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Title

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Permalink

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Journal

Journal of the American Academy of Dermatology, 6(4)

ISSN

0190-9622

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Publication Date

1982-04-01

DOI

10.1016/s0190-9622(82)80058-3

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General discussion on the use of oral retinoids in nodulocystic acne

P. E. Pochi, M.D.: Dr. Plewig, you mentioned that the pretreatment biopsy specimens were taken from uninvolved skin of acne patients. It struck me that the ultrastructural appearance of the follicular epithelium resembled that of comedonal structures rather than the normal picture in the sebaceous follicles; that is, the horny cell layer was thicker than usual, and intracytoplasmic lipid inclusions were apparent. More than that, however, I was surprised to notice that treatment with isotretinoin seemed to accentuate the abnormality, that is, it actually looked as if the horny layer was thicker still and that there were more lipid inclusions. I recall your previously published work showing that topically applied retinoic acid reverted these abnormal changes to a considerable degree.

G. Plewig, M.D.: All biopsies were taken from apparently normal skin from the upper back or forehead. Of course, these were patients who had severe acne. They were patients with conglobate acne and gigantic sebaceous follicles. Incidentally, in our biopsies, early lesions such as microcomedones or sometimes even small comedones were found. By no means do I want to leave the impression that the drug acts comedogenically.

P. E. Pochi, M.D.: I did not mean to imply that. It is just that the corneocytes seem to be more numerous and have more lipid inclusions after isotretinoin treatment. The response appears paradoxical, or at least not what one would expect from the presumed antikeratinizing effect of the drug.

G. Plewig, M.D.: Corneocytes from treated patients contained many lipid-like inclusions, much more than found in the same patient before the treatment is initiated. You can find these same changes, but to a much lesser degree in psoriasis. To that extent we have seen this only following the topical application of tretinoin. The electron micrographs that we published (*Acta Derm Venereol (Stockh)* 55(suppl 74):99, 1975) were from biopsy specimens taken from patients who were treated topically with tretinoin and did show very similar lipidlike materials in the corneocytes.

P. E. Pochi, M.D.: Is the effect that you see with oral isotretinoin, namely, a thicker follicular horny layer with more lipid inclusions, actually in contrast to what is seen with topical tretinoin?

G. Plewig, M.D.: That is very difficult to decide at present. My feeling about this is that lipid inclusions disappear, or are less prominent with time while the patient is still on the drug.

P. E. Pochi, M.D.: That might suggest a biphasic response, namely, an early accentuation of the pathologic change and then a subsequent reversal of the process.

J. J. Leyden, M.D.: Dr. Plewig, since we don't know of any direct antimicrobial effect, in your patients with gram-negative folliculitis were you able to correlate the disappearance of the gram-negative organisms with a reduction in sebum excretion? My concept is that patients who have gram-negative folliculitis have a bacterial overgrowth in their anterior nares which then spreads out over the face, colonizes inflamed skin, and induces lesions ranging from pustules to nodules. Gram-negative organisms require a fair amount of moisture. Possibly the decrease in gram-negative organisms was a consequence of the decrease in sebum. Also, did you culture the anterior nares to see if there was a decrease in organisms in that reservoir site?

G. Plewig, M.D.: We did not measure surface skin lipids. We judged the fall of seborrhea clinically. The patients with gram-negative infections required high doses of isotretinoin to respond satisfactorily. When we gave 1 or 2 mg/kg body weight, the gram-negative organisms were almost invariably eradicated from the skin surface and also from the anterior nares.

E. C. Gomez, M.D., Ph.D.: In the patients with a gram-negative folliculitis, the gram-negative organisms disappear and yet the *P. acnes* organisms remain. If this was the case, presumably sebum was not reduced enough to suppress the *P. acnes*.

G. Plewig, M.D.: That is correct. As a matter of fact, the *P. acnes* population came down to low levels, but when the gram-negatives disappeared, the *P. acnes* organisms increased again. However, they did not reach pretreatment levels. We interpret this increase as being due to the *P. acnes* bacteria occupying the ecologic niche which was formerly taken by the gram-negatives.

E. C. Gomez, M.D., Ph.D.: But at that time there was still clinical improvement?

G. Plewig, M.D.: Yes.

H. P. Baden, M.D.: In thinking about the reason for the prolonged remission of acne with isotretinoin therapy, could it be related to the mechanism of spontaneous remission, whatever that is? Is it conceivable that the mechanism of action of this drug is to accelerate some normal process that occurs in the sebaceous glands? What do we know that is different about the morphology or biochemistry of sebaceous glands at the time acne appears compared to what the gland is like at age 30? That, conceivably, might be the key to all of this.

A. R. Shalita, M.D.: To the best of my knowledge, there are no known differences when acne appears and disappears. Sebaceous secretion remains the same and the *P. acnes* counts remain the same. The only thing that could be different is whether or not there is a change in the follicle wall that makes it more or less susceptible to the effects of the irritating substances, but this is not known.

P. E. Pochi, M.D.: We do not really yet know why acne remains in remission after the drug is stopped. Presumably, as Dr. Baden has suggested, it is abetting those processes or operations that allows the disease to resolve spontaneously.

L. A. Schachner, M.D.: Dr. Shalita, you mentioned that you specifically counted nodular acne lesions larger than 4 mm in diameter. Did you count lesions smaller than 4 mm in diameter, specifically the papules and comedones, during isotretinoin therapy?

A. R. Shalita, M.D.: While we did not specifically count the other lesions, in general, the papules disappeared.

P. E. Pochi, M.D.: I would agree. While we have not enumerated small lesions such as papules, they did disappear, even more rapidly than the larger inflammatory lesions.

