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8th Georg Rajka International Symposium on Atopic Dermatitis: meeting report

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Summary

The 8th Georg Rajka International Symposium on Atopic Dermatitis was held in Nottingham in May 2014. The 3-day meeting featured a number of lectures by experts in the field of atopic dermatitis from around the world, as well as several original research presentations and a question and answer session. This paper aims to summarize the main oral presentations from the meeting, but is not meant to be a substitute for reading the conference proceedings and related references.

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The 8th Georg Rajka International Symposium on Atopic Dermatitis was hosted by Professor Hywel Williams and his team in Nottingham on 21–23 May 2014. New initiatives for this meeting included the preconference educational course on finding high-quality evidence on atopic dermatitis (AD), along with special efforts to minimize costs. The organizers had made strenuous efforts to bring in more colleagues from the Far East and had managed to make a number of bursaries available for trainees and those from developing countries. There was a deliberate plan to organize the meeting without any industrial sponsorship. Instead, senior industry partners and scientists were welcomed as equal delegates within the symposium.

At the 1977 World Congress of Dermatology in Mexico City, there was only one workshop on AD. Two years later, Professor Georg Rajka organized the first International Symposium on Atopic Dermatitis in Oslo. After he had hosted a series of meetings in Norway, the symposium was renamed in his honour and subsequent meetings have been held throughout the world. Knowing that he was unlikely to live long enough to come to Nottingham this year, the increasingly frail Professor Rajka wrote a letter in December 2012 to be read at the Nottingham meeting by his nephew, Dr Anders Galos. In this Professor Rajka described how he was very interested to see how the conference had expanded to a worldwide venture and that he had wanted to attend the meeting in Tanzania in 2012, but health problems precluded this. He talked of the many unresolved issues in the field of AD and the challenges and opportunities ahead. He also named and thanked numerous former colleagues and collaborators. Professor Rajka passed away in March 2013 aged 88, yet through this symposium his spirit and legacy live on.

Causes of atopic dermatitis: genetics and environment

Professor Alan Irvine delivered the first session on the genetics of AD. Understanding the pathogenesis is important for disease prevention, molecular phenotyping, developing new treatments and predicting treatment response. Earlier genetic studies examined linkage between AD and IgE responses[1] and risk variants in innate and adaptive immunity. What comes first: disrupted skin barrier or AD? A severe inherited barrier disruption is sufficient to cause AD. Mutations in the *SPINK5* gene increase serine protease activity and cause Netherton syndrome, but a functional mutation in the normal population increases AD risk.

Filaggrin (*FLG*) mutations cause ichthyosis vulgaris[2] and also predispose to AD.[3] There are multiple loss-of-function mutations, many of which occur in the population; some occur in families.[4] *FLG* mutations increase the risk of asthma, but only if eczema occurs in early life. In patients without *FLG* mutations, risk of AD is increased in people with low numbers of *FLG* repeats; conversely, a large copy number is protective.[5] Not everyone with a *FLG* mutation develops eczema; environmental factors are also important. Interaction with cats, in those with a predisposing *FLG* mutation, leads to eczema.[6] Furthermore, in contradiction of the popular hygiene

hypothesis, day care exposures and elder siblings actually increase risk by enhancing the effect of *FLG* mutations.[7,8] The subsequent discussion revealed how percutaneous exposure drives peanut allergy.

While *FLG* mutations increase AD risk in European populations, this is not so in Africa.[9] Dr Maria Bradley and colleagues searched for an 'African *FLG* gene' in an Ethiopian population using whole-exome sequencing.[10] Bradley hypothesized that *FLG* mutations may confer an evolutionary advantage, such as immunity via percutaneous exposure to infectious diseases or increased vitamin D production. However, instead of one common single gene or variant responsible for AD in Africans, they identified several new rare variants in different genes.

Dr Eung Ho Choi investigated barrier-related gene mutations in a Korean population using a new reverse blot hybridization assay.[11] While *FLG* mutations were not found to be important, the study identified a novel kallikrein (KLK)7 mutation and three mutations in *SPINK5*, not previously observed in Koreans.

