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CLINICAL REPORT

Rosacea Treatment with Intermediate-dose Isotretinoin: Follow-up with Erythema and Sebum Measurements

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Isotretinoin is one of the therapeutic options for rosacea. However, the response of erythema to treatment with isotretinoin is usually slow and incomplete with common (0.5–1 mg/kg/day) or low (10 mg/day) doses. This study investigated the efficacy of, and relapse on, 20 mg/day isotretinoin treatment in rosacea, with the aid of instrumental measurement of facial erythema and sebum levels. A 20 mg/day dose of isotretinoin was given for 4 months, and then the dose was tapered off within the following 6 months. A total of 25 patients were included in the study. Papule and pustule counts, erythema index, sebum level, dermatologist's and patient's erythema scores, and dermatologist's sebum scores were significantly lower in the first month of therapy compared with pretreatment values ($p < 0.05$). Within a median follow-up of 11 months (95% confidence interval: 8.4–13.5 months) 45% of patients had a relapse. In conclusion, 20 mg/day isotretinoin was rapidly efficient for reducing both inflammatory lesions and erythema in rosacea. ***Key words: rosacea; isotretinoin; dose; erythema; sebum.***

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Rosacea is a common, chronic facial dermatosis characterized by intermittent periods of exacerbation and remission. There is no curative treatment for this disease. Important in the management of rosacea is the continuity of the improvement obtained with a well-tolerated therapy. This goal may be achieved by a low-dose, relatively long-term therapy with isotretinoin, which is one of the few medications that is capable of treating more than one subtype of the disease (1). In several studies isotretinoin has been found to be effective at relatively high doses, such as 0.5–1 mg/kg or 40–60 mg/day (2–5). However, the drug was poorly tolerated by these patients as it caused xerosis of the skin and conjunctivae (3, 5, 6). In the 1990s and 2000s, experiences with low-dose isotretinoin in 3 studies were published (7–9).

To define the severity of rosacea in clinical trials, investigators used a range of methods that were mostly clinical, including lesion counts, scales or global assessments. More sophisticated instruments, such as a photoelectric reflectometer to measure colour intensity, have been utilized in 4 studies, only one of which evaluated the efficacy of 1 mg/kg/day isotretinoin in rosacea (4, 10). The aim of the current study was to monitor the efficacy of intermediate-dose isotretinoin therapy (20 mg/day) on rosacea by using standard measuring instruments for erythema and sebum (Mexameter® and Sebumeter®, respectively), in addition to various clinical parameters including side-effects and remission time associated with this dose regimen.

MATERIALS AND METHODS

Rosacea patients who did not respond to, or showed a relapse with, at least one mode of topical or systemic treatment, and who had no contra-indication for isotretinoin use, were included in the study whatever their lesion count.

The study was approved by the local ethics committee and written informed consent was obtained from each participant.

All rosacea treatments were withheld for 4 weeks prior to enrolment. Blood samples were drawn for lipid profile, liver and kidney functions and complete blood cell count before and during the treatment. Patients with ophthalmic symptoms were evaluated by the consultant ophthalmologist. The isotretinoin treatment protocol was as follows: in the first 4 months 20 mg/day, followed by 20 mg per every other day for 2 months, 20 mg twice weekly for the next 2 months and 20 mg once weekly for the last 2 months. Each patient was examined before treatment and monthly thereafter. Participants were advised not to apply any topical agents, such as emollients and/or sun protection products, to their face in the last 2 days before the visits. During each visit papules, pustules and nodules were counted, erythema and sebum levels were evaluated by the patients and by one dermatologist on an 11-point scale of 0–10, and the erythema and the sebum level on the face were measured by the same dermatologist using a Mexameter® MX 18 and Sebumeter® SM 815 (Courage and Khazaka Electronic GmbH, Köln, Germany), respectively. In order to prevent observer bias, at each visit erythema and sebum levels were evaluated initially and subsequent Mexameter measurements were recorded rapidly without any evaluation on the dermatologist's part. Patients were asked to assess the severity of erythema and seborrhoea on the day of the control examinations. All measurements and assessments of erythema and sebum were made at the same time of day and under similar conditions (22–24ºC, 39–42% humidity). Measurements of erythema and sebum were made on the mid-parts of the forehead, cheek, chin and nose tip. The area evaluated did not include active inflammatory lesions. The mean of these 4 measurements was calculated for each patient.

