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Management of congenital ichthyoses: European guidelines of care, part one

J. Mazereeuw-Hautier,[1] A. Vahlquist,[2] H. Traupe,[3] A. Bygum,[4] C. Amaro,[5] M. Aldwin,[6] A. Audouze,[7] C. Bodemer,[8,9] E. Bourrat,[8] A. Diociaiuti,[10] M. Dolenc-Voljc,[11] I. Dreyfus,[1] M. El Hachem,[10] J. Fischer,[12] A. Gånemo,[13] C. Gouveia,[14] R. Gruber,[15] S. Hadj-Rabia,[8,9] D. Hohl,[16] N. Jonca,[17] K. Ezzedine,[18] D. Maier,[19] R. Malhotra,[20] M. Rodriguez,[21] H. Ott,[22] D.G. Paige,[23] A. Pietrzak,[24] F. Poot,[25] M. Schmuth,[15] J.C. Sitek,[26] P. Steijlen,[27] G. Wehr,[28] M. Moreen,[29,30] E.A. O'Toole,[31] V. Oji[3,32] and A. Hernandez-Martin[33]

[1]Reference Centre for Rare Skin Diseases, Dermatology Department, Larrey Hospital, Toulouse, France
[2]Department of Medical Sciences, Uppsala University, Uppsala, Sweden
[3]Department of Dermatology, University Hospital of Münster, Von-Esmarch-Straße 58, D-48149 Münster, Germany
[4]Department of Dermatology and Allergy Centre, Odense University Hospital, Odense, Denmark
[5]Hospital de Egas Moniz, Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal
[6]Ichthyosis Support Group, PO Box 1242, Yateley GU47 7FL, U.K.
[7]Association Ichtyose France, Bellerive sur Allier, France
[8]Department of Dermatology, Reference Center for Genodermatoses and Rare Skin Diseases (MAGEC), Paris, France
[9]Institut Imagine, Université Descartes, Sorbonne Paris Cité, Hôpital Necker-Enfants Malades, Paris
[10]Dermatology Division, Bambino Gesù Children's Hospital-IRCCS, Rome, Italy
[11]Department of Dermatovenereology, University Medical Centre Ljubljana, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[12]Institute of Human Genetics, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[13]Department of Dermatology, Institute of Clinical Research in Malmö, Skåne University Hospital, Lund University, Malmö, Sweden
[14]Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[15]Department of Dermatology, Venereology and Allergology, Medical University of Innsbruck, Innsbruck, Austria
[16]Department of Dermatology, Hôpital de Beaumont, Lausanne, Switzerland
[17]Epithelial Differentiation and Rheumatoid Autoimmunity Unit (UDEAR), UMR 1056 Inserm – Toulouse 3 University, Purpan Hospital, Toulouse, France
[18]Department of Dermatology, Hôpital Henri Mondor, EA EpiDerm, UPEC-Université Paris-Est Créteil, 94010 Créteil, France
[19]Dermatology Department, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[20]Corneoplastic Unit, Queen Victoria Hospital NHS Trust, East Grinstead, U.K.
[21]Department of Ear, Nose and Throat, Hospital Universitario Son Espases, Palma de Mallorca, Spain
[22]Division of Pediatric Dermatology and Allergology, Auf Der Bult Children's Hospital, Hanover, Germany
[23]Department of Dermatology, Royal London Hospital, Barts Health NHS Trust, London, E1 1BB, U.K.
[24]Department of Dermatology, Venereology and Paediatric Dermatology, Medical University of Lublin, Lublin, Poland
[25]ULB-Erasme Hospital, Department of Dermatology, Brussels, Belgium
[26]Department of Dermatology and Centre for Rare Disorders, Oslo University Hospital, Oslo, Norway
[27]Department of Dermatology, Maastricht University Medical Centre, GROW Research School for Oncology and Developmental Biology, Maastricht, the Netherlands
[28]Selbsthilfe Ichthyose, Kürten, Germany
[29]Department of Dermatology, University Hospitals Leuven, Leuven, Belgium
[30]Department of Microbiology and Immunology, KU Leuven, Belgium
[31]Centre for Cell Biology and Cutaneous Research, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, U.K.
[32]Hautarztpraxis am Buddenturm, Rudolf-von-Langen-Straße 55, D-48147 Münster, Germany
[33]Department of Dermatology, Hospital Infantil Niño Jesús, Madrid, Spain

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Summary

These guidelines for the management of congenital ichthyoses have been developed by a multidisciplinary group of European experts following a systematic review of the current literature, an expert conference held in Toulouse in 2016 and a consensus on the discussions. They summarize evidence and expert-based recommendations and are intended to help clinicians with the management of these rare and often complex diseases. These guidelines comprise two sections. This is part one, covering topical therapies, systemic therapies, psychosocial management, communicating the diagnosis and genetic counselling.

Correspondence
Juliette Mazereeuw-Hautier.
E-mail: mazereeuw-hautier.j@chu-toulouse.fr

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Congenital ichthyoses (CIs) comprise a heterogeneous group of genetic diseases usually present at birth or appearing early in life. They affect the entire skin and are characterized by hyperkeratosis and scaling, often associated with skin inflammation.[1,2] The CIs are primarily monogenic diseases, with more than 50 genes identified to date, leading to a defective skin barrier. The classification is based on the clinical presentation and distinguishes basically between nonsyndromic (including common ichthyosis, autosomal recessive congenital ichthyosis, keratinopathic ichthyosis and other forms) and syndromic ichthyoses (Appendix S1; see Supporting Information).[3] CIs usually have a major effect on patients' quality of life (QoL) and therefore require lifelong treatment.

Currently there are no curative therapies, but various symptomatic treatment options exist. The only available guidelines for the management of CI are national guidelines from Germany.[4] We have developed European guidelines following a systematic review of the current literature, a guidelines conference and a consensus on the discussions. The recommendations are divided into two sections. Part one, presented here, covers topical therapies, systemic therapies, psychosocial management, communicating the diagnosis and genetic counselling. The second part will cover the management of complications and the particularities of some forms of CI.

Aim

These guidelines provide recommendations for the therapeutic management of CI. They may help to improve outcomes and QoL for patients.

Users

Dermatologists and other health professionals, including paediatricians, general practitioners, otolaryngologists, ophthalmologists, clinical geneticists, pharmacists, nurses, psychologists and podiatrists, and patient support groups and patients with CI.

Target group

These guidelines are aimed at the management of adults and children with CI.

Disclaimers and limitations

Therapeutic strategies need to be adapted depending on the healthcare system and local conditions. Moreover, readers are advised to keep up to date with newly published data.

Methods

In 2015, a European (16 countries) expert multidisciplinary group was formed, including 25 dermatologists, one paediatrician, one otorhinolaryngologist, one ophthalmologist, one clinical geneticist, one psychologist, one pharmacist, one dermatoepidemiologist and one nurse. This group is involved with the ichthyoses subthematic group of the European Reference Network for rare and undiagnosed skin disorders (ERN-Skin). Patients and families were also strongly involved, with the participation of the three representatives from patient support groups: one had CI and two had affected children. The AGREE II instrument (a 23-item tool comprising six quality-related domains)[5] was used to develop these guidelines.

