TREATMENT OF ACNE VULGARIS WITH TOPICAL VITAMIN A ACID

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SYNOPSIS

Based on current acne aetiopathogenesis, Vitamin A acid was used in an open clinical trial to treat 65 ambulatory patients with various severity of acne vulgaris. The patients were instructed to apply the 0.05% of the lotion once at night and 0.05% of the cream once in the morning. Seven patients (10.8%) did not complete the 5 months trial because of drug intolerance. Of the 58 patients who completed the trial, excellent to good results were obtained in three quarter of the series by the second month of treatment. These were accompanied by total reduction of acne lesions and the effect was more pronounced with the comedones and papules. Improvement continued after the second month and by the fifth month, nearly 90% of the patients were rid off acne lesions. However, therapeutically desirable topical side-effects such as erythema, desquamation, burning and pruritus were fairly severe during the first two months of treatment, but after the initial "flare up", they rapidly subsided. Thus despite the initial setback, the longterm effect of topical Vitamin A acid is excellent.

INTRODUCTION

One of the commonest skin diseases in young adults is acne vulgaris. While the milder forms of this pilosebaceous disorder are so frequently found in puberty as to be regarded as a physiological phenomenon, the more severe and persistent forms are a great source of unhappiness and social embarrassment, demanding medical attention.

In the past, the ambiguity and complexity of the aetiology and pathogenesis of this disease have lead to numerous ways and means of treatment, most of them without scientific basis. The results claimed for these treatment were variable and their longterm effect was not consistent. Recent studies have shown that the earliest change in the acne comedone formation is the failure of horny cells in the follicular epithelium to dehisce and extrude through the sebaceous ostium with the result that the

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adhesive expanding cell mass distends and ruptures the sebaceous follicle. The role of sebaceous excretory duct, microflora and lipid constitutents are of secondary importance (Plewig et al., 1971 (a); Knutson 1974). Based on this concept, the rational therapeutic apprach would be to correct this cellular cohesiveness and alter the follicular keratinisation.

Lately, Vitamin A acid (retinoic acid or tretinoin) applied topically, was able to effect this correction. It is able to penetrate into the depth of sebaceous follicle, thereby achieving a better than the usual superficial treatments with exfoliants and more importantly, it can accelerate formation of horny cells and increase incoherence in the horny cell lamella and finally eject the comedones from their bed (Plewing et al, 1971). Clinical trials with over 1000 patients have demonstrated the effectiveness of topical Vitamin A acid in various grades of acnes (Kligman et al., 1969; Wolff et al., 1970; Plewing et al., 1972); Eckstein et al., 1974). More than 70% of the patients treated achieved excellent to good results and within a relatively short time. Experience with this new drug in tropical condition was reported by Handojo & Susilorini (1973) who found it to be effective in various degrees of severity of acne vulgaris and good tolerance was observed by using different preparations (lotion and cream) of Vitamin A acid.

This paper presents the results and observations of a local clinical trial of Vitamin A acid in Singapore patients with various grades of acne vulgaris, most of whom did not respond to conventional therapy.

MATERIAL AND METHODS

An open clinical trial was carried out with 65 ambulatory patients attending the Skin Clinic, Singapore General Hospital during 1975-6 and suffering from acne vulgaris of all grades. After obtaining their consent, the patients' personal data and medical histories were obtained. All previous acne treatment were withdrawn, and Vitamin A Acid (all-trans-retinoic acid, tretinon) was used in this trial. Two preparations of Vitamin A acid were prescribed — "AIROL" Roche Lotion containing 0.05% of the active ingradient in a clear vehicle of equal parts of 95% ethyl alcohol and propylene glycol, and "AIROL" Roche Vanishing Cream containing 0.05% of Vitamin A acid in a washhole base of the oil-in-water emulsion type.

