Response to topical corticosteroid monotherapy in mycosis fungoides

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Background: Topical corticosteroids alone or in combination with other therapies are widely used to treat mycosis fungoides (MF), but data on response rates to their use as monotherapy in MF are limited.

Objective: To evaluate the efficacy of topical corticosteroid monotherapy in MF; compare sex, age, stage distributions, and histopathologic features between responders and nonresponders.

Methods: A retrospective cross-sectional review of patients with MF from 2013 to 2019 treated at Thomas Jefferson University was conducted. Patients with biopsy-proven MF, all stages, who received topical corticosteroid monotherapy were included. Response rates were determined by percent change in body surface area (BSA) involvement and modified Severity-Weighted Assessment Tool (mSWAT).

Results: Of the 163 patients with MF in our database, 23% (37/163) initially received topical steroid monotherapy. Of these, 73% (27/37) improved, with an average 65% decrease in BSA (67% in mSWAT); 27% (10/37) did not respond/progressed, with an average 51.6% increase in BSA (57% in mSWAT); and 33% (12/37) had a complete response (BSA, 0%) with prolonged topical steroid use. Early-stage MF and female sex were more represented in responders.

Limitations: Single-center retrospective design.

Conclusions: Topical steroid monotherapy in early-stage MF can produce measurable improvements in BSA and mSWAT scores and achieve complete remission in a limited subset of patients. (J Am Acad Dermatol 2021;84:615-23.)

Key words: body surface area; cutaneous T-cell lymphoma; topical corticosteroid.

Although no cure currently exists for mycosis fungoides (MF), various treatment algorithms based on the extent of disease are used for each stage.[1,2] Patients with early-stage disease often initially receive skin-directed therapies that include topical corticosteroids, topical retinoids, phototherapy (narrowband ultraviolet B and psoralen–ultraviolet A), topical chemotherapy, and radiotherapy.[3-7] Recalcitrant early-stage or advanced-stage MF requires systemic therapy and a multidisciplinary approach. Various combinations of skin-directed therapies, systemic retinoids, histone deacetylase inhibitors, interferon alfa, antibody-drug conjugates (brentuximab vedotin), monoclonal antibodies (mogamulizumab), and, ultimately, chemotherapeutic agents and hematopoietic stem cell transplants are used in the treatment of these patients.[1,2,8-17]

Topical corticosteroids are commonly used in the treatment of MF either alone, more often in the early

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limited stage (stages I-IIA), or in combination with other therapies in higher stages.[2] However, objective data on their efficacy as monotherapy in MF are limited. A 1998 prospective study of 79 patients with patch-stage MF and a follow-up 2003 study of 200 patients with patch and early plaque-stage MF reported high overall response rates to topical corticosteroids.[18,19] Despite showing efficacy in early-stage MF, neither of these studies defined how the response rates were measured and did not include higher MF stages. Furthermore, the characteristics of responder versus nonresponder cohorts were not fully interrogated, and patients who had received previous therapies were included. In this study, we performed a retrospective analysis of 37 patients with early- and late-stage MF who received front-line topical steroid monotherapy and quantified treatment response rates using changes in body surface area (BSA) and modified Severity-Weighted Assessment Tool (mSWAT). In addition, we performed a subgroup analysis to compare responders and nonresponders based on age, sex, stage distributions, and histopathologic features.

CAPSULE SUMMARY

- Data on the efficacy of topical steroid monotherapy in mycosis fungoides are limited, and the characteristics of responders versus nonresponders are not known.
- Overall, 73% of patients responded to topical steroid monotherapy, with an average 65% decrease in body surface area. Female sex and early-stage disease were more represented in responders.

