Effect of Topical Simvastatin Therapy on Patients with Psoriasis

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Abstract

Objective: Study the effect of simvastatin ointment on tissue expression of inflammatory mediators associated with pathogenesis of Psoriasis such as TNF-α, , IL-6 and ICAM-1.

Background: Psoriasis is a common and complex inflammatory disease, which was described as the chronic systemic T-cell-mediated inflammatory condition characterized by the skin and joint manifestation. The patients with psoriasis are usually presented with a white-silvery scaly lesion covering various parts of the body.

In psoriatic lesions, epidermal Keratinocytes produce a variety of inflammatory mediators, such as TNF-α, IL-6, ICAM-1 will stimulate the abnormal proliferation which will cause the psoriasis characteristics to appear.

Simvastatin is an anti-hyperlipidemic agent that acts by competitive, reversible inhibition of the HMG-CoA, the rate-limiting step in cholesterol biosynthesis.

Materials and Method: The study has been carried out on 44 patients suffering from mild to moderate chronic plaque psoriasis; patients with plaque psoriasis will be randomly divided into two groups, the first group was the Placebo group (n 22) whose patients have directed to have placebo plus topical steroid (***Dermosalic ointment***) ® (Betamethasone dipropionate 0.5 mg /g and salicylic acid 30 mg /g) two times for a period of 8 weeks.

The second group was the Simvastatin group (n-22) whose patients have been directed to have Simvastatin ointment 5% two times per day in addition to (***Dermosalic ointment***)® (Betamethasone dipropionate 0.5 mg /g and salicylic acid 30 mg /g) for a period of 8 weeks. Before and after the eight weeks; The skin biopsy samples have been taken from patients in the two groups at baseline and after eight weeks of treatment used to measure concentrations of TNF-α, IL-6, and ICAM-1.

Conclusion: The present study indicated the fact that Simvastatin ointment plus topical steroid improvement of psoriasis by reduce concentration of inflammatory mediators.

Keywords*: Simvastatin ointment , psoriasis, Topical steroid.*

Introduction

Psoriasis is a common and complex disease affecting about 2% to 3% of the world's population. [27] .was described as the chronic, systemic T-cell-mediated inflammatory condition associated with skin and joint manifestation. The patients with psoriasis are usually presented with a white-silvery scaly lesion covering various parts of the body. [29]. In psoriatic lesions, epidermal Keratinocytes produce a variety of inflammatory mediators, such as cytokine/chemokines [10]. At present, psoriasis is an immunological disorder associated with abnormal keratinocytes proliferation mediated by T-lymphocytes [(20, 15, 21)]. Psoriasis is related to an over expression of pro inflammatory cytokines

of Th1 cells, and under expression of Th2 cytokines. Now, the effects of cytokines in psoriasis pathogenesis are investigated. However, the biologic activities of cytokines in the in vitro ,to the in vivo models in psoriasis, there may be consider as much more complex interactions among individual cytokines in vivo than expected from the in vitro situation [18]. Circulating level of TNF-α is increased in psoriasis disease, and correlated with disease severity [5,3]. TNF-α regulating the ability of antigen-presenting cells (APS) similar to dendrites cells to activate T- cells. [28].

TNF- α stimulate the expression of C-reactive protein (acute phase response), cytokines such as IL-6 (responsible for T- cell proliferation, and Keratinocyte hyper proliferation); and chemokines such as CCL20 (recruitment of myeloid dendrites cells and T-17 cells) and IL-8 (for recruitment of neutrophils).in the up regulation of intercellular adhesion molecule-I (ICAM-1), TNF-α mediated of the infiltration of inflammatory cells similar to T-cells ,and monocytes to the skin. As the role of regulatory T- cells in the pathogenesis of psoriasis remains to be elucidated, IL-6 is thought to render effectors T- cells refractory to regulatory T-cell-mediated suppression. [12] · Plaque psoriasis is considered the commonest type of the disease accounting for 80%–90 % of all psoriasis conditions. The psoriatic lesion varies in diameter from one to several centimeters, which may be single or multiple lesions covering almost any part of a body [21]. The lesions are relatively spread bilaterally symmetrically and most often to be found in the lumbosacral area, knees, scalp, and elbows [8]. Topical types of treatment can used for any severity of psoriasis; with limitations based on patient compliance, specific patient needs, and therapy response. It is commonly accepted that a psoriasis-affected BSA (body surface area) of up to 20% is suitable and is best treated with topical agents using mono therapy. [24]. Topical corticosteroids, the most widely prescribed psoriasis treatment, are effective in the treatment of psoriasis due to their anti-inflammatory, ant mitotic, immunosuppressive and anti-purity properties. [17].