Patients were instructed to apply the lotion with a wad of cotton wool to affected areas once before retiring and to apply the cream very thinly over the same areas once in the morning. For those with a fair and more sensitive skin, initial treatment was application of lotion once a day only. They were informed of the expected therapeutic skin reaction which occurs in the first few weeks of the treatment. If skin irritation is too severe, the intervals between applications should be extended. Treatment should not be discontinued altogether if the side-effects are too intense or an early recovery is achieved. Proper precautions in the use of this drug and how to deal with them if they do occur, were explained before and during treatment.

Evaluation of acne treatment was done fortnightly for the first 8 weeks and monthly for the next three months. At each attendence, all the acne lesions (comedones, papules, pustules and nodulocysts) on both sides of the face were counted and scored as follows — No lesion = 0; 1 to 10 lesions = 1; 11 to 50 lesions = 2; More than 50 lesions = 3.

At the same time the major side-effects of treatment — Erythema, Desquamation, Burning and Pruritus were also recorded and scored as follows:- None = 0; Mild = 1; Moderate = 2; and Severe = 3. Other side-effects if encountered, were recorded.

Clinical improvement during treatment was graded as follows:- Excellent = regression of initial lesions by 75 - 100%; Good = regression of initial lesions by 50 - 74%; Moderate = regression of initial lesions by 25 - 49%; Insufficient = regression of initial lesions by 1 - 24%; No change = No regression of initial lesions; Worse = increase in initial lesions.

RESULTS

Fifty eight patients completed the 5 months clinical trial, the remainder 7 (10.8%) defaulted because of drug intolerance. The age, race, sex and occupation of the 58 patients are listed in Table 1. Majority in this trial were Chinese females (nurses) between the age

TABLE I: Personal Particulars of 58 Acne Patients

Sex	Females	53 (91.4%)
	Males	5 (8.6%)
Race	Chinese	39 (67.2%)
	Malays	10 (17.3%)
	Indians	8 (13.8%)
	Others	1 (1.7%)
Age (Years)	11 — 20 =	26 (44.8%)
	21 — 30 =	27 (46.6%)
	31 — 40 =	4 (6.9%)
	41 — 50 =	1 (1.7%)
Occupation	Nurses	24 (41.4%)
	Office Workers	13 (22.4%)
	Housewives	13 (22.4%)
	Students	6 (10.3%)
	Others	2 (3.4%)

groups of 11 to 20 and 21 to 30. Table II shows the face was predominantly affected (89.7%) and that the acne lesions were mostly of recent onset - between 6 months to 3 years (77.6%). Majority of the acne patients (69%) had greasy skin, and 17.2% had greasy and dry (mixed) skin texture.

Table III shows the total and mean scores as well as the percentage reduction of lesions from the initial score of COMEDONES, PAPULES, PUSTULES and NODULOCYSTS before and during the 5 months of Vitamin A acid treatment. Figure 1 demonstrates the total scores of the 4 types of acne lesions during the same period graphically. Reduction in lesions (total scores) were found in all 4 types of lesions but the rate was more rapid during the first 3 months and

TABLE II: Acne Lesions — Sites, Duration and Types of Skin (58 patients)

Sites:	Face Only	= 52 (89.7%)
	Face & Trunk	= 6 (10.3%)
Duration:	6 months to 1 years	= 25 (43.1%)
	1 + year to 3 years	= 20 (34.5%)
	3 + years to 5 years	= 8 (13.8%)
	More than 5 years	= 5 (8.6%)
Types of Skin:	Greasy	= 40 (69.0%)
	Dry	= 4 (6.9%)
	Mixed	= 10 (17.2%)
	Normal	= 4 (6.9%)

