

Review article

Important research questions in allergy and related diseases: nonallergic rhinitis: a GA²LEN paper

Nonallergic rhinitis (NAR) can be defined as a chronic nasal inflammation which is not caused by systemic IgE-dependent mechanisms. It is common and probably affects far more than 200 million people worldwide. Both children and adults are affected. However, its exact prevalence is unknown and its phenotypes need to be evaluated using appropriate methods to better understand its pathophysiology, diagnosis and management. It is important to differentiate between infectious rhinitis, allergic/NAR and chronic rhinosinusitis, as management differs for each of these cases. Characterization of the phenotype, mechanisms and management of NAR represents one of the major unmet needs in allergic and nonallergic diseases. Studies on children and adults are required in order to appreciate the prevalence, phenotype, severity and co-morbidities of NAR.

These studies should compare allergic and NAR and consider different age group populations including elderly subjects. Mechanistic studies should be carried out to better understand the disease(s) and risk factors and to guide towards an improved diagnosis and therapy. These studies need to take the heterogeneity of NAR into account. It is likely that neuronal mechanisms, T cells, innate immunity and possibly auto-immune responses all play a role in NAR and may also contribute to the symptoms of allergic rhinitis.

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Abbreviations: ARIA, Allergic Rhinitis and its Impact on Asthma; ASA, Aspirin; ECRHS, European Community Respiratory Health Survey; EGEA, Epidemiologic study on the Genetics and Environment of Asthma; FP5, European Union Fifth Framework Program; FP6, European Union Sixth Framework Program; GA²LEN, Global Allergy and Asthma European Network; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; NAR, nonallergic rhinitis; NSAID, nonsteroidal anti-inflammatory drugs; PRRs, pattern recognition receptors.

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Magnitude of the problem

Rhinitis is defined as an inflammation of the lining of the nose and is characterized by nasal symptoms including anterior or posterior rhinorrhea, sneezing, nasal blockage and/or itching of the nose (1).

Allergic rhinitis is the most common form of noninfectious rhinitis and is associated with an IgE-mediated immune response against allergens (2). Several nonallergic conditions can cause similar symptoms: infections, hormonal imbalance, physical and chemical agents, anatomical anomalies and the use of certain drugs (3). However, many patients have symptoms that mimic allergic rhinitis, with no definite causal factor and with a lack of demonstrated IgE-mediated allergy by skin prick tests and allergen-specific serum IgE (4). These patients have nonallergic rhinitis (NAR), sometimes ascribed to nonallergic, noninfectious rhinitis, and the prevalence in an adolescent/adult population with rhinitis is at least 25% (5–9). Although it is common, the prevalence in

early childhood and school-age children is not well known. Thus, there are well over 200 million people with NAR in the world, 50 million of them living in Europe.

Patients with NAR may be considered to be nonallergic because they have negative skin tests and serum-specific IgE. However, local IgE production and positive nasal provocation tests can be observed in some of these patients (10–13). The role of local IgE production in the inflammatory mechanisms of NAR is however unknown. So far, the definition of NAR is largely based on exclusion criteria, i.e. the absence of specific IgE to allergens and/or the absence of an infection. Several forms of rhinitis, based mainly on triggering agents, are commonly defined as NAR and a more univocal classification is therefore needed.

Allergic rhinitis is often associated with ocular symptoms and other co-morbidities including asthma. Asthma may be less common in patients with NAR (14).

Sinusitis and rhinitis frequently coexist and the correct terminology for sinusitis is now rhinosinusitis. Rhinosinusitis (including nasal polyps) is an inflammation of the

nose and the paranasal sinuses (15). Attempts have been made to define rhinosinusitis in terms of pathophysiology, microbiology, radiology, severity of symptoms and duration of symptoms (16–18). Rhinosinusitis represents a significant health problem with a large financial burden on society (19–21). Furthermore, the entity is rarely discussed in pediatric medicine, although upper respiratory complaints are common. The diagnosis of chronic rhinosinusitis cannot be made on the grounds of symptoms only (22). Epidemiologic data based on questionnaires for chronic rhinosinusitis are therefore limited and difficult to assess. As most epidemiologic studies on chronic rhinosinusitis are based on questionnaires, a large proportion of these patients may only have NAR without any significant sinus involvement.

