Multiple and Recalcitrant Warts Treated with Oral Acitretin

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Background: Acitretin, a synthetic retinoid, has been used to treat patients with psoriasis, Darier's disease, ichthyosis, keratosis pilaris etc. Some trials have suggested that oral acitretin may be useful for the treatment of warts.

Objective: The purpose was to determine whether oral acitretin is effective in the treatment of multiple and recalcitrant warts.

Methods: 25 patients with multiple and recalcitrant warts were enrolled. We administered acitretin, 30 mg daily in adults, and 0.5 mg/kg daily in children. At the end of the treatment, 21 patients were examined to determine the efficacy of the treatment.

Results: Of the 21 patients, 10 patients (48%) showed a complete response, 3 (14%) showed a moderate response, 4 (19%) showed a partial response, and 4 (19%) showed no response. Therefore, the patients showing more than a moderate response were 62% (13 of 21). An abnormal laboratory finding was not detected and adverse effects were common but tolerable in most patients.

Conclusion: Oral acitretin may be useful for the treatment of extensive and reclacitrant warts, especially verruca plantaris. (Ann Dermatol 16(2) 52~56, 2004)

Key Words: Acitretin, Multiple, Recalcitrant, Warts

INTRODUCTION

Warts are benign proliferations of skin and mucosa caused by human papilloma viruses and are estimated to affect approximately 0.85-10% of the population[1]. Most warts are asymptomatic and will resolve spontaneously with time. Since warts may cause cosmetic disfigurement or may be painful, treatment is sometimes needed. Multiple modalities are available for the treatment of warts, but none is uniformly effective. When warts are multiple and extensive, treatment is very difficult and multiple treatments often may be required[2].

Acitretin, a synthetic retinoid, has been used to treat patients with psoriasis, Darier's disease, ichthyosis, keratosis pilaris etc. and may help with extensive disabling hyperkeratotic warts. Sixteen out of twenty children with warts given etretinate at a dosage of 1 mg/kg per day showed complete regression of the disease without relapse[3]. So we used acitretin, principal metabolite of etretinate and investigated the efficacy and safety of it in patients with multiple and recalcitrant warts.

MATERIALS AND METHODS

We performed a clinical study of 25 patients (18 male, 7 female) with multiple warts, who visited the Department of dermatology, Chungnam National University Hospital between September, 1999 and July, 2001. All of the patients included the following; 1) the patients with more than 10 warts, 2) the patients with wart recurrence following other

Received April 19, 2004
Accepted for publication June 28, 20034

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This work was supported by Chungnam National University Hospital research fund, 2001.

treatment modalities given previously. Demographic data, including age, sex, site of wart, number of warts, type of warts, and previous therapy were recorded (Table 1). The patients visited for clinical evaluation every 2 weeks during the treatment. Acitretin (neotigason 10 mg/cap), 30 mg/day was administered in adults and 0.5 mg/kg/day in children. The dosage was tapered to 10 mg/day when the warts

Table 1. Summary of Clinical History of 25 Patients

Case	Age	Sex	Duration (months)	Type	Number	Site	Previous therapy	Treatment duration (weeks)	Total dose (mg)	Response	Follow up
1	6	M	12	v.v.	12	toe, foot	cryotherapy	14	1130	60%	recurred after 4 weeks
2	8	F	36	v.v.	above 20	foot, finger	cryotherapy, CO_2 laser	7	680	20%	
3	8	F	5	v.v.	above 20	finger, face	CO_2 laser	6	650	NR	
4	9	M	48	v.v.	above 10	knee, hand	CO_2 laser, cryotherapy	4	420	DO	
5	10	F	48	v.v.	13	finger, sole	CO_2 laser, cryotherapy, DNCB	8	980	NR	
6	11	M	48	v.v.	12	sole	CO_2 laser	13	1170	100%	not recurred
7	16	F	96	v.v.	13	finger	cryotherapy, excision	8	1480	100%	not recurred
8	17	M	36	v.v.	16	finger	CO_2 laser	8	1680	20%	
9	18	M	60	v.v.	11	finger	salicylic acid CO_2 laser	10	2100	40%	
10	22	M	48	v.v.	12	sole	cryotherapy	8	1680	70%	after cryotherapy, not recurred
11	27	M	4	v.v.	15	sole	cryotherapy	8	1680	NR	
12	28	M	96	v.v.	18	sole	CO_2 laser	9	1890	15%	
13	30	M	1	v.v.	13	sole	CO_2 laser	4	780	100%	recurred after 9 weeks
14	31	M	18	v.v.	16	toe, finger	salicylic acid, CO_2 laser	14	2640	100%	not recurred
15	22	M	24	v.v.,v.p.	above 10	sole, toe	cryotherapy	4	840	DO	
16	29	M	36	v.v.,v.p.	above 10	toe	CO_2 laser	8	1680	5%	
17	22	M	30	v.p.	12	finger	CO_2 laser	9	1690	100%	recurred after 8 weeks
18	38	M	72	v.p.	15	hand, sole	CO_2 laser DNCB	13	2430	100%	not recurred
19	57	F	36	v.p.	above 10	sole	CO_2 laser	4	840	DO	
20	20	M	12	v.p.	above 20	hand, sole	CO_2 laser	13	2220	100%	not recurred
21	24	F	12	v.p	above 20	sole	CO_2 laser	9	1690	100%	not recurred
22	18	M	120	v.p.	Above 10	sole	excision	10	1800	100%	not recurred
23	12	F	48	v.p.	above 10	sole	cryotherapy	15	1730	100%	not recurred
24	13	M	24	v.p.	15	sole	CO_2 laser	8	980	50%	after cryotherapy, not recurred
25	27	M	36	v.p.	above 10	sole	CO_2 laser	2	420	DO	

