Institution: Newcastle University

Unit of Assessment: UoA1

Title of case study: Increased range and adoption of evidence-based treatments for refractory moderate-to-severe atopic eczema

1. Summary of the impact

Atopic eczema is a disabling long-term skin condition affecting ~2% of the UK adult population. The mainstay of treatment remains topical steroids and moisturisers, but many adult patients with atopic eczema have resistant disease that can significantly impair quality of life. Newcastle University researchers conducted clinical trials that showed both whole-body ultraviolet B phototherapy and systemic (tablet) treatment with the immunosuppressant drug azathioprine were effective treatments for adults with atopic eczema resistant to standard topical treatments. UK and European guidelines written after 2008 recommend UVB phototherapy and azathioprine for atopic eczema, and survey data indicate that both are now widely used to treat the disease in the UK.

2. Underpinning research

Key Newcastle University researchers

The research was conceived and carried out by Professor Nick Reynolds (as Clinical Senior Lecturer and Professor from 2001); Dr Simon Meggitt (Honorary Clinical Lecturer and from 2005 Senior Clinical Fellow); and Professor Peter Farr, who at the time of the research was an Honorary Clinical Lecturer in the Department of Dermatology.

Background

Although often considered a disease of childhood, around 2% of adults in the UK have atopic eczema (dermatitis) (Herd et al 1996 PMID:8776352), representing over a third of all patients with the condition (Sandström Falk & Faergemann 2006 PMID:16648916). While many adult patients respond to treatment with topical steroids and moisturisers, a significant percentage have refractory disease although the prevalence of refractory moderate-to-severe atopic eczema in the UK has not been defined. In adults, refractory moderate-to-severe atopic eczema usually runs a prolonged and protracted course (Barker et al 2006 PMID:16990802) and is characterised by skin barrier dysfunction and chronic inflammation, typically affecting over 40% of the body surface area (R2, R3). The itching, associated loss of sleep and skin infections that accompany moderate-to-severe disease significantly impair quality of life.

Adults with moderate-to-severe atopic eczema refractory to topical treatments (including calcinuerin inhibitors) may be considered for phototherapy or systemic drug treatments. Currently ciclosporin is the only oral drug with a product licence for refractory atopic eczema. It should be used only for a limited period (the British National Formulary recommends two months maximum) because prolonged use is associated with hypertension, renal impairment and risk of cancer. However, symptoms recur within weeks when ciclosporin is discontinued.

In 2000 an independent systematic review (Hoare et al. 2000 PMID:11134919) highlighted the lack of therapeutic options for patients with refractory atopic eczema and underscored the need for scientifically robust testing of a range of treatments for the disease.

Newcastle research

Researchers in Newcastle University sought to address the issues highlighted by Hoare et al. and conducted trials of two distinct therapeutic approaches.

Ultraviolet B phototherapy: As narrowband ultraviolet B (UVB) is widely used to treat psoriasis, most dermatology units are equipped with phototherapy units though its efficacy for treating atopic eczema was previously unknown. In 1996, Farr led an open pilot study of narrowband UVB phototherapy for moderate-to-severe atopic eczema in adults (R1). That small study informed the design, by Farr and Reynolds, of the first randomised controlled trial (69 patients) comparing narrowband UVB to broadband UVA (as used in commercial sunbeds) and visible-light (placebo) for the treatment of refractory moderate-to-severe atopic eczema in adults. The results (R2) showed that narrowband UVB was an effective, well-tolerated treatment and the benefits were

maintained for several months after treatment ended. Over the course of 24 treatments, mean total disease activity (the sum of clinical scores of five clinical signs of eczema at six body sites) reduced by around one-third from baseline in UVB-treated patients, which was a statistically significant change when compared to placebo. In contrast, the reduction in disease activity after UVA treatment was smaller and not significant. The effectiveness of narrowband UVB was also reflected by improvements in the extent of disease and patient reported symptoms, as 90% of the UVB treated patients reported a reduction in itch over the treatment course, compared to 11% of the placebo group (R2).

Azathioprine: Following an open pilot study (the results of which were published in a review; Meggitt and Reynolds (2001) PubMed ID: 11488818), Reynolds and Meggitt designed and led the first parallel-group randomised controlled trial of azathioprine for moderate-to-severe atopic eczema in adults. This regional multi-centre trial was also the first to use pharmacogenetic-based dosimetry for a dermatological condition. Patient doses of azathioprine were based on their levels of the enzyme thiopurine methyl transferase (TPMT) which reflects their ability to metabolise the drug. The results were published in the *Lancet* in 2006 (R3). 63 patients participated in the trial, with 42 receiving azathioprine. Azathioprine significantly improved disease activity by 37% over 12 weeks of treatment compared to a 20% reduction in the placebo group. Again, objective improvements in disease activity were matched by improvements in body surface area affected, patient-oriented symptoms and quality of life scores. For example, itch scores reduced significantly (by 46%) in patients who received azathioprine compared to those who received placebo (R3). TPMT-based dosimetry reduced the dose administered to a subset of patients with no loss of efficacy and potential safety benefits (R3).

