PPAR-δ in *Abca12*$^{-/-}$ keratinocytes (Supplementary Figure S1 online). From our studies and the literature (Di-Poi *et al.*, 2002), PPAR-δ has been shown to have at least an anti-apoptotic role in *Abca12*$^{-/-}$ keratinocytes; however, it remains unclear whether the upregulation of PPAR-δ is in response to apoptosis or decreased ABCA12 expression.

Furthermore, we have measured the mRNA expression levels of other nuclear hormone receptors, including PPAR-α, PPAR-γ, retinoic acid receptor-α, liver X receptor-α, liver X receptor-β, RXR-α, and RXR-γ (Applied Biosystems). The mRNA level of RXR-α from *Abca12*$^{-/-}$ epidermis was shown to be significantly higher than that from wild-type epidermis (Supplementary Figure S1 online). The interaction between the upregulation of RXR-α and AKT activation in keratinocytes has not been reported. However, Wang *et al.* (2011) reported that RXR-α ablation in the epidermis enhances UV-induced apoptosis, which suggests that RXR-α has an anti-apoptotic function in keratinocytes. Thus, upregulation of RXR-α may also have an anti-apoptotic function in *Abca12*$^{-/-}$ keratinocytes.

In conclusion, the present data suggest that keratinocyte apoptosis is involved in the pathomechanisms of HI and that the AKT signaling pathway helps *Abca12*$^{-/-}$ keratinocytes to survive during the keratinization process. In light of this, activation of the AKT signal pathway may be to our knowledge, previously unreported strategy for treating keratinization disorders, including ichthyosis.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

We thank Ms Aoyanagi for her technical assistance. This work was supported in part by a grant-in-aid from the Ministry of Education, Science, Sports and Culture of Japan (Kiban A 23249058: to MA), a grant from the Ministry of Health, Labor and Welfare of Japan (Health and Labor Sciences Research Grants; Research on Intractable Disease: H22-177: to MA), and a grant-in-aid from the Japan Society for the Promotion of Science Fellows (to TY).

***Teruki Yanagi*[1], *Masashi Akiyama*[1,2], *Hiroshi Nishihara*[3], *Yuki Miyamura*[1], *Kaori Sakai*[1], *Shinya Tanaka*[4] *and Hiroshi Shimizu*[1]**

[1]Department of Dermatology, Hokkaido University Graduate School of Medicine, Sapporo, Japan; [2]Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [3]Laboratory of Translational Pathology, Hokkaido University Graduate School of Medicine, Sapporo, Japan and [4]Laboratory of Cancer Research, Department of Pathology, Hokkaido University Graduate School of Medicine, Sapporo, Japan
E-mail: makiyama@med.nagoya-u.ac.jp

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

REFERENCES

Abe R, Shimizu T, Shibaki A *et al.* (2003) Toxic epidermal necrolysis and Stevens-Johnson syndrome are induced by soluble Fas ligand. *Am J Pathol* 162:1515–20

Akiyama M, Sugiyama-Nakagiri Y, Sakai K *et al.* (2005) Mutations in lipid transporter ABCA12 in harlequin ichthyosis and functional recovery by corrective gene transfer. *J Clin Invest* 115:1777–84

Di-Poi N, Tan NS, Michalik L *et al.* (2002) Antiapoptotic role of PPARbeta in keratinocytes via transcriptional control of the Akt1 signaling pathway. *Mol Cell* 10:721–33

Jiang YJ, Lu B, Kim P *et al.* (2008) PPAR and LXR activators regulate ABCA12 expression in human keratinocytes. *J Invest Dermatol* 128:104–9

Mitsutake S, Suzuki C, Akiyama M *et al.* (2010) ABCA12 dysfunction causes a disorder in glucosylceramide accumulation during keratinocyte differentiation. *J Dermatol Sci* 60:128–9

Moskowitz DG, Fowler AJ, Heyman MB *et al.* (2004) Pathophysiologic basis for growth failure in children with ichthyosis: an evaluation of cutaneous ultrastructure, epidermal permeability barrier function, and energy expenditure. *J Pediatr* 145:82–92

