

Original Research Article

Effect of Acitretin on Serum Biomarkers Levels in Patients with Psoriasis

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Abstract

Psoriasis is a multifactorial, chronic, inflammatory skin disease of unknown etiology, associated with cytokines and adipokines serum levels changes that may influence disease pathogenesis.

To determine the effect of acitretin on serum IL-10, IL-23, adiponectin, Zn, Mg and copper levels in psoriasis patients.

A case control study that include 50 psoriasis patients, conducted in Tikrit Teaching Hospital. They received acitretin orally for 4 weeks duration course. IL-10, IL-23, adiponectin, Zn, Cu and Mg in serum for all patients determined at the time of enrollement in the study and after 4 weeks of treatment with the drug.

Acitretin reduced the mean PASI in 20 psoriatic patients from 20.97 before receiving treatment to 1.22 after receiving treatment ($P=0.000$). In addition, the mean serum levels for IL-10 reduced significantly ($P=0.000$) from (6.01 ± 4.17) pg/ml before treatment to (1.85 ± 0.54) pg/ml after treatment. Furthermore, Acitretin reduced the mean serum level for IL-23 from (72.08 ± 34.14) pg/ml pre-treatment to (66.1 ± 20.3) pg/ml, post-treatment ($P=0.423$). The mean serum levels of adiponectin in therapeutic group was lower (6.97 ± 3.06) µg/ml than that of baseline value (8.9 ± 3.96) µg/ml, but this result was statistically not significant ($p=0.114$). The mean serum levels of Zinc and copper in therapeutic group was lower than baseline value, but the difference was statistically not significant ($p>0.05$).

Key words: Psoriasis, Acitretin, Interleukin 10 , Interleukin -23, Adiponectin, Zinc, Copper, Magnesium.

الخلاصة

الصدفية مرض جلدي مزمن ومتعدد العوامل ولم يعرف سببه الحقيقي ويزامن مع تغيرات في السايتوكينات والاديبوكينات والتي تلعب دورا في امراضه. وقد كان البحث هو دراسة الحالات والشواهد وتم اجراءها في مستشفى تكريت التعليمي للفترة من بداية كانون ثاني ٢٠١١ لغاية ٢٠١١ تموز ٢٠١١. تم قياس انترليوكين ١٠ وانترليوكين ٢٣ والاديبونكتين والخاصين والنحاس والمغنسيوم في مصل جميع المرضى عند بدأ الدراسة وبعد ٤ اسابيع من العلاج.

ان استعمال استرتين لمدة اربع اسابيع ادى الى خفض مستوى انترليوكين ١٠ بعد العلاج وبفرق ذو قيمة معنوية... اما انترليوكين ٢٣ والاديبونكتين والخاصين والنحاس فقد انخفضت بعد العلاج عنها قبله ولكن ليست ذات قيمة معنوية. نستنتج من الدراسة ان الاسترتين علاج فعال للصدفية ويقلل انترليوكين ١٠ بفرق ذو قيمة معنوية.

Introduction

Psoriasis is a multifactorial, immuno-inflammatory skin disease of unknown etiology with chronic natural course [1]. Doctors have designated several types of psoriasis including erythrodermic, guttate, inverse, pustular and plaque clinical forms[2]. It is fundamentally a disease of human T

cell. The abnormal T cells in psoriasis lead to abnormal epidermal differentiation and hyperproliferation. Where as in normal skin the turnover of epidermis takes 21 to 28 days, in psoriatic plaques it takes 3 to 4 days [3]. T cells secrete or stimulate the production of powerful immune factors called cytokines [4]. Which are peptides, proteins or

glycoproteins that have a fundamental role in communication within the immune system and in allowing the immune system and host tissues cells to exchange information [5].

