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Glucosamine as a Novel Adjunctive Therapy in Symptomatic Oral Lichen Planus

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Abstract

Background:
Glucosamine (GlcN) is N-deacetyl amino sugar with immunoregulatory and anti-inflammatory effects, used for management of osteoarthritis and atopic dermatitis. Based on oral lichen planus (OLP) T-cell-mediated pathogenesis; GlcN seems to be a promising therapeutic agent.

Aim:
To evaluate clinical effectiveness of oral glucosamine sulphate as an adjunct to topical corticosteroids in OLP management and to investigate effect of this treatment modality on inhibitor kappa-B kinase alpha (IKKα) and interleukin-8 (IL-8) expression.

Methods:
Thirty patients with erosive/ atrophic OLP were randomly assigned into three equal groups. **Group I** received topical corticosteroid 4times/day and **Group II** received topical corticosteroid 2times/day. In both groups corticosteroids were combined with 500mg oral glucosamine sulphate 3times/day. **Group III** applied topical corticosteroid alone 4times/day. Clinical score (CS) and visual analogue scale (VAS) were calculated at baseline, 1, 2, 4, 6, 8 and 12 weeks. The immune expression of IKK-α and IL-8 in pre and post-treatment specimens was investigated.

Results:
Group I mean CS decreased significantly compared to groups II and III one week after treatment *($P < 0.001$)*. In the first 4 weeks, VAS dropped significantly from 8.7 (1.5) to 1.07 (1.46) in group I compared to other groups. All treatment regimens resulted in significant reduction in IKK-α and IL-8 expression. Exacerbation was reported in Groups II and III.

Conclusions:
Adjunctive use of glucosamine for erosive/ atrophic OLP induced more rapid initial response with lower rate of exacerbation than topical corticosteroids alone; and showed higher reduction in IKK-α and IL-8 expression in OLP lesions.

Key words: Glucosamine, IL-8, Nuclear Factor Kappa B, Oral Lichen Planus.

INTRODUCTION

Lichen planus (LP) is a chronic immune mediated mucocutaneous disorder [1]. Oral lichen planus (OLP) is variable; with four clinical forms: papular/reticular, plaque-like, and the most severe atrophic and erosive forms [2].

OLP is a T-cell-mediated disease; T helper-1 cells are stimulated to secrete IL-2 and IL-8 cytokines after antigen presentation by basal keratinocytes, with subsequent cytotoxic T-cells activation and basal keratinocyte apoptosis**.** Mast cell degranulation and matrix metalloproteinase activation are also involved [3].

Nuclear factor-kappa B (NF-κB) is a primary transcription factor found in almost all cell types in an inactive form bonded to inhibitor κB proteins (IκBs). Inhibitor κB kinase (IKK) complex (IKK-α and IKK-ß) is responsible for IκB phosphorylation and subsequent release of active NF-κB which acts as pivotal regulator of pro-inflammatory gene expression [4,5]. Studies reported that activation of NF-κB and its associated cytokines plays important roles in OLP exacerbation and remission [6,7].

Topical corticosteroids are considered the gold standard therapy for OLP. They have potent anti-inflammatory and immune-modulatory actions, including reduction in number and function of immune cells, such as lymphocytes, monocytes and neutrophils, they also decrease cytokines production [8,9].

A Cochrane review summarizing treatment modalities for OLP recommended research on new OLP therapies that focus on imbalance of immune response 10.

Glucosamine (GlcN) is an N-deacetyl amino sugar [11]**,** used as nutraceutical for management of osteoarthritis and atopic dermatitis due to its immunoregulatory capacity and anti-inflammatory effects [12]**.**

In mouse models, combined immune-suppressive therapy; GlcN with tacrolimus or with low dose cyclosporine resulted in reduction of T helper cytokines levels and chemokines expression, inhibition of inflammatory cells infiltration [13,14].

