Briefings from ACAAI 2008 Annual meeting

The Annual Scientific Meeting of the American College of Allergy, Asthma and Immunology, Seattle, WA, USA, 6–11 November, 2008

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The Annual Scientific Meeting of the American College of Allergy, Asthma and Immunology (ACAAI), was held in Seattle, WA, USA from the 6th to the 11th of November, 2008. With almost 4000 attendees, this annual happening is one of the highlights in the field of allergy and clinical immunology. People from many parts of the world are brought together in this yearly event, as the College has a strong global outreach program, supporting rising allergy societies. Moreover, international fellows-in-training (FIT) can apply for travel grants to come and present their work, and a whole FIT program is offered, with the FIT bowl competition as the utmost event for the fellows. As such, not only American allergists lecture at and attend the meeting, but also colleagues from Europe, Asia, Australia and Latin-America. Generally, the College meeting has a strong clinical flavor, with abundant and useful pearls for the practicing physician, but late-breaking new science is also presented, especially during the morning lectures. For the early risers there are meet-the-professor breakfasts, and in the afternoon attendees can book into workshops.

This year's meeting was preceded by some precongress courses, one of them on sublingual immunotherapy (SLIT) – lately a hot topic. On the first official congress day the classical literature review was presented. During the congress Richard Gower, ACAAI president, introduced the new Public Awareness and Education campaign, 'Find an Allergist, Find Relief', which is designed to increase the public's knowledge of the value of the services of trained allergists to control allergic rhinitis and asthma symptoms.

This article will focus on some details of the SLIT course, and on interesting take-home messages from the literature review course and a symposium on chronic urticaria (CU).

Sublingual immunotherapy course

The precongress course on SLIT was elegantly chaired by Ira Finegold (private practice, NY, USA), who gave the whole subject a special ambiance, picking trains as a special theme to build all talks around. The sessions were impressively well attended, showing the interest that exists among USA allergy experts in this field.

A wide variety of speakers from the USA, Europe and Latin America shared their knowledge on the subject with the audience. Moises Calderon (National Heart & Lung Institute, Imperial College London, UK) discussed the improved benefit of SLIT with a grass pollen tablet taken year after year, and stated that symptoms of allergic rhinitis were still clearly reduced even 1 year after termination of the treatment. Dr Harold Nelson (National Jewish Hospital, CO, USA) unrevealed the study design of a clinical trial that is actually undertaken at his center, and involves the administration of a multiple-allergen SLIT mixture in patients allergic to multiple inhalant allergens. Linda Cox (Allergy and Asthma Center, FL, USA) discussed some critical points relating to the obstacles that still remain before SLIT can be accepted in the USA. Bob Esch (Greer Laboratories™, NC, USA) uncovered the results of a USA SLIT study his laboratory had carried out, and explained the problems they met when attempting to obtain good results, as immunotherapy studies with pollen extracts always heavily depend on a good pollen season to show benefit of the treatment. Désirée Larenas-Linnemann (Hospital Médica Sur, Mexico City, Mexico), author of this article, spoke about alternative indications for SLIT: SLIT has been shown to reduce atopic dermatitis scores, especially in the mild-to-moderate group, after 9 months of treatment in a double-blind placebo-controlled trial. Oral allergy syndrome does not generally improve when successful SLIT is given for the cross-reacting pollen. SLIT for the pediatric age group has finally been proven to be effective, after some initial negative publications on this subject from a Dutch group of experts. The results of two large clinical trials

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in children, presented in the course of 2008, have taken away all doubts about the effectiveness of grass pollen SLIT in children, reporting improvement of over 30%.

SLIT with adjuvants can make the treatment more efficient, as Peter Creticos (John Hopkins Asthma and Allergy Center, MD, USA) demonstrated. Adjuvants that stimulate the Th1 and Tr responses are bacterial derivatives that stimulate the Toll-like receptors (TLRs). Another alternative under investigation is immunotherapy with peptides, which may prove promising.

The cost–effectiveness of the SLIT treatment, in which much higher doses have to be used than in subcutaneous immunotherapy, is another point of discussion.

Finally, SLIT seems to have less side effects than subcutaneous immunotherapy, but the last case-report of a 16-year-old girl who had an anaphylactic reaction and collapsed after an overdose of SLIT makes the medical world aware of the care that must be taken, even with SLIT.

