Systemic treatment for moderate-to-severe atopic dermatitis? A systematic review and recommendation

Jochen Schmitt –Centre for evidence-based healthcare, Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Germany

In many patients with moderate-to-severe atopic dermatitis (AD) disease activity requires systemic treatment to achieve adequate disease control. Various immunomodulating therapies are currently being used in patients with AD who do not respond to topical treatments and/or UV-therapy, including glucocorticosteroids, cyclosporin A (CsA), methotrexate (MTX), azathioprine (AZA), interferon-γ (IFN), intravenous immunoglobulin (IVIG), mycophenolate mofetil (MMF) and Traditional Chinese Herbal Medicine (TCHM).We aimed to systematically evaluate and critically appraise the efficacy and safety of systemic treatments for moderate-to-severe AD.

A systematic literature search was performed in MEDLINE, EMBASE and CENTRAL (until June 2012). Randomized controlled trials (RCT) evaluating systemic immunomodulating treatments for moderate-to-severe AD were included. Selection, data extraction, and trial quality assessment were performed independently by two reviewers. In accordance with the HOME (Harmonising Outcome Measures for Eczema) core outcome domains for AD-trials, outcomes concerning clinical signs, symptoms, health-related quality of life, and course of AD were extracted as efficacy outcomes. To compare safety data, the incidence rates (%) per patient per week for adverse event (AE), serious adverse event (SAE) and withdrawals due to AE or SAE were calculated.

Thirty-four trials were included, totaling 1,653 patients. CsA efficaciously improves clinical signs of AD in children and adults and is recommended as first line treatment for short-term use. AZA is recommended for short-term induction treatment and long-term treatment up to 24 weeks. Indirect comparisons suggest that the efficacy of AZA is lower than that of CsA. MTX may be considered as third line treatment option for short-term induction treatment and long-term treatment up to 24 weeks, but the evidence is limited. INF is also efficacious for severe AD, but safety and tolerability need to be monitored closely. MMF may be a treatment option for maintenance treatment of AD after induction treatment with CsA. Evidence for the other treatment options is either of low quality or indicates inferior efficacy.

This review provides evidence-based recommendations on systemic treatment for AD. However, most trials were small and short. To further increase our understanding of the best treatment options for patients with AD who cannot be adequately controlled with topical or UV treatments alone, large long-term head-to-head trials are needed. Furthermore, although prevalence of AD is highest among children, RCTs in children are missing for many relevant interventions, and more research in this age group is recommended.

Disease Modification Strategies for AD

Alain Taïeb, University of Bordeaux and INSERM 1035, Bordeaux, France

After so many years of debate about its pathophysiology, AD is now best considered as a model for inflammatory epithelial barrier diseases. The key discovery of a major effect of filaggrin mutation as a predisposing trait has ordered a puzzle of discordant views, and suggests that a disturbance in skin homeostasis can influence the regulation of organ innate immunity leading to uncontrolled adaptive responses and chronic inflammation. Most importantly, this epithelial pathophysiology based model indicates that interventions should be implemented according to disease stage and severity, from preclinical stage (no eczema, prevention+++), infantile eczema (revelation phase), flexural-chronic eczema (with various severity, including the very severe forms which need systemic intervention) to extracutaneous manifestations (asthma and rhinitis). A successful intervention based on this approach should limit asthma burden, not only atopic dermatitis.

The chronic auto-inflammatory phase of the disease is poorly influenced by modifications of the environment (irritants, allergens, stresses) and is now the major target for biologics, with the aim to return to more classical options after successful slowdown of cutaneous inflammation. Based on interventions already reported with existing biologics, there is no clear breakthrough in the field. Interestingly, other drugs blocking inflammation already used in other fields such as rheumatology have escaped investigation in AD and could be tested in a small pilot studies as a proof of concept for further drug development. On the other hand, the development of specific biologics for allergic TH2 mediated diseases is emerging targeting TH2 cytokine receptors (dupilumab, lebrikizumab), TSLP, pruritus associated cytokines such as IL31.