Topical corticosteroids when using for long-term, especially the more potent such as clobetasol, may also be associated with side effects in the skin such as (atrophy; contact dermatitis; hypertrichosis; folliculitis; hypopigmentation; perioral dermatitis; stria; telangiectasis; purpura traumatic ,and suppression of hypothalamic-pituitary-adrenal axis). [25, 13].

Inhibitors of HMG-CoA reductase (statins) are commonly used to control blood lipid disorder in medicine. Large clinical studies have shown that patient with or without coronary artery disease, statins significantly decrease cardiovascular morbidity and mortality.

It has also been reported that the use of HMG-CoA reductase inhibitors has

immunosuppressive effects. Statins are reductase inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A and besides treating dyslipidemia, pleiotropic anti-inflammatory and immune modulator effects have been found· [4,7].

statins has been report to cause a reduction in TNF-α, IL-6 ,and malondialdehyde (MDA), together with an increased in superoxide dismutase (SOD) act as antioxidant ,and cardio protective action. [22]

Because statins have different pleiotropic effects ; new unusual therapeutic modalities for various pathological disorders such as psoriasis; sepsis; alopecia; wound healing ,and inflammatory diseases are potentially.

Patients and methods:

The present study was conducted from period December-2018 to June- 2019. This study was permitted by Kufa university / College of medicine (Ethical Committee) for clinical trial. Samples were composed from the out patients clinic of Dermatology in AL-sadder teaching hospital clinic .

A total of 44 patients, 25 male, and 19 females were included in this study. patients with plaque psoriasis will be randomly divided into two group:

placebo group: twice daily placebo plus topical steroid **(Dermosalic ointment)®** were 22 patients (12 patients males; and 10 patients females).

Simvastatin group: Patients treated with (5 % simvastatin ointment) plus topical steroid **(Dermosalic ointment)®** were 22 patients (13 patients males; 9 patients females)

The libratory study has been conducted in the middle Euphrates cancer unite.

Collection of Samples

Samples of skin biopsy were taken from patients with psoriasis by using a punching tool(5 mm). Five mm of skin were obtained from each subject put into plain disposable tubes contain 10cc normal saline for Elisa was stored at -80˚C in the deep freezer until analysis. Other samples put in formalin for histopathology study.

Homogenization of Samples [30]

Place the tissue sample in eppendorf tube (1.5 cc) by using clean tools, and place it on ice as quick as possibly to prevent degradation with protease. After that add for each 5 mg weight pieces of skin tissue about 300 µL from extraction buffer to eppendorf tube on ice and homogenized manual for about 15 min.

After that Centrifuge by using ice micro centrifuge for 30 min at 14,000 rpm at 4C, when complete take the supernatant by using micropipette to a fresh eppendorf tube and store at -80C.

Statistical Analysis

Data of patients in both studied groups analyzed by using the statistical package version 25, IBM, US, 2017. Descriptive statistics of the variables and studied parameters presented as mean and standard deviation. Gender presented as frequencies and proportions with male to female ratio. Independent two samples students t-test was used to compare the mean difference of a parameter and also used to compare the mean age between both groups. Paired one sample T-test was used to compare the mean of a parameter before and after treatment in each group. Curve estimation, regression analysis was used to assess the correlation between PASI score from one side and each of ICAM-1, IL-6, and TNF-α after treatment from the other side in group 2. R-value which represented the correlation coefficient was calculated. Finally, results were presented in tables and figures with explanatory paragraphs for each using Microsoft Office Word Software for windows version 2013.