METHODS

This retrospective study was approved by the Thomas Jefferson University's institutional review board. All charts of initial patient visits to our dermatology and multidisciplinary cutaneous lymphoma clinics between 2013 to 2019 were reviewed. Patients with biopsy-confirmed MF, all stages, who received front-line topical corticosteroid monotherapy were included in the study. Patients with higher stages were included as they typically received topical corticosteroid monotherapy while undergoing appropriate staging studies. For higher stages, the outcome measure in this study was limited to the skin compartment. Patients must have received topical corticosteroid monotherapy with documented BSA involvement and mSWAT during at least 2 consecutive visits. Patients who previously received or were concurrently receiving additional treatments for MF, including other skin-directed or systemic therapies, were excluded from the study.

Age, sex, stage, BSA, and mSWAT score at initial and follow-up visits and duration of topical corticosteroid monotherapy were collected. Percent change in BSA (%BSA) and mSWAT from the first visit was calculated. Patients were documented as improving while using topical steroids if the %BSA decreased. Those with no change or an increase in %BSA were recorded as *no response* or *flaring*, respectively. All data points, regardless of the time period between clinic visits, were included for the no response/flare group. For patients who had an improvement, BSAs collected for 2 clinic visits 15 to 90 days apart were included in the analysis. Patients were stratified based on age, sex, and stage (according to skin, lymph nodes, visceral involvement, and blood [TNMB] classification) at diagnosis to evaluate any differences between the improved versus no response/flare groups.[20]

In addition, the skin biopsy samples taken at the start of topical steroid treatment from patients included in this study were collected and underwent a blinded review by a dermatopathologist who was not informed about the status of responsiveness for each case. This review assessed for histopathologic, molecular, and immunophenotype criteria and an overall likelihood of MF diagnosis. Furthermore, a retrospective review of patients' biopsy reports before the date of their MF diagnosis was conducted.

When indicated, a chi-square test of independence was performed to determine whether a statistically significant association between the responsiveness to topical steroid and a given variable exists. When patients had multiple biopsy samples taken from different anatomic sites during the initial visit, all biopsy samples were included in the blinded review. However, a single biopsy with more MF-like features was selected to count toward statistical analysis.

RESULTS

Our database included 163 patients with MF during the study period, of which 24% (39/163) were initially treated with topical steroid monotherapy. Of these, 37 patients were included in the study based on the inclusion criteria: 21 patients (57%) were men, and 16 patients (43%) were women; 29 patients (78%) were 60 years or older, and 8 patients (22%) were younger than 60 years at the time of diagnosis, with an overall average age of 65.8 years (Table I).

Abbreviations used:

%BSA:	percent change in body surface area
BSA:	body surface area
CR:	complete response
MF:	mycosis fungoides
mSWAT:	modified Severity-Weighted Assessment Tool
PR:	partial response
TCR:	T-cell receptor

Overall, 34 of 37 (92%) patients were treated with clobetasol propionate 0.05% cream or ointment, twice daily, alone or in combination with a lower-potency topical steroid, either desonide 0.05% or hydrocortisone 2.5%, for intertriginous or facial skin. Three of 37 (8%) patients were treated with either triamcinolone 0.1% (2/37, 5%) or mometasone 0.1% (1/37, 3%) ointments mainly because of issues with insurance coverage for clobetasol. The average time between visits for all patients was 79 days, with the mean of 49 days, and 76% (28/37) of the patients had at least 30 days between visits (Table I).

A total of 27 (73%) patients noticed an improvement in disease extent, with an average decrease of 65% in BSA and 67% in mSWAT values. In this group, 6 of 27 (22%) patients achieved a complete response (CR) (BSA involvement of 0%) in 15 to 90 days, of whom 67% had stage IA and 33% had stage IB disease (Table I). Twelve of 27 patients (44%) achieved CR over an average of 18.5 months, and 10 patients (37%) had a partial response (≥50% decrease in BSA) with prolonged topical steroid use. The remaining 5 patients had an improvement in BSA but did not meet criteria for CR or partial response (Fig 1, *A* and *B*).

