Lenalidomide for the Treatment of Resistant Discoid Lupus Erythematosus

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Background: Discoid lupus erythematosus (DLE) is a chronic, disfiguring disease that is characterized by scaly, erythematous, disk-shaped patches and plaques followed by atrophy, scarring, and dyspigmentation. It is refractory to standard therapies in a small population of patients. We investigated the use of lenalidomide, a thalidomide analogue, as a novel alternative therapy in 2 cases of refractory DLE and report our results.

Observations: Two patients with chronic, severe DLE were treated with low-dose lenalidomide. Improvement was noted within 1 month at a dosage of 5 mg/d in one case and was maintained for 10 months before the dosage was doubled to 10 mg/d for 12 months because of a slight worsening of symptoms. Clinical improvement was demonstrated by a sustained reduction in the Cutaneous Lupus Erythematosus Disease Area and Severity Index activity score, with no change in the Cutaneous Lupus Erythematosus Disease Area and Severity Index damage score. Within 5 months, oral prednisone therapy (60 mg/d) was tapered and discontinued; it was restarted at a low dosage (5 mg/d), however, to manage the symptoms of systemic LE. Of note, the patient experienced mild neutropenia after taking 10 mg/d of lenalidomide, which carries a black box warning regarding neutropenia; therefore, the complete blood cell count should be monitored weekly for the first 2 months and then monthly thereafter. The second case failed to show clinical improvement, and lenalidomide therapy was discontinued after 6 months.

Conclusions: Lenalidomide therapy is a potential alternative or adjunctive treatment for patients with severe, chronic DLE that is refractory to standard therapies. A larger study is needed to clarify its role in the treatment of DLE and other forms of cutaneous LE.


Discoid lupus erythematosus (DLE) is a clinical subtype of cutaneous LE (CLE) that typically presents as scaly, erythematous, disk-shaped patches and plaques followed by atrophy, scarring, and dyspigmentation. The lesions are chronic, disfiguring, and sometimes refractory to treatment. Approximately 25% of cases fail to respond to standard first-line systemic therapy with antimalarial agents. Among the alternative systemic therapies, thalidomide is an accepted treatment and has demonstrated clinical efficacy in up to 90% of recalcitrant cases in some studies. Its primary efficacy in CLE is thought to be related to the suppression of inflammatory mediators, including tumor necrosis factor (TNF), and inhibition of antigen presentation. Unfortunately, thalidomide is difficult to use long term because of its notorious adverse effects, including teratogenicity and peripheral neuropathy. Given thalidomide’s vast clinical potential to treat inflammatory and neoplastic conditions, efforts led to the development of a promising thalidomide analogue, lenalidomide (CC-5013 or Revlimid), in the mid-1990s. Lenalidomide has been approved by the Food and Drug Administration for the treatment of multiple myelomas and myelodysplastic syndrome as well as for the treatment of solid malignant neoplasms in clinical trials. Its potent anti-inflammatory and immunomodulatory properties may be via the inhibition of proinflammatory cytokine secretion such as TNF, T-cell costimulation, and antiangiogenic activity. In comparison to thalidomide, it is 2000-fold more potent as an inhibitor of TNF. Also, lenalidomide has a lower frequency of many of thalidomide’s common adverse effects (eg, sedation, constipation, and neuropathy), and preclinical stud-
ies have failed to show teratogenicity or mutagenesis in animals. One of the major adverse effects is myelosuppression (eg, neutropenia and thrombocytopenia), which has led to a black box warning and may occur at the doses (5-10 mg/d) that are needed for treatment of CLE. We initiated lenalidomide therapy at a dosage of 5 mg/d, observed results for at least 6 weeks, and then increased the dosage to 10 mg/d when necessary. An additional known adverse effect of lenalidomide therapy is increased risk of deep vein thrombosis, and antimalarial or anticoagulant agents such as aspirin should be prescribed as prophylaxis to decrease the risk of such events.10

Therefore, lenalidomide may be a potential alternative therapy for patients with CLE. Herein, we describe the treatment of 2 patients with severe recalcitrant generalized DLE with lenalidomide through a compassionate study. The study was begun before the drug was marketed in the United States, where it is now available with safety monitoring and restrictions similar to its analogue, thalidomide. Two compassionate investigational new drug applications based on a detailed treatment protocol were requested from the Food and Drug Administration in addition to institutional review board approval. Both patients were selected from the patient population under the care of the senior author (V.P.W.). The first patient was chosen based on her previous success with thalidomide therapy, which had to be discontinued secondary to neuropathy. The second patient was offered lenalidomide therapy because of the failure of most other treatments, including thalidomide. The offer was made approximately 6 months into the successful therapy of the first patient. Both patients gave written informed consent to the treatment.