Sun P, Wang XQ, Lopatka K *et al.* (2002) Ganglioside loss promotes survival primarily by activating integrin-linked kinase/Akt without phosphoinositide 3-OH kinase signaling. *J Invest Dermatol* 119:107–17

Thrash BR, Menges CW, Pierce RH *et al.* (2006) AKT1 provides an essential survival signal required for differentiation and stratification of primary human keratinocytes. *J Biol Chem* 281:12155–62

Uchida Y, Houben E, Park K *et al.* (2010) Hydrolytic pathway protects against ceramide-induced apoptosis in keratinocytes exposed to UVB. *J Invest Dermatol* 130: 2472–80

Wang XQ, Sun P, Paller AS (2001) Inhibition of integrin-linked kinase/protein kinase B/Akt signaling: mechanism for ganglioside-induced apoptosis. *J Biol Chem* 276:44504–11

Wang Z, Coleman DJ, Bajaj G *et al.* (2011) RXRalpha ablation in epidermal keratinocytes enhances UVR-induced DNA damage, apoptosis, and proliferation of keratinocytes and melanocytes. *J Invest Dermatol* 131:177–87

Yanagi T, Akiyama M, Nishihara H *et al.* (2008) Harlequin ichthyosis model mouse reveals alveolar collapse and severe fetal skin barrier defects. *Hum Mol Genet* 17:3075–83

Yanagi T, Akiyama M, Nishihara H *et al.* (2010) Self-improvement of keratinocyte differentiation defects during skin maturation in ABCA12-deficient harlequin ichthyosis model mice. *Am J Pathol* 177:106–18

See related commentary on pg 1790

Interpretation of Skindex-29 Scores: Cutoffs for Mild, Moderate, and Severe Impairment of Health-Related Quality of Life

Journal of Investigative Dermatology (2011) **131,** 1945–1947; doi:10.1038/jid.2011.138; published online 19 May 2011

TO THE EDITOR

Health-related quality of life (HRQL) is commonly assessed by means of standardized questionnaires and expressed in domain and overall HRQL scores. An important challenge is to interpret these scores correctly. What does a given score really mean? Although there is no standard approach, several methods exist to facilitate the interpretation of HRQL scores.

In a recently published study (Prinsen *et al.*, 2010), we identified

Abbreviation: HRQL, health-related quality of life

Table 1. Skindex-29[1] cutoff scores for mildly, moderately, and severely impaired HRQL

Impact of disease on HRQL for Skindex-29 domain and overall scores[2]	Correlation	Skindex-29 cutoff scores			AUC[3]		
		Mild	Moderate	Severe[4]	Mild	Moderate	Severe[4]
Symptoms	(*r*=0.54)	39	42	52	0.76	0.75	0.83
Emotions	(*r*=0.73)	24	35	39	0.87	0.86	0.88
Functioning	(*r*=0.79)	21	32	37	0.91	0.91	0.91
Overall	(*r*=0.75)	25	32	44	0.85	0.90	0.90

Abbreviations: AUC, area under the curve; HRQL, health-related quality of life.
[1]The domain scores and the overall score are expressed on a 100-point scale, with higher scores indicating a lower level of quality of life.
[2]The number of patients in each severity category varies, as it largely depends on the required number of responses to the Skindex-29 domains. The number of patients with mildly impaired HRQL ranged from 144–195; the number of patients with moderately impaired HRQL ranged from 73–104; and the number of patients with severely impaired HRQL ranged from 49–74.
[3]AUC: 0.50 indicates chance categorization and 1.00 indicates perfect categorization of a given Skindex-29 score to correctly classify mild, moderate, or severe impairment of HRQL.
[4]Cutoff scores and AUC coefficients for severely impaired HRQL as presented in the original article (Prinsen *et al.*, 2010).

clinically meaningful domain and overall cutoff scores for the Skindex-29 (Chren *et al.*, 1997a, b) by using an anchor-based method (Guyatt *et al.*, 2002). We related patient responses on the Skindex-29 to anchor questions, and we established cutoff scores by using receiver-operating characteristic analysis. As a result, we were able to determine cutoffs for severely impaired HRQL (Table 1).

In a commentary on the interpretation of HRQL scores, Chren (2010) stressed the relevance of Skindex-29 cutoff scores for mild and moderate degrees of effect in addition to the scores we presented for a severe degree of effect. In this letter, we will provide these additional cutoff scores.

