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Evaluation of acitretin side effects on Iraqi psoriatic patients

Ahmed H. Kadhim*'1 Dhia'a A. Hassan* Amer H. Chyad**
Abdulstaar M. Khudyar*

* Ministry of health , Baghdad ,Iraq ** department of physiology and pharmacology , College of Veterinary Medicine, Baghdad ,Iraq.

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Summary

Acitretin is the major metabolite of etretinate , an aromatic retinoid that formerly was approved for Psoriasis by exhibiting vitamin A activity. Acitretin was wildly used to improve plaque psoriasis and also for postural psoriasis and erthrodemic psoriasis .The present study focus on the evaluation of the common side effects of acitretin which makes a wide hesitation for Iraqi dermatologists to use it in treatement of psoriasis. Twenty psoriatic outpatient were treated with a dose of 25mg/ day for three continuous months in outpatient clinic of al- noor hospital during 2009 , their lipid profiles , liver and kidney function tests before starting treatment with acitretin considered as a control values. It was noticed that AST level increased significantly during 2nd and 3rd months of treatment and there is no significant change in S. Creatinine and BUN while TG increased significantly in 2nd and 3rd months of treatment.Cholesterol increased in the 3rd month of treatment. There is other important factors should be consider before evaluation the physiological changes may be caused by acitretin like smoking , alcohol intake , obesity and genetic association between psoriasis and other physiological change. However the changes that caused by administration of acitretin were relatively acceptable and not preventive measurement , but continuous monitoring (of TG , cholesterol , liver and kidney function test) still required regularly.

Key words: acitretin,etretinate,psoriatic patients,hesitation.

تقيم التأثيرات الجانبية لدواء الأسيترتين في الأشخاص المصابين بالصدفية

***أحمد حميدكاظم * ضياء عبد حسن ** عامر حكيم جياد**

* وزارة الصحة ,بغداد-العراق ** فرع الفسلجة والادوية كلية الطب البيطري

الخلأصة

الاسترتين هو احد اهم مركبات الايض للأترنيت , وهو علاج اثبت فعاليته في علاج انواع عديدة من داء الصدفية حيث يظهر فعالية تشابه فعالية الفيتامين (ا) في علاج الصدفية , الدراسة الحالية تحاول تقييم بعض تأثيرات الاسترتين المنتشرة مثل التأثير على فحوصات وظائف الكبد والكلى حيث ان هناك تخوفا وترددا لدى كثير من أطباء الجلدية العراقيين من تأثيراته الجانبية. الدراسة تناولت عشرين مريضا أعطوا جرعة فموية مقدارها (٢٥ ملغم) يوميا من الاستريتين لثلاث أشهر متتالية في العيادة الخارجية في مستشفى النور ببغداد خلال عام ٢٠٠٩ وتم متابعة وظائف الكبد والكلى ومستوى الدهون لدى هؤلاء المرضى قبل وبعد إعطاء الاسترتين, ولوحظ ان مستوى الـ(AST) ارتفع بشكل ملحوظ خلال الشهر الثاني والثالث من العلاج , ولم يكن هناك زيادة ملحوظة في مستويات الـ(S.Cratnine) والـ(BUN), من خلال الدراسة يتبين ان هناك عوامل عديدة يجب ملاحظتها قبل وصف الاسترتين لمرضى الصدفية مثل التدخين والسمنة و تناول الكحول ومتغيرات فسلجية اخرى , لكن التأثيرات الجانبية للاسترتين بقيت ضمن المستويات التي لاتمنع من استخدام الدواء مع ضرورة استمرار الفحوصات الدورية لوظائف الكبد والكلى ومستوى الدهون في الدم.

