J. Appl. Cosmetol. 11, 107-112 (October-December1993)

NORMALIZING EFFECT OF GAMMA-LINOLENIC ACID ON ETRETINATE-INDUCED HYPERTRIGLY-CERIDEMIA IN PSORIATIC PATIENTS: PRELIMINARY RESULTS.

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Receveid: *December 12, 1993.Presented at the "68° Congresso Nazionale SIDEV" Pisa, June 23-26, 1993*

Key Words: *Psoriasis; Etretinate; Gamma-linolenic acid; Hypertriglyceridemia.*

Synopsis

Retinoids are a group of synthesis compounds having vitamin A as their precursor. Among retinoids, etretinate is commonly used, alone or in combination with PUVA (8-methoxypsoralen+UVA), for diffuse and resistant psoriasis. However, eretrinate may induce local (severe skin dryness, flaking, cheilitis and fissures) and systemic side-effects. Among the systemic side-effects of etretinate, increased triglycerides, VLDLs, and cholesterol are frequently detected, which may cause treatment discontinuation. In the present paper 41 psoriatic patients undergoing Re-PUVA (Etretinate+PUVA) were considered. One month after the beginning of the therapy, 27 of them were additionally treated with gamma-linolenic acid, because of the dryness and itch induced by etretinate. During Re-PUVA treatment 11 out of these 27 patients showed increased triglyceride and cholesterol levels. A 2 month-treatment with gamma-linolenic acid induced an improvement of the cutaneous side-effects of eretrinate. Moreover, a statistically significant decrease of triglyceridemia ($p<0.01$) and cholesterolemia ($p<0.01$) was detected following the treatment with gamma-linolenic acid. These results demonstrate that association of gamma-linolenic acid is useful in contolling dyslipidemia if Re-PUVA treatment has to be continued to achieve clearing of psoriasis.

Riassunto

I retinoidi sono una famiglia di composti di sintesi che hanno il loro precursore nella Vit. A. I più diffusi in ambito terapeutico dermatologico sono l'etretinato, l'isotretinoina e l'acitretina. Questi farmaci agiscono promuovendo la differenziazione cheratinocitaria ed esercitano un effetto immunomodulatore. In particolare, l'etretinato trova indicazione, da solo o in associazione con PUVA-terapia (8-metossipsoralene+UVA), nel trattamento delle forme più estese e resistenti di psoriasi. L'etretinato, tuttavia, può indurre effetti collaterali sia locali (secchezza cutanea marcata, desquamazione, cheilite e ragadi) che generali. Tra gli effetti sistemici collaterali che l'etretrinato può indurre si rileva più frequentemente un innalzamento dei trigliceridi, delle VLDL e del colesterolo che possono indurre a sospendere la terapia prima del conseguimento di una risposta clinica soddisfacente. Nel presente lavoro vengono riportati i dati relativi al contollo dell' iperlipemia indotta da etretinato me-

diante l'impiego di acido gamma-linolenico per via generale. Tale acido grasso essenziale è stato impiegato in epoca recente per il controllo del prurito e della secchezza cutanea nei soggetti affetti da dermatite atopica; per questo motivo abbiamo ritenuto di utilizzarlo (480 mg/os/die) in un gruppo di 27 pazienti psoriasici che, in corso di trattamento con Etretinato (Etretinato 0,5 mg/Kg/os/die)+PUVA (Re-PUVA), avevano manifestato marcata secchezza cutanea e prurito, imputabili al retinoide. Ad un mese dall'inizio della terapia, 11 dei 27 pazienti affetti da secchezza cutanea e prurito avevano presentato anche anomalie del quadro lipidico, imputabili al trattamento con etretinato. Il trattamento con acido gamma-linolenico per 2 mesi, oltre a determinare un miglioramento degli effetti collaterali cutanei, ha indotto anche una riduzione statisticamente significativa della trigliceridemia ($p<0,01$) e della colesterolemia ($p<0,01$). Pertanto anche se gli innalzamenti di colesterolo e trigliceridi nella nostra casistica sono risultati, durante al terapia con etretinato, di moderata entità, l'utilizzo di acido gamma-linolenico ci ha permesso di continuare la terapia Re-PUVA con una certa sicurezza per il paziente. Come noto, infatti, la popolazione psoriasica risulta esposta ad un aumentato rischio di accidenti cardiovascolari, in associazione a diabete ed obesità, e l'ipertrigliceridemia iatrogena costituirebbe quindi un ulteriore fattore di rischio.

