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Atorvastatin and Placebo in Combination with Narrowband Ultraviolet B for Psoriasis Treatment

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Statins are the mainstay of treatment for hyperlipidemia, and they work by inhibiting 3-hydroxy-3-methylglutaryl coenzyme-A reductase, a key enzyme involved in the synthesis of cholesterol. However, statins also have immunomodulatory effects, which could be beneficial in psoriasis. The aim of the study was to evaluate the efficacy and safety of atorvastatin (ointment and systemic) either alone or in combination with narrowband ultraviolet B in the treatment of psoriasis. A controlled clinical study of 64 patients with psoriasis vulgaris who not receiving any line of treatment during the last month and their age ranged from 8 to 80 years. The studycarried out at outpatient clinic of Dermatology,Venereology and Andrology Department, Zagazig University Hospitals.All participants were subjected to full dermatological examination using (PASI) score which evaluates the severity of psoriasis. Patients were divided into four groups: group (I): applied topical atorvastatin ointment twice daily on the right side of the body (Ia) and placebo twice daily on the left side of the body (Ib) and received NBUVB sessions twice per week for 2 months.Group (II): 16 patients applied topical atorvastatin ointment twice daily for 2 months. Group (III): had taken atorvastatin tablet 40mg once daily for 2 months.Group (IV): 16 patients had taken atorvastatin tablet 40mg once daily and received NBUVB twice weekly for 2 months. During treatment, the patients were evaluated every 2 weeks in first month and every 4 weeks in the next month by a PASI score. Photographic records of psoriatic lesions obtained during each visit were processed. Regarding difference between PASI score pre & post treatments (ttt) in each group, there was a statistically significant increase in all groups in PASI score post ttt compared to pre ttt. The highest percent of increase were found among GI a & b (26.52% & 28.41% respectively).There were no statistical significant differences between the studied groups in the frequency of itching and no statistical significant correlation between therapeutic response and PASI before treatment,age or disease duration in all the studied groups. Atorvastatin calcium salt applied topically and systemic may act as a triggering factor of psoriasis.We suggested that statin should be avoided a cholesterol lowering agent in psoriatic patients.Also, it is not preferable to be used in patients treated byNBUVB.

Keywords: Psoriasis vulgaris, Atorvastatin, Itching, NBUVB and PASI score

INTRODUCTION

Psoriasis is a common chronic inflammatory skin disease characterized by abnormal proliferation/differentiation of keratinocytes and excessive immune cell infiltration in the dermis and epidermis.It is precipitated mainly by genetic and environmental factors(Ni and Lai 2020). The most common form, plaque psoriasis, occurs in80–90% of psoriatic patients, and is characterized by well-delineated, scaly, itchy,

erythematous plaques that commonly affect areas such as the elbows, knees, scalp and sacral region(Segaert et al. 2020).

The psoriasis-susceptibility (PSORS1) locus within the major histocompatibility complex (MHC) on chromosome 6p21 (location of the HLA genes) is considered a major genetic determinant of psoriasis. Among other MHC genes that have been associated with psoriasis, HLA- Cw6 is the most important allele for susceptibility to early onset psoriasis. HLA-Cw6 also demonstrates a strong association with guttate psoriasis. HLA-B17 may be associated with a more severe phenotype (Ogawa and Okada 2020). The Koebner phenomenon, i.e. the development of psoriatic lesions byinjury of the skin, is observed in nearly 25% of patientswithpsoriasis. Particular patients may be “Koebner-negative” at one point intime and later become “Koebner-positive”. Psoriatic lesions can also beinduced by other forms of injury, e.g. Sunburn and viral exanthem. The duration between the trauma andthe appearance of skin lesions is usually weeks (Furue et al. 2020).

