Professional Development Dermatology

UCD CHARLES INSTITUTE SEMINAR SERIES

Article and series in association with RELIFE MENARINI group

The big picture on atopic dermatitis

*Attendees at UCD's Charles Institute Seminar Series heard a presentation from **Prof Alan Irvine**, who provided the latest clinical perspectives on atopic dermatitis*

The Charles Institute, Ireland's national dermatology research and education centre, played host to a range of guest speakers who covered a variety of topics ranging from skin cancer to psoriasis, among others. The series, which was sponsored by RELIFE (part of the A.Menarini group), was designed to provide expert practical advice from a range of distinguished national and international experts in their respective fields and was chaired by Prof Desmond Tobin, Professor of Dermatological Science at UCD School of Medicine and Director of the Charles Institute of Dermatology.

The fifth presentation in the series was delivered by Prof Alan Irvine, Consultant Dermatologist at Children's Health Ireland and St James's Hospital, Dublin, who delivered a talk titled 'Atopic Dermatitis (AD) Comes of Age'. Prof Irvine highlighted the fact that AD is the most common inflammatory skin disease and he provided an overview of its many presentations and outcomes, as well as common associated comorbidities. Prof Irvine also outlined recent insights into the epidemiology of the condition and the potential for new therapies for AD that are currently in development.

Prof Alan Irvine

Prof Irvine began by stating that eczema is an "important condition" and pointed out that many of the attendees who are in patient-facing roles in their day-to-day work "will know what it is like for people who live with eczema" in terms of their quality of life. During his lecture, Prof Irvine focused on the importance of eczema as a condition, its causes, and potential therapeutic options.

"In terms of the global burden of disease, we are in a place now where the available treatments and available spend in any condition is huge, and is exponentially increasing," he explained. "In some way, we have to apply some health economics measures to determine what conditions are 'worthy' of the spend from public or third-party insurer money and one of the ways to do this is through health economics." In this context, Prof Irvine pointed out that dermatitis, and particularly atopic dermatitis, represents the largest global burden of skin disease and can be quantified as years lost due to disability or quality-adjusted life years measurements.

Consistent burden

Dermatitis is a consistent burden throughout all ages in life and dermatologists are increasingly seeing late-onset dermatitis as first presentations, Prof Irvine explained. He presented the seminar with overviews of how the condition impacts on both younger and older patients' lives. "Itch is the dominant symptom in pretty much everyone. Dryness is less of an issue, depending on the age group, and pain is an increasingly emerging symptom," said Prof Irvine. "That's something that dermatologists frequently don't discuss with their patients but when these patients are asked if they are experiencing pain, it is often reported as an issue." Other domains of impact include lifestyle in general, social interaction, intimacy, work life and sleeping patterns, he explained.

Prof Irvine provided a brief summary of epidemiological studies and told the attendees that different people's psychiatric profiles are affected differently by their conditions. "In eczema and atopic dermatitis, there is consistent sleep deprivation; there is also a definite impact in children in terms of conduct disorder, and anxiety and depression in adults." While rates of suicide are not increased in these patient populations, suicidal ideation rises, explained Prof Irvine. "We know that Th2 cytokines cross the blood-brain barrier but we do not know whether they have a direct effect here [in suicidal ideation], and that is an area that is open for study." The potential to develop neuropsychiatric comorbidities depends on the disease severity and the duration, Prof Irvine added.

"Psoriasis of more than 10 per cent body surface area is associated with a cardiovascular risk equivalent to an elevated cholesterol level," Prof Irvine continued. "In atopic dermatitis, the signal is not so strong and the type of systemic inflammation is different, and we are not exactly sure of these relationships. What we do know is, there is a greater risk of coronary artery disease, and if you have had long-term, significant eczema, independent of known cardiovascular risks, there is an independent risk and that is important to bear in mind."

Prof Irvine presented an overview of the various disease courses in atopic dermatitis and how these have changed over recent years, as well as some studies that chart lifetime patterns of eczema and the various levels of disease severity. "One of the most common questions we get in an eczema clinic is, 'will he/she grow out of it and if so, when?' It's a common and recurring refrain and generally speaking, the answer is that it is quite difficult to know. But the people with early-onset of severe, persistent eczema, these children can have the disease for life but there are other patterns, such as late childhood-onset eczema that disappears. There is also a cohort of those aged 60-plus years who have new onset of eczema. When you are in the clinic with a six-month-old child with eczema, it is hard to know which pathway is ahead of them."