TABLE III: Evaluation of Acne Lesions During Treatment

DURATION OF TREATMENT / TYPES OF LESION	BEFORE TREATMENT			ONE MONTH			TWO MONTHS		
	TOTAL SCORE	MEAN SCORE	PERCENTAGE REDUCTION OF LESIONS	TOTAL SCORE	MEAN SCORE	PERCENTAGE REDUCTION OF LESIONS	TOTAL SCORE	MEAN SCORE	PERCENTAGE REDUCTION OF LESIONS
COMEDONES	99	1.706	—	77	1.327	22.2%	41	0.706	58.6%
PAPULES	142	2.448	—	104	1.793	26.7%	55	0.94	61.3%
PUSTULES	61	1.052	—	54	0.931	11.5%	34	0.586	44.3%
NODULO-CYSTS	44	0.758	—	34	0.586	22.7%	17	0.293	61.4%

THREE MONTHS			FOUR MONTHS			FIVE MONTHS		
TOTAL SCORE	MEAN SCORE	PERCENTAGE REDUCTION OF LESIONS	TOTAL SCORE	MEAN SCORE	PERCENTAGE REDUCTION OF LESIONS	TOTAL SCORE	MEAN SCORE	PERCENTAGE REDUCTION OF LESIONS
15	0.258	84.8%	11	0.189	88.9%	8	0.137	91.9%
28	0.482	80.3%	20	0.344	85.9%	11	0.189	92.2%
12	0.206	80.3%	5	0.086	91.8%	3	0.051	95.1%
8	0.137	81.8%	5	0.086	88.6%	3	0.051	93.2%

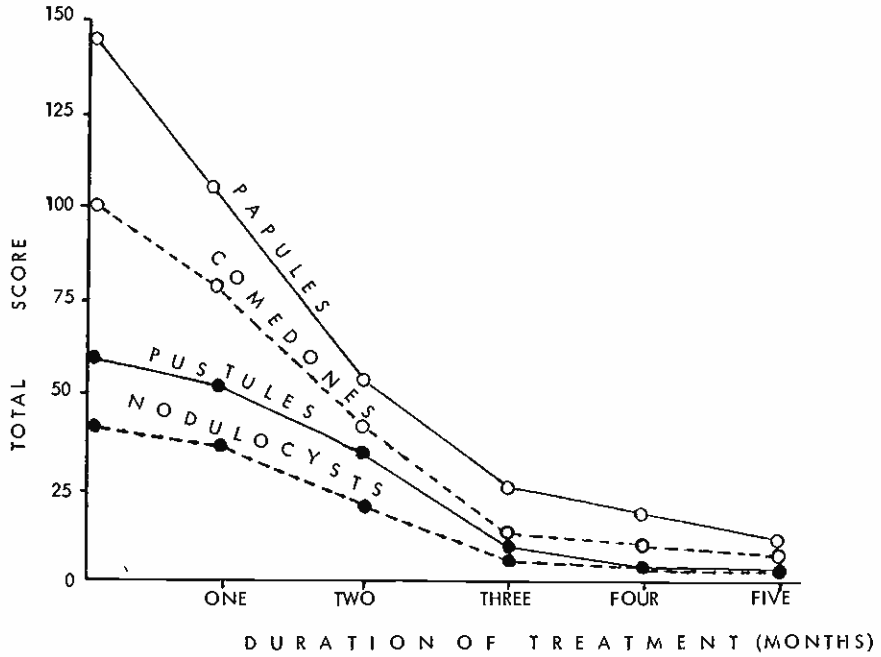

Fig. 1 Total scores of papules, comedones, pustules and nodulocysts during topical Vitamin A acid treatment.

more marked with Papules and Comedones than the other two. After the 3rd month, the reduction of lesions levels off and maintains at a very low score for the next 2 months. At this stage, most patients required very little or no topical Vitamin A acid. The therapeutic effects of "AIROL" on the acne lesions before and after treatment are shown in Figures 2 to 4 (A & B).

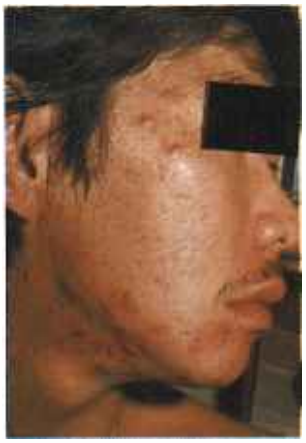

Fig. 2 (A) Before treatment.

