a new desensitization process.

White et al[28] describe 3 common situations in which the timing between ATAD, biologics, and surgery plays a crucial role:

1. A newly diagnosed patient should be evaluated for all affected organ dysfunctions and move to adequate therapy to achieve disease control in each aspect. Surgical evaluation should be performed upon computed tomography scan of the sinuses and careful evaluation with regard to possible treatment escalation should follow. Usually sinus surgery with/without ATAD would follow; however, biologic therapy might be suitable in selected cases. The publication refers to surgery as "debulking"; in other rhinology centers, a full ESS would certainly be used.
2. The patient with early polyp recurrence is an ideal candidate for ATAD, because aspirin therapy may have the best effect in patients with recent ESS, caused by an altered reaction severity upon ASA after sinus surgery.[93]

3. In case of persistent failure of surgical measures, the risks and benefits of ATAD or a biologic should be discussed, considering the patient's preferences, existing comorbidities such as cardiovascular disease, or the need for treatment with NSAIDs, or upcoming ESS. Similarly, Buchheit et al[94] proposed a treatment algorithm in which biologics are offered only after complete ESS and a trial of aspirin desensitization, given the high costs of biologics and lack of clear data on long-term safety.

Aside from medical reasons favoring one or the other treatment, the individual patient's expectations, likelihood of adherence to treatment, and subjective evaluation of the treatment regimen are to be respected in the NSAID-ERD–focused care pathway. Patients who are treated with ASA after an ATAD and skip their dose for more than 3 to 7 days gradually become intolerant again and then must be re-desensitized to ASA.[10,69] In addition, the long-term compliance to treatment is expected to be lower for medications prone to provoke side effects, as observed in previous studies.[54] Furthermore, patients have been asked to evaluate their previous treatment experiences in a retrospective fashion. Patients were asked about the efficacy and overall grading of either ATAD + surgery versus biologics or ATAD versus biologics + ATAD, and favored biologic treatment in terms of efficacy, well-being, and duration of disease control.[66,70] In a patient-centered approach, these experiences should also be respected in the overall evaluation and should be addressed in a more structured fashion in future study approaches.

COSTS FOR HEALTH CARE SYSTEMS

The highest direct costs of biologics are for the drugs themselves, whereas outpatient costs are the focus of ATAD. ASA is inexpensive and costs around €0.10 per tablet (daily dose) as Aspirin protect. The annual price for a daily therapy is therefore less than €40. The costs associated with the aspirin desensitization procedure (tolerance induction) depend on the health care system and eventually hospital-specific factors—as well as the insurance status of the patient—and are in the range of €1500 to €4000.[92,95,96]

For the 3 approved biologics (dupilumab, omalizumab, and mepolizumab) for CRSwNP, annual costs in Europe are estimated to range between €12,000 and €45,000 per patient.[97,98] Given that the average age of patients diagnosed with NSAID-ERD is around 30 years and that NSAID-ERD does not remit spontaneously, biologic therapy for an individual patient can cost from several hundred thousand to several million euros over the course of their lifetime.[87,92,95] There are currently no biosimilars for dupilumab, mepolizumab, and omalizumab on the European market. A biosimilar is expected to be the first for omalizumab, which could significantly reduce costs for the health care system. However, focusing solely on the direct costs is too short-sighted. The costs must be weighed against the effectiveness and the gain in quality of life, expressed by the "quality-adjusted life year," which stands for a year in perfect health.[99,100]

In 2008, Shaker et al[101] investigated the cost-effectiveness of ATAD in moderate to severe NSAID-ERD. The authors calculated the cost per quality-adjusted life year gained for outpatient ATAD in NSAID-ERD to be $6768. With various assumptions, ATAD always remained cost-effective in the low thousand-dollar range per quality-adjusted life year gained. The direct annual drug cost for ASA is less than €200, which is significantly lower than the cost of any biologic. No comprehensive cost-benefit analyses for CRSwNP exist for biologics to date. In a pharmacoeconomic study on asthma, the cost-effectiveness of omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab was determined. The authors concluded that prices should be reduced by at least around 60% to reach the cost-effectiveness threshold prices.[102] In summary, some questions remain about the true costs of both biologics and ATADs, but the cost difference in favor of ATADs compared with biologics is substantial. Soley based on a cost perspective, ATADs therefore appear to have an advantage, which, however, cannot lead to a clear positive assessment due to the lack of authorization and evidence to date.

