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# The Efficacy of Oral IMOD™ in Oral Licheh Planus Treatment; A Randonized, Double-Blind Placebo-Controlled Trial

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## ABSTRACT

**Objective**: A vast variety of local and systemic treatments have been utilized in the management of oral lichen planus (OLP). The efficiency of IMOD (an Iranian new immunomodulatory drug, containing selenium, carotene, and flavonoids) in the treatment of OLP was assessed.

**Methods** In a randomized double-blind placebo/controlled trial study, 40 individuals (who referred to the oral and maxillofacial department of the School of Dentistry) with lichen planus were registered. The study enclosed a three-month period of therapy by IMOD (480 mg/day) (n=20) or placebo (n=20), and a three-month follow-up period after drug interruption. Consequence measures contain pain or burning severity, clinical score, clinical global impression of change (CGIC) and patient global impression of change (PGIC). Unstimulated saliva levels of total antioxidant capacity (TAC), Malondialdehyde (MDA), uric acid and TNF-α were tested at the baseline and after treatment and calculated their changes. Statistical analysis of Mann-Whitney and unpaired student's t-test were used.

**Results**: There were no noteworthy changes between placebo and IMOD treaded groups in pain or burning severity, clinical score, CGIC and PGIC following 2,4,8,12, and 24 weeks following treatment and also in saliva TAC, MDA, TNF-α and uric acid changes.

**Conclusion**: IMOD lacks proper efficacy in the management of severe or very severe OLP lesions.

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## Introduction

OLP is a chronic inflammatory, autoimmune disorder with long clinical course. OLP is a complex disorder that genetics, environmental factors and style of life may be involved in its pathogenesis. This chronic disorder occurs in around fifth and six decades and mostly involve females than males. The low tendency for unexpected remission, high resistance to topical medications, and the tendency to malignant transformation of this disorder, have attracted much attention from researchers for research and study of OLP [1-4]. IMOD is an Iranian first-hand immunomodulator drug (international publication number: WO 2007/ 087825A1)

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with the source of herbal. It is formed from a mixture of ethanolic Rosa sp Urtica Dicica and Tanacetum Vulgare extracts, comprises selenium and urea, and having been exposed to a pulsed electromagnetic field [5].

TNF-α is a potent pro-inflammatory multifunctional cytokine that play a significant role in antitumor activity in vivo and many cell lines of tumor, immune modulation, in innate inflammation responses, control of cell proliferation (stimulates fibroblasts), differentiation (myeloid cells), activation (neutrophils), stimulates angiogenesis, effect on tissue remodeling, and has dual effect on apoptosis as a powerful activator and also anti-apoptotic signaling cascades [6]. In some autoimmune diseases, TNF-a concentration correlated with exacerbation and regression of diseases and may be used for monitoring [6].

Injury and destruction of the membrane of cells are performed by lipid peroxidation that its uncontrolled productions can occur in oxidative stress [7,8]. Oxidative stress indicates the imbalance between antioxidant defense systems and production of highly reactive oxygen and nitrogen species [9]. Reactive oxygen metabolites interact with polyunsaturated fatty acids and commence the lipid peroxidation process that is a consequence of oxidative stress. Therefore, Malondialdehyde (MDA) is a principal and most important supply that is considered as the final product of the polyunsaturation fatty acid oxidation and is appropriate for DNA damage as a biomarker and measurement of oxidative stress [10,11]. Uric acid is one of the furthermost main antioxidants in the fluids of the body, including saliva that forms more than 85% of both whole salivary stimulated and unstimulated salivary antioxidant capacity in individuals while it contributes to more than 50% of blood antioxidant capacity [12]

When the benefits of saliva as a possible diagnostic medium were detected, its usage for monitoring purposes and universal health has become a favourable aim in medical studies [13,14] Research on saliva is a dynamic field and has many advantages, including cost-effective means for monitoring, its collection is non-invasive simple and safe. Its repeated collections do not cause any discomfort for patients. Therefore, there has been increasing attention in saliva-based analyses in the past a few decades [9,15-18]

**Hypothesis/theory**

In our previous study, a single dose of IMOD was applied in an open-label before-after clinical trial study. Its results were dramatically positive on OLP [19]. In this study, Therefore, the aim is to evaluate the efficacy of this drug in a clinical trial on severe and very severe oral lichen planus lesions

**Methods and Patients**

This is a randomized double-blind placebo/ controlled trial study (Ethic No: IRCT138801191559N2) including 40 individuals (34 women and 6 men) aged 18-64 years who had oral lesions of OLP and referred to the oral and maxillofacial department of the School of Dentistry. Patients suffering from OLP were invited to participate in the study after full explanation of the aims of the trial in the local dialect. The formal recruitment process was completed when patients became fully aware of the content of the study consent form and signed it.