To the best of authors' knowledge, there are no published data regarding use of glucosamine in OLP management. Considering aforementioned properties of GlcN, we hypothized that combination therapy of GlcN and topical corticosteroid could improve efficiency or spare doses of corticosteroids. Thus we compared clinical efficiency of oral GlcN combined with standard or low dose topical corticosteroids to that of standard topical corticosteroid

alone in management of symptomatic OLP and assessed immune expression of IKK-α and IL-8 in OLP specimens.

MATERIALS AND METHODS

This prospective randomized three-arm comparison study was conducted in accordance with ethical principles provided by Declaration of Helsinki, approved by ethical committee, Faculty of Dentistry, Ain Shams University (FDASU-REC DO-91308) and all patients provided written informed consent. Study was registered at www.clinicaltrials.gov (ID- NCT02858297).

Selection of patients

Thirty patients with OLP were recruited from out-patient clinic, Department of Oral Medicine and Periodontology, Faculty of Dentistry, and Department of Skin and Venereal diseases, Faculty of Medicine, Ain Shams University. For each patient a marker lesion was identified, being the most severe then a punch biopsy was taken to confirm diagnosis of OLP.

Both genders (25-60 years) with clinically and histologically confirmed erosive/atrophic OLP and free from any systemic disease were considered eligible. While patients with history of drug induced lichenoid lesions or potential treatment for OLP (for less than 2weeks by topical or 4weeks systemic therapy) before start of study, pregnant or breast-feeding women, smokers and those with known hypersensitivity or adverse effects to treatment drugs were excluded. Losses of pliability or flexibility in tissues involved by oral lesions or histological signs of epithelial dysplasia or lichenoid lesions were also excluded.

Randomization, grouping and interventions

Patients who met eligibility criteria were randomized into three groups (10 patients each) using computer-generated randomization assignment and allocation concealment with sealed envelopes. **Group I** received topical triamcinolone acetonide 0.1% (**GEO ORALOG; Geopharma, Cairo, Egypt)** 4times/day combined with glucosamine sulfate 500mg capsules orally 3times/day **(Glucosamine; GlaxoSmithKline, Cairo, Egypt)** while **Group II** received combination of topical triamcinolone acetonide 0.1% 2times/day and glucosamine sulfate 500mg 3times/day. **Group III** patients applied topical triamcinolone acetonide 0.1% alone 4times/day and were considered the control group. All patients were treated for 8weeks then followed up for 4weeks after treatment termination. A single investigator blinded to type of treatment assessed outcome measures.

Clinical assessment

Clinical effectiveness primary outcomes were clinical scoring (CS) and visual analog scale (VAS); marker lesion in each patient was assessed for areas of reticulation, erosion, and ulceration by visual examination using (CS) according to Thongprasom et al. (2003**)** [15]**.** Patients ranked severity of pain on 100-mm (VAS) [16]**.**

Each patient was assessed at baseline, after 1, 2, 4, and 8 weeks then reassessed four weeks after treatment termination (12w). Side effects, abnormal vital signs or oral mucosa alteration were reported in each visit.

Immunohistochemical analysis

Punch biopsy specimens of approximately 5mm were taken from the marker lesion at baseline and at end of treatment (8w), then formalin fixed, embedded in paraffin, cut into 5μm thick sections and mounted on positively charged glass slides. Sections were then deparaffinized and re-hydrated with graded ethanol series to be stained using labeled streptavidin biotin immunohistochemistry assay. Primary antibodies used were: Monoclonal mouse anti-human IKK-α antibody ***(GeneTex, Ltd, UK)*** and monoclonal mouse anti-human CXCL8/IL8 antibody ***(Novus Biologicals, Ltd, UK)***.

- Slides were incubated with each primary antibody overnight at room temperature then immersed in horseradish peroxidase HRP-streptavidin at 37°C for 30minutes.
- After washing, color reaction was performed using 3,3-diaminobenzidine-4-hydrochloride, then slides were counter stained with Mayer s hematoxylin for 2minutes and mounted.
- In each positive section at least four microscopic fields showing highest immunopositivity were selected and photographed at 20X magnification. Photomicrographs were evaluated using image analysis software ***(Image J, 1.41a, NIH, USA)***.
- Area fraction of immunopositivity of IL-8 (calculated automatically representing percentage of immunopositive area to total area of microscopic field) and immunopositive cell counts of IKK-α for four different microscopic fields were measured then mean area fraction and count for each case was calculated.