3. References to the research (Newcastle authors in bold. Citations from Scopus, July 2013.)

R1. Hudson-Peacock MJ, Diffey BL & **Farr PM** (1996). Narrow-band UVB phototherapy for severe atopic dermatitis. *British Journal of Dermatology* 135(2):332. DOI: 10.1111/j.1365-2133.1996.tb01179.x **27 citations.**

R2. **Reynolds NJ**, Franklin V, Gray JC, Diffey BL & **Farr PM** (2001). Narrow-band ultraviolet B and broad-band ultraviolet A phototherapy in adult atopic eczema: a randomised controlled trial. *The Lancet* 357(9273):2012-2016. DOI: 10.1016/S0140-6736(00)05114-X. **113 citations.**

R3. **Meggitt SJ**, Gray JC & **Reynolds NJ** (2006). Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. *The Lancet* 367(9513):839-846. DOI: 10.1016/S0140-6736(06)68340-2. **81 citations.**

Key funding

NHS Research and Development, Northern and Yorkshire, UK.1994-7. £28,153. *Ultraviolet light (UV) therapy for atopic dermatitis: double blind, randomized trial of narrow band UVB (TLO1) versus UVA versus placebo.*

British Skin Foundation. Clinical Research Fellowship to Dr Meggitt. 2000-1. £40,372. *Randomised double blind controlled trial of azathioprine in moderate-to-severe atopic eczema.*

In 2007, Dr Meggitt was awarded the British Skin Foundation prize for the best British Skin Foundation funded research conducted in the previous 10 years.

Wellcome Trust. Funding for Professor Reynolds and Dr Meggitt. 2001- 4. £462,884. *Regulation of the calcineurin/NFAT pathway in human keratinocytes and inflammatory skin disease*

4. Details of the impact

Surveying current practice in the UK

To determine the extent of clinical adoption in the UK of UVB and azathioprine on treatment of adult patients with refractory moderate-to-severe atopic eczema outwith an acute flare, a survey of current clinical practice was conducted. This was done in June 2013 by Newcastle University researchers, through the UK Translational Research Network in Dermatology and the UK Dermatology Clinical Trials Network (Ev a). The design and implementation of the survey instrument was validated by an independent consultant. The 61 completed responses from 310

consultant dermatologists surveyed were in line with expectations for this type of research. Survey outcomes are discussed below for each of the treatments and should be seen in the context of the estimated number of new adult referrals in the UK per year. Responses from the consultant dermatologists surveyed revealed an estimated 28,400 new referrals for refractory moderate-to-severe atopic eczema in adults per year across the UK.

Narrowband UVB in guidelines and clinical practice

In 2012 a number of European dermatology societies, including the European Academy of Dermatology and Venereology, European Task Force on Atopic Dermatitis and European Society of Pediatric Dermatology, published a consensus set of guidelines on treatment of atopic eczema. On UV phototherapy they state:

> *'There is evidence that UV-therapy can be used in AE* [atopic eczema] *to relieve pruritus* [itch]*. Narrowband UVB seems to be most preferable'* (Ev b)… *'Narrow-band UVB was more effective than UVA'* (Ev b).

That recommendation cites and is largely based on Farr and Reynolds' 2001 trial results (R2): it is the only randomised controlled trial cited in support, and Reynolds' was a significantly larger study than the other two half-body comparison studies (which also reported later).

The results of the 2013 Newcastle run survey of UK practice indicated that phototherapy (using any one of a number of wavelengths of ultraviolet radiation) was the most popular first-line treatment option for moderate-to-severe refractory atopic eczema that was not controlled by topical treatment. Phototherapy was chosen by just under half (46%) of respondents, probably reflecting the widespread availability of phototherapy units. Of those considering this approach, over 93% selected narrowband UVB as their first choice, indicating that UVB phototherapy (trialled by Newcastle) has been widely adopted across the UK as a treatment for refractory atopic eczema. Based on the reported numbers of patients treated by the consultant dermatologists in the survey, it is estimated that about 8,200 patients are treated with or referred for narrowband UVB phototherapy each year in the UK.

Azathioprine in guidelines and clinical practice

The British National Formulary (BNF) is a standard resource for UK clinicians, aiding decisions on which drug to use when treating a particular disease. A full entry on azathioprine first appeared in the skin section of the Formulary in edition 59, March 2010 (Ev c). It states that azathioprine should be considered for severe refractory eczema, and there is accompanying dosing guidance based on the thiopurine methyl transferase (TPMT) activity of individuals, as first used by Newcastle researchers. TPMT is an enzyme present in humans that metabolises azathioprine and similar drugs. Genetic variation in the population means that the drug is broken down at different rates by different individuals. Patients with no TPMT activity should not receive the drug. The dosing guidance of 1-3mg/kg/day for normal or high TPMT activity, 0.5-1mg/kg/day for low TPMT activity reflects the doses used in the Newcastle University-led trial (R3). A British National Formulary clinical writer has stated,

> *'I can confirm that the paper by Meggitt SJ, et al …. Lancet 2006) was used, among others, to inform this content change* [the BNF entry on azathioprine for atopic eczema]*'* (Ev c).

