BRIEF RESEARCH COMMUNICATION

Comparison of the Effectiveness and Safety of Hydroxychloroquine and Methotrexate in the Treatment of Moderate-to-severe Oral Lichen Planus: A Pilot Study

Suboda Gnanarathne[1], Sanjeewani Fonseka[2], Supun S Manathunga[3], Ruwan Jayasinghe[4], Samadara Siriwardane[5]

Received on: 30 October 2023; *Accepted on:* 08 December 2023; *Published on:* 31 January 2024

Abstract

Aim and the background: Lichen planus (LP) is an autoimmune chronic inflammatory disorder. Oral lichen planus (OLP) affects the mucous membranes of the mouth. Mainstay of treatment is steroids. The aim of this study was to compare the effectiveness and safety of hydroxychloroquine (HCQ) and methotrexate (MTX) with standard treatment (systemic steroids) in the treatment of moderate-to-severe OLP.

Materials and methods: The study was conducted as a pilot study of a randomized, open-label, parallel-group, comparison trial assessing the efficacy and safety of systemic steroids (arm A), hydroxychloroquine (arm B), and methotrexate (arm C) in the treatment of moderate-to-severe OLP. Outcome measures were Guy's oral disease severity scoring system (Guy's ODSS) and chronic oral mucosal diseases questionnaire (COMD).

Results: Thirty patients between the ages 18 and 60 years with moderate-to-severe OLP completed the study. The reduction of the pain, site, activity, and total score of Guy's ODSS were statistically significant in arm C whereas pain, activity and total score of Guy's ODSS were statistically significant in arm A.

Conclusion: This study showed MTX was equally effective as standard treatment (systemic steroid) in the treatment of moderate-to-severe OLP. Therefore, it can be used in place of steroids to minimize the adverse effects of long-term systemic steroids. To see the difference between three arms, larger sample size is needed.

Clinical significance: Methotrexate could be considered as an effective treatment for moderate-to-severe OLP without having adverse effects of long-term systemic steroids.

Keywords: Hydroxychloroquine, Methotrexate, Oral lichen planus, Randomized clinical trial.

Journal of Oral Health and Community Dentistry (2023): 10.5005/jp-journals-10062-0178

Introduction

Lichen planus (LP) is a chronic inflammatory mucocutaneous disease with recurrent exacerbations with characteristic clinical and histopathologic features.[1] Although the pathogenesis and etiology of LP are uncertain, it is postulated to be an autoimmune disease in which basal keratinocytes undergo apoptosis due to CD4+ and CD8+ T lymphocyte attack, potentially triggered by viral or bacterial antigens, metal ions, drugs or physical factors.[2] Hepatitis C virus (HCV) seropositivity and genetic factors also appear to play a role in susceptibility to LP.[3]

Lichen planus can involve the skin, nails, and mucous membranes. Clinical subtypes of LP are termed based on the site of involvement and the morphology of the lesions (oral, nail, linear, annular, atrophic, hypertrophic, inverse, eruptive, bullous, ulcerative, LP pigmentosus, lichen planopilaris, vulvovaginal, actinic, LP-lupus erythematosus overlap syndrome, and LP pemphigoides).[4]

The most common variant of mucosal lichen planus is oral lichen planus (OLP).[5] There are six clinical types of OLP, that is, reticular, atrophic, papular, bullous, plaque and erosive types. The main symptoms of OLP are oral burning, soreness or pain, spontaneous or during chewing or tooth brushing that leads to considerable limitation of essential daily activities in many patients. Reticular lesions are usually asymptomatic unless accompanied by atrophic or erosive lesions.[6] Erosive OLP is a premalignant disease.[7]

The buccal mucosa is typically involved in 80–90% of OLP cases.[4] The borders and dorsum of the tongue and the gingiva are also commonly affected, whereas the palate (either hard or soft), the lips, and the floor of the mouth are less commonly affected.[7]

