BRIEF REPORT

Durability of Conventional Immunosuppressants in the Treatment of Oral Lichen Planus

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J Clin Aesthet Dermatol. 2025;18(12):45–49.

BACKGROUND: Oral lichen planus (OLP) is an inflammatory disease involving the oral mucosa. It affects roughly 0.5% to 2% of the global population and has an associated risk of oral squamous cell carcinoma. Treatment of moderate to severe OLP often requires immunosuppression. The durability of immunosuppressive medication is currently unknown and is important for understanding therapeutic testing needs. **OBJECTIVE:** We investigated traditional immunosuppressive drug survival in patients with OLP and evaluated potential discontinuation factors. **METHODS:** We retrospectively analyzed patients with OLP treated with methotrexate, mycophenolate, azathioprine, or cyclosporine. Time to medication discontinuation was evaluated using the Kaplan-Meier estimator, and Cox proportional hazards regression was used to compare the risk of discontinuing a medication between medications and across patient demographic and disease factors. **RESULTS:** We identified 125 treatment periods with mycophenolate (n=58), methotrexate (n=34), azathioprine (n=19), or cyclosporine (n=14). Most patients had erosive disease (92%), and median time (IQR) to discontinuation due to adverse events or inefficacy was 9.43 months (6.51-16.1). Overall, only cyclosporine was associated with higher risk of discontinuation compared to methotrexate (hazard ratio [HR]: 2.94; 95% confidence interval [CI]: 1.32-6.45). There was no evidence for risk differences across age or sex for the overall cohort. Within individual medication groups, age was associated with a small increased risk of discontinuing mycophenolate (HR: 1.05; 95% CI: 1.00-1.10) and a small decreased risk in cyclosporine (HR=0.94, 95% CI: 0.89-0.99). Otherwise, no demographic factors were associated with discontinuation. Treatment success was reported 8 times. **DISCUSSION:** Immunosuppressive medications were frequently discontinued after short time periods, and few were discontinued due to success. These data highlight the need for better systemic therapy in OLP. **KEYWORDS:** Autoimmune, lichen planus, oral lichen planus, immunosuppression, epidemiology, dermatology

Oral lichen planus (OLP) is a mucocutaneous inflammatory disease thought to be driven by a T-cell immune response, potentially to unknown antigens.[1] Approximately 0.5% to 2% of the global population is affected, and there has been an associated increased risk of oral squamous cell carcinoma, particularly among more severe inflammatory or ulcerative subgroups.[2,3] OLP is highly morbid, with one qualitative study noting that 69% of patients experienced significant impact on their activities of daily living.[4] Although first-line treatment involves the use of topical corticosteroids, the evidence for its efficacy is somewhat inconclusive, and our clinical experience suggests that many patients with moderate-to-severe OLP require additional systemic therapy. A Cochrane systematic review found no significant difference in clinical resolution between topical corticosteroids and placebo, though pain was more likely to be resolved using topical corticosteroids.[5] If topical therapies prove insufficient, severe disease may require treatment with immunosuppressive medications such as mycophenolate, methotrexate, azathioprine, and cyclosporine.[6] Currently, immunosuppressive medication durability in OLP is unknown. Medication durability can provide insight into tolerability and efficacy.[7] We also assessed for factors associated with discontinuation of treatment in the overall group and medication subgroups.

METHODS

We included patients seen at the University of Utah from January 1, 2010 to April 1, 2024 with a dermatologist-verified OLP diagnosis treated with methotrexate (MTX), mycophenolate mofetil (MMF), azathioprine (AZA), or cyclosporine (CsA). OLP diagnosis required OLP diagnosis over at least two visits and clinically congruent appearance. While we did not require histologic confirmation, most cases had confirmatory histology (68 of 91 [74.7%]). We excluded patients with concomitant systemic treatments (besides hydroxychloroquine/short-term oral corticosteroid), undocumented reason for treatment discontinuation, or multiple trials