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Sebumeter® SM 815 measurement

The Sebumeter affords direct photometric reading of the amount of lipids collected on a probe of opaque plastic strip after 30 s contact with the skin, and thus provides a measurement of the amount of lipids on the skin. This method of measuring sebaceous secretion, which has good repeatability and reproducibility, is based on the premise that lipids increase the transparency of opaque glass when in contact (11, 12). The transparency variation is measured by a photometer; recordable values lie between 0 and 350 μg/cm^2 and are referred to in this paper as the "sebum level" (SL).

Mexameter® MX 18 measurement

Erythema was measured photometrically using a Mexameter® 18, based on a remission principle. The special probe emits light of two defined wavelengths. One of these corresponds to the spectral absorption peak of haemoglobin. The other wavelength was chosen to avoid other colour influences (e.g. bilirubin). A receiver measures the light reflected by the skin. The "erythema index" (EI) was calculated by the instrument according to the formula: EI = 1000 log (red-remittance/green-remittance) (13). Results achieved could be in the range 0–999.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 14.0, with statistical significance set at $p < 0.05$. Mexameter and Sebumeter measurements were tested for normal distribution with the Kolmogorov–Smirnov test. All results showing normal distribution, monthly changes were compared by paired *t*-test. Descriptive statistics were given as mean ± standard deviation (SD). Wilcoxon's signed-rank test was used for within-subject comparisons of the patients' and dermatologist's erythema and sebum assessments and lesion counts, and descriptive statistics were given as medians. Correlation between the patient's and dermatologist's assessments and measurements was given as Pearson's correlation coefficients.

RESULTS

A total of 25 patients with papulopustular type rosacea were included in the study. Of these, 23 completed the 10-month treatment protocol; the remaining two patients were followed until the 8th and 9th months of therapy (Table SI; available from: http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1204). The two patients who dropped out of the study both reported that the hospital visits had become too much of an effort and had no medical complaints or findings preventing them from completing the study. There were 18 women and seven men; age range 28–65 years, mean age 46.2 ± 10.8 years. Disease duration ranged from 7 months to 25 years, with a mean of 4.8 ± 5.5 years. Five patients had received topical (metronidazole, azelaic acid, tetracycline) and 20 patients systemic (doxycycline, tetracycline) treatment for rosacea prior to isotretinoin therapy.

Before treatment the median count for papules was 9, pustules 1 and nodules 0. Pre-treatment values and monthly changes of EI, SL, and the scores during treatment can be seen in Figs 1–4. Papule and pustule counts (from 9 to 2 and from 1 to 0, respectively), EI, SL, dermatologist's erythema scores and sebum scores and patient's erythema scores were significantly lower in the first month of therapy compared with pre-treatment values (Figs 1–4, Table I). Significant decreases in papule counts (from 2 to 1.5) ($p = 0.038$) and in patient's erythema scores ($p = 0.01$) were also observed in the second month compared with the first month. After the second month of therapy, with the exception of the sebum level, none of the parameters mentioned above showed any statistically significantly differences compared with the previous month's values until the end of therapy.

Dermatologist's erythema scores were correlated both with patient's scores and EI in 10 out of the 11 evaluations. However, patient's erythema scores were correlated

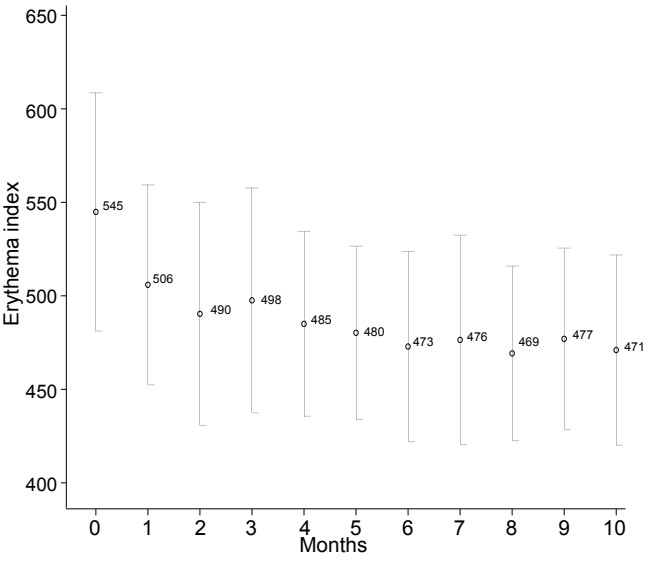

Fig. 1. Mean ± SD values of the erythema index (EI) measured by Mexameter® during therapy showing a significant decrease in EI in first month ($p = 0.002$, power: 0.77).