Diagnosis of OLP is made based on the clinical presentation; however, confirmation is done by oral mucosal biopsy.[4] Direct immunofluorescence studies may be needed in erosive OLP to differentiate it from other diseases (e.g., mucous membrane pemphigoid).[8]

[1]Department of Pharmacology, University of Peradeniya, Peradeniya, Central Province, Sri Lanka
[2,3]Department of Pharmacology, University of Peradeniya, Kandy, Peradeniya, Sri Lanka
[4]Department of Oral Medicine and Periodontology, Faculty of Dental Sciences, University of Peradeniya, Kandy, Peradeniya, Sri Lanka
[5]Department of Oral Pathology, Faculty of Dental Sciences, Peradeniya, Sri Lanka
Corresponding Author: Sanjeewani Fonseka, Department of Pharmacology, University of Peradeniya, Kandy, Peradeniya, Sri Lanka, Phone: +94718074979, e-mail: sanjeewani.fonseka@yahoo.com

How to cite this article: Gnanarathne S, Fonseka S, Manathunga SS, *et al*. Comparison of the Effectiveness and Safety of Hydroxychloroquine and Methotrexate in the Treatment of Moderate-to-severe Oral Lichen Planus: A Pilot Study. J Oral Health Comm Dent 2023;17(3):116–120.
Source of support: University Research Grant (URG/2022/46/M).
Conflict of interest: None

Currently used treatments are aimed at alleviating the symptoms, healing the lesions, reducing the risk of malignant transformation and prolonging the symptom-free intervals. Maintaining good oral hygiene and avoidance of mucosal trauma leads to regression of some lesions, without pharmacological interventions.[9]

Among currently used pharmacological treatments, topical steroids are considered to be the first-line agents for non-dysplastic and non-malignant lesions.[10] In severe OLP, intralesional and submucosal steroid injections, as well as systemic steroids are indicated.[11,12]

If systemic steroids are contraindicated, not tolerated or needed for a long period of time, other immunosuppressant and immunomodulatory agents, such as azathioprine, methotrexate (MTX), mycophenolate mofetil, cyclosporine, and hydroxychloroquine (HCQ) are used.[9]

Nevertheless, there is no uniform approach toward the management of OLP except for the widely used topical corticosteroids. The therapy varies greatly between clinicians and medical institutions.[13] Long-term corticosteroid use in moderate-to-severe OLP leads to many adverse outcomes. Therefore, it is necessary to have steroid-sparing agents in the treatment of OLP.

Hydroxychloroquine is an immunomodulatory agent considered to be effective in the treatment of OLP possibly through the anti-inflammatory effects of stabilizing lysosomal membranes[14] and the inhibition of prostaglandin synthesis and other hydrolytic enzymes.[15]

Methotrexate is a folate analogue with anti-inflammatory and immunosuppressive effects.[16] There is some evidence suggesting that it is also a valuable therapeutic option in longstanding erosive OLP.[17]

Both HCQ and MTX are less expensive, readily available, and long-term adverse effects monitoring is more feasible compared with most of the other steroid-sparing agents in current clinical practice. However, there is a scarcity of studies for evaluation of the effectiveness of either drug in the treatment of OLP.

Considering the necessity of effective and readily available steroid-sparing agents for patients requiring long-term systemic therapy, we intend to evaluate the effectiveness and safety of HCQ and MTX in the treatment of moderate-to-severe OLP with or without skin involvement in this study.

Materials and Methods

Study Design

The study was conducted as a pilot study of a randomized, open-label, parallel-group, comparison trial assessing the efficacy and safety of HCQ and MTX in the treatment of moderate to severe OLP with or without skin involvement. Ethical approval was taken from the Institutional Ethics Review Committee (2021/EC/83) and the Clinical Trial registration number is APPL/2022/007. Written informed consent was obtained from all subjects and the study was conducted in accordance with the Declaration of Helsinki.

