A Comparative Study between Intralesional Low Molecular Weight Chitosan and Triamcinolone Acetonide for Treatment of Erosive-Atrophic Oral Lichen Planus

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Abstract: Oral lichen planus (OLP) is a common chronic inflammatory mucosal disease in which T-cell mediated immune responses are implicated in the pathogenesis. Various treatments have been employed to treat symptomatic OLP, but a complete cure is very difficult to achieve because of its recalcitrant nature. Topical corticosteroids therapy of OLP has shown conflicting results in many reports. This study was conducted on twenty patients with symptomatic OLP were randomly assigned treatment with intralesional 1% low molecular weight chitosan or Triamcinolone Acetonide. The assessments were at weeks 0, 2, 4, 16 by appearance score, pain score, and TNF-α of the target lesions. Obtained results revealed appearance score, pain score, and TNF-α, were reduced in both groups. No significant differences were found between the treatment groups regarding the response rate and relapse. This study aimed to compare the effectiveness of topical intralesional 1% low molecular weight chitosan with topical intralesional Triamcinolone Acetonide in the treatment of oral erosive and atrophic lichen planus and level of TNF-α.

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1. Introduction

Oral lichen planus (OLP) is a relatively common chronic autoimmune inflammatory disease of mucosal surface with a variety of clinical manifestations including: reticular, papular, hyperkeratotic, atrophic, erosive, and bullous forms ***(Edwards & Kelsch, 2002)***. Among these forms, the long-standing erosive OLP is recalcitrant to medical management and more likely to be malignantly transformed into squamous cell carcinoma. Hence, OLP is considered to be a potentially malignant disorder and attracts many attentions of clinicians ***(Xiong et al., 2009).***

The TNF- α is a small cytokine with a molecular weight of only 17 kDa secreted from inflammatory cells such as activated monocytes, macrophages, and many other cells including B cells, T cells, mast cells, and fibroblasts during infection or trauma. It is a multifunctional cytokine that mediates inflammation, immune response, apoptosis and also has a significant role in normal development and homeostasis of several organs ***(Thongprasom et al., 2006).*** TNF has been found to be involved in the pathogenesis of many inflammatory or autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, psoriasis and lichen planus ***(Sugerman et al., 1996).***

The best treatment for this case includes the use of high-potency topical corticosteroids ***(Setterfield et al., 2000*** **and** ***Bruce & Rogers, 2007).*** It has been reported that topical corticosteroids, which have fewer side effects, are equally or even more effective than systemic corticosteroids ***(Lodi et al., 2005).*** The long-time use of the topical corticosteroids may also induce drug tolerance or insensitivity to the drugs ***(Valera et al., 2009),*** adrenal insufficiency ***(Levin & Maibach, 2002),*** pseudomembranous candidiasis **(*Gonzalez-Garcia et al., 2006*),** mucocutaneous atrophy (***Schoepe et al., 2006***), and Cushing's syndrome ***(Kumar et al., 2004).*** Moreover, a small proportion of people are allergic to corticosteroids ***(Foti et al., 2009),*** while some people are insensitive, or even resistant to corticosteroids, owing to the polymorphisms or mutations in the corticosteroids receptor gene ***(Charmandari et al., 2008).***

Natural products have served as a major source of drugs for centuries, and about half of the pharmaceuticals in use are derived from natural products ***(Clark, 1996).*** Among these materials, chitosan (poly-N-acetyl glucosaminoglycan), is a derivative of chitin, which is the second most abundant natural biopolymer, and which is a primary structural component of the exoskeleton of arthropods such as crustaceans, the cell wall of fungi, and the cuticle of insects. Chitosan is obtained by M-acetylating chitin, and it is biologically renewable,

biodegradable, biocompatible, nonantigenic, nontoxic, and biofunctional, and it can accelerate the wound healing process enhancing the functions of inflammatory cells, macrophages, and fibroblasts ***(Ueno et al., 2001*)**.

The chitosan inhibit formation of PGE2 and cyclooxygenase-2 (COX-2) induction accompanied by inhibition of TNF-α and IL-1β formation but enhancement of IL-10 generation (***Chou et al., 2003)***. Thermogelling chitosan/GP entraps and sustains release of a broad range of anti-TNF agents. Such delivery of disease-modifying therapy could establish a drug depot to treat local inflammation (***Shamji et al., 2009)***.