At the present time, one of the main areas of research in the psoriasis field concerns with the role of cytokines in the pathogenesis of this disease [1]. Psoriatic lesions have a type 1 cytokine profile (i.e., interleukin (IL)-2, interferon (IFN)- γ , and tumor necrosis factor (TNF)- α), without a significant component of type 2 cytokines (i.e., IL-4, IL-5, and IL-10) [6]. Interleukin 10 is a cytokine that play role in immune regulation in patients with psoriasis and exert anti-inflammatory action. Previous report suggests that IL-10 may have therapeutic implication depending on the basis of its induction and increase following treatment of psoriasis [7]. Th17 cells, a T cell subset, were with a role in psoriasis pathogenicity and IL-23 influence their proliferation [8]. Keratinocytes, macrophages and dendritic cells produces interleukin 10 [9].

Acitretin as systemic treatment approach for severe psoriasis exert anti-inflammatory and anti-proliferative function through effects on various cytokines [10]. The acitretin mechanisms of action at the cellular level are not well understood, however, the drug may interfere with natural retinoid intracellular metabolism and activation of retinoic acid nuclear receptors [11].

Acitretin, has relatively low affinity for RARs, but high affinity for CRABP, and has been shown to induce a shift in tretinoin binding from CRABPs to RAR γ heterocomplexes. This suggests that acitretin causes a redistribution of endogenous tretinoin from cytoplasmic to nuclear compartments, thereby indirectly potentiating retinoid activity [12].

However, a wide range of topical and systemic treatment approaches for psoriasis, still there is a gap in this disease therapy. Most of the effective treatment approaches for psoriasis are associated with severe side effects. But

acitretin was not associated with immunosuppression and cytotoxicity side effect of other systemic drugs that are used in the treatment of psoriasis thus this study conducted to evaluate the therapeutic effect of the drug in Iraqi population with psoriasis.

Materials and Methods

Study Design:

A case control, hospital-based study conducted in Tikrit Teaching Hospital from January 1, 2011 to July 31, 2011. Gender and age matched controls were recruited from individuals attending Dermatology Department accompanying their relative patients.

Study Population:

The patients were recruited from outpatient clinic of Dermatology Department. The study included 50 patients with psoriasis vulgaris those were diagnosed by consultant dermatologists according to standard criteria [13]. The psoriasis area and severity index [PASI] for each patient was determined by the same physicians. Of the total, 29 (58 %) were females, and 21 (42%) were males and their ages ranging from 12 to 60 years. The history as well as personal information about patients was obtained by questionnaire. All patients would not take any psoriasis treatments for at least one week before venous blood collection. Twenty three individuals from patients group receive acitretin as the only treatment for 30 days, three patients from them could not continue on that treatment, without giving any reason for their withdrawal, the remain twenty individuals from both genders (eleven female and nine male) the PASI was determined before and after treatment. Informed consent taken from all patients included in the study and the research protocol was approved by the Tikrit University College of Medicine Ethical Committee.

Fifty apparently healthy individual who's matching the patients group in age, sex and BMI, with no history of allergic and medical diseases were chosen from

Tikrit city citizens. Verbal agreement of the chosen patients was obtained before involvement in the study. Blood sample were obtained from the veins of tourniquet forearm of the patients, control and the therapeutic modulation groups, serum collected and stored at -30°C until the time of analysis. Samples showing haemolysis was discarded.

Measurements:

The IL-10, IL-23, adiponectin, Zn, Cu and Mg in serum for all patients, control and therapeutic modulation groups measurement were performed in Postgraduate Research Laboratory, Tikrit University College of Medicine. Adiponectin, IL-10 and IL-23 serum levels determined by ELISA method, while serum levels of zinc, magnesium and copper determined using colorimetric method. All the measurements were performed according to manufacturer's instruction for each kit [14].

Statistical Analysis:

All results were given as the mean and standard deviation. Data analysis was performed by SPSS statistical program (version 16). Differences between psoriasis and controls were tested by using T-test. Also, one way ANOVA was used to test the relation among the three groups (patients, control and therapeutic modulation group). Any P value less than 0.05 was considered significant.