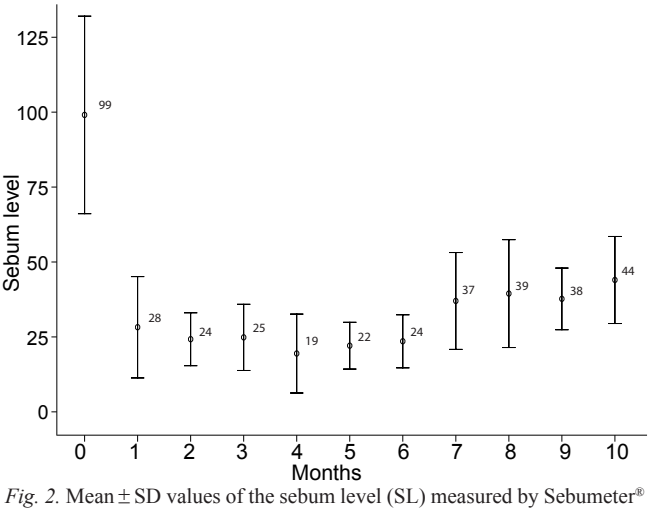

Fig. 2. Mean ± SD values of the sebum level (SL) measured by Sebumeter® during therapy showing a significant decrease in SL in first month ($p = 0.000$, power = 0.99).

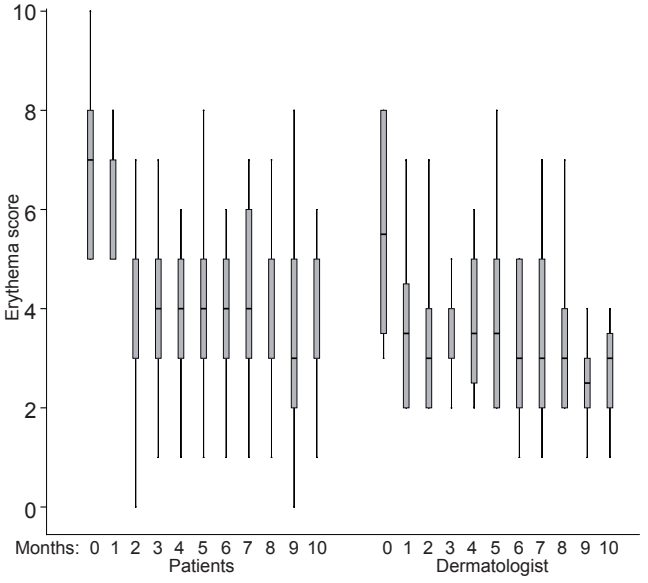

Fig. 3. Evaluation of dermatologist's and patient's median (range) erythema scores during therapy showing a significant decrease in scores in the first month [($p=0.000$, power:0.99) and ($p=0.042$, power=0.86), respectively]. Boxes include 25–75% values.

with the EI in only 3 evaluations. Dermatologist's sebum scores were correlated with SL in 8, and with patient's sebum scores in 3 evaluations whereas patient's scores were correlated in only 1 out of 11 evaluations with SL.

Follow-up findings

Isotretinoin treatment was continued in two of the 23 patients who had completed the 10-month study protocol (Table SI). One male patient requested continuation of therapy after completion of the 10-month protocol, as he was pleased to not have oily skin, on a dose of 20 mg once a week. In one female patient, disease progression was observed as the dose was lowered. Therefore she continued with a weekly 20 mg regimen in the 9th and 10th months and then switched to the same dose twice a week for a further 3 months instead of stopping the medication. The patient dropped out of the study at that time.

