Clinical Efficiency of Narrow Band-Ultraviolet B Phototherapy and Methotrexate Therapy and their effects on Serum Tumor Necrosis Factor-Alpha in Patients with Cutaneous Lichen Planus.

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Abstract

Objective: This study aimed to assess the clinical efficiency of Narrow Band-Ultraviolet B (NB-UVB) phototherapy and methotrexate (MTX) therapy and their effects on serum tumor necrosis factor-alpha (TNF-α) in patients with cutaneous lichen planus (CLP). Methods: The present cohort study was carried out on 60 patients with CLP who attended the Out-patient Clinics of the Dermatology, Department, Faculty of Medicine, Faculty of Medicine, South Valley University between May 2018 and December 2019.The included patients were indiscriminately classified into two treatment groups; group A (30 patients), received NB-UVB phototherapy for three months and group B (30 patients), received MTX therapy for three months. All the patients were assessed clinically and TNF-α before and after treatments. Results: There were no statistically significant differences between the two groups of treatment regard clinical improvement after treatment (P=0.149). Regarding levels of TNF-α, there was a statistically significant difference between the two treatment groups after treatment (P=0.024). There was a statistically significant reduction in TNF-α level after treatment in the MTX group. Conclusion: This study concluded that NB-UVB phototherapy and MTX therapy were clinically effective in the treatment of patients with CLP. MTX therapy was more efficient in the reduction of TNF-α level than NB-UVB phototherapy in patients with CLP.

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Running title: Serum Tumor Necrosis Factor-Alpha in Lichen Planus

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Conclusion: This study concluded that NB-UVB phototherapy and MTX therapy were clinically effective in the treatment of patients with CLP. MTX therapy was more efficient in the reduction of TNF-α level than NB-UVB phototherapy in patients with CLP.

Keywords: Lichen planus, Methotrexate, Narrow Band-Ultraviolet B

What is known?

The tumor necrosis factor-alpha (TNF-α) may have a role in the pathogenesis of lichen planus.

Narrow Band-Ultraviolet B (NB-UVB) phototherapy and methotrexate (MTX) therapy may be used for the treatment of lichen planus.

What is new?

NB-UVB phototherapy and MTX therapy were clinically effective in the treatment of patients with cutaneous lichen planus (CLP).

MTX therapy was more efficient in the reduction of TNF-α level than NB-UVB phototherapy in patients with CLP.

Introduction:

Lichen planus (LP) is a chronic disease that can affect the skin, nails, oral and genital mucosa, hair, scalp, conjunctiva, larynx, and pharynx that is inflammatory and autoimmune. The onset is typically acute, affecting the wrist, forearm, and leg flexor surfaces. Lacy, reticular, white lines known as Wickham striae frequently cover the lesions.[1] It could be idiopathic, or caused by certain medications or related to hepatitis C- virus infection, and other autoimmune diseases.[2] The lichenoid response, which may result in basal cell damage, may lead to immune responses to unknown external or self-modified antigens by T-cells. Keratinocytes cause damage by transmitting foreign or modified self-antigens on surfaces.[3]

A strong pro-inflammatory cytokine that causes acute process reactions is a tumor necrosis factor-alpha (TNF-α). It plays apart in cell proliferation, differentiation, apoptosis, immunity, and inflammation control. Also, it has a pivotal role in the growth and differentiation of different cell types and has antitumor activity, TNF-α, therefore, has an essential role in the local and systemic immunopathogenesis of LP.[4]

It has been reported that the serum levels of TNF-α were reported to be significantly increased in patients with LP, so TNF-α could play a crucial role in pathogenesis of LP.[5]

Narrow Band-Ultraviolet B (NB-UVB) may be an essential alternative therapy for lichen planus. NB-UVB reduces the cells of langerhans and causes cytokines and neuropeptides to develop and secrete. NB-UVB induces the production of anti-inflammatory cytokines and alters the expression of adhesion molecules which suppress TNF-α mediated inflammation.[6] Methotrexate (MTX) is an anti-metabolite utilized to treat several autoimmune inflammatory disorders. It suppresses the replication and function of T and B lymphocytes. It has both immunomodulatory and anti-inflammatory effects. These influences are mediated by the secretion of adenosine at sites of inflammation by fibroblasts and endothelial cells. Other potential influences of MTX activity in cutaneous disorders are inhibition of chemotaxis, suppression of monocyte/macrophage stimulation, and suppression of histamine release from basophils.[7] It has been found that MTX was an effective therapy for patients with LP.[8,9]

This study aimed to assess the clinical efficiency of NB-UVB phototherapy and MTX therapy and their effects on serum TNF-α in patients with cutaneous lichen planus (CLP).