We analyzed the data of our sample of 322 patients to identify optimal cutoff scores. Again, the Skindex-29 domain scores, and the overall score, were related to three types of patient-based anchors: (i) four global questions on the impact of disease on HRQL; (ii) a question on disease severity as perceived by the patient; and (iii) the results on the 12-item General Health Questionnaire, a standardized instrument to measure psychiatric morbidity. For complete methods, we refer to the original article (Prinsen *et al.*, 2010).

The four global questions relating to the impact of disease on HRQL showed the highest correlation with the domain and overall scores of the Skindex-29 (range 0.54–0.79). Cutoff scores associated with these anchors also showed the highest accuracy, as measured by the area under the curve receiver-operating characteristic statistic for mildly impaired HRQL (range 0.76–0.91) as well as for moderately impaired HRQL (range 0.75–0.91). On the basis of the results of these analyses, the optimal and most accurate Skindex-29 cutoff scores for mildly and moderately impaired HRQL could be determined (Table 1).

The relatively similar cutoffs of $\geqslant 39$ and $\geqslant 42$ points for mildly and moderately impaired HRQL, respectively, on the symptom domain, result from the lower correlation of that particular anchor question with the corresponding Skindex-29 domain score ($r = 0.54$). This is also visible in the lower accuracy of the symptom domain and, thereby, the lower discriminating capacity between patients who perceive mildly or moderately impaired HRQL (area under the curve = 0.76 and 0.75, respectively). From an analytical point of view, there is no apparent explanation for this lower correlation. We assume that patients experienced a difference between the meanings of ''symptoms'' as worded in the anchor question and ''symptoms'' as worded in the seven questions representing the symptoms domain of the Skindex-29.

The presented Skindex-29 cutoff scores for mildly, moderately, and severely impaired HRQL are generally higher than those presented in a study by Nijsten *et al.* (2009), who used a distribution-based method. In our anchor-based study, the Skindex-29 cutoff scores were determined by patients' assessments on their HRQL, whereas Nijsten *et al.* (2009) capitalized on the distribution of HRQL levels in the sample. Cutoff scores established by anchor-based methods depend on the particular anchor questions and their wording, but they are less dependent on the distribution of HRQL levels in the sample. As patients are grouped by their scores on anchor questions (i.e., mild, moderate, and severe impairment), the obtained cutoff scores are likely to show invariance across samples. This is one of the reasons for the popularity of anchor-based methods in HRQL research, particularly in determining minimal important differences and/or change in scores on a HRQL instrument.

By providing these additional cutoff scores, we hope to contribute to a meaningful interpretation of HRQL scores. To facilitate the application of the identified cutoff scores in clinical practice, it might be helpful, as a rule of thumb or memory aid, to round off the cutoffs for mild, moderate, and severe impairment to $\geqslant 20$, $\geqslant 30$, and $\geqslant 40$ points, respectively, for the domain and overall scores, with the exception of the symptoms domain.

As expressed in our original study, we recommend further research on the generalizability and, thereby, on the robustness of the cutoff scores of the Skindex-29.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

The original study was performed in nine dermatology outpatient clinics in the Netherlands. We thank all the dermatologists whose collaboration made the study possible.

Cecilia A.C. Prinsen[1], Robert Lindeboom[2] and John de Korte[1]

[1]Department of Dermatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands and [2]Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
E-mail: c.a.prinsen@amc.uva.nl

REFERENCES

Chren MM, Lasek RJ, Flocke SA *et al.* (1997a) Improved discriminative and evaluative capability of a refined version of Skindex, a quality-of-life instrument for patients with skin diseases. *Arch Dermatol* 133:1433–40

Chren MM, Lasek RJ, Quinn LM *et al.* (1997b) Convergent and discriminant validity of a generic and a disease-specific instrument to measure quality of life in patients with skin disease. *J Invest Dermatol* 108:103–7

Chren MM (2010) Interpretation of quality-of-life scores. *J Invest Dermatol* 130:1207–9

Guyatt GH, Osoba D, Wu AW *et al.* (2002) Methods to explain the clinical significance of health status measures. *Mayo Clin Proc* 77:371–83

