Institution: University of Sheffield

Unit of Assessment: 3C – Allied Health Professions: Biomedical science

Title of case study: Better Treatment and Prevention of Atopic Eczema

1. Summary of the impact

Research investigating genetic and environmental interactions leading to skin barrier breakdown in atopic eczema has delivered health benefits by improving the prevention and treatment of this condition. We found that established emollient formulations (e.g. Aqueous Cream BP) containing the harsh emulsifier sodium lauryl sulphate (SLS) damage the skin barrier in patients with atopic eczema and identified an underlying molecular mechanism. Consequently, the NICE Quality Standard and Guidelines now reflect our advice that Aqueous Cream should not be used as a leave-on emollient, SLS has been removed from all emollient formulations in the UK and we have helped develop the next generation of 'SLS-free' skin-care products. Medicines regulators including the Medicines and Healthcare products Regulatory Agency (MHRA) and New Zealand MedSafe have also issued new advice as a result of our research.

2. Underpinning research

Research led by Professor Cork (University of Sheffield since 1995) and Dr Tazi-Ahnini (University of Sheffield since 2000) in the Academic Unit of Dermatology identified genetic and environmental factors that lead to skin barrier breakdown in atopic eczema (atopic dermatitis). Studies showed that an increase in protease activity within the upper layers of the skin, attributable to genetic variants in protease and protease inhibitor genes, contributes to a major breakdown of skin barrier function [**R1, R2, R3**].

These researchers also observed that harsh soaps and the use of Aqueous cream BP ('Aqueous Cream') containing the detergent sodium lauryl sulphate (SLS) were associated with poor control of disease in children with atopic eczema. An audit of the number of cutaneous reactions to different types of emollient creams including Aqueous Cream showed that 56% of episodes of exposure to Aqueous Cream were associated with burning, stinging and redness of the skin, compared to 18% for all other emollients [**R4]**. This led to the conclusion that the SLS in Aqueous Cream was damaging the skin barrier and making the atopic eczema worse rather than better. Further research demonstrated that Aqueous Cream also caused severe damage to the skin barrier in people with a previous history of atopic dermatitis. SLS raises the pH of the upper layers of the skin leading to enhanced protease activity [**R5**], explaining why it causes exacerbation rather than improvement of symptoms [**R4**]. The increase in pH also inhibits the synthesis of the lipid lamellae, further worsening skin barrier dysfunction [**R5**]. These factors therefore feed a common pathway in skin barrier breakdown and the development of atopic eczema.

Education regarding the avoidance of harsh soap and detergents and the use of emollients is the first line therapy of atopic eczema. It was demonstrated that comprehensive education of parents and children with atopic eczema was essential in order to ensure avoidance of damaging environmental agents and correct use of emollients [**R6**].

The underpinning research has therefore identified genetic and environmental factors that lead to skin barrier breakdown in atopic eczema, has led to the development of new optimal emollient formulations and wash-products, and has provided education on how to use topical treatment to improve the treatment and prevention of atopic eczema

3. References to the research

R1. Vasilopoulos Y, Cork MJ, Murphy R, Williams HC, Robinson DA, Duff GW, Ward SJ, Tazi-Ahnini R. (2004). Genetic association between an AACC insertion in the 3'UTR of the stratum corneum chymotryptic enzyme gene and atopic dermatitis. *Journal of Investigative Dermatology.* 123: 62-66. doi: 10.1111/j.0022-202X.2004.22708.x

R2. Vasilopoulos Y, Cork MJ, Teare D, Marinou I, Ward SJ, Duff GW, Tazi-Ahnini R. (2007). A nonsynonymous substitution of cystatin A, a cysteine protease inhibitor of house dust mite protease, leads to decreased mRNA stability and shows a significant association with atopic dermatitis. *Allergy.* 62: 514-519. doi: 10.1111/j.1398-9995.2007.01350.x

