

Very low dose isotretinoin is effective in controlling seborrhea

Niedrig dosierte Isotretinoin-Therapie ist wirksam bei Seborrhö

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Schlüsselwörter

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Summary

Background: Excessive seborrhea, coarse-pored skin, minimal acne and oily scalp hair comprise a well-known clinical entity. It causes considerable concern, has social impact, and affects the quality of life in some individuals. Some patients seek treatment for seborrhea. No effective topical sebosuppressive medication is available. Oral isotretinoin is the only remedy for men. In women, oral isotretinoin is the most effective remedy, followed by antiandrogens.

Patients and methods: Eleven patients in three groups were treated for 6 months with very low dose isotretinoin. The influence on seborrhea was measured during oral treatment with 5 mg/d, 2.5 mg/d, or 2.5 mg 3× weekly.

Results: Sebum production, measured with Sebutape®, was reduced by up to 64%. Acne lesions regressed by as much as 84%. Follicular filaments were reduced by 66%. Microcomedones were reduced on average up to 86%. Quantitative bacteriology showed a reduction of *Propionibacterium acnes* but no increase of *Staphylococcus epidermidis*. Biopsies revealed a 51% reduction in sebaceous gland size. With Bentonite™, a reduction of lipids was demonstrated with 2.5 and 5 mg isotretinoin/d but not with 2.5 mg 3× weekly. There was a shift within the lipid fractions: triglycerides dominated, followed by squalenes and free fatty acids.

Conclusions: Good results were achieved in all patients. The small number of patients did not permit a statistical analysis of the three isotretinoin doses studied, but there was a tendency toward better results with the two higher doses.

Zusammenfassung

Hintergrund: Ausgeprägte Seborrhö, grobporige Haut, geringfügige Akne und fettiges Kopfhaar sind eine wohl bekannte Entität. Diese sollte Beachtung finden, da sie eine soziale Bedeutung hat und die Lebensqualität einiger Patienten beeinflusst. Teilweise konsultieren Patienten nur wegen der Seborrhö den Arzt. Keine effektive topische sebosuppressive Therapie steht zur Verfügung. Das einzig wirksame Mittel neben hormoneller Kontrazeption ist orales Isotretinoin.

Patienten und Methodik: Elf Patienten wurden in drei Gruppen jeweils über sechs Monate hinweg mit 13-*cis*-Retinsäure in sehr niedriger Dosierung behandelt. Bei oraler Gabe von 5 mg/Tag, 2,5 mg/Tag oder 2,5 mg 3mal wöchentlich wurde der Einfluss des Wirkstoffs auf starke Seborrhö untersucht.

Ergebnisse: Die mit Hilfe der Sebutape®-Methode gemessene Sebumproduktion verringerte sich im Laufe der Therapie im Gruppenschnitt um bis

zu 64 %. Akneeffloreszenzen nahmen bis zu 84 % ab. Follikelbiopsien ergaben einen mittleren Rückgang der Follikelfilamente bis zu 66 %. Die Zahl der Mikrokomedonen nahm durchschnittlich bis zu 86 % ab. Bakteriologische Untersuchungen ergaben eine Reduktion der Propionibakterien aber keine Zunahme von *Staphylococcus epidermidis*. Die Biopsien zeigten bis zu 51 % Reduktion des Talgdrüsengewebes. Mittels Bentonite™ konnte eine Reduktion der Lipide bei 2,5 mg und 5 mg Isotretinoin/Tag, nicht aber bei 2,5 mg 3mal wöchentlich nachgewiesen werden. Innerhalb der Lipidfraktionen gab es eine Verschiebung, prozentual machten die Triglyzeride den größten Teil aus, gefolgt von den Squalenen und freien Fettsäuren.

Schlußfolgerungen: Die Therapie zeigte bei fast allen Patienten gute Ergebnisse. Die Zahl der Patienten war nicht groß genug, um signifikante Ergebnisse zu erreichen. Es konnte keine deutliche Dosisabhängigkeit festgestellt werden, jedoch zeigte sich eine Tendenz zu günstigeren Resultaten in den beiden Gruppen höherer Dosierung (2,5 mg/Tag und 5 mg/Tag).

Disclosure

None of the three authors has had any commercial affiliation, neither currently nor over the past 10 years.

Introduction

Seborrhea is a common concern of acne patients and post-acne adults. Additionally, there is frequently minimal residual acne, especially of the face. Residual acne is difficult to define as there is no uniformly accepted terminology. It is a heterogeneous mixture of small papules, minimal folliculitis, and large-pored sebaceous follicles filled with either follicular filaments or showing early microcomedone formation.