Results

Effect of Acitretin on IL-10 Levels:

The mean serum levels for IL-10 reduced from (6.01 ± 4.17) pg/ml before treatment to (1.85 ± 0.54) pg/ml after treatment with acitretin for 30 days and the difference was statistically highly significant ($P=0.000$), Table 1. The post-treatment serum IL-10 mean value was not significantly ($p>0.05$) different from that in control group (1.48 ± 0.27) pg/ml, Table 2.

Effect of Acitretin on IL-23 Levels:

The mean serum IL-23 level before the treatment was (72.08 ± 34.14) pg/ml and reduced to (66.1 ± 20.3) pg/ml after treatment with Acitretin, however, this

result was statistically not significant ($P>0.05$). In addition, there was a significant difference ($P=0.00$) between IL-23 mean serum level after treatment with acitretin and control group (3.53 ± 8.71) pg/ml, Table 2.

Effect of Acitretin on Adiponectin Levels:

The serum mean value of adiponectin was reduced from (8.9 ± 3.96) $\mu\text{g/ml}$ before treatment to (6.97 ± 3.06) $\mu\text{g/ml}$ after treatment, but the reduction was statistically not significant ($p>0.05$). In addition, both pre- and post-treatment mean serum values of adiponectin were higher than that of control (6.89 ± 4.29) $\mu\text{g/ml}$, but the differences was statistically not significant ($p>0.05$), Table (2).

Effect of Acitretin on Zinc Levels:

The mean serum levels of Zinc in therapeutic group was (91.28 ± 13.01) $\mu\text{g/dl}$ before treatment and increased to (99.47 ± 11.62) $\mu\text{g/dl}$ after treatment, however, the difference was statistically not significant ($p>0.05$), Table 3. Furthermore, the mean serum levels of Zinc in control group was (93.95 ± 13.37) $\mu\text{g/dl}$, which was higher than pre-treatment level and lower than post-treatment level, but the differences was statistically not significant ($p>0.05$), Table (4).

Effect of Acitretin on Magnesium Levels:

The mean serum levels of Mg in therapeutic group was not significantly different from mean values before treatment (2.01 ± 0.08) mg/dl, post-treatment (2.09 ± 0.15) mg/dl and control group (2.03 ± 0.2) mg/dl, Tables 3 & 4.

Effect of Acitretin on Copper Levels:

The mean serum levels of copper in therapeutic group increased from (86.76 ± 3.9) $\mu\text{g/dl}$ before treatment to (94.43 ± 13.75) $\mu\text{g/dl}$ after treatment, however, the difference was statistically not significant ($p>0.05$), Table 3. However, both pre- and post-treatment mean serum values were significantly lower than that in control group (97.96 ± 19.67) $\mu\text{g/dl}$, Table (4).

Table 1: Mean serum levels of cytokines (IL-10, IL-23 and adiponectin) of therapeutic group in comparison to psoriatic patients

Variable	Psoriatic patients		After treatment		P value
	N	Mean $\pm$ SD	N	Mean $\pm$ SD	
IL-10 (pg/ml)	20	6.013 $\pm$ 4.17	20	1.857 $\pm$ 0.54	0.000
IL-23 (pg/ml)	20	72.089 $\pm$ 34.14	20	66.1 $\pm$ 20.3	0.423
Adiponectin (μg/ml)	20	8.907 $\pm$ 3.96	20	6.973 $\pm$ 3.06	0.114

Table 2: Mean serum levels of cytokines (IL-10, IL-23 and adiponectin) of the therapeutic group in comparison to controls

Variable	Control group		After treatment		P value
	N	Mean $\pm$ SD	N	Mean $\pm$ SD	
IL-10 (pg/ml)	20	1.489 $\pm$ 0.27	20	1.857 $\pm$ 0.54	0.635
IL-23 (pg/ml)	20	3.533 $\pm$ 8.71	20	66.1 $\pm$ 20.3	0.000
Adiponectin (μg/ml)	20	6.899 $\pm$ 4.29	20	6.973 $\pm$ 3.06	0.951

