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Use of two combination creams for the treatment of ichthyoses and ichthyosiform disorders

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Author contributions

Mazen Kurban planned the study. Samar Khalil, Carla Stephan, Divina J. Hasbani, Serena Saade, Tara Bardawil conducted surveys. Serena Saade submitted the study. Adele Chedraoui and Nelly Rubeiz entered the data. Mazen Kurban, Ossama Abbas, Samar Khalil and Serena Saade wrote the manuscript. Divina Hasbani and Carla Stephan did the literature review.

Competing interests

The authors declare no conflicts of interest.

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Abstract

Treatment options for ichthyosis and ichthyosiform disorders are limited and often unsatisfactory. Twenty-four patients used combination creams of 2% cholesterol with 2% lovastatin, and 10% glycolic acid with 0.025% tretinoin and 2% ketoconazole daily. At one month (n = 20), the average percent reduction in severity scores was 40%, and at three months (n = 10), it was 60.3%. Side effects were mainly mild irritation. These findings suggest that these two combination creams could be beneficial in the treatment of ichthyosiform disorders.

Keywords: ichthyosis; ichthyosiform disorders; cholesterol; statin; tretinoin

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Highlights

Treatment options for ichthyosis and ichthyosiform disorders are limited. However, a therapeutic regimen comprising of two combination creams, namely 2% cholesterol with 2% lovastatin, and 10% glycolic acid with 0.025% tretinoin and 2% ketoconazole, showed benefits in 24 patients with ichthyosis and ichthyosiform disorders.

Introduction

Ichthyoses and ichthyosiform disorders are a group of inherited and acquired disorders of keratinisation, in which the skin is covered by an excessive amount of scale, resulting in a thick but dysfunctional skin barrier [1, 2]. Hydrating and keratolytic agents are the mainstay of treatment, but unfortunately, the response is often unsatisfactory. Topical agents have been shown to benefit mild cases, but larger amounts applied can lead to side effects that decrease compliance. For example, emollients like urea can cause transient pruritus and burning when used in erythrodermic types of ichthyoses where cutaneous inflammation is a common feature. Similarly, keratolytics can cause burning, itching or irritation, and their use is not recommended on the face, flexural areas or fissures [3]. Combining keratolytics with a different moisturising vector, such as a cream-based ketoconazole, could be a promising alternative to decrease the side effects. In fact, previous studies have shown that combination creams can be more effective than higher concentrations of a single agent [4].

A double-blinded trial compared the efficacy of a cream mixture containing 5% lactic acid with 20% propylene glycol in a semi-occlusive cream, with either agent alone. The results demonstrated that the combination of two or more keratolytic agents and moisturizers in the same lipophilic cream base offers a synergistic effect in patients with lamellar ichthyosis, sparing them from the irritating higher concentrations of either agent alone [5].

In 2018, we published a case series of 15 patients with autosomal recessive congenital ichthyosis who were treated with a topical combination of glycolic acid (10–20%) and a combination cream of lovastatin (2%) and cholesterol (2%). This resulted in a significant reduction in disease severity scores of 33.7% at 2 months and 57.5% at 3 months [6]. The essential role of the "cholesterol sulfate cycle" in the development, maturation, and differentiation of keratinocytes has been demonstrated in patients with X-linked ichthyosis who have loss-of-function mutations in the steroid sulfatase gene (Figure 1) [7]. However, topical cholesterol has shown inconsistent results in X-linked ichthyosis as it fails to address the toxic metabolites generated in this cycle. Therefore, the addition of a topical statin to topical cholesterol inhibits the accumulation of metabolites from endogenous cholesterol production, improving skin differentiation.

