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EFFICACY AND SAFETY OF LOW DOSE ORAL ISOTRETINOIN FOR THE TREATMENT OF STEROID INDUCED ROSACEA- A RETROSPECTIVE STUDY

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Abstract

Background: The excessive, regular use of topical fluorinated steroids on the face often produces an array of skin complications, including an eruption clinically indistinguishable from rosacea-'steroid-induced rosacea like eruption ' or iatrosacea . Although it was believed that only high potency topical steroids could produce SIRD, it is important to note that topical hydrocortisone 1% can also cause such an eruption after prolonged use. **Objective:** To assess the efficacy and tolerability of low dose oral Isotretinoin for steroid induced rosacea- like eruption. **Methodology:** A retrospective registry/ photographic analysis of 30 patients enrolled between Jan 2013 to Jan 2014 was done at Cutis academy. Case records and photographs of 30 patients between the age group of 15- 45 years clinically diagnosed with steroid induced rosacea on low dose oral isotretinoin 20mg alternate days for 3 months were analysed. Patients were evaluated by a rosacea clinical score at weeks 0, 6, and 12 weeks. **Results:** A total of 30 patients (23females and 7 males) were enrolled in this study. The mean age of the study population was 30.1+/- 14.8 (14 to 45) years. Among the 30 patients, 2 dropped out due to side effects of treatment such as dryness and itching. According to seven point static score, Investigator global assessment of steroid induced rosacea eruption at baseline was 5.36+/- 1.1. This score decreased to 3.2 +/-0.8 at week 6, then 0.73 +/-0.6 at week 12.The difference of IGA between week 0, week 2, and week 6 was statistically significant.($p<0$-0001) . At baseline the 16 patients had ratings of 'severe' , 7 patients had ratings of 'moderate to severe', 2 patients had rating of 'moderate', 3 patients had rating of 'mild to moderate' .**Conclusion :** Low dose oral isotretinoin with cessation /avoidance of topical steroid use as well as the avoidance of other agents known to aggravate rosacea is proved to be an effective alternative mode of treatment of steroid rosacea like eruption.

KEYWORDS: Corticosteroids , Rosacea Dermatoses , Isotretinoin

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Introduction

The development of topical corticosteroids in 1951 opened new doors for dermatologists previously faced with treating intractable dermatoses.[1] Since then there is uncontrolled use (abuse) has been a common problem. The excessive, regular use of topical fluorinated steroids on the face often produces an array of skin complications, including an eruption clinically indistinguishable from rosacea-'steroid-induced rosacea like eruption ' or iatrosacea.(2,3)

The duration of use necessary to produce Steroid induced Rosacea Dermatoses can vary from days to several years. The average duration required to produce such adverse effect is 2 months, but may develop after only a few weeks of application of potent corticosteroids. Although it was believed that only high potency topical steroids could produce SIRD, it is important to note that topical hydrocortisone 1% can also cause such an eruption after prolonged use.[4-7]

The exact incidence of SIRD is not known, but it is believed to affect women more than men. The most common age at presentation is 40 to 50 years however, it has also been described in infants, children and elderly patients.[8]

Treatment for SIRD should include the discontinuation of all topical corticosteroids which usually leads to flare of the eruption. Anti-inflammatory oral antibiotics, topical clindamycin, topical erythromycin, topical metronidazole have been used as part of the treatment regimen.[9-11]

Isotretinoin is a Vitamin A analogue that has sebosuppressive, anti-inflammatory effects[12-14]. In this retrospective pilot study, the author presents the efficacy and tolerability of low dose isotretinoin in treating patients with SIRD during a 3 months treatment period.

Materials and Methods

A retrospective registry/ photographic analysis of 30 patients enrolled between Jan 2013 to Jan 2014 was done at Cutis academy. Case records and photographs of 30 patients between the age group of 15- 45 years clinically diagnosed with steroid induced rosacea on low dose oral isotretinoin 20mg alternate days for 3 months were analysed. Patients had been instructed to avoid topical corticosteroid use and other rosacea-aggravating substances including caffeine, spicy foods, alcohol, hot fluids. Oral antihistamines had been prescribed for symptomatic relief. Patient had not been taking oral antibiotics or any topical medications.

Patients were evaluated by a rosacea clinical score at weeks 0, 6, and 12 weeks. Investigator's global Assessment (IGA) of steroid –induced rosacea: seven point, static scoring system.

Numeric score	Definition	Description
0	Clear	No papules and/or pustules; no or residual erythema; no or mild telangectasia.
1	Minimal	Rare papules and /or pustules; residual to mild erythema; mild to moderate telangectasia.

