The Use of 5-Fluorouracil vs. Triamcinolone Intralesional Injection for Treatment of Oral Lichen Planus

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ABSTRACT

Oral lichen planus is a very common chronic mucomembraneous inflammatory disease of the oral cavity. 5-Fluorouracil (5-FU) has immunological properties by inhibiting thymidylate synthase. Several studies have been proved that 5-FU suppress T-cell activation in humans. The study aimed to investigate the immunomodulating effects of intralesional 5-FU as an immunosuppressant agent for treatment of oral lichen planus in comparing with triamcinolone injection. A randomized single-blind clinical study was performed. The study sample that consists of 40 patients were divided into two groups. Group A consists of 20 patients represent the control group and received 0.5 mL of triamcinolone acetonide per 1cm2 once weekly for 3 consecutive months. While group B consists of 20 patients received 0.5 mL of 5-FU per 1cm2 once weekly for 3 consecutive months (12 weeks). All patients were clinically evaluated every 1 month to assess the clinical response which were denoted by flattening of lesions, absence of new lesions and decrease in severity of irritation and burning sensation. The mean age of patients was 42±10.57; and male to female ratio was 2:3. The duration of OLP in the enrolled patients was varied from 4 months to 2 years. A statistically significant difference was observed comparing percent of oral lesion areas improvement between 5-FU group and Triamcinolone group. It was concluded that intralesional administration of 0.5 mL of 5-FU per 1cm2 in comparing to triamcinolone acetonide has been showed a superior significant buccal-healing effect of oral lichen planus by ameliorating the cytotoxic T cells (CD8+) damage by "thymidine-less death" mechanism.

Keywords: Oral lichen planus, 5-Fluorouracil, Triamcinolone, mucomembraneous.

INTRODUCTION

Oral lichen planus (OLP) is a very common chronic mucomembraneous inflammatory disease of the oral cavity found in 0.5%–1% of the population[1,2]. It mainly affects adult patients and is slightly more common in 4th and 5th decade females (65%)[1,2]. Oral lichen planus might occur in concomitant with or without skin lesions[3]. Oral lichen planus causes remain unknown, while the pathogenesis is generally well understood[2,4]. Histopathologically, OLP is a cytotoxic T cell ($CD8^+$)-mediated disease[5]. In epidermis and mucosal epithelium, basal cells are destroyed by an immune-mediated process in which migration of cytotoxic T cells together with smaller numbers of helper T cells, into the basal layers of the mucosal epithelium for destroying of the basal cells[5]. Sometimes oral lichen planus is asymptomatic and appears as a striae (reticular) or hyperkeratotic plaque[6,7]. However, there is burning sensation scales from mild discomfort to severe usually bilateral in atrophic, erosive (ulcers) and bullous forms[6,7]. There is no specific therapy for the underlying pathological process; all of the current treatments are actually symptomatic to control any flare up in the disease severity and its complications[8]. A wide variety of treatments have been used alone or in combination to treat OLP[9]. These agents are corticosteroids, immunosupressors like azathioprine, cyclosporine and levamisole, retinoids and its derivatives, PUVA therapy, and antifungals like griesofulvin[10,11].

The treatment of choice for primary cases of OLP is topical corticosteroids as a mouthrinse or a gel which are widely used and accepted[10,11]. Local complications that resulted from prolonged use of topical corticosteroids are; hypopigmentation of the applied area, blanching of the mucosa, and delayed wound healing[12,13]. For nonresponding cases to topical steroids or have adverse effects on systemic use, intralesional corticosteroids are reserved[10,11,14]. Intralesional injection delivers triamcinolone acetonide directly into the affected mucous membranes, minimizing systemic exposure and providing high local concentrations with prolonged duration of action[14-17]. The efficacy of intralesional triamcinolone acetonide have been demonstrated in several studies in alleviating pain and discomfort, as well as reducing severity and size of OLP lesions[18,19].

