EFFECT OF 13-CIS RETINOIC ACID ON CYSTIC ACNE IN SINGAPORE

Y C Giam
T Tan

Middle Road Hospital
Singapore 0718

Y C Giam, MBBS, M Med (Paed)
Senior Registrar

T Tan, MBBS, FRACP
Medical Director

SYNOPSIS

Roaccutane, 13-cis-Retinoic acid, an oral derivative of synthetic Vitamin A was used as a second line drug in 20 patients with severe nodulo-cystic acne. Of these, 15 were males and 5 were females. Patients received 0.5-1.0 mg/kg body-weight of Roaccutane, that is, 40-60 mg/day, for a total of 16 to 52 weeks.

Improvement was assessed by clinical means. By 12 weeks, 38% (7 patients) had cleared, the remaining cases continued to receive treatment and by 28 weeks, all cleared. When the patients were further divided into the one group with facial lesions and another with widespread lesions, including the chest and back, the study further confirmed the earlier response in the first group, 77% (7 of 9 patients) and the less rapid response, 72% (8 of 11 patients) by 28 weeks.

Follow up of 1 to 2 years showed that a prolonged remission was attained and that this was dose-related. Nine of 19 patients experienced mild acne. Adverse effects clinically were mild and biochemically were not detected.

INTRODUCTION

Acne vulgaris is common in Singapore, forming 15.7% of new dermatological cases seen annually in Middle Road Hospital. There is a small group of antibiotic-resistant nodulo-cystic acne which poses a cosmetic and social problem. Since Peck's original observations in 1979, the drug had been tried in several centres in Southeast Asia.

METHODS

This study assesses the efficacy of 13 cis-Retinoic acid in 20 severe nodulo-cystic acne patients with a follow-up of 1 to 2 years to confirm the reported prolong remissions attained.

20 patients with antibiotic resistant and cystic acne, (minimum of 10 cysts) entered into the study. All previous treatments were stopped for 1 week. The patients were started on 40 mg/day 13 cis-Retinoic acid, between 0.5-1.0 mg/body-weight in an open trial for 12 weeks. After 4 weeks, a few slow responders had the dose increased to 60 mg/day. The treatment was stopped when the lesions cleared. A follow-up of a further 1 to 2 years was undertaken. Clinical assessments were made on the grades of acne, counts of non-inflamed, superficial and deep inflamed lesions, photographic records, haematological and biochemical parameters. These included the liver function tests, urea and electrolytes, fasting cholesterol and triglyceride and urinalysis. Follow-ups were initially weekly, then fortnightly for 3 months, when the tests were repeated, and monthly subsequently. Adverse effects like dryness, chelitis, alopecia, atrophy, desquamation, conjunctivitis, facial dermatitis and pruritis were noted.

RESULTS

Of the the 20 patients, 15 were males and 5 were females. They include 14 Chinese (65%), 4 Malays (15%), 1 Indian (5%) and 1 Eurasian (5%). The racial distribution was similar to the general population. Advice regarding contraception was given to these 5 single females. Their average age was 20.8 years (range, 15-27 years) and the duration of acne was 4.3 years (range 1-10 years), with the lesions beginning at 16 years old. Associated medical illnesses included atrial septal defect, folliculitis keloidalis, which improved but later relapsed when treatment was stopped, and aplastic anaemia treated with stanozolol. Previous treatment included tetracycline, bactrim, dapsone and acne cream.

The attendance was good, except for the patient who died of aplastic anaemia 3 months later; there were no defaulters. There was a steady improvement of the acne grades with 38% (7 patients) clearance at 12 weeks and the treatment was gradually stopped; the slow responders continued to improve and cleared by 28 weeks. The dose in 2 cases were stepped up to 60 mg/day. 3 cases with extensive scars were treated for a total of 52 weeks and even the scars flattened.

From previous reports, it is known that the response of patients with only facial lesions differed from those with extensive lesions, therefore the patients were further divided into 2 groups. Group I included 11 patients with only lesions on the face and these included all the female patients. The response was much more rapid and by 12 weeks, 77% (7 out of 11 patients cleared). The remaining 2 cases had improved to 50% to 70% of their pretreatment grades and steadily cleared by 20 weeks. Group II consisted of 9 cases with extensive lesions of the face, chest and back. By 28 weeks there was an improvement in 72% (7 of 9 patients) and the remaining cleared only after 40 weeks of therapy. Most of the superficial and the deep inflamed lesions cleared faster. The non-inflamed lesions were slow to heal. The 3 cases were treated for 52 weeks in an attempt to improve the scars. This was later found to be unnecessary.

The term "Remission" in our study, is defined as an overall improvement of 90% of the acne. On follow-up, although 9 patients complained of the return of acne, these consisted of seborrhoea, small comedones, papules but not the initial large cysts that they had. This study confirmed that all were maintained in remission during the 1 to 2 years of follow-up. It was also noted that the patients who had longer courses of 13 cis-Retinoic acid sustained a longer acne-free period, often at least 6 to 8 months long. (Tables 1, 2, 3 and 4).