REPORT OF CASES

CASE 1

A 43-year-old African American woman presented with a 9-year history of refractory, generalized DLE and a 10-year history of systemic LE (SLE) with lesions characterized by erythematous and dyspigmented macules and papules, some with erosions and scale, on her face, scalp, back, and bilateral upper and lower extremities. The diagnosis of DLE was confirmed by skin biopsy findings. The symptoms of her SLE included persistent polyarthritis as well as intermittent fevers, abdominal pain, serositis, and mildly elevated liver function test results (aspartate aminotransferase and alanine aminotransferase). Baseline laboratory tests demonstrated a positive antinuclear antibody titer (1:320) with a nucleolar and speckled pattern, anti–double-stranded DNA antibody, and antidSAA antibody. Over the years, her DLE had failed to respond to several therapies, including topical corticosteroids, antimalarial agents (hydroxychloroquine, quinacrine, and/or chloroquine phosphate), dapsone, methotrexate, mycophenolate mofetil, rituximab, intravenous immunoglobulin, and azathioprine. Although she had some response to thalidomide therapy, it had to be discontinued because of peripheral neuropathy. Her concomitant medications for the DLE and SLE during this compassionate study included hydroxychloroquine, quinacrine, oral prednisone, and neurtontin.

The patient had a good clinical response within 1 month of starting lenalidomide therapy at a dosage of 5 mg/d, and the therapy was maintained at this dosage for 10 months. Between months 2 and 3, her oral prednisone therapy was successfully tapered (60 mg/d) and discontinued; however, it was restarted and continued at a low dosage (5 mg/d) for intermittent management of the SLE symptoms. At 10 months, the DLE activity increased slightly and the prednisone dosage was doubled to 10 mg/d; her condition was maintained with this regimen for an additional 12 months (Figure 1). At 22 months, the dosage was decreased to 5 mg/d because of sustained neutropenia, which had developed at a dosage of 10 mg/d. Of note, the patient had a history of neutropenia and lymphopenia in 2002, before use of this drug. Therefore, the neutropenia may have been attributable to SLE flares as well as to lenalidomide therapy.

During the 22 months of this regimen, the patient's clinical response was assessed as partial improvement based on the following measures: physical examination findings, general impression assessments on a visual analog scale of 0 to 10 by physician and patient (data not shown), and an objective assessment of therapeutic response using a recently validated scoring system, the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI).11 The CLASI has 2 separate scores: the activity score, which reflects erythema and scaling, and the damage score, which documents scarring and permanent dyspigmentation. There was a sustained reduction in the CLASI activity score, with no change in the CLASI damage score (Figure 1). Photodocumenty documented the improvement in the patient's skin lesions (Figure 2). Although the study has ended, the patient has continued to have diminished activity of her DLE at the 5-mg maintenance dose. However, the rapid initial improvement was followed by some worsening of skin disease, although not back to the level seen before initiation of therapy.

Pregnancy testing, routine laboratory tests (eg, complete blood cell count with differential, comprehensive metabolic panel, liver function tests, and urinalysis), and electrocardiography were performed at regular inter-
vals for safety monitoring, and the results were within normal limits with the exception of neutropenia, as noted above, and intermittent hypokalemia, which had been present at baseline. The findings of nerve conduction studies were abnormal at baseline but remained unchanged during the study, while the thalidomide-induced peripheral neuropathy symptoms resolved during lenalidomide therapy. There were no serious adverse events thought to be attributable to the use of the study drug.

CASE 2

A 40-year old African American woman presented with a 10-year history of severe refractory generalized DLE and SLE. Her lesions were characterized by erythema, scale, dyspigmentation, and scarring of her face, scalp, back, and extremities. Baseline laboratory tests demonstrated a positive antinuclear antibody titer (1:160), anti–double-stranded DNA antibody, and a low C4 level. The SLE manifested with recurrent flares of pleuritis, arthritis, and nephropathy. The DLE had failed to respond to several therapies, including antimalarial agents (hydroxychloroquine, chloroquine, and/or quinacrine), thalidomide, oral prednisone, dapsone, rituximab, methotrexate, azathioprine, and cyclosporine. The patient’s concomitant medications during the study included chloroquine, quinacrine, methotrexate, azathioprine, and oral steroids. Lenalidomide therapy was initiated at a dosage of 5 mg/d and was continued at that dosage for 6 months. The patient failed to show clinical improvement and experienced adverse events of unclear attribution, which precluded dose escalation. The events included mild leukopenia, which was likely related to SLE flares; mildly elevated liver function test results; cellulitis of the legs; and vasculitis. The lenalidomide therapy was discontinued at 6 months because of the lack of response of the CLE.

COMMENT

We describe the use of lenalidomide as an alternative therapy for DLE in 2 African American patients. The

![Figure 2. Photographs of patient 2 before and after the initiation of lenalidomide therapy. A and B, Facial erythema in discoid lupus erythematosus lesions at baseline. C, Diffuse erythema on back and arms at baseline. D, Erythema on the extensor aspect of the arms at baseline. E and F, Decreased erythema of facial lesions, with some repigmentation and hyperpigmentation of previously red areas after 7 and 8 months of treatment, respectively. G, Decreased erythema but increased pigmentation in the distribution of previous erythema on back and arms after 3 months of treatment. H, Decreased erythema, with increased pigmentation on the extensor aspect of the arms after 3 months of treatment.](image-url)
partial improvement of one of the patients suggests that lenalidomide may be useful as an alternative or adjunctive systemic therapy for patients with severe recalcitrant DLE with minimal or no systemic involvement or for patients who are not able to tolerate thalidomide. A larger case series or prospective study is needed to further evaluate the clinical effectiveness, biologic activity, and tolerability of this immunomodulator for DLE and other forms of CLE, which we hope to carry out in the future.

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REFERENCES