From the improved group, 4 patients eventually progressed to increased involvement over an average of 19 months. From the same group, 10 patients were started on additional treatment for prevention or persistent lesions. One patient with CR was started on phototherapy for prevention. The remaining 10 (27%) patients of the total 37 did not respond or progressed while receiving topical steroid monotherapy, with an average increase of 51.1% in BSA and 57% in mSWAT values over an average of 21.9 weeks.

Patient demographics and MF staging characteristics are shown in Fig 1, *C* and *D*. Changes in BSA are shown in waterfall plots based on sex, MF stage, and age (Fig 2). Male sex was slightly more prevalent in the BSA-progressed/no change group (P = .082) (Figs 1, *C* and *D*, and 2, *A*), and early-stage MF (stages IA and IB) was more represented in the BSA-improved group (P = .017) (Figs 1, *C* and *D*, and 2, *B*). Both groups had a higher proportion of patients 60 years or older, with an average age of 68.9 years in nonresponders and 64.7 years in responders (P = .296). (Fig 1, *C* and *D*, and 2, *C*). Similar results were seen based on changes in mSWATs (Supplemental Figs 1 and 2, available on Mendeley at https://data.mendeley.com/datasets/pd35n5xgvj/2).

Of the 37 patients included in the study, the skin biopsy samples from the start of topical steroid treatment for 34 patients were obtained, but we were not able to acquire the slides for the 3 remaining patients. Of these, 32 patients (94%) had a definitive or highly probable overall dermatopathology read, consistent with MF based on blinded biopsy review. The remaining 2 of 34 (6%) had a probable MF diagnosis. Overall, 78% (29/37) of all patients had a T-cell receptor (TCR) gene rearrangement study performed. Among these patients, the rate of positive TCR clonal rearrangement was 56% (5/9) in responders and 50% (10/20) in nonresponders (P = .782) (Table II). Immunophenotyping to determine $CD4^+$ T-cell predominance and CD7 expression on T-cells was performed in 78.8% (26/33) of all cases, and results did not significantly differ between responders and nonresponders. No significant associations were found for histopathologic features of lymphoid atypia, epidermotropism, and presence of Pautrier microabscesses between responders and nonresponders (Table II).

A review of clinical records and prior biopsies showed that 20 of 37 patients (54.1%) did not have any previous biopsies before the date of MF diagnosis. Other patients had previous diagnoses of parapsoriasis (11/37, 29.7%), spongiosis and/or perivascular dermatitis (3/37, 8.1%), pityriasis lichenoides chronica (2/37, 5.4%), and lichenoid dermatitis (1/37, 2.7%). Overall, 6 of 10 (60%) nonresponders and 11 of 27 (41%) responders had evidence of chronic skin involvement before progression to MF (P = .2965).

DISCUSSION

This study is the first to report quantifiable data on the degree of disease progression for patients with early- and late-stage MF who received first-line topical steroid monotherapy (Table I). Similar to previous studies, we found a high response rate (81%) to topical steroid monotherapy, mainly clobetasol, in early-stage MF. However, not surprisingly, there was a poor response (33.3%) to topical steroid monotherapy in patients with higher-stage MF (IIA and above). We observed that