Introduction

Psoriasis is a non-infectious , chronic inflammatory disease of skin , characterized by well – defined erythematous plaque with silvery scale , with a predilection for the extensor surfaces and scalp ,and a chronic fluctuating course (1). One to three percent of most population have psoriasis (2). In general Retinoid include three generation , its include natural compounds and synthetic derivative of retinol that exhibit vitamin A activity (3) . And if applied topically remains chiefly in the epidermis with less than 10% absorption into the circulation and then metabolized by the liver and excreted in bile and urine (4) in spite of the advantage of the remaining of the retinoid on the epidermis chiefly but this may produce erythema with wild peeling and dryness. (4). Acitretin is the major metabolite of etretinate , an aromatic retinoid that formerly was approved for Psoriasis but etretinate withdrawn from the market in 1998 because of its undesirable pharmacokinetics (3) (also see FDA website). Acitretin which represent 2^{nd} generation of retinoid(see FDA) consider quite effective in the treatment of psoriasis specially postular and erythroeic psoriasis (2) , and its wildly use to improve plaque psoriasis (4). Its inhibit psoriatic hyperkeratosis over 4- 6 weeks .(5) common toxicities include dry skin , cheilitis , hyperlipidemea and elevation of transaminases (6), dry lips and hair thinning or lost is common. (2) Its given at a dose of 25 – 50 mg / day (4) Or its given in dose 10 – 25 mg/ day (2) In general dose higher than 0.5 mg/kg/day may associated with greater side effect like loosing of all hair (2) Its more advantageous to start with low dose 10-25 mg/day. The overall rate of complete remssion is generally < 50%. higher doses (50 – 75 mg /day) result in more complete , responses but as associated with significantly increased side effect (7). The most important of these side effect is the dislipidymea because triglyceride may raise in nearly 25% of patient, and less commonly cholesterol and low density lipoproteins. In these time patient suffer from decreased high density lipoprotein. Elevation of transaminasescan occur also (7). Large percent of psoriatic patient in population which may reach 2% of general population(8) may lead to the appearance of these side effects more clear among poplation. While etritenate (first generation of retinoid) has undesirable pharmacokinetic in treating psoriasis (3) , acitretin(2^{nd} generation of retinoid) considered the safest systemic treatment of psoriasis (2). The aim of our study is to investigate these side effects of acitrtetin (dislipidymea , liver and kidney function test) in Iraqi psoriatic patient .

Material and methods

Twenty patients with a dermatologist – confirmed diagnosis of chronic psoriasis (13 male and 7 female , age rang 9- 60 years , 12 with BMI(body mass index) more than 30 and 3 with BMI more than 5 and 20 with BMI mor than 25, 10 smoker and 10 non smoker). All of these patients didn't currently used any systemic or phototherapy. All patient advice to avoid any drug can interfere with the tests result for 24 hr. before the test initiation , and if possible all drug should be stopped during these period. Also patients were instructed to stop eating 12-14 hr. before testing and the last meal most compose of low fat diet. Only water was permeated , also no alcohol should be taken 24 hr. before sample taken. The first samples were collected before treatment as a baseline level and then for three sequenced months after initiation of treatment of acitretin. All patient treated in fixed pattern of 25 mg /day of Neotigason® capsule (acitretin from Roch laboratory in Germany). Blood sample of 8ml were obtained by vein puncture and in EDTA free tubes, blood sample were left and at room temperature for 1/2 hr. for coagulation then centrifuged at 3000 rpm and the serum collected stored in deep freeze at -20 c until the time of analysis. Our

values expressed as mean ± SE (standard error) , to determine the differences between baseline values and after three months of treatment we use T-test and p value < 0.05 considered as significant difference.

Results

Table-1-shows that AST level increased significantly during 2nd and 3rd months of treatment and there is no significant change in S. Creatinine and BUN(tabele2) while TG increase significantly in 2nd and 3rd months of treatment(tabele3). AST levels increased significantly (P<0.05) during the 2nd (12.7%) and 3rd (15.08%) months of therapy with respect to baseline readings.

Table (1): Liver function tests(by masuring AST and ALT enzyme levels U/L) in patients received acitretin therapy for 3 months.

Liver Function Test		
Duration of Therapy	**AST (U/L)**	**ALT (U/L)**
Baseline	**12.60 ± 0.91**	**12.00 ± 0.61**
1 Month	**12.90 ± 0.82**	**11.75 ± 0.62**
2 Month	**14.20 ± 0.78 ***	**12.55 ± 0.55**
3 Month	**14.50 ± 0.85 ***	**12.70 ± 0.5**

Table (2): kidney function tests in patients received acitretin therapy for 3 months.