Table 3: Mean serum levels of (Zinc, Magnesium and Copper) of therapeutic group in comparison to psoriatic patients

Variable	Psoriatic patients		After treatment		P value
	N	Mean $\pm$ SD	N	Mean $\pm$ SD	
Zn (μg/dl)	20	99.475 $\pm$ 11.62	20	91.289 $\pm$ 13.01	0.083
Mg (mg/dl)	20	2.093 $\pm$ 0.15	20	2.013 $\pm$ 0.08	0.104
Cu (μg/dl)	20	94.436 $\pm$ 13.75	20	86.762 $\pm$ 3.9	0.089

Table 4: Mean serum levels of (Zinc, Magnesium and Copper) of therapeutic group in comparison to controls

Variable	Control group		After treatment		P value
	N	Mean $\pm$ SD	N	Mean $\pm$ SD	
Zn (μg/dl)	20	93.956 $\pm$ 13.37	20	91.289 $\pm$ 13.01	0.732
Mg (mg/dl)	20	2.037 $\pm$ 0.2	20	2.013 $\pm$ 0.08	0.615
Cu (μg/dl)	20	97.964 $\pm$ 19.67	20	86.762 $\pm$ 3.9	0.014

Discussion

Acitretin play a role in skin cells normal growth and reduces lesion formation in patients with psoriasis through prevention of growth of cell and keratinization [14].

The present study indicated that acitretin was effective in treatment of psoriasis vulgaris for a course of one month duration. This suggestion reached since acitretin reduced mean PASI value from (20.97) before receiving treatment to (1.21) post-treatment. In addition, the overall reduction in PASI mean was 94.2% of the baseline. Furthermore, acitretin treatment reduced the mean serum levels for IL-23 before the treatment of (72.08±34.14) pg/ml to (66.1±20.3) pg/ml after treatment; however, this result was statistically not significant. Although (55%) and (70%) of patients receiving acitretin treatment demonstrated a reduction in serum levels of IL-23 and adiponectin respectively. Taking together, these findings indicate that acitretin treatment for psoriasis is an effective treatment resulting in reduction of proinflammatory markers. Furthermore, the reduction and treatment response could be with individual variation.

It is postulated that acitretin acts through variable mechanisms which may be arranged in a sequences that leads to reduction in proliferation, immune response modulation, and anti-inflammatory effects [15-18].

Recent study report that psoriatic keratinocytes secreted high level of RANTES (CCL5), which can induces chemotaxis and activation of T cells, thus may play an important role in the pathogenesis of psoriasis. RANTES expression detected in supernatant of human keratinocytes cell line (HaCaT cells) stimulated with TNF- α and IFN- γ reduced, when cultured with Acitretin. Acitretin can inhibit proliferation and RANTES production of human epidermal keratinocytes, and the latter may be related to the inhibition of nuclear translocations of STAT1 and NF κ B [19].

Recently reported meta-analysis suggest that acitretin as an oral retinoid is approved for the treatment of psoriasis. It is unique compared to other systemic therapies for psoriasis such as methotrexate and cyclosporine in that it is not immunosuppressive. It is, therefore, safe for use in psoriasis patients with a history of chronic infection such as HIV, hepatitis B, hepatitis C or malignancy who have a contraindication to systemic immunosuppressive therapy and require systemic therapy because topical therapy is inadequate and they are unable to commit to phototherapy. Acitretin is one of the treatments of choice for pustular psoriasis. Even though Acitretin is less effective as a monotherapy for chronic plaque psoriasis, combination therapy with other agents, especially UVB or psoralen plus UVA phototherapy, can enhance efficacy [20-22]. However, Caproni et al [23] reported that serum levels of IL-17 and IL-22 are reduced by etanercept, but not by acitretin in psoriatic patients.

In conclusion, this study indicated that acitretin is an effective systemic treatment for psoriasis with limited side effects.

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