Side effects were minimal in this study. They were similar to other studies. There were mucosal and integumental effects, namely dryness of mouth, lips, nose, chelitis. Pruritis was a common complaint. Pyogenic granuloma-like lesions were not seen. However, one of the patients developed Pityriasis rosea but it was uncertain whether this was a side effect. There were no biochemical abnormalities (Table 5).

TABLE 1
LENGTH OF TIME FOR EFFECTIVE TREATMENT

Results

			CLEARANCE AT			
	Group	0 wk	12 wk	20 wk	28 wk	40 wk
I	Face	9	7 (77%)	9 (100%)		
II	Face Chest	11	0	4 (36%)	8 (72%)	11 (100%)

TABLE 2

Results

	Group	Relapses	Remission
I	Face (8)	4 (50%)	8 (100%) 18 — 24 mths
II	Face, Chest, Back (10)	5 (50%)	10 (100%) 6 — 24 mths

TABLE 3
FACIAL LESIONS

Case	Sex	Duration (week)	Clearance 12 wks	Relapse	Remission
1	F	40	C*	Nil	2 yrs
2	M	36	C	Nil	2 yrs
3	M	32	C	Some folliculitis	1 yr
4	F	28	C	Nil	2½ yrs
5	F	28	50%	Few papules at 2 yrs	2½ yrs
6	M	24	75%	2 small cysts at 6 mths	2 yrs
7	F	16	C	Few papules at 1 mth	2 yrs
8	F	12	C	Nil	3 mths (died)
9	M	10	C	Nil	1½ yrs

*C — cleared

TABLE 4
FACE, CHEST, BACK LESIONS

Case	Duration (weeks)	Clearance (28 wks)	Relapse	Remission
1	52	50%	Papules at 2 mths	2 yrs
2	52	90%	Papules at 6 mths	2 yrs
3	52	90%	Nil	2 yrs
4	28	C*	Papules at 7 mths	6 mths
5	28	C	Nil	6 mths
6	28	C	Nil	1 yrs
7	28	C	Defaulted	Nil
8	24	C	Nil	2 yrs
9	20	C	Nil	6 mths
10	16	C	Papules at 6 mths	6 mths
11	12	C	Papules at 8 mths	8 mths

*C — Cleared

TABLE 5
ADVERSE REACTIONS OF 13-CIS RETINOIC ACID

	Side Effects	No. of Cases	Onset (week)
1a	Dry lips	20	1 — 2
1b	Dry mouth	18	1 — 2
1c	Dry nose	13	2 — 3
1d	Epistaxis	2	8
2	Chelitis	20	2 — 3
3	Pruritis	14	3 — 10
4	Thin skin	6	6 — 20
5	Desquamation	5	3 — 20
6	Facial dermatitis (erythema)	3	4
7	Conjunctivitis	2	4
8	Alopecia	1	24
9	Pityriasis rosea like	2	24
10	Pyogenic granuloma like	0	0
11	Biochemical	0	0

DISCUSSION

The exact action of 13-cis-Retinoic acid on acne is unknown but it has an action on all 4 aspects of acne pathogenesis. Suppression of sebum production, changes in follicular epithelium, decrease in Propionibacterium acnes density and anti-inflammatory effects have been reported (Kings 1982, Goldstein 1982, Stewart 1982).

Our results confirmed those of other workers (Peck 1979, Farell 1980, Jones and Cunliffe 1983, van der Meeren 1983, Strauss 1984) (Table 6). All these workers have also studied dose response of 13-cis-Retinoic acid on cystic acne and the drug had been found to be effective at all 3 doses 0.1 mg/kg, 0.5 mg/kg and 1.0 mg/kg body weight. It was also realised that Peck's dose of 2.0 mg/kg was high.

The lower overal success with 0.1 mg/kg suggested that it was inadequate as a single agent for an initial course of treatment. Trials with 0.5 mg/kg and 1.0 mg/kg proved that though the final results were the same, more side effects were encountered with the latter.

Though the treatment periods were variable, compared to the studies of others, the results were similar. For the Asian population, a dose of 0.5 mg/kg body weight of 13-cis-Retinoic acid appeared adequate for a period of about 16-20 weeks, like the American experience, while truncal lesions would do better with a longer period of 24-28 weeks. Reports of other workers demonstrated that prolong remissions with 0.5 mg/kg occurred despite stopping the drug, and this had been a similar experience with our study.