Participants

The participants were males and females aged 18–60 years with histologically confirmed moderate-to-severe OLP with or without skin involvement (a pain score of 6 or greater on a VAS of 0–10).

The following categories of patients were excluded from the study: patients who did not give consent, patients with psychiatric disorders, pregnant, or lactating women (to exclude pregnancy in premenopausal women, treatment was commenced after the next menstrual period or if still unsure, after a negative urine hCG test), patients with contraindications for HCQ or MTX, patients with poorly controlled diabetes, patients with retinal diseases, patients with other dermatological conditions in addition to OLP, patients who have received treatment for LP previously.

Patients were recruited from the Oral Medicine Clinic, University (Dental) Hospital Peradeniya, Sri Lanka. The study was conducted at the Oral Medicine Clinic, Faculty of Dental Sciences, University of Peradeniya.

Sample Size

The pilot study consisted of three study arms. A sample size of 10 was taken to each arm with a total sample size of 30.

Arm		*No. of patients*
A	Standard treatment	10
B	Hydroxychloroquine	10
C	Methotrexate	10

The trial was conducted for a total period of 12 weeks per patient including a recruitment visit and six fortnightly follow-up visits.

Randomization Procedure

Stratified randomization was used to ensure that the total sample size was equally distributed in the three treatment arms. All participants were given a trial number.

Interventions

At the oral medicine clinic, patients with a clinical suspicion of OLP routinely undergo the following investigations; full blood count, liver function tests, fasting blood sugar and oral mucosal incisional biopsy.

After assessing the baseline investigation reports and the biopsy report, patients were selected for the study based on the eligibility criteria.

Informed written consent was obtained by an investigator who was not directly involved in routine patient care. Then patients were allocated to three study arms (arms A, B, and C).

The three arms consisted of:

Arm A: Systemic steroid therapy (oral prednisolone 1 mg per kg bodyweight daily: Rednisol tablets USP 5 mg manufactured by UNICURE REMEDIED PRIVATE LIMITED, India, marketed by EMAR PHARMA (PVT) LTD, Sri Lanka) at the beginning of the study. The dose was tapered when the patient was responding, and the time of dose adjustments was documented.

Arm B: HCQ (Hydroxychloroquine Sulfate USP 200 mg, State Pharmaceuticals Manufacturing Corporation (SPMC), and Sri Lanka.) was given at a dose of 200 mg daily at night for a period of 12 weeks. Also, oral prednisone 0.25 mg per kg bodyweight in a tailing off dose was given for the first 2 weeks to bridge the time for the activating of HCQ.

Arm C: MTX (Methotrexate tablets BP 2.5 mg (INTERMETO) manufactured by INTERMED, India, Distributed By State Pharmaceuticals Manufacturing Corporation (SPMC), Sri Lanka) was commenced at a dose of 5 mg once a week (Sunday). Guided by the

clinical assessment of disease improvement and investigations for side effects (mentioned later), the MTX dose was increased by 2.5 mg every 2 weeks (if needed) depending on the clinical response and the adverse events, up to a maximum weekly dose of 10 mg, which was continued for the rest of the study period.

Folic acid (Folic acid tablets BP 1 mg manufactured by CIPLA LTD., Distributed By State Pharmaceuticals Manufacturing Corporation (SPMC), Sri Lanka) supplementation was continued for the duration of MTX therapy at a dose of 1 mg once a week (Wednesday).

In addition to those treatments, oral prednisone 0.25 mg per kg bodyweight in a tailing off dose was given for the first 2 weeks to bridge the time for the activating of MTX.

All three arms received chlorhexidine mouthwash (Chlorhexidine gluconate solution 4% w/v manufactured by UNILAB CHEMICALS and Pharmaceuticals Pvt. Ltd, India, distributed by, State Pharmaceuticals Manufacturing Corporation (SPMC), Sri Lanka) twice a day. After 2 weeks, the mouthwash was discontinued as it may irritate the buccal mucus with long-term use.