Patient with moderate to severe disease may need phototherapy or systemic, the location of the disease and the presence of psoriatic arthritis also affect the choice of therapy,psoriasis of face ,hand and foot can be debilitating functionally or socially and more aggressive treatment approach is needed(Armstrong et al.,2013).A combination product containing calcipotriene and betamethasone dipropionate is available for this use. With proper adherence, considerable improvement with topical therapies may be seen in as little as one week, though several weeks may be required to demonstrate full benefits (Alinia et al. 2017).Severe psoriasis requires phototherapy,cyclosporine,anti-TNF systemic therapies, retinoid, methotrexate or biological agent include sadalimumab, etanercept, infliximab, anti-interleukin(IL)12/23 antibody, ustekinumab, and the anti-IL-17antibody secukinumab ,Improvement usually occurs within weeks(Falto-Aizpurua et al. 2020). Common forms of phototherapy include broadband ultraviolet B (BB-UVB), narrowband ultraviolet B (NB-UVB), ultraviolet A1 (UVA1), ultraviolet A2 (UVA2), psoralen plus ultraviolet A (PUVA), and excimer laser used alone, or in combination with topical and/or systemic medications in the treatment of psoriasis (Krenitsky et al. 2020).

Statins are classified into two categories based on their chemical structure.Statin can either be fungal-derived or synthetically produced. Lovastatin, pravastatin, and simvastatin are fungal-derived statins, while atorvastatin, cerivastatin, fluvastatin, pravastatin, pitavastatin, and rosuvastatin are fully synthetic compounds (Shuhaili et al. 2017). Systemic atorvastatin were found to improve the clinical outcome in patients with psoriatic skin lesions. Clinically, the effectiveness of these treatments were confirmed by the significant reduction in PASI score (Mosiewicz et al. 2013).But, there is a paucity of trials investigating the effects of atorvastatin on psoriasis severity and there is insufficient evidence that the use of atrovastatin as an adjunctive therapy can reduce the severity of psoriasis (Ramessur and Gill, 2017).

Therefore, the aim of the study was to evaluate the efficacy and safety of atorvastatin (ointment and systemic) either alone or in combination with narrowband ultraviolet B in the treatment of psoriasis.

MATERIALS AND METHODS

A controlled clinical trial that carried out at outpatient clinic of Dermatology,Venereology and Andrology Department, Zagazig University Hospitals during the period from October 2019 to July 2020.This study wasapproved by Dermatology Council Ethical Committee and Institutional Review Board (IRB), Faculty of Medicine Zagazig University.

Inclusion and exclusion criteria:

Inclusion and exclusion criteria were patients with psoriasis vulgaris who not receiving any line of treatment during the last month, theirage ranged from 8–80 years both sexes were involved. While,pregnancy or breast-feeding,patients with hypersensitivity to atorvastatin calcium salt, patients with photosensitivity, xerodermapigmentosum, systemic lupus erythermatosus, basal cell nevus syndrome, previous history of melanoma and skin cancer (BCC, SCC) were excluded from this study.

All participants were subjected to the following full dermatological examination for extension and severity of psoriatic plaques viapsoriasis area and severity index (PASI) score which evaluates the severity of psoriasis in relation to erythema (E), infiltration (I), and desquamation (D). Each of which are graded from 0-4 according to severity where 0 means no involvement and 4 refers to very severe involvement. Also with assessment of the whole body of each patient : the head (H), the upper limb (U), the trunk (T) and the lower limb (L)

that are corresponding to 10%, 20%, 30% and 40% of the total body surface area respectively. The surface area affected (A) is graded from 0-6 corresponding to the following scale: (0= no involvement, 1= <10%, 2= 10-29%,3= 30-49%, 4= 50-69%, 5= 70-89% 6= 90-100%).

Therapeutic intervention:

64 patients were divided into four equal groups:Group (I):16 patients applied topical atorvastatin ointment twice daily on the right side of the body (Ia) and placebo twice daily on the left side of the body (Ib) and received NBUVB sessions twice per week for 2 months. Group (II): 16 patients applied topical atorvastatin ointment twice daily for 2 months.Group (III): 16 patients had taken atorvastatin tablet 40mg once daily for 2 months.Group (IV): 16 patients had taken atorvastatin tablet 40mg once daily and received NBUVB twice weekly for 2 months.