Kidney Function Test		
Duration of Therapy	**BUN(µmol/L)**	**S.Creatinine(µmol/L)**
Baseline	**4.64 ± 0.22**	**71.60 ± 3.68**
1 Month	**4.63 ± 0.22**	**73.25 ± 3.4**
2 Month	**4.64 ± 0.22**	**73.05 ± 3.8**
3 Month	**4.75 ± 0.19**	**73.80 ± 4.41**

Table (3): Lipid Profile in patients received acitretin therapy for 3 months.

Lipid Profile		
Duration of Therapy	**Triglycerides(mg/dL)**	**S.T.Cholesterol(mg/dL)**
Baseline	**1.48 ± 0.19**	**4.56 ± 0.83**
1 Month	**1.58 ± 0.14**	**4.52 ± 0.70**
2 Month	**1.71 ± 0.13 ***	**4.68 ± 0.75**
3 Month	**1.79 ± 0.15 ***	**4.82 ± 0.78 ***

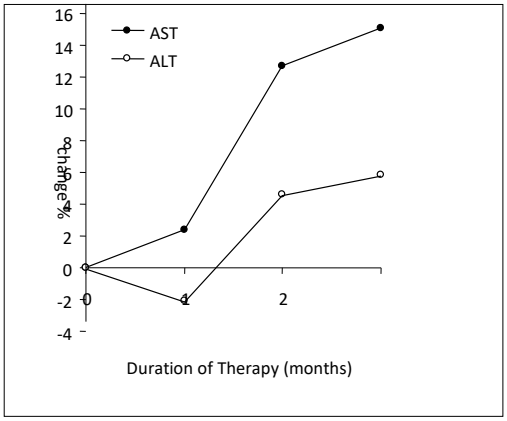

Fig. (1): Percent change in liver transaminases in patients treated with acitretin for 3 months.

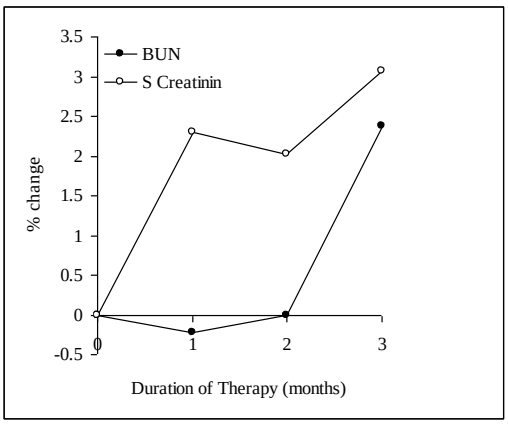

Fig. (2): Percent change in blood urea and serum creatinine in patients treated with acitretin for 3 months.

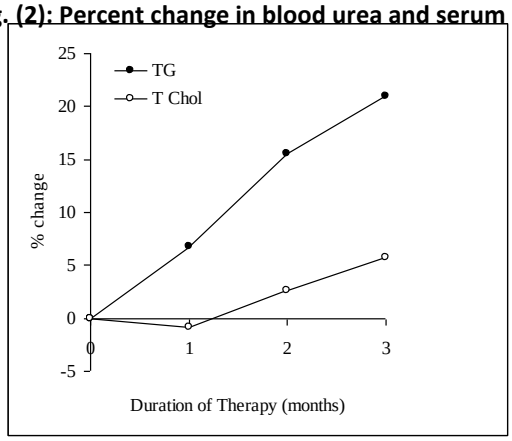

Fig. (3): Percent change in serum triglycerides and total cholesterol in patients treated with acitretin for 3 months.