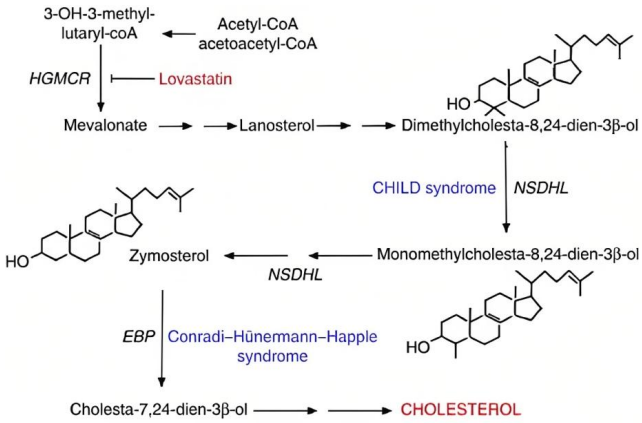

Figure 1 Metabolism and mechanism of action of natural retinoids

In this study, we included 24 patients with treatment-resistant ichthyoses and ichthyosiform disorders. Two types of creams were administered to the participants: a lovastatin-cholesterol combination cream and a combination cream containing glycolic acid (10%), tretinoin (0.025%), and ketoconazole (2%). Ketoconazole functions by inhibiting cholesterol production through CYP51 inhibition and the degradation of retinoids by blocking their CYP26-mediated catabolism. The potential benefits of 2% topical ketoconazole for the management of ichthyosiform disorders have been demonstrated in a case of CHILD syndrome, where the patient experienced a 90% resolution of skin lesions and minimal recurrence after four years [8].

Materials and methods

The Department of Dermatology at the American University of Beirut Medical Center is a referral center for genodermatoses in Lebanon and the Middle East region. For this study, we recruited 25 Middle Eastern patients with ichthyosis and ichthyosiform disorders, 17 of whom were products of consanguineous marriage. We included patients of all ages, genders, and types of ichthyosis, regardless of their past or current treatments. Pregnant females were excluded from the study. Prior to the study, many of our patients had been using emollients and creams containing varying concentrations of urea and glycolic acid with suboptimal responses. All topical therapies were discontinued at the start of the study. Only one patient was on oral isotretinoin therapy, but they had to be excluded from the study due to severe irritation that developed within one week of introducing our topical creams.

The study was approved by the Institutional Review Board of the American University of Beirut Medical Center (Ethics approval number: BIO-2018-0356). All patients provided their written informed consent.

Patients in the study were instructed to apply the treatment creams on specific areas selected by both the patient and the physician. The combination cream of lovastatin, 2%-cholesterol, 2% was applied every morning, followed by a glycerol-based moisturizer every afternoon. The combination cream of glycolic acid, 10%-tretinoin, 0.025%-ketoconazole, 2% was applied nightly or every other night depending on tolerability. The amount of cream applied depended on the surface area involved, with patients using up to five adult finger-tip units a day per cream.

Patients were scheduled for monthly visits during which they were provided with the study creams, their skin was scored, and photographs were taken. The primary outcome was the clinical improvement observed after 2 and 3 months of treatment, and some patients continued treatment beyond 3 months. However, due to the Lebanese revolution that began in October 2019 and the COVID-19 pandemic of 2020, some patients were unable to come to the clinic for their monthly visits.

Scoring system

We utilized the same severity scoring system employed in our previous study6 and assessed five distinct criteria during each visit: (1) skin thickness and/or scaling; (2) pain, pruritus, and/or discomfort; (3) erythema; (4) impact of the condition on the ability to perform daily functions; and (5) the patient's subjective severity scoring, which refers to the patient's own assessment of the severity of their condition. Each criterion was given a score from 0 to 20, with 0 denoting the absence of symptoms and 20 representing the most severe symptoms (Table 1). At each visit, patients were examined by both Dr. Mazen Kurban, a specialist in genodermatoses, and Dr. Samar Khalil, who has conducted clinical research on ichthyosis with Dr. Kurban for years.