Age of onset

Prof Irvine summarised data from epidemiological studies on the typical age of adult onset of the condition in a wide range of populations and ethnicities and stated: "The bottom line is, about 25 per cent of everybody who has eczema or atopic dermatitis did not have it when they were under the age of 18 years." In terms of causes, he told the attendees there is a complex and interacting pathogenesis in eczema between skin barrier dysfunction and the most predominant microbiome, staph aureus, and Th2 cytokines, "all of which drive itch, which makes all of these more amplified," he told the attendees.

Further elaborating, he told the seminar: "Essentially, we are seeing I IL-4 and IL-13 driven T memory cells that react," he said. "So it's a different response and it has to be that way, when you think about it. These allergic responses have evolved from past times, when people were being bitten by parasites and they needed to scratch them off quickly, or cough them up, or vomit them, so the Th2 reactions are therefore designed for quick expulsion of parasites — they are not meant to be switched on for 25, 40 or 60 years, for example, because that would be tremendously damaging physiologically. In our modern environment, they are switched on for a very long time, for whatever complex concoction of reasons."

He also described the frustration of patients around allergy testing for atopic dermatitis: "Allergy testing for a barrier dysfunction — it's the wrong way around," said Prof Irvine. "There is so much misinformation around this. It's very frustrating for patients and they can spend a lot of money on allergy testing, but it is really an add-on — it's important, but avoidance will not 'fix' eczema by itself."

Prof Irvine concluded his talk by telling the attendees: "The onset of atopic dermatitis, particularly in children, persists into adulthood but there are many, many different variations. There is a huge risk of type 2 comorbidities and type 2 inflammation is the dominant inflammation.

"There are dominant cytokines and they drive itch and barrier dysfunction, and they can be blocked using monoclonal antibodies. The therapeutic landscape is going to change dramatically in the next number of years and that is going to be very disruptive."

Triggers

During a lively Q&A session after Prof Irvine's presentation, he described atopic dermatitis as "very much a condition of urbanisation" and suggested that there are multiple triggers for this, such as diesel fumes, loss of microbiome diversity and increased exposure to detergents, all of which can drive inflammatory responses. Prof Tobin raised the point of huge genetic variation in skin, which is seen in different populations and how their skin reacts when they relocate to highly-urbanised areas. He also drew a comparison with skin pigmentation. "The melanocortin 1 receptor, which controls the amount of brown/black melanin we produce… in Africa, there is a 'brake' against polymorphism in that gene, and essentially so, because to lose that pigmentation in a high-UV area would be absolutely catastrophic. Therefore, it seems odd that with filaggrin — given its location as a key survival element, especially if it occurs prior to a person's reproductive peak — that such a deficit would be tolerated through selective evolutionary pressures."

Prof Irvine responded: "The question is, if you are heterozygous in some areas, is there an advantage? There are some examples — for instance, sickle cell is somewhat protective against malaria as a trait, but not as a disease. There is also a theory that CF could be protective against salmonella, but we're not quite sure about that," continued Prof Irvine. "There is a heterozygous advantage in melanocortin, because paler skins make better vitamin D, so there are some heterozygote advantages. We don't know if there is a heterozygous advantage for filaggrin. You could look at that with genomics and whether it is genetic drift, or positive selection pressure — there does not seem to be positive selection pressure on it. It seems to be a highly-mutable gene."

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Prof Tobin also pointed out that in locations of a child's face that are affected by atopic dermatitis, sebum-rich areas seem to provide a protective effect. "Sebum is thought to contain antimicrobials and complex chemicals — human sebum is even more remarkable than other mammals' sebum. In a therapeutic context, is there anything there that could be applied via mimics of sebum that may be more volatile on dryer skin?"

Prof Irvine concurred and responded: "Researchers have looked at vernix caseosa and its protein structure in this regard… it could be very useful, but it is incredibly difficult to synthetically replicate vernix or sebum, but it does make a lot of sense to pursue that," he said. "Researchers are also looking at biotherapy, for similar reasons."

Speaking with the ***Medical Independent (MI)*** following his presentation, Prof Irvine commented on the need for therapeutic advances in eczema. "There are no formally-approved and reimbursed treatments for eczema in Ireland at the moment. I think next year will be huge, with several options coming online, but at the moment there are no new treatments available."

Prof Irvine concluded by complimenting the diagnostic skills of GPs who treat and refer patients with skin conditions. "I think GPs are very good at diagnosing atopic dermatitis," he told MI. "Often, there can be under-treatment mild eczema because of a fear of steroid use, by GPs or pharmacists. But generally speaking, diagnostic dilemmas are not a big thing in primary care — these physicians normally get it spot-on."

Relife has had no input into the content of the series or article.