INTRODUCTION

Retinoids are a family of synthesis compounds having vitamin A as their precursor (1,2).
Among retinoids, etretinate (3,4), isotretinoin (5) and acitretin (6) are most commonly used in dermatologic treatment.
These drugs act on the keratinization process by enhancing the differentiation of keratinocytes and inhibiting their proliferation. In addition, they influence the immunomodule killer lymphocytes (7) and neutrophils (8) (chemotaxis reduction). The main field of use of retinoids includes psoriasis, some skin T-lymphomas, and other diseases characterized by keratinization changes, such as ichthyosis, Darier's disease, palmoplantar keratodermas, and acne cystica and conglobata.
Specifically, etretinate is recommended for diffuse and resistant psoriasis, and is used alone or in combination with PUVA or topical drugs (9). However, etretinate may produce systemic and local side-effects (severe skin dryness, flaking, cheilitis, and fissures). Among the possible systemic side-effects of etretinate, increased triglycerides, VLDLs, and cholesterol are most frequently detected (10,11,12). As a result, treatment must be discontinued before a satisfying clinical response is obtained.
This paper deals with data on the response of etretinate induced hyperlipemia to the systemic administration of gamma linolenic acid. This essential fatty acid was used in a group of patients treated with etretinate+PUVA (Re-PUVA) to reduce skin dryness due to etretinate.

MATERIALS AND METHODS

A group of 41 male patients with diffuse psoriasis was treated with Re-PUVA (Etretinate* 0.5 mg/kg/ orally given daily in combination with 8-methoxypsolaren (**) 0.6 mg/kg orally given three times a week.

Before treatment, all patients had normal hematochemical values, specifically for serum lipids (cholesterol < 200 mg/dl, triglycerides < 150 mg/dl). During treatment, 27 patients developed severe skin dryness and itching.
A further hematochemical examination, performed a month after the beginning of treatment, detected hypertriglyceridemia and hypercholesterolemia due to etretinate treatment in 19 patients. Specifically, 11 patients out of 27 with skin dryness and itching also showed lipid imbalance.
The maximun peaks for cholesterol and triglycerides were, respectively, 348 mg/dl and 322 mg/dl, while they exceeded 210 mg/dl and 150 mg/dl in all other patients (Tables 1 and 2).
Re-PUVA treatment had to be continued due to persistent psoriatic lesions. In order to control skin dryness and itching induced by etretinate, patients were orally given gamma linolenic acid (***) (480 mg/daily), which had been already used to control skin dryness and pruritus in Atopic Dermatitis. Gamma-linolenic acid 480 mg were orally used daily for at least two months in the patients considered.

(*) Tigason®, Roche
(**) Oxsoralen®, Lifepharma
(***) Efagel®, Mavi

RESULTS

Gamma linolenic acid proved effective in controlling skin dryness and itching in 15 patients out of 27. The statistical analysis of data revealed a statistically significant increase both in cholesterolemia ($p < 0.01$) and triglyceridemia ($p<0.01$) after a one-month treatment with etretinate (Table 3). An hematochemical examination, performed about three months after beginning of Re-PUVA and about 60 days after the beginning of treatment with gamma linolenic acid, revealed a decrease in cholesterolemia and triglyceridemia in 7 out of 11 patients (Tables 1 and 2). The overall analysis showed a statisti-

Table I.

BLOOD CHOLESTEROL CHANGES IN PSORIATIC PATIENTS AFTER TREATMENT WITH ETRETINATE AND AFTER ADMINISTRATION OF GAMMA LINOLENIC ACID (ANALYSIS DATA, MG/DL).

PATIENTS	BASIC LEVEL	AFTER ETRETINATE	AFTER ETRETINATE PLUS GAMMA-LINOLENIC ACID
1) F.F. 58ys	200	348	288
2) M.A.45ys	195	251	184
3) P.A. 25ys	185	221	190
4) C.A. 55ys	190	271	188
5) C.G. 44ys	190	292	280
6) R.G. 28ys	179	225	190
7) P.P. 58ys	200	295	245
8) S.G. 36ys	187	267	281
9) P.A. 59ys	182	232	185
10) G.V. 36ys	190	228	178
11) C.Z. 37ys	197	275	195

Table II.

TRIGLYCERIDEMIA CHANGES IN PSORIATIC PATIENTS AFTER TREATMENT WITH ETRETINATE AND AFTER ADMINISTRATION OF GAMMA LINOLENIC ACID (ANALYSIS DATA, MG/DL).