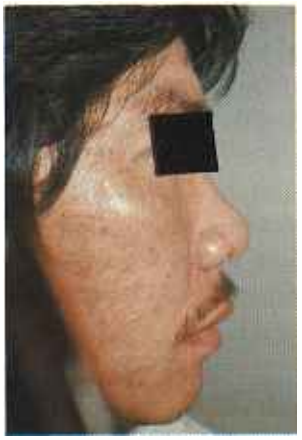

Fig. 2 (B) 6 weeks after treatment.

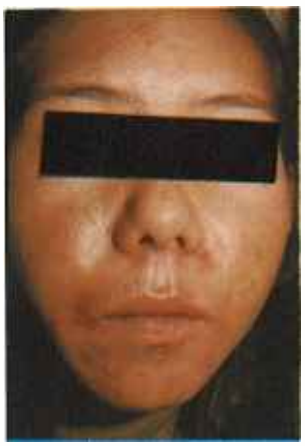

Fig. 3 (A) Two weeks after treatment — Note increase erythema, desquamation and pustulation.

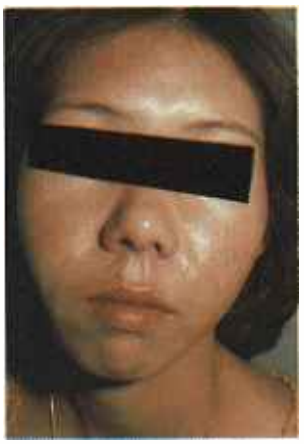

Fig. 3(B) 10 weeks after treatment — Note the smooth glossy skin.

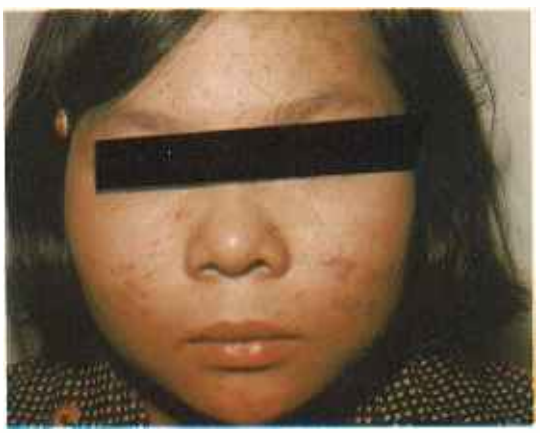

Fig. 4 (A) Before treatment.

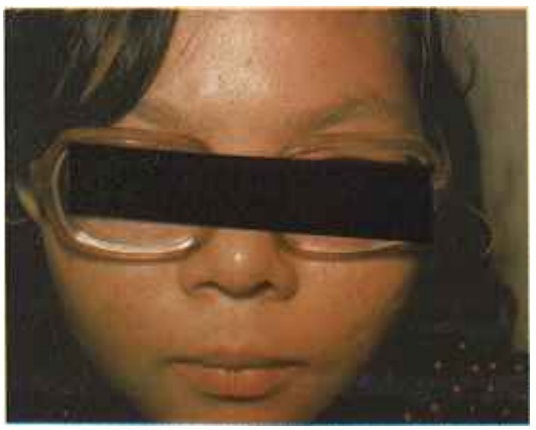

Fig. 4 (B) 8 weeks after treatment.