A vast heterogeneity exists in patients with NAR, but phenotypic characterization is lacking because the disease has not yet been assessed globally and existing studies are fragmented. Furthermore, age-related considerations are necessary.

Recommendations for specific diagnostic criteria and treatment options for NAR are often lacking compared with those addressing allergic rhinitis (23).

The treatment of NAR is another unresolved problem. Many studies have found that NAR inconsistently benefits from treatments effective in allergic rhinitis (24, 25). However, patients with NAR may respond differently to treatments depending on their phenotype. Some forms of NAR react favorably to treatment with capsaicin without any known change in inflammatory cells (26–28).

Unresolved questions

Nonallergic rhinitis is common and probably affects more than 200 million people worldwide. Both children and adults are affected. However, its exact prevalence is unknown and its phenotypes need to be evaluated using appropriate methods for diagnosis and management. It is important to differentiate between infectious rhinitis, NAR and chronic rhinosinusitis, as management differs for each of these cases.

Studies in children and adults are needed to appreciate the prevalence, phenotype, severity and co-morbidities of NAR. These studies should compare allergic and NAR and consider different age group populations including young children and elderly subjects.

Mechanistic studies should be carried out to better understand the disease(s) and risk factors and to guide towards an improved diagnosis and therapy. These studies need to take the heterogeneity of NAR into account. It is possible that neuronal mechanisms, T cells, innate immunity and possibly auto-immune responses all play a role in NAR and also contribute to the symptoms of allergic rhinitis. Prospective viral epidemiology may help differentiate between the infectious and hyperreactive components.

Study of NAR

Epidemiologic studies

The epidemiologic definition of rhinitis has been difficult in large population studies where the characterization of nasal symptoms has not been the primary objective. Objective tests for the diagnosis of IgE-mediated allergy (skin prick tests, allergen-specific serum IgE) can be used (29–31). In both developed and developing countries, a large percentage of patients with an epidemiologic definition of 'allergic rhinitis' do not have positive skin tests or serum-specific IgE (5–9, 32, 33). Future studies should encompass not only clinical symptoms and immune response tests but also nasal function and eventually specific nasal challenge (34). More specifically-designed epidemiologic studies are needed to fully appreciate the prevalence of NAR. In these studies, co-morbidities should be considered.

In birth cohorts, many children have NAR (35–37) but the phenotype is unclear. More longitudinal and cross-sectional data are needed to define these patients.

Prevalence and severity of NAR in adolescents and adults. Studies such as the European Community Respiratory Health Survey (ECRHS) (38) or the Epidemiologic Study on the Genetics and Environment of Asthma (EGEA) (39) include patients with allergic and NAR. Among the subjects already enrolled in these studies, some of these phenotypes have already been collected. Analyses on factors associated with NAR should be conducted on aspects not previously addressed.

The newer Global Allergy and Asthma European Network (GA²LEN) questionnaire on the epidemiology of allergic diseases is currently being carried out in 22 centers. This questionnaire has been designed with a specific interest in nasal symptoms, as previous studies such as the ECRHS and EGEA were focused on asthma. This questionnaire can identify subjects with nasal symptoms but is unable to differentiate patients with allergic, NAR or rhinosinusitis due to the fact that these conditions cannot be accurately differentiated using questionnaires only. As for the second phase of ECRHS-I (40), in the GA²LEN study, a random sample of subjects will be invited to participate. A more detailed questionnaire on nasal symptoms, risk factors, triggers, skin tests and allergen-specific serum IgE will enable the differentiation of patients with allergic and NAR rhinitis. The severity of symptoms and their duration (intermittent/persistent rhinitis), as defined by Allergic Rhinitis and its Impact on Asthma (ARIA), together with a statement of associated co-morbidities should also be included. In some selected centers, nasal challenges with allergens and nonspecific triggers as well as nasal CT-scans will be carried out to assess the presence of local IgE immune responses, NAR triggers or rhinosinusitis.

