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Effect of Acitretin on Penile Erection in Psoriatic Male Patients

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ABSTRACT

Background: Psoriasis vulgaris (PV), a systemic immune-mediated disease, comprises chronic inflammation stimulated by psychiatric, genetic, and environmental factors. Acitretin is a systemic retinoid that has been approved for the treatment of PV. There have been some case reports indicating that retinoids may cause sexual dysfunction.

Objective: To assess the effect of acitretin therapy on penile erection in psoriatic male cases.

Patients and Methods: This study comprised a total number of 31 male patients with psoriasis who were treated with acitretin for at least 2 months. All cases were asked to complete International Index of Erectile Function (IIEF-5) questionnaire before and 2 months from treatment with acitretin. Lesions were scored based on psoriasis area and severity index (PASI) score and Physician Global Assessment (PGA). The dosage of acitretin was 0.5 mg/kg/day, in form of capsules, route of administration was oral for duration of 2 months.

Results: When IIEF grades were compared before and after two months of therapy, it was observed that the number of patients with second, third and fourth grades was significantly higher after therapy, while the number of patients with the first grade was significantly lower after therapy. Erectile dysfunction was detected in 11 patients before treatment, all of them were grade 2 and in 27 patients after two months of therapy.

Conclusion: Acitretin is associated with a great risk of erectile dysfunction when administrated in treatment of psoriatic male patients and had showed a significant drop in IIEF scores after two months follow up.

Keywords: International Index of Erectile Function, Acitretin, Penile Erection, Psoriatic Male, Psoriasis Area and Severity Index.

INTRODUCTION

Psoriasis vulgaris (PV) is a chronic dermatosis of unknown etiology with relapsing course. Its worldwide prevalence is 2% [1]. PV has been recorded to be stimulated by several environmental factors [2]. Approximately 85% of patients present with plaque psoriasis. Other types of PV involve guttate, erythrodermic, inverse and pustular psoriasis [3].

It is known that there is no a complete cure for PV, on the other hand there are different therapeutic modalities that could treat the manifestations including topical agents for mild cases, phototherapy for moderate cases and systemic drugs for severe cases [4]. Most of treatment options have significant side effects, however acitretin and other retinoids are non-immunosuppressive drugs with relatively less side effects [5].

Acitretin is a synthetic retinoid, which is a pharmacological active metabolite of etretinate. Now acitretin has been approved by Food and Drug Administration (FDA) as a promising therapeutic modality in the context of severe PV and also can be used in treatment of generalized pustular psoriasis and exfoliating erythrodermic psoriasis. Acitretin side effects including teratogenicity, hyperlipidemia, pruritus and dryness of mucous membranes and erectile dysfunction have been reported [6].

Erectile dysfunction is defined by difficulty getting and keeping an erection enough to have sexual intercourse. It may be due to organic cause, psychogenic cause or drug use. Recently, acitretin effect on penile erection became an important topic to be studied as acitretin may cause erectile dysfunction and this side effect should be considered before starting treatment [7].

Aim of the work was to evaluate the effect of acitretin treatment on penile erection in psoriatic male cases.

PATIENT AND METHODS

This prospective comparative study was conducted in Dermatology and Andrology outpatient clinic of Mansoura University Hospitals (from February 2021 to February 2022) and included thirty-one male psoriatic patients aged from 20 to 55 years in whom acitretin was indicated and included patient took acitretin at least for 60 days with regular sexual relationship. But we excluded patients with psychiatric disorders, diabetes, hypertension, systemic disorders, penile disorders, hyperlipidemia, history of using other systemic drug for psoriasis as methotrexate and history of substance abuse.

Methods

All cases were subjected to full history taking that included personal history (name, age, sex, occupation, residence), present history (onset, course, duration of PV, predisposing factors), history of medications (nature, route of administration, dosage, duration, effects and adverse events), family history of PV and past history of any medical and surgical conditions as well as any dermal disorder.

Complete general examination was done to rule out any systemic disorders and we assessed triglycerides level (TG) and cholesterol level. Full dermatological examination was done including skin, hair, nails and mucous membranes to evaluate the type of PV, distribution and severity and to rule out autoimmune

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skin disorders. Lesions were scored based on PASI score.

The Psoriasis Area and Severity Index (PASI)

The PASI, which is considered the best approach, is usually used for evaluation of severity of psoriasis as well as treatment efficacy. It is composed of four parameters that should be assigned: erythema, thickness, scaliness and affected area in the four body sections (head and neck, trunk, upper limbs, and lower limbs) resulting in a score with values between zero and 72. A PASI Score less than ten defined PV as mild, between ten and twenty as moderate and above twenty as severe [8].