Patients and methods:

Patients:

The current study was a cohort clinical trial. It was conducted between May 2018 and December 2019 on sixty patients with CLP who were enrolled in the Outpatient Clinics at Dermatology Department, Faculty of Medicine, Faculty of Medicine, South Valley University between May 2018 and December 2019. The study received the approval of Scientific and Ethics Committees at the Faculty of Medicine, South Valley University. Informed consent was taken from the participants after detailed clarifications of the nature of this study.

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Inclusion criteria: Patients with CLP diagnosed clinically.

Exclusion criteria: CLP patients with other autoimmune diseases like systemic lupus, rheumatoid or mixed connective tissue diseases, alcoholic diseases, heart diseases or liver diseases, blood cell disorders such as anemia or leucopenia, bone marrow dysfunction, nursing or pregnant women, kidney disease, infants or children, photo-exaggerated patients, previous NB-UVB therapy or systemic therapy in 6 months prior to the first LP therapy, history of dysplastic nevi, malignant skin lesions, and drug-treated patients causing photosensitivity or cutaneous pigmentations within 60 days before the initiation of NB- UVB therapy.

Treatment protocol:

The included patients were indiscriminately classified into two group; Group A; 30 patients received two sessions of NB-UVB weekly for 3 months with the dose of 100 mJ /cm2 and the dose of NB-UVB for 310-315 nm with a total emission limit of 312 nm. Group B; 30 patients received methotrexate 15mg per week orally in 3 divided doses 12 hours apart for 3 months. Folic acid 1mg daily in days before and after days of MTX dose was taken.

Methodology:

All included subjects were subjected to the following:

History details and demographic data: Personal history (sex, age, occupation, residence, marital status, and special habits of medical importance), history of present illness (beginning, course, duration of the disease, progress, symptoms, exacerbating, and relieving factors), past history of similar lesions, skin cancer, systemic disease or drug history and family history of LP or autoimmune disease.

Physical examination: An overall assessment involving weight, height, body mass index (BMI) estimation, and blood pressure measurement. Clinical skin examination: a complete dermatologic examination was

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performed to determine cutaneous LP and to determine the extent and distribution of the disease.

Laboratory investigations:-

1. **Investigations before starting treatment (baseline investigations):** Serum TNF-α, differential complete blood picture (CBC), renal function testing, hepatitis C serology, and liver function testing.
2. **Investigations after three months of treatment:** Serum TNF-α.
3. **Repeated liver function tests and CBC** : for patients of methotrexate treatment group during treatment (at 2nd, 4$^{\text{th}}$, 8$^{\text{th}}$, and 12$^{\text{th}}$ weeks).

ΤΝΦ-α μεασυρεμεντ: Enzyme-linked immunosorbent assay (ELISA) investigated serum TNF-α according to the instructions of the manufacturer with the commercial package of Sinogen Clon Biotech co., ltd. (TNF-α) ELISA package.

Evaluation of the patients after three months of treatment: Patients were evaluated according to the clinical response into; Complete (total lesions and pruritus disappearance), partial (over 50 percent lesion clearance and no or moderate residual pruritus), and no response (less than 50 percent lesion clearance and/or significant residual pruritus).[10]

Statistical analysis: The researcher processed, coded, and evaluated the data with version 21 of the SPSS. Descriptive statistics: Means were calculated, standard deviation, inter-quartile range (IQR), and percentages. The chi-square test was utilized to compare frequency distribution variations between different groups. The independent t-testing analysis was performed to compare the means by which data for the continuous variables were usually distributed, while the median data variations that do not meet normal distribution were tested by the Mann Whitney U test. P-value < 0.05 was considered significant.