2	Mild	Few papules and /or pustules; mild erythema to moderate telangectasia.
3	Mild to moderate	Distinct number of papules and/or pustules; mild to moderate erythema,mild to moderate telangectasia.
4	Moderate	Pronounced number of papules and/or pustules; moderate erythema, mild to moderate telangectasia.
5	Moderate to severe	Many papules and/or pustules, occasionally large inflamed lesions; moderate erythema; moderate telangectasia.
6	Severe	Numerous papules and/or pustules occasionally with confluent areas of inflamed lesions; moderate or severe erythema and telangectasia.

Average duration of steroid usage in these patients was 3 months and most of the patients had used mid potent steroids. Digital photographs of the face were obtained using identical camera settings and lighting conditions at each follow up session. Photographic assessment was done by a single non treating physician and were evaluated clinically for erythema, papules and pustules using Investigator's global Assessment .

All recorded data were entered using MS Excel software and analyzed using SPSS 22 version software for determining the statistical significance. Results are expressed in descriptive statistics. The data is scores, non-parametric tests are used for analysis. To compare the scores at two different point of time Wilcoxon Signed rank test is used. To compare the overall improvements from First visit to Third weeks of treatment Friedman's chi-square used. p-value of <0.05 was considered to be statistically significant.

Results :

A total of 30 patients (23females and 7 males) were enrolled in this study. The mean age of the study population was 30.1+/- 14.8 (14 to 45) years. Among the 30 patients, 2 dropped out due to side effects of treatment such as dryness and itching. According to seven point static score, Investigator global assessment of steroid induced rosacea eruption at baseline was 5.36+/- 1.1. This score decreased to 3.2 +/-0.8 at week 6, then 0.73 +/-0.6 at week 12.The difference of IGA between week 0, week 2, and week 6 was statistically significant.(p<0-0001) (fig1). At baseline

the 16 patients had ratings of 'severe' , 7 patients had ratings of 'moderate to severe', 2 patients had rating of 'moderate', 3 patients had rating of 'mild to moderate' .

The most common treatment-related cutaneous adverse events were chelitis , xerosis, photosensitivity and mild itching sensations. These complaints were reported by 7 of the 30 patients which led 2 of the patients to discontinue treatment. No other treatment-related serious adverse events were reported.

Table 1: Frequency Distribution Investigator's global Assessment (IGA) of steroid – induced rosacea of Study population in First Visit

First Visit		Frequency	Percent
Mild to moderate	3	3	10.7
Moderate	4	2	7.1
Moderate to severe	5	7	25
Severe	6	16	57.1
Total		28	100

Table 2: Frequency Distribution Investigator's global Assessment (IGA) of steroid – induced rosacea of Study population in Second visit (6^{th} week)

6^{th} week		Frequency	Percent
Minimal	1	3	10.7
Mild	2	3	10.7
Mild to moderate	3	10	35.7
Moderate	4	12	42.9
Total		28	100.0

Table 3: Frequency Distribution Investigator's global Assessment (IGA) of steroid – induced rosacea of Study population in Third Visit (12^{th} week)

12^{th} week		Frequency	Percent
Clear	0	15	53.6
Minimal	1	7	25.0
Mild	2	6	21.4
Total		28	100.0

Table 4: Descriptive Statistics of scores

Descriptive Statistics	First Visit	Second visit (6^{th} week)	Third Visit (12^{th} week)
n	28	28	28

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Minimum	3	1	0
Maximum	6	4	2
Mean	5.286	3.107	0.679
SD	1.013	0.994	0.818
Median	6	3	0
IQR (Q1-Q3)	5 – 6	3 – 4	0 – 1
Mode	6	4	0

Figure 1 : Graph wise distribution of treatment score at different time of visits

