UNANSWERED QUESTIONS ON
EXACERBATIONS OF ASTHMA AND RHINITIS:
A GA\textsuperscript{2}LEN WORKSHOP REPORT

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Abstract

Although, novel approaches towards asthma control are regularly proposed in the literature and incorporated in guidelines, avoidance and/or treatment of exacerbations continues to represent an unmet need. This is especially true for exacerbations in which viral presence is confirmed and/or the asthma phenotypes which are driven only by respiratory infections. This suggests that more research is needed to improve understanding of the mechanisms underlying exacerbations and assess potential therapeutic alternatives. On March 2006, members of the GA²LEN work-package on ‘exacerbations of respiratory allergy’ took part in a workshop aimed at identifying research gaps that are amenable to further studies. The conclusions of the workshop are reported herein.

Keywords: Asthma, rhinitis, exacerbation, infection, respiratory virus
INTRODUCTION
On March 2006, members of the GA\textsuperscript{2}LEN work-package 2.2.3 on ‘exacerbations of respiratory allergy’ took part in a workshop aimed at identifying research gaps that are amenable to further studies. The conclusions of the workshop and comments of the work-package are reported herein.

Although, novel approaches towards asthma control are regularly proposed in the literature (1-4), and incorporated in guidelines (5), avoidance and/or treatment of exacerbations continues to represent an unmet need. This is especially true for exacerbations in which viral presence is confirmed and/or the asthma phenotypes which are driven only by respiratory infections (6). This suggests that more research is needed to improve understanding of the mechanisms underlying exacerbations and assess potential therapeutic alternatives.

DEFINITIONS
A major problem in exacerbation research is the lack of concrete definitions and an overlap between the concepts of ‘exacerbation’ and ‘lack of control’(7). Rapid symptom progression and clinically significant changes from a previous baseline are clinical tools efficiently used by physicians; epidemiological and clinical trial definitions often rely on indirect measures such as drug or health care utilization, however, these are retrospective. Inconsistent or retrospective definitions may lead to a series of problems, such as when attempting to include or group patients in therapeutic trials or designing intervention algorithms. The problem becomes more pronounced when allergic rhinitis is also taken into account: although asthma and rhinitis are literally considered as one disease (8), the concept of ‘allergic rhinitis exacerbations’ is, to say the least, vague. Nevertheless, respiratory viruses, the major trigger of asthma exacerbations, also induce symptoms in allergic rhinitis patients, although discrimination from viral rhinitis is uncertain. Definition, pattern recognition, natural history and pathophysiology of virus-induced upper respiratory tract disease in allergic patients are important research priorities. Clearer definitions are also needed for virus-associated asthma phenotypes in childhood, based upon exacerbation characteristics.
**METHODOLOGICAL ISSUES**

Respiratory viral infections are the major triggers of acute asthma exacerbations, both in children and adults (9, 10). A limiting factor in understanding and evaluating asthma exacerbations is the ability to detect respiratory viruses. In this respect, molecular tools that have appeared in the last few years and are rapidly evolving are of particular value. Nevertheless, optimization and validation of such methodologies is still lacking. The usefulness of quantitative versus qualitative approaches, or viral presence versus proliferation/viability, are among currently evaluated issues. Sampling techniques as well as appropriate biological materials for virus detection and isolation and finally clinical (symptoms and signs) and paraclinical information (e.g. endoscopy, imaging) which would give the highest diagnostic accuracy, are subjects that require attention.

**EPIDEMIOLOGY**

Studies showing a very high prevalence of viral infections in association with asthma exacerbations have been conclusive. However, until now, few studies have attempted to compare infection and consequent exacerbation rates between countries, urban or rural environment, or other life-style parameters. It is possible that part of the variability in reported asthma prevalence might be explained by differential virus circulation in communities, as well as the closely associated herd antiviral immunity. As an interesting example, school attendance is strongly associated with asthma exacerbations, through viral infections which spread rapidly as soon as children return to school after vacation (11).

