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Arotinoid Ro 13-6298 and Etretin: Two New Retinoids Inferior to Isotretinoin in Sebum Suppression and Acne Treatment

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Thirty patients have been treated with either etretin, the main derivative of etretinate, or arotinoid Ro 13-6298, a polyaromatic retinoid, or isotretinoin. Sebum production was measured before and during the treatments. While no change was observed in the patients treated with etretin, a reduction of 33% of the sebum excretion rate was observed for those treated with arotinoid Ro 13-6298 but only after long treatment periods of 20 to 30 weeks. The sebum excretion rate decreased by 92% in the patients treated with isotretinoin. Four patients suffering from severe nodulocystic acne were treated with arotinoid Ro 13-6298 for 2–5 months without improvement. Substantial improvement, however, resulted after a subsequent treatment with isotretinoin; sebum production decreased markedly as well. This study suggests that neither etretin nor arotinoid Ro 13-6298 will replace isotretinoin in the treatment of severe nodulocystic acne. (Received September 6, 1985.)

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Isotretinoin, one of the early synthesized retinoids of the first non-aromatic generation is until now the only retinoid with marked sebosuppressive property. Its "miraculous" effect on severe nodulocystic acne is well documented in numerous reports (1, 2, 3, 4, 5). In addition, it has been used in other follicular dermatoses such as rosacea, gram-negative folliculitis (6, 7) etc. Etretinate, a mono-aromatic retinoid from the second generation is marketed in several European countries and used in the treatment of psoriasis and keratotic genodermatoses. It has little or no sebosuppressive effect (8) and has therefore a far less beneficial effect in acne. Several new retinoids are currently used in clinical studies: etretin (Ro 10-1670) the free acid derivative analogue and main metabolite of etretinate seems to be therapeutically similarly effective as etretinate (9) and, due to its shorter elimination rate (10) of great interest for clinical use. Arotinoid ethyl ester (Ro 13-6298) is a polyaromatic retinoid also in clinical studies. Its therapeutic properties are not well established so far, but it seems to be useful in psoriasis (11, 12) cutaneous T cell lymphomas (13) and psoriatic arthritis (14). The potential benefit of these two new drugs in the treatment of acne patients has not been evaluated yet.

It is important to determine the exact spectrum of action in humans of each retinoid, since it cannot strictly be extrapolated from animal experiments. We have studied the sebosuppressive activity of etretin and arotinoid ethyl ester. In addition, arotinoid was administered to four acne patients to evaluate its effectiveness as compared to isotretinoin. We thought this to be of interest since arotinoid ethyl ester is active in the range of microgram per kg, has antiinflammatory properties, is active on acne conglobata and cystic acne (15) and suppresses seborrhea (11), and does not increase serum triglycerides.