Details of the literature searches and the methodology of the conference are provided in Appendix S2 (see Supporting Information). Levels of evidence (LoE) and grades of recommendation (GoR) were evaluated using the Scottish Intercollegiate Guidelines Network guidelines (Appendix S3; see Supporting Information). Our review of the literature revealed a very low number of randomized controlled trials, which included small heterogeneous groups of patients without standardization of outcome measures.[6] Most articles were case reports or small series. For some topics, there were no data in the literature. Therefore, the level of evidence was often restricted to categories 3 and 4 (expert opinion). These recommendations are presented in Table S1 (see Supporting Information) and are mentioned in the text.

Plans for updating the guidelines

An update of these guidelines and literature search will be necessary every 5 years after publication. For future updates we will use a formal and consistent wording of recommendations. To ensure their availability and dissemination, the guidelines and their revisions will be disseminated via ERN-Skin, as well as the patient support groups (https://ichthyosis-eu.freemore.com).

Topical and systemic therapies

The different therapeutic options are described below. The choice of treatment depends on the morphology (i.e. scaling, hyperkeratosis), the disease distribution, the presence or absence of inflammation or erosions, the disease severity and the age of the patient.

Topical therapy

Topical agents represent the first-line treatment. They help to reduce scales, skin discomfort and pruritus, and may improve the general appearance of the skin. Their effect on barrier dysfunction is variable.[7] Topical agents are considered to be essential and are used by almost all patients. They are recommended by all experts,[8–10] even though evidence from the literature is weak. Clinical studies have evaluated the effects of topical agents on scaling (and sometimes erythema and pruritus) on the body but not specifically on the scalp or palmoplantar skin. A variety of topical agents are available (Table 1). They can be used as monotherapy or in combination with oral retinoids. The choice of a specific agent is based on the various parameters described above (LoE 4, GoR D): availability, formulation and texture, possibilities for reimbursement and costs. Unpleasant smell or a very greasy consistency of ointments needs to be avoided. Finally, the preferences of the patients are decisive, considering that the therapeutic outcome is largely dependent on therapy compliance, as application of topical therapies is time consuming and demanding.[11]

Emollients

Emollients act via skin hydration, lubrication and occlusion.[12] Many emollients are available and their properties vary according to formulation and lipid-to-water content ratio. There are no studies comparing different emollients. In clinical practice, the preferred emollient varies among patients. Application of emollients is recommended for all ichthyoses (LoE 1, GoR B), as often as necessary, at least twice a day and ideally after bathing to improve skin hydration (LoE 3, GoR D).[9] Except for transient minor symptoms such as itching or a burning sensation, moisturizers are safe.[8,13,14] As they may not be well tolerated, emollients containing urea are not recommended on inflamed skin, flexural areas or erosions (LoE 3, GoR D).[1] Increased skin permeability may increase the risk of allergic contact dermatitis.[15] Large applications of occlusive pure ointments are not recommended as they may further impair heat tolerance and promote maceration and infections, particularly in hotter climates (LoE 4, GoR D).[9] For patients with thick scaling or hyperkeratosis, we suggest addition of other agents (LoE 1, GoR B).

Table 1 Topical agents used in congenital ichthyoses

Hydrating agents	Urea (< 5%)
	Propylene glycol (< 20%)
	Dexpanthenol
	Macrogol 400
	Glycerol (i.e. glycerine)
Lubricating agents	Petrolatum/Vaseline
	Paraffin
Keratolytic agents[a]	Urea (≥ 10%), up to 40%
	Propylene glycol (> 20%)
	Alpha-hydroxyacids (lactic acid, glycolic acid) (5–12%)
	Salicylic acid (2–5%), up to 25%
Topical retinoids	Topical retinoids (tazarotene, adapalene)
Other topical agents	Calcipotriol (vitamin D analogue)
	N-Acetylcysteine[b]

[a]All keratolytics must be used with caution in children (risk of absorption). [b]The addition of fragrances may partially lessen the strong odour.

Keratolytics

The superiority of keratolytics over emollients in removing scales and hyperkeratosis has been demonstrated in a few studies.[13,16–21] These studies included urea (≥ 10%), alpha-hydroxyacids (5–12%), propylene glycol (> 20%) and salicylic acid (> 2%), alone or in combination. There is no evidence to conclude which is the best keratolytic agent or which is the best combination. In clinical practice, urea is the most frequently used agent; its concentration may be increased up to 20%, even 40% in localized areas of thick scale or hyperkeratosis. Keratolytics are usually applied once or twice daily and can be tapered depending on the response (LoE 1, GoR B). Side-effects include itching, burning sensation and irritation. Application on the face, flexures and areas of fissuring is not recommended, as keratolytics may induce irritation (LoE 1, GoR B).[8] Systemic absorption and toxicity must be taken into account considering the epidermal barrier defect,[22] especially in children. Therefore, all keratolytics must be avoided in newborns and young infants (LoE 3, GoR D), although the exact age limit is not well defined. We recommend strict contraindication of salicylic acid for children under the age of 2 years, and to restrict the application once daily to limited areas for older children.[23–27] Urea (≥ 10%) is not recommended before the age of 1 year, except once daily on limited areas such as the palms and soles.

Topical retinoids

Topical tazarotene demonstrated efficacy in a small open study of 12 patients with CI[28] and one patient with severe X-linked recessive ichthyosis;[29] adapalene was used in a patient with epidermolytic ichthyosis (EI).[30] Topical tazarotene may also be used for ectropion (see part two). Although a meta-analysis including pregnant women who were exposed to topical retinoids was reassuring,[31] and repeated topical administration on limited areas is unlikely to induce systemic effects,[32] the use of topical retinoids is contraindicated during pregnancy (LoE 1, GoR B).

Other topical agents

Other topical agents may be useful (LoE 3, GoR B). Calcipotriol, a vitamin D derivative, has demonstrated efficacy in adults[33] but is limited by a maximum weekly dose of 100 g.

N-Acetylcysteine, a thiol derivative used as a mucolytic agent, showed efficacy in a small case series.[34] However, the sulfuric smell may be very unpleasant. The addition of fragrances may partially lessen the strong odour, but may also expose to the risk of sensitization.

Targeted topical therapy

There is now evidence that topical therapy can be designed to address disease pathogenesis specifically. For example, in CHILD syndrome (congenital hemidysplasia with ichthyosiform erythroderma and limb defects), the understanding of the pathophysiology of the skin manifestations (two major mechanisms: deficiency of cholesterol and toxic accumulation of aberrant steroid precursors) enabled use of the combination of topical cholesterol with a topical statin to reverse the ichthyotic phenotype.[35–37]

Bathing

Cleaning of the skin is of utmost importance to remove scaling and residual ointments, to lessen discomfort and for hygiene. Most patients use bathing, which may be more effective in removing scale; others prefer showers. We can recommend the following modalities (LoE 4, GoR 4). Mild soaps or soap-free cleansing bases may be used. Daily lukewarm baths (30 min or more) are recommended.[8,10] Scales may then be removed by gently rubbing (e.g. with sponges, microfibre cloths or pumice stone).[10] Moisturizing additives, colloidal preparations, baking soda (3–6 g L^{-1}) or saltwater baths (normal saline 0·9%) can provide additional benefits.[10,38–40]

Antiseptics should not be used routinely, except in CI with recurrent skin infections such as keratitis–ichthyosis–deafness (KID) syndrome or Netherton syndrome (NS). In these patients, they can be used two to three times a week (LoE 4, GoR D). Several antiseptics may be used: biocides such as chlorhexidine (dilution 5 parts in 1000–10 000), octenidine 0·1%, polyhexanide 0·1%, potassium permanganate (dilution 1 part in 10 000) or diluted bleach baths (0·005% solution).[9,10] Iodine-based antiseptics are not recommended (risk of thyroid dysfunction). Antiseptics should be rinsed to avoid irritation. Balneotherapy and hydrotherapy with thermal waters may be useful (LoE 2+, GoR C); they have shown benefits in a single uncontrolled study.[41] Studies are needed to test the benefits of steam baths.