Treatment of oral lichen planus (OLP) remains a great challenge for clinicians. This study aimed to compare the effect of topical intralesional 1% low molecular weight chitosan with topical intralesional corticosteroids in the treatment of oral erosive and atrophic lichen planus and level of TNF-α.

2. Materials and Methods

A prospective randomized trial was carried out in the Department of oral medicine, Faculty of Dentistry, Tanta University, 6th October University. All patients gave written informed consent. Twenty patients were assessed according to the eligibility requirements.

The inclusion criteria were as follows:

1. Clinical diagnosis of OLP (Presence of painful and atrophic-erosive oral Lesions).
2. Age between 20-60 years
3. Ability to complete the present clinical trial.

The exclusion criteria were:

1. Pregnant or breast feeding women (pregnancy test for women of child bearing age).
2. Lichenoid reactions caused by certain drugs or dental amalgam.
3. Therapy for OLP in the 6 months prior to the study.
4. Patient doesn't have hepatitis C [after the patients' medical histories were recorded, the patients were given hepatic screening as published elsewhere ***(Carrozzo et al., 1996)*]**.
5. Presence of candidiasis before treatment.
6. Contraindications for corticosteroid use (immunodeficiency or severe heamatological alterations).

The two study drugs (1% intralesional LMW chitosan & 5-10 mg/ml intralesional TA) were prepared. Determination of whether a patient should be treated by intralesional TA (group I) aqueous suspension or 1% LMW chitosan (group II) were made by reference to a stastistical series based on a random number table drawn up by a professor of statics.

Both 1% LW Chitosan & TA 5-10 mg/ml injected at once weekly interval over 3- 4 weeks /every 4 weeks (maximum of 0.1 ml /1 square cm of tissue per injection) **(*McCreary & McCartan, 1999*)** 0.5 ml TA (40 mg/ml).

Clinical assessment:

The responses of Atrophic-errosive OLP to intralesional 1% LMW chitosan and TA were evaluated on basis of erosive area and pain or burning sensation. All values for erosive area and pain or burning sensation were assessed and recorded at baseline, 2, 4, 16 weeks by 2 independent researches who were blinded to the medication for the whole treatment duration.

The pain or burning sensation was self-assessed by patient using a 10- cm line visual analog scale (VAS). Patients marked the point from 0 (no pain) to 10 (extreme pain) representing their present pain perception.

Each patient was examined at the beginning of treatment, and then after 2, 4, 6, 8 weeks and 4 months of therapy. The clinical data were scored according to the criteria used by ***Thongprasom et al., (1992):***

Score 5 = white striae with erosive area more than I cm
Score 4 = white striae with erosive area less than 1 cm
Score 3 = white striae with atrophic area more than I cm
Score 2 = white striae with atrophic area less than I cm
Score I =mild white striae, no erythematous area
Score 0 = no lesion, normal mucosa

The pain was scored by visual analogue scale (VAS), a well documented method of pain assessment ***(Martin & Greenberg, 2003):***

The severity of pain and pain sensation was evaluated according to following scales:
Scale 0: no pain: VAS=0
Scale 1: mild pain: 0< VAS≤3.5
Scale 2: moderate pain: 3.5 <VAS≤7
Scale 3: severe pain: 7< VAS≤10.

Patients were asked to score their intensity of pain at each visit. Pain scores ranged from 0 (no pain) to 10 (extreme pain).

Estmation of the serum level of TNF-alpha:

3 cm venous blood samples were collected from all patients before treatment and after 2 weeks, 1 and 4 months from treatment and centrifuged at a rate of 3000 r.p.m to separate the serum which were stored at -70ºC till analysis.

TNF-alpha was estimated by Enzyme Linked Immunosorbent Assay (ELISA) using commercially available human TNF-alpha kits manufactured by Bender medsystems CO. ELISA was performed according to manufacture's instruction. The microtitre plate was read at 450nm. The sensitivity of

TNF ELISA was 1.5 pg/ml. All samples were assayed in duplicate.

