

Original article

GA²LEN (Global Allergy and Asthma European Network) addresses the allergy and asthma ‘epidemic’

Allergic diseases represent a major health problem in Europe. They are increasing in prevalence, severity and costs. The Global Allergy and Asthma European Network (GA²LEN), a Sixth EU Framework Program for Research and Technological Development (FP6) Network of Excellence, was created in 2005 as a vehicle to ensure excellence in research bringing together research and clinical institutions to combat fragmentation in the European research area and to tackle Allergy in its globality. The Global Allergy and Asthma European Network has benefited greatly from the voluntary efforts of researchers who are strongly committed to this model of pan-European collaboration. The network was organized in order to increase networking for scientific projects in allergy and asthma around Europe and to make GA²LEN the world leader in the field. Besides these activities, research has also been carried out and the first papers are being published. Achievements of the Global Allergy and Asthma European Network can be grouped as follows: (i) those for a durable infrastructure built up during the project phase, (ii) those which are project-related and based on these novel infrastructures, and (iii) the development and implementation of guidelines. The major achievements of GA²LEN are reported in this paper.

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Allergic disease in Europe

The Global Allergy and Asthma European Network (GA²LEN), a Sixth EU Framework Program for Research and Technological Development (FP6) Network of Excellence, was created as a vehicle to ensure excellence in research bringing together research and clinical institutions to combat fragmentation in European allergy and asthma research. Allergic diseases including allergic rhinitis, asthma, rhino-conjunctivitis, gastrointestinal symptoms, urticaria and eczema are among the most common chronic diseases in the world (1) and rank first in Europe. Their prevalence continues to grow with one child in three now affected by an allergic disease. Trends indicate that half of all Europeans will suffer from allergy by 2015. There is significant under-diagnosis and under-treatment in all areas of allergy, with the majority of patients left untreated according to existing medical standards. Some allergies may exceptionally be fatal. Patients with

allergic diseases usually have impaired social life, work and school performance (2–4) which may be severe and debilitating. Many allergic patients present with co-morbidities or develop them during the course of the disease (5). Co-morbidities increase the complexity of management as well as the costs.

As the prevalence of allergic disease has already reached more than 35% in the age group of the working population, it is of utmost importance to look at both the costs of treatment for the European Union (EU) health-care systems as well as the socio-economic costs which occur due to under-treatment. The direct costs for the healthcare system clearly relate to the stage of the disease. The treatment in allergic rhinitis often costs < 30–50 €/day on average, while persistent severe allergic asthma (a consequence of earlier undertreatment) can cost over 30 €/day for treatment only (6). Early treatment to avoid progression of disease is therefore an important issue, also from an economic point of view. However, in many EU member states, allergic rhinitis is still not regarded as a severe disease and medications are not reimbursed. This has led to the unfortunate situation that far less than half of the population with allergic rhinitis is correctly diagnosed and treated. This circumstance has severe socio-economic implications. Allergic rhinitis, similar to a common cold, impairs mental capacities and learning by up to 30%. This disease, therefore,

Abbreviations: EAACI, European Academy of Allergology and Clinical Immunology; EFA, European Federation of Allergy and Airway Diseases Patients Association; ERS, European Respiratory Society; FP6, Sixth EU Framework Program for Research and Technological Development; GA²LEN, Global Allergy and Asthma European Network (an FP6 project); SCUAD, severe chronic upper airway disease; WP, Work Package.

has a severe impact on work productivity (7). Indirect costs induced by allergic rhinitis alone are far higher than expected (8). Recent calculations by GA²LEN and EAACI show that they range in the order of 100 billion € lost to Europe's industry, simply due to lost working hours (9). According to this calculation and a recent study (8), on average, treatment costs of 50 €/day can save over 50 €/day of loss in working time. Allergic diseases and asthma are the only major noncommunicable diseases which often start early in life and continue throughout life (10). This impacts the socio-economic consequences of allergic diseases since long-term costs should be projected and school learning disability (4) is difficult to modelize.