TABLE IV: Evaluation of Side-effects of Vitamin A Acid Therapy

DURATION OF TREATMENT / TYPES OF SIDE-EFFECTS	ONE MONTH			TWO MONTHS		
	TOTAL SCORE	MEAN SCORE	Percentage of severity	TOTAL SCORE	MEAN SCORE	Percentage of severity
ERYTHEMA	128	2.21	73.6%	76	1.31	43.7%
DESQUAMATION	123	2.12	70.9%	79	1.36	45.4%
BURNING	110	1.89	63.8%	75	1.29	43.1%
PRURITUS	113	1.94	64.5%	71	1.22	40.8%

THREE MONTHS			FOUR MONTHS			FIVE MONTHS		
TOTAL SCORE	MEAN SCORE	Percentage of severity	TOTAL SCORE	MEAN SCORE	Percentage of severity	TOTAL SCORE	MEAN SCORE	Percentage of severity
62	1.07	35.6%	26	0.45	14.9%	8	0.13	4.6%
41	0.71	23.5%	25	0.43	14.4%	6	0.10	3.4%
37	0.63	21.2%	23	0.39	13.8%	5	0.08	2.8%
37	0.63	21.2%	22	0.37	12.6%	4	0.06	2.3%

TABLE V: Evaluation of Clinical Improvement (n = 58)

RESULTS	1st mth No. pat.	(%)	2nd mth No. pat.	(%)	3rd mth No. pat.	(%)	4th mth No. pat.	(%)	5th mth No. pat.	(%)
EXCELLENT	6	(10.3)	16	(27.6)	25	(43.1)	22	(37.9)	23	(39.7)
GOOD	11	(19.0)	23	(39.6)	21	(36.2)	22	(37.9)	31	(53.4)
MODERATE	21	(36.2)	16	(27.6)	8	(13.8)	8	(13.8)	4	(6.9)
INSUFFICIENT	10	(17.2)	0	(0)	2	(3.4)	3	(5.2)	0	(0)
NO CHANGE	8	(13.8)	1	(1.7)	0	(0)	3	(5.2)	0	(0)
WORSE	2	(3.4)	2	(3.4)	2	(3.4)	0	(0)	0	(0)

TABLE IV shows the total and mean scores as well as the percentage of severity (Mean Score divided by the maximium score of 3 X 100) of 4 major side-effects of therapy — Erythema, Desquamation, Burning and Pruritus during the 5 months of treatment. These were all most intense during the first two months but rapidly subsided to neglible therafter. Erythema and Desquamation are the most important side-effects seen in over 70% of all patients. Other side-effects were not observed. Clinical improvement during treatment, though slow at first, was impressive and sustained. As shown in TABLE V, Excellent to Good results were observed in 29.3%, 67.2%, 79.3% 75.8% and 93.1% of this series during the 1st, 2nd, 3rd, 4th and 5th months respectively. Relapses were common in those (12%) who discontinued the treatment prematurely, but they were easily controlled on retreatment.

DISCUSSION

Acne vulgaris is a multifactorial disease dependent upon many pathogenetic mechanisms for its expression. Recent research has shown that the formation of acne comedone depends on hereditary predisposition (Gotz et al., 1974; Krebs & Fasler 1974); high sebum production (Pochi & Strauss 1974); androgen stimulation (Pochi & Strauss 1969; Barranco 1973; Winkler & Zaun 1972); the expanded role of follicular microbial flora e.g. C. acnes, Staph. Albus, P. ovale, (Puhvel & REisner, 1972; Edwards et al., 1975); inincreased in free fatty acids (Kellum 1968); host factors (Rajka 1970); external agents (Mills & Kligman 1975) and the alternation in follicular wall and keratinization (Plewig 1972). Based on current concepts of acne pathogenesis, therapeutic approach is multilateral and specific drugs could be used to reduce the formation of acne comedones. Besides dietary control, which is often disputable in its effectiveness, topical treatment with skin cleansers, antiseptics, antibiotics and peeling (desquamating) agents have been in popular use. External acne treatment also includes irradiation with ultraviolet light, Grenz rays, Xrays (Braun-Falco & Lukacs 1973), the use of comedo squeezer and lancet knife and the application of carbon dioxide slush. Internal treatment includes the use of hormones (oestrogens), steroids and antibiotics such as tetracyclines, tetracyline derivatives or erythromycins.