In patients with rhinitis and/or asthma, another study in the context of GA²LEN is prospectively associating nasal and bronchial symptom variability with the presence and/or quantity of presumed triggers, including viral infections.

Birth cohorts: prevalence and severity of NAR in children. Long-term studies on children are appropriately carried out with birth cohorts. It has already been observed in some cohorts that many children with nasal symptoms are not allergic (35, 36). GA²LEN has made a special effort to coordinate a large number of European birth cohorts (41, 42). In cohorts analyzing nasal symptoms, the prevalence and risk factors of NAR can be assessed.

Allergic and NAR in elderly people. It has been proposed that allergic rhinitis is less common in subjects over 60 years of age than in younger subjects, possibly because the 'allergic epidemics' started more recently. However, in tree pollen allergy, many monosensitized subjects develop symptoms in old age (43, 44). On the other hand, NAR appears to be more common in subjects over 50 years of age than in younger ones (8). It is therefore of great interest to study subjects over 50 years of age to define the prevalence and the phenotype of rhinitis.

Gender differences. A number of studies have shown gender differences in the prevalence of wheeze and asthma (45) as well as in allergic and NAR. To examine the effect of gender-specific differences in environmental exposures and allergic and NAR prevalence and severity in puberty, large populations need to be investigated.

Co-morbidities. Allergic rhinitis is often associated with asthma and a global perspective is needed (46, 47). In some studies, it has been found that NAR is also associated with asthma (7, 14, 48). However, the importance of the association between the two sites of the airways needs to be better assessed comparing allergic and nonallergic patients, particularly in patients with uncontrolled asthma (49, 50).

For more than 80 years, the coexistence of asthma and chronic rhinosinusitis has been noted in the medical literature (51–53). The debate still remains as to whether chronic rhinosinusitis is a precipitating factor for bronchial asthma. Patients with severe and/or uncontrolled asthma have more severe nasal symptoms and CT-scan abnormalities than other patients (54–56). However, large multicentric studies are needed to better understand the association between the upper and lower airways in patients with severe asthma.

Social consequences

Like asthma (57), allergic rhinitis is known to affect social, school and professional life as well as sleep

(58–60). However, there is no existing study on NAR. It is important to compare patients with allergic and NAR and to assess the importance of the social impact of NAR using generic (61) and disease-specific questionnaires on quality of life (such as the rhinitis-specific quality-of-life questionnaire) (62, 63), sleep (58), school/work performance, allergy-specific work productivity and activity impairment (64).

Phenotype of NAR

Persistence and severity. The severity of NAR can be assessed using a visual analogue scale (65), quality of life and sleep questionnaires and the ARIA classification (2, 66, 67). Persistence can be assessed using ARIA criteria.

Occupational rhinitis and asthma. Occupational rhinitis is common and may be IgE or non-IgE mediated. With low molecular weight agents, nonimmunologic mechanisms are of importance (68). In patients with occupational rhinitis to high-molecular weight agents, the IgE immune response needs to be tested. T-cell responses may differ in occupational rhinitis and asthma (69).

Local IgE response. Local IgE response should be studied by nasal challenge with allergens (12). Local IgE production should be tested and compared in allergic and NAR (70–72).

Non-allergic triggers and pollutants. The upper airway occupies a sentinel position with respect to the physical and chemical qualities of the inspired atmosphere. Responses of the upper airway can be acute or chronic, as well as primary (sensory) or secondary (physiologic) (73–75). Nasal obstruction has been documented in response to a variety of agents, including acetic acid vapor, ammonia (76), chlorine (77, 78), mixed volatile organic compounds (79) or cold air (80).

However, it is often difficult to differentiate between acute, repeated acute (81) and chronic exposures such as outdoor air pollution which can induce nasal inflammation and symptoms in both adults and children (82–85). More data are needed on a global scale to appreciate these effects. The role of passive smoking is still a matter of debate, but subjects exposed for a long time to environmental tobacco smoke have an increased prevalence of rhinitis (86, 87).