Results:

This study was carried out on 60 patients with CLP; the mean age of all included patients was 34.3 ± 2 years. There were no significant differences between the patients in the two treatment groups regarding age, sex, marital status, special habits, occupation, and residence (P>0.05).

Regarding the level of clinical response; there were no significant differences between NB-UVB group and MTX group (P=0.149). The level of clinical response to the different treatment models was illustrated in table 1. Among NB-UVB group, about two-thirds of cases (36.7% each) showed either complete response to treatment or no response and only one quarter (26.6%) showed partial response to treatment. For the MTX group, half (50%) of cases showed partial response to treatment, about one-third (30%) showed complete response and only one-fifth (20%) of them showed no response to treatment. This relationship was a statistically insignificant (P >0.05). **Table 1, Fig 1, 2**

Regarding level of TNF-α, there were no significant differences between NB-UVB group and MTX group before treatment (P=0.147), while a significant difference was between NB-UVB group and MTX group after treatment (P=0.024). There were no statistically significant differences between the two groups in the median TNF-α level before treatment (P>0.05). **Table 2**

On the other hand, there were statistically significant differences between the two groups in the median TNF-α levels after treatment (P=0.024). Furthermore, for repeated measure analysis (before vs. after treatment); the median level of TNF-α decreased significantly after treatment in the MTX group by 12 pg/ml (P=0.001). Notwithstanding the median TNF-α increased insignificantly after treatment in the NB-UVB group by 1.5 pg/ml (P>0.05). In respect to the percent change in the level of TNF-α in response to treatment, the level of TNF-α decreased significantly after treatment in the MTX group by 41% compared with only 0.8% in the NB-UVB group (P= 0.021). **Table 2**

In the NB-UVB group; a significant high positive correlation was between TNF-α levels before and after treatment (r=0.60; P<0.001). In the MTX group; there was a significant mild positive correlation between TNF-α levels before and after treatment (r=0.22; P=0.039). In the NB-UVB group; there was a significant high positive correlation between TNF-α levels before and after treatment (r=0.60; P<0.001). In the same

way, In the MTX group; there was a significant mild positive correlation between TNF-α levels before and after treatment (r=0.22; P=0.039). **Fig 3, 4**

In the NB-UVB group; there were no statistically significant differences in the median TNF-α levels between different clinical response groups neither overall (P>0.05) nor pairwise (complete (35 (39) pg/ml), partial (21 (33) pg/ml) and (40 (76) pg/ml), respectively. In the MTX group; there was no statistically significant difference in the median TNF-α levels between different clinical response groups neither overall (P>0.05) nor pairwise (complete (20 (26) pg/ml), partial (28 (16) pg/ml) and (25 (16) pg/ml), respectively. In respect to the percent change in the level of TNF-α in response to treatment for different clinical response levels, in the NB-UVB group; there was statistically significant difference in the median percent change of TNF-α levels between different clinical response groups overall (P= 0.016). For pairwise comparisons, patients with complete response had 2% changes vs. 22% change in cases with partial response and this was statistically insignificant (P>0.05). Unlike, patients with partial response had 22% change vs. -25% change in cases with no response and this was a statistically significant (P=0.009). Likewise, patients with complete response had 2% change vs. -25% change in cases with no response and this was a statistically significant (P= 0.001).

Table 3

Discussion:

While CLP may exhibit spontaneous improvement over time, systemic treatments are required for several patients due to persistent of itching and cosmetic issues, especially in a generalized pattern. Numerous modalities of treatment for CLP were used as corticosteroids (topical and systemic), retinoids, MTX, azathioprine, cyclosporine, phototherapy, and biologics. However, there are no formal care guidelines based on facts yet.[11]

In the current study, among NB-UVB group, 36.7% of patients showed complete response to treatment and 26.6% of patients had partial response to treatment.

