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Evaluation of Acitretin in the Treatment of Multiple Recalcitrant Common Warts: a Pilot Study

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Abstract

Background: Oral acitretin, a synthetic compound of retinoids, seems to be a promising modality in treating warts. To the best of our knowledge, no studies regarding its use have been performed on Egyptian patients.

Objectives: Evaluating the role of acitretin in the treatment of multiple recalcitrant common warts.

Patients and Methods: Forty adult patients with multiple recalcitrant warts were treated with oral acitretin [20 with 1 mg/kg/day for 3 month (group A), 20 with 0.5 mg/kg/day for 3 months (group B), and 20 served as controls and were given placebo (group C)].

Results: Oral acitretin was found to be a statistically significant therapy compared to placebo in treating warts. Total clearance of lesions was noted in 70% of group A compared to 80% in group B and none in group C. A non significant difference between group A and B was noted. However, there was a significant relation between the clinical response and the duration of disease, as the longer the duration of the disease, the higher was the percentage of patients showing complete response to therapy.

Conclusions: Acitretin can be used as an effective non-invasive alternative form of therapy for multiple recalcitrant common warts.

Keywords: Acitretin; Human papilloma virus (HPV); Recalcitrant; Multiple; Wart

Introduction

Warts are the cutaneous manifestations of human papilloma virus (HPV) that may exist in different forms. Common warts (verruca vulgaris), plantar (verruca plantaris), flat (verruca plana), and genital (condylomata acuminata) are some of the clinical manifestations of HPV infection [1]. Approximately 23% of warts regress spontaneously within 2 months, 30% within 3 months, 65% to 78% within 2 years and 35% tend to be recalcitrant-either showing no response to treatment or having prompt recurrences after treatment [2,3].

There are multitudes of treatment opinions regarding the combative therapies of warts in the form of destructive therapies as surgical excision, cryosurgery, carbon dioxide lasers, electro-cauterization), the topical application of keratolytics and antimitotic agents [4] or immunotherapy which is either specific as anti-HPV vaccination (not available in Egypt) or non-specific as MMR vaccination, BCG vaccination and zinc sulphate [5,6]. These methods are either aggressive or require long treatment duration, multiple sittings, and are often associated with recurrences. Unfortunately, even with years of medical research on this subject, no treatment has yet proven 100% effective for a cure. It was therefore, important for several investigators to find an effective systemic therapeutic regimen for treating warts [7,8].

During the past years, retinoids have been proposed as promising alternative treatment for warts [9]. Acitretin, a synthetic 2nd generation oral retinoid, has been used with dramatic clinical improvement in the management of extensive warts. The dose of oral acitretin used in literature was either 0.5 mg/kg body weight/day for 3 months [10] or 1 mg/kg body weight/day for 1 month [11].

The use of oral acitretin in the treatment of recalcitrant warts is under studied in literature where most reports were in the form of case studies [4,6]. To the best of our knowledge, no studies regarding its use on Egyptian patients with warts have been performed. In view of this, the present study was performed to evaluate the role of oral acitretin in the treatment of multiple recalcitrant common warts on a relatively larger number of patients, than those reported in literature that showed no response to traditional lines of treatment.

Patients and Methods

Patients

After screening 128 patients with multiple warts randomly, 79 fulfilled the inclusion criteria. Nineteen patients skipped some of the follow up sessions, so they were excluded from the analysis and we were left with 60 adult patients who completed the study. Patients were recruited from the Dermatology out-patient clinics of the National Research Centre and Zagazig University Hospitals. All patients gave an informed consent to participate in this work. The study was approved by the research ethics committee of the National Research Center, Giza, Egypt.

The study included 32 males and 28 females with multiple recalcitrant common warts that were refractory to conventional therapies including (e.g. cryotherapy, electrocautery, salicylic acid, trichloroacetic acid, podophyllin, and radiofrequency). The clinical diagnosis was based on the appearance of multiple discrete, hyperkeratotic, verrucous, hyperpigmented papules measuring 2-5 mm in diameter (measured by a planimetry). Histological confirmation of the diagnosis was done to all patients. Children, pregnant females or those intending to become pregnant, those with abnormal blood count

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profile, liver and renal function tests, total protein, albumin, and lipid profile were excluded.

All patients were subjected to detailed history taking, dermatological clinical examination for the type of warts, and sites of involvement as well as laboratory investigations. Photographic documentation (Panosonic LZ8 camera, 8.1 megapixel, China) for each patient before and after the course of treatment was done to compare and evaluate the clinical response and side effects of the treatment.

Methods

In this prospective randomized open clinical trial, patients were randomly assigned to 3 groups:

Group (A): included 20 patients that were treated with a high dose of oral acitretin (1 mg/kg body weight/day) for 3 months.

Group (B): included 20 patients treated with a low dose of oral acitretin (0.5 mg/kg body weight/day) for 3 months.

Group (C): included 20 patients that served as controls and were given identically looking placebo capsules for a total duration of 3 months.

All patients in the acitretin treated groups were comparable in terms of age, sex, size and number of warts with the placebo group.