Moreover, it is not known whether these agents act as inducers of NAR or triggers of nonspecific nasal hyperreactivity. Triggers of NAR include temperature changes (88), diesel and car exhaust, tobacco smoke, perfumes and fragrances, incense, cleaning products, newsprint, hairspray, as well as alcoholic beverages and spicy foods (89).

The different causes and triggers of NAR should be studied by questionnaire and environment assessment, and by using appropriate tests (in particular, challenge).

Moreover, nasal biopsies taken from subjects living in different environments are of importance in understanding the mechanisms of NAR.

However, critical issues underlying the interface between air quality science, stakeholder participation and policy development should be envisaged to promote scientific-based recommendations (90, 91).

Mechanisms: inflammatory mechanisms

Inflammation and cell persistence. Several important questions still remain to be answered concerning the inflammatory cells that contribute to allergic and NAR. These questions include the following points: cells limiting inflammatory responses and their regulation (92); possible defect in regulatory cells in allergy; possibility to induce physiologic anti-inflammatory molecular and cellular events; activation of dendritic cells; and role of eosinophils which is still unclear (93). Another important problem is the lack of appropriate biomarkers to diagnose and monitor allergic and nonallergic patients. However, new therapeutic tools may help to shed light, at least on some of these issues. For instance, the use of anti-IL-5 monoclonal antibody therapy may clarify under which conditions eosinophils are critical cellular elements in pathogenesis. A recent study indicated that eosinophils are critical in chronic rhinosinusitis with nasal polyps expressing high levels of IL-5 (94). Earlier *in vitro* studies suggested that anti-IL-5 treatment induces eosinophil apoptosis in nasal polyp explants (95).

Nasal biopsy studies have shown the phenotype of nasal tissue in allergic rhinitis (96, 97). However, less is known about biopsies in NAR (11, 26, 98, 99) although histological findings in NAR show a strong interaction between infiltrating mononuclear cells and the mucosal epithelium (100). Nasal biopsies of patients with allergic and NAR should be compared to assess the cell types involved. Moreover, apoptosis and its mechanisms are key elements in understanding the persistence of inflammatory cells in allergic and NAR (101).

T cell-mediated mechanisms. Patients with allergic rhinitis have an IgE-mediated response involving Th2 and T regulatory cells (T_{Reg}). Epithelial cells are important in allergic and NAR (100).

T cells and epithelial cells are likely to contribute to the commencement and progression of NAR. Based on our current understanding of the mechanisms of chronic inflammation in the upper airways, viral and/or bacterial infection may prime and activate epithelial cells and initiate a chemokine cascade in attracting T cells, neutrophils and eosinophils to the nasal mucosa. The function of a novel T-cell subset characterized by the secretion of IL-17 and named Th17 cells (102) may be a key factor in the progression of NAR. The major cytokine released by Th17 cells, IL-17A, stimulates

fibroblasts, macrophages, endothelial and epithelial cells to produce a variety of inflammatory mediators, e.g. IL-1, IL-6, IL-8, TNF- α and chemokines which are potent inducers of inflammation (102).

T regulatory cells are essential in the regulation of allergic diseases (103). The CD4⁺ CD25⁺ T_{Reg} cells, also called constitutive T_{Reg} cells, inhibit the activation of effector T cells. These cells, along with CD4 and CD25 expression, are also associated with the transcription factor FoxP3 (104). There is some evidence in adults that constitutive CD4⁺ CD25⁺ T_{Reg} cells and inducible IL-10- and TGF- β -secreting Tr1 cells represent overlapping populations. CD4⁺ CD25⁺ T_{Reg} cells normally inhibit Th2 cytokine expression and the proliferation of peripheral blood mononuclear cells from nonatopic donors, in response to allergen. This suppression has been shown to be associated with the control of allergic disease (105).