Preparation of topical atorvastatin ointment:

Materials:Atorvastatin calcium (Epico.co.(10th of Ramadan city, Egypt)

Soft paraffine, dimethyl sulfoxide (DMSO) and peppermint oil (El-Gomhoria Co. Cairo, Egypt)

Method:1% of atorvastatin were added to the melted base of ointment (Soft paraffine, dimethyl sulfoxide (DMSO) as a penetration enhancer and peppermint oil to improve the smell of ointment),mix all ingredients till the ointment congeal. Preparation obtained from the department of Pharmaceutics Technology at Zagazig University.

The NB-UVB Therapy:

Patients received NB-UVB sessions twice per week for 2 months.The NB-UVB source was eight NB fluorescent tubes (Philips TL100, Hamburg, Germany) with a spectrum of 310-315nm and maximum wave length 311nm installed in a Wildman UV-100 unit, the initial dose of UVB was determined according the schedule of NB-UVB, and increased by 20% every session till the minimal erythema dose was achieved.The dose increment in NBUVB depends on erythema response. The erythema response is assessed before the next phototherapy session and can be graded as no erythema, mild and barely perceptible erythema (grade 1), moderate and well-defined asymptomatic erythema (grade 2) and severe painful erythema persisting for more than 24 h (grade 3). In case there is no erythema, the dose is increased by 20% of the last dose. In the presence of grade 1 erythema, the previous dose is maintained and subsequent dose increment is reduced to 10%. In case of grade 2 erythema, postpone one treatment, repeat previous dose at next visit and reduce to 10% increment, while in case of grade 3 erythema, no treatment is offered until recovery and further treatment is given by reducing exposure dose by half and 10% increment thereafter.

Evaluation of clinical response:

The patients were evaluated every 2 weeks in first month and every 4 weeks in the next month by a PASI score. Photographic records of psoriatic lesions obtained during each visit were processed.All visits were held in the same clinical study room, and photos were taken with a camera under similar conditions.

Follow up:

All patients were followed up for 1 month aftertheend of treatment course. All the data were collected in sheets and tables for statistical analysis.

Statistical Analysis

The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 18.0.Qualitative data were represented as frequencies and relative percentages. Chi square test was used to calculate difference between qualitative variables.Kruskal Wallis test was used to calculate difference between quantitative variables in more than 2 groups in not normally distributed data.PairedWilixocon test was used to calculate difference between quantitative variables in the same group in 2 different times in not normally distributed data.Spearman's correlation coefficient used to calculate correlation between quantitative variables.

RESULTS

The study was conducted on 64 patients with psoriasis coming to dermatology and andrology outpatient clinic in ZUH.Regarding difference between PASI score pre & post ttt in each group, there was a statistically significant increase in all groups in PASI score post ttt compared to pre ttt. The highest percent of increase were found among G I a & b (26.52% & 28.41%, respectively) (Table1).The attainable results showed that there was no statistical significant correlation between therapeutic response and PASI before treatment,age or disease duration in all the studied groups(Table 2).

Table 1: PASI score pre & post ttt among the studied groups:

Variable	Group Ia (*n*=11^)	Group Ib (*n*=11^)	Group II (*n*=13^)	Group III (n=14^)	Group IV (n=15^)	KW	P
Pasi: Pre *Mean ± SD* *Median* *Range*	 17.98 ± 3.79 17 13.5 - 23	 16.65 ± 2.89 15.3 12.5 – 20.8	 4.89 ± 2.75 4.8 2 – 10.5	 6.76 ± 3.65 5.8 1.8 – 12.9	 23.47 ± 15.24 18 8.8 – 43.6	50.6	<0.001 **
P versus Ib P versus II P versus III P versus IV	0.49 NS <0.001** <0.001** 0.90 NS	--- <0.001** <0.001** 0.66 NS	---- --- 0.19 NS <0.001**	-- -- -- <0.001**	-- -- -- --		
Pasi: Post *Mean ± SD* *Median* *Range*	 22.44 ± 3.95 22.6 17.7 – 27.1	 21.26 ± 3.84 18.7 17.7 - 27.1	 5.96 ± 3.93 4.8 2 – 12.9	 7.76 ± 4.47 6.4 2.4 – 14.6	 24.33 ± 16.15 18 9.2 – 45.8	50.6	<0.001 **
P versus Ib P versus II P versus III P versus IV	0.67 NS <0.001** <0.001** 0.69 NS	--- <0.001** <0.001** 0.39 NS	---- --- 0.19 NS <0.001**	-- -- -- <0.001**	-- -- -- --		
Paired W	2.96	2.95	2.53	2.97	2.18		
P	0.003**	0.003**	0.01*	0.002**	0.04*		
% of Change	26.52%	28.41%	18.40%	14.52%	3.20%		