The chemotherapeutic antimetabolite drug 5-fluorouracil (5-FU) is widely used in the treatment of solid tumors since 1957; including cancers of the colorectal, esophagus, stomach, breast, liver, pancreas, and head and neck[20]. 5-Fluorouracil requires activation because it is inactive in its parent form, and the activation occurs through a complex series of enzymatic reactions[21]. 5-Fluorouracil, a pyrimidine analog, induces cytotoxicity either by inhibiting thymidylate synthase (TS) enzyme through formation of covalently bound ternary complex or by disrupting RNA and DNA synthesis directly through misincorporating

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its metabolites[22]. 5-Fluorouracil has immunological properties by inhibiting thymidylate synthase[23]. Several studies have been proved that 5-FU suppress T-cell activation in mice and humans[24-26].

The present work aimed to explore the immunomodulating effects of intralesional 5-FU as an immunosuppressant agent for treatment of oral lichen planus in comparing with triamcinolone injection.

METHODOLOGY

Study design: This randomized single-blind clinical study was performed at dentistry clinics in Baghdad, Iraq, between September 2024 and June 2025. Patients who were visited the clinic with oral lichen planus were approached and those with white lines Wickham striae (WS) were selected. Patients were fully informed of the study protocol and informed consent was obtained from all participants before starting the study. Ethical and scientific committees in college of pharmacy and college of dentistry, Mustansiriyah University were approved the study.

Inclusion criteria: The inclusion criteria were as follows: Adult patients (≥ 18 years); patients who presented with symptomatic bilateral white lines Wickham striae OLP with or without generalized lichen planus; OLP patients who diagnosed by both clinical (morphology of oral mucosa) and histopathological (biopsy) approaches.

Exclusion criteria: The exclusion criteria were as follows: Patients with chronic systemic diseases like, diabetes mellitus, liver disease, renal disease, autoimmune disease, cardiovascular diseases, and hematological disease; pregnancy or breastfeeding; presence of genital lichen planus; infections; patients having any drug-induced lichenoid reactions; recent history of local buccal therapy in the past 2 weeks or systemic therapy approximately in the past month ; drug hypersensitivity; association of different variety of buccal lesions; histopathologic finding of epithelial dysplasia.

Study sample: The study sample that consists of 40 patients were divided into two groups. Group A consists of 20 patients represent the control group and received 0.5 mL of triamcinolone acetonide per 1cm^2 once weekly for 3 consecutive months. While group B consists of 20 patients received 0.5 mL of 5-FU per 1cm^2 once weekly for 3 consecutive months.

Intralesional procedure: Triamcinolone acetonide 40mg/mL injectable suspension USP, 5 mL multiple dose vial (Kenalog®, Bristol-Myers Squibb Pharmaceuticals Ltd) was used in the study for group A. 5-Fluorouracil (as Fluorouracil sodium) 50mg/mL injectable solution USP, 1g/20ml multiple dose vial (5-FU, Ebewe Pharma Austria) was used in the study for group B.

The lesion areas were sterilized by povidone-iodine (betadine®) gargle 1% oral solution as antiseptic. 1-mL Insulin syringe with fixed needle 31-guage was used to inject each of the drugs by the same practitioner at the center of the lesion without local anesthetic. Abstention from drinking and eating for at least 30 minutes was a necessary instruction to all patients after each injection. Additionally, patients were asked to enhance their oral hygiene as well as avoidance of spicy or coarse food. Patients were also asked to not use any buccal medications during the treatment course. Nikon D7500 20.9MP DX-Format 4K Ultra HD DSLR intraoral digital camera (Tokyo, Japan) was used for photographing the oral lesions.

Assessment of patients: Demographic profiles of participants including; age, gender, smoking status, drinking status, allergy to drugs, family history of skin and oral lichen planus, history of other oral diseases were recorded before starting the study. Blood samples were collected before the starting of therapies (baseline investigations) for all patients to assess and measure; complete blood count (CBC), renal function tests, liver function tests, random serum glucose and glycated hemoglobin. All investigations were repeated every 4 weeks.

Outcome measurement: All patients were clinically evaluated every 1 month to assess the clinical response which were denoted by flattening of lesions, absence of new lesions and decrease in severity of irritation and burning sensation.