Table I. Patient demographics, BSA, and mSWAT scores

Patient	Sex	Age, y	Stage at diagnosis	BSA before, %	BSA after, %	BSA % change	mSWAT before	mSWAT after	mSWAT % change	Days between visits
1	**F**	**64**	**IA**	**0.25**	**1**	**300**	**0.25**	**1**	**300**	**434**
2	**M**	**23**	**IA**	**1.25**	**2.25**	**80**	**1.25**	**2.25**	**80**	**295**
3	**M**	**72**	**IA**	**5.5**	**9**	**64**	**5.5**	**9**	**64**	**35**
4	**M**	**66**	**IA**	**3.9**	**6**	**54**	**3.9**	**8**	**105**	**623**
5	**M**	**90**	**IIIA**	**87**	**96.5**	**11**	**87**	**96.5**	**11**	**33**
6	**F**	**64**	**IVA2**	**58.75**	**60.5**	**3**	**100.75**	**112.5**	**12**	**19**
7	**M**	**72**	**IIB**	**1**	**1**	**0**	**25**	**25**	**0**	**12**
8	**M**	**88**	**IIIB**	**21**	**21**	**0**	**91**	**91**	**0**	**16**
9	**M**	**87**	**IA**	**90**	**90**	**0**	**1.5**	**1**	**−33**	**30**
10	**M**	**63**	**IA**	**0.25**	**0.25**	**0**	**0.25**	**0.25**	**0**	**35**
11	M	44	IA	12	11.75	−2	12	12	0	15
12	F	74	IIB	46	39	−15	70.5	40	−43	28
13	M	67	IA	3	2.5	−17	2.5	2	−20	51
14	M	61	IIB	29.75	24.75	−17	36.25	26	−28	19
15	F	36	IB	10	8	−20	10.925	9	−18	56
16	F	83	IA	9.5	7.2	−24	9.5	7.2	−24	51
17	M	75	IA	10	7	−30	10.27	7.28	−29	19
18	M	37	IA	7	4.25	−39	7	4.25	−39	42
19	F	60	IA	2	1	−50	2	1	−50	65
20	F	33	IB	68.25	26	−62	68.25	43.5	−36	42
21	F	56	IA	1.44	0.5	−65	2	0.5	−75	42
22	M	68	IA	3	1	−67	3	1	−67	56
23	M	72	1A	3	1	−67	3	1	−67	19
24	F	42	IA	3.25	1	−69	3.25	1	−69	49
25	F	80	IA	9	2.75	−69	9	2.75	−69	70
26	M	66	IB	8	2	−75	10	2	−80	77
27	M	67	IB	42.5	7	−84	42.5	7	−84	63
28	F	73	IA	5.75	0.5	−91	5.75	0.5	−91	63
29	M	70	IB	75	5	−93	82	10	−88	70
30	M	81	IB	20	1	−95	21	1	−95	65
31	M	78	IB	10	0.26	−97	10	0.26	−97	89
32	F	76	IA	11	0	−100	2	0	−100	18
33	F	68	IA	3	0	−100	0.5	0	−100	37
34	M	60	IB	60	0	−100	60	0	−100	44
35	F	78	IB	0.25	0	−100	11	0	−100	65
36	F	56	IA	2	0	−100	3	0	−100	84
37	F	86	IA	2.25	0	−100	2.25	0	−100	90

The sex, age, stage at diagnosis, BSA before and after treatment, mSWAT score before and after treatment, %BSA change, %mSWAT change, and days between visits are presented for the 37 patients included in the study. Ten patients had no response/flared (bold), and 27 patients improved with topical corticosteroid monotherapy. The %BSA change for each patient corresponds to the waterfall plots.
BSA, Body surface area; *F*, female; *M*, male; *mSWAT*, modified Severity-Weighted Assessment Tool.

topical steroid monotherapy can achieve complete remission in patients with early-stage MF. In our study, the response rate to topical steroid monotherapy was shown by an average of 65% measurable decrease in BSA (67% in mSWAT) in responders and an average of 51.1% increase in BSA (57% in mSWAT) in nonresponders to treatment. The collected data can guide clinicians regarding how much average improvement in BSA to expect with topical steroid monotherapy.

In a subgroup analysis of responders versus nonresponders, we found that early-stage MF (stages IA and IB) was more represented in the BSA-improved group. Furthermore, all patients with early-stage disease with significant cutaneous involvement (BSA of 20% to 75%, n = 6), had a marked response to topical steroid monotherapy. For higher stages, the outcome measure in this study was limited to the skin compartment. Interestingly, patients with disease up to stage IIB responded to topical corticosteroid treatment, at least partially. Higher stages (IIIA-IVA2) were more prevalent in the progressed/no change group. Our data support findings of previous studies that topical steroid monotherapy is an appropriate treatment in early-stage MF and may be effective in a select group