Treatment of the scalp

Most patients present with scalp desquamation, sometimes with adherent thick scales requiring treatment. Foams, solutions and shampoos are cosmetically more acceptable than gels and ointments but may be less effective. The application of a layer of emollient or keratolytic (washable preparation) may be necessary (for a few hours or overnight), with variable weekly periodicity (LoE 4, GoR D).[10] Plastic occlusion may enhance efficacy, but transfollicular penetration of active substances is much higher than elsewhere and must be taken into account, particularly in children.[42,43] After shampooing, scales must be gently removed with combs.[44] Some centres use a professional hair steamer for better removal of adherent scales with hot water vapour. In CI with fragile skin or brittle hairs (e.g. NS or trichothiodystrophy), more gentle procedures are recommended.

Treatment of palmoplantar keratoderma

Some patients present with disabling palmoplantar keratoderma (PPK), predisposing to fissuring and pain. In cases of moderate-to-severe PPK in adults, high concentrations of keratolytics in ointment formulations may be used for a limited period (salicylic acid up to 25% or urea up to 40%).[9] For children see the precautions in the paragraph on keratolytics. We can recommend to use these agents once or twice daily after protection of fissures and surrounding skin (i.e. using petroleum jelly), with or without a plastic film (with caution) in order to improve effectiveness and with manual removal of excess callus[9] (which may require podiatrists) (LoE 4, GoR D). In cases of milder forms, topical tazarotene may be used (LoE 4, GoR D).

Systemic therapy

Systemic therapy may be considered in addition to topical therapies, in case they are insufficiently effective or patients need respite from excessive topical treatment (LoE 2, GoR D).[8,10,45,46] Systemic therapy in CI is based mainly on oral retinoids. Other types of systemic therapy, such as ciclosporin,[47] have been tried, but they cannot be recommended. Novel therapies targeting skin inflammation could be candidates for future clinical studies, especially for CI with severe inflamed skin such as NS (see part two). Retinoids are analogues of vitamin A that act principally via an 'antikeratinizing' effect (Appendix S4; see Supporting Information).[48,49] Four systemic retinoids can be considered for treatment of CI: isotretinoin, alitretinoin, etretinate (no longer available in Europe) and acitretin. Moreover, retinoid acid metabolism-blocking agents were effective in clinical studies on CI, but did not progress to the market.[50,51]

Acitretin

Efficacy and therapeutic indications Retinoids revolutionized the lives of many patients with severe CI, especially harlequin ichthyosis (HI) and lamellar ichthyosis (LI). Evidence of retinoid efficacy came from old trials with etretinate, before the introduction of acitretin. Acitretin is the drug of choice (LoE 2, GoR D): it is the main retinoid used in Europe and is the only one approved by the European Medical Agency (EMA) for treating CI.[52] The efficacy of acitretin has been demonstrated in a few pilot studies and from numerous case series.[53–63] Acitretin is effective in removing scales and thinning hyperkeratosis. Other effects include improvement of hypohidrosis,[64] hair regrowth, improvement of ectropion and

eclabion, improvement of hearing and shortening of the daily time spent on skincare.[8,10,45,46] Acitretin is especially relevant for patients with thick scales (i.e. LI and HI), but it is also useful for milder forms such as severe X-linked recessive ichthyosis.[50,65] In EI the results are much better for patients with *KRT10* mutations than those with *KRT1* mutations, who may even deteriorate on retinoids (Appendix S5; see Supporting Information).[57]

Dosage and scheduling Acitretin is administrated orally (10- or 25-mg capsules) once daily and should be prescribed only by dermatologists experienced in its management (LoE 2, GoR D). The optimal dosage of acitretin varies between patients and depends on the type of CI (LoE 2, GoR D). Most patients do not require more than 0·5 mg kg^{-1} per day and may be maintained on doses as low as 10–25 mg per day. Higher doses of up to 1 mg kg^{-1} per day may be needed in adults with very severe ichthyosis, for example LI. The maximum dosage approved by the EMA is 75 mg per day. Of note, patients with marked erythroderma, such as those with EI (Appendix S5; see Supporting Information) and NS, should be treated with caution.[66] They may need only a low retinoid dose (< 25–30 mg per day in adults), otherwise skin irritation fragility or blistering may occur. Patients may start with a low dose (i.e. 10 mg for adults) once daily or every second day. The effect should be evaluated after a few weeks and the dosage may be gradually increased until there is sufficient improvement with tolerable side-effects (LoE 2, GoR D). A too rapid dose escalation may increase the risk for side-effects, making the patient negative towards continued acitretin therapy. After stabilization of the desired effects, the dosage may be tapered to the lowest effective dose.[55] The therapeutic effects of acitretin persist only for a short time after discontinuation of the medication. Long-term therapy may be interrupted during humid and hot weather (LoE 4, GoR D).

Specific situation of children There is no minimum age for the use of retinoids (for the neonatal period see part two). The treatment should be prescribed in collaboration with a paediatrician or a dermatologist specialized in paediatric dermatology (LoE 2, GoR D). In most countries, there are no paediatric formulations, but the appropriate dosage can be prepared by the pharmacist. As acitretin is light sensitive, capsules should be opened away from daylight or added to breast milk in a bottle protected by aluminium foil. The efficacy of acitretin in children is documented in a few small case series of various disorders of keratinization, essentially in LI, congenital ichthyosiform erythroderma[53,60–63] or HI.[67–74] It is recommended to reserve retinoids for those with a severe phenotype and functional impairment. The daily dose should be kept as low as possible, < 1 mg kg^{-1} per day, ideally close to 0·5 mg kg^{-1} per day, in order to limit the potential adverse effects (LoE 2, GoR D).