R3. Vasilopoulos Y, Sharaf N, di Giovine F, Simon M, Cork MJ, Duff GW, Tazi-Ahnini R. (2011). The 3'-UTR AACCins5874 in the stratum corneum chymotryptic enzyme gene (SCCE/KLK7), associated with atopic dermatitis; causes an increased mRNA expression without altering its stability. *Journal of Dermatological Science.* 61: 131-3. doi: 10.1016/j.jdermsci.2010.11.013

R4. Cork MJ, Timmins J, Holden C, Carr J, Berry V, Tazi-Ahnini R, Ward SJ. (2003). An audit of adverse drug reactions to aqueous cream in children with atopic eczema. *Pharmaceutical Journal.* 271: 747-748.

R5. Danby S, Al Enezi T, Sultan A, Chittock J, Kennedy K, Cork MJ. (2011). The effect of aqueous cream BP on the skin barrier in volunteers with a previous history of atopic dermatitis. *British Journal of Dermatology*. 165: 329-334. doi: 10.1111/j.1365-2133.2011.10395.x

R6. Cork MJ, Britton J, Butler L, Young S, Murphy R, Keohane SG. (2003). Comparison of parent knowledge, therapy utilization and severity of atopic eczema before and after explanation and demonstration of topical therapies by a specialist dermatology nurse. *British Journal of Dermatology.* 149: 582-589. doi: 10.1046/j.1365-2133.2003.05595.x

4. Details of the impact

Impact on health

The National Eczema Society (NES) charity, which supports people with eczema, highlights the substantial improvements to eczema patient wellbeing that have resulted from our work [**S1, S2**].

Recommendations by NICE agreed with the conclusions that Aqueous Cream BP should never be used as a leave-on emollient; the NICE guidance on atopic eczema in children [**S3**] cited this research. This advice has been further reinforced in the NICE Quality Standard for atopic eczema issued in 2013 [**S4**], which is based on the NICE atopic eczema guideline of 2007.

Our Aqueous Cream research has also been recognised and acted upon by medicine regulators internationally. The New Zealand Medicines Safety Authority quoted R5 stating. "*These papers highlight the importance of not using products containing SLS, such as Aqueous Cream, as leave-on emollients as they may act to exacerbate skin damage, rather than support skin barrier function*" [**S5**]. Other regulators including the Medicine and Healthcare products Regulatory Agency (MHRA) have issued advice regarding the adverse effects of Aqueous Cream [**S6**].

Commercial impact

As a result of these research-led changes, the costs of healthcare have changed in practice. The NES has followed our research using it in their campaign to remove cheap, ineffective, harmful emollients, such as Aqueous Cream, from formularies. "*These products not only exacerbate diseases such as atopic eczema but may even contribute to its development. They are also a false economy because Aqueous cream often makes atopic eczema worse leading to referral to dermatologists*" [**S1, S2**]. The sales of Aqueous Cream have fallen 70% since 2009 [**S1**].

All of the UK companies previously producing emollients containing SLS have now removed the SLS and replaced it with a less harmful emulsifier. NES sources state that: "*The logo 'SLS Free' now appears on all of these emollients – a direct consequence of your research. Similar re-formulations of emollient products are taking place internationally*" [**S1, S2**].

As a result of our research, companies producing skin-healthcare products have invested in research and development, working with us to design and test new and improved formulations that are now in production. We have spent the past 15 years developing completely new products to produce an optimal repair of the defective skin barrier in atopic dermatitis, initially through a spinout company (Molecular Skin Care), but more recently with a [text removed for publication] investment by [text removed for publication] [**S7**]**.** We have performed randomised control clinical studies demonstrating the benefits of the new formulation compared with existing formulations. This product is now going into production [**S1, S2**].