Statistical analysis

Data were tabulated in excel sheet to be analyzed by ***SPSS -Version 20 (SPSS Inc., Chicago, IL, USA)***. We used Fisher exact test to compare between categorical data, one way ANOVA test to compare between groups regarding numerical data and Fridman test to compare between follow up periods within each group. Significance level was set at $P \leq 0.05$.

RESULTS

Thirty patients (20 females and 10 males) with mean age 52.5(6.8) were enrolled and committed to treatment protocol throughout the twelve weeks study period. All patients had bilateral lesions on buccal mucosa and 12 patients had other lesions in tongue and lip. Nineteen patients (63.3%) had history of specific OLP treatments including topical, intra-lesional and systemic steroids, while remaining were treated with topical anti-inflammatory, antifungal and analgesics.

Patients' age, gender and disease characteristics (duration, frequency of exacerbation and morphological subtypes) are displayed in **(Table 1)**. Group I showed highest percentage of erosive morphological subtype and group III patients had highest mean number and frequency of disease exacerbation, however no statistically significant baseline differences were found between groups before initiation of treatment regarding all characteristics.

Clinical improvement was observed in all groups as reduction in lesion size and severity **(Fig.1).** (**Table 2)** demonstrates that mean (CS) and (VAS) as well as (IKK-α)

immunopositive cells and mean area fraction of (IL-8) were reduced significantly from baseline to eighth week of treatment for all groups *(P = 0.0001)*. However, CS decreased from 4.5(0.849) to 2.9(1.44) in group I after one week treatment, and mean CS was statistically significant different from mean CS in group II 3.33(0.67) and in group III 3.5(0.84) in this visit**.** Group I also showed VAS reduction from 8.7(1.5) after one week, to 3.38(2.1) in second week and to 1.07(1.46) in third week and the differences were statistically significant when compared with mean VAS in other two groups.

By end of follow up period CS in Group I decreased to 0(0.47), while in Group II it decreased from 1.2(0.42) to 1(0.47) and in Group III it changed from 1(0.58) to 1(0.67) although the differences were statistically insignificant. In follow up visits, VAS did not change in Groups I and II and patients remained pain free, but in Group III it increased to 0.2(0.63). Group I showed least mean CS **(Fig 2)** and VAS **(Fig 3)** during follow up.

IKK-α and IL-8 antigens were expressed in subepithelial lymphocytes before treatment in all groups. While after treatment period, it showed a higher significant reduction in group I followed by group II then group III **(Fig. 4).**

Table 1: Baseline characteristics of the patients enrolled in each study group

Baseline Characteristics	Group I	Group II	Group III	*P* value
Age [Mean(SD)]	54.7 (5.9)	48.2 (8.3)	54.6 (6.3)	0.07
Sex [n (%)]				
Male	2 (20%)	6 (60%)	2 (20%)	0.12
Female	8 (80%)	4 (40%)	8 (80%)	
Disease duration (Month) [Mean(SD)]	23.7 (23.8)	23.8 (22.0)	53.7 (37.9)	0.11
Number of exacerbations [Mean(SD)]	7.7 (7.5)	7.9 (7.3)	13.5 (11.8)	0.38
Frequency of exacerbations/months	0.4 (0.4)	0.5 (54.2)	0.9 (0.6)	0.11
History of previous treatments [n (%)]	6 (60%)	6 (60%)	7 (70%)	0.99
Morphological Subtype [n (%)] Erosive	8 (80%)	5 (50%)	5 (50%)	0.48
Atrophic	2 (20%)	5 (50%)	5 (50%)	

Table 2: Treatment effect on mean clinical score (CS), mean visual analogue scale (VAS), immunopositive cell counts of (IKKα) and the area fraction of immunopositivity of interleukin-8 (IL-8)