Messages from the literature review course

Basic & clinical immunology

In the field of basic immunology, an article from Dostert *et al.* [1] regarding the underlying mechanisms of asbestosis and silicosis of the lung was reviewed. In 2006, Drenth *et al.* had already elucidated part of the innate immunity cascade [2]: mature IL-1β is produced by cleavage of its precursor, the pro-IL-1β, by caspase 1. In turn, capsase 1 is activated by the Nalp3 inflammasome. Asbestos and silica particles cause frustrated phagocytosis, with subsequent generation of reactive oxygen species. Reactive oxygen species are important danger signals that activate the Nalp3 inflammasome, which then cause IL-1β release and inflammation. Anakinra, the IL-1 receptor antagonist, is effective in the treatment of autoinflammatory syndromes, and the present study suggests that it might help to slow down the progression of these inflammatory lung diseases.

In the field of clinical immunology, some articles were published on the role of TLRs and TLR signaling pathways in primary immunodeficiency [3]. An autosomal recessive disorder was described with clinical and laboratory characterization of 28 children with IRAK-4 deficiency. The children had an early onset of pyogenic infections, and 43% had a fatal outcome. However, there were no more deaths after the age of 8 years. Moreover, no fungal, viral or parasitic infections were detected. The clinical picture of nine children with MyD88 deficiency is strikingly similar to that of IRAK-4 deficiency. Here, the immunodeficiency also improves with age.

On the contrary, defects in TLR-3 and its signaling (UNC-93 mutations) resulted in encephalitis caused by herpes simplex virus-1 in children under 5 years of age. In addition, once the children grew up, no further events were reported.

For common variable immunodeficiency (CVID), TACI mutations have been described. However, even with today's state-of-the-art, it is still not recommended to sequence CVID patients for this mutation. In contrast, in an article published in *Blood* this year [4], it stated that it is worthwhile to obtain the B-cell subsets, as this will identify high-risk patients: a severe reduction in switched memory B cells is related to increased splenomegaly and granulomatous disease, important causes of death in CVID.

Environmental & occupational disorders

Mark Dykewics (St Louis University Medical School, MO, USA) reviewed the publications in the field of environmental and occupational disorders. Choi *et al.* studied the optimal conditions for the removal of house dust mites, dog dander and pollen allergens using mechanical laundry [5]. Allergen load was best reduced by high water temperature, but also by augmenting the number of rinses. This may be important when it is not feasible to use high water temperature.

Last year, the Inner City Asthma Study (ICAS) showed that a successful reduction of cockroach and mite exposure could lead to a significant decrease in asthma symptoms, with benefit sustained throughout 1 year follow-up. Pongracic *et al.* analyzed the isolated mouse data from that same study [6], and found that mouse allergen is prevalent in inner-city homes. Moreover, it is an independent risk factor for asthma morbidity, and environmental intervention reduced mouse allergen levels and asthma-related sleep and activity disturbances.

Palacin *et al.* reported on the detection of lipid transfer protein (LTP), Tri a 14, sensitization in 60% of patients with baker's asthma. In a subsequent publication, they described oral allergy syndrome to kiwi in seven of 20 patients with baker's asthma, who all had positive specific IgE and skin-prick testing to kiwi. Moreover, using ELISA and ELISA inhibition, in approximately half of the patients

cross-reactive carbohydrate determinants and thiol-proteases homologous to Act d 1 were responsible for wheat–kiwi cross-reactivity [7].

Asthma & chronic obstructive pulmonary disease

James T Li (Mayo Clinic, MN, USA) reviewed once again the latest data on long-acting β-agonists (LABAs). A systematic review of 27 studies in chronic obstructive pulmonary disease (COPD) patients demonstrated LABA plus an inhaled corticosteroid reduced the risk of respiratory death compared with LABA alone, and the long-acting anticholinergic, tiotropium, decreased the risk of COPD exacerbation compared with LABA. However, care must be taken with this drug class in COPD, as a meta-analysis of the use of anticholinergics in COPD reconfirmed that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, myocardial infarction and stroke [8]. The systematic review by Quon *et al.* [9] on COPD exacerbations concluded that systemic corticosteroids, antibiotics and noninvasive positive pressure ventilation are all effective in reducing treatment failures.

