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Lenalidomide for refractory cutaneous manifestations of paediatric systemic lupus erythematosus

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Abstract

Objective—Cutaneous manifestations of paediatric systemic lupus erythematosus (pSLE) cause significant morbidity. Lenalidomide, a thalidomide analogue, has shown promise treating cutaneous LE (CLE) in adults. Our objective was to evaluate lenalidomide's efficacy and safety in treating refractory cutaneous manifestations of pSLE.

Methods—We performed a retrospective chart review of 10 adolescents who received lenalidomide for recalcitrant CLE. Information was gathered at drug initiation and 6-month follow-up. The Wilcoxon matched-pairs signed-rank test was used to assess change in quantitative parameters of disease activity.

Results—Nine subjects were female and six African-American. Indications for lenalidomide treatment included alopecia, nasal and oral ulcers, extensive malar rash, discoid lesions, bullous lesions, panniculitis, cutaneous vasculitis, and Raynaud's phenomenon with digital ulcerations. Within 6 months, all patients demonstrated complete or near resolution based on physician report. Prednisone dose decreased from a mean 23.5 mg (SD±13.3) to 12.25 mg (SD±9.2) ($P=0.008$). ESR decreased from a mean 29 mm/hr (SD±31.5) to 17 mm/hr (SD±18.1) ($P=0.004$). Lenalidomide was well-tolerated.

Conclusion—Lenalidomide is an effective and safe treatment for a spectrum of dermatologic conditions in pSLE. Its use may allow reduction in prednisone dose and decreased disfigurement. Prospective study is needed to clarify lenalidomide's role in treating cutaneous manifestations of SLE.

Introduction

Cutaneous manifestations are common in systemic lupus erythematosus (SLE), causing significant morbidity. Skin involvement occurs in up to 85% of patients and can be extensive, disfiguring, and recalcitrant to traditional therapy.^{1, 2} The goals of treatment are to reduce activity and minimize damage. Management typically includes a combination of sun protective measures, antimalarials, topical and systemic corticosteroids, and immunosuppressant or immunomodulatory therapies.^{3, 4} Thalidomide has proven to be effective in the treatment of cutaneous lupus erythematosus (CLE), but its use is limited by fetal teratogenicity and the potential for peripheral neuropathy.^{5, 6} Lenalidomide, a thalidomide analogue, has also shown promise in adults with greater potency and a more favorable side effect profile compared to thalidomide.⁷⁻¹⁰ Though their mechanism of action is not completely understood, both agents appear to have anti-inflammatory and immunomodulatory properties.^{11, 12} The aims of this study were to evaluate and report the safety and clinical efficacy of lenalidomide in the treatment of refractory cutaneous manifestations of paediatric SLE.

Methods

We retrospectively analyzed records of 10 adolescents started on lenalidomide between 2008 – 2013 specifically for treatment of recalcitrant cutaneous manifestations of SLE. Lenalidomide dosing was 5-12.5 mg daily. One subject was initially taking thalidomide 100 mg daily before being switched to lenalidomide. Patients were evaluated at drug initiation and at 6-month follow-up using a standardized case report form. Information collected included race, gender, age and disease manifestations at time of SLE diagnosis, age and cutaneous manifestations at lenalidomide initiation, concurrent medications, prednisone dose, and laboratory parameters, including white blood cell count (WBC), neutrophil count (ANC), lymphocyte count (ALC), and sedimentation rate (ESR).

Quantitative data were expressed as mean $\pm$ standard deviation. The Wilcoxon matched-pairs signed-rank test was used to compare quantitative parameters obtained at 6-month evaluation from baseline. Patients with missing values were excluded from that particular analysis. Statistical analyses were performed using GraphPad Prism (Version 6.0; GraphPad Software, Inc., La Jolla, CA). Results were considered significant if $P < 0.05$. The study protocol was approved by Duke University Health System Institutional Review Board.

Results

Nine subjects were female and 6 were African-American (Table 1). Average age at diagnosis was 12.5 years ($SD \pm 3.3$). Average age at lenalidomide initiation was 16.9 years ($SD \pm 3.8$). All subjects started the medication for treatment of skin disease, including scarring alopecia, nasal and oral ulcers, extensive malar rash, diffuse maculopapular eruption, discoid lesions, bullous lesions, panniculitis, and severe Raynaud's phenomenon with digital ulcerations. One patient initially received thalidomide before switching to lenalidomide 28 months later due to complaints of numbness over her anterior shin with a normal EMG.

Within the first 6 months of treatment with lenalidomide, all 10 subjects demonstrated excellent response with near or complete resolution of cutaneous manifestations based on physician report. Lenalidomide maintained the remission in skin disease achieved on thalidomide in the one patient. No subject experienced a cutaneous flare on continued lenalidomide therapy. At the time of chart review, mean duration of therapy was 18 months. Prednisone dose was decreased in 8/10 of patients (Table 1), from a mean of 23.5 mg (SD ± 13.3) to a mean of 12.25 mg (SD ± 9.2) at 6 months ($P=0.008$). ESR also decreased from a mean of 29 mm/hr (SD ± 31.5) to a mean of 17 mm/hr (SD ± 18.1) at 6 months ($P=0.004$). Only one patient started a new disease-modifying antirheumatic drug (azathioprine) during the 6-month follow-up period. The remaining subjects stayed on steady doses of other immunosuppressants.

Lenalidomide exhibited a favorable side effect profile, even when used in conjunction with other immunosuppressive agents. There were no significant changes in WBC, ANC, or ALC values from baseline to 6-month follow up (all $P>0.05$). We further describe the treatment of two patients with lenalidomide for severe, recalcitrant CLE to illustrate its efficacy and tolerability.