CS [Mean (SD)]	Group I	Group II	Group III	*P* value
Base	4.5 (0.8)	4 (0.9)	3.9 (0.8)	0.26
Week 1	2.9 (1.4)[a]	3.3 (0.6)[b]	3.5 (0.8)[b]	0.59
Week 2	1.9 (1.1)	2.1 (0.5)	2.1 (1.1)	0.79
Week 4	1.1 (1.1)	1.4 (0.6)	1.6 (0.9)	0.16
Week 8	0.8 (0.4)	1.2 (0.4)	1 (0.5)	0.18
***P* value**	**<0.001*** **<0.001***	**<0.001***		
Week 12	0 (0.4)	1 (0.4)	1 (0.6)	0.92
VAS [Mean (SD)]				
Base	8.7 (1.5)	7.8 (1.8)	7.55 (1.7)	0.25
Week 1	3.3 (2.1)[b]	4.3 (1.6)[a]	3.87 (1.5)[a]	0.61
Week 2	1.07 (1.4)[b]	1.2 (1.1)[b]	1.4 (1.04)[a]	0.47
Week 4	0	0.1 (0.3)	0.1 (0.3)	0.59
Week 8	0	0	0	0.92
***P* value**	**<0.001***	**<0.001***	**<0.001***	
Week 12	0	0	0.2 (0.6)	0.36
IKK-α [Mean (SD)]				
Before treatment	11.9 (1.5)[a]	13.3 (1.8)[ab]	14.3 (1.4)[b]	0.01
After treatment	5.1 (0.9)[a]	6.5 (1.03)[ab]	7.6 (1.8)[b]	0.001
***P* value**	**<0.001***	**<0.001***	**<0.001***	
% Change	**57.1 (6.8)**[a]	**50.2 (6.0)**[ab]	**46.6 (11.8)**[b]	**0.03**
Il-8 [Mean (SD)]				
Before treatment	8.9 (5.1)	7.9 (3.7)	4.6 (2.7)	0.059
After treatment	2.8 (1.7)	2.03 (1.3)	1.3 (0.8)	0.075
***P* value**	**<0.001***	**<0.001***	**<0.001***	
% Change	**0.8 (0.3)**	**0.6 (0.3)**	**0.4 (0.62)**	**0.69**

a) *Significant at *P* value <0.001

b) Similar superscript letters indicate no significant differences.