FUNDING: No funding was provided for this article.
DISCLOSURES: Dr. Hopkins is supported by a career development award from the Dermatology Foundation and has received consultation fees from Priovant Therapeutics. The remaining authors have no conflicts of interest relevant to the contents of this article.
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of the same immunosuppressant (only the first trial was included). In patients who used multiple unique immunosuppressants at nonoverlapping time points (eg, MTX that was transitioned to MMF due to lack of efficacy), each trial was considered individually. Descriptive statistics included medians/interquartile ranges (IQR) and counts or percentages. Group comparisons were made using Kruskal-Wallis (continuous variables) and chi-square test (categorical variables). Time to medication discontinuation was evaluated using Kaplan-Meier estimator, and Cox proportional hazards regression was used to compare the risk of discontinuing a medication between medications and across different demographic factors.[8,9] Our primary outcome was hazard of medication discontinuation due to adverse event or medication failure. Secondary analyses included an age- and sex-adjusted model for the primary outcome, individual evaluations of failure due to adverse events, medication failure, and medication success (ie, patient remission). Analyses were performed across medication groups and the overall cohort, as well as by individual medications. All analyses were performed in Stata v17.1, StataCorp, and $p<0.05$ was considered significant.

RESULTS

We identified 125 OLP treatment periods, which included treatment with MMF (n=58), MTX (n=34), AZA (n=19), and CsA (n=14), by 91 patients. Of these patients, 68 (74.7%) had confirmatory biopsies. The remaining patients had clinically consistent disease noted by a dermatologist with extensive OLP experience. Reasons for lack of confirmatory biopsy included: diagnoses that occurred prior to our current record availability, skin biopsies confirming lichen planus and OLP was assumed to be related, and nonconfirmatory biopsies but the clinician felt the oral disease was clinically consistent. Sixty-five patients had only one treatment period, 18 had two, and 8 had three treatment periods. MMF and MTX were used most during the first treatment period and overall, but AZA was most used during the second period (Supplemental Table 1). Overall, median (IQR) patient age was 63.1 years (55.4-71.6), 78.4% were female, and 85.6% were White (Table 1). Most had erosive disease (92.0%). Adjunctive therapy use (ie, hydroxychloroquine or oral corticosteroid) was similar between treatment cohorts. Treatment was discontinued in 113 treatment periods. Reasons for discontinuation included: adverse events or treatment failure (n=79), treatment success (n=8), lack of efficacy (n=27), and adverse events (n=52). Median (IQR) time to discontinuation overall was 9.43 months (6.51-16.1). Median time to discontinuation was highest for the first trialed immunosuppressant (10.1 months; 6.67-16.8), and decreased for the second (6.51 months; 3.45-47.2) and third (5.06 months; 0.89-N/A). Only CsA was associated with an increased risk for discontinuation compared to methotrexate (hazard ratio [HR]: 2.66; 95% CI: 1.25-5.65), including after adjusting for age and sex (HR: 2.94; 95% CI: 1.36-6.32) (Table 2, Figure 1). Across all medications and within each individual medication, we found no evidence for factors influencing hazard of discontinuation, save a small age effect in MMF and an imprecise, but large, impact on smoking for CsA (Table 2). We also evaluated if having failed one immunosuppressant increases the odds of failing the subsequent medication, but we did not find evidence for this (Table 2). Patients were concomitantly on hydroxychloroquine in 51 of 125 (40.8%) treatment periods. We found no evidence for decreased risk of discontinuation with hydroxychloroquine use (HR: 0.76; 95% CI: 0.48-1.19) nor an increased risk of treatment success (HR: 1.63; 95% CI: 0.36-7.41).

When analyses were stratified by individual medications, treatment discontinuation due to treatment failure occurred more often in men (HR: 1.91; 95% CI: 1.05-3.45) but otherwise estimates were similar. Corticosteroid rescue was identified 19 times. We identified no differences in steroid rescues across medications nor by patient and disease demographics. Discontinuation due to treatment success occurred in 8 treatment periods. We found no evidence for differences in chance of success across medication groups nor demographic factors.