For criterion number (4), which pertains to the impact of the condition on the ability to perform daily functions, we utilized the Dermatology Life Quality Index. We obtained a score out of 30, which was subsequently converted to a score out of 20. When applicable, questions were posed to parents of small children (e.g., "Over the last month, how often did you observe your child itching their skin

lesions?"). It is important to note that we used the Dermatology Life Quality Index score to assess the impact on daily life, rather than the Children's Dermatology Life Quality Index score, because we anticipated recruiting more adults, but most of our participants turned out to be younger than 16 years old. The level of improvement during follow-up was evaluated by the percentage reduction in the total severity score as compared to the baseline score. A reduction of 0% to 9.9% was classified as a poor response; 10.0% to 24.9% was categorised as a fair response; 25.0% to 49.9% was regarded as a good response; 50% to 74.9% was considered a very good response; and 75% to 100% was deemed as an excellent response. The primary outcomes of the study were changes in the average severity scores (compared to baseline) at 1, 2 and 3 months of follow-up. The secondary outcomes were changes in the average severity scores (compared to baseline) at 4, 5 and 6 months of follow-up, and the rates of adverse events.

Statistical analysis

The data were presented in terms of means and percent change.

Results

A total of 24 patients completed at least 1 month of treatment. Of the 24 study participants, half (n = 12) were male. The average patient age was 8.8 years (range, 1 month-26 years). The median age was 7.5 years. The characteristics of the study participants are summarised in Table 2

Primary outcomes

The average severity score at baseline was 52. During the follow-up, 20, 18, and 10 patients came to the clinic at 1, 2, and 3 months, respectively. The average severity scores were 31.2 at 1 month, 28.7 at 2 months, and 20.6 at 3 months. The average percentage reductions in the severity scores were 40% at 1 month (good response), 44.8% at 2 months (good response), and 60.3% at 3 months (very good response) (Table 3).

Overall, at 1 month, 3 patients (15%) had an excellent response; 7 patients (35%) had a very good response; 5 patients (25%) had a good response; 4 patients (20%) had a fair response; and 1 patient (5%) had a poor response. At 2 months, 4 patients (22.2%) had an excellent response; 5 patients (27.8%) had a very good response; 6 patients (33.3%) had a good response; 2 patients (11.1%) had a fair response; and 1 patient (5.6%) had a poor response. At 3 months, 3 patients (30%) had an excellent response; 6 patients (60%) had a very good response; 1 patient (10%) had a good response; and no patient had a poor or fair response. (Figures 2–5, Supplementary Figures 1–7). The scores of the patients are detailed in Supplementary Table 1.

Table 1 Scoring system

Criterion	Maximum score
Skin thickness/ scaling	20
Pain/ Pruritis/ Discomfort	20
Erythema	20
Impact of the condition on the ability to perform daily functions	20
Patient severity scoring	20
Total	100

Table 2 Characteristics of the study participants

Patient ID	Age	Gender	Disease	Consanguineous parents
1	7 months old	Male	Lamellar ichthyosis	Yes
2	11 months old	Male	Lamellar ichthyosis	Yes
3	21 years old	Male	Lamellar ichthyosis	Yes
4	10 years old	Male	Lamellar ichthyosis	Yes
5	1 years old	Male	Ichthyosis hystrix	Yes
6	9 years old	Male	Unknown ichthyosiform disorder	Yes
7	3 years old	Female	KID syndrome	No
8	4 years old	Female	Lamellar ichthyosis	Yes
9	16 years old	Male	Lamellar ichthyosis	Yes
10	15 years old	Male	Lamellar ichthyosis	Yes
11	21 years old	Female	Lamellar ichthyosis	Yes
12	1 years old	Female	Lamellar ichthyosis	No
13	5 years old	Male	Lamellar ichthyosis	Yes
14	3 years old	Female	Lamellar ichthyosis	Yes
15	13 years old	Male	Lamellar ichthyosis	No
16	10 years old	Male	Lamellar ichthyosis	No
17	7 years old	Male	Lamellar ichthyosis	No
18	26 years old	Female	CHILD syndrome	No
19	13 years old	Female	Lamellar ichthyosis	Yes
20	12 years old	Female	Lamellar ichthyosis	Yes
21	7 years old	Female	Lamellar ichthyosis	Yes
22	1 months old	Female	Lamellar ichthyosis	Yes
23	5 years old	Female	X-linked ichthyosis	No
24	8 years old	Female	Erythrokeratodermia variabilis	Yes