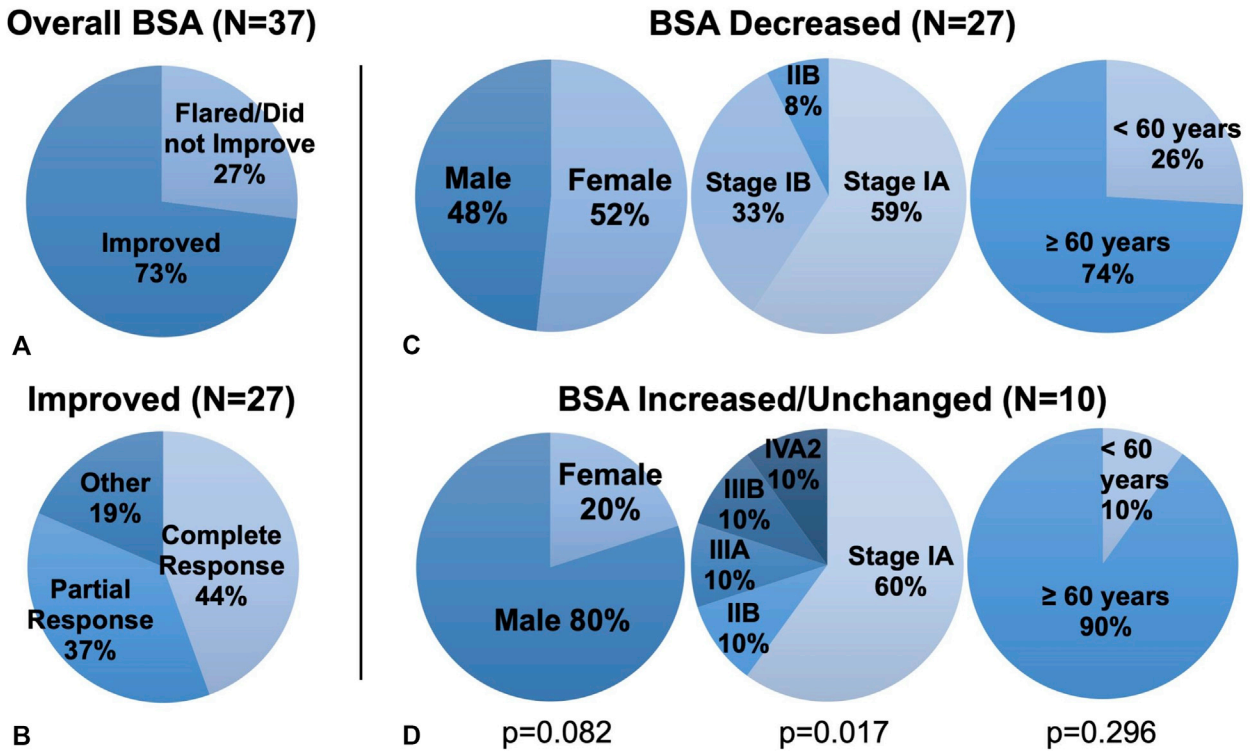

Fig 1. Patient characteristics based on changes in BSA. **A**, Overall, 73% (27/37) of patients had an improvement in BSA, and 27% (10/37) flared or did not response to topical corticosteroid monotherapy. **B**, From the improved group, 44% (12/27) had a complete response (BSA involvement 0%), and 37% had a partial response (≥50% decrease in BSA) with prolonged topical corticosteroid use. **C**, Sex, MF stage, and age distribution in patients with reduced BSA involvement. **D**, Sex, MF stage, and age distribution in patients with increased or unchanged BSA involvement. *BSA*, Body surface area; *MF*, mycosis fungoides.

of patients with stage IIB MF. Further studies can evaluate BSA improvement with topical steroid monotherapy versus in combination with other skin-directed therapies.