DISCUSSION

We found that immunosuppressive medications for this OLP cohort were frequently discontinued, due to adverse events and treatment failure but infrequently for treatment success. The median time to these events was 9.43 months, which is shorter than what has been observed when using these medications for other indications like bullous pemphigoid.[10] For example, median drug survival in this study was 20.4 to 72.2 months compared to 9.43 months in our cohort.[10]

We generally found no evidence for differences in immunosuppressive durability between medications, except for CsA, suggesting that no one medication had better efficacy or safety profiles. We suspect that the difference seen in CsA may be driven in part by use of this medication as a short-term medication (with a goal to use for ≤12 months typically). However, this was difficult to fully assess in this database and survival times tended to be lower than 1 year. In a different OLP cohort, Myers et al[11] similarly found no difference in adverse event prevalence between MMF, MTX, and AZA in OLP. However, their cohort did experience treatment-limiting adverse events less frequently (16.0-27.8%). The reason for this is unclear, but may stem from our cohort having a high prevalence of severe disease, as evidenced by the high prevalence of erosive disease. Although the male patients in our cohort appeared to have a higher hazard of treatment failure, we could not identify a clear reason for this.

This study has important limitations. First, all cases came from a single institution with limited racial or ethnic representation, limiting generalizability. There is also a potential for misclassification, given that 25% of cases did not have a biopsy available. Furthermore, most cases were severe with erosive subtype disease, which may alter drug survival. For example, with more severe erosive disease, smaller improvements may be considered grounds for discontinuation, whereas in more moderate disease, these improvements might be more acceptable and the medication may be more likely to be continued. We found no evidence for differences in drug survival by erosivity, but this confounding may remain, and generalizability is limited. The order of immunosuppressant usage may affect subsequent treatment periods. We attempted to account for this, but it is possible that other treatments that were not reported (ie, used by a referring physician or prior to our current electronic medical record time period). Lastly, direct comparisons between medications are limited by the retrospective nature and likely confounding by indication.

Overall, our results highlight that patients with OLP frequently encounter adverse events,

TABLE 1. Demographic information, disease characteristics, and treatment information