It has been found that the clinical efficiency of NB-UVB in a retrospective study among 20 patients for the treatment of widespread CLP was 55% patients (full responses) and 20% patients (partial responses).[10]

A retrospective study examined the efficiency of UVB for the treatment of generalized CLP in 50 patients. According to their findings, 70% of the patients achieved a full response, 85% of those were still in remission. The authors deduced that NB-UVB is a safe and effective alternative line for treatment of generalized LP.[12]

Also, it has been reported that treatment of 16 generalized traditional therapy resistant CLP patients with NB-UVB 3 times weekly achieved a full response in 68.75% patients and partial response in 12.5% patients. The authors found that an increased number of sessions were correlated with a substantial increase in the overall response.[13]

While for the MTX group, 50% of patients showed partial response to treatment and 30% of patients showed complete response. In agreement with our findings, MTX therapy was effective for complete clearance of the lesions of CLP in more than 90% of the patients.[8]

According to our knowledge, this was the first study that evaluated the effect of MTX on the serum levels of TNF-α among CLP patients. In the current study, there was a statistically significant difference between the two treatment groups in the median TNF-α level after treatment. Furthermore, the median level of TNF-α decreased significantly after treatment in the MTX group. The median TNF-α was increased insignificantly after treatment in the NB-UVB group. Also, the level of TNF-α in the MTX group decreased significantly after treatment by 41% in response to treatment, compared with only 0.8% in the NB-UVB group, that suggests the molecular action of MTX on inflammatory diseases by inhibiting cytokine production induced by T cell activation.[14]

In the current study, in the NB-UVB group; for pairwise comparisons, patients with complete response had 2% changes vs. 22% change in cases with partial response and this was statistically insignificant. Unlike, patients with partial response had 22% changes vs. -25% changes in cases with no response and this was a

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statistically significant. Likewise, patients with complete response had 2% change vs. -25% change in cases with no response and this was statistical significant. This may be explained by the effect of NB-UVB in the production of anti-inflammatory cytokines and alternations in the expression of adhesion molecules that inhibit TNF-α mediated inflammation.[6]

In the MTX group; for pairwise comparisons, patients with complete response showed 68% decrease in the level of TNF-α compared with 29% decrease in cases with partial response and this was statistically significant. Moreover, patients with complete response showed 68% decrease in the level of TNF-α compared with 22% decrease in cases with no response and this was statistically significant. Contradictory, patients with partial response showed 29% decrease in the level of TNF-α compared with 22% decrease in cases with no response and this was statistically insignificant. However, it has been found that serum levels of TNF-α were found to be significantly increased in patients with CLP [5], and MTX was an effective therapy for patients with CLP [8,9], there is no previous study assessed the effect of MTX in the reduction of TNF-α level in patients with CLP.

The significant increase in serum TNF-α level in patients with CLP may be caused by local and systemic productions of the TNF-α by several cell types. TNF-α may be secreted by lymphocytes (T and B), macrophages, natural killer cells, langerhans cells, monocytes, mast cells, fibroblasts, endothelial cells, and keratinocytes.[15] The significant efficacy of MTX in the reduction of serum TNF-α level in patients with CLP may be related to its ability to suppress replication and function of lymphocytes (T and B), inhibition of chemotaxis, suppression of monocyte /macrophage stimulation, and inhibition of histamine release from basophils.[11]

Anyway, these findings need further evidences on several comprehensive large-sized multicenter clinical studies and to be more evidenced by further assessments of the non-lesional and lesional tissue expressions of TNF-α before and after NB-UVB phototherapy and MTX therapy in patients with CLP.

This study concluded that NB-UVB phototherapy and MTX therapy were clinically effective in the treatment of patients with CLP. MTX therapy was more efficient in the reduction of TNF-α level than NB-UVB phototherapy in patients with LP. TNF-α could be an essential cytokine in the pathogenesis of CLP.

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Table 1: Clinical response differences between the studied groups.

	NB-UVB Group (No.=30)	MTX Group (No.=30)	Total (No.=60)	P-value*
Level of clinical response	Level of clinical response	Level of clinical response		= 0.149
Complete	11 (36.7%)	9 (30%)	20 (33.3%)	
Partial	8 (26.6%)	15 (50%)	23 (38.3%)	
No	11 (36.7%)	6 (20%)	17 (28.4%)	

*Chi-square test was used in comparing the proportion difference between groups.

