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Objective Assessment of Isotretinoin-Associated Cheilitis: Isotretinoin Cheilitis Grading Scale

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Abstract

Importance—Isotretinoin remains an effective treatment for severe acne. Despite its effectiveness, it includes many side effects, of which cheilitis is the most common.

Objective—To develop an objective grading scale for assessment of isotretinoin-associated cheilitis,

Design—Cross-sectional clinical grading study.

Setting—UC Davis Dermatology clinic.

Participants—Subjects were older than 18 years old and actively treated with oral isotretinoin.

Exposures—Oral Isotretinoin.

Main outcomes and Measures—We developed an isotretinoin cheilitis grading scale (ICGS) incorporating the following four characteristics: erythema, scale/crust, fissures, and inflammation of the commissures. Three board-certified dermatologists independently graded photographs of the subjects.

Results—The Kendall's coefficient of concordance (KCC) for the ICGS was 0.88 ($p < 0.0001$). The Kendall's coefficient was 0.72 ($p < 0.0001$) for each of the four characteristics included in the grading scale. An image-based measurement for lip roughness statistically significantly correlated with the lip scale/crusting assessment ($r = 0.52$, $p < 0.05$).

Conclusion and Relevance—The ICGS is reproducible and relatively simple to use. It can be incorporated as an objective tool to aid in the assessment of isotretinoin associated cheilitis.

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Keywords

Acne; Teledermatology

Introduction

Acne is one of the most prevalent dermatological diseases and studies indicate that up to 95% of adults experience acne at some point in their life [1–2]. Acne has social, psychological, and psychiatric impacts on those it affects [3]. Since its introduction to the market in the 1982, isotretinoin has remained the most effective treatment for severe acne and targets all four factors involved in the pathogenesis of acne [4–6]. Despite its effectiveness it has multiple side effects. Notably, cheilitis remains the most common side effect reported with isotretinoin use [7–9].

Current treatment relies on the use of hydrating and emollient products to alleviate symptoms of isotretinoin-associated cheilitis. However, there is a dearth of grading systems to clinically assess the characteristics and severity of the cheilitis, making evidence-based research of potential interventions challenging. One study investigating the use of evening primrose oil supplementation to treat and prevent xerotic cheilitis associated with isotretinoin use utilized a Tewameter TM300 to measure transepidermal water loss (TEWL) and a corneometer to measure moisture content of the lip [5]. A comparative evaluation using photography was also conducted using a quartile grading scale with 1=poor (0%–25%), 2=moderate (26%–50%), 3=good (51%–75%), 4=excellent (76%–100%) [5]. While elegantly performed, this method of evaluation utilizes equipment that is not readily available to all practitioners. Another study that investigated the potential use of oral vitamin E supplementation as a treatment for isotretinoin-related dryness of the mucosal surfaces found an overall decrease in these side effects, including cheilitis, relative to control [10]. However, an objective and clinically based grading scale is needed to assist in relatively quick clinical evaluation and the reproducibility of future studies.

In this study, our goal was to create a reproducible, comprehensive, and objective grading scale that can be utilized to grade isotretinoin associated cheilitis.

Methods

This study was approved by the Institutional Review Board at the University of California, Davis. Each subject provided written informed consent. Sixteen subjects were recruited from the Dermatology Clinic at the University of California, Davis. The average age of the subjects was 21.6 ± 5.39 years of age. There were a total of eleven males and five females in this study. Each subject was prescribed and actively taking oral isotretinoin at the time of photography. Subjects were asked to refrain from application of any products for the day of their visit and photography. Before the photograph, the subject's face was cleansed with alcohol swabs. Following this, a high-resolution facial photograph was taken with the 3D BTBP Clarity Pro Facial Modeling & Measurement System (Brigh-Tex BioPhotonics, San Jose, CA).

The facial modeling and measurement system combines multi-spectral light with skin mapping technology to create a surface map of the face and lips through the use of facial recognition parameters and biometrics. A lip dryness measure was calculated based on alteration of surface reflection. For each pixel within the lip region the local neighborhood average intensity was measured. We then calculated how much brighter the pixel intensity was compared to the local average. Pixels with a result lower than the local average were assigned a 0 to remove the effect of lip wrinkles from the measurement (pixels darker than the local average). The final figure provided is the average of the measurement described above for every pixel within the lip region.