CHARACTERISTIC	TOTAL (n=125)	MYCOPHENOLATE (n=58)	METHOTREXATE (n=34)	AZATHIOPRINE (n=19)	CYCLOSPORINE (n=14)	*p*-VALUE
Age, years, median (interquartile range [IQR])	63.1 (55.4-71.6)	61.6 (55.6-73.8)	65.0 (56.3-70.9)	59.1 (55.0-71.1)	57.8 (44.2-71.6)	0.72
Sex, n (%)						
Female	98 (78.4)	45 (77.6)	24 (70.6)	16 (84.2)	13 (92.9)	0.34
Male	27 (21.6)	13 (22.4)	10 (29.4)	3 (15.8)	1 (7.1)	
Race, n (%)						
Asian	2 (1.6)	1 (1.7)	0 (0.0)	1 (5.3)	0 (0.0)	0.87
Black	3 (2.4)	1 (1.7)	1 (2.9)	0 (0.0)	1 (7.1)	
Hispanic	2 (1.6)	1 (1.7)	1 (2.9)	0 (0.0)	0 (0.0)	
White	107 (85.6)	49 (84.5)	29 (85.3)	16 (84.2)	13 (92.9)	
Unknown	11 (8.8)	6 (10.3)	3 (8.8)	2 (10.5)	0 (0.0)	
Ethnicity, n (%)						
Non-Hispanic	114 (91.2)	52 (89.7)	30 (88.2)	18 (94.7)	14 (100.0)	0.87
Hispanic	2 (1.6)	1 (1.7)	1 (2.9)	0 (0.0)	0 (0.0)	
Unknown	9 (7.2)	5 (8.6)	3 (8.8)	1 (5.3)	0 (0.0)	
OLP duration, months, median (IQR)	40.3 (19.6-74.5)	31.1 (19.2-53.0)	57.0 (21.2-129.2)	40.3 (27.2-63.2)	38.2 (15.6-77.3)	0.06
Erosive OLP, n (%)						
No	10 (8.0)	5 (8.6)	4 (11.8)	1 (5.3)	0 (0.0)	0.55
Yes	115 (92.0)	53 (91.4)	30 (88.2)	18 (94.7)	14 (100.0)	
Bridge steroid, n (%)						
No	108 (86.4)	51 (87.9)	30 (88.2)	15 (78.9)	12 (85.7)	0.77
Yes	17 (13.6)	7 (12.1)	4 (11.8)	4 (21.1)	2 (14.3)	
Rescue steroid, n (%)						
No	106 (84.8)	47 (81.0)	30 (88.2)	17 (89.5)	12 (85.7)	0.73
Yes	19 (15.2)	11 (19.0)	4 (11.8)	2 (10.5)	2 (14.3)	
Hydroxychloroquine, n (%)						
No	74 (59.2)	38 (65.5)	18 (52.9)	10 (52.6)	8 (57.1)	0.60
Yes	51 (40.8)	20 (34.5)	16 (47.1)	9 (47.4)	6 (42.9)	
Medication discontinued: AE or failure, n (%)						
No	47 (37.6)	19 (32.8)	17 (50.0)	8 (42.1)	3 (21.4)	0.21
Yes	78 (62.4)	39 (67.2)	17 (50.0)	11 (57.9)	11 (78.6)	
Medication discontinued: treatment failure, n (%)						
No	98 (78.4)	43 (74.1)	28 (82.4)	16 (84.2)	11 (78.6)	0.73
Yes	27 (21.6)	15 (25.9)	6 (17.6)	3 (15.8)	3 (21.4)	
Medication discontinued: AE, n (%)						
No	73 (58.4)	36 (62.1)	22 (64.7)	8 (42.1)	7 (50.0)	0.34
Yes	52 (41.6)	22 (37.9)	12 (35.3)	11 (57.9)	7 (50.0)	
Medication discontinued: treatment success, n (%)						
No	117 (93.6)	54 (93.1)	32 (94.1)	18 (94.7)	13 (92.9)	0.99
Yes	8 (6.4)	4 (6.9)	2 (5.9)	1 (5.3)	1 (7.1)	
Treatment duration, months, median (IQR)	6.7 (2.1-23.8)	7.8 (2.3-25.8)	6.5 (2.3-17.0)	19.8 (2.1-55.3)	3.7 (1.3-6.7)	0.088

Comparisons across groups were performed using Kruskal-Wallis for continuous variables and chi-square for categorical variables.
Patient age was reported at the time of medication initiation.
AE: adverse event; OLP: oral lichen planus

TABLE 2. Cox-proportional hazard ratios across study

	OVERALL HR (95% CI)	METHOTREXATE HR (95% CI)	MYCOPHENOLATE HR (95% CI)	AZATHIOPRINE HR (95% CI)	CYCLOSPORINE HR (95% CI)
Medication					
Methotrexate	REFERENCE				
Mycophenolate	1.22 (0.69-2.17)				
Cyclosporine	**2.94 (1.34-6.45)**				
Azathioprine	1.01 (0.47-2.17)				
Failure of prior immunosuppressant					
First immunosuppressant			REFERENCE		
Second immunosuppressant	1.02 (0.60-1.74)	1.11 (0.32-3.87)	0.84 (0.30-2.39)	1.60 (0.33-7.70)	1.48 (0.41-5.33)
Third immunosuppressant	1.09 (0.39-3.00)	N/A	1.21 (0.29-5.05)	3.14 (0.41-24.2)	**N/A**
Age	1.01 (0.99-1.02)	1.01 (0.98-1.03)	**1.05 (1.00-1.10)**	1.04 (0.98-1.09)	**0.94 (0.89-0.99)**
Sex					
Female			REFERENCE		
Male	1.45 (0.86-2.44)	1.61 (0.80-3.24)	1.37 (0.48-3.90)	1.48 (0.30-7.22)	2.75 (0.31-24.7)
Erosive disease					
No			REFERENCE		
Yes	0.84 (0.36-1.93)	0.64 (0.23-1.83)	1.76 (0.23-13.3)	0.33 (0.04-2.79)	Insufficient data
Ever smoker					
No			REFERENCE		
Yes	0.87 (0.49-1.56)	0.72 (0.33-1.58)	0.66 (0.19-2.23)	2.00 (0.24-16.3)	**14.9 (1.32-168)**