Patient 1

A 13-year-old African American female was diagnosed with SLE at 11 years of age with lymphopenia, direct Coomb's positive hemolytic anemia, oral ulcers, and positive antinuclear (ANA), anti-double-stranded deoxyribonucleic acid (dsDNA), anticardiolipin, and anti-beta-2 glycoprotein antibodies. Lenalidomide 5 mg daily was started for extensive alopecia (Figure 1a) and nasal and oral ulcers refractory to treatment with hydroxychloroquine, oral prednisone, and topical corticosteroids.

The patient demonstrated good clinical response within 6 months with complete hair regrowth after 9 months (Figure 1b) of starting lenalidomide. Her lenalidomide dose was increased to 10 mg daily after 8 months of treatment for recurrence of panniculitis. Her panniculitis resolved with the higher lenalidomide dose. Over the course of 14 months, her prednisone was successfully tapered from 30 mg daily to 7.5 mg daily without the addition of other immunosuppressive therapy. There were no serious adverse events attributable to the use of lenalidomide.

Patient 2

A 21-year-old Caucasian male was diagnosed with SLE at 16 years of age with malar rash, photosensitivity, nephritis, positive ANA, and positive anti-dsDNA antibody. Lenalidomide 10 mg daily was initiated for extensive malar rash (Figure 2a) and cutaneous vasculitis of the extremities recalcitrant to hydroxychloroquine and oral prednisone. The patient exhibited marked improvement within 1 month (Figure 2b), with complete resolution of cutaneous disease after 6 months of lenalidomide treatment. He was started on azathioprine 100 mg daily and his oral prednisone increased after 5 months of therapy due to serologic flare with elevated anti-dsDNA antibody titer and hypocomplementemia, but no flare in skin disease. Prior to the disease flare, his prednisone was successfully tapered from 40 mg daily to 15 mg daily. There were no serious adverse events attributable to the use of lenalidomide.

Conclusions

Skin disease is highly prevalent among children and adolescents with SLE and can be disfiguring. We report our clinical experience with lenalidomide in the treatment of refractory cutaneous manifestations of paediatric SLE. We observed a high rate of near or complete remission in cutaneous disease within 6 months of lenalidomide therapy. Its use also allowed for reductions in prednisone. Lenalidomide was well tolerated and did not cause significant changes in WBC, ANC, or ALC values. Though lenalidomide was extremely effective in treating recalcitrant cutaneous manifestations, it did not prevent systemic disease flare in one patient. The risk and nature of flare in cutaneous disease after lenalidomide withdrawal is also unknown.

Lenalidomide was both effective and safe for the treatment of a spectrum of dermatologic conditions in this small, retrospective study in paediatric SLE. It may be used alone or as adjunctive therapy. Prospective study of lenalidomide is needed to further clarify its role in the treatment of cutaneous manifestations of SLE.

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Figure 1. Patient 1 at lenalidomide initiation (a) with extensive alopecia and nasal and oral ulcers refractory to hydroxychloroquine, daily prednisone, and topical corticosteroids and then 9 months after lenalidomide therapy (b) with complete hair regrowth. She color-treated her hair.

Figure 2. Patient 2 at lenalidomide initiation (a) with extensive malar rash and cutaneous vasculitis refractory to hydroxychloroquine and daily prednisone and then 1 month after lenalidomide therapy (b) with near complete resolution of malar rash.

Patient demographics and clinical characteristics

Table 1

Patient	Age ^a (years)	Race	Sex	Cutaneous Manifestations	Lenalidomide Dose (mg daily)	Concurrent Treatments	Initial Prednisone Dose (mg daily)	6 month Prednisone Dose (mg daily)	Initial ESR (mm/hr)	6 month ESR (mm/hr)	Initial WBC (cells/mm ³)	6 month WBC (cells/mm ³)		
1	13	AA	F	extensive alopecia	panniculitis nasal, oral ulcers	5-10	HCQ TCS	30	15	6	3	10,800	6,500	
2	21	C	M	malar rash	cutaneous vasculitis	10	HCQ AZA	40	25	4	3	4,800	6,000	
3	22 ^b	AA	F	discoid lesions	extensive alopecia nasal, oral ulcers	10	HCQ TCS	20	10	11	10	3,700	1,900	
4	10	AA	F	extensive alopecia	Raynaud's phenomenon	digital ulcerations	5	HCQ CYC IV RTX BOS PTX	30	10	38	26	10,400	3,700
5	21	C	F	malar rash	extensive alopecia	cutaneous vasculitis nasal, oral ulcers	12.5	None	5	0	22	12	4,000	3,200
6	17	C	F	panniculitis	cutaneous vasculitis	5-10	HCQ	20	2.5	15	N/A	10,300	N/A	
7	17	AA	F	malar rash	bullous lesions nasal, oral ulcers	10	HCQ MMF	30	20	50	45	5,800	8,100	
8	15	AA	F	panniculitis		5	HCQ MMF	40	20	109	48	3,100	9,400	
9	17	C	F	oral ulcers		5	HCQ	0	0	16	3	5,500	6,100	
10	16	AA	F	discoid lesions	extensive alopecia	5	HCQ MMF	20	20	18	6	4,900	2,300	

AA, African American; AZA, azathioprine; BOS, bosentan; C, Caucasian; CYC, cyclophosphamide; ESR, sedimentation rate; HCQ, hydroxychloroquine; IV, intravenous; MMF, mycophenolate mofetil; PTX, pentoxifylline; RTX, rituximab; TCS, topical corticosteroids; WBC, white blood cell

^aAge at lenalidomide initiation

^bPatient previously treated with thalidomide for 50 months, discontinued due to left anterior shin numbness