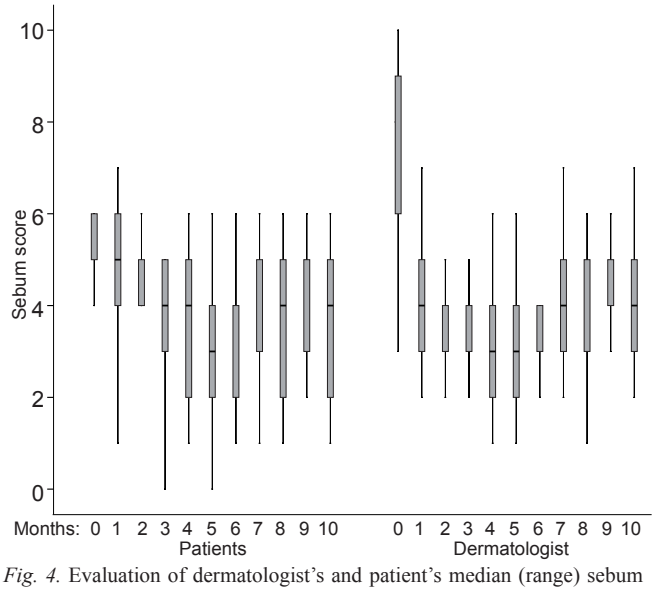

Fig. 4. Evaluation of dermatologist's and patient's median (range) sebum scores during therapy showing a significant decrease in dermatologist's scores in the first month ($p=0.000$, power=0.99). Boxes include 25–75% values.

For the remainder of the 21 patients, in whom the treatment could be stopped at the end of tenth month, the cumulative dose was 3,480 mg. A second course of isotretinoin therapy was needed in 4 patients; after remission times of 2, 3, 7 and 11 months. Various topical agents were given to another 5 patients, two of whom received cosmetics for erythema alone. The mean number of inflammatory lesions (papules and pustules) at restart of therapy with isotretinoin and topical agents were 7.5 ± 3.7 and 5.2 ± 4.8, respectively. In the group that did not require re-treatment 2.4 ± 2.8 lesions were present at the end of follow-up. Statistical analysis showed that, after a median follow-up of 11 months (95% CI: 8.4–13.5 months), 9 patients (45%) experienced a relapse, which was defined as the reappearance of, or significant increase in, rosacea symptoms (erythema and/or papulopustular lesions) (Table I). Patients showing relapse were not different by means of the disease duration and pre-treatment inflammatory lesion counts from those who were not showing relapse.

Adverse effects

Cheilitis was observed in 23 patients, in 4 of whom it was quite severe. Marked desquamation of the face was associated with severe cheilitis in 3 patients. In one patient the daily dose had to be reduced to "every other day" after 2 months instead of after 4 months due to this side-effect. Pruritic dermatitis, in the form of erythema with fine desquamation, developed in the forearms of two patients in the second and third months of therapy. One patient experienced exacerbation of the rosacea in the first month of therapy, which subsided in the next month. Although significant increases were seen in serum triglyceride and cholesterol levels in patients who had normal pretreatment triglyceride ($n=20$) and cholesterol levels ($n=16$) ($p=0.004$ and $p=0.023$, respectively), this side-effect was successfully managed by dietary measures alone or the use of an antilipidaemic medication (atorvastatin, 20 mg/day) in only two patients. No significant further increases in lipid profile were observed in participants who were already hyperlipidaemic before initiation of the study.

DISCUSSION

Isotretinoin is an established therapy in the management of rosacea. The efficacy of the drug has been attributed to its sebosuppressive (2, 7) and anti-inflammatory ef-

Table I. *Median inflammatory lesion counts and outcomes of the patients during isotretinoin therapy (*n = *23–25)*

Dose level		I				II		III		IV			
Months	M0	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	Follow-up[a]	Relapse
Counts	11	2	2	2	1	0	0	0	0	0	1	11	45%

[a]median of the months.

I: 20 mg/day; II: 20 mg/every other day; III: 20 mg twice a week; IV: 20 mg/week.

Note: Papule and pustule counts were significantly lower [(p=0.000, power=0.99) and (p=0.001, power=0.96), respectively] in the first month of therapy compared with the results of pre-treatment.

fects (8). The effectiveness of isotretinoin in rosacea has been shown in several studies of doses of 0.5 mg/kg or more (2–5). Promising results with low-dose isotretinoin have also been reported (7–9). However, in all of these reports disease severity was only determined clinically, with no instrumental measurements being used. In addition, the remission rate with the low-dose regimen has been reported in only one study (7).