Role of GA²LEN

The Global Allergy and Asthma European Network has had a clear mandate from the EU not to primarily conduct research but rather to create a durable infrastructure facilitating future research in allergy and ensuring a systematic dissemination policy. For this purpose, GA²LEN was given the task to create, amongst others, centralized structures like flexible web platforms for secure communication and an office managing the network and overviewing the multiple assets in knowledge of the different GA²LEN partners, enabling them to optimally synchronize their research efforts. Creating these structures has been complex since not only many technical and legal aspects had to be solved but also a whole new atmosphere of trust had to be created. Since data and knowledge are the main assets of every researcher, it is evident that combining data from different partners is extremely useful for increasing society's knowledge, but is a sensitive issue regarding intellectual property rights. This is why a network is needed to fully understand all aspects of these diseases. This whole infrastructure is now established and could be used for other EU research programs in allergy, eventually saving public money by facilitating the processes.

The Global Allergy and Asthma European Network has conducted activities covering all aspects of allergy including fundamental, clinical, translational and epidemiological research and has turned results into clinical guidelines for health professionals and information for patients and the public. The ability to coordinate Europe-wide studies involving patients from different environments and leading different lifestyles is fundamental if scientists are to understand the causes of allergic diseases, their development through life and ultimately how to treat them more effectively, reducing the socioeconomic burden associated with allergies.

New research questions exist in allergic diseases and asthma, and some of them have been considered by GA²LEN (11). These include nonallergic rhinitis (12), drug allergy (13) and chronic rhinosinusitis (14).

The existing GA²LEN network

GA²LEN is a multidisciplinary research network (15–17).

Its vision is to address all aspects of allergic diseases in order to create a better understanding of allergic diseases among the general public, patients, health professionals and policymakers and to develop the highest standards for clinical care with the final goal of reducing the burden of allergy and asthma for patients and society in Europe.

Mission statement. The Global Allergy and Asthma European Network is a network created by research and clinical institutions for research and clinical institutions to address asthma and allergy in its totality, from basic and translational research to its implementation into clinical practice, with the aim of setting the highest standards for the harmonized clinical care of allergy and asthma patients. The Global Allergy and Asthma European Network aims to enhance the quality and relevance of European research and to disseminate best practice and knowledge to health professionals, patients and policy makers. Understanding factors and mechanisms of allergic diseases will contribute to developing better health care and improving the quality of life of more than 80 million Europeans with allergies.

GA²LEN members include:

- 27 research centers and 60 Collaborating centers.
- 500 researchers in 25 countries.
- Nine research topics from fundamental research to clinical guidelines.
- The European Academy of Allergology and Clinical Immunology (EAACI).
- The European Federation of Allergy and Airway Diseases Patients Association (EFA).
- Two small and medium enterprises.

GA²LEN achievements

The network was organized in order to increase networking for scientific projects in allergy and asthma around Europe and to make GA²LEN the world leader in the field. Besides these activities, research has also been carried out and the first papers are being published. Global Allergy and Asthma European Network achievements in general can be grouped as follows: those for a durable infrastructure built up during the project phase, and those which are project-related and based on these novel infrastructures.

GA²LEN infrastructure

The Global Allergy and Asthma European Network is governed democratically by the Assembly where all partners have equal voting rights. In between Assemblies, an Executive Committee organizes the workflow and takes the necessary decisions. The daily workflow is managed by

employed staff at the GA²LEN office, supervised by the Secretary General. The Global Allergy and Asthma European Network is a registered trademark and has created its own legal entity GA²LEN e.V. to ensure sustainability independent of the duration of the EU commitment. However, the infrastructure created by GA²LEN cannot be self-supporting for long periods without extra funding, and depends, at least partly, on its future use in research programs. The infrastructure is durably built up and is based mainly on the following platforms.

- Secure web platform for secure data and knowledge exchange and storage.
- Knowledge on biobanking.
- Secure SharePoint® IT platform for simplifying collaboration without data loss independent of localization.
- Clinical trials platform with novel instruments to ensure a higher quality of clinical trials.
- Administrative platform for supporting partners in the distribution of financial and human resources and accounting.
- Office support platform for synchronizing research efforts among partners avoiding redundant research efforts in the consortium.

Project-related research work

Quality management. Standards in allergy clinical care and diagnostic procedures (e.g. skin prick tests) (18) have been published. Several Position Papers increasing the standardization of methods have been published by members of Working Packages, most of them in collaboration with EAACI:

- Aspirin challenges (19).
- Atopy patch tests (20).
- Eczematous reactions to foods in atopic dermatitis (21).
- Exercise-induced asthma in sports (22, 23), in collaboration with the European Respiratory Society (ERS).
- Nonspecific provocation tests (24).