HR: hazard ratio

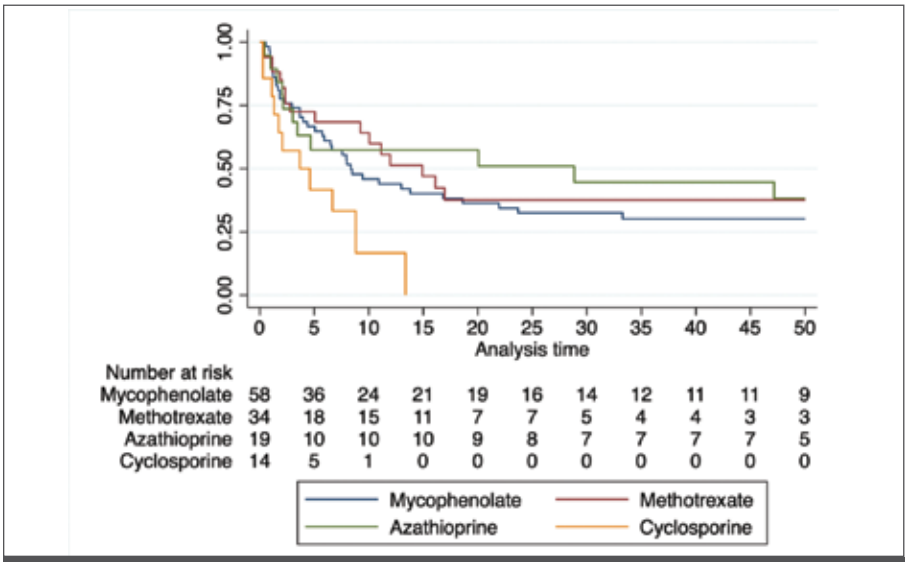

FIGURE 1. Survival from adverse event/side effect or treatment inefficacy by medication

SUPPLEMENTAL TABLE 1. Frequency of medication use across treatment periods

IMMUNOSUPRESSSANT PERIOD	METHOTREXATE n=34	MYCOPHENOLATE n=58	AZATHIOPRINE n=19	CYCLOSPORINE n=14
First, n (%)	27 (29.7)	49 (53.9)	5 (5.5)	10 (11.0)
Second, n (%)	5 (19.2)	6 (23.1)	11 (42.3)	4 (15.4)
Third, n (%)	2 (25.0)	3 (37.5)	3 (37.5)	0 (0.0)

Percents are from row frequencies (ie, percent of medication trials for that treatment period attributed to that medication).

treatment failure, and low immunosuppressive durability. These data underscore the difficulty of treating this condition and the need for more effective treatments with favorable safety profiles. Promisingly, cases of excellent treatment response to Janus kinase inhibitor (JAKi) therapy are emerging. For example, we recently reported a 10-patient case series reporting the effectiveness of upadacitinib, an oral JAKi, in the treatment of recalcitrant OLP,[12] and additional cases of successful treatment using upadacitinib[13] and deucravacitinib, a tyrosine kinase 2 inhibitor, have been recently reported.[14] Conversely, a recent clinical trial of secukinumab failed to demonstrate efficacy in lichen planus subtypes, including OLP.[15] However, further prospective clinical trials are needed.

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