The ICGS was as follows: **Erythema**- 0= no involvement, 1= mild erythema, 2= moderate erythema, 3= severe erythema, **Scale/Crust**- 0= no involvement, 1= mild scale/crust, 2= moderate scale/crust, 3= severe scale/crust, **Fissure**- 0= no fissures, 1= one fissure, 2= two-four fissures, 3= greater than 4 fissures, **Commissure**- 0= no involvement, 1= mild involvement (erythematous or scaly), 2= moderate involvement (erythematous and scaly, lichenification, severe fissuring), 3= severe involvement (more extensive erythema) (Table 1).

Three independent board-certified dermatologists graded isotretinoin-associated cheilitis from the photographs of subjects. A reference guide with example photographs of different grades for each characteristic was compiled. Each of the three dermatologists was given the reference guide and a group training session was conducted on a training set of isotretinoin-associated cheilitis photographs. Following this training, the three dermatologists graded the lips on forward-facing images of subjects actively receiving isotretinoin treatment. Figure 1 shows examples of mild, moderate, and severe cheilitis presented to the dermatologists for grading.

Statistical analyses were performed by calculating the inter-rater reliability through the calculation of an interclass correlation coefficient (ICC) and the Kendall's coefficient of concordance (KCC) [11] among the three graders. A Spearman rank-order correlation was utilized to assess the relationship between computerized grading and the clinical grading scale. Significance was set to $p = 0.05$.

Results

The inter-rater KCC for the cheilitis characteristics included in the grading scale are shown in Table 2: 0.73 for erythema ($p < 0.0001$), 0.72 for scale/crust ($p < 0.0001$), 0.75 for fissures ($p < 0.0001$), 0.81 for commissures ($p < 0.0001$), and 0.88 for the overall score ($p < 0.0001$). The ICC for the overall ICGS was 0.8 with 95% CI = (0.63, 0.90). In a subset of the subjects studied, a photograph before and after initiation of isotretinoin was utilized to assess whether the presence of before photographs would affect the grading and inter-rater reliability. The usage of a before photographs (prior to initiation of isotretinoin) did not alter the inter-rater concordance as it remained unchanged with the KCC at 0.77 ($p = 0.001$) and the ICC at 0.78 with 95% CI = (0.52, 0.91).

The image-based measurement for lip roughness statistically significantly correlated with the lip scale/crusting assessment ($r = 0.52$, $p < 0.05$).

Discussion

In this study, we present a reproducible grading scale that can be used for assessing isotretinoin-associated cheilitis. These results indicate a high inter-rater agreement for total score and each individual clinical characteristic, validating the reproducibility of the overall scale itself as well as the individually graded characteristics.

The facial modeling and measurement tool was able to correlate the measure of surface roughness with the scale/crust grading. Facial modeling and analysis is a growing field in which clinical comparisons have moved beyond simple photography. The development of tools to reproducibly assess facial features will help reduce inter-rater differences and make clinical studies more standardized.

Despite the strength of the ICGS, there are certain potential limitations regarding its applications. As the ICGS did not include parameters for assessing secondary infection, it cannot be utilized in a clinical scenario involving concern for infection. This study was limited to subjects who were currently receiving treatment with isotretinoin; therefore, our scale may not be applicable to other forms of cheilitis, such as actinic cheilitis, lip-licker cheilitis, or angular cheilitis. Further studies are needed to assess if the ICGS can be adapted to other forms of cheilitis.

The ICGS is straightforward in addition to being reproducible; it can easily be incorporated as a grading tool into future research to objectively investigate the effectiveness of treatments for isotretinoin-associated cheilitis. There have been various studies investigating potential treatments for isotretinoin-associated cheilitis, including vitamin E supplementation, evening primrose supplementation, and administering lower doses of isotretinoin in an attempt to mitigate side effects. Yet, there are currently no evidence-based effective or preventative treatment options for isotretinoin associated cheilitis [5, 10, 12–13]. Therefore there is a significant need for the development of novel treatment options. The scale presented here will greatly aid in this area of research.