COMBINATION OF SIMULTANEOUS ATAD AND BIOLOGICS

In a study at Brigham and Women's Boston Hospital, 24 of 98 patients reported concomitant use of ATAD and a biologic.[86] In fact, the choice does not necessarily have to be dichotomous. Even more so, ATAD and T2 biologics can have a synergistic effect when used in combination. T2 biologics help sufficiently in difficult cases where the response to ATAD is partial, but not enough to rule out the need for further therapy. Especially in the initial phase of an ATAD (induction phase), T2 biologics can also prevent a worsening of the clinical manifestations of NSAID-ERD and thus make the ATAD possible in the first place.

In particular, patients with NSAID-ERD with severe bronchial asthma or pronounced urticaria due to manifest overproduction of PGD_2 and LTE_4 may require the addition of a T2 biologic to tolerate a daily NSAID dosage in the context of ATAD.[95] Some data suggest that the effect of T2 biologics goes beyond the prevention of exacerbated reactions and has the potential to induce NSAID tolerance: of 33 patients who underwent an ASA provocation test before and after 6 months of anti-IgE therapy with omalizumab, 56% developed complete NSAID tolerance.[103] In another study, the effectiveness of 6 months of treatment with dupilumab in inducing tolerance to ASA was demonstrated.[80] Furthermore, a reduction in LT was shown in patients with CRSwNP after treatment with dupilumab.[73] The induction of tolerance toward higher dosages of NSAID must be looked at more thoroughly in the future when evaluating overall treatment success.

DISCUSSION

In the treatment of NSAID-ERD, ATAD and biologics play a decisive role alongside basic therapy with topical glucocorticoids and other standard therapeutic measures. The possible use of these 2 therapeutic options should be weighed up individually for each patient.

The clinical characteristics of the disease play a major role in decision making. In at least 50% of patients with NSAID-ERD, asthma meets the criteria for difficult to control severe asthma with standard therapy, which is the criterion used to indicate the start of biological treatment regardless of whether it is an NSAID-ERD or NSAID-tolerant asthma and is also a contraindication for starting ATAD. If only CRSwNP is severe and not the asthma, the recent acceptance of the use of omalizumab, mepolizumab, and dupilumab in the treatment of severe

CRSwNP based on its relevant therapeutic efficacy seems to require a deeper consideration in centers where ATAD is a viable option.

In meta-analyses on efficacy and safety, 24 randomized controlled trials evaluating 7 different biologics were included in addition to the 5 randomized controlled trials on ATAD.[82] Dupilumab add-on therapy uniquely ranks among the most beneficial for all outcomes studied. To cite 2 prominent studies, a *post hoc* analysis of the study cohort from the SINUS-24 and SINUS-52 studies, which led to the approval of dupilumab for the indication CRSwNP, a reduction in visual analog scale score from 7.99 to 4.39 after half a year was observed among patients with NSAID-ERD. A *post hoc* analysis of the SYNAPSE approval study for mepolizumab also showed that patients with NSAID-ERD did not perform significantly differently from patients without NSAID-ERD in terms of visual analog scale and sinonasal outcome test-22 scores, thus significantly reducing disease burden. In contrast to similar protocols for biologic studies, however, it is very difficult to pool the data on ATAD due to the differences in the study protocol (total daily ASA dose in the top-up and maintenance phase, treatment duration) and different primary end points.[84] In addition, most of the studies conducted have a retrospective study design. The longest retrospective study showed that 85% of patients were still taking aspirin daily 10 years after desactivation because they were able to achieve a very good or good improvement in the control of their CRS and/or asthma symptoms and in the improvement of their quality of life.[10,87] Although the study results on the effect of ATAD on the need for revision surgery are not yet conclusive, there is a consensus that ATAD has a protective effect on the regrowth of nasal polyps after ESS and also reduces the existing polyp burden.[69] The ability to smell is also improved by ATAD in 40% to 60% of patients with NSAID-ERD [86] although improvements in olfactory function are generally considered to be more of a strength of biologics.

Because patients with NSAID-ERD were only a subset of the population with CRSwNP included in phase III clinical trials with biologics, more studies on the efficacy of biologics in NSAID-ERD and data on their cost-effectiveness are needed. Real-world evidence studies of biologics in CRSwNP are being conducted internationally, capturing endotypes, phenotypes, and relevant biomarkers to answer questions such as which biologic provides the best results, which biomarker predicts response to therapy, and how long treatment should be continued.[104] The latter question is important to identify information on potential disease-modifying effects of biologics in CRSwNP and NSAID-ERD. Several studies already suggest that biologics may not only be supportive in enabling ATAD induction but may also support the development of tolerance to NSAIDs.[103,105,106] However, more research is needed on how ATAD leads to success and why some patients benefit more than others from ASA desactivation.