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Table 3 Severity scores at baseline and during follow-up appointments

	Baseline	1 month	2 months	3 months	4 months	5 months	6 months
Number of patients	24	20	18	10	8	5	1
Severity score	52	31.2	28.7	20.6	20.6	12.2	25
Percentage change in severity score	–	40%	44.8%	60.3%	60.3%	76.5%	51%

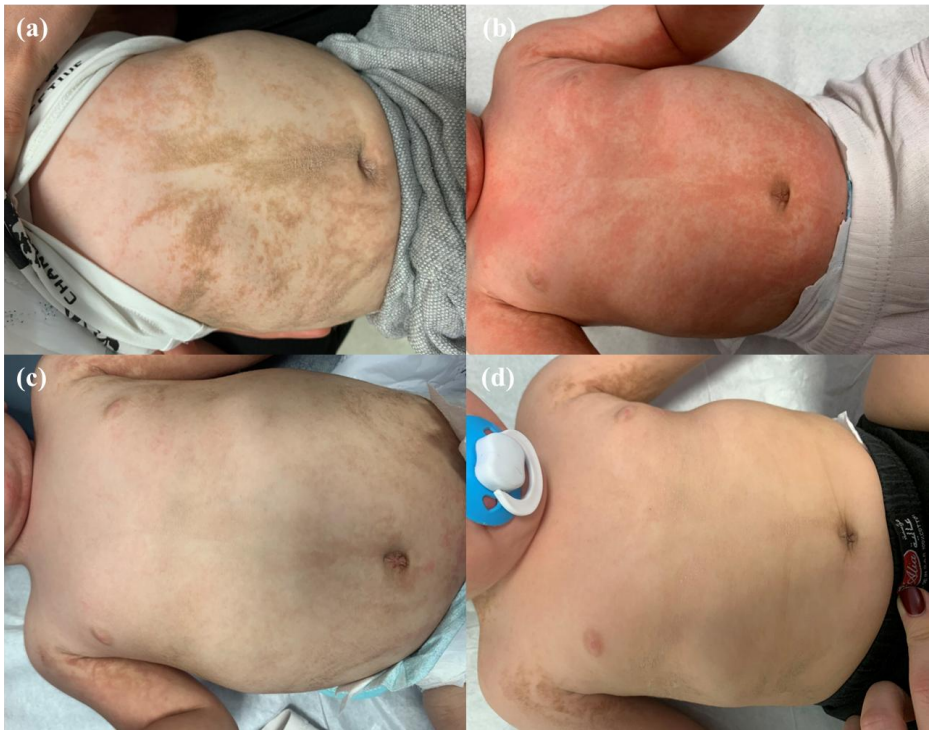

Figure 2 Patient ID-5. (a) Before treatment; (b) 2 months after treatment; (c) 3 months after treatment; (d) 5 months after treatment, with an excellent response.