GA²LEN epidemiologic survey. This is a new study that is being carried out by GA²LEN members and some collaborative centers in order to assess the prevalence of allergic and airway diseases. It will be used to assess the prevalence and impact on the quality-of-life (EuroQOL) of various diseases including severe asthma and severe chronic upper airway disease (SCUAD). This study is extending the methods of the European Community Respiratory Health Survey (ECRHS) to study a wider age range and to include other conditions such as chronic rhino-sinusitis. It will also indicate the trends of prevalence and severity of allergic diseases and asthma in

Europe. Collaborative GA²LEN studies have led to harmonize methods within the network and to better understand the relationships between paracetamol use or selenium and asthma (25, 26).

GA²LEN birth cohorts. This study is unique in the world, extremely innovative and expanding outside Europe. It has attempted to combine the data of many European birth cohorts dealing with asthma and allergic diseases in a single database in order to analyse several risk factors and severe diseases (27, 28). About 41 420 participants from 24 birth cohorts from 20 centers in 9 countries were pooled and 50 risk and protective factors considered. A first pooled analysis focusing on pet keeping and allergic diseases has been completed. The study tested the possibility of conducting meta-analyses on data pooled from the Birth Cohorts which will be published in 2009 (29). New birth cohorts from non European countries will be incorporated later this year. It is expected that this study will form the basis for questions which cannot be answered by individual birth cohorts.

Gender. A number of studies have shown gender differences in the prevalence of wheeze and asthma. One review examined published results on gender differences in childhood and adolescent asthma incidence and prevalence, to define current concepts and to identify new research needs (30). This review suggested that sex hormones play an important role in the development and outcome of the allergic immune response (asthma in particular) and helped the development of the GA²LEN epidemiologic survey questionnaire.

GA²LEN nutrition. An extensive review reported the studies on interactions between allergic immune response (asthma in particular) and nutrition. It raised a serious methodological problem associated with international studies of nutrition, relating to how items for food frequency questionnaires could be selected to provide adequate information on a wide variety of diets. A GA²LEN food frequency questionnaire was drawn up and successfully piloted in 5 countries representing widely divergent diets. It helped the development of the GA²LEN epidemiologic survey questionnaire (31).

GA²LEN DARE. Viral infections represent the most common cause of severe asthma exacerbations (32). However, there is an urgent need to collect nasal samples in children with a high cross-center reproducibility. One important issue in this respect is the discomfort caused to patients, especially children, and their acceptance of the test. A pilot study has been carried out in some GA²LEN centers to validate the methodology. An extended study is in process.

Regulatory T-cells (Tregs). Regulatory T-cells or 'Tregs' have a key role in immunological tolerance to allergens.

Tregs are assumed to have a regulatory, suppressive role on T-cells from other types (such as Th1 and Th2) that trigger pathogenic reactions. A GA²LEN Work Package (WP) reviewed current evidence on the role of Tregs in allergic and healthy immune responses to allergens. Studies showed that allergen-specific Tregs are less present in allergic patients and that specific immunotherapy seems to increase these cells. As part of the GA²LEN WP, it was found that beekeepers have a tolerance to venom associated with the expansion of IL-10-producing Tr1 cells and the use of multiple suppressive factors (33).

Moreover, the European Treg Survey was to define a common protocol for assessing the presence of Tregs in blood. The survey also provides data for further analysis. A protocol was generated and validated in an experienced laboratory (SIAF, Davos, Switzerland), which then supported laboratories in all other centers. The protocol covers the entire procedure: definition of the primers, tests and material used including cell culture and reagents, and validation data with respective genes of interest.

Pollution. Environmental epidemiology specially focuses on human health risks related to exposures in the general (nonoccupational) environment (34). In recent years, several studies in Europe have associated within-city contrasts in air pollution with various health end points including mortality in cohort studies of adults, and respiratory morbidity in cross-sectional and cohort studies of children. Many of these studies have used NO₂ contrasts as the primary exposure variable, which raises the issue of whether such associations are uniquely found for NO₂ *per se*, or whether NO₂ acts as a surrogate for a complex mixture of combustion pollutants primarily derived from vehicular traffic (35–37).