A large number of adverse effects had been

TABLE 6
13-CIS RETINOIC ACID

Comparison with Other Studies

Author	No. of Patients	Dose	Clearance	Relapse	Remission
Peck et al (1979)	14	2 mg/kg (16 wks)	13/14 pts	Nil	100% at 20 mths (14 pts)
Farrell (1980)	15	0.1, 0.5, 1 mg/kg (12 wks)	14/16 pts	Nil	On follow-up
Jones, Cunliffe (1980)	82	0.1, 0.5, 1 mg/kg (16 wks)	60-80%	Relapse in 0.1 mg/kg gp	80% (9/12) at 7 mths 12/19 at 24-30 mths
van der Meeren (1983)	58	0.5, 1 mg/kg (24 wks)	Good	Nil	43% (25 pts) at 24 wks 22/58 pts at 15 mths
Strauss (1984)	150	0.1, 0.5, 1 mg/kg	Good	40% in 0.1 mg/kg 10% in 1 mg/kg	Better with 0.5 — 1 mg/kg
Giam/Tan (1984)	20	0.5 to 1 mg/kg	Good	Mild	100%

reported. These include elevations of serum triglycerides (Lyon 1982, Daneshmend 1983, Marsden 1983, Zech 1983) and increase in the level of liver enzymes. These were not seen in our study. The lower meat diet and lower level of consumption of alcohol might have helped in this case. The teratogenic side effects continue to require monitoring in our females as none have been pregnant so far. The mucosal effects of chelitis were noted to be bothersome to the patients but could be controlled with vaseline creams. Ophthalmologic side effects (Velantic 1983) and neovascular nodules (Ensink 1983, Exner 1983) were not noted (Table 7).

In conclusion, 13-cis-Retinoic acid is a breakthrough in the treatment of cystic acne in our population. The majority of patients experienced impressive improvement clinically and psychologically. Even the slow responders continued to improve with therapy. A dose of 0.5 mg/kg for 16-20 weeks appears to be effective.

TABLE 7
13-CIS RETINOIC ACID

Adverse Effects
Comparison with Other Studies

Author	Dry Lips	Dry Nose	Conjunctivitis	Chelitis	Desquamation	Pruritis	Biochemical
Cunliffe (1980)	Nil	Nil	Nil	30%	20%	Nil	↑SGOT ↑S. Protein ↑ESR
van der Meeren (1983)	100%	42%	33%	76%	75%	57%	Nil –
Farrel (1983)	Nil	50%	50%	100%	3%	57%	↑LDH ↑TG
Strauss (1984)	93%	78%	58%	93%	50%	68%	↑LDH ↑TG (with 1.0 mg. bw)
Glam/Tan (1984)	100%	90%	10%	100%	25%	70%	NIL

REFERENCES

1. Peck GI, Olsen TG, Yoder FY: Prolonged remission of cystic and conglobate acne with 13-cis retinoic acid. N Engl J Med 1979; 300: 329-33.
2. King K, Jones DH, Daltrey D, Cunliffe WJ: A double blind study of 13-cis retinoic acid on acne, sebum excretion rate and microbial population. Br J Dermatol 1982; 107: 583-90.
3. Goldstein JA, Grunite H, Mescon H, Pochi HE: Isotretinoin in the treatment of acne. Histologic changes, sebum production and clinical observations. Arch Dermatol 1982; 118: 555-8.
4. Steward ME, Benoit AM, Stranieri AM, et al: Effect of oral 13-cis retinoic acid at three dose levels on sustainable rates of sebum secretion and on acne. J Am Acad Dermatol 1983; 8: 532-8.
5. Farrell LN, Strauss JS, Stanieri AM: The treatment of severe cystic acid with 13-cis Retinoic acid. J Am Acad Dermatol 1980; 3: 602-11.
6. Jones DH, Cunliffe WJ: Effect of 13-cis Retinoic acid on acne treatment and follow-up. Br J Dermatol 1981; Suppl 19: 20.
7. Jones DH, King K, Miller AJ, Cunliffe WJ: A dose response study of 13-cis Retinoic acid in acne vulgaris. Br J Dermatol 1983; 108: 333-43.
8. Cunliffe WJ, Miller AJ. Retinoid Therapy. M T P Press Ltd, 1984: 203.
9. van der Meeren HLM, van der Schroeff JG, Stinjen T, et al: Dose related retationship in Isotretinoin therapy for conglobate acne. Dermatologica 1983; 167: 299-303.
10. Strauss JS, Rapini RP, Shalita AR, et al: Isotretinoin therapy for acne: Results of multi-centre dose response study. J Acad of Dermatol 1984; 10: 490-6.
11. Lyons F, Laker MF, Marsden JR, et al: Effect of oral 13-cis retinoic acid on serum lipids. Br J Dermatol 1982; 107: 591-5.
12. Daneshmend TK, Paisey R: Isotretinoin (13-cis Retinoic acid) and serum lipids. Br J Dermatol 1983; 108: 124-31.
13. Marsden JR, Shuster S, Laker MF: Isotretinoin and serum lipids. Lancet 1983; i: 134.
14. Valentic JP, Ban RJ, Weinstein GD: Inflammatory neovascular nodules associated with oral isotretinoin treatment of severe acne. Arch Dermatol 1983; 119: 871-2.
15. Ensink BW, Pevan Voorst Vader: Ophthalmological side effects of 13-cis Retinoic therapy. Br J Dermatol 1983; 108: 627.
16. Exner JH, Dahal S, Pochi PE: Pyogenic Granulomalike acne lesion during isotretinoin therapy. Arch Dermatol 1983; 119: 808-11.