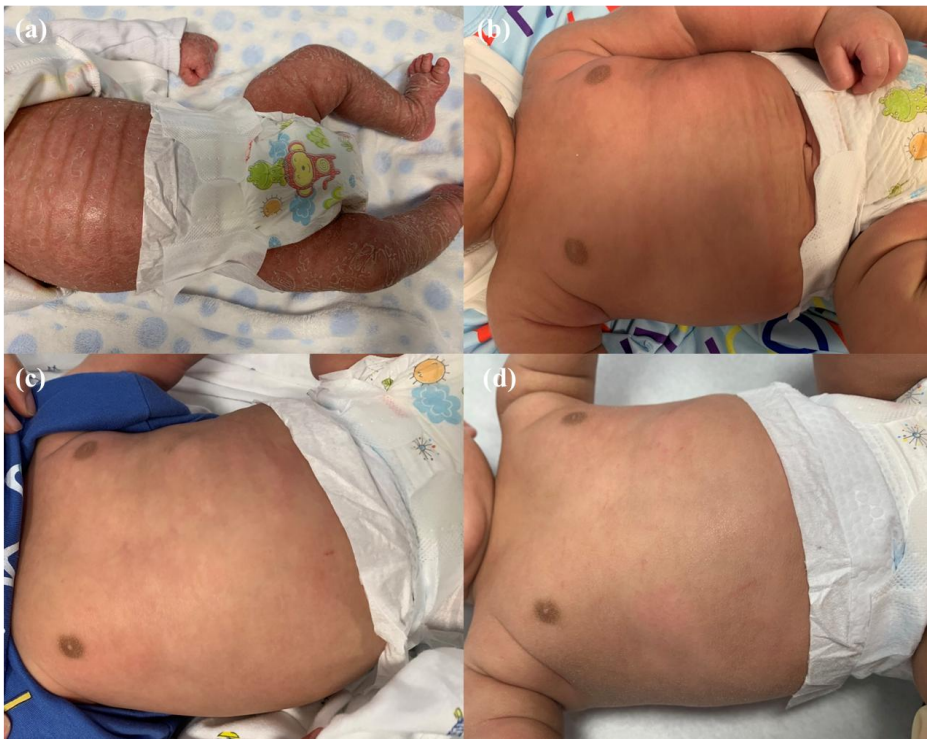

Figure 3 Patient ID-2. (a) Before treatment; (b) 2 months after treatment; (c) 3 months after treatment; (d) 5 months after treatment, with an excellent response.

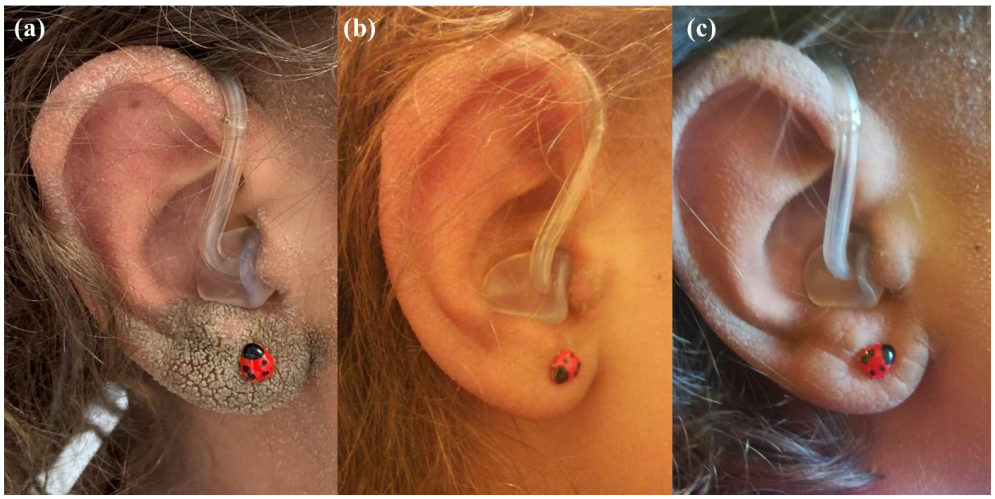

Figure 4 Patient ID-7. (a) Before treatment; (b) 2 months after treatment with an excellent response; (c) 4 months after treatment with a good response.

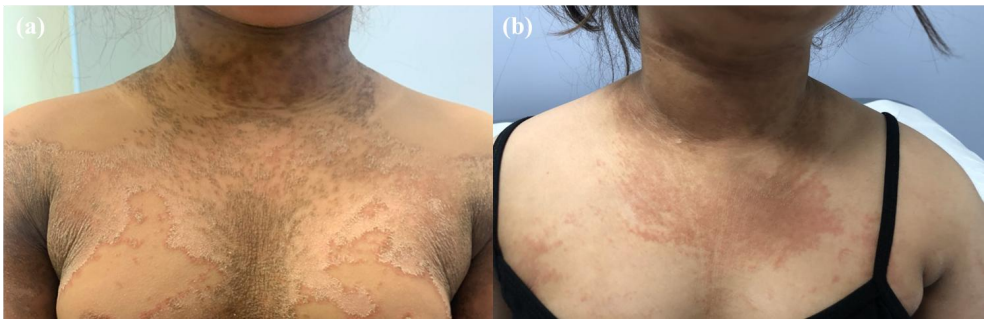

Figure 5 Patient ID-24. (a) Before treatment; (b) 3 months after treatment with a very good response.