Follow up assessment:

Patients with complete disappearance of the erosion at 1-week had 1-month and 2- month follows ups to detect recurrence. Meanwhile, patients who did not get a complete response were assessed every week for another 3- weeks. If there is no evidence of erosion and the VAS was 0, the treatment was stopped. The patients who still had erosion after 1-month of treatment were referred for other therapies including topical immunosupressant or systemic corticosteroids.

3. Results:

Twenty patients [5 males and 15 females] completed the study, 10 in group I with mean age 45.9± 9.91 and 10 in group II with mean age 48.7± 11.48 (Table 1).

Two cases of acute pseudomembranous candidiasis were found in the TA group (gave antifungal) and this complication was not reported in the chitosan group. No adverse effect was observed in two groups.

Results showed that there was a significant reduction of the mean of TNF-α, VAS and criteria of clinical data which continued up to the end of the 4 months evaluation period as compared to the mean baseline value in groups I and II (Table 2, 3 and 4 Figure 1,2, 3 and 4).

Data showed that the mean difference of TNF-α, VAS and criteria of clinical data at baseline was statistically insignificant between all treated groups. At all evaluation periods ANOVA test showed statistically insignificant difference between the two treated groups.

Table (1): Mean values of age and sex, among the study groups

Time of assessment	Group I (n=10)	Group II (n=10)	
	Mean± SD	Mean± SD	
Age	45.9±9.91	48.7±11.48	0.566
Sex	7 female/3 male	8 female/2 male	1.000

Table (2): Mean values of tumor necrosis factor α (TNFα) among the study groups at base-line, 2 weeks, 1 and 4 months post-intralesional injection.

Time of assessment	GroupI (n=10)	GroupII (n=10)	t-test P
	Mean± SD	Mean± SD	
	15.54±6.41	16.56±7.19	0.749
2 weeks (2)	13.2±5.54	13.9±6.83	0.277
1 month (3)	10.69±4.68	8.42±3.40	1.240
4 months (4)	8.9±2.7	7.1±1.4	1.844
F-test **P** **Scheffe test**	3.357* 0.029 1 vs 2, 3 & 4, P***	7.199** 0.001 1 vs 2, 3 P*** 1 vs 4 P**	

Significance: *P<0.05. **P<0.01, ***P<0.001

Table (3): Mean values of visual analogue scale (VAS), among the study groups at base-line, 2 weeks, 1 and 4 months post-intralesional injection.

Time of assessment	Group I (n=10)	Group II (n=10)	F-test P Scheffe test
	Mean± SD	Mean± SD	
At base-line (1)	5.20±1.13	5±0.94	0.673
2 weeks (2)	2.2±0.63	2.4±0.51	0. 449
1 month (3)	1±0.47	0.6±0.516	0.087
4 months (4)	0.40±0.51	0.30±0.48	0.660
F-test **P** **Scheffe test**	83.755*** 0.0001 1 vs 2, 3 & 4, P***	112.651*** 0.0001 1 vs 2, 3, & 4, P***	

Significance: *P<0.05. **P<0.01, ***P<0.001

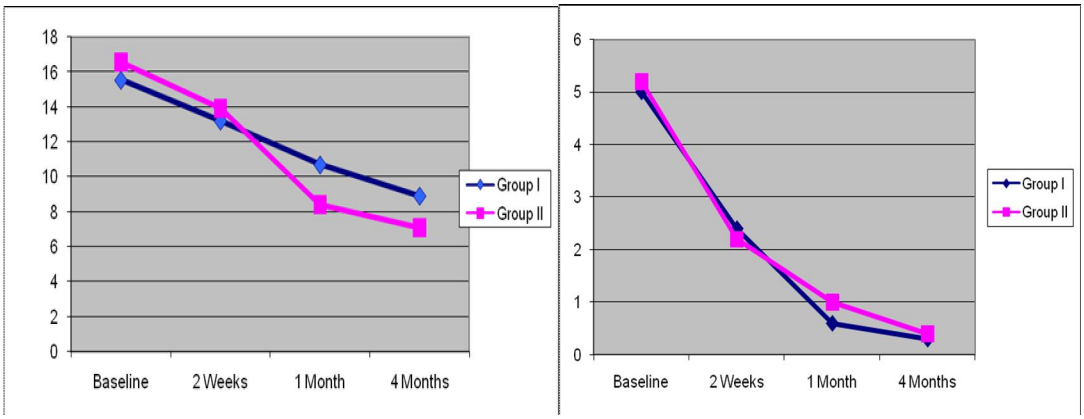

Figure 1: a, Mean values of tumor necrosis factor α (TNFα) among the study groups at base-line, 2 weeks, 1 and 4 months post-intralesional injection. b, Mean values of visual analogue scale (VAS), among the study groups at base-line, 2 weeks, 1 and 4 months post-intralesional injection.