Such patients with annoying seborrhea of face and scalp coupled with residual minimal acne often receive no appropriate treatment. The facial lesions are not severe enough to warrant a regular dose of oral isotretinoin or a course of systemic antibiotics. Furthermore, antibiotics are often not helpful. Such patients often have gone through a long list of topical remedies including adapalene, isotretinoin, tretinoin, antibiotics, benzoyl peroxide, and combinations thereof.

We therefore decided to treat such patients with a very low dose of oral isotretinoin for 6 months irrespective of their bodyweight. Multiple evaluations including clinical inspection and laboratory testing, not performed in a previous group of patients, were carried out.

Materials and Methods

Eleven patients were treated in our acne clinic. Four patients received 5 mg iso-

tretinoin daily, five patients 2.5 mg daily, and two patients 2.5 mg 3x weekly irrespective of bodyweight for 6 months. Isotretinoin was available as 2.5 mg capsules (Roaccutan®).

Ten patients reported having had acne during puberty and oily skin ever since. Ten patients had used multiple topical and systemic acne treatments, while four had received at least one course of oral isotretinoin.

At the start of this treatment, none of the patients had been on oral isotretinoin within the previous 4 months, or on oral antibiotics or topical acne therapy within the previous 4 weeks.

Women were thoroughly informed about the teratogenicity of oral isotretinoin. All precautions and safety measures, well documented in the literature and by the manufacturer, were strictly followed.

All women were on oral contraceptives when we first saw them. Despite hormonal replacement for more than 6 months, they had persistent seborrhea and minor acne. For those who wished to use facial cosmetics, the following items were provided for use *ad libitum*, but no other topical treatment was allowed: Neurogena® clear facial soap, Dermatop® Basis Cream, Roc® Fond de

Table 1: Timing of clinical and laboratory tests.

Tabelle 1: Zeitplan der klinischen Untersuchungen und Labortests.

| | Before Rx | Month | | | |
|-------------------------------|-----------|-------|---|---|---|
| | | 0.5 | 2 | 4 | 6 |
| Seborrhea grading | + | | + | + | + |
| Sebutape® | + | | + | + | + |
| Bentonite™ | + | | + | + | + |
| Cyanoacrylate | + | | + | + | + |
| Biopsy | + | | | | + |
| Bacteriology | + | | + | + | + |
| Lesion count | + | | + | + | + |
| Blood count, Chemistry | + | + | + | + | + |
| Side effects | | + | + | + | + |

teint hydratant fluid as a facial cover, unguentum molle for dry lips.

Lesion Count

All noninflammatory and inflammatory lesions on the left side of the face were counted by two physicians and expressed as medians (Tables 1 and 10).

Blood Count, Chemistry

Fasting values were determined 5 times (Table 1) – cholesterol, triglycerides, alkaline phosphatase, GOT, GPT, gamma-GT, alpha-amylase, bilirubin, complete blood count.

Grading of Seborrhea

Facial seborrhea and scalp hair oiliness were graded subjectively by the patient and objectively by the physicians 4 times (Tables 1, 2). The degree of severity was graded on an arbitrary scale from 6 to 1 (6 = highest grade of seborrhea/oiliness; 1 = nil).

Sebum Analysis

Sebutape®

This technique is used to measure the excretion of sebum from follicular infundibula and sebaceous ducts. It is described in detail elsewhere [1]. In short, a hydrophobic polymer film (Cuderm Corporation, Dallas, USA; or Hermal Pharmaceutic Laboratory, Oak Hill, USA) was placed on the left side of the forehead for 1 h, then fixed with formaldehyde steam for 7 min. The Sebutape® was mounted on black cardboard and photographed at standard magnification. The measurement equates sebum excretion, expressed as follicles per cm²; sebum excretion rate (SER) per follicle in arbitrary units (AU) per cm²/h; and total sebum excretion rate (TSER) in AU/cm²/h. A computerized technique was used (S.K.I.N. Inc., Conshohocken, USA).

Bentonite™

Sebum was collected on four occasions (Table 1) with clay in 10% ethanol with 0.2% carboxymethylcellulose over a 3.5 × 2.5 cm area on the right side of the forehead. Details of this technique are described elsewhere [2]. Lipids were extracted and gravimetrically assayed on a precision scale (quantitation), and lipid composition was qualitatively analyzed by high-power thin-layer chromatography (HPTLC). Lipid extraction fol-

Table 2: Degree of seborrhea of face and scalp. Subjective rating on an arbitrary scale from 6 to 1 (6 = severe; 1 = nil).