Other studies examined the influence of early-life events. Dr Sébastien Barbarot interrogated two large French birth cohorts to investigate the effect of prematurity on AD risk.[12] Contrary to the hypothesis that extreme prematurity increases risk due to an impaired skin barrier, those with a gestational age < 29 weeks had a 50% lower risk. Possible mechanisms include shorter exposure to T helper (Th)2 cytokines during pregnancy or induction of tolerance through the impaired skin barrier. During the subsequent discussion it was suggested that the skin microbiota differed due to long periods in an incubator, or that genetic factors causing prematurity may be protective.

In 1998 a questionnaire-based study in schoolchildren found that hard water increased AD risk.[13] However, the recent Softened Water Eczema Trial found that water softeners did not improve established eczema.[14] So does hard water influence the risk of developing eczema? To answer this question, Dr Carsten Flohr and colleagues from King's College London studied 1303 U.K. infants aged 3 months, performing skin examinations, SCORing Atopic Dermatitis (SCORAD) severity assessments and *FLG* skin barrier gene mutation status, as well as measuring skin barrier function by transepidermal water loss (TEWL).[15] Water hardness and calcium carbonate and chlorine concentrations were provided by local water companies for each study participant. Twenty-four percent of children had eczema. Hard (vs. soft) water increased eczema risk by 45% at 3 months, with a significant further increase in children carrying a *FLG* mutation. Hard water also impaired skin barrier function, as measured by TEWL, even in children without eczema. As little is known about the effects of calcium carbonate on skin barrier function, and as the public health implications of these findings are likely to be significant, there is the need for an intervention study, using water softeners from birth. In the subsequent discussion, Professor Mike Cork pointed out that conventional ion-exchange water softeners substitute sodium for calcium and increase pH. As the latter is known to impair skin barrier function, a new type of water softener might have to be developed for the proposed intervention study, which lowers not only the water calcium carbonate concentration but also the pH.

Environmental influences were reported in animal and human studies. Dr Caoimhe Fahy studied flaky-tailed mice, an animal model for AD,[16] and compared open-air conventional cages with cleaner conditions in individually ventilated cages.[17] Both environments were specific pathogen free. The mice in the conventional environment had greater severity of skin disease, with improvement when moved to the clean environment.

Dr Annice Heratizadeh reported a small double-blinded placebo-controlled trial of patients with AD sensitized to *Dactylis glomerata* grass pollen.[18] Controlled grass pollen exposure was compared with clean air. The exposure group had a greater increase in objective SCORAD than controls and a higher local SCORAD on exposed sites. Controlled exposure to airborne allergens in those with extrinsic IgE-mediated AD caused a deterioration, implying the need for allergen avoidance.

Dr Jonathan Silverberg compared two U.S. studies on the climatic effects on AD. In a large study of over 90 000 children from the U.S. National Survey of Children's Health 2007–8, 13% of children had AD.[19] Overall, in areas of greater ultraviolet (UV) exposure there was less eczema; higher temperature and humidity were protective; and higher precipitation was harmful. Looking at the most common combinations of climate variables, areas with high temperature in combination with high UV had decreased odds of eczema, whereas areas with high humidity and precipitation and low UV had increased odds. In contrast, a second study of 6000 children with AD showed that higher relative humidity worsened control and greater UV exposure and higher temperatures caused more persistent eczema.[20] From the contrasting results he concluded that there were differences between the cohorts and short- and long-term climatic variables.

Day one concluded with presentations from our veterinary colleagues. Dr Rosanna Marsella studied percutaneous induction of peanut allergy in atopic and nonatopic beagles.[21] Dogs sensitized by application of peanut paste under occlusion to the axillae for 8 weeks underwent cutaneous and oral challenge. All dogs developed cutaneous symptoms, which were worse in atopic dogs. Anaphylaxis is rare in dogs. The aim is to develop this model for eventual vaccine development.

Dr Wolfgang Bäumer presented a novel dog model of AD in Maltese beagles by sensitizing young dogs to house dust mite.[22] The researchers then applied house dust mite to a clipped area on the dogs' abdomens, with video monitoring of scratching behaviour. The subsequent discussion revealed that, as in humans, prevalence of canine AD is increasing. Sensitization to human owners can occur, although testing is not performed as owners get very upset.