**Intervention allocation (Randomization) and blinding**

The patient and those who conducted the study were not cognizant of the state of the patients with regard to getting the drugs or placebo. For this to occurred, the patients were blind by using a placebo which was similar to the drug in outward but the add-up

is a biologically inert matter. To blind those who conducted the study, the person who delivered or checked the study drug was different from those who examined the patients and all drug packages were identified by unique numbers. Finally, the randomisation table was concealed from research staff by using closed envelops.

**Inclusion and Exclusion Criteria**

The inclusion criteria were the presence of white, reticular/papular symmetric or bilateral, histologically confirmed liquefaction degeneration of the basal layer, and band-like infiltration of mononuclear inflammatory cells, just beneath to connective tissue.

The exclusion criteria were pregnancy/nursing, systemic diseases, presence of dysplasia in histological analysis, use of any topical or systemic medication in the past six months, including the use of vitamin supplements history of chemotherapy or radiotherapy,

**Intervention**

This study had two arms: oral IMOD (Pars Roos Co, Tehran, Iran), 120 mg (1capsule) every 6 hours for 3 months and placebo (starch), 1 capsule every 6 hours, for 3 months.

Patients were advised to take the medicine (IMOD or placebo) with a glass of water one hour after a meal.

**Follow-up assessments**

Patients were visited every other week during the first month and every month during the following five months by two oral and maxillofacial specialists during the study period. Patients were followed-up for another period of three months (post-treatment follow-up period) after completing drug treatment period. All the patients were visited by oral and maxillofacial specialists at the end of the study.

**Measurement of variables**

Intensity of pain and burning sensation during the week prior to the assessment time was measured through a 5-point rating numerical scale from no to very severe pain or burning sensation (0 = no, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe).

The oral lesions were clinically graded based on the following grading scale: 0 = normal mucosa without lesion, 1 = reticular lesion with atrophic area less than 1 centimetre, 2 = reticular lesion with atrophic area more than 1 centimetre, 3 = reticular lesion with erosive area less than 1 centimetre, 4 = reticular lesion with erosive area more than 1 centimetre.

Clinical Global Impression of Change (CGIC) was measured through a 10-point scale on which the clinician-rated the change observed in the patient's overall status since the first follow-up visit and Patient Global Impression of Change (PGIC) was measured at the end of treatment period and when the follow up finished at the end of study through a 10-point scale on which patients themselves rated any changes observed in their overall status since the beginning of the study. The scores on this scale varied from 10: "much improved" to 0: "much worse".

Unstimulated saliva samples were collected before and 24 weeks after intervention without chewing movements through expectoration under resting conditions, in a quiet room between 9 a.m. and 12 p.m., and at least 90 minutes after the last intake of food or drink. The specimens were kept at -80ºC until determining of TNF-α, oxidative stress, total antioxidant capacity and uric acid.

Total Antioxidant Capacity (TAC) of saliva was determined by measuring its ability to decolourization of ABTS radical cation according to previous fully described methods and the assay calibrated with Trolox [20]. Saliva MDA level was determined by a method based on reaction with thiobarbituric acid (TBA) at 90 - 100°C.[15]

Uric acid was measured calorimetrically by TOOS method using affiliated kit (Pars Azmoon, Karaj, Iran).
TNF-α was assessed by using ELISA technology using a commercially available kit (Zelbio GmbH, Ulm, Germany).

**Statistical Analysis:**
Analyses were performed using SPSS software version 16 (SPSS Inc. Chicago, IL, USA). The statistical analysis of the t-test and Mann-Whitney test were used. $P < 0.05$ was considered statistically significant.

**Results:**
The number of men and women and also the number of smokers, married and their age was approximately equal in both groups (Table 1)
Statistical evaluation of data using Mann-Whitney test displayed that there were no significant differences between placebo and IMOD treaded groups in pain or burning severity, clinical score, clinical and patients Global Impression of Change at 2,4,8,12, and 24 weeks following treatment and AUC of these parameters (Table 2).
The differences in unstimulated salivary lipid peroxidation (MDA), total antioxidant Capacity (TAC), TNF-α and uric acid (UA) levels and their changes between IMOD and Placebo treated groups were not significant (Table 3).
There was no side effect in each group after intervention.