As a self-administered assessment of 11-point, visual analogue scale (VAS) score was used to assess mouth pain and burning sensation. Patients were asked to mark their pain and describe their symptoms on a VAS score ranging from (0 = no burning sensation, no pain) to (10 = severe burning sensation, extreme pain).

Mucosa assessment was denoted as score 1 for mild erythema, score 2 for moderate erythema and score 3 for severe erythema. Moreover, lesion size assessment was denoted as score 1 for lesion size ≤0.5 cm^2, score 2 for lesion from >0.5 cm^2 to 1 cm^2, and score 3 for lesion area >1 cm^2. Assessment of the severity of OLP was measured by Thongprasom's score ranging from (0 = no lesion, normal mucosa) to (5 = white striae with erosive area >1 cm^2).

Treatment effectiveness was established when there are no white striae (except very mild cases), no erythematous or inflammation areas, and no occurrence of other symptoms.

Adverse reaction assessment: Patients were informed that, if any serious adverse reactions and/or complications occurred, they should stop the therapy, and knowing the researches to exclude them from the study. Fortunately, no one had serious adverse reactions and/or complications. If *Candida ablicans* infection had appeared, topical antifungal oral gel like Miconazole have been used. If symptoms reappeared, patients were informed to contact the researches following the end of treatment course[27].

Sample size: Calculation of the sample size was given 38 patients would have been needed (effect size of 0.5, type I error of 0.05, and power of 85%). So, this study enrolled 40 patients.

Statistical analysis: Data were analyzed using the SPSS (Statistical Package for the Social Sciences, version 28.0, SPSS Inc. Chicago, Illinois, USA)[28]. The means, standard errors, standard deviations from mean, and 95% confidence intervals were used as descriptive statistics. one-way ANOVA used to test statistical differences within each group, T-test paired for comparison between the study groups. A P-value < (0.05) was considered to be significant, and a P-value < (0.01) was considered to be highly significant[29,30].

RESULTS AND DISCUSSION

The Results of the current work demonstrated that there were non-statistically significant differences between the studied groups in values relating to the age (in years), gender, smoking habit, Alcohol consumption, allergy to drugs, family history of skin and oral lichen planus, history of other oral diseases. In addition, there were no statistically significant differences between the study groups in values relating to renal function tests, complete blood count, liver function tests in addition to random serum glucose and glycated hemoglobin.
The mean age of patients was 42±10.57; and male to female ratio was 2:3. The duration of OLP in the enrolled patients was varied from 4

months to 2 years. Out of 40 patients, 19 patients had only oral lesions, and 21 patients had mucosal and skin lesions.

The study abbreviates the results by this simple equation $\Delta (T_0 - T_f)$ to focus on the reduction of the lesion areas; where, T_0, before starting treatment; T_f, after the end of the treatment; Δ, percentage reduction: mean alteration in the mucosal region post-treatment(mm^2). So, results were demonstrated by percent.

The response to treatment was considered to be excellent if there was an overall 75-100% improvement; good if there was an overall 50-74% improvement; and poor if there was an overall less than 50% improvement.

A statistically significant difference was observed comparing percent of oral lesion areas improvement between the two groups. Table (1) showed that there was a significant difference between 5-FU group and

Table 1. Percent of Improvement for treatment groups.

Percent of Improvement		Excellent	Good	Poor	P-Value [a]
		$\Delta (T_0 - T_f) = \%$	$\Delta (T_0 - T_f) = \%$	$\Delta (T_0 - T_f) = \%$	
After 1 month	Triamcinolone	60%	26%	14%	0.002*
	5-Fluorouracil	67%	18%	15%	0.002*
P-Value [b]		0.039*	0.023*	0.130 [NS]	
After 2 months	Triamcinolone	67%	21%	12%	< 0.001**
	5-Fluorouracil	71%	21%	8%	< 0.001**
P-Value [b]		0.045*	0.669 [NS]	0.025 *	
After 3 months	Triamcinolone	72%	16%	12%	< 0.001**
	5-Fluorouracil	82%	13%	5%	< 0.001**
P-Value [b]		0.019*	0.042 *	0.017*	

[a] comparison performed by one-way ANOVA test, [b] comparison performed by T-test paired between the study groups. NS: Non-significant, (*) significant, (**) highly significant differences ($p<0.01$). Excellent if there was an overall 75-100% improvement; good if there was an overall 50-74% improvement; and poor if there was an overall less than 50% improvement.