Mechanisms of atopic dermatitis

The second morning began with Professor Lisa Beck's outstanding overview of the mechanisms of AD. Current areas of

interest are the interactions between barrier defects and defects in adaptive and innate immunity.

Filaggrin mutations causing skin barrier defects are associated with AD and a number of allergic disorders.[4] The association of *FLG* mutations with peanut allergy in individuals without AD has also strengthened the theory that percutaneous sensitization plays an important role in food sensitization. Filaggrin mutations are also associated with increased risk for eczema herpeticum, but not for staphylococcal infections, suggesting an association with viral susceptibility.

Many other skin barrier proteins are also being investigated. Recent research has revealed the importance of tight junctions in the stratum granulosum and their component transmembrane proteins, the claudins.

The Th2 and Th1 pathways have been studied in AD, and the roles of Th22 and Th17 cytokines in defects of adaptive immunity are currently under investigation.[23] Toll-like receptor (TLR)2 is the focus of research into defects of innate immunity. TLR2 expression is reduced in AD.[24] TLR2 is also involved in herpes simplex infections. Professor Beck also discussed the interaction between TLR2, the skin barrier, Th2 and cytokines of the adaptive immunity and described the roles of histamine-independent pruritogens[25,26] and microbial flora.[27]

Invited speaker Professor Mike Cork discussed factors affecting the skin barrier and the influence of products applied to the skin. He detailed the importance of filaggrin, maintaining low pH, natural moisturizing factor (NMF) and protease inhibitors (e.g. SPINK5) in the normal skin barrier.[28] Proteases, which break down corneodesmosomes, are switched off by low pH. In a defective barrier, there is decreased NMF, water and filaggrin and a defective lipid lamella. He described the role of occlusive emollients in decreasing TEWL, humectants, which increase hydration, the potential to correct lipid abnormalities, and the importance of mild surfactant properties and normalizing pH.

Professor Hitoshi Mizutani presented his work on an objective quantitative scratching sound detection system using a wristwatch-type sound detector.[29–31] Studies have shown a difference between itch reporting and scratching behaviour, but the need for objective measurement of pruritus was widely acknowledged by the delegates.

Dr Dagmar Simon investigated the role of interleukin (IL)-17 and other Th17 cytokines in AD, allergic contact dermatitis and irritant contact dermatitis.[32] All three clinical types show similar signs, and Th17 seems to be contributory. IL-17, as well as IL-22, may play a role in skin remodelling in these conditions.

The atopy patch test (APT) is often used in studies of AD pathogenesis. Dr Dave Koole sought to validate the APT as an *in vivo* model for AD.[33] His study showed that although the APT is a good tool for studying AD, differences exist between this and chronic AD lesions.

Professor Yoshiki Tokura presented his team's work on the proteomics of the stratum corneum from patients with intrinsic and extrinsic AD (IAD and EAD) and ichthyosis vulgaris, and healthy controls.[34] The proteins and metabolites identified were divided into categories according to their roles (e.g. inflammatory substances, stratum corneum constituents).

The study found that albumin was greatest in EAD, but was also increased in IAD compared with ichthyosis vulgaris. Filaggrin was decreased in EAD compared with IAD and controls; KLK5 and KLK7 were increased in AD compared with controls; and dermcidin was decreased in AD. There were also decreased sweat-gland-derived proteins in AD, indicating reduced sweating.

Two studies investigated the role of autoreactivity. Dr Susanne Hradetzky presented a study on the autoallergens thioredoxin and α-NAC (α-chain of the nascent polypeptide-associated complex) in AD.[35–37] These can induce proinflammatory cytokines such as IL-10 and IL-1β. Dr Lennart Roesner and colleagues found elevated numbers of autoallergen-specific interferon-γ-producing CD8+ cytotoxic T cells, implicating them in the pathogenesis of AD.[38]

Dr Mayte Suárez-Fariñas studied the AD transcriptome using RNA sequencing in an effort to overcome the limitations of the widely used microarray method. TREM-1 (triggering receptor expressed on myeloid cells), a dendritic cell receptor, was identified only by RNA sequencing, and its role in AD was discussed.[39]

Dr Anna De Benedetto investigated the effects of histamine on tight junctions and barrier function.[40] Histamine receptor 1 and 4 blockade improved tight-junction function, suggesting a previously unrecognized role for antihistamines in improving epidermal barrier function.