Exacerbation rates have increased in Europe over the last decade, according to results of the ECRHS (12), however, we do not know to what extent this may reflect an increase in viral prevalence or changes in viral ecology. In this respect, although human rhinoviruses (RV) are the agents most frequently associated with asthma exacerbations, it is still unclear whether this reflects the preponderance of these agents as respiratory pathogens, or a particular propensity to induce bronchoconstriction and wheezing.
INTERACTIONS

There is no doubt that a multitude of factors are involved in the development of rhinitis and asthma exacerbations. Both clinical and experimental evidence suggest that respiratory viruses are coupled and/or interact with aeroallergens, air pollutants, climatic factors and more to induce or complicate respiratory symptoms and exacerbate rhinitis or asthma (13). Atopic allergic individuals may be more prone to such effects. Several years ago it was demonstrated that viral infections enhance allergen-induced inflammatory responses, eosinophil recruitment, histamine release and late phase airway responses (14). However, not all clinical and experimental settings have reached the same conclusion. For instance, there are studies that failed to show any synergistic or even additive effect between viral infection and allergen exposure and even one in which a protective role of allergen exposure against viral infection was shown (15).

Moreover, the relative contribution of each factor, the sequence of events that lead to an exacerbation, the natural history and mechanisms of such interactions would need to be better understood in order to be able to design improved therapeutic strategies. In this respect, longitudinal studies with robust designs, assessing in parallel potential inducers as well as confounders are necessary. Novel virus sampling techniques, but also information on personal exposure to pollutants and allergens, implementing temporal and geographical distribution models, would greatly contribute towards this task.

MECHANISMS

Although mechanistic studies have a very wide scope in respect to potential research directions, issues around the innate immune response to viral infections may provide the next step in understanding and subsequently intervening in virus-induced exacerbations. Recent data suggest that impaired antiviral immunity is closely associated with the development, expression and/or consequences of an acute asthma exacerbation (16). Such antiviral responses are regulated and affected by a multitude of cells and mediators and, although the respiratory epithelium retains a central role, the relative contribution of each individual element requires attention. Several interferon-associated genes are
upregulated soon after exposure of epithelial cells to RV; deficient production of IFN-α, IFN-β, IFN-γ and IFN-λ may help explain the impaired antiviral responses in atopic individuals, which are in turn associated with exacerbations (17-19). Pattern recognition, e.g. by Toll-like receptors, and effector molecules, such as the antimicrobial defensins, are certainly promising fields. The possibility that one or more viral infections could be able to switch the epithelial response to a remodeling phenotype is yet another concept that may provide a link between disease exacerbation and persistence (20). A detailed review on the mechanisms of virus-induced asthma exacerbations has been published by GAALEN (26). Finally, models combining virus-induced pathophysiology with other triggers may offer additional information and identify common or distinct pathways.

**THERAPEUTIC INTERVENTIONS**

Treatment of an exacerbation after its initiation, has not changed for the last several years, comprising of bronchodilation, systemic steroids and supportive oxygenation (5). However, it is interesting to note that many major trials on preventive asthma medications and/or strategies are using exacerbations as a major outcome (21). *In-vitro* studies have shown that many widely used drugs, including antihistamines, glucocorticosteroids and long acting b2-agonist-steroid combinations, can block inflammatory mechanisms induced by virus infections in airway epithelial cells (22, 23), although these results have not been paralleled by equally convincing clinical data. In general, treatment of virus-associated asthma exacerbations with systemic steroids or high doses of inhaled steroids is less effective than the control of persistent asthma, suggesting that during virus-induced asthma exacerbations a relative steroid resistance may occur. It is probable that selection of populations, phenotypes, age groups, severity stage and/or other strategic parameters may affect effectiveness. Currently explored strategies include the leukotriene receptor antagonist montelukast given intermittently for mild cases or intravenously upon exacerbations (4, 24), and steroid-LABA combinations, either fluticasone-salmeterol at high doses aiming to achieve complete asthma control (1), or the budesonide-formoterol combination, following disease activity in order to prevent exacerbation development (3). Future possibilities include antiviral and new anti-inflammatory drugs, which, however, will require time in order to prove their safety and efficacy. Recently arrived or coming soon, biologicals such as anti-IgE and anti-TNF respectively
seem promising; their full potential is still to be explored. Interest in macrolides has recently re-emerged, based on the results of a study showing improved symptoms and lung function in patients receiving telithromycin during an acute asthma exacerbation (25).

CONCLUSIONS

Exacerbations of asthma and rhinitis are currently receiving considerable attention, as more information on their epidemiology, mechanisms and precipitating factors becomes available. Increasing understanding and but also awareness on the consequences of this aspect of asthma and rhinitis may minimize morbidity, mortality and health expenses and relieve many actual or potential patients, providing improved quality of life.


(5) GINA. Global strategy for asthma management and prevention. 2006.