Tabelle 2: Grad der Seborrhö von Gesicht und Kopfhaut. Subjektive Bewertungsskala von 6 bis 1 (6 = stark; 1 = keine).

| | Isotretinoin Dose mg | Degree of Seborrhea | | Regression % |
|------------------|----------------------|---------------------|---------|--------------|
| | | Grades 6 to 1 Mean | | |
| | | Month 0 | Month 6 | |
| F A C E | 5/d | 5.0 | 1.5 | 70 |
| | 2.5/d | 5.0 | 2.8 | 44 |
| | 2.5/3× week | 5.5 | 4.0 | 27 |
| H A I R | 5/d | 4.5 | 2.3 | 49 |
| | 2.5/d | 4.8 | 3 | 38 |
| | 2.5/3× week | 5 | 3.5 | 30 |

lowed a modified Folch technique [3]. Controls included Soxhlet analysis. Chromatography employed a CAMAG TM Linomat IV (Muttentz, Switzerland). Lipid extracts were placed on HPTLC plates and quantitated using a CAMAG TM-TLC scanner II and CAMAG TM CAT S3 software [4].

Bacteriology

The technique of *Williamson and Kligman* [5] was used 4 times (Table 1). Sterile glass cylinders of 2.2 cm in diameter were held onto the left cheek, and buffered 0.1% Triton-X-100 was used. From pooled samples, agar plates were incubated for aerobes, and tripticase soy

Table 3: Sebutape®. Sebum excretion rate (SER) in arbitrary units (AU/cm²/h). Means and standard deviation.

Tabelle 3: Sebutape®. Sebum Exkretionsrate (SER) in willkürlichen Einheiten (arbitrary units) (AU/cm²/h). Mittelwert und Standardabweichung.

| Isotretinoin | | Sebum Excretion Rate in Arbitrary Units per cm ² /h | | | |
|--------------|----|--|----|----|----|
| | | SER (AU)/cm ² /h | | | |
| | | Months | | | |
| Dose mg | | 0 | 2 | 4 | 6 |
| 5/d | M | 67 | 30 | 32 | 33 |
| | SD | 31 | 8 | 14 | 15 |
| 2.5/d | M | 143 | 55 | 79 | 52 |
| | SD | 66 | 56 | 80 | 34 |
| 2.5/3× week | M | 105 | 64 | 41 | 43 |

Table 4: Bentonite™ clay technique and HPTLC. Percent lipids before treatment. Means and standard deviations, but no confidence intervals.

Tabelle 4: Bentonite™ und HPTLC. Prozentuale Lipidverteilung vor Therapie. Mittelwert und Standardabweichung, keine Konfidenzintervalle.

| Isotretinoin Dose mg | Chol | FFA | TG | Chol Est | SQ | n-Alk |
|----------------------|-------------|---------------|---------------|---------------|-------------|--------------|
| 5/d | 1.87 ± 1.31 | 25.28 ± 10.19 | 35.30 ± 8.85 | 15.26 ± 12.67 | 0.65 ± 1.21 | 21.07 ± 7.46 |
| 2.5/d | 1.97 ± 1.32 | 26.48 ± 9.18 | 38.72 ± 10.73 | 13.65 ± 5.95 | 2.44 ± 4.86 | 18.29 ± 9.65 |
| 2.5/3× week | 1.80 | 23.89 | 36.85 | 12.38 ± | 1.73 | 22.74 |
| M ± SD | 1.90 ± 1.30 | 25.57 ± 9.38 | 37.14 ± 10.06 | 14.01 ± 8.95 | 1.66 ± 4.15 | 20.11 ± 8.79 |

Chol = cholesterol; Chol Est = cholesterol esters; FFA = free fatty acids; n-Alk = n-alkanes; SQ = squalene; TG = triglycerides

agar plates for anaerobes. The number of bacteria per cm² was calculated separately for staphylococci (Bio Mérieux) and anaerobes (Rapid ANA II system). A semilogarithmic scale of median was used.