Prevention and consequences of atopic dermatitis

Prevention of AD remains an important area of research. Evidence suggests that there is potential to prevent development of AD, either antenatally or in early life.

Invited speaker Dr Robert Boyle discussed prevention of AD through dietary interventions.[41] Evidence supports the use of probiotics, specifically *Lactobacillus rhamnosus*, in the last few weeks of pregnancy and during lactation in high-risk families.[42] No particular adverse events have been recorded, although Dr Boyle cautioned against starting too early during pregnancy: probiotics can induce proinflammatory cytokines and could theoretically induce adverse effects in the developing foetus. Probiotics do not seem to affect the risk of allergic sensitization, and further research is required on their mechanism of action.

The delegates discussed the possibility that prolonged lactation increases risk of AD. The benefits of breastfeeding are well known, but maternal diet may impact on the composition of breast milk, and this needs further study. Recent work has found that treatment of parasitic infections antenatally (but not postnatally) increases the risk of AD in the infant.[43,44]

Dr Joanne Chalmers presented the Barrier Enhancement in Eczema Prevention study, a pilot feasibility study of intensive emollient application in high-risk infants, starting within the

first 3 weeks of life and continued for 6 months.[45] Intervention showed some benefit, although this was not a primary outcome and the results need cautious interpretation. The study confirmed the feasibility for a larger-scale randomized controlled trial (RCT).

Professor Yukihiro Ohya presented an RCT comparing proactive and reactive management, from birth to 32 weeks, for prevention of AD.[46] A significant protective effect was found with the proactive approach, and TEWL was also significantly less.

Comorbidities in eczema of itch, sleep disturbance, chronic inflammation and steroid use may affect growth. Dr Silverberg's meta-analysis of nine large-scale American population-based studies revealed a transient association with short stature in adolescence, which resolved in adulthood.[47] The only signal linking AD and shorter stature was sleep disturbance and loss, suggesting a role for interventions for sleep problems.

Dr Matthew Ridd presented a questionnaire-based cohort study on the association with adolescent behavioural problems.[48] There were weakly positive associations between early-onset/clearing eczema and late-onset eczema and hyperactivity, and between early-onset/clearing eczema and conduct disorder. This requires further investigation.

Outcome measures for atopic dermatitis

Research to establish the optimum outcome measures for clinical trials on AD is ongoing. Dr Eric Simpson delivered a clear overview of the international effort for consensus on measuring AD by the Harmonising Outcome Measures for Eczema (HOME) collaboration. The international group had concluded that both the Eczema Area and Severity Index (EASI) and SCORAD are valid instruments. The EASI was found to be the best instrument for the dimension of signs, but for the dimension of signs and symptoms the best instrument has not yet been identified. Use of SCORAD is encouraged when needed.[49] Definitions of early AD, disease flares and long-term control are lacking, and outcome measures are even harder to define. The HOME collaboration is working to identify instruments to measure the core outcomes domains for inclusion in all AD trials using a systematic approach.[50,51]

Professor Phyllis Spuls presented a study from the HOME symptoms group that reviewed all RCTs in AD from 2000 to 2013.[52] Itch and sleep loss are the most commonly reported symptoms in clinical trials; however, this is usually as part of a composite score and not individually. Dr Laura Beate von Kobyletzki and colleagues sought patients' perspectives on the importance of signs and symptoms in determining treatment response.[53] A questionnaire-based study of patients and parents of children in 28 countries revealed that itch and pain were rated as most important. Scratch marks, sleep disturbance, signs of inflammation, extent and area were also considered important measures of treatment effects.

Dr Masaki Futamura presented a systematic review of clinical trials that used Investigator Global Assessment (IGA) as an outcome measure.[54] Although IGA is required for new drug approvals in the U.S.A., it is not validated and needs standardization.

Undergraduate Miss Anh Tran compared outcome measures for severity and quality-of-life scores.[55] Although the study was performed in a limited number of patients, she found that EASI alone had high inter- and intrarater reliability. None of the severity scores correlated with quality-of-life scores except for SASSAD (the Six Area, Six Sign Atopic Dermatitis severity score), with moderate correlation to Skindex-29.