Table 1: Basal characteristics of subjects in IMOD and placebo-treated groups.

| | IMOD | Placebo | P-value |
|---|---|---|---|
| Sex=Female: n (%) | 16 (80) | 18 (90) | 0.38 |
| Age (x□ ± SD) | 52±9.9 | 49.1±9.9 | 0.35 |
| Married n (%) | 20(100) | 19(95) | 0.50 |
| Non-smoker: n(%) | 18 (90) | 17 (85) | 0.84 |

**Discussion:**
Generally, patients with OLP are the most non-infectious patients that referred to oral and maxillofacial department. Its pathogenesis is not clearly known and therefore has no definitive cure at present. At this time, corticosteroids are gold standard for treatment of OLP. Due to the chronic nature and high recurrence rate of OLP, long-term local and topical use of corticosteroids is often necessary, which may be caused candidiasis, mucosal thinning (atrophy), delayed wound healing, tachyphylaxis, discomfort and ultimately poor patient collaboration are amongst the complications of local corticosteroids [21].
IMOD is an immunomodulatory herbal origin drug that is an enriched mixture of extracts with selenium, a substantial trace element that has a crucial role in guarding cells from oxidative stress. IMOD has undergone three phases of clinical trial without any significant adverse effects and has been shown to increase CD4 lymphocytes after one to three months of use, a long-term effect that can be maintained for a long time after discontinuation. So, it can be used in immunological disturbances [5]. Therefore, in the first phase, for OLP treatment, by designing a study with before and after method, in 85% of the lesions were shown to some degree of clinical improvement [19]. Since no harm was observed in the original studies and also previous study, in order to confirm the effectiveness of this drug, as an optional drug in the treatment of OLP, at this stage, by increasing the dose, we re-examined its effectiveness. Due to the good response obtained in the first phase of the study, our hopes for finding a drug with few side effects that can cause remission this chronic disorder, which has the potential for malignant transformation, increased. At this stage, for evaluating the efficacy of this herbal drug, in addition to changing the type of study and the dose of medication, patients were included in the study who mentioned the severity of the lesion pain as severe or very severe. After diagnosis of OLP based on clinical and histopathological criteria, about a quarter of patients did not report severe or

very severe pain and were not included in the study. Five patients rejected from doing the study after reading the entry agreement form. It should be noted that in this study, in addition to informed written signatures, patients were discussed in detail and oral strict promises were made from them to complete the study in any situation, and in three cases where patients came from other cities with accompanied, this promise was also made from them. So, we had no elimination patients after we started the study.

The primary intent for patients with OLP treatment is remission their diseases, secondary is, the lasting this phenomenon. Due to this issue in previous and present studies, we followed the patients for three months after cessation of the treatment [21]. While following up for applying tacrolimus 0.1% and intralesional triamcinolone acetonide injection were two weeks [22].

The reason for lasting remission is the prevention of chronicity that shows a crucial role in malignant transformation. Of course, the real cause of this process is unclear; however, chronicity is very important. our study failed to show any significant difference in study variables between the two groups. One of the possible reasons for this, may be that since stress plays an important role in this disease, and patients in both groups were monitored regularly during this period, therefore, could provide relief their stress that influenced the outcome of the study. This is why clinical trial studies are superior to case control studies. It can also be suggested that this herbal immunolatory drug is not effective on severe and very severe lesions.

In recent decade, various forms of imbalance between oxidants and antioxidants values in the blood and saliva of participants with OLP including, augmented oxidative stress status against inequity in the antioxidant protection system or an increase full antioxidant capacity of saliva in OLP compared with control group either meaningfully decreasing of serum total antioxidant defense in participants with OLP than healthy individuals, and that significantly increasing of saliva of Malondialdehyde (MAD), the product of lipid peroxidation in different studies, all demonstrate importance of oxidative stress status state in etiopathogenesis of OLP [23]. In some autoimmune diseases, TNF-a concentration correlated with exacerbation and regression of diseases and may be used for monitoring [6]. In this, randomized double-blind placebo-controlled clinical trials, with the changes in drug dose that was performed, in addition of TNF-α, total oxidant and antioxidant capacity (Stress oxidative status) and uric acid for further controlled study were also assessed. Two criteria that had not been assessed in previous studies and we applied in the present study were ‘’clinical and patient Global Impression of Change’’.