In 2011 the British Association of Dermatologists published guidelines on the safe and effective prescription of azathioprine for a variety of dermatological conditions. On use of the drug for atopic eczema, the guidelines state:

> *'Although azathioprine is not licensed for use in atopic eczema, there is now strong evidence (from two RCTs) for a statistically significant and clinically meaningful response to azathioprine. Both studies used the drug as oral monotherapy in moderate-to-severe, refractory disease.'* (Ev d)

The Newcastle University trial (R3) was the larger of the two studies referred to and was the only one to employ dosing based on the TPMT activity of patients. The guidelines specifically highlight the importance of TPMT assessment in the clinic for avoiding drug toxicity. This trial was also cited as significant underpinning evidence in an influential 2011 systematic review of several studies in which azathioprine had been used off-label for treatment of skin diseases. The review contains a

'strong clinical recommendation … for azathioprine in atopic dermatitis' on the basis of high-quality level A evidence (Ev e).

The Newcastle run 2013 survey of UK dermatologists (Ev a) indicated that azathioprine has been widely adopted in the UK as a treatment of moderate-to-severe refractory atopic eczema. Systemic therapy was the most popular second-line treatment option chosen by 49% of respondents, and it was also the second most popular first-line treatment option, chosen by 36% of respondents. Of those considering systemic therapy, azathioprine was the most popular first-line choice of drug (46% of respondents). There is evidence that because of its better safety profile than ciclosporin, azathioprine is facilitating longer-term control of symptoms (for example suppression of itching) in patients. Thus, the median length of azathioprine treatment reported in the survey was 13 - 24 months compared with three to six months for ciclosporin - the next most commonly used drug. Almost 95% of respondents agreed/strongly agreed that TPMT level at baseline should guide the choice of initial dose, a dosing strategy pioneered by Newcastle. Based on the reported numbers of patients treated by the consultant dermatologists in the survey, it can be estimated that about 4,470 patients begin treatment with azathioprine each year in the UK.

Beyond the UK, the 2012 European guidelines on treatment of atopic eczema recommend that azathioprine be considered for moderate-to-severe disease. They state (citing R3 as supporting evidence):

> *'Azathioprine may be used (off label) in AE* [atopic eczema] *patients, if ciclosporin is either not effective or contraindicated. Patients should be screened for TPMT activity before starting azathioprine therapy to reduce the risk for bone marrow toxicity by dose adaptation. The suggested dose range is 1–3 mg⁄kg bw⁄day.' (Ev f)*

There is little data on the extent of use of azathioprine in the adult patient population across Europe, but a recently published survey of paediatric dermatologists across the continent found that the drug was prescribed as a first-line treatment in a fifth of cases of severe eczema in children (Ev g).

5. Sources to corroborate the impact

Ev a. Survey of UK dermatologists that were members of the UK Translational Research Network in Dermatology or the UK Dermatology Clinical Trials Network (June 2013).

Ev b. Journal of the European Academy of Dermatology and Venereology (2012): Guidelines for treatment of atopic eczema (atopic dermatitis) – Part I. DOI: http://dx.doi.org/10.1111/j.1468-3083.2012.04635.x. (Quotation from page 1053, column 2.)

Ev c. Statement from a science writer at the British National Formulary.

Ev d. British Journal of Dermatology (2011): British Association of Dermatologists' guidelines for the safe and effective prescribing of azathioprine. http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Azathioprine%20guidelines%202011.pdf. (Quotation from page 714, column 2.)

Ev e. Schram ME, Borgonjen RJ, Bik CM, van der Schroeff JG, van Everdingen JJ, & Spuls PI (2011). Off-label use of azathioprine in dermatology: a systematic review. *Archives of dermatology* 147(4): 474-88. DOI: http://dx.doi.org/10.1001/archdermatol.2011.79. (Quotation from page 474, column 2.)

Ev f. Journal of the European Academy of Dermatology and Venereology (2012): Guidelines for treatment of atopic eczema (atopic dermatitis) - Part II. DOI: http://dx.doi.org/10.1111/j.1468-3083.2012.04636.x. (Quotation from page 1180, column 1.)

Ev g. Proudfoot LE, Powell AM, Ayis S, Barbarot S, Baselgatorres E, Søndergaard Deleuran M, Fölster-Holst R, Gelmetti C, Hernández-Martin A, Middelkamp-Hup MA, Oranje AP, Patrizi A, Rovatti G, Schofield O, Spuls P, Svensson A, Vestergaard C, Wahlgren CF, Schmitt J, Flohr C; The European Dermato-Epidemiology Network (EDEN). The European treatment of severe atopic eczema in children taskforce (TREAT) survey. Br J Dermatol. (2013) doi: http://dx.doi.org/10.1111/bjd.12505