Treatment of atopic dermatitis

The final day of the meeting focused on management strategies for AD.

Professor Alain Taïeb described the evolution in medical advances over the last 200 years and the more recent progression from evidenced-based to translational and personalized medicine.[56] He proposed that AD comprises many different endophenotypes and may represent several genetically/epigenetically different subgroups.[57] An approach for developing new therapies is to adapt treatments for rare diseases; for example, could a protease inhibitor for Netherton syndrome work in AD? Despite numerous studies, success remains elusive. Subsequent discussion highlighted the importance of publishing negative results to avoid time-wasting repetition. Drug development is slow, with only 10% of new molecules reaching the market. There are numerous drugs in development targeting different facets of the disease: barrier restoration, itch controllers, oral and topical anti-inflammatory drugs, new biologics and even mesenchymal stem cells. Management strategies must be targeted to specific disease phases: primary prevention in the initiation phase, a revelation phase (infantile eczema), a chronic phase and an extracutaneous phase.[58] Interventions should also limit asthma, not only AD. Potential therapeutic strategies include decreasing epidermal innervation (there is evidence of increased innervation in AD skin), targeting allergic cytokines, including IL-31[59,60] and thymic stromal lymphopoietin,[25] and conducting trials of existing biologics.

Helen Nankervis presented her update of the Health Technology Assessment systematic review.[61,62] She explained the importance of seeing the whole picture to target future research appropriately. She included 287 new RCTs on eczema treatments and divided them into different therapeutic categories. There is evidence of benefit with proactive topical corticosteroids, tacrolimus and pimecrolimus to prevent flares, systemic treatment in adults, phototherapy and patient education. However, no benefit was found with twice-daily topical corticosteroids vs. once-daily dosing, or with linoleic acid, ion exchange or antibiotics in noninfected eczema. Areas identified as requiring further research included emollient use to decrease the severity of eczema and flares over time. This work is freely available online as the GREAT Database (www.greatdatabase.org.uk).

Professor Jochen Schmitt presented a systematic review of systemic treatment, including 34 trials involving 1653 adult

and paediatric patients.[63] Most of the trials were small and of short duration, reporting standards were low and there was methodological and clinical heterogeneity. Fourteen were on ciclosporin and three on azathioprine. Current evidence suggests ciclosporin as first-line, azathioprine as second-line and methotrexate as third-line treatment. One suggested regimen was induction of remission with ciclosporin, with mycophenolate mofetil as maintenance. Interferon could be considered with close monitoring of adverse events.[64] Systemic steroids, intravenous immunoglobulin, montelukast and traditional Chinese herbal medicine are not currently recommended. A small study of omalizumab in severe AD found that the only responders had no filaggrin mutations.[65] The ensuing discussion revealed a gulf between current practice and best evidence, with many choosing methotrexate as the first-line treatment due to its favourable side-effect profile.

Dr Ting Seng Tang reviewed the literature on subclinical inflammation and management strategies for initial clearance of AD and their impact on long-term control.[66] A literature search, identifying 26 studies on areas such as barrier dysfunction, subclinical inflammation and bacterial colonization, concluded that even nonlesional skin was abnormal in AD. Only one study examined treatment of subclinical inflammation. Inadequate early control increased the relapse rate. Further work is required to establish how aggressive to be with treatment and the duration required in the induction period.

A potential barrier to control is fear of topical corticosteroids, 'corticophobia'.[67] Dr Hélène Aubert-Wastiaux investigated this phenomenon in French dermatologists, paediatricians and pharmacists.[68] It was originally described in asthma,[69] and more recent studies reveal that 40–70% of patients are corticophobic. All groups, but especially pharmacists, had concerns about treatment. She concluded that patient corticophobia could be induced by an exaggerated warning, and suggested that updated evidence-based information defining a clearer risk–benefit ratio would be helpful in educating healthcare professionals.