Table (4): Mean values of criteria of clinical data, among the study groups at base-line, 2 weeks, 1 and 4 months post-intralesional injection.

Time of assessment	GroupI (n=10) Mean± SD	GroupII (n=10) Mean± SD	F-test P Scheffe test
At base-line (1)	4.1±0.73	4.3±0.67	0.535
2 weeks (2)	2.3±0.48	2.4±0.516	0. 660
1 month (3)	0.7±0.48	0.60±0.516	0.660
4 months (4)	0.40±0.51	0.40±0.51	1.00
F-test P Scheffe test	96.321*** 0.0001 1 vs 2, 3 & 4, P***	105.637*** 0.0001 1 vs 2, 3,&4, P***	

Significance: *P<0.05. **P<0.01, ***P<0.001

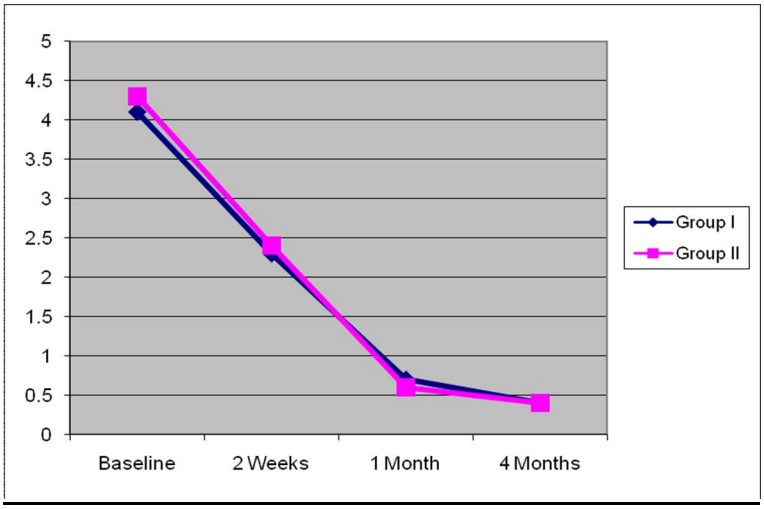

Figure 2: Mean values of criteria of clinical data, among the study groups at base-line, 2 weeks, 1 and 4 months post-intralesional injection.