The importance of skin as an initiating factor for priming the immune system towards a dysregulated TH2 adaptive response suggests to use this route for desensitization in addition to interventions targeting the more tolerogenic gut immune system. The manipulation of the microbiome holds a great promise in this respect as an adjuvant to promote allergen tolerance or influence desensitization. In addition to immune targets, factors that may restore epidermal environment constitute interesting therapeutic tools from emollients to possible gene therapy or gene modification. Concerning areas of importance that have been relatively overlooked, we should try to influence the inflammatory skin pattern towards less pruritogenic effects, and thus we need to better understand pruritus and pruritogenic inflammation. Also, limiting the amplification loop of disease by attacking abnormal regulatory mechanisms which perpetuate skin autoinflammation is probably as important in allergic disorders as already shown in autoimmunity.

Patient Education & Support Groups

Roberto Takaoka, Department of Dermatology, University of Sao Paulo
Medical School Hospital, Sao Paulo, BRAZIL

Despite great advancements in our understanding of the immunologic mechanisms and skin barrier defects involved in the pathogenesis of atopic dermatitis, the management of this chronic skin disease often remains a challenging and frustrating problem for both patients and doctors. In a recent poll conducted on the Internet, 80% of patients and parents responded negatively when asked if they were satisfied with the treatment given by their doctors. A common complaint was that doctors were unable to explain the disease properly and consequently failed to provide proper care. Atopic dermatitis is a complex disease and time constraint limits the amount of information a doctor can provide during the consultation.

Educational programs for patients and parents can improve the understanding about the disease and improve adherence to treatment. But explaining how the disease works and what medication to use is also not enough. Doctors and the educational team should go beyond the disease and have a broader view of the many aspects involved in the pathological process. These include psychological, environmental, social, financial, and cultural aspects. Patients should also have a more realistic expectation about the treatment and should not expect a swift and miraculous cure.

Supports groups for patients and parents can be extremely helpful in addressing important medical, psychological and social issues involved in this complex disease. Support groups break isolation and provide a space where patients can share common experiences and collectively learn how to better treat and cope with the disease. An active collaboration that involves doctors, patients and their families, and a multidisciplinary educational team, should be established for the development of an effective therapy for atopic dermatitis.

Involving patients in atopic dermatitis care and research

Kim Thomas and Amanda Roberts, Centre of Evidence Based Dermatology, University of Nottingham, UK

Background

Patient involvement in research has become fashionable in recent years, but many researchers and patients find it hard to work together in a meaningful and mutually-beneficial way. Patient involvement in research, when done well, can ensure that the right questions are asked, that they are answered in the right way, and that the resulting evidence will be relevant to the needs of those who need it most.

This session will reflect on some of the lessons learned in engaging with eczema patients as partners in research at the Centre of Evidence Based Dermatology, with particular reference to the eczema Priority Setting Partnership..

Priority setting partnership

The eczema Priority Setting Partnership worked with patients and healthcare professionals to identify, and prioritise important questions about the use of eczema treatments that had not already been answered by research (these were known as treatment uncertainties). A steering group comprising patients, clinicians, researchers and a James Lind Alliance representative (providing infrastructure and process) oversaw the priority setting partnership. Key stakeholder organisations and individuals were contacted to ensure participation of eczema patients, their carers, and healthcare professionals caring for eczema patients.

What we did

Using online and paper surveys, 493 participants submitted up to five eczema treatment uncertainties. This yielded 1,070 uncertainties, which were refined and collated by the steering group. Uncertainties known to have been answered by previous research, and those not relevant to the treatment of eczema, were removed, giving a short list of 732 uncertainties.

In the second stage, 514 participants each selected up to ten uncertainties of the short-listed uncertainties to create a ranked list.

The ranked priorities were subdivided into uncertainties that were prioritised by all participants, and those prioritised by patients and health professionals separately, to ensure adequate representation of all participants' views. This resulted in 14 prioritised uncertainties; four that were priorities for both patients and healthcare professionals, five that were priorities for patients, and five that were priorities for health care professionals.