Cyanoacrylate

Follicular biopsies were obtained 4 times (Table 1) from the right cheek of patients by using superpotent glue (Praktikus R No 708 OL11) according to the method of Marks and Dauber [6]. With this technique, the superficial portion of the stratum corneum and follicular filaments (casts) and vellus hairs are re-

moved. Eukitt® embedded specimens were evaluated microscopically, using a fixed circular area of 0.7 cm in diameter (0.38 cm² circle): follicular filaments with 1 to 2 hairs; microcomedones with 2 to 4 hairs; and vellus hairs (1 hair only). The data are expressed as n/cm².

Biopsies

Before and after 6 months of therapy, 3-mm biopsies were secured from the right temple, formalin-fixed, and stained with hematoxylin and eosin. Sebaceous gland size was measured using a computer-generated fine network of horizontal and vertical lines following the

guidelines of Bahmer and Körner [7], allowing a very precise determination of surface area (Table 1).

Side Effects

Subjective and objective side effects were recorded at each visit (Table 1).

Statistics

The small number of patients did not permit the use of standard analysis. Wherever applicable, means, medians and standard deviations are provided. It is emphasized that the data are meant to be descriptive.

Results

Grading of Seborrhea

All patients reported a decrease in both seborrhea of facial skin and scalp hair oiliness with ongoing treatment. The subjective data are shown in Table 2. It was one of the purposes of the study to examine this particular parameter. The decrease of seborrhea seemed to follow a dose response.

Sebutape®

All patients in the three groups had fewer lipid-producing follicles, expressed as sebum excretion rate per arbitrary unit per cm²/h (Table 3) or total sebum excretion rate in AU/cm²/h (data not shown).

Bentonite™

Lipids extracted from clay before and at the end of treatment showed a reduction

Table 5: Bentonite™ clay technique and HPTLC. Summary of % change of lipids after treatment.

Tabelle 5: Bentonite™ und HPTLC. Prozentuale Veränderung der Lipidverteilung nach Therapie.

| Isotretinoin Dose mg | Chol | FFA | TG | Chol Est | SQ | n-Alk |
|----------------------|------|-----|-----|----------|-----|-------|
| 5/d | +18 | -30 | -33 | +20 | -60 | +35 |
| 2.5/d | + 5 | +20 | - 9 | - 8 | -65 | +61 |
| 2.5/3× week | +22 | +25 | -17 | - 6 | -40 | - 8 |

Chol = cholesterol; Chol Est = cholesterol esters; FFA = free fatty acids; n-Alk = n-alkanes; SQ = squalene; TG = triglycerides; + = % increase over pretreatment values; - = % decrease over pretreatment value

Table 6: Cyanoacrylate skin surface biopsy. Follicular filaments and microcomedones before and during treatment with three isotretinoin doses. Means and standard deviations.

Tabelle 6: Cyanoacrylat-Oberflächenbiopsie. Follikelfilamente und Mikrokomedonen vor und während der Therapie mit drei Isotretinoindosierungen. Mittelwert und Standardabweichung.

| Isotretinoin Dose mg | Type of Lesion | | Month | | | | Reduction % |
|----------------------|----------------------|----|-------|-----|-----|-----|-------------|
| | | | 0 | 2 | 4 | 6 | |
| 5/d | Follicular filaments | M | 161 | 107 | 108 | 105 | 35 |
| | | SD | 102 | 85 | 70 | 73 | |
| | Microcomedones | M | 36 | 15 | 8 | 14 | 62 |
| | | SD | 24 | 16 | 8 | 15 | |
| 2.5/d | Follicular filaments | M | 86 | 53 | 49 | 29 | 66 |
| | | SD | 36 | 16 | 40 | 11 | |
| | Microcomedones | M | 18 | 12 | 8 | 3 | 86 |
| | | SD | 6 | 8 | 4 | 2 | |
| 2.5/3× week | Follicular filaments | M | 47 | 42 | 47 | 37 | 22 |
| | Microcomedones | M | 8 | 5 | 5 | 3 | 67 |

Table 7: Evaluation of sebaceous gland biopsies from the right temple in mm² per mm epidermal surface before and at the end of a 6-month therapy with three different doses of isotretinoin. Regression expressed as difference in %. Means and standard deviations.