To make patients otherwise uniform, all patients were given a leaflet containing beneficial lifestyle modifications and advised to adhere to those measures. Patients were given a leaflet with the adverse effects of prednisolone, HCQ or MTX, according to the drug, the patient was receiving. The trial pharmacist was in charge of handing over the drugs and advising patients.

All patients were given the contact details of the Department of Pharmacology, Faculty of Medicine, University of Peradeniya and Oral Medicine Clinic, University (Dental) Hospital Peradeniya. If a patient has been admitted to a hospital for medical care/in need of taking some other drugs, the relevant medical officer was kindly asked to contact the department. The nature of the study was explained to the patient. All concurrent drugs that the patient is on were continued.

Outcome Measures

The baseline assessment of participants consisted of sociodemographic details, past medical and dental history, lifestyles related to LP and results of routine investigations which are routinely carried out in the clinic (full blood count, serum glutamic oxaloacetic transaminase (SGOT)/serum glutamic pyruvic transaminase (SGPT), serum creatinine, and fasting blood glucose) and documentation of all skin and oral lesions. The oral lesions were documented and numbered on a diagram. A minimum of six photographs were taken from the oral cavity to cover the six areas; left buccal mucosa, right buccal mucosa, palate, dorsal surface of the tongue, ventral surface of the tongue, and the floor of the mouth.

All patients were reviewed every fortnight for a total duration of 12 weeks. At each visit (including the baseline), the assessment of participants consisted of:

- Documentation of all skin and oral lesions. The oral lesions were documented and numbered on a diagram. A minimum of six photographs were taken from the oral cavity to cover the six areas; left buccal mucosa, right buccal mucosa, palate, dorsal surface of the tongue, ventral surface of the tongue, and the floor of the mouth.
- The Guy's Oral Disease Severity Scoring system (Guy's ODSS) which was initially proposed by Escudier et al.
- Chronic Oral Mucosal Diseases Questionnaire (COMD) to assess patients' quality of life.
- Investigations: Full blood count, SGOT/SGPT, serum creatinine, and fasting blood glucose to assess the adverse effects of medications.

Patients comorbid with well-controlled diabetes, if recruited for the study were initially assessed and followed up during the study period by a consultant physician. Bacterial or fungal infections, if developed, were treated accordingly.

All adverse events encountered by the patient during the duration of the trial were documented.

Statistical Methods

Linear regression models with interactions were used to assess whether the reduction of the site score, activity score, pain score, and total score in Guy's ODSS as well as the reduction of raw score in COMD are associated with the treatment arm.

The significance of the association between the reduction of site score, activity score, pain score, total score, raw score, and the treatment arm was assessed using the beta coefficients of the interaction terms.

$$score = \beta_0 + \beta_1 \cdot arm_2 + \beta_2 \cdot arm_3 + \beta_3 \cdot visit\ no \cdot arm_1 + \beta_4 \cdot visit\ no \cdot arm_2 + \beta_5 \cdot visit\ no \cdot arm_3$$

where β_0 is the intercept of the model, β_1 and β_2 are the coefficients associated with the treatment arm and β_3 to β_5 are the coefficients of interaction terms associated with the treatment arm and the visit.

Differences between the coefficients were assessed using linear hypothesis testing with F statistic.

A *p*-value less than 0.05 was considered statistically significant.

Results

Fifty-five patients were recruited and thirty patients between ages 18 and 60 years with moderate-to-severe OLP completed the study. The recruitment and follow-up of the patient is shown in Figure 1.

Table 1 shows the baseline demographic and patient's habits about the use of tobacco and betel chewing.

The initial mean values and mean score reduction per visit of pain, site, activity, and total scores of Guy's ODSS are given in Table 2. The reduction of the pain, site, activity and total score of Guy's ODSS were statistically significant in arm C whereas pain, activity and total score of Guy's ODSS were statistically significant in arm A. There was no significant reduction in any of the scores of Guy's ODSS in arm B.