Adverse effects Teratogenesis is the main adverse effect.[75–77] Pregnancy prevention must be performed carefully in all women of childbearing potential (LoE 2, GoR D) (Appendix S6; see Supporting Information). Many decades of treatment experience exist, and the adverse effects of retinoids are well known (Table S2; see Supporting Information). They vary in frequency and severity and are dose dependent. Common reversible effects include mucosal dryness, blood abnormalities (e.g. lipids or liver tests) and hair loss. Long-term musculoskeletal adverse effects are the main source of concern. In adults, spinal and extraspinal hyperostosis and calcifications of tendons and ligaments have been reported, but they cannot be differentiated from age-induced bone changes. The majority of patients were on retinoids for many years or had taken etretinate previously.[53,78–92]

The risk for skeletal anomalies seems to be higher if a high cumulative dose of retinoids, previous treatment with etretinate (longer half-life and prolonged bone exposure) and old age are present. The risk of osteoporosis is controversial. It was reported after long-term therapy with etretinate.[92,93] A short-term prospective study with acitretin[94] and a retrospective study of 23 patients treated with acitretin or etretinate for various disorders of keratinization, followed over a long period,[53] did not reveal osteoporosis. Osteoporosis in CI may be due to vitamin D deficiency,[95] which is often associated with ichthyosis (see part two).[96]

In children, various skeletal anomalies including premature closure of the epiphyses were reported in association with high dosages of etretinate (up to 2·5 mg kg^{-1} per day).[97–101] Nevertheless, no baseline studies are available. Such anomalies were not found in two series of children on long-term etretinate therapy[102,103] or on both etretinate and acitretin.[53,62] No growth delay was reported on retinoids. Rather, severely affected children with failure to thrive as a result of chronic disease had improved growth after starting retinoids.[98] In summary, risk–benefit analysis of acitretin shows it to be considered favourable, even though potential adverse effects may be problematic.

Monitoring Regular monitoring is necessary and recommended by the EMA (LoE 2, GoR D) (Table S2; see Supporting Information).

Interactions and contraindications Interactions of acitretin with other drugs and contraindications are presented in Appendix S7 (see Supporting Information).

Other retinoids (alitretinoin and isotretinoin)

Alitretinoin and isotretinoin have the advantage of more rapid clearance than acitretin. There is no proper comparative study with acitretin. Alitretinoin has been reported as effective in reducing erythema in a small series of patients with CI[104] and some case reports.[105,106] Efficacy on scaling was reported for a few patients at a high dose.[107] Side-effects include headache, benign intracranial hypertension and hypothyroidism. The effectiveness of isotretinoin in LI and EI has been demonstrated in an open-label study[108] and in case reports including patients with HI.[67,72,109] High doses of isotretinoin are necessary[108] and the safety profile seems to be poorer than with

acitretin, with a well-established risk for intracranial hypertension, myalgia, muscle stiffness and tenderness.[110] The main concern is related to skeletal toxicity, which, in contrast to acitretin, is clearly reported for isotretinoin.[111–113] Isotretinoin was also reported to be associated with a possible exacerbation of corneal neovascularization in KID syndrome.[114]

Therefore, we recommend the choice of acitretin for long-term therapy, due to its approval by the EMA, its efficacy and its safety profile. In cases of female patients considering a future pregnancy or in the rare event of hypersensitivity to aromatic retinoids,[115] alitretinoin or isotretinoin should be preferred (LoE 2, GoR D).

Specific situation of syndromic ichthyosis

Patients with syndromic ichthyosis may be candidates for oral retinoids (LoE 2, GoR D) (Appendix S8; see Supporting Information), even in cases of liver involvement (such as Chanarin–Dorfman syndrome)[116,117] or eye symptoms (KID syndrome).[118–124] However, they should be monitored for side-effects more closely.

Psychosocial management, communicating the diagnosis and genetic counselling

Congenital ichthyoses may have a profound impact on QoL from childhood to adult age, for the patient and their family.[125–131] The identified factors influencing QoL are related to physical health, daily life and relations with others or oneself.[126] The importance of each individual parameter varies among patients with CI, but cutaneous pain emerged as the most significant factor influencing QoL, followed by skin scaling and sex (female).[130] It was demonstrated that the burden of the disease was related to domestic life (skincare, housework, clothing), educational and professional lives (rejection and bullying by other children at school, workplace discrimination) and leisure and sports activities. The patient's economic resources were constrained by ichthyosis.

The expenses that can be covered by national health systems and disability allowances vary greatly among European countries, but the expense of moisturizing creams is often the main contributor to the financial impact of the disease.[11,132] Living with a child with CI may also be a difficult situation for parents because ichthyosis is a rare and not well-known skin disease, the consequences of which are often underestimated by the medical profession and the general public. Therefore, we recommend to assess QoL and burden of disease (LoE 3, GoR D) using ichthyosis-specific questionnaires[131,133] (if available in the appropriate language) or dermatology QoL questionnaires such as the (Children's) Dermatology Life Quality Index.[134]

Due to the effect of CIs on QoL and daily life, psychological support is strongly recommended and is an important part of ichthyosis care, although the effects of psychosocial interventions on ichthyosis outcomes have not been tested. Ideally, psychosocial management should be offered as soon as possible, then throughout life, for children, adults and families; it should be adapted to their needs and expectations (LoE 4, GoR D). Psychosocial support should be provided by a psychologist, but it may involve other healthcare providers involved in the patient's care, such as dermatologists, social workers or specialist nurses. Relevant complications should be addressed honestly, not only during a life-threatening situation such as HI at birth, but also for mating and sexuality during puberty and later on. Support of affected individuals or parents may prevent or alleviate psychological trauma and allow an appropriate response to hurtful comments.

During the neonatal period it is very important to permit maternal–infant attachment with facilitation of close physical contact between the baby and the parents (LoE 4, GoR D).[135–137] This mother–child contact and, even more, the experience of the following cutaneous separation from the mother are particularly important for the child to recognize itself as 'me' and to develop its 'skin ego'. Family therapy may be useful if feelings of guilt or reproach are shown by parents. The situation of siblings must be taken into account as they may feel abandoned (LoE 4, GoR D). It may be very useful to provide patient or family group interviews. Due to the financial burden, it is necessary to inform families about reimbursement opportunities, ideally via the involvement of a social worker (LoE 4, GoR D). The physician in charge and the social worker could also work together to provide evidence that CI can be a disability and help with appropriate professional orientation.

Educational interventions ('ichthyosis schools') may be very useful to improve treatment adherence and lessen fears and misconceptions (LoE 3, GoR D).[138] Nevertheless, formal and structured multidisciplinary educational programmes have been established in a minority of European countries, and there are very few data evaluating their impact.[139] Patients must be informed about the national patient support groups that exist in many European countries and allow support from other families and sharing of individual experiences (LoE 4, GoR D). Healthcare providers should inform patients and families about the patient support groups and give their contact details (https://ichthyosis-eu.freemore.com).