Results

Effect of simvastatin on inflammatory mediators

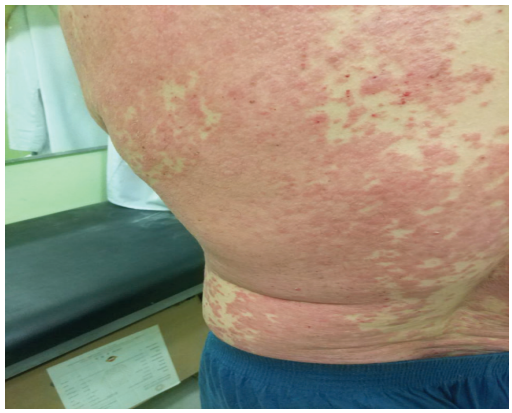
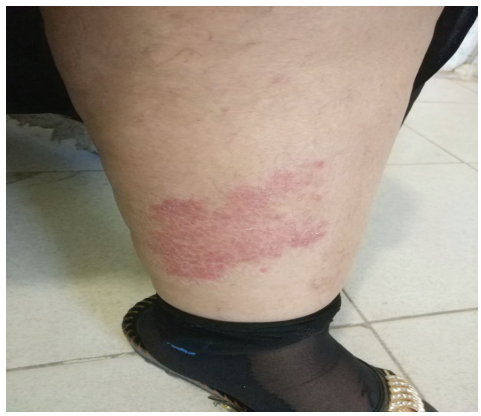
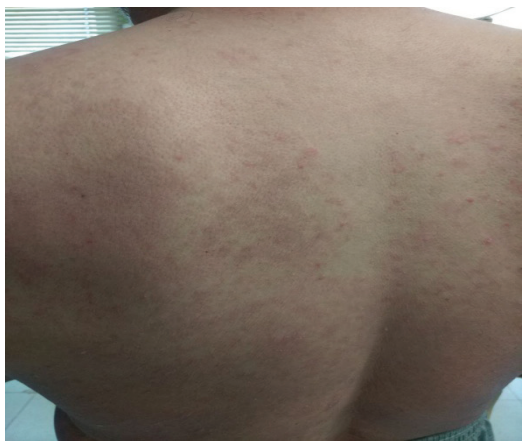
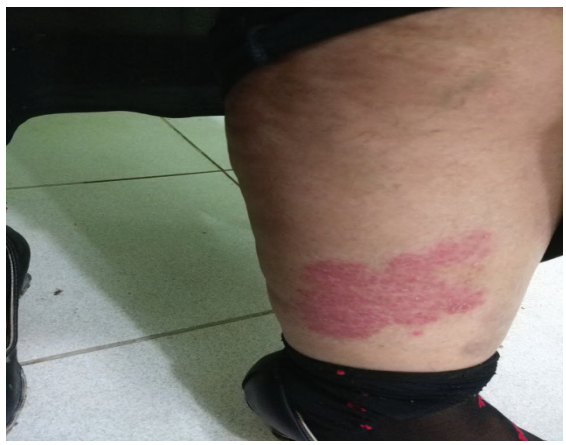
There were not statistically significant difference in baseline of inflammatory mediator values TNF-α ,IL-6 and ICAM-1 between both groups. there were a statistically significant decrease ($p<0.05$) in TNF-α ,IL-6 and ICAM-1 after 8 weeks of simvastatin treatment in comparison with baseline in simvastatin treated group, and with that of placebo treated group after 8 weeks .

parameter	Placebo group baseline	Placebo group 8weeks	Simvastatin group baseline	Simvastatin group 8weeks
TNF-α Pg/ml	15.85(6.14)	4.73(1.88)	12.09(5.21)	7.79(3.81)
IL-6 Pg/ml	77.14(26.54)	29.12(13.10)	52.71(23.18)	9.03(4.22)
ICAM-1 Pg/ml	1.08(0.14)	0.98(0.35)	0.99(0.17)	0.85(0.18)