The lack of consensus with regards to the assessment of severity of rosacea is an important issue that requires further investigation (14, 15). One of the objectives of this study was to evaluate the benefit of utilizing measuring device in the follow-up of rosacea.

The results show that 20 mg/day isotretinoin treatment significantly reduced papule/pustule counts and erythema in rosacea over a period of 4 weeks. Although not statistically significant, a further decrease in EI was observed until the fifth month. Improvements in erythema and inflammatory lesion count were preserved when the dose was decreased to 20 mg once weekly. A well-known effect of isotretinoin, sebum suppression, was also rapidly observed. Side-effects of 20 mg/day isotretinoin in rosacea patients, xerosis and hyperlipidaemia, were minor and well-tolerated. Xerosis was prominent in 4 of 25 patients. Patient compliance with the regimen was good.

There are very few reports of low-dose isotretinoin use for rosacea, two of which are studies evaluating the efficacy of 10 mg/day (7, 8). A third report is of a dose of 10 or 20 mg/day in 12 patients (9). The latter dose, 20 mg/day, may be called an "intermediate dose".

In our study 20 mg/day isotretinoin significantly decreased lesion counts in the first month. This immediate effect on papules and pustules is well known with 0.5–1 mg/kg/day dose (3), however with a 10 mg/day isotretinoin dose, this efficacy was only seen as late as the ninth to 16th weeks of treatment (7, 8). Although never completely eradicated during treatment, a significant improvement in erythema was also observed in our study in the first month. In trials with 10 mg/day isotretinoin, the earliest reduction in erythema was observed by the ninth to sixteenth week (7, 8), indicating a slower effect achieved with 10 mg/day. On the other hand, doses higher than 20 mg/day also showed a slow effect on the resolution of erythema (3–5). Marsden et al. (4) speculated that an irritancy-related erythema resulting from the xerosis caused by 1 mg/kg isotretinoin could replace the erythema of rosacea and prevent early resolution of this symptom. Perhaps an intermediate dose of 20 mg/day may be preferred to both lower and higher doses for more rapid relief of erythema. This dose also seems to be effective as rapidly as the higher doses in reducing the inflammatory lesions.

Within a mean follow-up time of 11 months, 45% of our patients underwent relapse. Longer remission times have been reported with higher isotretinoin doses (0.5–1 mg/kg, for 3–6 months) (3). Similar to the acne, remission times in rosacea may be related to the cumulative dose. With a treatment regimen of 10 mg/day isotretinoin for 4 months, Ertl et al. (7) observed that a 75% decrease in papulopustular lesion count and 38% decrease in erythema were preserved at 4 months of follow-up. Hofer's use of the continuous "micro-dose" isotretinoin showed that a dose of 34.2 mg/week kept the disease under control (9). He observed immediate recurrence when the individually determined dose was stopped. Nevertheless, this regimen provided lower DLQI scores in patients.

Instrumental evaluation of rosacea symptoms

Use of the Mexameter confirmed the dermatologist's observation of the significant decrease in erythema. Correlation of the instrument's values with the dermatologist's scores was better than the ones with the patient's scores, reassuring the dermatologist's clinical evaluation.

Patients' sebum scores correlations with the dermatologist's scores and with the SL were found to be rather poor. Some other authors also found discrepancies between subjective assessment of sebum and amount of sebum excretion (16, 17). Compared with the dermatologist's assessment, the Sebumeter enabled earlier detection of an increase in sebum levels and was thus helpful in better evaluation of the dose-dependent course.

In conclusion, isotretinoin 20 mg/day was effective in reducing rosacea symptomatology starting from the first month of therapy. The drug was well tolerated and no relapse was observed in more than half of the patients in the 11 months of follow-up. This study is the first to present data about relapse with 20 mg/day isotretinoin in rosacea. Further research is required into whether the cumulative dose had an effect on relapse.

The present study is also the first to use the Mexameter and Sebumeter to evaluate the efficacy of the isotretinoin in rosacea. Patient's assessments of erythema and sebum on a scale of 0–10 may not be sufficiently valid for evaluation and/or monitoring of the disease. Use of standard instruments may help doctors and investigators to make more accurate and objective evaluations in patients with rosacea.

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The authors declare no conflicts of interest.

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