A significant advance in acne therapy in recent years has been the introduction of topical Vitamin A acid (retinoic acid or tretinoin), which acts at the very basic formation of acne comedo thereby supersedes previous treatment that are not only elaborate, time-consuming and inconstant in their results but they also possess many unwanted side-effects. Although oral administration of Vitamin A has long been known to have a profound effect upon keratinization, very high doses nearing toxic level are required (Straumfjord 1943). However if applied topically, Vitamin A acid (a derivative of Vitamin A) is also effective in skin diseases associated with abnormal cornification (Stuttgen 1962). When used in acne vulgaris, it produces a dramatic effect by its ability to reduce comedones and papulopustules by inducing the formation of horny cells which no longer stick together and by inhibiting the synthesis and quality of cement substance which binds horny cells into solid impactions, thus attacking the disease at the very point of its origin. (Kligman et al., 1969).

Many clinical trials involving over 1000 patients have confirmed the effectiveness of topical Vitamin A acid in the treatment of acne comedones and papulopustules. (Christiansen et al., 1974; Mills & Marples 1972; Schumacher & Stuttgen 1971; Pelwig et al., 1971 (b); Weitgasser 1972). Excellent to good results were obtained in over 70% of patients while about 10% were found ineffective during the 6 to 8 weeks of therapy. Our results in this trial was in agreement with others. Excellent to good results were recorded by more than 70% of the patients after the second month of treatment. This results are also shown in the total and mean scores of the 4 types of lesions — comedones, papules, pustules and nodulocysts. As noted by others, patients in our series with comedones and papules respond more dramatically than the other two. Even after the lesions have subsided, prophylactic treatment with Vitamin A acid could maintain the appearance of new ones.

The therapeutic effect of Vitamin A acid often causes alarm to the patients because of transient worsening of acne during the first few weeks of treatment and this have caused 7 of our patients to drop off the trial. This "flare up" is caused by the inflammatory restructuring of the comedones — silent and closed comedones are "compressed" into a short period by treatment and are eliminated while papules may pustulate and desquamate with attending erythema, burning and pruritus (Plewig 1972). Because we had warned our patients before and during the trial of these reactions and also the benefit of continued treatment, our drop-off rate (10.8%) was comparatively lower. Studies with ^{3}H-labelled thymidine, Plewig & Fulton, (1972) found that Vitamin A acid causes proliferation of stratum germinativum, follicular duct and comedo epithelium, the cell passage time being reduced to 3 days. Others also found that Vitamin A acid achieves this cellular changes by controlling the genetic system in the nucleus by stimulating the epidermal DNA synthesis and RNA polymerase (Christopher & Fraun-Falco 1968). The rapid cellular turnover in the epiidermis reduces the adherence of the horn-cell lamellae to one another and the loose but accelerated thrust of these cells detaches the comedo from the follicular wall and ejects it out (Kligman et al., 1969). In addition, Vitamin A acid also inhibits the formation of tonofilaments and keratohyalin as well as the release of lysosomal enzymes with the result of marked decrease in cohesiveness of the comedo horny cells (Bingle et al., 1961; Bowling & Wald 1960; Plewig et al., 1971).

Side-effects from topical application of Vitamin A acid such as erythema, desquamation, burning and pruritus, though therapeutically desirable, are unfor-

tunately common. In this series, after the first month of treatment, the percentage of severity of the 4 common skin reactions ranged from 63 to 74%, after the second month, the percentage of severity reduced to between 40 to 45%. From the third month onwards, the severity of all 4 side-effects were markedly less. The results obtained here using the 0.05% of the lotion and 0.05% of the cream are an improvement to those obtained in the earlier days when higher concentration of Vitamin A acid was used (Pedace & Stoughton 1971). In an attempt to reduce these irritant side-effects an new aromatic ethylamide derivative of Vitamin A acid (retinoid acid) was recently introduced. Although the side reactions due to topical application are less than the original drug, its efficacy in acne treatment was much inferior (Handojo 1977).

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