Skin diseases

The next review provided an update on skin diseases. In atopic dermatitis, the single most important gene in predicting the presence and severity of the disease is the filaggrin gene. Alterations in filaggrin cause abnormalities in the epidermal barrier. Filaggrin null mutations are significantly associated with mild-to-moderate atopic dermatitis in childhood, but they are quite rare. As it becomes increasingly clear that the barrier permeability abnormality in atopic dermatitis is not an epiphenomenon, but the driving force of the disease activity, clear indications for treatment can be given. Elias *et al.* emphasized the importance of wet dressings and ceramide-containing cream in the treatment of atopic dermatitis [10]. Probiotic use can still not be openly recommended. Eventually these agents might have a preventive effect, as use in the pregnant mother during the last trimester of pregnancy showed a reduction of atopic dermatitis in the child, but this field is still under investigation.

Nikkel seems to be the 'allergen of the year' for contact dermatitis. An interesting review confirmed that nikkel does not only act as a contact allergen, but that it can also give inflammatory responses in remote skin (cell-phone syndrome and low-dose dietary exposure) [11].

A new classification for urticaria is proposed, distinguishing between acute and physical urticaria versus CU. The latter can then be subdivided into chronic autoimmune urticaria and the real idiopathic urticaria; this last one characterized by a negative autologous serum skin test.

Rhinitis & rhinosinusitis

Dr Dana Wallace (Nova Southeastern University, FL, USA) presented the latest evidence in the area of rhinitis and rhinosinusitis in her very clear and practical style. In 2008, some articles were published that showed how all upper airways are interconnected, speaking in terms of reflexes and inflammation. The presence of a nasosinal reflex is proposed by Baroody *et al.*, who have shown that a nasal allergen challenge can provoke inflammation in the maxillary sinus [12]. Nasal allergy is related to serous otitis media. In patients with serous otitis media, the investigators demonstrated Eustachian tube dysfunction after nasal allergen challenge, both in adults and in children.

In patients with allergic rhinitis, cigarette smoking is associated with a greater risk of incident asthma 10 years later, with a relationship between the number of pack years and a rise in the odds ratio for the development of asthma. Allergen immunotherapy reduced this risk.

With the use of intranasal noninhaled carbon dioxide for the symptomatic treatment of seasonal allergic rhinitis (this was already shown to be effective for migraine), 85% of patients had at least a 25% reduction of symptoms, and 25% had a 75% improvement in symptoms. This was accomplished by blowing CO_2 in one nostril for 10 s, and asking the patient to breath through the mouth.

A combination local treatment of azalastin and a topical steroid for seasonal allergic rhinitis was more effective in reducing symptoms than single drug treatment. This finding is in line with the recommendations of the updated practice parameters on allergic rhinitis [13].

A meta-analysis of individual patient data was performed to examine the usefulness of antibiotics for adults with clinically diagnosed acute rhinosinusitis. Common signs and symptoms do not distinguish between patients who will benefit from a course of antibiotics with or without intranasal corticosteroids for their sinusitis and those who will not, and nor does the duration of the disease. However, purulent discharge in the oropharynx and the severity of symptoms might do. Another randomized, placebo-controlled study showed the same – that

improvement within 15 days was not different in the placebo or active groups. Topical mupirocin may be beneficial in patients following sinus surgery and in patients with recalcitrant chronic rhinosinusitis, but antifungal irrigation is of no benefit. The noninvasive marker of inflammation, intranasal nitric oxide, might be a useful indicator for successful antibiotic treatment of acute bacterial rhinosinusitis [14].

Vaccines, antibiotics & microorganisms in relation to allergy

Among 11,531 children who received at least four doses of diphtheria, pertussis and tetanus, the risk of developing asthma was decreased if the first dose was given after 2 months of age. However, care must be taken when interpreting these data, because in the majority of the children with delayed application of the first dose, this was carried out due to the presence of an infection and fever, two factors that by themselves could have been the cause of the protective effect, instead of the vaccine delay.

Prolonged clarithromycin therapy significantly reduced airway concentrations of IL-8 and neutrophil accumulation and improved the quality of life in patients with severe asthma. This effect was especially marked in those with noneosinophilic asthma; however, the beneficial effect is only present during the treatment.