We have also been working with other pharmaceutical companies to develop optimal wash products, for use in regimens to prevent the development of atopic eczema. We have worked with Johnson & Johnson to develop and test an optimally formulated SLS-free range of baby care products (including 'Top to Toe' baby wash). Johnson and Johnson funded a knowledge exchange scheme (£718,000) with the University of Sheffield to exploit biochemical and biophysical assays of skin barrier function developed by the group [**S8**]. With our collaborators (Professor Dame Tina Lavender's group in Manchester) and Johnson and Johnson in the USA we have conducted a programme of clinical trials to evaluate all of the products that we put on babies' skin [**S9, S10**]. Since 2008, Johnson and Johnson have invested many £millions in research and development of these products and have seen sales of their products 'Top-To-Toe Bath' increase by 15% and 'Extra Sensitive Wipes' increase by 8% [**S8**]. The key enabler in these sales increases was verification of the findings from the clinical trials that these products were safe to use from birth.

Public understanding has improved. Educating children with atopic eczema and their parents regarding the importance of avoiding all harsh soaps and detergents, and how to use the correct emollient products, was evaluated in our 2003 audit [**R6**]. This paper was cited by both NICE 2007 and NICE 2013 as evidence for the crucial role of education in the treatment of atopic eczema [**S3, S4**]. Regarding our work NES states that: "*Education regarding the use of topical treatments is one of the interventions that has transformed the lives of children and adults with atopic eczema. The Sheffield team, led by Professor Michael Cork, have made a major contribution in this area*" [**S1, S2**].

5. Sources to corroborate the impact

S1. CEO of *The National Eczema Society* (NES) support letter (on file).

S2. http://www.eczema.org/ageous

S3. NICE Atopic Eczema Guidelines, CG57-issued December 2007 (http://guidance.nice.org.uk/CG57). Although published in 2007, this guideline remains valid. There have been no updates.

S4. NICE Quality Standards 44, Atopic Eczema in Children published September 2013. Full guidance is found here: http://guidance.nice.org.uk/QS44. Specific guidance on avoidance of sodium lauryl sulphate containing emollient is found here: http://tinyurl.com/okra5rj

S5. New Zealand Medicines and Medical Devices Safety Authority (NZ MEDSAFE) Aqueous Cream – Moisturiser or Irritant? March 2012; Prescriber Update 2012; 33(1): 4. http://www.medsafe.govt.nz/profs/PUArticles/PDF/PrescriberUpdate_March_2012.pdf

S6. MHRA UK Public Assessment Report (March 2013). Aqueous cream: may cause skin irritation, particularly in children with eczema, possibly due to sodium lauryl sulfate content. Drug Safety Update, volume 6, issue 8, Article A2. http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON254804

S7. [text removed for publication] support letter (on file) regarding the development of optimal emollient formulations.

S8. Johnson & Johnson support letters (on file). Details of the partnership between the University of Sheffield and J&J are described, including figures for investment in Research and Development and the impact of research on sales of J&J baby skin care products.

S9. Lavender T, Bedwell C, O'Brien E, Cork MJ, Turner M, Hart A. Infant skin-cleansing product versus water: A pilot randomized, assessor-blinded controlled trial. *BMC Pediatr*. 2011 May 13; 11:35. doi: 10.1186/1471-2431-11-35 This pilot study (n=100 randomised to 2 groups) provided data to inform an extensive trial of Johnson and Johnson's® *baby top-to-toe*™ wash.

S10. Lavender T, Bedwell C, Roberts SA, Hart A, Turner MA, Carter LA, Cork MJ. Randomized, Controlled Trial Evaluating a Baby Wash Product on Skin Barrier Function in Healthy, Term Neonates. *J Obstet Gynecol Neonatal Nurs.* 2013 Feb 19. doi: 10.1111/1552-6909.12015. Newborn bathing with *baby top-to-toe*™ wash product (n=159) was compared to water alone (n=148) in a powered, randomised, trial. No difference was found between the two regimes and the data can be used to reassure and inform parental choice of wash protocols.