L. A. Schachner, M.D.: Dr. Plewig, do you have any comments on the ability of retinoids to decrease the comedo and papule count?

G. Plewig, M.D.: We have not looked carefully into this question.

F. L. Meyskens, Jr., M.D.: The response you see with isotretinoin is almost like a hormonal response. We frequently see responses like this in estrogen-treated breast cancer, or in response to an antiestrogen such as tamoxifen. The patients who respond the best are frequently those who have an initial flare-up suggesting a biphasic response. I wonder whether the effect of retinoids is mediated by an androgen receptor in the target organ, the sebaceous gland. Is it known whether the androgen receptor in the skin of individuals is abnormal?

P. E. Pochi, M.D.: Individuals with severe acne

and high sebum levels have a higher content of androgen receptors in their skin. Whether these are merely a reflection of greater sebaceous gland size in skin is not known. But I don't believe that isotretinoin is antiandrogenic. Did your question imply that?

F. L. Meyskens, Jr., M.D.: There are two ways to look at it. One, does tretinoin compete on a competitive basis with an androgen receptor? Secondly, does isotretinoin function as an antiandrogen, either through an androgen receptor or through some other receptor, analogous to estrogen receptor modulation by progesterone in breast cancer? I am just tossing this out as an idea.

P. E. Pochi, M.D.: It is not very likely. Other androgen-responsive tissues are unaffected by isotretinoin; there is no reduction of gonadotropins or of testosterone, and, on the basis of what Dr. Gomez presented, there does not seem to be a peripheral antiandrogenic effect at the sebaceous gland site.

F. L. Meyskens, Jr., M.D.: But you only get acne when you are a teenager.

P. E. Pochi, M.D.: Most cases of acne do occur in the teen years, but some persist or even begin well after this time.

E. C. Gomez, M.D., Ph.D.: In addition to direct inhibition of the binding of dihydrotestosterone to the androgen receptor, the other point of possible antiandrogen action on sebaceous cells is, of course, blockage of the conversion of testosterone to dihydrotestosterone. We have looked at isotretinoin, and it had no effect on the 5α -reductase. Inhibition of binding to the receptor hasn't been evaluated. As I mentioned, although the molecules are very different, Feldman, Voigt, and Hsia (*J Biol Chem* **252**:3324, 1977) did describe an estrogen-binding protein from rat preputial gland, and tretinoin proved to be a competitive inhibitor for estrogen binding in this system. So there may be some sort of molecular configuration that allows a retinoid to resemble an estrogen.

P. E. Pochi, M.D.: It doesn't inhibit 5α -reductase activity, although it could conceivably inhibit binding, but then if it did, the pigmentation and the hair growth of the hamster flank organ would be suppressed, and Dr. Gomez has shown that they aren't. The effect on the sebaceous gland cells is quite selective.

I. M. Freedberg, M.D.: I have heard something this afternoon that struck me. We all are acquainted with the phenomenon in which patients with psoriasis get better from the head down. Apparently those of you who have studied retinoids in acne see that this drug works from the head down—the face gets better before the back. What does this mean?

A. R. Shalita, M.D.: Dr. Windhorst, do you have

any information as to the distribution of the drug? It seems to me that that might account for this phenomenon. Is a high concentration delivered to the face and less to the back and chest?

D. B. Windhorst, M.D.: I don't know.

J. S. McGuire, M.D.: I have a question that might help Dr. Baden with his quandary about acne being less prevalent with age. It clearly doesn't have anything to do with sebum production, since sebum production remains elevated with age. I wonder if individuals with age could become tolerant to products of *P. acnes*, or whether their cellular immune response might fall. Cell-mediated immunity is known to diminish with age. Has anyone in the group looked at this?

A. R. Shalita, M.D.: Rather the opposite holds true. Those people who have the worst acne are the ones that appear to have depressed cellular immunity. However, we have not looked to see whether or not cellular immunity changes as acne clears.

F. L. Meyskens, Jr., M.D.: Is the skin developed from top to bottom embryologically, and, if so, could the earlier response in the face being more primordial, be pushed by isotretinoin to earlier maturation?

P. E. Pochi, M.D.: I believe that the epidermal appendages develop embryologically in a cephalocaudal direction, although I seriously doubt if that is why the drug works better on the face than on the trunk.

G. Plewig, M.D.: I think we do not have enough

information to discuss this question. Lesions have to be the same if you want to compare responsiveness of face vs trunk, and most of the lesions are probably not the same. On the back they are sometimes the size of a walnut, but they are much smaller on the face.

A. M. Kligman, M.D., Ph.D.: I think that all the things that you have discussed reflect nonspecific anti-inflammatory effects. The retinoids seem to be able to suppress inflammation in some unknown way. The fall in *P. acnes* density is usually explained by their being deprived of sebum owing to atrophy of the sebaceous glands. But all of us who are dermatologists must wonder why experimental models are not being developed to evaluate the anti-inflammatory effects. For example, we can pretty much reproduce the nodule of acne conglobata by injecting ground-up comedones. We could create lesions of different severity and then determine their rate of resolution when retinoids are given. Another model which is feasible to study in humans is the production of pustules by the topical application of potassium iodide. We have studied the suppressive effect of tetracycline and isotretinoin on these pustules. I cannot confirm the antipustular effect of tetracycline. I also could not demonstrate suppression of pustules with high doses of retinol given orally. Unfortunately, these controversies are all too common and suggest that we need better models.