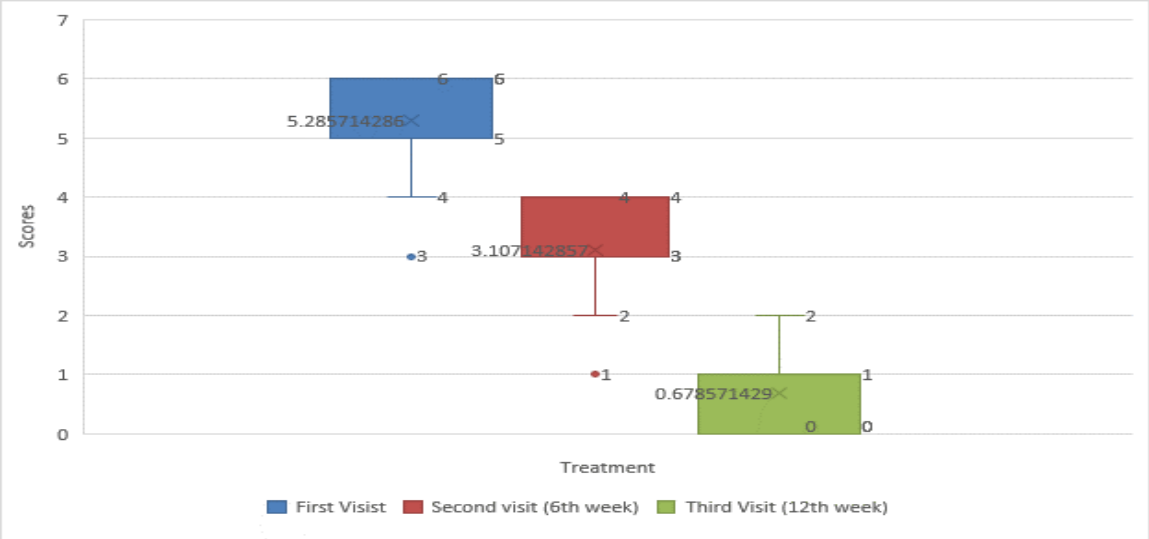

Table 5: Comparison of Scores from first visit to second visit of treatment

Visit	n	Min	Max	Mean	SD	Median	IQR	Wilcoxon Signed rank (z)	p-value
First Visit	28	3	6	5.286	1.013	6	5-6	- 4.963	< 0.05
Second Visit	28	1	4	3.107	0.994	3	3-4		

In First visit Median = 6 with IQR = 5-6, and after the Second visit Median = 3 with IQR = 3-4, Wilcoxon Signed rank (Z) = - 4.963 and p-value=0.000 <0.05, Therefore, there is a statistically significance difference.

Table 6: Comparison of Scores from first visit to third visit of treatment

Visit	n	Min	Max	Mean	SD	Median	IQR	Wilcoxon Signed rank (z)	p-value
First	28	3	6	5.286	1.013	6	5-6	- 4.675	0.000003
Third	28	0	2	0.679	1.013	0	0-1		

In First visit Median = 6 with IQR = 5-6, and after third visit Median = 0 with IQR = 0-1, Wilcoxon Signed rank (Z) = - 4.675 and p-value=0. .000003<0.05 . Therefore, there is a statistically significance difference.

Table 7: Comparison of scores from First visit to third visit of the treatment

Visit	Mean	SD	Median	IQR	Mean Rank	Friedman Test (chi-square)	df	p-value
First	5.286	1.013	6	5-6	3	56.0	2	< 0.05
Second	3.107	0.994	3	3-4	2			
Third	0.679	0.818	0	0-1	1			

The median with IQR in first visit was 6 (5-6), in second visit 3 (3-4) and in third visit 0 (0-1) with mean rank 3, 2, 1 in first, second and third visit respectively. There was a statistically significant difference in the treatment from first visit to third visit, Friedman's chi-square =56.0 with p=0.000 <0.05.

Discusssion :

Steroid-induced rosacea-like dermatitis(SIRD) is caused by prolonged use of topical steroids on the face. It is an uncomfortable and painful condition. The primary lesion in SIRD consists of pinpoint, red or flesh-colored papules, pustules or papulovesicles. Eventually, patients develop persistent and diffuse erythematous and edematous skin with numerous telangiectatic vessels. Based on location of eruption , there are 3 types of SIRD: perioral, centrofacial and diffuse. Patients experience a sensation of tightness, moderate stinging or burning, and dryness that can be intensely pruritic.[15,16]

The pathogenesis of SIRD and its rebound phenomenon is multifactorial but can be partially explained by several hypothesis. One hypothesis is that the immunosuppressive effects of a topical steroids, functional may facilitate the overgrowth of various bacteria, yeast, demodex mites, or other microorganisms in pilosebaceous glands, resulting in inflammatory reactions that produce papules and pustules. These microorganisms may subsequently act as superantigens. Withdrawal from use of topical steroids and their immunosuppressive effects then enables a superantigen-mediated immunologic response with an accompanying proinflammatory cytokine release .[17] Secondly, steroid induced rosacea like dermatitis has been described as intolerance reaction of seborrheic skin to topically applied steroids. The seborrheic type of skin seems to be an essential factor because in some experimental studies, application of potent steroids to healthy skin rich in sebaceous glands has resulted in typical rosacea-like symptoms.[8] The third hypothesis for steroid- induced rosacea like eruption is that the vasoconstrictive effect of corticosteroids inhibits the release of endothelium derived relaxing factor, a natural dialator. Vasoconstriction leads to build up of various metabolites,