Tabelle 7: Messungen der Talgdrüsengröße von der rechten Schläfe in mm² pro mm Hautoberfläche vor Therapie und am Therapieende nach 6 Monaten mit drei Isotretinoindosierungen. Regression als prozentuale Differenz ausgedrückt. Mittelwert und Standardabweichung.

| Isotretinoin Dose mg | | Month | | Difference % |
|----------------------|----|-------|------|--------------|
| | | 0 | 6 | |
| 5/d | M | 0.41 | 0.27 | 29.75 |
| | SD | 0.18 | 0.12 | |
| 2.5/d | M | 0.50 | 0.35 | 30.20 |
| | SD | 0.20 | 0.15 | |
| 2.5/3× week | M | 0.37 | 0.16 | 51.50 |

with 5 mg and 2.5 mg isotretinoin, but not with 2.5 mg 3× weekly. A dose-related lipid reduction was observed. In the group on 5 mg isotretinoin/day, a 60 % reduction of the lipids was achieved (from 0.66 to 0.26 µg). In the group on 2.5 mg isotretinoin/day, a 22 % reduction of the lipids was achieved (from 0.46 to 0.35 µg). In the group on 2.5 mg isotretinoin 3× weekly, only a 3 % reduction of lipids was achieved.

The qualitative lipid composition before treatment is shown in Table 4. This demonstrates the accuracy of the Bentonite™ technique coupled with HPTLC.

The qualitative lipid changes after 6 months of therapy are given in Table 5. There was a relative increase in cholesterol and a decrease in triglycerides and squalenes.

Cyanoacrylate

Follicular filaments are possible precursors of comedones. Typically, they are present in high numbers in acne-prone areas of the skin (Table 6). In this study, follicular filaments regressed with treatment. The same was observed for microcomedones (Table 6).

Biopsies

In all patients, sebaceous gland size regressed with treatment (Table 7).

Bacteriology

The two common types of facial resident flora were identified, staphylococci and *Propionibacteria*. Details for *Staphylococcus epidermidis* are given in Table 8. No increase of this organism was found.

In contrast, *Propionibacterium acnes* was reduced by logarithmic numbers with 5 mg and 2.5 mg isotretinoin. Counts for the lower dose of 2.5 mg 3× weekly were very low to begin with and are reported only for accuracy (Table 9).

Lesion Count

With 5 mg isotretinoin, the noninflammatory lesions regressed from 16.6 to 4.7 (−72 %) and inflammatory lesions from 6.0 to 1.0 (−84 %) after 6 months (Table 10). With 2.5 mg isotretinoin, the figures were 6.3 to 2.3 (−64 %) and 3.0 to 2.8 (−8 %) (Table 10). With 2.5 mg isotretinoin 3× weekly, the figures were 8.0 to 3.0 (−64 %) and 8.0 to 12.0 (+15 %) (Table 10).

Blood Count, Chemistry

No abnormalities were seen before or during treatment in all three groups for any of the parameters. Particularly cholesterol and triglycerides remained within normal limits.

Side effects

Pharmacological effects were observed for all three doses. These were minimal compared to those seen in other patients on higher doses of isotretinoin, when 0.5–1.0 mg/kg are used. Dry facial skin was seen (objectively) or reported (subjectively) in all patients, as was the typical retinoid-associated cheilitis or dry vestibulitis. Dryness was mild and easily controlled by the emollients provided to the patients.

Retinoid-associated facial redness was seen in 8/11 patients, dryness of eyes and conjunctivitis in 3/11 patients, mostly seen in the 5 mg/d isotretinoin group and to a lesser degree in the 2.5 mg/d group. Neither side effect was reported with 2.5 mg 3× weekly.

Discussion

Two key messages can be found. First, very low dose isotretinoin is effective in controlling seborrhea and improves persistent facial follicular lesions. Isotretinoin improves many parameters, providing a smooth and almost lesion-free skin with which patients are universally satisfied. Second, this amount of isotretinoin does not lead to major changes in blood chemistry and other laboratory tests.

Teratogenicity remains a problem. Isotretinoin, like all other retinoids, is teratogenic. There are no exceptions to this rule. It is presently unknown if there is a cut-off at very low doses.

The established Sebutate[®] technique and the more sophisticated Bentonite[™] technique were suitable to demonstrate lipid inhibition. This confirms previous work from clinical studies [8], from experimental work with comedonal lipids [9] and also from *in vitro* studies using cultivated sebocytes [10]. Where the cut-off values are remains open for discussion. The lowest dose of 2.5 mg 3× weekly had some sebosuppressive effects. In another study, similar very low doses of 0.5 mg isotretinoin daily were used. Histologically and with sebum analysis, suppressive effects on sebaceous glands were shown (unpublished personal data).

The precursor lesions of acne and persistent mild acne or acne-like lesions improved, as could be shown with the cyanoacrylate technique. Morphometric analysis of sebaceous glands from facial biopsies attested the efficacy of isotretinoin to reduce the sebocyte population

and their lipid production. Bacteria are only indirectly inhibited by isotretinoin, *Propionibacteria* more so than *Staphylococcus epidermidis* [8]. Precisely this happened with the very low isotretinoin doses used in this study.