In previous and present applying of IMOD, no significant side-effects or adverse reactions were reported in patients while using systemically drugs for erosive/ulcerative OLP lesions followed with the threat of severe or untoward adverse reactions [24-26]. This study did not also display any significant difference in (MDA), (TAC), TNF-α, and (UA) levels between the two groups.

These results can be logical because when the clinical criteria do not change, the paraclinical criteria do not change as well. It may also be suggested that since IMOD is a modulator of the immune system, its effect on (MDA), (TAC), TNF-α, and (UA) is different from that of immunosuppressive drugs such as corticosteroids.

The limitation of this study was that a few of patients were interested to be in case group that was inconsistent with the RCT study. Time-consuming and long-term was the time to evaluate the clinical criteria of the study.

Table 2. Primary outcomes in IMOD and Placebo treated groups

| | Pain or burning severity | | | Clinical score | | | Clinical Global Impression of Change (CGIC) | | | Patient Global Impression of Change (PGIC) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | IMOD | Placebo | P value | IMOD | Placebo | P value | IMOD | Placebo | P value | IMOD | Placebo | P value |
| Base | 4 (1) | 4 (1) | 0.485 | 5(1) | 4.5 (1) | 0.141 | 203 (34) | 205 (36) | 0.588 | 184 (39) | 182 (34) | 0.566 |
| Week 2 | 4 (1) | 3 (1) | 0.120 | 3.5(1.75) | 4 (1) | 0.871 | 9 (2) | 9 (0.75) | 0.857 | 9 (3) | 8.5 (1.75) | 0.526 |
| Week 4 | 3 (1) | 3 (2) | 0.580 | 4 (2) | 3 (2) | 0.088 | 9 (1) | 9 (0.75) | 0.603 | 8 (3) | 8.5 (1.75) | 0.504 |
| Week 8 | 3 (2) | 2.5 (1) | 0.363 | 2.5 (1) | 2 (1) | 0.605 | 9 (1) | 8 (1) | 0.360 | 8 (3) | 8 (1.75) | 0.315 |
| Week 12 | 2 (1) | 3 (2) | 0.406 | 3 (2) | 2 (1.75) | 0.087 | 8 (2) | 8 (1) | 0.334 | 7 (3) | 8 (1) | 0.336 |
| Week 24 | 2 (1) | 2 (3) | 0.942 | 2 (3) | 2 (2) | 0.827 | 7 (4.5) | 7.5 (2) | 0.837 | 8 (4.5) | 6 (3) | 0.537 |
| AUC | 68(19) | 68.5(21) | 0.671 | 72 (37) | 62 (31) | 0.421 | 6 (3) | 5 (4.5) | 0.433 | 4 (3) | 3 (3) | 0.093 |

Data were expressed as Median (IQR= interquartile range) and statistically analyzed by Mann-Whitney test. AUC: Area under the curve

Table 3: Salivary Lipid Peroxidation (MDA), Total Antioxidant Capacity (TAC), TNF-α and Uric Acid in IMOD and Placebo treated groups

| | MDA (mmol/ml) | | | TAC (mmol/l Trolox) | | | TNF-α (ρg/ml) | | | Uric acid (mg/mL) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | IMOD | Placebo | P value | IMOD | Placebo | P value | IMOD | Placebo | P value | IMOD | Placebo | P value |
| Before Intervention | 2.74± 0.59 | 2.93± 0.55 | 0.813 | 8.79± 1.73 | 9.65± 1.68 | 0.723 | 20.56± 1.07 | 32.65± 8.69 | 0.706 | 4.10± 0.51 | 3.68± 0.65 | 0.615 |
| After 24 weeks Intervention | 1.74± 0.27 | 1.35± 0.41 | 0.413 | 10.29± 1.73 | 10.21± 1.63 | 0.975 | 19.15± 1.90 | 20.62 ± 3.36 | 0.175 | 3.87± 0.46 | 3.81± 0.47 | 0.922 |
| Changes | -1.00±0.57 | -1.70± 0.79 | 0.471 | 1.50± 2.30 | 0.56± 1.71 | 0.746 | -1.41±2.43 | -12.04 ± 5.86 | 0.106 | -0.22± 0.31 | 0.13± 0.33 | 0.440 |

Data were expressed as mean ± SEM and statistically analyzed by t-test

**Conclusion**: IMOD lacks proper efficacy in the management of severe or very severe OLP lesions.

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