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Original Article

Comparison of efficacy of oral methotrexate and acitretin for generalized lichen planus

Ghafoor Ullah, Muhammad Ziaulhaq, Farhad Ali

Department of Dermatology, Hayat Abad Medical Complex Peshawar, Gaju Khan Medical College Swabi.

Abstract

Objective To compare the efficacy of oral methotrexate and acitretin in the treatment of generalized lichen planus.

Methods The study comprised 36 participants of both sexes who were between the ages of puberty and maturity. It was determined that the efficacy of oral methotrexate 15 mg/week was defined by 50% elimination of mucocutaneous lesions after 12 weeks of treatment. There were four weeks of data collection for nausea and weakness, as well as for haemoglobin (Hb), white blood cell count (WBC), and serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and a safety assessment.

Results The mean age of the patients in Group 1 is 54years and 52.5years in Group 2, while the mean weight in Group 1 is 71.9 kg and 72.2 kg in Group 2. Methotrexate was shown to be effective with marked improvement in 33.3% and slight improvement in 38.9% of patient. While acitretin showed marked improvement in 33.3% and slight improvement in 33.3% of patients. Patients with mucosal involvement in group 1 were (N=6) and (N=7) in group 2. The overall side effects reported with acitretin group were slightly higher than methotrexate group.

Conclusion In our study, methotrexate and acitretin was proven to be both beneficial and safe for the vast majority of participants.

Key words
Acitretin, methotrexate, lichen planus.

Introduction

Lichen planus is violaceous, polygonal, pruritic, flat-topped, papules and plaques. Lichen planus (LP) is a chronic mucocutaneous condition caused by an unknown cause that is most commonly observed on the lower back, body folds, oral mucosa, and on the scalp.[1] It is recurrent and is treated with post-inflammatory hyperpigmentation.[2] LP can be classified into subtypes based on the morphology and distribution of the lesions.[3] It is estimated that it affects 0.5-2% of the general population, with no racial differences in the prevalence of the disease. It is more common among adults in their middle ages, and in some cultures, females outnumber males by a factor of 2:1.[2,4]

Even though it has been linked to human leukocyte antigen (HLA) DR1, hepatitis B and C, as well as cytokine profiles, it is unknown what causes liver disease. Hereditary, viral, or autoimmune factors have all been suggested. T lymphocytes activation is thought to be the cause of the ailment, which is classified as an autoimmune illness.[2] It's a long-term condition. Oral LP cases that have been present for a long

Address for correspondence
Dr. Ghafoor Ullah, Assistant Professor
Dermatology Unit, Hayatabad Medical Complex
Peshawar, Pakistan.
Ph: 03339189230
Email: dr_ghafoorullah@yahoo.com

period of time are related with squamous cell carcinoma.[5]

Dermatologists are faced with a difficult LP treatment dilemma that requires their expertise.[8] Corticosteroids, tacrolimus, retinoid, cyclosporine, photo chemotherapy, azathioprine, cyclophosphamide, mycophenolate mofetil, hydroxychloroquine, thalidomide, dapsone, and gold are some of the current topical and systemic LP medications.[7,8] These therapeutic approaches are effective, but their significant toxicity prevents them from being used for an extended period of time. New medications are always being developed in order to provide appropriate disease control while also having fewer side effects and being more cost-effective.

Methotrexate (MTX) inhibits dihydrofolate reductase. It has anti-inflammatory and immunomodulatory properties, and it is used in the treatment of cancer (an enzyme involved in denovo pyrimidine production).[9] It has been shown to be effective in the treatment of lichen planus in multiple studies because it lowers the number of activated T cells and lessens the skin's immunological mediated reaction.[10,11] MTX is inexpensive, widely available, and typically safe. In the treatment of cutaneous lichen planus, Etretinate metabolite acitretin is the most abundant and is metabolised to a substantial extent. The drug is deemed essentially as effective as etretinate, since it is eliminated from the body significantly more quickly and has a therapeutic effect that is similar to that of etretinate.[4,6]

Methods

During the March 2019 to September 2020, a randomized controlled trial was conducted in the department of Dermatology Hayat Medical Complex Peshawar. Approved by the Institutional Ethical Committee. LP was diagnosed clinically in 36 people of either gender, aged 15 or above, with histological confirmation in doubtful cases and less than three months of disease duration, who were included in the study. All of these patients had haemoglobin levels more than 10g/dl, white blood cell counts greater than 4000/mm^3, platelet counts greater than 150,000/mm^3, ALT levels less than 35IU/L, with the exception of those who were pregnant, had a history of diabetes, kidney failure, chronic liver disease, had a positive HBSAg/HCV infection, and had received a topical treatment within the previous two weeks.