In our opinion, too little attention has so far been paid to patient-centered treatment. It goes without saying that patients should be involved in the decision as to whether ATAD or biologic therapy or a combination of both should be carried out. Some patients are afraid of a renewed NSAID-induced reaction and therefore refuse ATAD. In a survey of centers treating patients with NSAID-ERD, about half of the 109 patients were reluctant to start ATAD. The reasons given were as follows: 45% had concerns about long-term use of ASA, 27% were concerned about safety, 19% said their doctor had not recommended it, and 9% believed that the procedure was too expensive.[85] However, despite study data to the contrary, there are still patients who fear the effects of biologics on their immune system, especially in the absence of long-term safety data. In a survey of 98 patients with NSAID-ERD,[86] 60% of patients who discontinued an ATAD prematurely cited "adverse effects" as the reason, whereas in the biologics group 49% of those who discontinued therapy cited "lack of efficacy" as the most common reason for discontinuation. However, future studies should differentiate between the individual biologics, because there appear to be differences between the individual mAbs.[107] In one study, the serum IgE level was a biomarker for treatment success with biologics in NSAID-ERD, which could indicate the presence of different NSAID-ERD subendotypes[108] and raises the question of which NSAID-ERD endotypes would benefit more from ATAD and which would benefit more from biologic therapy. In a nasal secretion analysis, 3 subtypes of NSAID-ERD were defined, characterized by (1) a low inflammatory burden, (2) a high proportion of cytokines from T_H2 cells, and (3) a comparatively low proportion of T2 cytokines and a high proportion of T1 and T3 cytokines.[109]

Further research into biomarker-based endotyping and responder analyses is required, to be able to make individual treatment decisions. In addition, the results of the individual biologics phase 3 studies are not directly comparable, due to the different inclusion criteria,[110] and this applies even more to ATAD. The issue of insufficient diagnostic proof of NSAID-ERD in the biologic studies (no NSAID-ERD confirmed by controlled challenge, but purely based on anamnestic information) has already been addressed.[69,95]

The ambition is currently being redefined in chronic diseases. Nowadays, the traditional medical model, in which medicine is simply reactive, is no longer sufficient. Currently, medicine does not just cure, but tries to prevent, improve the quality of life, adapt itself to the individual, predict the evolution, and put the patient in the center of the disease. In obstructive airway diseases, the recent use of biologics is slowly but surely inducing a shift from the downstream firefighting approach to a more predict-and-prevent approach, aimed to reduce airway and people remodeling, and eventually achieve clinical remission.[82]

Our current perspective is that the therapeutic goal in NSAID-ERD should be complete remission of all the 3 underlying conditions: CRSwNP, asthma, and aspirin intolerance. Also, after 100 years of studying the natural history of the disease, we should aim to improve the prognosis of recently diagnosed patients with severe NERD. We can now predict and prevent airway remodeling, corticosteroid side effects, severe, even life-threatening asthma attacks, surgeries, hospitalizations, overall impaired quality of life, and other potential complications, by early introduction of disease-modifying drugs, ATAD, and/or biologics, as summarized in Figure 1.[82]

So, considering this new approach, this review advocates for the 5P Medicine[111] in NSAID-ERD, with the 5P standing for

- **Personalized:** Assess specific therapies for each patient (ATAD and/or biologics), depending on the severity of the underlying diseases, other conditions and associated risk factors, and patient preferences.
- **Predictive:** Analyze the future risk of developing complications of the diseases and/or of their treatments.
- **Preventive:** Make decisions that prevent the appearance of severe asthma attacks, loss of lung function, CRSwNP