Communication of the diagnosis to the family should be offered as soon as the diagnosis is known (LoE 4, GoR D). Explaining a diagnosis of severe ichthyosis is a delicate situation and therefore may be best performed in a multidisciplinary consultation, ideally involving a psychologist. Genetic counselling must be offered to the family and patient by the clinical geneticist (LoE 4, GoR D). The role of the clinical geneticist is to calculate the risk for other family members or an expected child to be affected or not, and to answer questions concerning prenatal testing or predictive or preimplantation diagnosis if convenient and available.[140]

References

1 Traupe H, Fischer J, Oji V. Nonsyndromic types of ichthyoses – an update. *J Dtsch Dermatol Ges* 2014; **12**:109–21.

2 Vahlquist A, Fischer J, Törmä H. Inherited nonsyndromic ichthyoses: an update on pathophysiology, diagnosis and treatment. *Am J Clin Dermatol* 2018; **19**:51–66.
3 Oji V, Tadini G, Akiyama M *et al.* Revised nomenclature and classification of inherited ichthyoses: results of the first ichthyosis consensus conference in Sorèze 2009. *J Am Acad Dermatol* 2010; **63**:607–41.
4 Oji V, Preil M-L, Kleinow B *et al.* S1 guidelines for the diagnosis and treatment of ichthyoses – update. *J Dtsch Dermatol Ges* 2017; **15**:1053–65.
5 Brouwers MC, Kho ME, Browman GP *et al.* AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010; **182**:E839–42.
6 Hernández-Martin A, Aranegui B, Martin-Santiago A *et al.* A systematic review of clinical trials of treatments for the congenital ichthyoses, excluding ichthyosis vulgaris. *J Am Acad Dermatol* 2013; **69**:544–9.
7 Hoppe T, Winge MCG, Bradley M *et al.* X-linked recessive ichthyosis: an impaired barrier function evokes limited gene responses before and after moisturizing treatments. *Br J Dermatol* 2012; **167**:514–22.
8 Vahlquist A, Gånemo A, Virtanen M. Congenital ichthyosis: an overview of current and emerging therapies. *Acta Derm Venereol* 2008; **88**:4–14.
9 Fleckman P, Newell BD, van Steensel MA *et al.* Topical treatment of ichthyoses. *Dermatol Ther* 2013; **26**:16–25.
10 Oji V, Traupe H. Ichthyosis: clinical manifestations and practical treatment options. *Am J Clin Dermatol* 2009; **10**:351–64.
11 Dreyfus I, Pauwels C, Bourrat E *et al.* Burden of inherited ichthyosis: a French national survey. *Acta Derm Venereol* 2015; **95**:326–8.
12 Lodén M. The clinical benefit of moisturizers. *J Eur Acad Dermatol Venereol* 2005; **19**:672–88.
13 Lykkesfeldt G, Høyer H. Topical cholesterol treatment of recessive X-linked ichthyosis. *Lancet* 1983; **2**:1337–8.
14 Blanchet-Bardon C, Tadini G, Machado Matos M *et al.* A. Association of glycerol and paraffin in the treatment of ichthyosis in children: an international, multicentric, randomized, controlled, double-blind study. *J Eur Acad Dermatol Venereol* 2012; **26**:1014–19.
15 Al Malki A, Marguery M-C, Giordano-Labadie F *et al.* Systemic allergic contact dermatitis caused by methyl aminolaevulinate in a patient with keratosis-ichthyosis-deafness syndrome. *Contact Dermatitis* 2017; **76**:190–2.
16 Küster W, Bohnsack K, Rippke F *et al.* Efficacy of urea therapy in children with ichthyosis. A multicenter randomized, placebo-controlled, double-blind, semilateral study. *Dermatology* 1998; **196**:217–22.
17 Tadini G, Giustini S, Milani M. Efficacy of topical 10% urea-based lotion in patients with ichthyosis vulgaris: a two-center, randomized, controlled, single-blind, right-vs.-left study in comparison with standard glycerol-based emollient cream. *Curr Med Res Opin* 2011; **27**:2279–84.
18 Kempers S, Katz HI, Wildnauer R *et al.* An evaluation of the effect of an alpha hydroxy acid-blend skin cream in the cosmetic improvement of symptoms of moderate to severe xerosis, epidermolytic hyperkeratosis, and ichthyosis. *Cutis* 1998; **61**:347–50.
19 Gånemo A, Virtanen M, Vahlquist A. Improved topical treatment of lamellar ichthyosis: a double-blind study of four different cream formulations. *Br J Dermatol* 1999; **141**:1027–32.
20 Pope FM, Rees JK, Wells RS *et al.* Out-patient treatment of ichthyosis: a double-blind trial of ointments. *Br J Dermatol* 1972; **86**:291–6.
21 Buxman M, Hickman J, Ragsdale W *et al.* Therapeutic activity of lactate 12% lotion in the treatment of ichthyosis. Active versus vehicle and active versus a petrolatum cream. *J Am Acad Dermatol* 1986; **15**:1253–8.
22 Nguyen V, Cunningham BB, Eichenfield LF *et al.* Treatment of ichthyosiform diseases with topically applied tazarotene: risk of systemic absorption. *J Am Acad Dermatol* 2007; **57** (5 Suppl.):S123–5.
23 Madan RK, Levitt J. A review of toxicity from topical salicylic acid preparations. *J Am Acad Dermatol* 2014; **70**:788–92.
24 Chiaretti A, Schembri Wismayer D, Tortorolo L *et al.* Salicylate intoxication using a skin ointment. *Acta Paediatr* 1992; **86**:330–1.
25 Ramírez ME, Youseef WF, Romero RG *et al.* Acute percutaneous lactic acid poisoning in a child. *Pediatr Dermatol* 2006; **23**:282–5.
26 Ward PS, Jones RD. Successful treatment of a harlequin fetus. *Arch Dis Child* 1989; **64**:1309–11.
27 Germann R, Schindera I, Kuch M *et al.* [Life-threatening salicylate poisoning caused by percutaneous absorption in severe ichthyosis vulgaris]. *Hautarzt* 1996; **47**:624–7 (in German).
28 Hofmann B, Stege H, Ruzicka T *et al.* Effect of topical tazarotene in the treatment of congenital ichthyoses. *Br J Dermatol* 1999; **141**:642–6.
29 Cotellessa C, Cuevas-Covarrubias SA, Valeri P *et al.* Topical tazarotene 0.05% versus glycolic acid 70% treatment in X-linked ichthyosis due to extensive deletion of the *STS* gene. *Acta Derm Venereol* 2005; **85**:346–8.
30 Ogawa M, Akiyama M. Successful topical adapalene treatment for the facial lesions of an adolescent case of epidermolytic ichthyosis. *J Am Acad Dermatol* 2014; **71**:e103–5.
31 Kaplan YC, Ozsarfati J, Etwel F, *et al.* Pregnancy outcomes following first-trimester exposure to topical retinoids: a systematic review and meta-analysis. *Br J Dermatol* 2015; **173**:1132–41.
32 Buchan P, Eckhoff C, Caron D *et al.* Repeated topical administration of all-*trans*-retinoic acid and plasma levels of retinoic acids in humans. *J Am Acad Dermatol* 1994; **30**:428–34.
33 Kragballe K, Steijlen PM, Ibsen HH *et al.* Efficacy, tolerability, and safety of calcipotriol ointment in disorders of keratinization. Results of a randomized, double-blind, vehicle-controlled, right/left comparative study. *Arch Dermatol* 1995; **131**:556–60.
34 Bassotti A, Moreno S, Criado E. Successful treatment with topical N-acetylcysteine in urea in five children with congenital lamellar ichthyosis. *Pediatr Dermatol* 2011; **28**:451–5.
35 Paller AS, van Steensel MAM, Rodriguez-Martín M *et al.* Pathogenesis-based therapy reverses cutaneous abnormalities in an inherited disorder of distal cholesterol metabolism. *J Invest Dermatol* 2011; **131**:2242–8.
36 Kiritsi D, Schauer F, Wölfle U *et al.* Targeting epidermal lipids for treatment of Mendelian disorders of cornification. *Orphanet J Rare Dis* 2014; **9**:33.
37 Elias PM, Williams ML, Feingold KR. Abnormal barrier function in the pathogenesis of ichthyosis: therapeutic implications for lipid metabolic disorders. *Clin Dermatol* 2012; **30**:311–22.
38 Schmid MH, Korting HC. The concept of the acid mantle of the skin: its relevance for the choice of skin cleansers. *Dermatology* 1995; **191**:276–80.
39 Pootongkam S, Nedorost S. Oat and wheat as contact allergens in personal care products. *Dermatitis* 2013; **24**:291–5.
40 Milstone LM. Scaly skin and bath pH: rediscovering baking soda. *J Am Acad Dermatol* 2010; **62**:885–6.
41 Bodemer C, Bourrat E, Mazereeuw-Hautier J *et al.* Short- and medium-term efficacy of specific hydrotherapy in inherited ichthyosis. *Br J Dermatol* 2011; **165**:1087–94.
42 Ogiso T, Shiraki T, Okajima K *et al.* Transfollicular drug delivery: penetration of drugs through human scalp skin and comparison of penetration between scalp and abdominal skins *in vitro*. *J Drug Target* 2002; **10**:369–78.