Blood sampling

Venous blood samples were withdrawn from each patient on the initial visit before treatment and then monthly after the administration of therapy for a total of 3 months to assess blood counts, fasting lipid profile (triglycerides, cholesterol), liver function tests (AST, ALT), total protein, albumin, and blood sugar levels for diabetic patients.

Follow up

Evaluation of the clinical response to therapy was performed for all subjects during the administration of treatment by two different physicians. Response to therapy was considered as follows: complete response: 100% clearance of lesions, partial response: reduction in the warty area by 50%, and no response: no change in the lesions [12]. Follow up of the patients was continued for six months after completion of therapy to detect recurrence.

Statistical analysis

Patients were also instructed to report any side effects from the administration of the medication as gastrointestinal symptoms in the form of nausea, diarrhea, and abdominal pain, mucocutaneous symptoms as cheilitis, xerosis, skin peeling, photosensitivity, or alopecia, neurologic as headache, and ocular symptoms as dry eyes.

Results

This pilot study included 60 patients, 32 males (53.3%) [10(50%) males in group A, 10(50%) in group B, and 12 (60%) in group C] and 28 females (47.7%) [10(50%) females in group A, 10 (50%) in group B and 8 (40%) in group C]. Their ages ranged from 19-49 years with a mean ± standard deviation (SD) of 32.3 ± 8.7 years (mean ages in groups A, B and C were 30.3 ± 8.6 years, 33.2 ± 8.4 years, and 33.5 ± 9.9 years respectively). Mean ± SD of the duration of the disease was 17.9 ± 6.8 months in group A, 17.6 ± 5.2 months in group B, and 12.8 ± 5.8 months in group C. As regards the site of affection, 28 (46.6%) patients had warts on their hands and 32 (53.3%) on foot. No significant difference was detected as regards age, gender, duration of the disease or site of distribution of warts between the studied groups (P-value >0.05).

On comparing both group A and B with the control group (group C) as regards the complaint of the patients, we recorded that in both groups, 24 (60%) patients complained from the cosmetic appearance of the warts, versus 12 (60%) patients in group C, 12 patients (30%) complained of pain versus 6 (30%) patients in group C, and 4(10%) patients complained of itching versus 2(10%) patient in group C with a non-significant difference between them (P-value >0.05).

Side effects were noted more in group A as 8 patients (40%) versus 6 patients (30%) in group B suffered from xerosis and chelitis, however, with a non-significant difference between both groups (P-value > 0.05).

Comparison between the studied groups as regards clinical response to therapy

On comparing the clinical response to therapy in each of Group A and B with the control group, a highly significant difference was noted, as surprisingly, none of the controls showed any spontaneous regression (P-value <0.05). Oral acitretin resulted in total clearance of lesions in 70% of the patients in group A (Figure 1) and 80% among group B (Figure 2). Moreover, partial response was detected in 10% of the patients in each of group A and B while no improvement of the lesions in either the size or the number of lesions was noted among Group C.

However, a non-significant difference was noted on comparing both Group A and B together as regards the clinical response to therapy (P-value >0.05) (Table 1). There was also a non-significant difference between the two groups as regards the response to therapy in relation to age, sex, or the complaint of the patients (P-value >0.05). Nevertheless, there was a highly significant relation between the clinical response and the duration of disease, as the longer the duration of the disease, the higher was the percentage of patients showing complete response to therapy (P-value < 0.05) (Table 2).

Discussion

In the current study, we present 40 patients with multiple recalcitrant common warts who were treated with different doses of oral acitretin and were compared with 20 patients who received

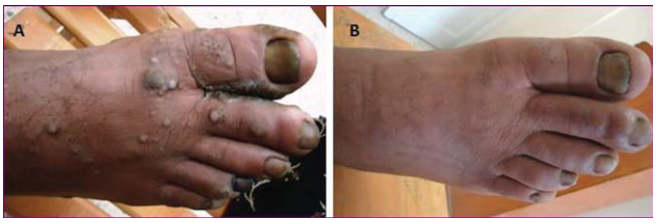

Figure 1: Multiple warts in a patient of the high dose acitretin-treated group: (a) Before treatment. (b) After treatment with complete resolution of warts.

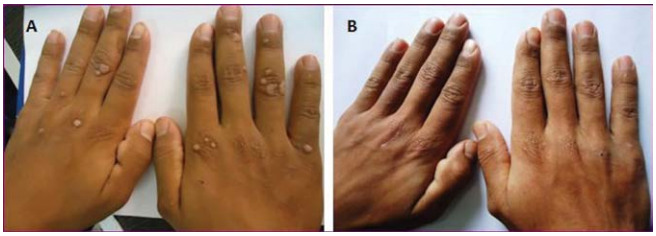

Figure 2: Multiple warts in a patient of the low dose acitretin-treated group: (a) Before treatment. (b) After treatment with complete resolution of warts.

Response	Group A N=20		Group B N=20		P-value	Significance
	Number	%	Number	%		
Complete (N=30)	14	70	16	80	>0.05	NS
Partial (N=4)	2	10	2	10		
No (N=26)	4	20	2	10		

NS: non-significant

Table 1: Comparison between the two treated groups as regards clinical response to therapy.