Following the clinical evaluation, patients were divided into below three groups based on the location of their involvement,

- Skin and mucosal lesions are present in Group A patients.
- Patients in Group B are individuals who have only mucosal involvement and no other symptoms.
- Individuals with skin lesions are classified as Group C patients (more than 10 lesions).

Baseline tests such as haemoglobin, white blood cell count, platelet count, as well as ALT levels, were performed on the patient. At the start of the study, 18 patients received 5 mg of methotrexate and 18 additional patients received 10 mg of acitretin, followed by a repeat tests a week later to determine the effectiveness of the treatment. Patients with normal blood cell counts received 15mg of methotrexate weekly and 50mg of acitretin daily for four weeks. The treatment was continued until the damage was completely healed or for a maximum of 12 weeks, whichever occurred first, and then it was discontinued completely. Folic acid was administered to all patients at a dose of five milligram per day. Each patient was observed

Table 1

Characteristics	*Methotrexate (N=18)*	*Acitretin (N=18)*	*p-value*
Age (mean)	54 ± 13.8	52.5 ± 14.3 SD	0.8850
Gender (M/F)	12/6	10/8	0.7332
Weight in kg (mean)	71.9 ± 13.9 SD	72.2 ± 14.8 SD	0.7989
Duration of LP (months) (mean)	5.6 ± 3.02 SD	6.2 ± 3.5 SD	0.5497
Mucous Membrane Involvement	6 (33.3%)	7 (38.9%)	0.5000

for a total of three months after being admitted to the hospital.

It was determined whether the medication was effective by a decrease in the number of mucocutaneous lesions noticed during the second, fourth, eighth, and twelfth weeks of treatment. After 12 weeks of treatment, it was determined that the medicine was effective when skin lesions were cleared at a rate more than 50% at the maximal dose. After one week, and then at the 2nd, 4th, 8th, and 12th weeks of the study, haemoglobin, white blood cell count, platelet count, as well as ALT levels, were taken. All of the information was gathered through the use of a proforma that was created expressly for this purpose.

SPSS was employed (version 25). Standard deviations were used to represent quantitative data (age), whereas frequencies and levels were used to show qualitative outcomes (gender, efficiency, and safety). The information was divided into three categories based on the location of the lesions (mucosa, skin, both skin and mucosa).

Results

Out of 36 patients of lichen planus, the demographics characteristics of all the participants of the study are recorded and shown in **Table 1**.

The efficacy of both the drugs, namely, methotrexate and acitretin are analysed and evaluated. Chi square tests are performed to demonstrate the association between the two drugs. The resulted p value is less than 0.05; hence the test is significant statistically **Table 2**.

Table 2

Efficacy Assessment	*Methotrexate (N=18)*	*Acitretin (N=18)*	*P value*
Remission	2 (11.1%)	2(11.1%)	0.5000
Marked Improvement	6(33.3%)	6(33.3%)	0.5000
Slight Improvement	7(38.9%)	6(33.3%)	0.5000
No Change	2 (11.1%)	2(11.1%)	0.6987
Worsening	1 (5.6%)	2(11.1%)	0.5000

Table 3

Side Effects	*Methotrexate (N=18)*	*Acitretin (N=18)*	*p-value*
Dry lips (cheilitis)	3	4	0.5000
Dry mouth	6	8	0.3666
Dry nose	2	3	0.5000
Dry eyes (conjunctivitis)	2	2	0.6987
Dry skin	5	4	0.5000
Scaling (palms/soles)	2	5	0.2009
Hair loss	4	6	0.3556
Fragile nails	6	6	0.6377

The reported side effects of both methotrexate and acitretin are recorded and shown in **Table 3**.