43 Vázquez Martinez JL, Stanescu S, Castrillo Bustamante S *et al.* Unrecognized transcutaneous severe salicylate intoxication in an infant. *Pediatr Emerg Care* 2015; **31**:e8.
44 Shwayder T. Disorders of keratinization: diagnosis and management. *Am J Clin Dermatol* 2004; **5**:17–29.
45 Digiovanna JJ, Mauro T, Milstone LM *et al.* Systemic retinoids in the management of ichthyoses and related skin types. *Dermatol Ther* 2013; **26**:26–38.
46 Happle R, van de Kerkhof PC, Traupe H. Retinoids in disorders of keratinization: their use in adults. *Dermatologica* 1987; **175** (Suppl. 1):S107–24.
47 Ho VC, Gupta AK, Ellis CN *et al.* Cyclosporine in lamellar ichthyosis. *Arch Dermatol* 1989; **125**:511–14.
48 Törmä H. Regulation of keratin expression by retinoids. *Dermatoendocrinol* 2011; **3**:136–40.
49 Vahlquist A, Duvic M. *Retinoids and Carotenoids in Dermatology*. New York: Informa Healthcare U.S.A. Inc., 2007.
50 Verfaille CJ, Vanhoutte FP, Blanchet-Bardon C *et al.* Oral liarozole vs. acitretin in the treatment of ichthyosis: a phase II/III multicentre, double-blind, randomized, active-controlled study. *Br J Dermatol* 2007; **156**:965–73.
51 Vahlquist A, Blockhuys S, Steijlen P *et al.* Oral liarozole in the treatment of patients with moderate/severe lamellar ichthyosis: results of a randomized, double-blind, multinational, placebo-controlled phase II/III trial. *Br J Dermatol* 2014; **170**:173–81.
52 Ormerod AD, Campalani E, Goodfield MJD *et al.* British Association of Dermatologists guidelines on the efficacy and use of acitretin in dermatology. *Br J Dermatol* 2010; **162**:952–63.
53 Katugampola RP, Finlay AY. Oral retinoid therapy for disorders of keratinization: single-centre retrospective 25 years' experience on 23 patients. *Br J Dermatol* 2006; **154**:267–76.
54 Macbeth AE, Johnston GA. Twenty-one years of oral retinoid therapy in siblings with nonbullous ichthyosiform erythroderma. *Clin Exp Dermatol* 2008; **33**:190–1.
55 Steijlen PM, Van Dooren-Greebe RJ, Van de Kerkhof PC. Acitretin in the treatment of lamellar ichthyosis. *Br J Dermatol* 1994; **130**:211–14.
56 Steijlen PM, van Dooren-Greebe RJ, Happle R *et al.* Ichthyosis bullosa of Siemens responds well to low-dosage oral retinoids. *Br J Dermatol* 1991; **125**:469–71.
57 Virtanen M, Gedde-Dahl T, Mörk NJ *et al.* Phenotypic/genotypic correlations in patients with epidermolytic hyperkeratosis and the effects of retinoid therapy on keratin expression. *Acta Derm Venereol* 2001; **81**:163–70.
58 El-Ramly M, Zachariae H. Long-term oral treatment of two pronounced ichthyotic conditions: lamellar ichthyosis and epidermolytic hyperkeratosis with the aromatic retinoid, Tigason (RO 10-9359). *Acta Derm Venereol* 1983; **63**:452–6.
59 Nassif PW, Nakandakari S, Fogagnolo L *et al.* Epidermolytic hyperkeratosis: a follow-up of 23 years of use of systemic retinoids. *An Bras Dermatol* 2011; **86** (4 Suppl. 1):S72–5.
60 Kullavanijaya P, Kulthanan K. Clinical efficacy and side effects of acitretin on the disorders of keratinization: a one-year study. *J Dermatol* 1993; **20**:501–6.
61 Blanchet-Bardon C, Nazzaro V, Rognin C *et al.* Acitretin in the treatment of severe disorders of keratinization. Results of an open study. *J Am Acad Dermatol* 1991; **24**:982–6.
62 Lacour M, Mehta-Nikhar B, Atherton DJ *et al.* An appraisal of acitretin therapy in children with inherited disorders of keratinization. *Br J Dermatol* 1996; **134**:1023–9.
63 Zhang X-B, Luo Q, Li C-X *et al.* Clinical investigation of acitretin in children with severe inherited keratinization disorders in China. *J Dermatolog Treat* 2008; **19**:221–8.
64 Haenssle HA, Finkenrath A, Hausser I *et al.* Effective treatment of severe thermodysregulation by oral retinoids in a patient with recessive congenital lamellar ichthyosis. *Clin Exp Dermatol* 2008; **33**:578–81.
65 Bruckner-Tuderman L, Sigg C, Geiger JM *et al.* Acitretin in the symptomatic therapy for severe recessive x-linked ichthyosis. *Arch Dermatol* 1988; **124**:529–32.
66 Hartschuh W, Hausser I, Petzoldt D. [Successful retinoid therapy of Netherton syndrome]. *Hautarzt* 1989; **40**:430–3 (in German).
67 Rajpopat S, Moss C, Mellerio J *et al.* Harlequin ichthyosis: a review of clinical and molecular findings in 45 cases. *Arch Dermatol* 2011; **147**:681–6.
68 Shibata A, Akiyama M. Epidemiology, medical genetics, diagnosis and treatment of harlequin ichthyosis in Japan. *Pediatr Int* 2015; **57**:516–22.
69 Lawlor F, Peiris S. Harlequin fetus successfully treated with etretinate. *Br J Dermatol* 1985; **112**:585–90.
70 Rogers M, Scraf C. Harlequin baby treated with etretinate. *Pediatr Dermatol* 1989; **6**:216–21.
71 Arjona-Aguilera C, Albarrán-Planelles C, Jiménez-Gallo D. Treatment of harlequin ichthyosis with acitretin. *Actas Dermosifiliogr* 2015; **106**:759.
72 Chang LM, Reyes M. A case of harlequin ichthyosis treated with isotretinoin. *Dermatol Online J* 2014; **20**:2.
73 Harvey HB, Shaw MG, Morrell DS. Perinatal management of harlequin ichthyosis: a case report and literature review. *J Perinatol* 2010; **30**:66–72.
74 Singh S, Bhura M, Maheshwari A *et al.* Successful treatment of harlequin ichthyosis with acitretin. *Int J Dermatol* 2001; **40**:472–3.
75 Grote W, Harms D, Jänig U *et al.* Malformation of fetus conceived 4 months after termination of maternal etretinate treatment. *Lancet* 1985; **1**:1276.
76 Kietzmann H, Schwarze I, Grote W *et al.* [Embryonal malformation following etretinate therapy of Darier's disease in the mother]. *Dtsch Med Wochenschr* 1986; **111**:60–2 (in German).
77 Lammer EJ. Embryopathy in infant conceived one year after termination of maternal etretinate. *Lancet* 1988; **2**:1080–1.
78 Mørk NJ, Kolbenstvedt A, Austad J. Efficacy and skeletal side effects of two years' acitretin treatment. *Acta Derm Venereol* 1992; **72**:445–8.
79 Mørk NJ, Kolbenstvedt A, Austad J. Skeletal side-effects of 5 years' acitretin treatment. *Br J Dermatol* 1996; **134**:1156–7.
80 Mørk N-J, Austad J, Kolbenstvedt A. Bamboo spine mimicking Bekhterev's disease caused by long-term acitretin treatment. *Acta Derm Venereol* 2006; **86**:452–3.
81 Rood MJ, Lavrijsen SPM, Huizinga TWJ. Acitretin-related ossification. *J Rheumatol* 2007; **34**:837–8.
82 Gualtierotti R, De Marco G, Marchesoni A. An overlooked cause of back pain and stiffness. *Rheumatology* 2013; **52**:985.
83 Ruby LK, Mital MA. Skeletal deformities following chronic hypervitaminosis A: a case report. *J Bone Joint Surg Am* 1974; **56**:1283–7.
84 Körner WF, Völlm J. New aspects of the tolerance of retinol in humans. *Int J Vitam Nutr Res* 1975; **45**:363–72.
85 Gerber A, Raab AP, Sobel AE. Vitamin A poisoning in adults: with description of a case. *Am J Med* 1954; **16**:729–45.
86 DiGiovanna JJ, Helfgott RK, Gerber LH *et al.* Extraspinal tendon and ligament calcification associated with long-term therapy with etretinate. *N Engl J Med* 1986; **315**:1177–82.
87 Melnik B, Glück S, Jungblut RM *et al.* Retrospective radiographic study of skeletal changes after long-term etretinate therapy. *Br J Dermatol* 1987; **116**:207–12.
88 Halkier-Sørensen L, Andresen J. A retrospective study of bone changes in adults treated with etretinate. *J Am Acad Dermatol* 1989; **20**:83–7.