Duration (Months)	Complete Response (Number=30)	Partial Response (Number=4)	No Response (Number=6)	P-value	Significance
Mean ± SD	20 ± 4.4[a]	10 ± 2.8[a]	9.7 ± 0.6	0.001	HS
HS:highly significant, **a**:significance between complete and partial response					

Table 2: Relation between the clinical response in both group A and B and the duration of the disease.

placebo. Acitretin was found to be more effective than placebo in the treatment of the condition. A total clearance of warts was noted in 70% of patients treated with 1 mg/kg/day for 3 months with no relapse at a 6-month follow-up. These results are in agreement with the case reported by Choi et al., [11] using the same dose of acitretin without any recurrence. On the other hand, Choi et al., [4] , when using the same dose of acitretin, reported considerable regression of the warts after 1 month with total clearance of the lesions after 2 months of therapy after which acitretin was stopped. However, there was a relapse 1 month after the cessation of therapy.

Moreover, we also noted complete clearance of lesions in 80% of patients administering 0.5 mg/kg/day of acitretin for 3 months. This was also in accordance with several case studies in literature as those reported by Krupa Shankar and Shilpakar, [10] using the same dose of acitretin without any recurrence and Chen and Tzung, [8] who used the same dose of acitretin but for 6 months, which is a longer period than that in the present study, and demonstrated complete clearance of the lesions with no recurrence in their 6 months follow up period. Also Kaliyadan and Dharmaratnam, [3] used the same dose of acitretin for 3 months but in combination with cryotherapy once weekly and demonstrated complete clearance of lesions with no recurrence in their 5 months follow up period. While partial clearance of warts was observed in some of our patients, yet the rapid clinical response as well as the painless and convenient nature of acitretin therapy was acceptable to all of them.

Spontaneous remission of warts, particularly common warts, occurs in up to two-thirds of patients within two years; others persist for years [13]. In the present study, we expected some of the patients in the control group to show any signs of spontaneous regression in their lesions during the follow up period. However, interestingly none of them did. We believe that factors related to the patient's overall immune status play a role and that preservation of nonspecific immunity is prerequisite for spontaneous regression of common warts. Moreover, a longer follow up period is needed to reach such a finding.

Our findings of the good clinical response of common warts to oral acitretin, either in the form of complete or partial response, is very interesting and deserves further investigation. This difference in clinical response and rate of recurrence between our study and the previous studies may be related to the interaction of certain subtypes of HPV and their response to acitretin. A variety of different strains and variants of HPV have been identified based on DNA studies and serological detection of type-specific antibodies against HPV capsid antigens. Over 118 types of papillomavirus have been identified and individuals are likely to be infected by multiple types. The different types can behave synergistically to facilitate concurrent or subsequent infection with another type. Others can act antagonistically to interfere with one another [1].

At the meantime, the clinical improvement observed in our patients could be explained by the fact that retinoids exert a wide range of diverse biological effects on cells, including the regulation of growth and differentiation. An inverse relationship was previously reported between concentrations of retinoids and HPV deoxyribonucleic acid (DNA) within infected epithelial cells, suggesting an effect on viral replication [4,14].

Apart from being a potent immune modulator by inhibiting dermal micro-vascular endothelial cells and neutrophil migration, the mechanism of action of retinoids, is also likely related to the effect that they have on the keratinization process. Acitretin normalizes epidermal cell proliferation, differentiation and cornification. It is thought to exert these effects by interfering with the expression of epidermal growth factor genes [4,15].

In this study, a highly significant relation was also noted between the clinical response and the duration of disease, as the longer the duration of warts, the more liable was the clinical response to oral acitretin with either the high or low dose. Human papilloma virus replication is related to the state of keratinocyte differentiation [15]. We speculate that the older the warts are, the greater the keratinization will be and the possible proliferations of the cutaneous and mucosal epithelium. Retinoids by altering keratinization, are capable of inhibiting the replication and assembly of HPV within the affected cells. Worthy of note is the fact that retinoids reduce the bulk of hyperteratotic warts and substantial clinical improvement is achieved [8].

Side-effects are generally seen in most patients receiving acitretin and usually disappear when the dosage is reduced or the medicine is withdrawn [15]. Side effects in our patients were more apparent in those who received high doses of acitretin in the form of cheilitis and xerosis that improved with petroleum jelly and moisturizing cream.

We believe that there are several limitations in this study one of which is the small sample size of the patients and the difficulty in keeping either the patients or the investigators blind to retinoid therapy as the lips on the active principle confess through desquamation and fissuring. Further studies on a larger scale are required to confirm or refute our findings.

Conclusion

To sum up, acitretin can be used as an effective, fairly well-tolerated, and non-invasive alternative form of therapy for multiple recalcitrant warts that could bring about physical and psychosocial dysfunction [4,11]. Further studies on a larger scale of patients are required in the future to determine its effectiveness in treating a broad range of other benign and cancerous lesions induced by HPVs [16]. Genotyping of HPV could be of value to know which subtypes will be more responsive to acitretin treatment than others to get better results without recurrence. However, such studies would imply the study of thousands of patients, and the cost benefit ratio has to be weighed.

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