including nitric oxide , a potent vasodialator. When the corticosteroid is no longer present the diameter of the vessels actually enlarge beyond their original diameter because of the accumulation of nitric oxide. This potentiates erythema, burning and itching seen in rebound

phenomenon of steroid induced rosacea like eruption.[17] However this hypothesis may not be supported by recent reports that described marked reduction in endothelial nitric oxide synthase and serum levels of nitric oxide metabolities in animals given long term glucocorticoid treatments.[18,19] Another theory postulates that topical steroids may inhibit collagen synthesis, leading to dermal atropy. The decrease in supporting connective tissue allows for the passive dilation of blood vessels and easier visualisation of dermal capillaries that clinically manifest as prominent telangectasia with background erythema.[8]

Role of oral low dose isotretinoin in treatment of steroid induced rosacea can be attributed to its sebosupressive, anti-inflammatory and also its role in decreasing the P.acnes population.[20] Isotretinoin induces cell cycle arrest apoptosis of sebocytes through what appears to be an RAR – independent mechanism. Neutrophils gelatinase associated lipocalin(NGAL), which functions in immune defense and induces apoptosis of murine B lymphocytes, was recently shown to mediate isotretinoin induced apoptosis.Isotretinoin was found to upregulate NGAL expression in sebaceous glands as well as cultured sebocytes. [21]
Since steroid-induced rosacea like dermatitis has been described as an intolerance reaction of seborrheic skin to topically applied steroids, oral isotretinoin can be a logical choice in SIRD.

Oral retinoids influence dermal components such as cutaneous capillaries and dermal inflammatory cells in addition to their well known action on keratinizing epithelia. In particular, they reduce elevated skin temperature, inhibit the motility of neutrophils and eosinophils and their migration into the epidermis, decrease DNA synthesis of human lymphocytes by blocking their response to lectins and stimulate Lngerhans cells, monocytes
and macrophages in various in vitro and in vivo models.[22] On this basis, they act as anti inflammatory drug. This supports the role of isotretinoin in treating inflammatory reaction that produce erythema, papules and pustules characteristic of steroid induced dermatitis.

In this study, we describe the efficacy of low dose oral isotretinoin 20mg on alternate days for a duration of 12 weeks in the treatment of steroid induced rosacea like eruption. There are various studies which supports the effectiveness of oral isotretinoin.

Amy et.al has studied that an average dosage of 2 to 5 mg daily (often given as a 10-mg dose 2 or 3 times weekly) for 3 months has been found to be effective in treating steroid induced rosacea.[8]

In another study M. Usla et al studied that 20 mg/day isotretinoin treatment significantly reduced papule/pustule counts and erythema in rosacea over a period of 4 weeks. Improvements in erythema and inflammatory lesion count was wee preserved when the dose was decreased to 2 mg once weekly.[20]

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An average dosage of 2 to 5 mg daily (often given as a 10 mg dose 2 or 3 times weekly) for 3 months has been found to be effective in steroid induced rosacea. Low dose isotretinoin has also been studied for acne rosacea, with doses of 10 mg per day demonstrating effectiveness in treating telangectasia, erythema, papules and pustules.[23] Continuos micro doses as low as 20 to 30mg per week after low daily doses of isotretinoin for 4 to 6 months also prevented relapse in rosacea patients.[24] These observations indicate that low dose isotretinoin might be useful for treating steroid – induced rosacea like eruption.

Conclusion :

In this study, we describe the efficacy of low dose oral isotretinoin 20mg on alternate days for steroid-induced rosacea-like eruption. Although 2 of the 30 recruited patients discontinued the treatment due to local side-effects of isotretinoin treatment, the remaining 28 patients all showed improvement of their rosacea symptoms as evidenced by decreased rosacea clinical score. Not only the erythema but also the papulopustular lesions in steroid-induced rosacea-like eruption improved after low dose isotretinoin therapy treatment. Low dose oral isotretinoin with cessation /avoidance of topical steroid use as well as the avoidance of other agents known to aggravate rosacea is proved to be an effective alternative mode of treatment of steroid rosacea like eruption. Further double-blind, vehicle-controlled studies are needed to confirm the efficacy and tolerability of low dose oral isotretinoin for the treatment of steroid-induced rosacea-like eruption.

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