Antibiotic use early in a child's life is an independent risk factor for wheezing – maybe because neonatal use of antibiotics changes the gut flora.

Viruses were studied in relation to the development of asthma in small children in the Childhood Origins of Asthma (COAST) study. It was concluded that wheezing with a rhinovirus infection at the age of 1 or 2 years augments the risk for asthma at the age of 6 years by a much greater degree than respiratory syncitial virus infection. In patients with asthma, the presence of human rhinovirus was demonstrated by reverse transcriptase-PCR. Human rhinovirus causes a remodeling in asthma by changing the local production of growth factors.

Chronic urticaria

Chronic urticaria is a heterogeneous disease: almost half of the patients have immunoglobulin (Ig) G autoantibodies to IgE or to the high-affinity IgE receptor. These autoantibodies can be shown by various methods – none are completely conclusive. In this symposium some tests to show the presence of autoantibodies in CU were discussed:

- Autologous serum skin test can be positive. Autologous serum skin test positivity is not always due to the autoantibodies, as depletion of the serum of IgG does not turn the test negative in all patients. It is probable that some other serum factors that can degranulate the mast cells are picked up by this test.
- Basophil histamine release by serum from patients with CU is another test that can be carried out. Interestingly, the serum of some of the patients does release histamine on stimulus (responders), but the serum of almost half of the patients does not (nonresponders). After the urticaria goes into remission, the nonresponders start to show more normal patterns of histamine release, but, in addition, in the responders, a rise in histamine release can be detected on remission. However, there is no correlation with the presence or absence of autoantibodies as detected by ELISA.
- In almost half of the CU patients, the IgG autoantibodies mentioned above can be detected by western blot or ELISA. However, there is no correlation with disease severity or prognosis.

At the end of the presentation, the monoclonal anti-IgE, omalizumab, was discussed as an alternative treatment for recalcitrant chronic idiopathic urticaria. Double-blind, placebo-controlled study results were shown, with reduction in symptoms of the patients already being demonstrated from the second week on, reaching a plateau with an approximate 70% reduction in symptoms at around the sixth to eighth week of treatment, and coming back to baseline slowly in the course of 2–3 months after omalizumab was withdrawn. These clinical data correlate with the basophil histamine release test, which shows a normalization of the histamine release when the patients respond to omalizumab, and again a reduction in the response of the basophils when the monoclonal antibody is stopped.

Conclusion

The 2008 Annual Meeting of the ACAAI was a very well attended meeting in which a broad array of subjects in relation to allergy, asthma and immunology were presented. As the meeting has a strong practical focus, it might not only be valuable for allergists, but also for other physicians who treat patients with allergies, such as general physicians, pediatricians and

Executive summary

- Sublingual immunotherapy is gaining interest among American allergists.
- Studies have shown efficacy on a worldwide level, but US studies are still not reaching positivity for primary efficacy variables.
- Sublingual immunotherapy is safer than subcutaneous immunotherapy, but even so anaphylaxis might occur with overdosing.
- The role of Toll-like receptors (TLRs) and TLR signaling pathways in primary immunodeficiencies became better known after some cases of deficiencies in these molecules.
- Long-acting bronchodilators (LABAs), in combination with inhaled corticosteroids, reduce the risk of death in chronic obstructive pulmonary disease, in comparison with LABAs alone.
- Inhaled anticholinergics in chronic obstructive pulmonary disease are associated with a significantly increased risk of cardiovascular death, myocardial infarction and stroke.
- The discussion on the usefulness of antibiotics and topical corticosteroids in sinusitis is still ongoing.
- Prolonged treatment with clarithromycin improved control in chronic severe asthma.
- Chronic idiopathic urticaria: autologous serum skin tests and some laboratory tests might indicate the presence of autoantibodies, but there also seem to be other factors involved in mast-cell degranulation.
- The annual congress of the American College of Allergy, Asthma and Immunology presents an excellent opportunity to update one's knowledge on the state-of-the-art in allergic diseases and basic and clinical immunology.

otorhinolaryngologists, and a parallel program for allied health makes it also very useful for medical administrators, nurses and the like.

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