Occupational exposure. Occupational exposures have a considerable impact on asthma and rhinitis in adult life in Europe (38, 39). New occupational allergens and irritants, including cleaning agents (40), have been identified and prevention strategies need to be developed (38). In addition, GA²LEN and other networks of European researchers are developing initiatives to focus on specific occupations such as health care professionals and cleaning workers. Furthermore, not only dermatologists and chest physicians should be made aware of the impact of occupational exposures on asthma and allergies but also pediatricians. The latter group is of uppermost importance for the prevention of occupational asthma and allergies in atopic teenagers, as it was recently shown by researchers of the GA²LEN network that atopic adolescents do not take into account their disease when opting for a job (41). Furthermore, particularly exposures early in professional life are shown to be important for the development of occupational allergies and asthma (42). So far, only a limited number of studies among adolescents exist. This is partly due to the fact that adolescent research requires the interdisciplinary involvement of

specialists in the field of pediatric and adult epidemiology. Previously, such collaborations were rarely undertaken and were established within the GA²LEN network. As a result, occupational exposures will be implemented in the existing European birth cohort studies in the near future when the participants reach working age.

Sensitization and symptoms. Not all subjects with an IgE immune response against inhalant allergens present symptoms (43). Epidemiologic studies in the general population show that asymptomatic sensitized subjects make up 15–20% of the EU population (44–46). Understanding the reasons for symptoms in IgE sensitized subjects is of critical importance. Global Allergy and Asthma European Network members have studied the mechanisms underlying the association of symptoms and IgE in birch and *Parietaria* pollen sensitized subjects. In contradistinction with the general population, selected patients underwent a nasal challenge and it was found that few subjects are sensitized without symptoms. The enrolment of subjects was therefore slower than expected and first results are expected within a year.

Remodeling in asthma and rhinitis. Nasal remodeling is less extensive than bronchial remodeling in allergic subjects. The reasons for these differences were discussed in a review published by GA²LEN members (47). A longitudinal clinical trial was performed in order to evaluate the relationships between pro-inflammatory and pro-remodeling mediators, and the severity and control of asthma in a pediatric population followed over 1 year. A positive correlation between some of these biomarkers (FeNO, eosinophils, IL-8) and the number of exacerbations that occurred during the 1 year follow up in moderate asthmatics was demonstrated (48). This study suggests the need to perform large prospective studies to confirm the importance of measuring specific biomarkers to assess sub-clinical airway inflammation and disease control in patients with asthma.

GA²LEN chronic rhinosinusitis. Many reports including the US CDC suggest that rhinosinusitis is as common as allergic rhinitis, leading to considerable costs. In fact, the exact prevalence of chronic rhinosinusitis is unknown. The GA²LEN project uses the epidemiologic study to assess the real prevalence of chronic rhinosinusitis. Protocols for clinical studies have been conducted in nine Ear-Nose-Throat GA²LEN centers in eight countries. A common database so far includes 1200 cases of chronic rhino-sinusitis. It appears of importance to expand the number of centers carrying out this study. The phenotypes of patients with chronic rhinosinusitis and nasal polyposis need to be defined, on clinical as well as biological grounds, and the mechanisms behind those phenotypes elucidated (14).

GA²LEN Search. The Severe Asthma Research In Children protocol has begun between Oslo (KH Carlsen) (49)

and Karolinska (G Hedlin). It aims to recruit children with severe asthma and to follow them in order to better define the phenotype of these patients as well as the natural history.

GA²LEN Olympic study. Several GA²LEN centers have recruited athletes who participated in the Beijing Olympic games in order to assess allergic diseases and asthma and to attempt to predict outcomes during the games (50). After analysis of the results of the study, it is expected that this will form the basis for a wider study in future Olympic games. Moreover, a longitudinal follow up of the patients is important since some athletes develop persistent airflow limitation.

Quality of life. Quality of life is impaired in patients with allergic diseases. Two reviews examined clinical trials in which quality-of-life was investigated in allergic rhinitis and asthma (51, 52). These studies helped the design of new trials.