Diagnosis of early-stage MF can be challenging, and early biopsies may be interpreted differently by pathologists. We performed a blinded secondary dermatopathologist review of patients' biopsy samples at enrollment to ensure correct diagnosis and to compare histopathologic features in responder versus nonresponder cohorts. This review showed that nearly all enrolled patients had histopathologic features consistent with MF. We found no statistically significant association between response to topical steroid monotherapy and histopathologic/immunophenotypic features or TCR clonality. However, lack of data on TCR clonality and immunophenotyping for some patients was a limitation in this analysis.

Patients with MF can present with chronic skin conditions and ambiguous pathologies before progression to MF. Such patients may receive topical steroid treatment for various durations before being diagnosed with MF. In our cohort, although a higher fraction of nonresponders had chronic skin conditions before progression to MF, the difference between nonresponders and responders did not reach statistical significance (60% vs 41%, respectively; $P = .2965$).

Additionally, we compared groups based on sex and age. Although difficult to accurately measure, lower compliance may explain the higher prevalence of men in the progressed/no change group. Men may be noncompliant or less willing to consistently apply a topical corticosteroid to affected areas. These results emphasize the importance of educating patients, particularly men, regarding regular use of topical steroids. There was no difference in age distribution between the improved and progressed/no change groups, with most patients 60 years or older.

This study was limited to 1 center and included primarily early-stage MF, with possible higher compliance due to specialized care in a multidisciplinary setting or close follow-up. To conduct