Nijsten T, Sampogna F, Abeni D (2009) Categorization of Skindex-29 scores using mixture analysis. *Dermatology* 218:151–4

Prinsen CA, Lindeboom R, Sprangers MA *et al.* (2010) Health-related quality of life assessment in dermatology: interpretation of Skindex-29 scores using patient-based anchors. *J Invest Dermatol* 130:1318–22

Infliximab Infusions for Netherton Syndrome: Sustained Clinical Improvement Correlates with a Reduction of Thymic Stromal Lymphopoietin Levels in the Skin

Journal of Investigative Dermatology (2011) **131,** 1947–1950; doi:10.1038/jid.2011.124; published online 9 June 2011

TO THE EDITOR

Netherton syndrome (NS) is a severe autosomal recessive skin disorder caused by mutations in serine protease inhibitor Kazal-type 5 (*SPINK5*), which encodes the lymphoepithelial Kazal-type-related inhibitor (LEKTI) (Chavanas *et al.*, 2000). Lack of LEKTI causes stratum corneum detachment secondary to the hyperactivity of epidermal proteases, which leads to skin barrier defect, thus facilitating allergen penetration and contributing to atopy in NS. Affected individuals have chronic and severe skin inflammation and allergic manifestations, including atopic dermatitis–like lesions and elevated serum IgE levels. Recent studies have shown that thymic stromal lymphopoietin (TSLP) and tumor necrosis factor-alpha (TNF-α) are overexpressed in the LEKTI-deficient epidermis of NS patients and *SPINK5*-null mice (Briot *et al.*, 2009). This is due to unrestricted activity of epidermal proteases, including kallikrein 5, which activates PAR2 signaling in keratinocytes, leading to NF-κB activation and TSLP expression (Briot *et al.*, 2010). TSLP is produced by keratinocytes as well as airway epithelial cells and is necessary and sufficient for inducing atopic response in mice (Yoo *et al.*, 2005; Li *al.*, 2006). It regulates innate immunity and polarizes T cells toward a T helper type 2 (Th2) phenotype through the conditioning of antigen-presenting cells (Soumelis *et al.*, 2002; Soumelis and Liu, 2004). TNF-α and IL-1 (Lee and Ziegler, 2007) induce expression of TSLP, which can synergize with these pro-inflammatory cytokines to amplify pro-Th2 cytokine secretion by activated mast cells (Allakhverdi *et al.*, 2007). These data suggest that a therapeutic approach targeting these key molecules could reduce skin inflammation in NS.

The data and procedures reported in this article were in accordance with the institutional ethical requirements of the University Hospital of Geneva, Switzerland. The study was conducted in adherence with the Declaration of Helsinki Principles. Written informed consent was obtained from the patient, a 25-year-old woman who consulted for an extensive pruritic dermatitis that had been evolving since birth and was associated with ichthyosis, asthma, food allergies, and high levels of IgE ($3,660\ \mathrm{kU\ l^{-1}}$). The recurrent, severe inflammatory flares were unresponsive to systemic dapsone, topical steroids, tacrolimus, and pimecrolimus. The presence of diffuse xerosis, a pattern of ichthyosis circumflexa (Figure 1a), and outbreaks of severe vesicular and pustular lesions led to the diagnosis of NS, which was supported by the absence of epidermal LEKTI detection (Figure 1c, d). *SPINK5* molecular analysis identified a homozygous mutation leading to a premature termination codon in exon 12, thus confirming the diagnosis of NS. Histological analysis of skin sections revealed an acanthotic and spongiotic epidermis with subcorneal accumulation of neutrophils (Figure 1e). A lymphohistiocytic infiltrate with neutrophils and eosinophils was present in the superficial dermis, whereas the density of mast cells was similar to that in normal skin. Because TNF-α is critical for neutrophil skin emigration (Groves *et al.*, 1995) and skin mast cell

Abbreviations: LEKT1, lymphoepithelial Kazal-type-related inhibitor; NS, Netherton syndrome; SPINK5, serine protease inhibitor Kazal-type 5; Th2, T helper type 2; TNF-α, tumor necrosis factor-α; TSLP, thymic stromal lymphopoietin