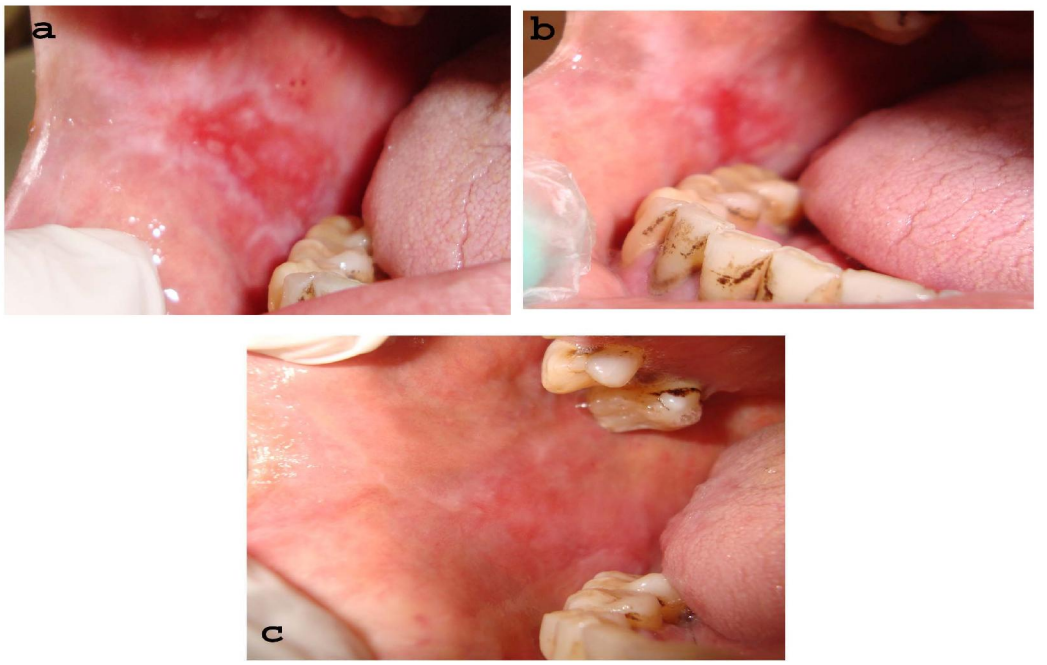

Figure 3: a) The buccal mucosa showed erythematous and ulcerative, b) Clinical response after 2 weeks treatment with of 1% of chitosan, c) Clinical response after 2 months treatment with of 1% of chitosan

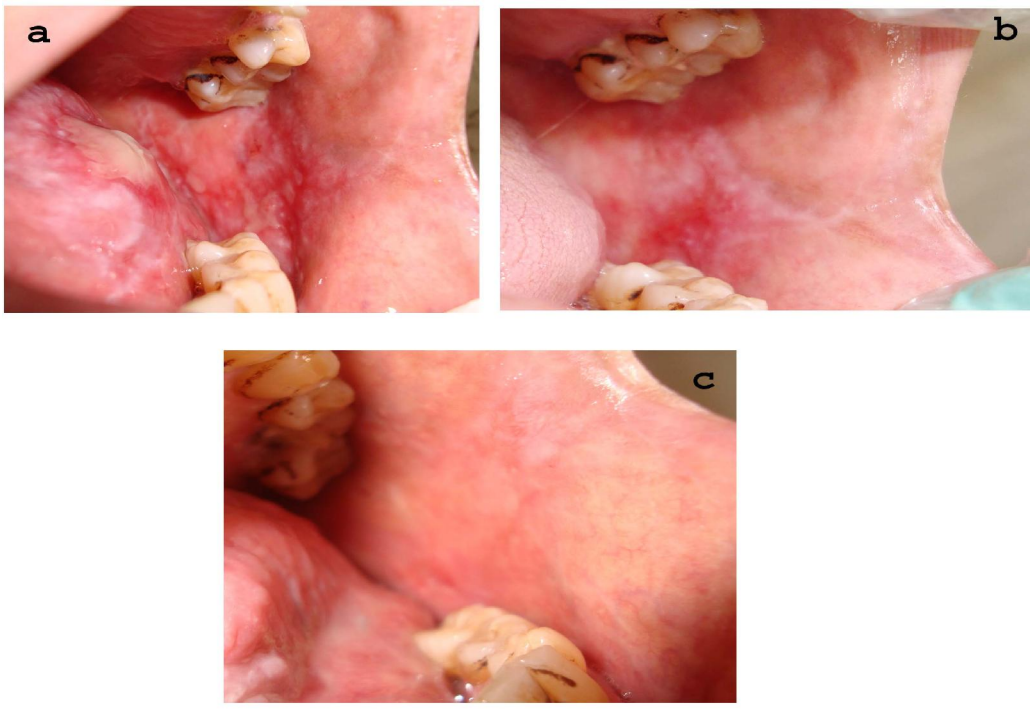

Figure 2: a) The buccal mucosa showed erythematous and ulcerative, b) Clinical response after 2 weeks treatment with of triamcinolone acetonide, c) Clinical response after 2 months treatment with of triamcinolone acetonide

4. Discussion

The management of erosive lichen planes remains challenging. Existing therapies predominantly provide symptom control rather than induce remission. Topical corticosteroids are the mainstay in treating mild to moderately symptomatic lesions. Options (presented in

terms of decreasing potency) include 0.05% betamethasone valerate gel, 0.05% fluocinonide gel, and 0.1% triamcinolone acetonide ointment ***(Vincent, 1991).*** The use of topical steroids has fewer side effects than systemic administration. The disadvantages of topical steroids include: candidiasis, thinning of the oral mucosa, compliance problem, and discomfort while applying. In Topical formulations of the more potent corticosteroids can cause adrenal suppression if used in large amounts for prolonged periods ***(Edwards & Kelsch, 2002)***, so in the present study we use lowest-potency steroid.