The initial values and the reduction of score per visit in each treatment arm in raw score of COMD are given in Table 3. None of the arms showed a statistically significant reduction in COMT scores.

Regarding adverse events, two patients who were on standard treatment were noted to develop hyperglycemia, however, none has stopped the treatment due to adverse effects of the treatments.

Discussion and Conclusion

This is a pilot study of a randomized, open-label, parallel-group, comparison trial assessing the efficacy and safety of HCQ and MTX in the treatment of moderate-to-severe OLP. There are no proper guidelines for the treatment of lichen planus. Steroids in the form of topical and systemic are the mainstay of treatment but due to high risk of adverse events, need for steroid-sparing agents raises. In this study, it was shown that MTX can be used safely and effectively in place of larger dose of systemic steroids. On the other hand, HCQ also showed a good response clinically, but it was not statistically significant most probably due to small sample size.

In this pilot study, there was a large dropout rate due to transportation and financial concerns of patients. The majority

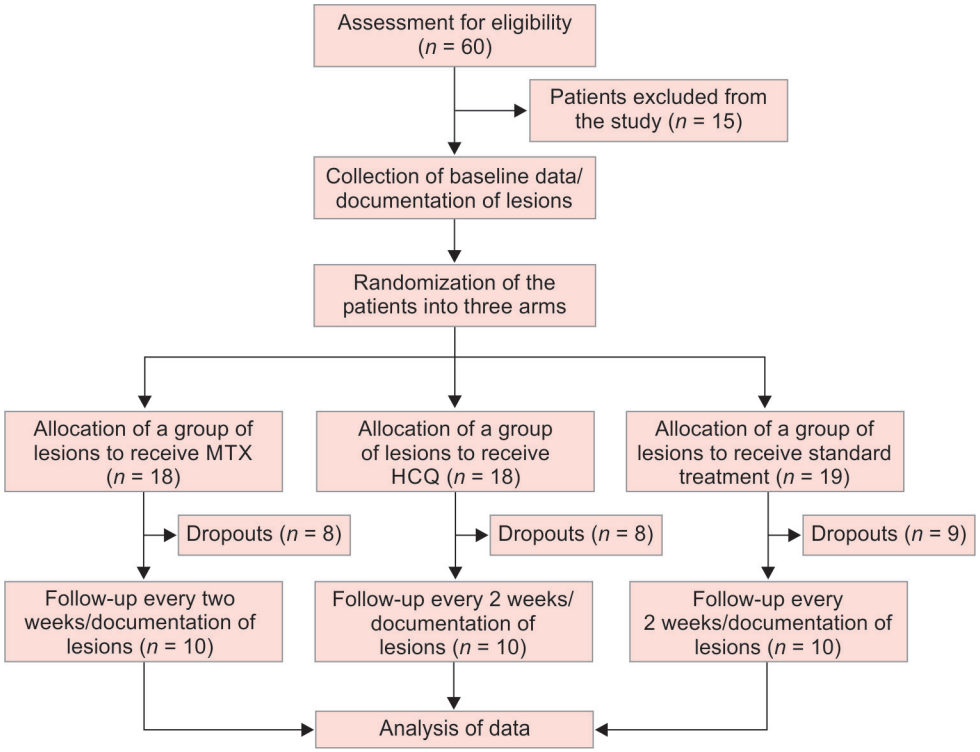

Fig. 1: Recruitment and follow-up of the patients (*n* = number of patients)

Table 1: Baseline demographic and social data

	Treatment arms		
	A (standard treatment)	*B (HCQ)*	*C (MTX)*
Age range	18–60 y	20–56 y	18–58 y
Gender			
Male	7 (70%)	6 (60%)	6 (60%)
Female	3 (30%)	4 (40%)	4 (40%)
Tobacco use			
Cigarette	2 (20%)	3 (30%)	3 (30%)
Cigar	0	0	0
Bidi	0	0	0
Betel chewing	2 (20%)	1 (10%)	3 (30%)