PATIENTS	BASIC LEVEL	AFTER ETRETINATE	AFTER ETRETINATE PLUS GAMMA-LINOLENIC ACID
1) F.F. 58ys	138	310	165
2) M.A.45ys	130	192	133
3) P.A. 25ys	135	322	145
4) C.A. 55ys	125	220	140
5) C.G. 44ys	132	195	189
6) R.G. 28ys	98	187	135
7) P.P. 58ys	145	195	175
8) S.G. 36ys	130	173	180
9) P.A. 59ys	100	196	139
10) G.V. 36ys	135	199	135
11) C.Z. 37ys	136	179	132

cally significant decrease in triglycerides ($p<0.01$), which had nearly returned to their normal level (Table 3). Cholesterolemia still exceeded its basic level ($p<0.02$), even though it was considerably lower than its average level measured after a one-month treatment with etretinate and before treatment with gamma linolenic acid ($p<0.01$) (Table 3).

(19). In addition, they are known as being able to play immunomodulating role on several cell populations (macrophages, langerhans cells, neutrophils, eosinophils, circulating lymphocytes), also by normalising the production of some cytokines (IL-2, leukocyte migration inhibition factor) (20,21). The increase in cholesterol and triglyceride levels is one of the side effects of

Table III.

CHANGES IN SERUM LIPID LEVELS (MG/DL) AFTER TREATMENT WITH ETRETINATE AND WITH ETRETINATE PLUS GAMMA LINOLENIC ACID..

	CHOLESTEROL	TRIGLYCERIDES
Basic level	190,45+7	127,64+15,05
After etretinate	264,09+38,52*	215,27+52,27*
After gamma linolenic acid	218,54+45,03	151,64+21,33

* $p<0.01$ increase after 30 days of etretinate compared to both the basic and final levels

DISCUSSION

All retinoids in general, and, specifically, etretinate are able to modulate keratinocyte growth and differentiation (14).

Retinoids are regarded being able to perform such regulatory functions by changing the genomic expression of target cells (15). They may exert an influence on the ribonucleic acid, which promote changes in the expression of specific proteins (16).

However, their effects on keratinocyte growth and differentiation do not seem to depend on a modified binding with EGF (17). Furthermore, auto radiographic investigations sbowed that, in psoriatic patients, etretinate causes a reduced incorporation of tritiated thymidine and an enhancement of DNA synthesis time in keratinocytes (18).

On clinical ground, this turns into a marked decrease in keratin production. Retinoids are thought to exert an anti-inflammatory effect and to influence the metabolism of arachidonic acid the systemic administration of retinoids, and of etretinate in particular.

Usually, the increased lipid level is persistent during the entire period of treatment with etretinate. Lipide are expected to return to their basic level 4-8 weeks after treatment is discontinued (22).

Studies on lipoprotein fractions during etretinate treatment may show an increase in both triglycerides and their VLDL fraction in some patients. As regards the changes in cholesterol during etretinate treatment, evidence is obtained of an increase first in the VLDL and then in the LDL fraction. Also, it should be taken into account that HDL cholesterol decreases slightly after treatment with etretinate, and with isotretinoin combined with acitretin. The above-mentioned changes in lipid levels due to etretinate may result from the following:

1) Increased VLDL synthesis or reduced catabolism of VLDL into intermediate and low density lipoproteins (23, 24).

2) Increased synthesis of these lipoproteins, as

occurs in diabetes hyperlipemia and familial hypertriglyceridemia. This hypothesis is also supported by the knowledge of the hypolipidemic effects of the eicosapentaenoic acid (omega-3 fatty acid) on retinoid-induced hypertriglyceridemia (25, 26).

Gamma linolenic acid (omega-6 fatty acid contained in borage oil) may be assumed to cause a considerable decrease in triglycerides (and in cholesterol) in psoriatic patients treated with etreninate, through the inhibition of VLDL production by the liver.

Despite, cholesterol and triglyceride slight increase during etretinate treatment, in the cases under consideration, Re-PUVA treatment was safely continued by using gamma linolenic acid. As is known, psoriatic patients are more exposed to cardiovascular disorders associated with diabetes and obesity (27-29). Further investigations are needed to elucidate these preleminary results through a more detailed analysis of the lipid metabolism of psoriatic patients treated with Re-PUVA and gamma linolenic acid.

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