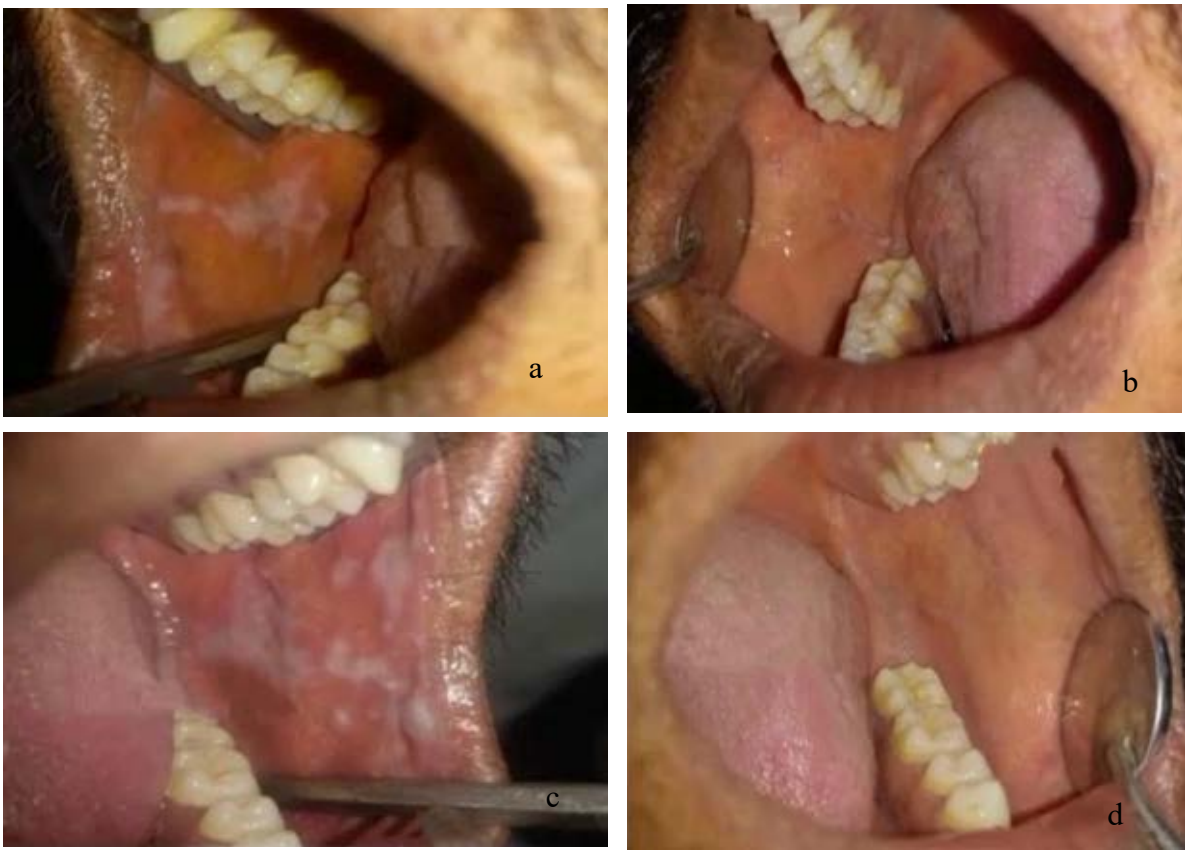

Figure 1. The appearance of lesions on buccal mucosa. (a) Before treatment with triamcinolone acetonide. (b) After treatment with triamcinolone acetonide. (c) Before treatment with 5-FU. (d) After treatment with 5-FU.