The T cell-mediated regulation of NAR should be investigated and compared with allergic rhinitis (98). The following experiments may be useful in exploring the nature of NAR. The co-culture of T cells with nasal epithelial cells and sinus epithelial cells should be performed as well as the investigation of T cell and epithelial cell activation-related surface ligands, cytokines and chemokines. The investigation of the contribution of Th17 T_{Reg}, Th1 and Th2 cytokines to the development of NAR and the determination of their mechanisms of action should be focused. Furthermore, the epithelial cell response to these T-cell subsets and their effector cytokines and surface molecules should be investigated. Nose-infiltrating T cells and nasal epithelial cells can both be isolated and characterized and compared with healthy subjects, allergic rhinitis, NAR and chronic rhinosinusitis. The *in vivo* relevance of the findings should be confirmed by the direct demonstration of these cells and their effector molecules in sinus and nasal tissues. Moreover, *in vivo* T-cell reactivity against certain allergens, such as *Betula verucosa* allergen 1, should be tested using patch tests with non-IgE binding recombinant *Betula verucosa* allergen 1 fragments (106).

Auto-immune responses. Allergy symptoms are usually triggered by an IgE-mediated mechanism, but they can also be elicited by self-antigens (107). Two classes of self-antigens can be involved in allergic reactions: human proteins with extended sequence homology to environmental allergens (108) and self-antigens without any sequence homology to IgE-binding proteins (109).

The first class includes phylogenetically highly-conserved proteins such as manganese-dependent superoxide dismutase (MnSOD), acidic P₂ ribosomal protein, cyclophilin, thioredoxin and profilin. This class most likely induces symptoms through molecular mimicry between shared B- and T-cell epitopes present in homologous pairs of molecules (110–112). Based on the solved crystal structures of the environmental allergens MnSOD,

cyclophilin and thioredoxin, reactivity to self-antigens showing sequence homology with environmental allergens can be clearly traced back to conserved amino acid residues clustered on the surface of the IgE-binding molecules. All of these proteins, except profilin, are able to stimulate T cells in sensitized individuals and to induce strong skin test reactions *in vivo*. Moreover, human MnSOD is sufficient to elicit eczematous reactions, if applied to healthy skin areas of atopic eczema patients in atopy patch tests (113). These findings strongly support a pathogenic role of self-antigens in perpetuating eczematous reactions.

The second class of IgE-binding self-antigens can be obtained by screening a human lung cDNA library displayed on a phage surface with the allergen-specific serum IgE of patients suffering from long-lasting allergic diseases. This class spans a vast variety of structures without sequence homology to known allergens. Although not yet analysed in detail, some of the cDNA sequences show a high degree of sequence identity and cross-reactivity to environmental allergens (107), as shown by a retrospective analysis of the sequences.

Much more is not yet known about the auto-reactivity of self-antigens without sequence homology to environmental allergens. It is still unclear as to whether they are able to directly induce a B-cell switch towards IgE production, or if the observed IgE-binding capability is a result of cross-reactivity with unidentified environmental allergen structures. Because all individuals have total IgE in serum, it would be interesting to screen human cDNA libraries with the serum IgE of NAR patients to clarify whether IgE-mediated auto-reactivity to self-antigens such as 'hidden allergens' can contribute to the pathology of NAR.

Mechanisms: infections, innate immunity and dendritic cells

The nasal mucosa is frequently exposed to bacterial and viral infections. Infectious rhinitis, most often caused by respiratory viruses and characterized as a 'common cold', may trigger both allergic (114, 115) and NAR in addition to asthma (116). However, the role of viruses in the development of persistent rhinitis has not been adequately assessed. In community studies, the duration of the common cold has been quoted to be a few days, but occasionally up to several weeks: it is not clear whether such prolonged illness may in fact be the expression of pre-existing or concurrent nasal hyperresponsiveness.

Airway epithelial cells, the primary site of human rhinovirus infection, provide a link between the innate and specific immune response to rhinoviruses. A single layer of epithelial cells separates the host tissues from luminal bacteria. The immune system has innate and adaptive components, which cooperate to protect the host against infections. The innate immune system consists of functionally distinct 'modules' that have

evolved to provide different forms of protection against pathogens (117). The immediate activation of innate immunity relies on the detection by the host of conserved microbial motifs known as pathogen-associated molecular patterns, comprising diverse molecules from bacteria and viruses, such as lipopolysaccharide, peptidoglycan, flagellin and lipoproteins (118). The understanding of innate immunity has increased enormously with the discovery of many microbial sensors called 'pattern recognition receptors' (PRRs). The toll-like receptor and NOD receptor families of PRRs appear to play essential roles in mucosal homeostasis, and alterations may contribute to the pathogenesis of NAR.