MTX; methotrexate, NB-UVB; Narrow Band-Ultraviolet B.

Ταβλε 2: ΤΝΦ-α διφφερενςες βετωεεν τηε στυδιεδ γρουπς.

	NB-UVB (No.=30)	MTX (No.=30)	P-value*
ΤΝΦ-α (πγ/μλ)	ΤΝΦ-α (πγ/μλ)		
Before treatment	138.16 ± 49.7$^{\$}$	119.06 ± 40.2	= 0.147
	31.5 (88) $^{\$}$	37 (88)	
After treatment	131.18 ± 49.1	26.24 ± 3.9	= 0.024*
	33 (81)	25 (17)	
P-value**	= 0.517	= 0.001*	
% χηανγε ιν ΤΝΦ-α	% χηανγε ιν ΤΝΦ-α		= 0.021*
	-1.48 ± 0.9	-26.19 ± 13.2	
	-0.8 (19)	-41 (17)	

* Mann Whitney U-test was used in comparing the median difference between groups

**Related Sample Wilcoxon Sign test was used in comparing the median difference between groups. $^{\$}$ Mean ±

SD and Median (IQR)

MTX; methotrexate, NB-UVB; Narrow Band-Ultraviolet B, TNF; tumor necrosis factor.

Ταβλε 3: ΤΝΦ-α λεελ αςςορδινγ το ςλινιςαλ ρεσπονσε βετωεεν τηε στυδιεδ γρουπς

	NB-UVB (No.=30)	P-value**	MTX (No.=30)	P-value**
Λεελ οφ ΤΝΦ-α αφτερ τρεατμεντ (μεδιαν (IXP»	Λεελ οφ ΤΝΦ-α αφτερ τρεατμεντ (μεδιαν (IXP»	Λεελ οφ ΤΝΦ-α αφτερ τρεατμεντ (μεδιαν (IXP»	Λεελ οφ ΤΝΦ-α αφτερ τρεατμεντ (μεδιαν (IXP»	Λεελ οφ ΤΝΦ-α αφτερ τρεατμεντ (μεδιαν (IXP»
Complete	35 (39)	P1=0.098	20 (26)	P1=0.123
Partial	21 (33)	P2=0.069	28 (16)	P2=0.396
No	40 (76)	P3=0.459	25 (16)	P3=0.209
P-value*	= 0.426		= 0.215	
Λεελ οφ ΤΝΦ-α % ςηανγε (μεδιαν (IXP»	Λεελ οφ ΤΝΦ-α % ςηανγε (μεδιαν (IXP»	Λεελ οφ ΤΝΦ-α % ςηανγε (μεδιαν (IXP»	Λεελ οφ ΤΝΦ-α % ςηανγε (μεδιαν (IXP»	Λεελ οφ ΤΝΦ-α % ςηανγε (μεδιαν (IXP»
Complete	2 (11)	P1=0.068	-68 (55)	**P1=0.003***
Partial	22 (66)	**P2=0.009***	-29 (24)	P2=0.242
No	-25 (81)	**P3=0.001***	-22 (15)	**P3=0.001***
P-value*	**= 0.016**		**< 0.001**	

*Kruskal Wallis test was used in comparing the median difference between groups

**Post-hoc test for pairwise comparisons

—P1 (Complete vs. Partial), P2 (Partial vs. No), P3 (Complete vs. no)

MTX; methotrexate, NB-UVB; Narrow Band-Ultraviolet B, TNF; tumor necrosis factor.

Figure legends:

Fig. 1. Male patient 60 years old presented with CLP on his dorsal aspect of both hands; a) before treatment by NB-UVB, b) after treatment by NB-UVB.

Fig. 2. Female patient 27 years old presented with CLP on her right lower limb; a) before treatment by MTX, b) after treatment by MTX.

Fig. 3. Correlation between TNF-α level before and after NB-UVB treatment.

Fig. 4. Correlation between TNF-α level before and after MTX treatment.

Group: Methotrexate