

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

J. Mazereeuw-Hautier¹, 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^{15,8,9}, 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-Martin³³

¹Reference Centre for Rare Skin Diseases, Dermatology Department, Larrey Hospital, Toulouse, France

²Department of Medical Sciences, Uppsala University, Uppsala, Sweden

³Department of Dermatology, University Hospital of Münster, Von-Esmarch-Straße 58, D-48149 Münster, Germany

⁴Department of Dermatology and Allergy Centre, Odense University Hospital, Odense, Denmark

⁵Hospital de Egas Moniz, Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal

⁶Ichthyosis Support Group, PO Box 1242, Yateley GU47 7FL, U.K.

⁷Association Ichtyose France, Bellerive sur Allier, France

⁸Department of Dermatology, Reference Center for Genodermatoses and Rare Skin Diseases (MAGEC), Paris, France

⁹Institut Imagine, Université Descartes, Sorbonne Paris Cité, Hôpital Necker-Enfants Malades, Paris

¹⁰Dermatology Division, Bambino Gesù Children's Hospital-IRCCS, Rome, Italy

¹¹Department of Dermatovenereology, University Medical Centre Ljubljana, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

¹²Institute of Human Genetics, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

¹³Department of Dermatology, Institute of Clinical Research in Malmö, Skåne University Hospital, Lund University, Malmö, Sweden

¹⁴Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

¹⁵Department of Dermatology, Venereology and Allergology, Medical University of Innsbruck, Innsbruck, Austria

¹⁶Department of Dermatology, Hôpital de Beaumont, Lausanne, Switzerland

¹⁷Epithelial Differentiation and Rheumatoid Autoimmunity Unit (UDEAR), UMR 1056 Inserm – Toulouse 3 University, Purpan Hospital, Toulouse, France

¹⁸Department of Dermatology, Hôpital Henri Mondor, EA EpiDerm, UPEC-Université Paris-Est Créteil, 94010 Créteil, France

¹⁹Dermatology Department, Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

²⁰Corneoplastic Unit, Queen Victoria Hospital NHS Trust, East Grinstead, U.K.

²¹Department of Ear, Nose and Throat, Hospital Universitario Son Espases, Palma de Mallorca, Spain

²²Division of Pediatric Dermatology and Allergology, Auf Der Bult Children's Hospital, Hanover, Germany

²³Department of Dermatology, Royal London Hospital, Barts Health NHS Trust, London, E1 1BB, U.K.

²⁴Department of Dermatology, Venereology and Paediatric Dermatology, Medical University of Lublin, Lublin, Poland

²⁵ULB-Erasme Hospital, Department of Dermatology, Brussels, Belgium

²⁶Department of Dermatology and Centre for Rare Disorders, Oslo University Hospital, Oslo, Norway

²⁷Department of Dermatology, Maastricht University Medical Centre, GROW Research School for Oncology and Developmental Biology, Maastricht, the Netherlands

²⁸Selbsthilfe Ichthyose, Kürten, Germany

²⁹Department of Dermatology, University Hospitals Leuven, Leuven, Belgium

³⁰Department of Microbiology and Immunology, KU Leuven, Belgium

³¹Centre 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.

³²Hautarztpraxis am Buddenturm, Rudolf-von-Langen-Straße 55, D-48147 Münster, Germany

³³Department of Dermatology, Hospital Infantil Niño Jesús, Madrid, Spain

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Summary

Correspondence

Juliette Mazereeuw-Hautier.

E-mail: mazereeuw-hautier.j@chu-toulouse.fr

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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.

Conflicts of interest

J.M.H. is a consultant for Arrow. The other authors declare no conflicts of interest.

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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 dermatoeidemiologist 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).

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 ($\geq 10\%$), 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 ($\geq 10\%$) is not recommended before the age of 1 year, except once daily on limited areas such as the palms and soles.

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 ($\geq 10\%$), 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

^aAll keratolytics must be used with caution in children (risk of absorption). ^bThe addition of fragrances may partially lessen the strong odour.

Topical retinoids

Topical tazarotene demonstrated efficacy in a small open study of 12 patients with CI²⁸ 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 adults³³ 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 callus⁹ (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

elabion, 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 administered 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 acitretin⁹⁴ 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 CI¹⁰⁴ 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 study¹⁰⁸ and in case reports including patients with HI.^{67,72,109} High doses of isotretinoin are necessary¹⁰⁸ 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 Charnarin–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

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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.