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Comparative responsiveness of cutaneous lupus erythematosus patients to methotrexate and mycophenolate mofetil: a cohort study

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Keywords

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To the editor,

For patients with antimalarial-refractory cutaneous lupus erythematosus (CLE), methotrexate (MTX) and mycophenolate mofetil (MMF) are frequently used.[1] Although surveys show providers have medication preference by CLE subtype which includes acute, subacute (SCLE), and discoid (DLE), there is a lack of evidence-based research comparing response between these medications across subtypes.[2, 3] We retrospectively reviewed our Institutional Review Board-approved prospective CLE database. CLE subtype was determined by clinical evidence and expert opinion of V.P.W. according to the Gilliam classification.[4]

The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) has been established as a responsive outcome measure, with an improvement in the activity (CLASI-A) score of 50% defining clinically significant and meaningful improvement.[5] We thus defined a medication response or non-response as a reduction in CLASI-A score of ≥50% or <50% after starting the medication, or chart documentation of response or non-response as evaluated by V.P.W. Discontinuations due to side effects were analyzed separately (Table 1).

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Conflicts of interest: University of Pennsylvania owns the copyright for the CLASI

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One hundred and ninety one patients with SCLE and DLE were identified in the database. Seventy-three took MTX and/or MMF with at least 1 visit after initiation of MTX or MMF at least 2 months apart in order to determine response. This included 34 patients with concomitant SLE. The other subtypes and other systemic immunosuppressive medications were not powered for analysis and were excluded. Forty-four patients (60%) had CLASI-A data available. The responses for the remaining patients were determined by chart abstraction.

Mean response rate was 64.8% (95% CI 54.2-75.4%). No statistically significant difference was found in the rate of response to MTX or MMF when comparing SCLE vs DLE ($p>0.05$) (Table 2). Results suggest that MMF may be more effective in DLE than MTX, but our sample was not powered to show this ($p=0.175$). Difference in response rate for MTX vs MMF for combined subtypes was not significantly different ($p=0.446$), suggesting comparable response rates overall. Two SCLE and no DLE patients who previously failed MMF subsequently responded to MTX. Alternatively, two SCLE and three DLE patients who previously failed MTX responded to MMF.

We compared response rates to MTX and MMF within and between SCLE and DLE, and did not find substantial differences. This suggests similar efficacies for these medications between subtypes. Other factors may then influence medication selection, such as side effect profiles, disease course, and comorbid conditions.

Limitations include that this is a refractory university cohort with a high proportion of concomitant SLE. Additionally, approximately 40% of patients did not have objective CLASI-A data to demonstrate response, so some subjectivity was introduced by using V.P.W's expert opinion and chart abstraction. There were no differences in the populations of patients with or without CLASI-A data. Additionally, V.P.W.'s assessments always concurred with CLASI-A response. Together, these support that the chart abstraction was reliable when CLASI-A scores were not available.

European guidelines list MTX as second-line and MMF as third-line. Our results suggest comparable response rates between MTX and MMF. However, other considerations such as immunosuppression level were considered in creating the guidelines.[1] Further randomized controlled studies are needed to assess whether MMF may work better than MTX in DLE, as well as further characterize and compare effectiveness of immunosuppressive medications within and between subtypes.

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List of abbreviations used

CLE	cutaneous lupus erythematosus
SLE	systemic lupus erythematosus

SCLE	subacute cutaneous lupus erythematosus
DLE	discoid lupus erythematosus
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLASI-A	Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity
MTX	methotrexate
MMF	mycophenolate mofetil

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Table 1.

Rates of discontinuation of medications due to side effects

Medication	SCLE	Most common SE[a] causing discontinuation in SCLE	DLE	Most common SE causing discontinuation in DLE
MTX	7/25 (28%) [b]	Nausea/diarrhea	3/16 (19%)	Increased transaminases
MMF	6/13 (46%)	Nausea/diarrhea	5/32 (16%)	Nausea/diarrhea

[a] side effect (SE)

[b] percentages are for rate of discontinuation due to side effects from all instances of that medication use within the population subset

Table 2:

Comparison of response rates for each medication between SCLE and DLE

Medication	Response Type	SCLE	DLE	p-value from Fisher's exact test[a]
MTX		n=18[b]	n=13	0.262
	Responders	13 (72%)	6 (46%)	
	Non-responders	5 (27%)	7 (54%)	
MMF		n=7	n=27	>0.999
	Responders	5 (71%)	19 (70%)	
	Non-responders	2 (29%)	8 (30%)	

[a] Statistical analysis was performed using Fisher's exact test 2x2 tables using GraphPad Prism™ Version 8.4.3.

[b] n values do not include patients who discontinued each medication due to side effects

MTX = methotrexate

MMF = mycophenolate mofetil