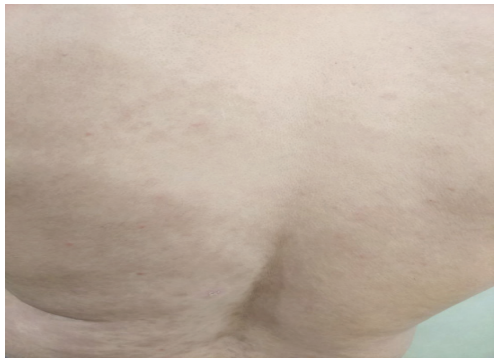
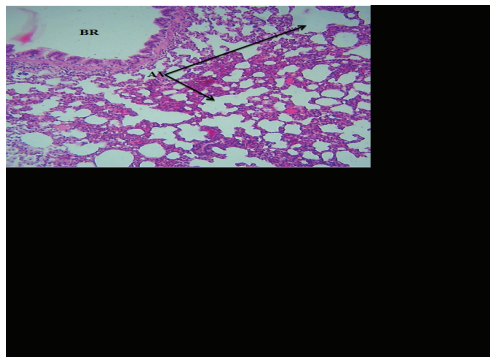
change of TNF-α, IL-6 and ICAM-1 concentration (pg/ml) of psoriatic patients of the simvastatin and placebo groups. Data expressed as mean ± SD (N=22 in each group) using paired T-test.

The Mean Differences of ICAM-1, IL-6 and TNF level in both groups after treatment :

Parameter	Group	N	Mean	SD	P-Value
ICAM-1 Pg/ml	**Placebo**	**22**	0.10	0.03	**0.007***
	Simvastatin	**22**	0.14	0.06	
IL-6 Pg/ml	**Placebo**	**22**	44.97	3.26	**0.364***
	Simvastatin	**22**	42.10	5.31	
TNF-Alpha Pg/ml	**Placebo**	**22**	11.12	3.34	**0.001***
	Simvastatin	**22**	4.30	2.65	
***significant**					

	Simvastatin group	**Placebo group**
At base-line		
After 2weeks		

Cont... **The Mean Differences of ICAM-1, IL-6 and TNF level in both groups after treatment :**

After 8weeks		

Discussion

Psoriasis is considered common recurrent Th1mediated chronic troublesome disease [2]. The recent studies indicated the anti-inflammatory and immunomodulatory effects of statins and used for treatment autoimmune disease , therefore encouraging used of statins for treatment psoriasis [26].

The current study shows a significant reduction of inflammatory mediator such as TNF-Alpha,IL-6 and ICAM-1 levels in both groups '. Compared to baseline concentrations in groups treated with simvastatin and placebo after 8 weeks of therapy, the decline in TNF-Alpha,IL-6 and ICAM-1 concentrations was more significant in simvastatin groups than in placebo group.

[1,] who documented a significant decrease in TNF-α and ICAM-1 in psoriatic hyperlipidemic patients after 8 weeks of getting simvastatin orally. , to best of our knowledge there is no previous research to compare our result with it. [9] the current study showed that simvastatin could reduce the proliferation, apoptosis, TNF-α, IL-6, and vascular endothelial growth factor secretion both in VSMC and macrophage, which is induced by TNF-alpha activated EC.

[19] reported a significant reduction in IL-6 in patients with acute bacterial infection relative to the control group after receiving simvastatin treatment. [6] this study investigated the relationship between the levels of IL-6, tumor necrosis factor-alpha (TNF- α) , and visfatin or simvastatin usage, in the gingival crevicular fluids (GCFs) of diabetic patients with chronic periodontitis; were showed the levels reduced due to simvastatin usage.

The study by [14] revealed a significant reduction in plasma ICAM-1 in patients with hyper-lipoproteinemia following simvastatin treatment. Furthermore, [11] reported that in patients with hypercholesterolemia, simvastatin therapy significantly reduced ICAM-1 relative to patients taking bezafibrate for six months.

Conclusion

The present study indicated the fact that Simvastatin ointment plus topical steroid improvement of psoriasis by reduce concentration of inflammatory mediators.

Financial Disclosure: There is no financial disclosure.

Conflict of Interest: None to declare.

Ethical Clearance: All experimental protocols were approved under the Department of Pharmacology and therapeutics/College of medicine/ University of Kufa, Iraq and all experiments were carried out in accordance with approved guidelines.

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