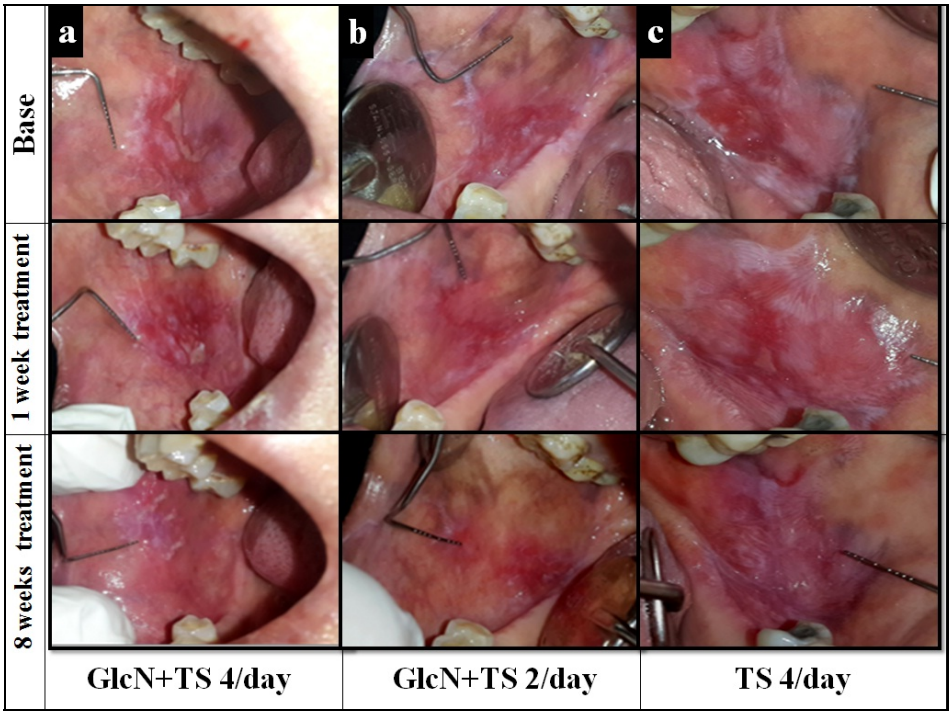

Figure 1 Clinical changes in oral lichen planus lesions in three patients treated by **(a)** combination of Glucosamine and topical steroids 4 times/day (GlcN+TS 4/Day) **(b)** combination of Glucosamine and topical steroids 2 times/day (GlcN+TS 2/Day) or **(c)** topical steroid alone 4 times /day (TS 4/Day) at baseline, after 1 week and after 8 week treatments.