^: The rest of cases dropped out of the study.

SD: Standard deviation, KW: Kruskal Wallis test Paired W: Paired Wilcoxon test

NS: Non significant (P>0.05) *: Significant (P<0.05) **: Highly significant (P<0.01)

Table 2: Correlationbetween therapeutic responseand PASI score, age or duration among the studied groups:

Variable	Percent of Change of PASI After Treatment									
	Group Ia (*n*=11^)		Group Ib (*n*=11^)		Group II (*n*=13^)		Group III (n=14^)		Group IV (n=15^)	
	r	P	r	P	r	P	r	P	r	P
Age	0.42	0.20 NS	0.01	0.97NS	0.03	0.91NS	0.06	0.85NS	0.30	0.28 NS
Duration	0.52	0.06 NS	0.04	0.88 NS	0.09	0.77NS	0.38	0.14NS	0.50	0.06 NS
PASI (severity before ttt)	0.47	0.09NS	0.55	0.08NS	0.24	0.43NS	0.14	0.64NS	0.48	0.07NS

r: Spearman correlation coefficient, NS: Non significant (P>0.05) .

Table 3: Side effects of ttt among the studied groups:

Side effect	Group I (*n*=11)		Group II (*n*=13)		Group III (n=14)		Group IV (n=15)		χ^2	p
	No	%	No	%	No	%	No	%		
Itching: *No* *Yes*	 9 2	 81.8 18.2	 10 3	 76.9 23.1	 10 4	 71.4 28.6	 11 4	 73.3 26.6	0.41	0.94 NS
Burning sensation: *No* *Yes*	 9 2	 81.8 18.2	 11 2	 84.6 15.4	 7 7	 50 50	 12 3	 80 20	5.52	0.14 NS
Erythema: *No* *Yes*	 4 7	 36.4 63.6	 7 6	 53.8 46.2	 12 2	 85.7 14.3	 10 5	 66.7 33.3	6.93	0.07 NS
Developm-ent of new lesions: *No* *Yes*	 0 11	 0 100	 11 2	 84.6 15.4	 10 4	 71.4 28.6	 5 10	 33.3 66.7	21.46	<0.001 **

χ^2: Chai square test. NS: Non significant (P>0.05)

**: Highly significant (P<0.01)

There were no statistical significant differences between the studied groups in the frequency of itching.However, burning sensation was more significant in group III (50%). Erythema was recorded more in group I and II (63.6% & 46.2%) compared to other groups. And development of new lesions was more frequent in group I & IV (100% & 66.7%)versus group II & III (15.4%, 28.6%) respectively (Table 3).