Table 8: *Staphylococcus epidermidis* colony forming units (cfu) per cm² skin surface (left cheek) before and during treatment with three doses of isotretinoin. No persistent change. Means and standard deviations.

Tabelle 8: *Staphylococcus epidermidis*. Koloniebildende Einheiten (cfu) pro cm² Hautoberfläche (linke Wange) vor und während der Therapie mit drei Isotretinoindosierungen. Keine persistente Verminderung. Mittelwert und Standardabweichung.

| Isotretinoin Dose mg | | Month | | | |
|----------------------|----|---------|-----------|-----------|-----------|
| | | 0 | 2 | 4 | 6 |
| 5/d | M | 2.105 | 697.103 | 996.947 | 1.399.737 |
| | SD | 2.105 | 1.045.161 | 1.562.224 | 2.367.309 |
| 2.5/d | M | 379.158 | 217.895 | 115.263 | 134.105 |
| | SD | 517.647 | 140.186 | 88.485 | 95.767 |
| 2.5/3× week | M | 522.895 | 528.947 | 605.263 | 544.737 |

Table 9: *Propionibacterium acnes*. Colony forming units (cfu) per cm² skin surface (left cheek) before and during treatment with three isotretinoin doses. Reduction on a logarithmic scale with the two higher doses, but not with the lowest dose. Means and standard deviations.

Tabelle 9: *Propionibacterium acnes*. Koloniebildende Einheiten (cfu) pro cm² Hautoberfläche (linke Wange) vor und während der Therapie mit drei Isotretinoindosierungen. Logarithmische Reduktion bei den beiden höheren Dosierungen, nicht bei der niedrigsten Dosierung. Mittelwert und Standardabweichung.

| Isotretinoin Dose mg | | Months | | | |
|----------------------|----|------------|------------|-----------|---------|
| | | 0 | 2 | 4 | 6 |
| 5/d | M | 4.689.474 | 11.057.987 | 3.567.921 | 270.921 |
| | SD | 7.928.377 | 12.374.619 | 6.138.445 | 199.652 |
| 2.5/d | M | 9.462.842 | 6.600.021 | 4.691.052 | 568.428 |
| | SD | 14.395.289 | 12.754.201 | 8.188.777 | 465.297 |
| 2.5/3× week | M | 97.842 | 55.263 | – | 737 |

– = data not available

Table 10: Lesions (mean) before and at end of treatment for comedones (noninflammatory) and papules/pustules (inflammatory). The 5 mg dose of isotretinoin is more effective than the 2.5 mg dose. No consistent results were obtained with the lowest dose (2.5 mg 3× weekly).

Tabelle 10: Hautläsionen (Mittelwert) vor und nach Therapie für Komedonen (nicht-entzündlich) und Papeln/Pusteln (entzündlich). 5 mg Isotretinoin ist wirkungsvoller als 2,5 mg Isotretinoin täglich. Die niedrigste Dosierung (2,5 mg an drei von sieben Tagen) zeigte keine konstanten Ergebnisse.

| Isotretinoin Dose mg | Lesion Type | Lesion Count | | Reduction % |
|----------------------|------------------|--------------|---------|-------------|
| | | Month 0 | Month 6 | |
| 5/d | Non-inflammatory | 16.6 | 4.7 | 72 |
| | Inflammatory | 6 | 1 | 84 |
| 2.5/d | Non-inflammatory | 6.3 | 2.3 | 64 |
| | Inflammatory | 3 | 2.8 | 8 |
| 2.5/3× week | Non-inflammatory | 8.0 | 3.0 | 64 |
| | Inflammatory | 8.0 | 12.0 | +15 |

Quantitation of facial lesions demonstrated effectiveness at least for the 5 mg and 2.5 mg isotretinoin dose per day, but not for the 2.5 mg dose 3× weekly.

Side effects were minimal and presented no reason for any of the patients to stop the 180 days of oral treatment.

Therapy must be discussed in the context of pharmaco-economic considerations. Today, as isotretinoin has become less expensive, very low doses mean that treatment is reasonably economical. It would be of interest to compare these costs with other treatment regimens, but this was not the purpose of the present study. Very low dose treatment recommendations mandate adequate formulations and the reintroduction of much smaller capsules, as were previously available. <<<

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