HCQ, hydroxychloroquine; MTX, methotrexate

Table 2: Data of outcome measures of the pain score, site score, activity score and total score the of the Guy's ODSS

	Pain score		*Site score*		*Activity score*		*Total score*	
Arm	*Initial mean value*	*Mean reduction per visit*	*Initial mean value*	*Mean reduction per visit*	*Initial mean value*	*Mean reduction per visit*	*Initial mean value*	*Mean reduction per visit*
A (standard treatment)	7.21	0.34*	2.89	0.14	4.14	0.31*	14.25	0.80*
B (HCQ)	7.52	0.65	3.75	0.29	4.99	0.48	16.28	1.44
C (MTX)	6.50	0.88*	4.02	0.57*	4.82	0.71*	15.35	2.18*

HCQ, hydroxychloroquine; MTX, methotrexate; Significant *p*-values < 0.05*

of patients were unwilling to be followed up with every 2 weeks appointments. Additionally, we observed that some patients skipped follow-up appointments after observing some improvement in their illness. Consequently, there was a dropout rate of roughly 50%. The patients would have been more compliant with the trial if the follow-up visits had been scheduled at intervals of 1 month.

Table 3: Data of raw scores of the COMD

	Raw score	
Arm	*Initial mean value*	*Mean reduction per visit*
A (standard treatment)	43.72	0.36
B (HCQ)	39.30	2.36
C (MTX)	38.73	3.67

HCQ, hydroxychloroquine; MTX, methotrexate; Significant *p*-values < 0.05*

Another drawback of the study is not being able to have an equal prednisolone dose to all the patients, as tolerance to prednisolone differs from patient to patient. Therefore, we have to adjust the dose according to the requirements of patients.

None of the patients who were on MTX or HCQ arms developed any adverse events. However, patients with impaired glucose tolerance had a tendency to develop diabetes mellitus with oral prednisolone.

It would be preferable if we could conduct the study as a single- or double-blind study to minimize the biases in the evaluation of outcomes. However, this is challenging because HCQ is administered daily whereas MTX is prescribed on a weekly basis. To comply with the blinding techniques, we therefore need to develop three placebo drugs.

This study sheds light into the immunomodulatory drugs in the treatment of moderate-to-severe OLP. This study would be further expanded to give more evidence on the topic.

Clinical Significance

Methotrexate could be considered as an effective treatment for moderate-to-severe OLP without having adverse effects of long-term systemic steroids.

Manufacturer Name

REDNISOL tablets USP 5 mg is manufactured by UNICURE REMEDIED PRIVATE LIMITED, India, marketed by EMAR PHARMA (PVT) LTD, Sri Lanka.

Hydroxychloroquine sulfate USP 200 mg is manufactured by State Pharmaceuticals Manufacturing Corporation (SPMC), Sri Lanka.

Methotrexate tablets BP 2.5 mg (INTERMETO) is manufactured by INTERMED, India, distributed by State Pharmaceuticals Manufacturing Corporation (SPMC), Sri Lanka.

Folic acid tablets BP 1 mg is manufactured by CIPLA LTD., distributed by, State Pharmaceuticals Manufacturing Corporation (SPMC), Sri Lanka.

Chlorhexidine gluconate solution 4% w/v is manufactured by UNILAB CHEMICALS and PHARMACEUTICALS PVT LTD, India, distributed by, State Pharmaceuticals Manufacturing Corporation (SPMC), Sri Lanka.

Ethical Approval

Ethics Review Committee, Faculty of Medicine, University of Peradeniya (2021/EC/83).

WHO trial registry number (Universal trial number): APPL/2022/007.

Orcid

Suboda Gnanarathne https://orcid.org/0009-0009-6463-3791
Sanjeewani Fonseka https://orcid.org/0000-0003-0262-4776
Ruwan Jayasinghe https://orcid.org/0000-0002-8054-4301

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