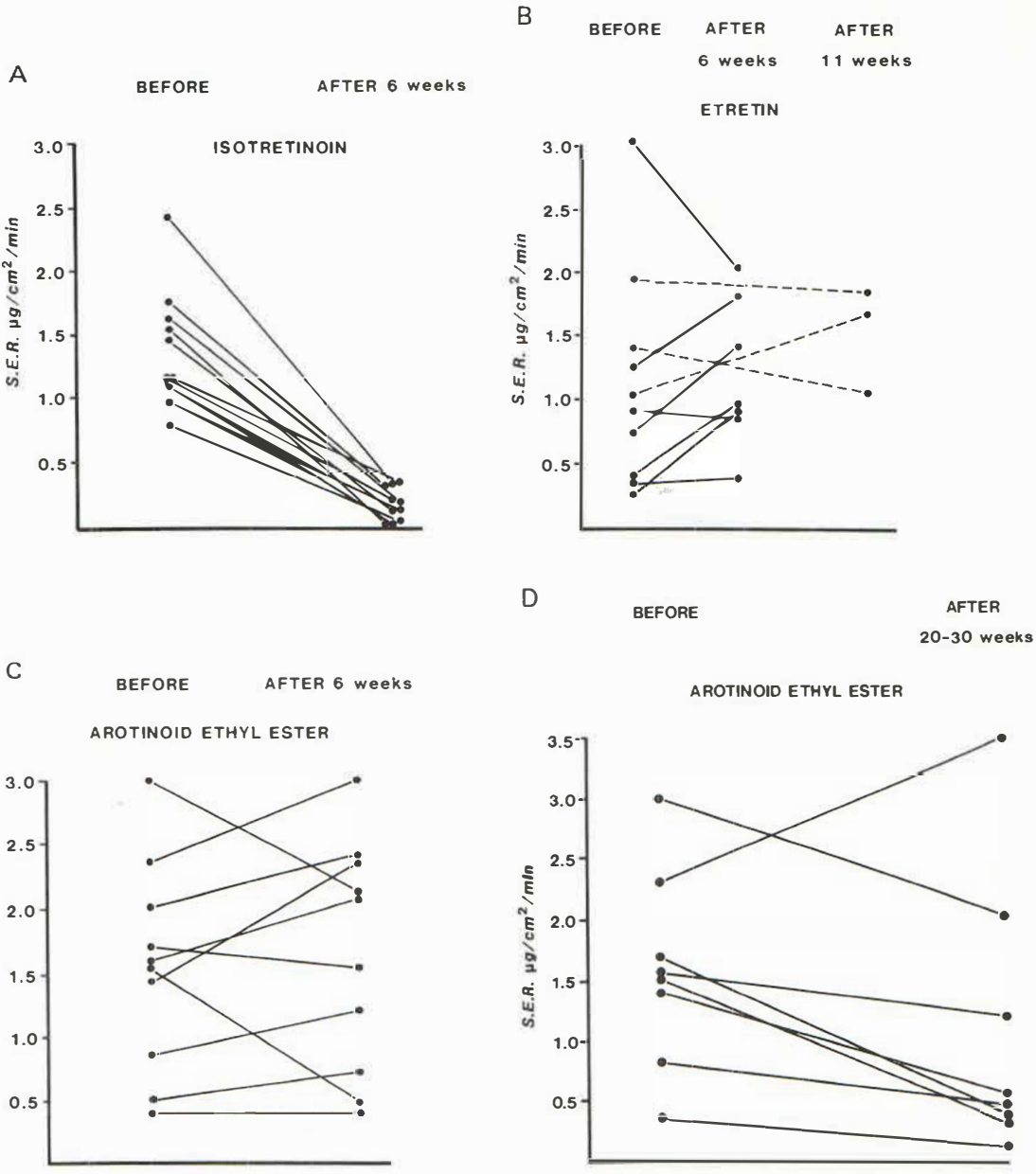

Fig. 1 A. Sebum excretion rate (SER) in 10 acne patients treated with isotretinoin. Important decrease of SER (92.6%) after 6-week treatment.

Fig. 2 B. Sebum excretion rate (SER) in 10 psoriasis patients before and 6 weeks after treatment with etretin. Three of them had a second measurement after 11-week treatment. Slight increase of SER after 6-week treatment, no changes in 3 patients controlled after 11-week treatment.

Fig. 1 C. Sebum excretion rate (SER) in 10 psoriasis patients treated with arotinoid ethyl ester. No change of SER after 6-week treatment.

Fig. 1 D. Sebum excretion rate (SER) decreased in 8 psoriasis patients treated with arotinoid ethyl ester for 20–30 weeks.

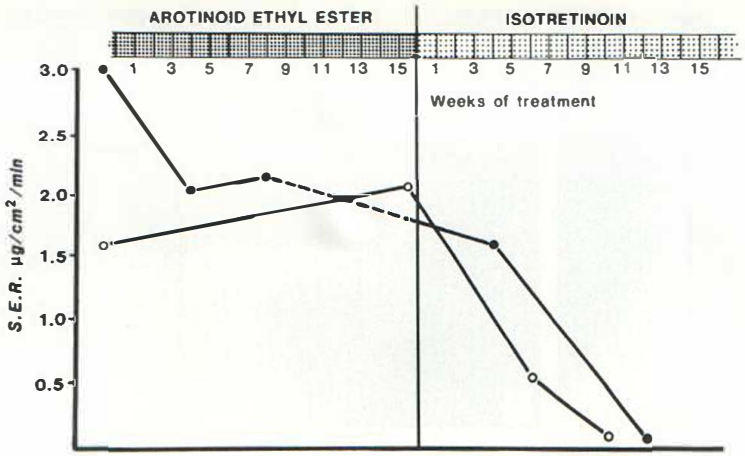

Fig. 2. Sebum excretion rate (SER) before and during treatment with arotinoid ethyl ester and isotretinoin in acne patients (○, patient 2, ●, patient 3).