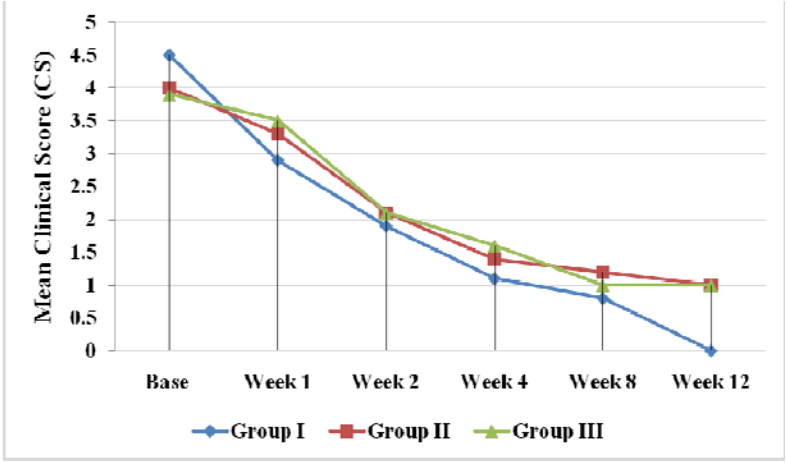

Figure 2 Changes of mean (CS) over study period

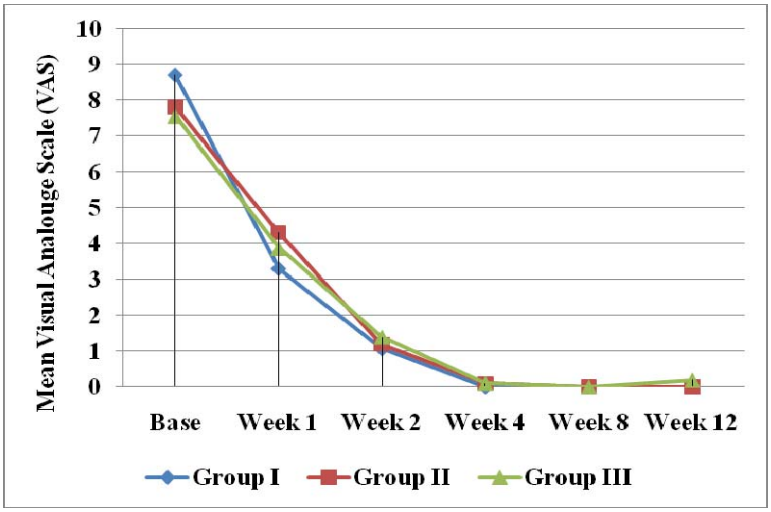

Figure 3 Changes of mean (VAS) over study period

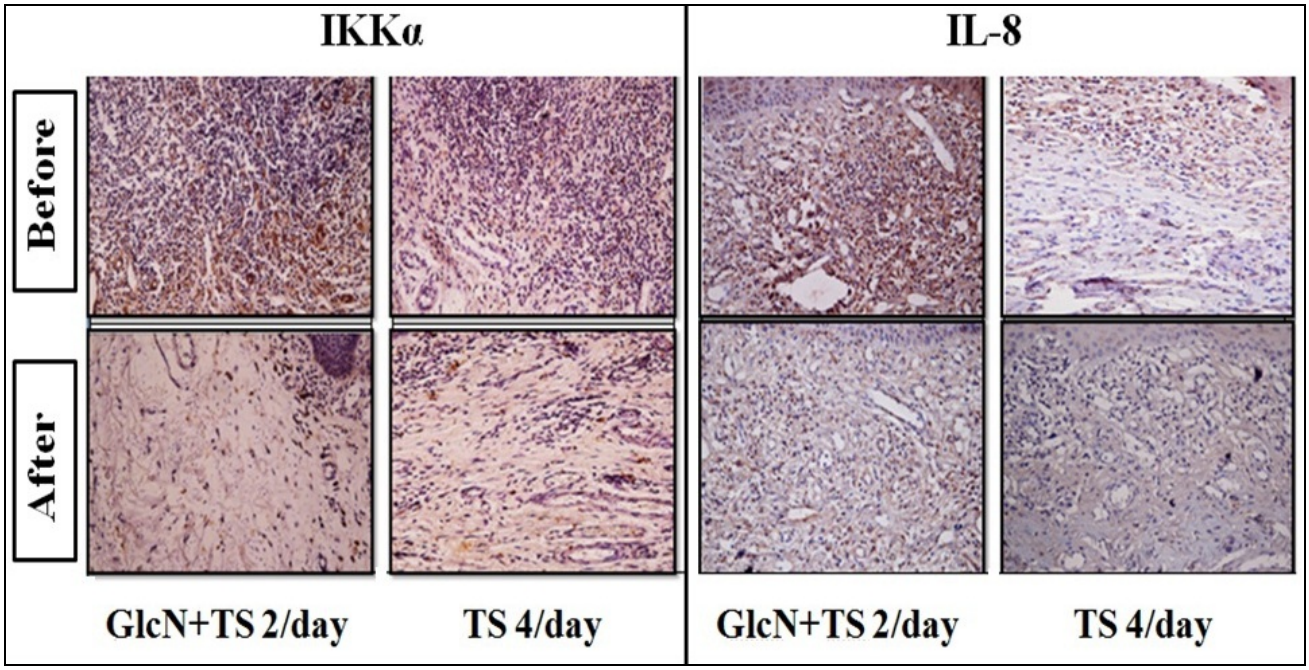

Figure 4 Photomicrographs comparing IKK-α and IL-8 immunopositivity in OLP lesions before treatment and reduction after treatment in a patient treated with combination of Glucosamine and topical steroids 2 times/day (GlcN+TS 2/Day) and another patient treated with topical steroid alone 4 times /day (TS 4/Day) *(original magnification 40X)*

DISCUSSION

We hypothesized that GlcN might be effective in management of symptomatic OLP considering GlcN mode of action, OLP pathophysiology and reported effective use of GlcN in management of atopic dermatitis which has similar pathogenesis to lichen planus.

Both subjective patients perception of pain and objective scoring of lesion were recorded at each visit to detect early differences between groups and after a treatment free observational period to investigate treatment maintenance effect.

Disease characteristics and mean of all measured scores at baseline revealed no statistically significant differences between the three groups, indicating that changes observed are mainly due to effect of used treatment.

Results of current study revealed that standard topical corticosteroid therapy (4times/day) combined with oral glucosamine (3times/day) showed early improvement and significant reduction in pain after 2weeks of treatment and pain totally disappeared after 4weeks, while standard topical corticosteroid therapy alone showed the least improvement and higher exacerbation.

Jin, et al.2015 compared between low dose cyclosporine combined with glucosamine and cyclosporine alone in treatment of atopic dermatitis and found that there was significant clinical improvement with combination treatment than with cyclosporine alone [17], similar results were seen in an earlier study by Kwon, et al. in 2013 [18]. Their results were consistent with present study since combination therapy with glucosamine revealed better results.

Exacerbation of lesions during treatment free period was reported in group II and group III patients only in consistent with a previous study on triamcinolone acetonide 0.1%, in which exacerbation was reported within 3 9 weeks after treatment cessation [19].