Discussion

In this study approximately 35% of patients have higher TG level than normal and 25% of patient with cholesterol level higher than normal untill before acitretin treatment initiation. It was founded that AST level increased significantly ($p < 0.05$) during the second (12.7%) and third (15.08%) months of therapy with respect to baseline reading (table,1and fig,3). While there is no significant change in *ALT* levels during the coures of therapy (table,1and fig,3). This is may be due to the metabolism of acitretin occurs mainly in the liver and takes too long time (4) while the concern for liver toxicity in psoriasis has been supported by research suggesting that significant liver damages are three times more likely in these patients when compared with rheumatoid arthritis RA at the same dosage of retinoid treatment , and liver cirrhosis

may occurs without significant increases in transaminase (9and10). Also there is established facts about the high prevalence of dislipidemia in psoriatic patient (11,12and13) some of those patient on lipid lowering drug like (HMG- CO A reductase inhibitors) and nicotinic acid which in turn may cause elevation in hepatic transaminases or lead to abnormal liver function test(14). Triglycerides (TG) levels increased significantly ($p<0.05$) during the second (15.45%) and third (20.95%) month of therapy with respect to baseline reading. While cholesterol levels increased significantly during the third month(5.7%) of therapy with respect to the baseline reading (table,3and fig,3). It has been found that obesity is common in patient with psoriasis , occurring up to two times more often in psoriatic patient than general population.(15 and 16). As far as the directionality of the psoriasis – obesity association is concerned. A prospective study recently suggested that obesity could be a risk factor for incident psoriasis(17). However , others suggest that lifestyles associated with psoriasis may favor obesity (16).In spite of that, the connection between obesity and psoriasis has not yet been fully determined unlike the decreased prevalence of obesity typically found in populations of patents with other sever form of chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease (IBD), the prevalence of obesity in patients with psoriasis increased with disease severity.(18,19and20). The most important thing is that obesity is associated with propensity to develop dislipidemea.(21and22). As with obesity, controversy existed whether dislipidemea is consequence of or a risk factor for psoriasis (16and17). In general there is atherogenic dislipidemea profile in psoriatic patients as in this results .Excess adipose tissue lead to over production of inflammatory cytokines (TNF – alpha and IL – 6) associated with parallel decreased in anti-inflammatory adipokines , especially adiponectins [adipose – specific hormones involved in obesity] (23). To explain the role of adeponectin , low level of adiponectin lead to increase body mass index BMI and triglyceride level due to inverse correlation between adiponecin with BMI and TG (24). From other hand there is negative correlation between obesity and adiponectin level , So obese psoriatic patient tend to have more BMI and TG level than healthy individual (25and26), so all of these changes may consider as a marker of inflammation which is common in psoriasis and in turn these changes promote lipolysis and a proatherogenic lipid profile. (11,12and13). Furthermore a genetic predisposition of dislipidemia in psoriasis may exist. Although most of the lipid profile study do not consider psoriasis disease duration , a Swedish study may be the first one to evaluate lipid profile at the onest of diagnosis(within 12 month) and showed an abnormal lipid profile(13) and when we detect abnormal lipid profile at the onset of psoriasis this suggest that they may be genetically acquired,(27and28). This is relatively compatible with our investigation which show that nearly 35% of patients have higher TG level than normal and 25% of patient with cholesterol level higher than normal untill before acitretin treatment initiation. Some studies try to test the hypothesis that transient impairment of glucose and lipid hematostasis might be sustained by the effect of retinoid on adipocytes function and particulary on the production of resistin and adiponectin two adipose – specific hormone involved in obesity(29and30). In fact it has been reported that retinoic acid and vitamin A reduce the expression of both in rodent white adipocytes, (31and32). In this researching trip we notice that cholesterol level decreased in the first month of treatment with acitretin The decrement of cholesterol mean value during the first month of acitretin therapy agree with the thought that acitretin cause down regulation of expression of apolipoprotien A-1 mRNA ,a major component of HDL- cholesterol, and this decrement may occur by all – trance retinoid. These fact established by some studies on rat hepatocyte.

(31,32&33). Also, there is another interfering factor like smoking which is more common in psoriatic patient than in general population (1.3 to 2.1), (34) and approximately 80% of psoriatic patient had smoked cigarette before the onset of psoriasis (35). So this may lead to increases in triglyceride level and have opposite effect on HDL – C . (36&37). There are other important factors should be consider before using like smoking , alcohol intake , obesity and genetic association between psoriasis and other physiological change. Eventually the changes that caused by acitretin using were relatively acceptable and not preventive measurement , but continuous monitoring (of TG , cholesterol , liver and kidney function test) still required regularly.

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