89 Archer CB, Griffiths WA, MacDonald L. Spinal hyperostosis and etretinate. *Lancet* 1987; **1**:741.
90 White SI, MacKie RM. Bone changes associated with oral retinoid therapy. *Pharmacol Ther* 1989; **40**:137–44.
91 Van Dooren-Greebe RJ, Lemmens JA, De Boo T *et al.* Prolonged treatment with oral retinoids in adults: no influence on the frequency and severity of spinal abnormalities. *Br J Dermatol* 1996; **134**:71–6.
92 Torkamani N, Phal P, Savarirayan R *et al.* Concomitant extraspinal hyperostosis and osteoporosis in a patient with congenital ichthyosis. *Clin Cases Miner Bone Metab* 2016; **13**:157–9.
93 DiGiovanna JJ, Sollitto RB, Abangan DL *et al.* Osteoporosis is a toxic effect of long-term etretinate therapy. *Arch Dermatol* 1995; **131**:1263–7.
94 McMullen EA, McCarron P, Irvine AD *et al.* Association between long-term acitretin therapy and osteoporosis: no evidence of increased risk. *Clin Exp Dermatol* 2003; **28**:307–9.
95 Neema S, Mukherjee S, Vasudevan B *et al.* Vitamin D deficiency after oral retinoid therapy for ichthyosis. *Pediatr Dermatol* 2015; **32**: e151–5.
96 Frascari F, Dreyfus I, Rodriguez L *et al.* Prevalence and risk factors of vitamin D deficiency in inherited ichthyosis: a French prospective observational study performed in a reference center. *Orphanet J Rare Dis* 2014; **9**:127.
97 Halkier-Sørensen L, Laurberg G, Andresen J. Bone changes in children on long-term treatment with etretinate. *J Am Acad Dermatol* 1987; **16**:999–1006.
98 Ruiz-Maldonado R, Tamayo L. Retinoids in disorders of keratinization: their use in children. *Dermatologica* 1987; **175** (Suppl. 1):S125–32.
99 Prendiville J, Bingham EA, Burrows D. Premature epiphyseal closure:a complication of etretinate therapy in children. *J Am Acad Dermatol* 1986; **15**:1259–62.
100 Milstone LM, McGuire J, Ablow RC. Premature epiphyseal closure in a child receiving oral 13-*cis*-retinoic acid. *J Am Acad Dermatol* 1982; **7**:663–6.
101 Glover MT, Atherton DJ. Etretinate and premature epiphyseal closure in children. *J Am Acad Dermatol* 1987; **17**:853–4.
102 Glover MT, Peters AM, Atherton DJ. Surveillance for skeletal toxicity of children treated with etretinate. *Br J Dermatol* 1987; **116**:609–14.
103 Paige DG, Judge MR, Shaw DG *et al.* Bone changes and their significance in children with ichthyosis on long-term etretinate therapy. *Br J Dermatol* 1992; **127**:387–91.
104 Onnis G, Chiaverini C, Hickman G. Alitretinoin reduces erythema in inherited ichthyosis. *Orphanet J Rare Dis* 2018; **13**:46.
105 Prasad SC, Bygum A. Successful treatment with alitretinoin of dissecting cellulitis of the scalp in keratitis-ichthyosis-deafness syndrome. *Acta Derm Venereol* 2013; **93**:473–4.
106 Werchau S, Toberer F, Enk A *et al.* Keratitis-ichthyosis-deafness syndrome: response to alitretinoin and review of literature. *Arch Dermatol* 2011; **147**:993–5.
107 Gånemo A, Sommerlund M, Vahlquist A. Oral alitretinoin in congenital ichthyosis: a pilot study shows variable effects and a risk of central hypothyroidism. *Acta Derm Venereol* 2012; **92**:256–7.
108 Baden HP, Buxman MM, Weinstein GD *et al.* Treatment of ichthyosis with isotretinoin. *J Am Acad Dermatol* 1982; **6** (4 Pt 2 Suppl.):S716–20.
109 Gilgor RS, Chiaramonti A, Goldsmith LA *et al.* Evaluation of 13-*cis* retinoic acid in lamellar ichthyosis, pityriasis rubra pilaris and Darier's disease. *Cutis* 1980; **25**:380–1.
110 Chroni E, Monastirli A, Tsambaos D. Neuromuscular adverse effects associated with systemic retinoid dermatotherapy: monitoring and treatment algorithm for clinicians. *Drug Saf* 2010; **33**:25–34.
111 Ellis CN, Pennes DR, Hermann RC *et al.* Long-term radiographic follow-up after isotretinoin therapy. *J Am Acad Dermatol* 1988; **18**:1252–61.
112 Pennes DR, Martel W, Ellis CN *et al.* Evolution of skeletal hyperostoses caused by 13-*cis*-retinoic acid therapy. *AJR Am J Roentgenol* 1988; **151**:967–73.
113 Lamb RC, Lang J, Terron-Kwiatowski A *et al.* Avascular necrosis of the hip and diffuse idiopathic skeletal hyperostosis during long-term isotretinoin treatment of epidermolytic ichthyosis due to a novel deletion mutation in KRT10. *Br J Dermatol* 2014; **171**:913–15.
114 Hazen PG, Carney JM, Langston RH *et al.* Corneal effect of isotretinoin: possible exacerbation of corneal neovascularization in a patient with the keratitis, ichthyosis, deafness ('KID') syndrome. *J Am Acad Dermatol* 1986; **14**:141–2.
115 Vahlquist A, Lööf L, Nordlinder H *et al.* Differential hepatotoxicity of two oral retinoids (etretinate and isotretinoin) in a patient with palmoplantar psoriasis. *Acta Derm Venereol* 1985; **65**: 359–62.
116 Srinivasaraghavan R, Krishnamurthy S, Chandar R *et al.* Acitretin-responsive ichthyosis in Chanarin-Dorfman syndrome with a novel mutation in the ABHD5/CGI-58 gene. *Pediatr Dermatol* 2014; **31**:612–14.
117 Israeli S, Pessach Y, Sarig O *et al.* Beneficial effect of acitretin in Chanarin-Dorfman syndrome. *Clin Exp Dermatol* 2012; **37**:31–3.
118 Patel V, Sun G, Dickman M *et al.* Treatment of keratitis-ichthyosis-deafness (KID) syndrome in children: a case report and review of the literature. *Dermatol Ther* 2015; **28**:89–93.
119 Zhang X, He Y, Zhou H *et al.* Severe ichthyosis-related disorders in children: response to acitretin. *J Dermatolog Treat* 2007; **18**:118–22.
120 Bondeson M-L, Nyström A-M, Gunnarsson U *et al.* Connexin 26 (GJB2) mutations in two Swedish patients with atypical Vohwinkel (mutilating keratoderma plus deafness) and KID syndrome both extensively treated with acitretin. *Acta Derm Venereol* 2006; **86**:503–8.
121 Maintz L, Betz RC, Allam J-P *et al.* Keratitis-ichthyosis-deafness syndrome in association with follicular occlusion triad. *Eur J Dermatol* 2005; **15**:347–52.
122 Sahoo B, Handa S, Kaur I *et al.* KID syndrome: response to acitretin. *J Dermatol* 2002; **29**:499–502.
123 Nazzaro V, Blanchet-Bardon C, Lorette G *et al.* Familial occurrence of KID (keratitis, ichthyosis, deafness) syndrome. Case reports of a mother and daughter. *J Am Acad Dermatol* 1990; **23**:385–8.
124 Wolfe CM, Davis A, Shaath TS *et al.* Visual impairment reversal with oral acitretin therapy in keratitis-ichthyosis-deafness (KID) syndrome. *JAAD Case Rep* 2017; **3**:556–8.
125 Gånemo A, Lindholm C, Lindberg M *et al.* Quality of life in adults with congenital ichthyosis. *J Adv Nurs* 2003; **44**:412–19.
126 Mazereeuw-Hautier J, Dreyfus I, Barbarot S *et al.* Factors influencing quality of life in patients with inherited ichthyosis: a qualitative study in adults using focus groups. *Br J Dermatol* 2012; **166**: 646–8.
127 Gånemo A. Quality of life in Swedish children with congenital ichthyosis. *Dermatol Rep* 2010; **2**:e7.
128 Gånemo A, Sjöden P-O, Johansson E *et al.* Health-related quality of life among patients with ichthyosis. *Eur J Dermatol* 2004; **14**: 61–6.
129 Kamalpour L, Gammon B, Chen K-H *et al.* Resource utilization and quality of life associated with congenital ichthyoses. *Pediatr Dermatol* 2011; **28**:512–18.