Mucosal surfaces contain specialized dendritic cells capable of sensing external stimuli, such as environmental stimuli and pathogens, and of mounting appropriate local responses depending on the nature of the elements encountered. In the absence of pathogens, mucosal dendritic cells either ignore the antigen or induce regulatory responses. Upon recognition of microorganisms that invade the mucosal barrier, mucosal dendritic cells mount robust protective immunity (119). Nasal innate immunity and the phenotype of nasal mucosal dendritic cells should be studied in NAR and compared with allergic rhinitis.

Mechanisms: neurogenic mechanisms

The nose provides defensive and homeostatic functions requiring rapid responses to physical and chemical stimuli (120). As a result, it is armed with a complex nervous system that includes sensory, parasympathetic and sympathetic nerves. Sensory nerves transmit signals from the mucosa, generating sensations such as pruritus, motor reflexes such as sneezing and parasympathetic and sympathetic reflexes that affect the glandular and vascular nasal apparatuses (121). Reflexes directed to the nose are also generated by inputs from other body regions. Neural function can be chronically upregulated in the presence of mucosal inflammation, acutely with an allergic reaction, or even in the absence of inflammation, as in the case of NAR. Upregulation of the nasal nervous system can occur at various levels of the reflex pathways. This can result in exaggerated responses (neural hyperresponsiveness), as well as in an increased capacity for the generation of neurogenic inflammation, a phenomenon that depends on the release of neuropeptides on the antidromic stimulation of nociceptive sensory nerves. The molecular mechanisms of hyperresponsiveness are not understood, but several inflammatory products appear to play a role. Neurotrophins, such as the nerve growth factor (122), are prime candidates for mediators of neural hyperresponsiveness.

Interrelationships between neurogenic and immune mechanisms of NAR should be studied using nasal biopsies, nasal challenge with various neuropeptides (123) and animal studies.

Mechanisms: pharmacologic mechanisms (ASA)

Aspirin (ASA) and nonsteroidal drugs are considered to be common triggers of NAR and asthma. Although these triggers could be potentially avoided, the presence of ASA-sensitivity is a hallmark of unusually severe rhinosinusitis and asthma (124, 125). The greater severity of rhinosinusitis in ASA-hypersensitive patients is reflected by characteristic cellular profiles of the airway inflammation with a high degree of tissue eosinophilia and frequent association with nasal polyposis. The mechanisms of ASA-induced reactions and associated chronic inflammation are thought to be nonimmunologic, but related to abnormalities in arachidonic acid metabolism (including both prostaglandin deficiency and leukotriene overproduction). The mechanism of ASA-induced asthma and rhinosinusitis should be clearly differentiated from other adverse allergic reactions to single nonsteroidal anti-inflammatory drugs (NSAIDs), most commonly presenting as urticaria (126). Understanding the pathophysiologic mechanism of the increased severity of upper airway inflammation in patients with ASA-sensitivity could lead to novel therapeutic approaches to other nonimmunologically-mediated diseases characterized by tissue eosinophilia (e.g. nonallergic asthma). ASA-induced respiratory disease has been widely studied in some GA²LEN centers, but further studies addressing the pathogenesis of hypersensitivity to NSAIDs and underlying severe airway inflammation are warranted.

Proteomics and genomics

Since the completion of the human genome, the interest of the scientific community has evolved towards understanding the human proteome. Genomic and proteomic data will facilitate our understanding of the functions of proteins in diseases and the discovery of novel drug target proteins and biomarkers of diseases as well as the impact of environmental triggers in rhinitis (127). The proteomics of nasal secretions and other fluids from the respiratory tract can provide a very potent tool to dissect allergic and NAR (128–133). The analysis of these fluids is challenging because of the low protein content and the presence of mucopolysaccharides. Data on the global proteome of these fluids are available, leading the path to their use for a biomarker discovery program. Genomic analyses can be carried out on the cells of nasal fluid or biopsy specimens (134–136).