Observed synergistic clinical effect of GlcN with topical corticosteroid therapy could be attributed to its ability to suppress T-cell functions by enhancing apoptosis of activated T-cells, decreasing production of T helper cytokines, stimulating T regulatory cells and blocking NF-κB dependent signaling pathway with subsequent production of pro-inflammatory cytokines (IL-1, IL-6, IL-8 and TNF-α) [13,17].

Immunohistochemical analysis of both IKK-α and IL-8 was done for better understanding of GlcN effect on a critical step of nuclear factor-kappa B signaling in OLP. Pretreatment biopsy specimens revealed predominance of IL-8 and IKK-α in all groups which reduced significantly regardless type of treatment. Karatsaidis et al., 2007 found that IKK-α was strongly up-regulated in erythematous OLP compared to normal oral mucosa [20]. Moreover, Zhou et al, (2009) [21] and Ge et al, (2012) [6] reported that there was strong expression of NF-κB in infiltrated lymphocytes in OLP. Also Nottingham et al, (2014) found that over-expression of IKK-α and IKK-β induced NF-κB activation [22]. The present study results were also in accordance with a study used IL-8 as a marker to detect response of OLP to anti-angiogenic therapy and found that there was marked decrease in IL-8 [23]. These results support the role of NF-κB and pro-inflammatory cytokines in OLP pathogenesis.

Adjunctive GlcN therapy in group I had higher percentage changes regarding IKK-α and IL-8 than standard corticosteroid therapy in group III, but was statistically significantly different in IKK-α only. This may be attributed to glucosamine direct effect on early event in signaling pathway producing earlier clinical response, while corticosteroid alone act on later event after IL-8 production.

CONCLUSION

Glucosamine sulfate could be considered a novel adjunctive immunomodulatory agent in management of OLP inducing more rapid initial response and lower rate of recurrence even with substandard dose of topical corticosteroid. More comparative randomized clinical trials with longer follow up periods are required to investigate clinical effect of combination between low dose of systemic corticosteroid and GlcN in severe cases of OLP and other mucocutaneous immune mediated diseases and to compare GlcN effect with other immunomodulatory agents as calcinurin inhibitors. Moreover, pharmacological preparation and testing of topical GlcN delivery system for oral use would be a future research era.

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CONFLICT OF INTEREST:

The authors declare that they have no conflicts of interest.

REFERENCES

[1] Gupta, S. Jawanda, M.K. Oral Lichen Planus: An Update on Etiology, Pathogenesis, Clinical Presentation, Diagnosis and Management. *Indian J Dermatol*. 2015, *60*, 222 229.

[2] Mollaoglu, N. Oral lichen planus: a review. *Br J Oral Maxillofac Surg.* 2000, *38*, 370 377.

[3] Sugerman, P.B., Savage, N.W., Walsh, L.J., Zhao, Z.Z., Zhou, X.J., Khan, A. The Pathogenesis of Oral Lichen Planus. *Crit Rev Oral Biol Med*. 2002, *13*, 350 365.

[4] Li, Q., Verma, I.M. NF-kappaB regulation in the immune system. *Nat Rev Immunol.* 2002, *2*, 725 734.

[5] Hansberger, M.W., Campbell, J.A., Danthi, P., Arrate, P., Pennington, K.N., Marcu, K.B. IkappaB kinase subunits alpha and gamma are required for activation of NF-kappaB and induction of apoptosis by mammalian reovirus. *J Virol*. 2007, *81*,1360 1371.

[6] Ge, Y., Xu, Y., Sun, W., Man, Z., Zhu, L., Xia, X. The molecular mechanisms of the effect of Dexamethasone and Cyclosporin A on TLR4 /NF-κB signaling pathway activation in oral lichen planus. *Gene*. 2012, *508,* 157–164.

[7] Zhang, D., Wang, J., Li, Z., Zhou, M., Chen, Q., Zeng, X. The Activation of NF-κB in Infiltrated Mononuclear Cells Negatively Correlates with Treg Cell Frequency in Oral Lichen Planus. *Inflammation*. 2015, *38*, 1683 1689.