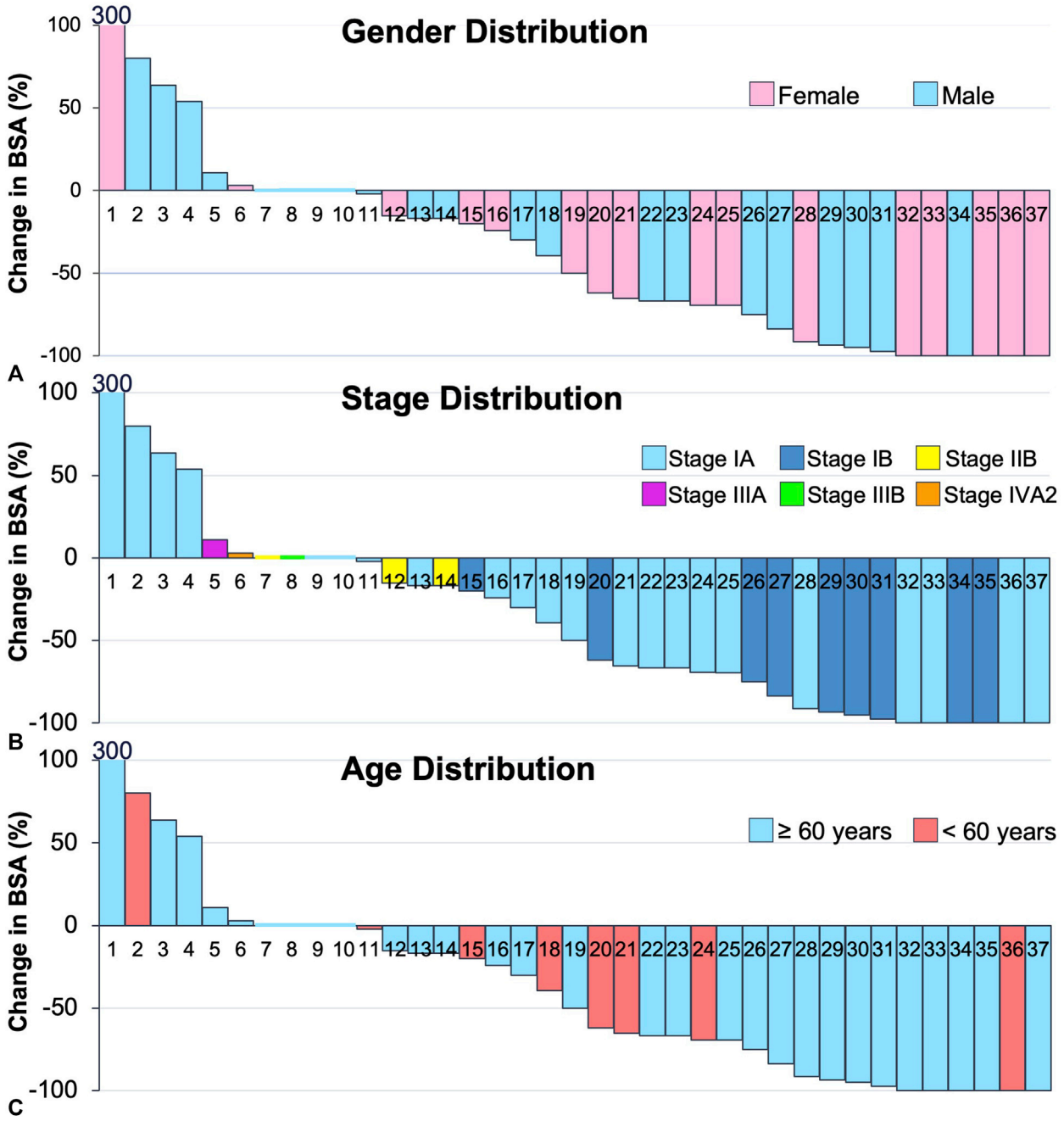

Fig 2. Changes in BSA based on (**A**) sex, (**B**) stage, and (**C**) age. A total of 37 patients were included in the waterfall plot analysis and arranged in order from the greatest increase in BSA to the greatest decrease in BSA. Patients were stratified based on sex, MF stage, and age.

this retrospective study, use of a variable time period between visits was an inevitable limitation. Furthermore, although patients were instructed to apply topical medications twice daily, we had no independent way of verifying the correct frequency of applications at home. Our small sample size is another limitation, which remains an issue for this center and others. The low threshold to add treatments to topical steroids in patients with MF with persistent skin symptoms limits the number of patients receiving topical steroid as monotherapy. Finally, inherent limitations for this and other studies of early MF are challenges in diagnosing the early stages and categorization of patients with smoldering skin conditions that mimic or precede MF.

Table II. Histopathologic, molecular, and immunophenotypic characteristics of patient biopsy samples at time of enrollment

	Histopathologic				Molecular	Immunophenotype		
Patient	Superficial lymphoid infiltrate	Lymphoid atypia	Epidermotropism	Pautrier microabscesses	Clonal TCR	$CD4^+$ T-cell predominance	$<10\%$ $CD7^+$ T-cells	Overall read consistent with MF
Flared/did not improve								
1	Yes	No	No	No	Positive	No	No	Probable
2	Yes	Yes	Yes	No	Positive	No	No	Highly probable
3	Yes	Yes	Yes	No	Negative	No	Yes	Yes
	Yes	Yes	Yes	No	Suspicious	No	Yes	Yes
4	Yes	No	No	No	Negative	No	No	Highly probable
	Yes	No	Yes	Yes	Indeterminate	No	No	Highly probable
5	Yes	No	Yes	Yes	Negative	No	No	Highly probable
6	Yes	Yes	Yes	Yes	Positive	Yes	Yes	Yes
	Yes	Yes	Yes	Yes	Positive	Yes	Yes	Yes
7	Yes	Yes	Yes	Yes	Positive	Yes	Yes	Yes
	Yes	Yes	Yes	No	Positive	Yes	Yes	Yes
	Yes	Yes	Yes	Yes	Positive	Yes	Yes	Yes
8	Yes	Yes	Yes	Yes	Indeterminate	No	No	Yes
9	Yes	Yes	No	No	NP	NP	NP	Highly probable
10	Yes	Yes	Yes	Yes	Positive	Yes	Yes	Yes
	Yes	Yes	Yes	Yes	Positive	Yes	Yes	Yes
Improved								
11	No slide				NP			
12	Yes	Yes	Yes	No	Positive	Yes	No	Yes
	Yes	Yes	Yes	No	Positive	Yes	No	Highly probable
13	Yes	Yes	Yes	Yes	Positive	No	No	Yes
14	Yes	Yes	No	No	Positive	Yes	Yes	Yes
	Yes	Yes	Yes	No	Positive	Yes	Yes	Yes
15	Yes	No	Yes	Yes	Negative	No	No	Yes
	Yes	Yes	Yes	Yes	Negative	Yes	No	Yes
16	Yes	No	Yes	Yes	Indeterminate	Yes	No	Yes
17	Yes	Yes	Yes	Yes	NP	Yes	NP	Highly probable
	Yes	No	No	No	NP	Yes	No	Highly probable
	Yes	Yes	Yes	Yes	NP	Yes	No	Yes
18	Yes	No	Yes	No	Indeterminate	NP	NP	Yes
19	No	No	Yes	No	Positive	NP	NP	Probable
20	Yes	No	Yes	Yes	Negative	Yes	Yes	Yes
21	Yes	Yes	Yes	Yes	Negative	No	No	Yes
	Yes	Yes	Yes	No	Negative	Yes	No	Yes