Secondary outcomes

At 4 and 5 months, 8 and 5 patients attended follow-up appointments, respectively. The average severity scores were 20.6 at 4 months and 12.2 at 5 months. The average percentage reductions in the severity scores were 60.3% at 4 months and 76.5% at 5 months. Only one patient visited the clinic at 6 months and had an average severity score of 25 with a 51% percentage reduction from baseline, indicating a very good response (Table 3).

Adverse effects were reported by 6 patients (25%) and mainly consisted of mild erythema, scaling, and burning. These effects were managed by adjusting the frequency of application. One patient who was on oral isotretinoin experienced severe irritation within 1 week of starting the creams, and their symptoms did not improve with fewer weekly applications of the creams. This patient withdrew from the study and was excluded from the analysis. No other patient discontinued the use of the creams due to reported side effects.

The remaining patients who were unable to attend clinic appointments were contacted by phone and reported compliance with the use of the creams and no side effects.

Discussion

Cholesterol plays a crucial role in the development of the skin barrier, and mutations in genes associated with cholesterol metabolism have been linked to various types of ichthyoses [6, 7]. Previous studies have demonstrated the efficacy of topical cholesterol, either alone or in combination with lovastatin, in the treatment of certain skin disorders, such as X-linked ichthyosis, CHILD syndrome, and autosomal recessive congenital ichthyosis [6, 9–14]. This combination cream not only provides the skin with exogenous cholesterol but also inhibits the aberrant endogenous cholesterol synthesis pathway (through the statin) and prevents the accumulation of toxic metabolites, making it an effective treatment option for ichthyoses [6, 12, 13].

Glycolic acid and tretinoin, both keratolytic agents, have the ability to promote shedding of excess skin and facilitate better absorption of the cholesterol and lovastatin cream. Additionally, retinoids play a crucial role in regulating cell growth, differentiation, and apoptosis [15]. Recent studies suggest that ketoconazole, another component of the cream, has anti-inflammatory properties, and it can inhibit cholesterol production and degradation of retinoids [16–19].

In this study, we evaluated the effectiveness of two combination creams in treating ichthyosis and ichthyosiform disorders. The first cream contains 2% lovastatin and 2% cholesterol, while the second cream contains 10% glycolic acid, 0.025% tretinoin, and 2% ketoconazole. To the best of our knowledge, this combination of active ingredients has not been studied before in this context. Results showed an average reduction in severity scores of 40% at 1 month (good response), 44.8% at 2 months (good response), and 60.3% at 3 months (very good response).

Adverse effects were mild and easily manageable, primarily involving irritation related to the night cream.

Limitations

Limitations of our study include the relatively small number of participants. Unfortunately, due to the Lebanese revolution that commenced in October 2019, as well as the COVID-19 pandemic in 2020, some patients were unable to visit us monthly. As a result, we made phone calls to these patients to ensure treatment adherence and monitor for side effects. It should be noted that all patients were able to attend at least one follow-up visit. Another limitation of our study is the subjective nature of the scoring system, which involves a patient-reported improvement percentage. Furthermore, a future step would be to conduct this study with a larger number of patients and examine the histological changes induced by the cream combinations in patients with ichthyosis. Additionally, the study lacks a control group, and future research could benefit from its inclusion. Although

our findings were not robust enough to support our claims, they can still contribute to the existing body of research and inform future studies.

Conclusion

Based on our study, it can be concluded that there is potential benefit in using a treatment regimen that combines 2% cholesterol with 2% lovastatin, along with another combination of 10% glycolic acid with 0.025% tretinoin and 2% ketoconazole, for the treatment of ichthyoses and ichthyosiform disorders.

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