Why this is important

This open and transparent process allowed patients and healthcare professionals the dominant voice in determining future research priorities. This is an important step for ensuring that publicly-funded research addresses the most important questions and uses limited resources wisely. All treatment uncertainties have been published and disseminated to research funders to guide future research priorities for funding. Many of the priority areas are now being addressed by ongoing research.

State of the Art Understanding of Mechanisms in Atopic Dermatitis

Lisa Beck - University of Rochester Medical Center, USA

Atopic dermatitis (AD) is the most common inflammatory skin disease affecting > 14% of children and ≈ 10% of adults in the US. Hypotheses proposed to explain the pathogenesis of this disease are numerous and not entirely compatible. At the risk of being seen as an "outlaw," I am going to propose general concepts that have emerged in hopes that this will give you a broader view of the "Sherwood Forest" rather than just the band of "merry men" within. Murine and human mechanistic studies as well as genetic analysis have strongly implicated a role for skin **barrier**, cutaneous **immune** responsiveness (innate and adaptive) and **pruritic** pathways in AD development. There seems to be little debate that these abnormalities are commonly observed in our patients – the conflict arises when considering which is primary and/or dominant.

The observation that AD patients' *nonlesional* skin is xerotic, physiologically impaired (as highlighted by increased TEWL, a more alkaline pH) and susceptible to topical irritants have long implicated an epithelial defect as a central feature of this disease. The stratum corneum (SC) is dysfunctional in AD as the result of one or more of the following defects; reduced/altered levels of SC lipids, dysregulated proteases/antiproteases and acquired or genetic defects in structural proteins such as filaggrin, loricrin and other epidermal differentiation complex genes. Null mutations in filaggrin (*FLG*) and copy number variants have been strongly linked to AD and several subphenotypes (early-onset, severe/persistent, and eczema herpeticum). Tight junctions (TJ), found just below the SC within the stratum granulosum regulate the paracellular passage of ions and solutes and also appear to be defective in AD. The assumption from these observations is that a leaky epidermal barrier would promote greater immunologic responsiveness either by greater penetration of allergens, antigens, irritants and/or microbes or greater access and activation of LC/DCs to the skin surface to sense these "outlaws". This remains a very active area of research.

Although barrier defects are likely key initiating factors, immune dysregulation and in particular Th2 polarization, is also critical for the development of AD. This is highlighted by strong association of AD with other Th2-driven, allergic disorders, the dramatic elevation in Th2 biomarkers such as serum total IgE, TARC, eotaxin-3, periostin, peripheral eosinophilia, and the sensitization to large number and range of environmental, microbial and even self antigens. More recent studies have also identified T22 cells and in intrinsic AD subjects, Th17 cells can be been found. The induction of an adaptive Th2 immune response is likely the consequence of local tissue factors and less frequently the consequence of genetic mutations in Th2 pathway genes. Epithelial cells and the innate lymphoid cell (ILC2 or nuocyte) are thought to provide key signals (IL33, TSLP, IL25) that activate the LC/DC and initiate the development and recruitment of Th2 cells. These epithelial "adjuvants" (aka Robin Hoods) are secreted in response to mechanical injury, enzymatic actions (either directly or through the signaling of PAR receptors)

or by triggering innate immune receptors such as TLRs. Considering this one could imagine that the itch-scratch cycle might bias an individual toward a Th2 response. Is this in fact the "itch that rashes" or the rash that itches?

Less is known about what drives the intractable pruritus, which is a major factor accounting for the low quality of life scores measured in patients. Several candidate pruritogens have emerged. Probably the most extensively studied is IL31 which is increased in the skin and blood of patients with AD. It is produced by T cells (Th2, T22 and other subsets) and mast cells and may act on a number of cells including eosinophils. More recently epithelial-derived TSLP has been shown to directly communicate with a subset of TRPA1-positive sensory neurons to trigger itch.

Only a highly skilled "swordsman/woman" will know whether barrier, immune or itch is in the center of the bullseye.