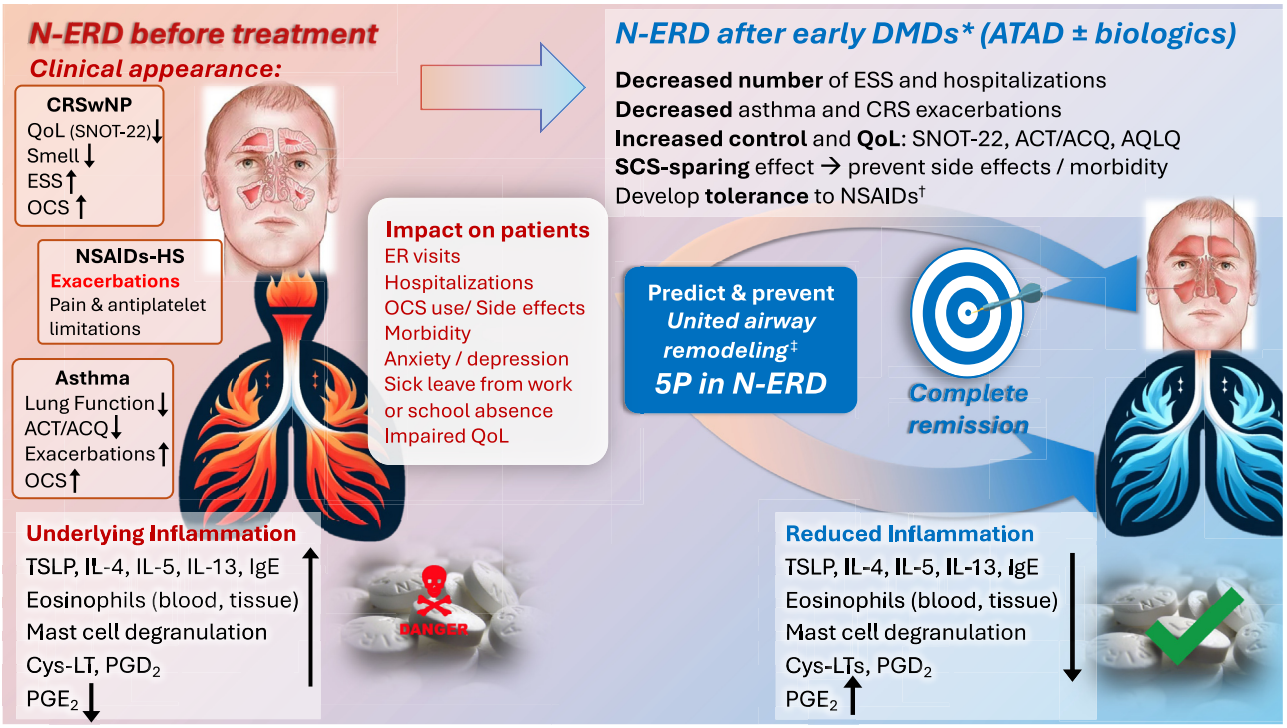

FIGURE 1. *5P*, Predictive, personalized, preventive, participatory, populational; *ACT/ACQ*, asthma control test/questionnaire; *AQLQ*, asthma quality of life questionnaire; *DMD*, disease-modifying drug; *ER*, emergency room; *HS*, hypersensitivity; N-ERD, NSAID-ERD; *PGE2*, prostaglandin E2; *QoL*, quality of life; *SCS*, systemic corticosteroid; *SNOT-22*, sino-nasal outcome test-22. *There is evidence on efficacy of DMDs in N-ERD at any time, but the benefits are higher, and the overall morbidity is reduced by early treatment. †Limited data available for change in tolerance after biologics but likely for ATAD. ‡Adapted from Couillard et al.[111]

recurrence, and side effects (systemic corticosteroids) of used medication mainly.

- **Participatory:** Try to put the patient at the center of the health care system, teaching and providing appropriate tools, so that the patient can participate in the responsibility for his or her health care.
- **Populational:** Must ensure access to health care for the entire population. Hence, in those countries worldwide where biologics are not yet available or the access to them is limited for many patients, ATAD is still a valid option in severe patients without contraindications, as a disease-modifying strategy.

CONCLUSIONS

Clinical observations, and the limited data obtained from clinical trials, show that patients with NSAID-ERD respond differently than NSAID-tolerant patients to biologics, a finding supporting further specific studies aimed to analyze optimal therapeutic options for patients with NSAID-ERD. ATAD still represents a valid option where available, in selected candidates, with or without biologics, in a personalized fashion, and including patient's preference (5P medicine in NSAID-ERD). Early use of disease-modifying drugs should be considered, given that the debut occurs usually in the third to fourth decade of life, and spontaneous remission is exceptional at most. So, complete disease remission with treatment is currently the ultimate goal in patients with NSAID-ERD.

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