Dr Ellen van den Bogaard presented the case for reintroducing coal tar in AD treatment.[70] It is one of the oldest dermatological treatments, and although used predominantly for psoriasis elsewhere, in the Netherlands it is used mainly for eczema. Cosmetic issues, local irritation, folliculitis and potential carcinogenicity have facilitated its decline. However, two large studies found no increase in cancer risk.[71,72] Its therapeutic effects are due to polycyclic aromatic hydrocarbons and are mediated via the aryl hydrocarbon receptor, a ligand-activated transcription factor. Application of coal tar to *in vitro* skin models decreases the effects of Th2 cytokines, restores expression of epidermal proteins and accelerates epidermal differentiation.[73]

Dr Eric Simpson presented the results of early-phase clinical trials with dupilumab, a fully humanized monoclonal antibody that blocks the IL-4/IL-13 receptor ligand system. It is administered as a once-weekly subcutaneous injection.[74] The most common side-effects were nasopharyngitis and headaches, and there were no significant differences in adverse effects overall between treatment and placebo. Treatment showed good efficacy, with the greatest improvements with the highest dose of 300 mg. Addition of topical corticosteroids increased efficacy, with no increase in adverse events.[75]

Dr Lee Zane, representing Anacor Pharmaceuticals, introduced AN2728, a boron-based small-molecule 251-kDa phosphodiesterase inhibitor with anti-inflammatory properties.[76–79] Early-phase studies found that twice-daily dosing at 2% was safe and tolerable over a 4-week period. Low levels were found in the blood, and the most common side-effects were mild-to-moderate application-site reactions, which resolved spontaneously. There were good improvements in clinical scores, suggesting this to be a useful nonsteroidal treatment for mild-to-moderate AD.

Two presentations examined biomarkers in AD. Biomarkers provide a quick, objective way of monitoring disease activity, both in the clinic and for drug development. To characterize the best biomarkers for AD, Dr Judith Thijs tested inflammatory markers in 31 patients before and after 2 weeks of potent topical steroids.[80] Thymus and activation-regulated chemokine (TARC) was the most promising, showing good correlation with disease severity. However, a combination of biomarkers was better than TARC alone. Dr Emma Guttman-Yassky further explored the use of biomarkers, including not only cytokines and chemokines, but also histological features, such as hyperplasia and protein expression.[81] These permit objective assessment of treatment response and should be incorporated into early clinical trials.

The final afternoon commenced with the awards for best oral presentation and poster. The Sheriff of Nottingham, County Councillor Jackie Morris, presented carved wooden apples made of wood from Sherwood Forest to Dr Carsten Flohr for his work on hard domestic water[15] and Dr Uffe Nygaard for the best poster, on IL-33 and skin barrier function.[82]

Professor Johannes Ring spoke briefly on the International Society for Atopic Dermatitis (ISAD), founded in 2013 with the aim to pursue excellence in clinical care, research, education and training in the field of AD. ISAD decides where the international symposium is to be held every 2–3 years, with the next symposium in Brazil in 2016.

Invited speaker Professor Roberto Takaoka presented results of an online survey from Brazil showing that 80% of patients were dissatisfied with their AD treatment. Furthermore, 82·5% thought that doctors did not know how to treat AD! Eighteen RCTs and two systematic reviews have shown that patient and parent/carer education is beneficial.

The multiple dimensions of AD are difficult to address within a limited consultation time. In the speaker's dermatology department, doctors and nursing staff have introduced evening and weekend workshops for patients and parents. These allow more time for explanations and questions. Education is reciprocal for both patients and doctors. There are projects such as calendars made from prints of children's drawings, and origami to help minimize scratching. The online survey is yet to be repeated, to see whether there has been any improvement in patient satisfaction. Professor

Takaoka shared the link to his helpful website, used by patients to access information (www.aada.org.br).

Professor Kim Thomas and patient representative Amanda Roberts discussed patient involvement in research. The Priority Setting Partnership for eczema was organized by the Centre of Evidence Based Dermatology in Nottingham, supported by the James Lind Alliance.[83] It involved both patients and healthcare professionals, and online surveys were used to identify and prioritize uncertainties in eczema management. Professor Thomas described the process from inception to completion. This yielded 14 top uncertainties to direct future research.

Amanda Roberts explained the importance of patient involvement in research and the significance of Priority Setting Partnerships. She described her perspective on the doctor–patient relationship and the problems of time constraints in consultations, and conflicting advice from professional and lay sources.