130 Dreyfus I, Bourrat E, Maruani A *et al.* Factors associated with impaired quality of life in adult patients suffering from ichthyosis. *Acta Derm Venereol* 2014; **94**:344–6.
131 Dufresne H, Hadj-Rabia S, Méni C *et al.* Family burden in inherited ichthyosis: creation of a specific questionnaire. *Orphanet J Rare Dis* 2013; **8**:28.
132 Styperek AR, Rice ZP, Kamalpour L *et al.* Annual direct and indirect health costs of the congenital ichthyoses. *Pediatr Dermatol* 2010; **27**:325–36.
133 Dreyfus I, Taïeb C, Barbarot S *et al.* IQoL-32: a new ichthyosis-specific measure of quality of life. *J Am Acad Dermatol* 2013; **69**:82–7.
134 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**:210–16.
135 Ripmeester P, Dunn S. Against all odds: breastfeeding a baby with harlequin ichthyosis. *J Obstet Gynecol Neonatal Nurs* 2002; **31**:521–5.
136 Anzieu-Premmereur C. The skin-ego: dyadic sensuality, trauma in infancy, and adult narcissistic issues. *Psychoanal Rev* 2015; **102**:659–81.
137 Cho E-S, Kim S-J, Kwon MS *et al.* The effects of kangaroo care in the neonatal intensive care unit on the physiological functions of preterm infants, maternal–infant attachment, and maternal stress. *J Pediatr Nurs* 2016; **31**:430–8.
138 Lorig K. Partnerships between expert patients and physicians. *Lancet* 2002; **359**:814–15.
139 Dufresne H, Hadj-Rabia S, Taïeb C *et al.* Importance of therapeutic patient education in ichthyosis: results of a prospective single reference center study. *Orphanet J Rare Dis* 2013; **8**:113.
140 Fischer J, Traupe H. [Clinics and genetics of ichthyoses]. *Med Genet* 2014; **26**:427–42 (in German).

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Classification of congenital ichthyoses: non-syndromic and syndromic forms.

Appendix S2 Methodology of the literature searches and consensus conference.

Appendix S3 Levels of evidence and grades of recommendation.

Appendix S4 Pharmacodynamics of oral retinoids.

Appendix S5 Treatment of epidermolytic ichthyosis with oral retinoids.

Appendix S6 Pregnancy prevention programme for women of childbearing age.

Appendix S7 Interactions and contraindications of acitretin.

Appendix S8 Use of oral retinoids in syndromic ichthyoses.

Table S1 Use of topical and systemic therapies, psychosocial management, communicating the diagnosis and genetic counselling: recommendations with level of evidence and grade.

Table S2 Main adverse effects of acitretin, precautions and monitoring.