The interest of developing proteomic research on nasal fluid in NAR is based on previous data indicating that the proteome of this fluid is affected in seasonal allergic rhinitis and modified by pharmacologic treatment (128–132). Nasal fluid is a readily-accessible biological fluid whose composition may alter as a consequence of disease. Research on biomarkers in NAR can therefore be conducted using high throughput profiling technologies such as those combining chromatography on chip (SEL-

DI[®]) or on magnetic microbeads (Clinprot[®]; Bruker Daltonics, Bremen, Germany) followed by a mass spectrometry time-of-flight profile (137). These approaches on multiple samples could be combined with more powerful analytic techniques using electrophoresis and mass spectrometry (2DE, LC-MS/MS). The ultimate goal of this proteomic research would be to identify and validate protein changes to enable a differentiation of patients with allergic and NAR rhinitis.

Genetic studies

Once NAR phenotypes are characterized, genetic studies will be performed and allergic and NAR compared. Single nucleotide polymorphisms together with functional studies in relevant cytokines and their receptors remain to be elucidated.

Clinical trials

GRADE evaluation of clinical trials in NAR. A systematic review of what is currently known about the evidence from clinical studies, in particular clinical trials in NAR, will be conducted (138). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be used to assess the quality of evidence of the clinical studies on NAR.

Proposal for clinical trials in NAR. Once phenotypes are defined, randomized clinical trials will be carried out with current or novel therapies determined by mechanistic studies. Short- and long-term treatments will be examined. In long-term treatments, only patients with persistent NAR will be enrolled, as patients with intermittent NAR may be symptom-free within a month after starting the trial.

How EU projects can help

The EU has led a large number of projects on allergic and related diseases. Their methods and results are of importance both in the design and performance of new studies, and it appears that the expertise gained in these projects could be essential for the understanding and treatment of NAR.

The methods and results of several projects focusing on air pollution and respiratory health should be examined. These include the ECRHS-I and II (FP3, FP4 and FP5) (38, 139), AIRALLERG (Effects of outdoor and indoor air pollution on the development of allergic disease in children, FP5) (140, 141), Health effects of particles from motor engine exhaust and ambient air pollution, FP5 (142), PATY (Pollution and the young combined analyses of cross-sectional studies of respiratory health of children and air pollution, FP5) (143–145) and Respiratory Allergy and Inflammation due to Air Pollution (FP5) (146).

BioAir (FP5), a longitudinal assessment of clinical course and biomarkers in severe chronic airway disease, has used modern clinical measurements and the exploitation of new molecular methods to define biomarkers of chronic airway inflammation and remodeling. The methods developed and standardized can be used for the assessment of the inflammation of NAR.

The Global Allergy and Asthma European Network (FP6) is a network of European centers of excellence in allergy. It consists of 26 partners and over 80 collaborating centers (147). In GA²LEN, interaction is optimal between allergists, pediatricians, ENT physicians, epidemiologists, methodologists and basic scientists. All methods required for a project on allergic and related diseases are regularly used in the network. A GA²LEN epidemiologic study is currently being performed in 22 centers using a questionnaire on nasal symptoms (110 000 subjects are being recruited from the general population). This epidemiologic study can be used to characterize the NAR phenotype, co-morbidities and social consequences. Skin tests are standardized between GA²LEN centers (148). The use of standardized extracts optimized by

CREATE (149) will improve the detection of allergic patients. GA²LEN has made a particular effort to coordinate birth cohorts in allergy (41, 42). Networks on ASA-induced asthma and rhinitis (124) or on exacerbations of asthma and rhinitis have been established in GA²LEN. Methodologists are members of GA²LEN and can evaluate trials using the GRADE approach (150, 151). A clinical center network has been established within GA²LEN. Moreover, GA²LEN has official interactions with AllerGen NCE (Canada) and the research can be expanded to non-European centers.

GABRIEL (FP6) is important in genetic studies. Moreover, policies such as AIRNET (91, 152, 153) supporting the Clean Air for Europe program (154), and Towards Healthy Dwellings in Europe (90) should be considered.

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