The subsequent discussion considered the specific problems of teenagers with AD.

Question and answer session

The symposium concluded with a question and answer session with delegates' presubmitted questions, answered by an expert panel: Professor Alan Irvine, Professor Jon Hanifin, Professor Kristian Thestrup-Pedersen, Dr Kenji Kabashima, Dr Carsten Flohr and Professor Amy Paller.

Question 1: 'What are the key differences between those whose eczema resolves and those whose persists lifelong?'

Answer: There is no clear answer so far. While 50–60% outgrow their eczema, early-onset, severe disease persists. Possible explanations include increased sebum production and microbiome changes at puberty, or compensation of barrier dysfunction. Longitudinal studies with collection of biomarker data are required.

Question 2: 'How many phenotypes of eczema have been identified and how well are they characterized?'

Answer: The literature gives no clear answers; however, phenotypes may change throughout life. Early onset is usually associated with severe disease and food allergies. Intrinsic and extrinsic eczema are recognized, and AD may represent a spectrum of clinical phenotypes. It may become more important to describe these phenotypes with the introduction of the biological agents.

Question 3: 'Please advise on management of Afro-Caribbean children with chronic lichenified eczema.'

Answer: These patients tend to have chronic eczema with a more papular component and lichenification. Similar appearances occur in Asian patients. Suggestions for treatment included moderate topical corticosteroids under occlusion with ichthammol paste bandages or wraps. Another suggestion was salicylic acid 6% and triamcinolone ointment for a maximum of a few months. A small cohort of patients receiving alitretinoin for prominent hand involvement showed improvement in other parts of the body. Ciclosporin is another option. Occlusion is essential when using topical treatment, but caution is required with potent corticosteroids on darker skin due to the risk of depigmentation. Cryotherapy has been successful for nodular prurigo in Japanese patients.

Question 4: 'Does early aggressive treatment of eczema alter its subsequent course?'

Answer: Studies of proactive treatment are encouraging, but experience suggests that patients do not comply. One approach, used in Japan, is admission of those with early-onset eczema for aggressive corticosteroid treatment, for 1–4 weeks until clear, with subsequent proactive treatment. Problems with proactive treatment include corticophobia among patients and professionals, and delayed referral to secondary care. Two delegates shared their experience of the efficacy of proactive treatment. General practitioners may impede care by underprescribing, or by reluctance to prescribe regimens they consider too aggressive. Cosmesis and aesthetic acceptance of topicals are not important to infants; they can be treated as aggressively as necessary. The role of health visitors in detecting and appropriate referral was discussed. Individuals with eczema have a 35% risk for irritant hand dermatitis and 30% risk for pompholyx. Flares of eczema may be associated with immune stimulation, for example by vaccination.

Question 5: 'Are there any associations between adult atopic dermatitis and diet?'

Answer: Food allergies in adults with AD are considered rare but do exist, and can be involved in AD flares and chronicity, with significant improvements seen following removal of the culprit food allergen from the patient's diet. Some specialized centres have therefore started to run joint adult allergy–dermatology clinics. Skin prick testing and specific IgE levels are insufficient for the diagnosis of IgE-mediated food allergy, and food challenges are often needed as the gold-standard diagnostic test. Although good population-based data on the prevalence of immediate-type food allergies among adults with AD are missing, there are concerns that more adults are developing *de novo* food allergies, some in the context of existing AD, and this is an area for future investigations.

Question 6: 'Methotrexate is used for atopic dermatitis, despite being unlicensed. Could you advise when and how it is used and whether it would be a relevant comparator for a clinical trial?'

Answer: The only licensed systemic treatment for AD is ciclosporin, and this is only for patients aged over 16 years

and for only 8 weeks. The European TREAT survey (TREatment of severe Atopic eczema in children Taskforce),[84] conducted among more than 700 dermatologists, allergists and paediatricians in eight countries, found that ciclosporin was by far the most common first-line systemic treatment for severe recalcitrant AD in children. However, a recent study conducted among adults with severe AD,[85] which compared methotrexate with azathioprine, suggested that both treatments are viable alternatives to ciclosporin. Methotrexate also has a more favourable side-effect profile than ciclosporin and azathioprine. It is therefore likely to become more commonly used in both adults and children. However, an RCT in children is required, as virtually all the evidence for treatment efficacy in this area comes from adults. Methotrexate is an emerging alternative strategy and, while unlicensed, is increasingly used in some centres. In severe disease, subcutaneous methotrexate was suggested from the outset. Subcutaneous administration provides higher bioavailability, and dosing should be adjusted accordingly. Problems in clinical trials include difficulties with blinding, dosing issues and slow onset of response.