v.v.: verruca vulgaris, v.p.: verruca plantaris, NR: no response, DO: drop out

cleared to 10% of the initial size. Complete blood count and liver function tests were done every 2 to 3 weeks. The response to therapy was graded using the following grades: complete response (100% cleared), moderate response (50 - 99%), partial response (10-49%) and no response (<10%). The same physician evaluated each patient at every visit. Up to 17 months after the discontinuation of therapy, recurrence was acquired via telephone contact. Statistical evaluation of the results was undertaken with the independent T-test (SPSS ver.10).

RESULTS

The mean age of the cases was 21 years (range 6 to 57 years old). The mean duration of warts was 40 months, ranging from 1 month to 10 years. The site of warts was sole (n=15), finger (n=8), hand (n=3), toe (n=3), face (n=1), knee (n=1). The type of warts was verruca vulgaris (n=14), verruca plantaris (n=9), and both (n=2). All patients had experienced previous treatment failure and CO_2 laser, cryotherapy, surgical excision, salicylic acid, DNCB therapy were in order (Table 1).

The therapy was completed by 21 of the 25 patients. Four patients were dropped out because of noncompliance. Of 21 patients, 10 patients (48%) showed a complete response, 3 (14%) showed a moderate response, 4 (19%) showed a partial response, and 4 patients (19%) showed no response (Table 2) Therefore, the patients showing more than a moderate response were 62% (13 of 21). Of them, 3 patients partially recurred after the discontinuation therapy. The regressive change of the warts was noted in 4 to 6 weeks after administration. The mean duration of treatment was 9.2 weeks, ranging from 4 to 15 weeks. There was considerable regression of the warts on the soles (Fig. 1 & 2). Most of residual lesions were cleared by cryotherapy. Significant difference of response rate was found in the type of warts; in verruca plantaris, response rate was 89.4%, but in verruca vulgaris, it was only 43.8% (p=0.007).

Abnormal laboratory findings were not detected and adverse effects were common but tolerable in most patients. The most commonly reported adverse effects were cheilitis, xerosis, dry mouth, and headache (Table 3).

Table 2. Treatment Response of 21 Patients Treatment Outcome

	No. of patients (%)
Complete response (100% cleared)	10 (48%)
Moderate response (50-99%)	3 (14%)
Partial response (10-49%)	4 (19%)
No response (<10%)	4 (19%)

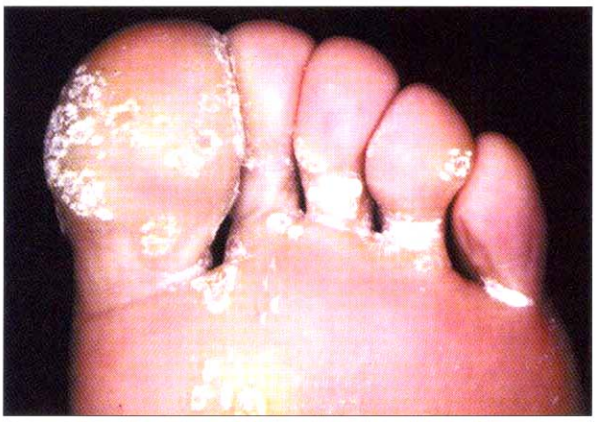

Fig. 1. Before the treatment.