Discussion

This trial was conducted to evaluate the efficacy of MTX with acitretin in the treatment of Lichen planus. The oral MTX effective as a monotherapy for Lichen planus Turan *et al*.[11] A small number of lichen planus patients have been treated with topical clobetasol dipropionate and tacrolimus ointments after being exposed to MTX.[10]

According to our findings, men are more likely than women to suffer from lichen planus, which

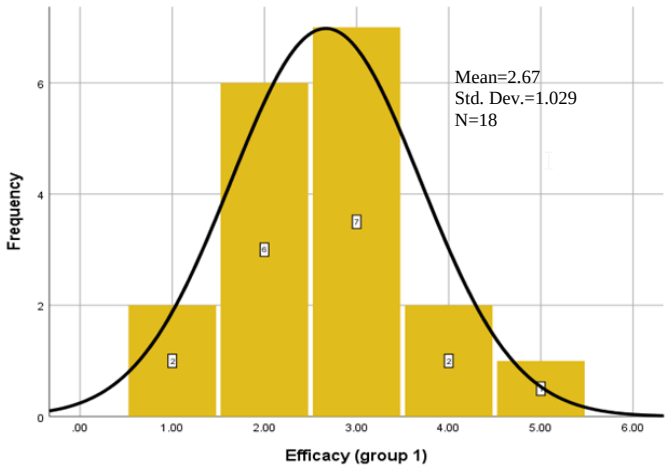

Figure 1

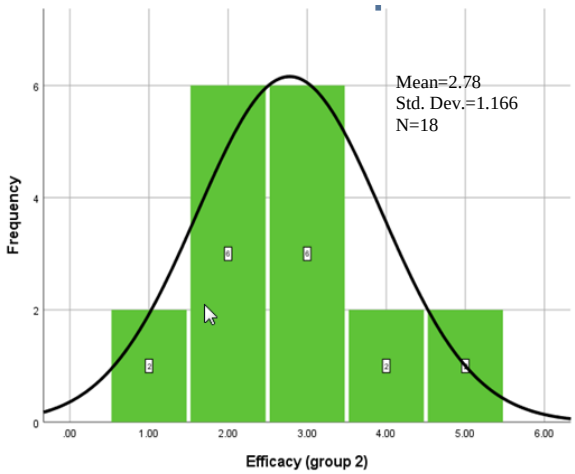

Figure 2

In **Figure 1**, The histogram showed the efficacy level of methotrexate higher as compared to acitretin histogram **(Figure 2)**.

is a genetic condition. The females accounted for the vast majority of lichen planus cases Turan *et al*.[11] It was discovered in this study that those in the 40-60 year age range had the highest incidence of disease which is consistent with earlier studies. According to Abdallat *et al*.,[2] the majority of lichen planus patients were between the ages of 34 and 59 when they were diagnosed. According to the findings lichen planus was found to be more prevalent among people between the ages of 30 and 50 years.[4]

The 65% of patients with cutaneous LP also had oral mucosal ulcers Anber *et al*.[12] lichen planus mucosa was found in 13 out of the 20 patients who participated in our investigation, which is identical to the previous findings. Oliveira *et al*.[13] conducted a retrospective study of 110 LP patients and discovered that 32 and 72% of them had isolated lichen planus. In our study, we noticed that 7.3% of our patients had isolated oral mucosal lichen planus, despite the fact that Brazilian oral LP data indicates that isolated oral mucosal LP occurs in 15-35% of all lichen planus cases.[13] Possibly as a result of the smaller number of participants in this study (36 as opposed to 110 in the Brazilian study), the results are more unpredictable than they otherwise would be as previously mentioned, geographical contrasts between Pakistan and Brazil could be another probable explanation for the disparity in percentages between the two countries. The findings of an Egyptian study, which revealed that 8% of patients had oral mucosal involvement, also contribute to the notion of regional variation in cancer treatment.[12] Our findings are similar to those of an Egyptian study, which can be explained by the fact that environmental elements are distributed in the same geographic regions in both nations. It also lends support to the notion that the prevalence of oral lichen planus varies from one region of the world to another, as demonstrated by this study.

In our investigation, 13 patients in group 1 and 12 cases in group 2 had a reduction in the number of LP lesions of up to 100%, while in Turan *et al*. study's the reduction was 91%.

Thirteen pilot trials demonstrated a reduction in the number of lesions of LP of more than 90%. Overall, 36.4% of patients in our experiment were judged ineffective after receiving the medicine, whereas only 9% of patients in Turan and colleagues' studies were declared ineffective after receiving the treatment.