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References

1. Collier CN, Harper JC, Carfardi JA, et al. The prevalence of acne in adults 20 years and older. *J Am Acad Dermatol.* 2008; 58(1):56–9. [PubMed: 17945383]
2. Inglese MJ, Mahave T, Lobesa M, et al. The pharmacoeconomics of acne treatment: where are we heading? *J Dermatolog Treat.* 2008; 19(1):27–37. [PubMed: 18273722]
3. Halvorsen JA, Stern RS, Dalgard F, et al. Suicidal ideation, mental health problems, and social impairment are increased in adolescents with acne: a population-based study. *J Invest Dermatol.* 2011; 131(2):363–70. [PubMed: 20844551]

4. Jones H, Blanc D, Cunliffe WJ. 13-cis retinoic acid and acne. *Lancet*. 1980; 2(8203):1048–9. [PubMed: 6107678]
5. Park KY, Ko EJ, Kim IS, et al. The effect of evening primrose oil for the prevention of xerotic cheilitis in acne patients being treated with isotretinoin: a pilot study. *Ann Dermatol*. 2014; 26(6): 706–12. [PubMed: 25473222]
6. Zouboulis CC, Bettoli V. Management of severe acne. *Br J Dermatol*. 2015
7. Blasiak RC, Stamey CR, Burkhart CN, et al. High-dose isotretinoin treatment and the rate of retreatment, relapse, and adverse effects in patients with acne vulgaris. *JAMA Dermatol*. 2013; 149(12):1392–8. [PubMed: 24173086]
8. Rademaker M. Adverse effects of isotretinoin: A retrospective review of 1743 patients started on isotretinoin. *Australas J Dermatol*. 2010; 51(4):248–53. [PubMed: 21198520]
9. Rao PK, Bhat RM, Nandakishore B, et al. Safety and efficacy of low-dose isotretinoin in the treatment of moderate to severe acne vulgaris. *Indian J Dermatol*. 2014; 59(3):316. [PubMed: 24891681]
10. Goforoushan F, Azimi H, Goldust M. Efficacy of vitamin E to prevent dermal complications of isotretinoin. *Pak J Biol Sci*. 2013; 16(11):548–50. [PubMed: 24498826]
11. Kendall, M. Rank Correlation Methods. 2. London: Charles Griffin & Co. Ltd; 1955.
12. Bergler-Czop B, Brzezinska-Wcislo L. The new therapy schema of the various kinds of acne based on the mucosa-skin side effects of the retinoids. *Cutan Ocul Toxicol*. 2012; 31(3):188–94. [PubMed: 22103810]
13. Kus S, Gun D, Demicay Z, Sur H. Vitamin E does not reduce the side-effects of isotretinoin in the treatment of acne vulgaris. *Int J Dermatol*. 2005; 44(3):248–51. [PubMed: 15807739]

Figure 1.
Examples of median isotretinoin cheilitis grading scores: A) 2, B) 4, C) 7, D) 8.

Table 1

Grading Scale used for assessment of isotretinoin associated cheilitis

Clinical Criteria	Score Descriptions
Erythema	0-No involvement 1- Mild erythema 2 -Moderate erythema 3-Severe erythema
Scale/Crust	0-No involvement 1- Mild scale/crust 2-Moderate scale/crust 3-Severe scale/crust
Fissure	0-No fissures 1-One fissure 2-Two to four fissures 3-Greater than four fissures
Commissures	0-No involvement 1- Mild involvement: erythematous or scaly 2 -Moderate involvem entherythematous and scaly, lichenified, mild fissuring 3 -Severe involvement: more extensive erythema, scale, and lichenification or any of those with severe fissuring
Total Score	Ranges from 0 to 12

Table 2

Inter-rater Agreements of Cheilitis Characteristics

Characteristics	Kendall's Coefficient of Concordance	p-value
Erythema	0.73	<0.0001
Scale/Crust	0.72	<0.0001
Fissures	0.75	<0.0001
Commissures	0.81	<0.0001
Overall Total Score	0.88	<0.0001