MATERIAL AND METHODS

Sebum excretion rate

Sebum excretion rate (µg/cm²/min) was measured according to a modified photometric technique (16). Three groups were studied each receiving one of the retinoid: etretin, arotinoid ethyl ester or, as control, isotretinoin. Ten acne patients were treated with isotretinoin 0.5 mg and 1.0 mg/kg/day. Measurements were made before and six weeks after the beginning of the treatment. Ten male psoriasis patients, 20–52 years of age, were treated with etretin (Ro 10-1670) 0.3–1.0 mg/kg/day. SER was measured before treatment and after six weeks; in three cases SER was studied after 11 weeks of treatment as well. Ten other male psoriasis patients, 36–85 years of age, were treated with arotinoid (Ro 13-6298) 0.7–1.5 µg/kg/day. SER measurements were made before and after six weeks of treatment. Eight patients had another measurement between the 20th and 30th week of treatment.

Arotinoid ethyl ester in cystic acne patients

Four patients with severe cystic acne gave their consent to treatment with arotinoid ethyl ester for a period of 2 to 5 months with a mean dose of 1 µg/kg/day. Arotinoid ethyl ester was subsequently stopped and replaced by isotretinoin. SER was measured before and during retinoid treatment in three of the patients.

RESULTS

Sebum excretion rate

Fig. 1A shows the sebosuppressive effect of isotretinoin in acne patients. The average sebum excretion rate before treatment was 1.35 µg/cm²/min. After treatment for 6 weeks with isotretinoin SER was reduced to an average value of 0.1 µg/cm²/min, which represents a decrease of 92.6%.

Etretin-treated patients (Fig. 1B) had before treatment an average SER level of 0.99 µg/cm²/min, which increased after a treatment of 6 weeks to 1.25 µg/cm²/min, in the 7 patients studied, which represents an increase of 10.2%. SER was also measured after 11 weeks' treatment in 3 patients and was 1.56 µg/cm²/min. They had a SER level of 1.46 µg/cm²/min before treatment.

The average pretreatment SER level in the patients treated with arotinoid ethyl ester (Fig. 1C) was 1.54 µg/cm$_2$ min and after a treatment of 6 weeks 1.52 µg/cm²/min. Eight patients were evaluated between the 20th and 30th week of treatment (Fig. 1D); SER level was then 1.01 µg/cm²/min which represents a decrease of SER of 33.4%.