The Physician Global Assessment (PGA) and affected body surface area (ABSA)

With the benefit of being easier for utilization, the PGA and ABSA may be an alternative for PASI score as PASI has considerable limitations as it is difficult to be applied and to be interpreted. So, the PGA measures the qualities of the plaques present over the whole-body giving values ranging from zero to five in which zero is clear and 5 is severe. The ABSA could be described as the percentage of the affected area in which one percent corresponds to the palm, fingers, and thumb area of each patient [9].

International Index of Erectile Function (IIEF)

Entire cases were asked to complete IIEF-5 questionnaire before and 2 months after treatment with acitretin. The IIEF-5 questionnaire consisted of 5 questions. The patients were given a score between 1 and 5 based on their responses. (IIEF-5) questionnaire's possible score ranges from 5 to 25. Patients with score range from 5 to 7 were considered having severe erectile dysfunction, patients with score range from 8 to 11 were considered having moderate erectile dysfunction, patients with score range from 12 to 16 were considered having mild to moderate erectile dysfunction, patients with score range from 17 to 21 were considered having mild erectile dysfunction and patients with score range from 22 to 25 were not be considered having erectile dysfunction [10,11].

The Treatment Course

The dose of acitretin was 0.5 mg/kg/day, in form of capsules, route of administration was oral for duration of 2 months. Then after two months the follow up was done to assess penile erection following the treatment course of acitretin.

Ethical approval:

Mansoura Medical Ethics Committee of Mansoura Faculty of Medicine gave its approval to this study (IRB approval: MS.21.01.1349). All participants gave written consent after receiving all information. The Helsinki Declaration was followed throughout the study's conduct.

Statistical Analysis

The collected data were analysed by utilizing the SPSS program (version 22). Normal distribution of numerical data was assessed by Kolmogorov-Smirnov test. Normally distributed numerical data were presented as mean±SD and compared by utilizing paired samples t-test. Categorical data were presented as number (percentage) and their comparison was conducted by utilizing Wilcoxon test. All data were considered statistically significant if P value was ≤ 0.05.

RESULTS

Thirty-five patients were assessed for eligibility in the current study; four patients were excluded and the remaining 31 patients who met the inclusion criteria were enrolled and analyzed. Table **(1)** shows the mean age of patients and the mean values of cholesterol, TG, and PASI.

Table (1): Mean values of age-cholesterol, triglyceride, and PASI

Age (years)	39.4 ± 9.1
Cholesterol (mg/dl)	182.9 ± 12.4
TG (mg/dl)	139.4 ± 8.6
Psoriasis area and severity index	29.1 ± 6.9

Table **(2)** shows comparison of IIEF scores before and after two months of therapy and reveals that the scores were significantly lower after two months of therapy.

Table (2): A comparison of the IIEF scores before and after therapy

	Mean + SD	**P value**
Before	21.84 ± 1.13	< 0.0001*
After	17.35 ± 3.3	

* Significant.

When IIEF grades were compared before and after two months of therapy, it was observed that the number of patients with second, third and fourth grades was significantly higher after therapy, while the number of patients with the first grade was significantly lower after therapy as shown in table **(3).**

Table (3): A comparison of the IIEF grades before and after therapy

	Before	**After**	**P value**
Score 1 (22-25) No	20 (64.5%)	4 (12.9 %)	< 0.0001*
Score 2 (17-21) Mild	11 (35.5%)	13 (41.9 %)	
Score 3 (12-16) Moderate	0	12 (28.7%)	
Score 4 (8-11) Severe	0	2 (6.5%)	

* Significant.

DISCUSSION

Psoriasis is a chronic, multifactorial immune-mediated skin disorder featured by development of erythematous, scaly, pruritic and occasionally painful plaques [12]. PV is activated when genetic and/or environmental factors stimulate plasmacytoid dendritic cells, with a subsequent formation of several proinflammatory cytokines, comprising tumor necrosis factor (TNF)-α, interferon-γ, interleukin (IL)-17, IL-22, IL-23 and IL1β. Many of such cytokines trigger keratinocyte hyperproliferation, that maintains a cycle of chronic inflammation [13]. PV is accompanied by an increase in the possibility of several co-morbidities such as psoriatic arthritis, cardiac diseases, diabetes, overweight, and ulcerative colitis in comparison with the general population [14]. It is theorized that early systemic therapy targeting pro-inflammatory cytokines accompanied by PV pathogenesis improve skin manifestations and decrease systemic inflammation, as a result improving long-term results via reducing of the progression of comorbidities [15].