Severe asthma. The GA²LEN Severe Asthma group was the continuation of the BioAir FP5 project. The global definition of severe asthma is unclear since in developed countries where effective drugs are available and affordable, severe asthma may be classified using response to treatment. On the other hand, in countries where drugs are not available and/or affordable, severity should be based on different outcomes. Moreover, severity and control of asthma are different terms which also need a global definition. There is an urgent need for a global definition of severe and uncontrolled asthma. This would contribute to filling the gaps in knowledge and improve the translation and dissemination of knowledge into guidelines and policies. A WHO consultation has been approved for April 8–9, 2009. It will be funded by GA²LEN and the report will be available before the end of 2009.

Clinical trials. Two large randomized, placebo-controlled clinical trials have been performed in the GA²LEN network (53, 54). The study of intermittent allergic rhinitis is of critical importance since this phenotype of allergic rhinitis has never been studied before. This will have an impact on the development of guidelines for allergic rhinitis (53).

Genetics and biobanking

In the WP on 'genetics, genomics and post genomics', activities have been focused on methodological aspects related to networking genetic collections and on improving biological sampling for 'omics' approaches. Work has been performed regarding quality management and preanalytical sampling issues in biological resources, benefiting from the input of the EU MolPage project. Seminars and training have been organized (55). A paper has been published with a practical proposal to trace biological

collections to favor collaborations (56). A web-based tool is currently being set up to help researchers in the respect of legal requirements for the exchange of biological material (Human Sample Exchange Regulation Navigator). Developments are being planned to continue in conjunction with the EU BBMRI (Biobanking and Biomolecular Resources Research Infrastructure) project.

The feasibility of studies on the genetics of asthma severity has been explored. A very comprehensive data base has been constructed for the meta-analysis of linkage studies for asthma, and the coherence of the results with recent genome-wide association (GWA) results from the Gabriel EU project suggests that this approach is complementary and could be developed further for other phenotypes.

A high level international research seminar on 'post genome respiratory epidemiology II: an interdisciplinary challenge', recently co-organized with ERS, has allowed geneticists, epidemiologists, clinicians, immunologists and statisticians to explore avenues of future interdisciplinary research.

Guidelines and consensus

ARIA in collaboration with GA²LEN and AllerGen. ARIA (Allergic Rhinitis and its Impact on Asthma) is an initiative carried out in collaboration with WHO which proposed the first evidence-based document on the management of allergic rhinitis. An update began by the publication of various papers on new aspects of allergic rhinitis which had not been considered before [alternative and complementary medicine (57), sports (58)] or on updates [links between asthma and rhinitis (59), pharmacologic treatments (60, 61), environmental control (62), immunotherapy (63)]. Most of these papers were published as part of GA²LEN. The ARIA 2008 update, collecting all the new information between 2001 and 2007, was published in collaboration with GA²LEN and AllerGen. The full-length document has already been translated into Chinese, Japanese, Spanish and Vietnamese. The executive summary has also been translated into over 25 languages. It was felt that the ARIA guidelines should be available in primary care since most patients with allergic rhinitis consult in this setting (64, 65). The pocket guide has therefore been published in collaboration with Wonca (World Organization of General Practitioners), IPCRG (International Primary Care Respiratory Group) and the patient's organization EFA (66).

Urticaria guidelines. Allergy and skin should represent an interdisciplinary approach as has been proposed by GA²LEN (67). Urticaria guidelines have been produced in collaboration with EAACI and the European Dermatology Federation (68, 69). This is the result of a consensus reached during a panel discussion at the second International Consensus Meeting on Urticaria, 2004. A new consensus was carried out in December 2008

(Berlin). The World Allergy Organization joined the group. The publication is pending.

GRADE guidelines. A Guidelines working group is revising current guidelines in the field of asthma and allergy according to the GRADE recommendations. In collaboration with ARIA (Allergic Rhinitis and its Impact on Asthma), the guidelines on allergic rhinitis and the links of rhinitis and asthma are being developed. This will be the first international guideline based on GRADE (70), the methodology approved by WHO.

Conclusions

With the creation of the GA²LEN infrastructure, the EU has offered European allergists ideal platforms to

synchronize research efforts and to guarantee de-fragmentation of the research landscape. All tools and platforms are in place and can be used for further multi-national EU research projects in allergy. With these tools, GA²LEN's vision to address all aspects of allergy can be further pursued. Continued use of the GA²LEN infrastructure will help to lower the socioeconomic costs of allergies and asthma in the EU.

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