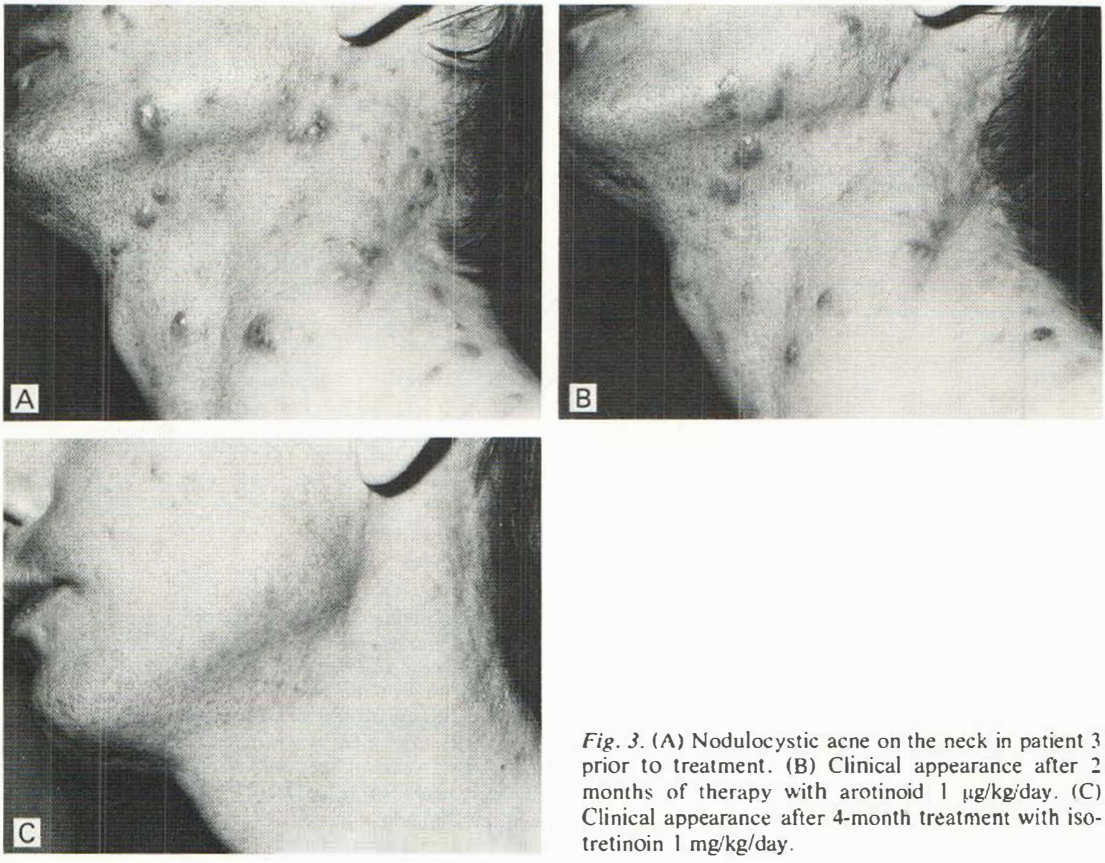

Fig. 3. (A) Nodulocystic acne on the neck in patient 3 prior to treatment. (B) Clinical appearance after 2 months of therapy with arotinoid 1 μg/kg/day. (C) Clinical appearance after 4-month treatment with isotretinoin 1 mg/kg/day.

Arotinoid ethyl ester in cystic acne patients

Patient 1, a 22-year-old woman received 0.5 μg/kg/day of arotinoid for one month and as there was no improvement, the dosage was increased to 1 μg/kg/day. After these two months the acne had worsened and had involved previously unaffected areas. This flare up was very similar to what sometimes happens with isotretinoin. She refused to continue with isotretinoin.

Patient 2 was a 38-year-old man suffering from severe nodulocystic acne involving face and trunk since adolescence. He was treated with arotinoid in a daily dosage of 1.25 μg/kg/day for 5 months. No clinical improvement was obtained. He was then given isotretinoin 1 mg/kg/day for 5 months. Considerable improvement was obtained and no inflammatory lesions recurred. SER measurements showed that, contrary to isotretinoin, arotinoid ethyl ester did not induce decrease in SER (Fig. 2).

Patient 3, a 23-year-old man, with severe nodulocystic acne particularly on the neck (Fig. 3 A) was treated with arotinoid 1 mg/kg/day for 2 months. He failed to improve (Fig. 3 B). Then isotretinoin 1 mg/kg/day was given. After 4 months, the acne had completely healed (Fig. 3 C). SER values (Fig. 2) again showed that isotretinoin had by far a better sebosuppressive effect than arotinoid ethyl ester.

Patient 4, a 26-year-old woman, with severe cystic acne had been treated with isotretinoin 1 mg/kg/day for one month only. She stopped this treatment for personal reasons. SER value 4 weeks after cessation of isotretinoin was 0.56/μg/cm^2/min. Arotinoid treatment 1

μg/kg/day was started two months after cessation of isotretinoin. We observed no improvement of the acne lesions during three months of arotinoid treatment; moreover, the SER was 2.14 μg/cm²/min after 2 months and then 1.47 μg/cm²/min after 4 months of arotinoid treatment; both values are higher than that observed after isotretinoin. This patient is continuously treated with isotretinoin.

The patients had slight cheilitis during the arotinoid period but evident cheilitis during the isotretinoin period.

DISCUSSION

The marked inhibitory effect on sebaceous glands with significant decrease of SER of about 90% is certainly the main factor for the impressive clinical response of severe acne with isotretinoin. In our study this decrease was 92.6% and well in accordance with other SER studies measured using other (17, 18) methods. This demonstrates that the photometric method used in this study can be applied to the screening of sebosuppressive effect of new retinoids in humans.

Etretinate has a weak or insignificant sebosuppressive effect. Goldstein (8) found a SER decrease of 16% after 6 weeks of treatment. Etretin, the free acid of etretinate was found in our study to increase SER in about 10% which cannot be regarded as significant. Both results can be considered as quite similar according to the methods used. It can be said therefore that etretin appears to be very similar to etretinate with regard to sebum excretion and probably to the clinical efficacy in acne. This is not surprising since etretin represents the active compound, etretinate being the pro drug (9, 10).

Arotinoid ethyl ester was found to have a slight sebosuppressive effect of about 30% but only after a long treatment period of 20–30 weeks. It is interesting that despite this slight sebosuppressive effect, it was not useful in the treatment of patients with severe cystic acne, even when given up to 5 months. This contrasted sharply with the rapid improvement when these patients were given isotretinoin. We do not believe that the lack of sebosuppressive effect was due to a low arotinoid ethyl ester dosage since (i) a patient was given up to 1.5 μg/kg/day. It is well established that the arotinoid ethyl ester Ro 13-6298 is active on human skin in dose ranges of about 1 μg/kg body weight; (ii) isotretinoin has been found to decrease sebum excretion even at 100 μg/kg/day.

Therefore our study shows that the two new retinoids under clinical study, etretin and arotinoid ethyl ester, will not compete with isotretinoin in the treatment of acne patients.

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