Steroids use is contraindicated in patients who are breast feeding, and used with caution in patients with herpetic infections, glaucoma, pregnancy, HIV infection, tuberculosis, diabetes mellitus, candidiasis, and hypertension ***(Sharma et al., 2008).*** Because of these clinical problems and immunopathogenesis of OLP, we sought to identify a topical immunomodulatory drug for treatment of this disorder as an alternative when topical glucocrticoid is ineffective or contraindicated. The current study was carried out to compare the efficacy of intralesionl chitosan for erosive lichen planes with respect to an intralesional triamcinolone acetonide.

TNF-α which is one of the proinflammatory cytokines, has been reported to play a role in the pathogenesis and inflammatory process of OLP ***(Thongprasom et al., 2006).*** In the present study, both groups had a decrease in TNF- α compared to the baseline values. This reduction can be contributed to the anti-inflammatory effect of both chitosan and TA. Chitosan inhibits prostaglandin E2 (PGE2), by suppressing cycloxygenase (COX2) induction and activity, and it also suppresses the TNF-α and the IL-1β. In addition, it also increases the anti-inflammatory cytokine IL- 10 ***(Chou et al., 2003 and Okamoto et al., 2002).*** The suppressing effect of chitosan against the TNF- α was also demonstrated by ***Shamji et al., (2009),*** who showed the ability of chitosan to release a broad range of anti-TNF agents. Fluocinolone acetonide 0.1% have a beneficial effect on the reduction of TNF-α expression by inhibiting the synthesis of this cytokine ***(Thongprasom et al., 2006)***. Furthermore, ***Rhodus et al., (2006)*** found that patients with lichen planus who were treated with 0.1% dexamethasone oral rinse for 6 weeks, the levels of cytokines such as TNF-alpha, IL-1-alpha, IL-6, and IL-8 were decreased significantly.

In the current study, IL CH and IL TA groups showed a significant reduction of clinical signs (erosion , appearance score) which was maintained until the end of the study period when compared to baseline levels. The reduction in clinical signs in the presence of chitosan could be attributed to the anti-inflammatory effect chitosan (***Chou et al., 2003 and Okamoto et al., 2002)***. Repeated oral administration of LMW chitosan in rats accelerated gastric ulcer healing by formation of granulation tissue and angiogenesis in the ulcerated part ***(Ito et al., 2000)***.

Current treatments for OLP are aimed at alleviating pain and eliminating the lesions. In the current study, both the tested groups had an improvement in clinical symptoms (pain, burning sensation) (VAS score) of both groups as compared to the elevated score of the baseline at all evaluation periods. Chitosan provided excellent pain relief in cases who received the agent topically over open wounds such as burns, skin abrasions, skin ulcers and skin graft areas which occurs as a result of absorption of proton ions released from the inflammatory site, while the main analgesic effect of chitin is the absorption of bradykinin which is the main substance related to pain (***Okamoto et al., 2002).***

In the present study, two cases of acute pseudomembranous candidiasis were found in the TA group and this complication was not reported in the chitosan group. These data could be attributed to the actual antifungal effect of chitosan ***(Senel et al., 2000).*** Chitosan reduces hydrophobicity and adhesion of candida albicans to cells which are important virulence factors related to colonization of the soft tissues of host or acrylic surfaces present in the oral system and prevents the development of mucositis (***Azcurra et al., 2006***).

In addition, potent topical corticosteroids used for long periods, or in excessive quantities, can cause atrophic effects, inhibiting the synthesis of collagen in connective tissue ***(Setterfield et al., 2000)***. Chitosan inhibited the degradation of extracellular matrix, stimulated the expression of type I collagen and up-regulated alkaline phosphatase ***(Zhang et al., 2007).***

On conclusion; the topical intralesional chitosan injection is as effective as TA for erosive OLP, which suggests that topical intralesional chitosan injection can be a promising therapeutic alternative for erosive OLP, especially for those insensitive, or even resistant, to glucocorticoids. In addition; the use of the 1% LMW chitosan should be encouraged, investigated in larger RCTs, assessed using quality of life measures and also tested with other drugs for the treatment of OLP.

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