Acitretin (ACI) is a retinoid, which is a pharmacological active metabolite of etretinate. Now acitretin is approved by FDA for treatment of severe PV and also can be used in the management of generalized pustular psoriasis [16]. Retinoids are a class of compounds that derive from vitamin A. Vitamin A plays an essential role in the context of immune system regulation, cellular growth, differentiations, proliferations, and embryonic development. Further actions of retinoids involve immunological anti-inflammatory actions, promotion of apoptotic cell death, and suppression of tumour promotion [17].

In recent years, there are limited number of researches in the context of the actions of retinoids on the male reproduction. Such researches are mainly reliant on tests and literatures, and the majority of which consider retinoids to be safe from andrology point of view. They are based on the broad spectrum of retinoid utilization and explanation of whether retinoids action on male reproduction is urgently required. Confirming whether acitretin interferes with the reproduction of adult males with PV is an essential problem which needs immediate solution [18].

The side effect of acitretin on females is well defined as it is absolutely contraindicated in pregnancy due to its teratogenic effect and pregnancy is discouraged for three years after discontinuation of the drug, while in males it is used safely without notable adverse effects [19]. Data on the effects of acitretin on sexual functions are limited. Recently, acitretin effect on penile erection become an important topic to be studied as acitretin may cause erectile dysfunction and this side effect should be considered before starting treatment [7].

Our study aimed to evaluate the acitretin effect on penile erection in psoriatic male cases. This study was conducted on 31 adult male cases with psoriasis treated with acitretin for at least 2 months. The patients were recruited from Dermatology and Andrology outpatient clinic of Mansoura University Hospitals.

The mean age of patients was (39.4±9.1) years old with mean values of cholesterol (182.9±12.4) mg/ dl, TG (139.4±8.6) mg/ dl and PASI mean value (29.1±6.9). By comparison of IIEF scores before and after two months of therapy, our study demonstrated that the scores were significantly lower after two months of therapy ($P < 0.0001$). When IIEF grades were compared before and after two months of therapy, it was observed that the number of patients with second, third and fourth grades was significantly higher after therapy, while the number of patients with the first grade was significantly lower after therapy ($p< 0.0001$). Erectile dysfunction was detected in 11 patients (35.5 %) before treatment, all of them were grade 2 and in 27 patients (87 %) after two months of therapy, Grade II was found in thirteen cases, grade III in twelve cases and grade IV in two cases).

The mechanism by which acitretin causes erectile dysfunction is unclear but this may be explained by the inhibition of the activity of testosterone by retinoids by binding to the same site at the receptor molecule [20], or may be related to deficiency in testosterone as a result of isotretinoin therapy which has an essential role in the continuation of normal sexual functions [21-23]. However, there have also been studies that documented no isotretinoin-related changes in hormone levels [24-26], so it may not be a reasonable explanation due to controversial results of studies.

Many researchers addressed the effects of acitretin on spermatogenesis. Parallel to this study, a study had documented significant effect on spermatogenesis in male managed with all-trans-retinoic acid (ATRA) [27]. In accordance with the current study, **Topal and Otunctemur** [7] demonstrated that acitretin may cause erectile dysfunction and believe that patients should be informed of this potential side effect before initiating treatment.

Zakhem and his colleagues[28] had found relationship between dose of acitretin and suppression of fructolysis, which assesses sperm motility. These finding is in agreement with the current study. Likewise, erectile dysfunction was recognized in a 39-year-old patient with psoriasis after 45 days of initiation of acitretin therapy [29]. As well, two more case reports noted the association of sexual dysfunction and the use of etretinate [28,30].

In accordance to results of this study, in a study conducted on rats, the authors suggested that neonatal retinoid exposure may have affected sexual parameters due to the binding of nuclear steroid receptors [31]. In contrast, **Sengör and his colleagues**[32] had found no effect of different doses of acitretin on spermatogenesis; but this study was done on rats.

LIMITATIONS

Small number of patients due to unwilling of patients to take part in such a study, and it was difficult to convince them to participate. Absence of control

group. Inability to evaluate hormone levels due to defect in facilities. Large number of exclusion criteria had to be selected, as many factors may cause erectile dysfunction.

CONCLUSION

In conclusion, acitretin is associated with a great risk of erectile dysfunction when administrated in treatment of psoriatic male patients and had showed a significant reduction in IIEF scores after two months follow up.

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