Continued

Table II. Cont'd

Patient	Histopathologic				Molecular	Immunophenotype		
	Superficial lymphoid infiltrate	Lymphoid atypia	Epidermotropism	Pautrier microabscesses	Clonal TCR	$CD4^+$ T-cell predominance	$<10\%$ $CD7^+$ T-cells	Overall read consistent with MF
22	Yes	Yes	Yes	Yes	Negative	No	No	Highly probable
23	No Slide				NP			
24	Yes	Yes	No	No	Positive	No	No	Highly probable
	Yes	Yes	Yes	No	Negative	No	Yes	Highly probable
25	Yes	Yes	Yes	Yes	Positive	NP	NP	Yes
26	Yes	Yes	Yes	Yes	Negative	No	Yes	Yes
	Yes	Yes	Yes	No	Negative	No	Yes	Yes
27	Yes	Yes	Yes	No	Negative	No	NP	Yes
28	Yes	No	Yes	Yes	NP	NP	NP	Highly probable
	Yes	No	No	No	NP	NP	NP	Highly probable
29	Yes	Yes	Yes	Yes	Negative	No	No	Highly probable
30	Yes	No	Yes	Yes	Positive	Yes	No	Yes
	Yes	No	Yes	No	Positive	Yes	Yes	Yes
31	Yes	Yes	Yes	No	NP	No	No	Highly probable
	Yes	Yes	Yes	No	NP	Yes	Yes	Yes
32	Yes	No	Yes	No	NP	NP	NP	Highly probable
33	Yes	Yes	Yes	Yes	Positive	Yes	No	Yes
34	Yes	No	No	No	NP	NP	NP	Highly probable
35	Yes	Yes	No	No	Positive	No	No	Highly probable
36	No Slide				Negative			
37	Yes	Yes	Yes	No	Positive	No	No	Yes
P value	N/A	.8499	.3360	.7549	.7817	.2760	.6482	.4531

The skin biopsy samples from the start of topical steroid treatment of 34 patients underwent blinded review by a dermatopathologist. *P* values for each category are calculated to compare nonresponders (patients 1-10) with responders (patients 11-37).

MF, Mycosis fungoides; *N/A*, not applicable; *NP*, not performed; *TCR*, T-cell receptor.

CONCLUSIONS

Our results show a measurable improvement in MF disease activity, predominantly in early-stage patients, receiving front-line topical steroid monotherapy. Additional studies are needed to compare topical corticosteroid monotherapy against other skin-directed therapies and evaluate duration of response and clinical or histopathologic factors influencing response to topical steroids. The results of such studies, and our results, can guide appropriate treatment for patients with MF.

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