DISCUSSION

Psoriasis is a chronic debilitating and stigmatizing skin disorder associated with significant physical and psychological comorbidities (Wannianget al., 2020).Psoriasis could be considered a disorder of both innate and adaptive immune system as the pathogenesis involves T lymphocytes, with subsequent keratinocyte hyperproliferation in the epidermis. The epidermis is regarded as an active component in innate immune responses and capable of inducing adaptive immunity (Cibrianet al., 2020).Narrow band ultraviolet B (NB-UVB) (wavelength 311–313 nm) has largely replaced the use of BB-UVB (290–320 nm) due to its greater efficacy and remission duration at lower cumulative doses resulting in a reduction of associated long-term complications.UVB exerts its effects by damaging nuclear DNA within epidermal-dermal junctional cells leading to apoptosis and cellular death of keratinocytes, immune cells, and fibroblasts (Krenitsky et al., 2020).Statins are the mainstay of treatment for hyperlipidemia, and they work by inhibiting 3-hydroxy-3-methylglutaryl coenzyme-A reductase, a key enzyme involved in the synthesis of cholesterol. However, statins also have immunomodulatory effects, which could be beneficial in psoriasis(Socha et al.,2020).

This study was conducted on 64 patientsof psoriasis vulgaris,they were collected from the dermatology and andrology outpatient clinic in Zagazig University Hospitals (ZUH).The studied cases were divided into 4 groups as follow: Group I: all patients were instructed to apply topical atorvastatin on right side and placebo on left side and received NBUVB twice weekly; Group II: was treated with topical atorvastatin; Group III:was treated withsystemic atorvastatin 40 mg; and Group IV:was treated withsystemic atorvastatin 40 mg + NBUVB. The duration of treatment was 2 months. The study was aimed to evaluate the efficacy and safety of atorvastatin (ointment and systemic) either alone or in combination with narrow band ultraviolet B in the treatment of psoriasis.

Our results showed a significant increase in PASI score post treatment compared to pretreatment in all groups. The highest percent of increase in PASIwas found among Group I (topical atorvastatin in theright side and placebo in the left side in combination with NBUVB). This means that nearly all groups of patients worsen with treatment with atorvastatin either topical or systemic even when combined with NBUVB and the worst results were among patients treated by combined topical atorvastatin and NBUVB. There was no correlation between therapeutic responseand age, duration or disease severity in all the studied groups.

This results of our study came in agreement with three cases reports by (Jacobi and Highet 2003;Cozzani et al., 2009 ;andArdeshna et al., 2017) those reported worsen of preexisting psoriasis and developing of new lesions in psoriatic patients who suffered from hypercholesrolemia and took statins, atorvastatin, simvastatin and pravastatin, as cholesterol lowering drugs, besides their antipsoriatic treatment like methotrexate and cyclosporine, patients resolved only after discontinuation of statin.Chua et al., (2017) who concluded that systemic atorvastatin 40 mg was not able to produce an additional benefit compared to psoriatic patients applying topical steroid alone.In addition, topical simvastatin was not associated with significant impacts in the treatment of psoriasis (Iraji et al., 2014).

In contrast to the results of our study, different studies reported decrease in progression of psoriasis with systemic statin intake (simvastatin 10mg, 40mg) when used either alone or in combination with topical treatment leading to improvement of psoriasis (Shirinsky and Shirinsky, 2007, Naseri et al., 2010, Brauchli et al., 2011 and Ghazizadehet al., 2011).In one study, the addition of systemic atorvastatin 20 mg to standard therapy improved the severity of psoriasis (Vasiuk et al., 2010).

From all previously mentioned studies and results, it is now obvious that there is controversy about the effects of statin on psoriasis. These studies recommended addition of statin to treatment of psoriasis, suggested that statin therapy depend on a variety of mechanisms. Which include down-regulation of lymphocyte function-associated antigen-1, inhibition of leukocyte endothelial adhesion, extravasation and natural killer cell activity, inhibition of pro-inflammatory cytokines such as tumor necrosis

factor-alpha and interleukin-1 and -6, lowering of C-reactive protein, promotion of shifting from Th1 to Th2 cells and inhibition of Th1 cytokine receptors on T cells (Mosiewicz et al., 2013).

CONCLUSION

Atorvastatin calcium salt applied topically and systemic may act as a triggering factor of psoriasis.We suggested that statin should be avoided a cholesterol lowering agent in psoriatic patients. Also, it is not preferable to be used in patients treated by NBUVB.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

AUTHOR CONTRIBUTIONS

All author contributed in all parts of the paper.

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