This gap can be explained by the fact that only patients with generalised LP were included in the Turan *et al*.[11] study, and generalized lichen planus is a type of LP that responds well to medications, which explains the difference. We recruited patients with a variety of different types of LP for our comparison study. A number of LP types, such as LP pigmentosus, LP hypertrophicus, and other follicular LP, have been found to be highly resistant to therapy, according to study. Apart from that, whereas the dosages used by Turan and colleagues[11] ranged from 15 mg to 20 mg/week, depending on the severity of the disease, we used a standard 15 mg/week dose, regardless of the severity or type of the disease, which may account for our study's higher medication inefficiency rate.

Patients with isolated cutaneous involvement in the current study demonstrated their success in up to 60% of cases in each group, however, Turan *et al*.[11] revealed their effectiveness in 82% of cases in the preceding study, which included patients with isolated cutaneous involvement. One explanation for the huge disparity in the percentages of patients with isolated skin involvement could be due to the fact that a bigger number of patients with isolated skin involvement had been enrolled in their investigation. We found that LP was beneficial in treating patients who had both mucosal and cutaneous complaints, according to our research. Overall response rates of more than 90% were reported in the Turkish experiment, with one patient (9%) reporting dual involvement rates of more than 90%. This finding of efficacy is consistent with the findings of our research on the subject. While the percentage of dual involvement patients who achieved efficacy varies statistically significantly between the two studies, this variation is primarily due to the vastly different sample sizes between the two studies. In the Turkish investigation, there was no distinction made between cutaneous and mucosal lesions, and there was no evidence that such a distinction had been made. Another large-scale investigation found no difference in the interaction between cutaneous and oral LP with methotrexate and acitretin in either the short or long term.

Conclusion

According to the findings of our study, methotrexate and acitretin were both useful and safe for the vast majority of those who took part.

References

1. Pittelkow MR, Daoud MS. lichen planus. In: Wolff K, Goldsmith LA, Katz SI, editors. *Fitzpatrick's Dermatology in General Medicine, 7th ed.* McGraw-Hill, New York; 2008: 244-48.
2. Abdallat SA, Maaita TJ. Epidemiological and clinical features of lichen planus in Jordanian patients. *Pak J Med Sci*. 2007;**23**:92-4.
3. Perry D, Fazel N. Zosteriform lichen planus. *Dermatol Online J*. 2006;**12**:3.
4. Khondker L, Wahab MA, Khan SI. Profile of lichen planus in Bangladesh. *Mymensingh Med J*. 2010;**19**:250-3.
5. Crincoli V, Di Bisceglie MB, Scivetti M,Lucchese A, Tecco S, Festa F. Oral lichen planus: update on etiopathogenesis, diagnosis and treatment. Immunopharmacol *Immunotoxicol*. 2011;**33**:11-20.
6. Bermejo-Fenoll A, Sanchez-Siles M, López-Jornet P,Camacho-Alonso F, Salazar-Sanchez N. Premalignant nature of oral lichen planus. A retrospective study of 550 oral lichen planus patients from SouthEastern Spain. *Oral Oncol*. 2009;**45**:e54-6.
7. Sharma S, Saimbi CS, Koirala B. Erosive oral lichen planus and its management: a case series. *J Nepal Med Assoc*. 2008;**47**:86-90.
8. Kalmar JR. Diagnosis and management of oral lichen planus. *J Calif Dent Assoc*. 2007;**35**:405-11.
9. Bangert CA, Costner MI. Methotrexate in dermatology. *Dermatol Ther*. 2007;**20**:216-28.

10. Jang N, Fischer G. Case Series. Treatment of erosive vulvovaginal lichen planus with methotrexate. *Australas J Dermatol*. 2008;**49**:216-9.
11. Turan H, Baskan EB, Tunali S, Yazici S, Saricaoglu H. Methotrexate for the treatment of generalized lichen planus. *J Am Acad Dermatol*. 2009;**60**:164-6.
12. Anbar TE, Barakat M, Ghannam SF. A clinical and epidemiological study of lichen planus among Egyptians of al-Minya province. *Dermatol Online J*. 2005;**11**:4.
13. Oliveira Alves MG1, Almeida JD, Balducci I, Guimarães Cabral LA. Oral lichen planus: A retrospective study of 110 Brazilian patients. *BMC Res Notes*. 2010;**3**:157.