[8] Leung, D.Y.M, Bloom, J.W. Update on glucocorticoid action and resistance. *J Allergy Clin Immunol*. 2003, *111*, 3 22.

[9] Thongprasom, K., Dhanuthai, K. Steriods in the treatment of lichen planus: a review. *J Oral Sci.* 2008, *50*, 377 385.

[10] Thongprasom, K., Carrozzo, M., Furness, S., Lodi, G. Interventions for treating oral lichen planus. *Cochrane Database Syst Rev*. 2011:CD001168.

[11] Distler, J., Anguelouch, A. Evidence-based practice: review of clinical evidence on the efficacy of glucosamine and chondroitin in the treatment of osteoarthritis. *J Am Acad Nurse Pract*. 2006,*18*, 487 493.

[12] Reginster, J.Y., Neuprez, A., Lecart, M.P., Sarlet, N., Bruyere, O. Role of glucosamine in the treatment for osteoarthritis. *Rheumatol Int*. 2012, *32*, 2959 2967.

[13] Kim, C.H., Choi, Y.S., Cheong, K.A., Lee, A.Y. Mechanism underlying the effect of combined therapy using glucosamine and low-dose cyclosporine A on the development of atopic dermatitis-like skin lesions in NC/Nga mice. *Int Immunopharmacol.* 2013, *15*, 424 432.

[14] Kim, C.H., Cheong, K.A., Park, C.D., Lee, A.Y. Therapeutic effects of combination using glucosamine plus tacrolimus (FK-506) on the development of atopic dermatitis-like skin lesions in NC/Nga mice. *Scand J Immunol*. 2012, *75*, 471 478.

[15] Thongprasom, K., Luengvisut, P., Wongwatanakij, A., Boonjatturus, C. Clinical evaluation in treatment of oral lichen planus with topical fluocinolone acetonide: A 2-year follow-up. *J Oral Pathol Med*. 2003, *32*, 315 322.

[16] Scott, J., Huskisson, E.C. Graphic representation of pain. *Pain.* 1976, *2*, 175 184.

[17] Jin, S.Y., Lim, W.S., Sung, N.H., Cheong, K.A., Lee, A.Y. Combination of glucosamine and low-dose cyclosporine for atopic dermatitis treatment: a randomized, placebo-controlled, double-blind, parallel clinical trial. *Dermatol Ther*. 2015, *28*, 44 51.

[18] Kwon, H.B., Ahn, B.J., Choi, Y., Jin, S.Y., Cheong, K.A., Lee, J. Combination of glucosamine improved therapeutic effect of low-dose cyclosporin A in patients with atopic dermatitis: A pilot study. *J Dermatol*. 2013, *40*, 207 210.

[19] Laeijendecker, R., Tank, B., Dekker, S.K., Neumann, H.A.M. A comparison of treatment of oral lichen planus with topical tacrolimus and triamcinolone acetonide ointment. *Acta Derm Venereol*. 2006, *86*, 227 229.

[20] Karatsaidis, A., Hayashi, K., Schreurs, O., Helgeland, K., Schenck, K. Survival signalling in keratinocytes of erythematous oral lichen planus. *J Oral Pathol Med*. 2007, *36*, 215 222.

[21] Zhou, G., Xia, K., Du, G., Chen, X., Xu, X., Lu, R. Activation of nuclear factor-kappa B correlates with tumor necrosis factor-alpha in oral lichen planus: A clinicopathologic study in atrophic-erosive and reticular form. *J Oral Pathol Med*. 2009, *38*, 559 564.

[22] Nottingham, L.K., Yan, C.H., Yang, X., Si, H., Coupar, J., Bian, Y. Aberrant IKKα and IKKβ cooperatively activate NF-κB and induce EGFR/AP1 signaling to promote survival and migration of head and neck cancer. *Oncogene* 2014, *33*, 1135–1147.

[23] Mahmoud, M.M., Afifi, M.M. Anti-angiogenic therapy (bevacizumab) in the management of oral lichen planus. *Eur J Oral Sci.* 2016, *124*, 119 126.