Triamcinolone group regarding percentage improvement calculated as percent Δ ($T_0 - T_f$) = %. Table 1 also illustrated that there was a significant difference between the two groups and within the same group each month. Figure (1) depicted appearance of lesions on buccal mucosa before and after with triamcinolone acetonide and 5-FU.

The reticular structure of oral lichen planus is typically characterized by the presence of Whickham striae (symmetrical white hyperkeratotic striae) in the oral mucosa associated with burning sensation and decreased quality of life[31]. OLP considered as a multifactorial disease; and currently there is no established cure or treatment focuses on the immune process that relating to its pathogenesis[32]. The best of current treatment modalities available nowadays for management of oral lichen planus is corticosteroids, which have been extensively used, but unfortunately, many patients suffering from unwanted adverse drug reactions[33].

Up to researchers' knowledge, there is the first study tried 5-FU in patients with OLP in comparing with triamcinolone acetonide. The researches aimed to study a well-known antimetabolite with immunosuppressant effects to treat a difficult condition with marked annoyance and morbidity.

The immune effect of 5-FU has been extensively studied, particularly in mice[24-26]. 5-FU has an effect on adaptive immunity as well as innate immunity (monocytes, or specifically macrophages)[34]. The effect of 5-FU on $CD8^+$ T-cell has been proved [34]. Moreover, IL-1β/IL-1R pathway signal for $CD8^+$ T-cell recruitment; 5-FU has been denoted to counteract IL-1β/IL-1R pathway that is activated in chronic inflammation[35]. So, this study was focused on a new agent that decreases the immune response that occur in the pathogenesis of OLP to ameliorate buccal lesions, as well as, improve the quality of life for the patients.

5-Fluorouracil is inactive in the "parent form" and enters into cells through a carrier-mediated transport system (facilitated transport)[20]. 5-FU requires activation (transformation) to numerous active ribosyl and deoxyribosyl nucleotide metabolites via a complex series of enzymatic reactions[23]. When 5-FU entering into the cells, it is converted directly to 5-fluorouridine monophosphate (5-FUMP) by phosphoribosyl transferase (PRPP), or converted indirectly to 5-fluorouridine (5-FUR) then to 5-FUMP by uridine phosphorylase (UP)[25]. By phosphorylation, 5-FUMP is then converted to 5-fluorouridine diphosphate (5-FUDP)[26]. Then to transform to the active metabolite that damaging RNA, 5-FUDP converted to 5-fluorodeoxyuridine triphosphate (5-FUTP) by nucleoside-diphosphate kinase (NDPK)[24]. Moreover, transformation to the active metabolite that damaging DNA; firstly, 5-FUDP converted to 5-fluoro-2′-deoxyuridine-5′-monophosphate (5-FdUMP, 5-fluorodeoxyuridine monophosphate) by ribonucleotide reductase (RNR); finally, 5-FdUMP forms with thymidylate synthase (TS) a covalently bound ternary complex[20,23,24]. When 5-FdUMP inhibit thymidylate synthase, the reduced folate 5,10-methylenetetrahydrofolate (N_5, N_{10}-Methylene-FH_4) cannot be converted to dihydrofolic acid (FH_2), a critical reaction for the de novo biosynthesis of deoxythymidine monophosphate (dTMP)[26, 34-36]. dTMP needed for DNA synthesis and cell growth [20]. Inhibition of DNA synthesis results from inhibition of thymidylate synthase through "thymidine-less death" [25,34,37]. This study suggest that 5-FU heal oral lichen planus lesions by "thymidine-less death" mechanism in the cytotoxic T cells ($CD8^+$).

CONCLUSION

Intrlesional administration of 0.5 mL of 5-FU per 1cm² in comparing to triamcinolone acetonide has been showed a superior significant buccal-healing effect by ameliorating the cytotoxic T cells ($CD8^+$) damage by "thymidine-less death" mechanism; representing a possible promising drug for treatment of oral lichen planus.

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Potential Conflicts of Interest: None

Competing Interest: None

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