Question 7: The panel was asked for their experience of corticosteroid addiction and rebound effects on stopping

Answer: The panel felt that this is a very rare adverse effect, which can occur when patients have unlimited access to corticosteroids. It can be differentiated from a recurrence of AD because the skin looks red, there is a burning sensation – uncommon with eczema – and there may be papulopustules. The term 'vasoplegia' has been used for patients with red and painful face caused by corticosteroids overuse. Patients can tell the difference. The panel have not seen this phenomenon in children. Similar symptoms have been reported by people using topical corticosteroids as bleaching agents. Suggested treatments included slow weaning, with change to calcineurin inhibitors, tetracyclines and topical soothers, and emotional support. Another option is the new topical preparation, brimonidine tartrate, for rosacea-related facial erythema. The practice of mixing topical corticosteroids in emollients was also discussed; however, there is no evidence to support this treatment and there are concerns that dilution will reduce efficacy.

Question 8: 'What advice do you have on difficult-to-treat patients, resistant to multiple treatments?'

Answer: Treatment options include a tapering course of oral corticosteroids, subcutaneous methotrexate or recruitment into clinical trials (e.g. for dupilumab).

Another suggestion was to revisit the diagnosis and consider biopsy. Hair- and feather-bearing pets may cause constant re-exposure to allergens, and withdrawal of the pet may be beneficial. Other options include intensive management to repair the skin barrier, reduction of re-exposure to allergens, or immunotherapy for those with hay fever and asthma.

Fig 1. Dr Jonathan Silverberg receives the Rajka Medal from Dr Susanne Rajka, with Professor Johannes Ring (left) and Professor Hywel Williams (right).

Final reflections

In addition to the oral presentations, there were 88 poster presentations on the mechanisms, causes, prevention and treatment of AD from researchers throughout the world. All of the abstracts, for both oral and poster presentations, have been published in a special online supplement of this journal.[86] Delegates had opportunities to socialize at the drinks reception, during a guided tour of Nottingham University Gardens and at the Conference Dinner. In the predinner presentation, Professor Rajka's widow, Dr Susanne Rajka, spoke about her memories of the symposium and awarded the first Rajka Medal to Dr Jonathan Silverberg for outstanding work by a young researcher in the field of AD (Figs 1 and 2). Throughout the meeting, the academic sessions started and ended with music that Professor Williams had composed, played and recorded specially for the meeting, including a theme song that depicted the misty mediaeval forests of Nottinghamshire. The musical highlight was the first performance of the Georg Rajka Song, superbly executed in the dulcet tones of a Welsh baritone, accompanied by a gospel-choir-style chorus

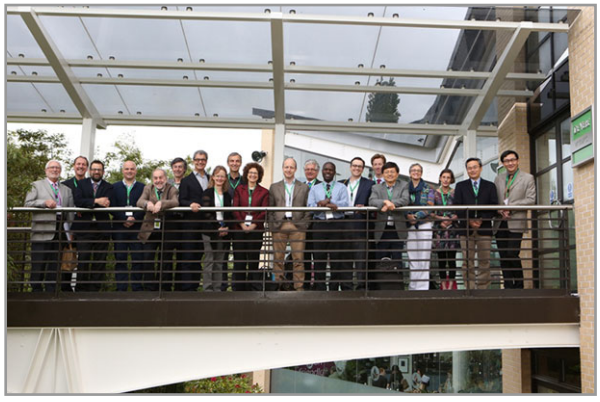

Fig 2. Faculty of the 8th Georg Rajka International Symposium on Atopic Dermatitis.

comprising senior academics and clinicians from the world of dermatology. For those who missed the conference, a short clip of the performance and other conference songs are available via the University of Nottingham website.[87]

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