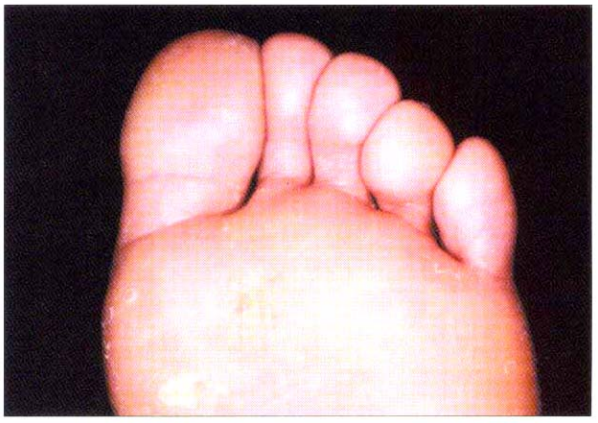

Fig. 2. After the treatment at 12 weeks.

DISCUSSION

The ideal treatment modality of warts would be effective, painless, safe, least time-consuming, and inexpensive. Multiple modalities are available, but none is uniformly effective.

Table 3. Adverse Effects During the Therapy

Side effects	No. of patients (%)
Cheilitis	19 (90%)
Xerosis	10 (47%)
Dry mouth	5 (24%)
Headache	2 (10%)
Back pain	2 (10%)
Nail change	2 (10%)
Hair loss	1 (5%)
Fatigue	1 (5%)

Salicylic acid in various concentration and different bases is the most commonly used therapy to treat warts[4]. Therapeutic effects are enhanced by removing surface keratin or by occlusion with adhesive plasters. It may cause irritation of the surrounding skin.

Liquid nitrogen cryotherapy is one of the commonest treatments used when patients are referred to a dermatologist. Cryotherpay can be applied with a cotton bud or a cryo-spray. Cryotherapy is usually repeated at 1-3 weekly intervals. Cryotherapy showed 44-80% cure rate, but is very painful and may leave scarring, ulceration, or pigment alteration[4,5].

If cryotherapy is not successful then various other options are available. Immunotherapy with topical application of diphencyprone[6] or squaric acid dibutylester[7] can be effective. Treatment may need to be done repeatedly before a response is obtained. Intralesional bleomycin[8] using a solution containing 1 mg/mL of bleomycin can be injected into the wart or pricked through with a lancet. This treatment is quite painful. Surgical excision, CO_2 laser ablation[9] or curettage and cautery of troublesome and resistant warts can be attempted but the risk of scarring and recurrence in the scar can be a problem. Pulse dye laser treatment[10], by theoretically targeting the rich capillary network in the wart, is sometimes effective.

Other treatments such as oral high-dose cimetidine[11], oral levamisole[12], oral retinoid[3], topical 5-fluorouracil[13], and topical imiquimod[14] can be tried.

Oral retinoids are known to influence epidermal proliferation, normalize the keratin polypeptide profile, and diminish the cohesive properties between keratinocytes. Lutzner et al.[15] proposed that retinoid was able to inhibit replication and assembly of the virus by altering keratinization. And Gross et al.[16] suggested that retinoid could induce the reduction in the number of virus particle and the disappearance of viral DNA. But in both reports[15,16], warts were recurred when treatment was stopped, so they insisted that retinoid was effective in the reduction, but it was not curable. But Gelmetti et al.[3] reported that 80% showed complete regression of the warts without recurrence.

In our study, 62% of patients showed moderate response (>50%). This result is not superior to that of other treatment modalities. But our study had been done in patients whom other modalities had already failed and we had experienced only 3 patients recurred after the discontinuation of treatment. We think that retinoid may induce immunomodulation as like other previous reports[17,18] and alter keratinization process, so debulking and halting progression.

The adverse effects of acitretin include cheilitis, xerosis, hair loss, pruritus, nail change, hepatotoxicity, increased serum lipid levels, teratogenicity and so on[19]. In our study, most reported adverse effects were mucocutaneous changes (cheilitis, xerosis, dry mouth) and well tolerable in most patients. Administration of acitretin, together with varying amounts of alcohol, gives a dose-dependent formation of etretinate[20]. Owing to the teratogenic potential of acitretin, fertile women especially should be informed about the importance of strict alcohol abstinence during treatment and for at least 2 months after stopping therapy. Acitretin In case of non-compliance with alcohol abstinence, a post-therapy contraceptive period of 2-3 years should be recommended[20].

Poor prognostic factors are age of onset, duration before treatment, and type of warts[1,2]. In our study, only the type of warts influenced prognosis. Mahrle and Alexander[1] reported that verruca plantaris and periungual warts showed less cure rate and more recurrence rate. But in our study, verruca plantaris showed an 89.4% improvement.

CONCLUSIONS

Oral acitretin was well tolerated and effective in treating patients whose warts were extensive and had failed to respond to other modalites. Oral acitretin may be useful for the treatment of extensive and

recalcitrant warts, especially verruca plantaris.

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