

Dermatologic Adverse Effects of Lenalidomide Therapy for Amyloidosis and Multiple Myeloma

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Objectives: To examine dermatologic adverse effects of lenalidomide in patients with amyloidosis and multiple myeloma and to determine whether the adverse effects are different when lenalidomide is used alone compared with when it is used in combination with dexamethasone.

Design: Retrospective review of medical records.

Setting: Tertiary referral center.

Patients: Seventy-five patients with multiple myeloma and 23 patients with amyloidosis participating in clinical trials.

Intervention: In the 75 patients with multiple myeloma, lenalidomide was the treatment in 24 and lenalidomide and dexamethasone in 51. In the 23 patients with amyloidosis, lenalidomide was used alone.

Main Outcome Measures: The frequency, type, severity, and time of onset of all skin eruptions that were temporally related to lenalidomide treatment were recorded.

Results: In the patients with amyloidosis treated with lenalidomide, 10 (43%) had rashes. In the patients with multiple myeloma, rashes occurred in 7 (29%) of those receiving lenalidomide alone and in 15 (29%) of those receiving lenalidomide and dexamethasone. The rashes were characterized as morbilliform, urticarial, dermatitic, acneiform, and undefined. Severe rashes required permanent discontinuation of lenalidomide therapy in 2 patients. In 23 patients (72%), rashes occurred in the first month after therapy was initiated; however, delayed-onset rashes occurred in 9 (28%).

Conclusions: The prevalence of dermatologic adverse effects in patients receiving lenalidomide was higher in those with amyloidosis than in those with multiple myeloma. The prevalence of skin eruptions was not diminished by the concurrent use of systemic corticosteroids. Most skin eruptions were mild and did not necessitate withdrawal of lenalidomide therapy.

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LENALIDOMIDE IS AN ORAL bioavailable analogue of thalidomide belonging to a class of immunomodulatory drugs. Compared with thalidomide, it has been reported to have more potent immunomodulatory, antiangiogenic, and antitumor activities and a better safety profile.¹

Currently, phase 2 clinical trials are studying the efficacy of lenalidomide for the treatment of amyloidosis. First-line therapies for amyloidosis include melphalan-based chemotherapy, autologous stem cell transplantation, and high-dose dexamethasone therapy.²⁻⁵ Trials involving thalidomide for the treatment of amyloidosis have shown that, although thalidomide has activity in primary systemic (AL) amyloidosis, it also has high rates of complications and toxic effects.^{6,7} In 1 investigation that used thalidomide and dexamethasone when the first-line therapies failed or relapse occurred, the combination was effective for treating amyloidosis, but the low tolerability of thalidomide limited its applicabil-

ity.⁸ Lenalidomide may be better tolerated and is therefore being investigated for the management of amyloidosis.

Lenalidomide is a promising treatment for multiple myeloma; it appears to have direct and indirect effects on myeloma cells, including the ability to induce apoptosis, inhibit myeloma cell growth, and inhibit angiogenesis.⁹ Several studies⁹⁻¹¹ have shown its efficacy for treating multiple myeloma. Lenalidomide has shown considerable activity in relapsed and refractory myeloma, as monotherapy and in conjunction with dexamethasone.¹² The ability of lenalidomide to reduce the level of the monoclonal protein in myeloma also makes it an attractive option for primary amyloidosis, although more data on response duration and toxic effects are needed.¹³ Thalidomide has been used to treat multiple myeloma; studies of the combination of thalidomide and dexamethasone for multiple myeloma have shown excellent response rates.^{14,15} However, the use of thalidomide in multiple myeloma has been asso-

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ciated with dizziness, peripheral neuropathy, constipation, birth defects, leukocytopenia, blood clotting, deep venous thrombosis, and pulmonary embolism.¹⁶ In addition to these adverse effects, the dermatologic adverse effects of thalidomide can be disconcerting.¹⁷ Lenalidomide is related to thalidomide, but, when used in place of thalidomide, it appears to be at least as effective and to have fewer adverse effects. When used in combination with dexamethasone, lenalidomide has been reported to reduce the monoclonal cancer protein cells by more than half in more than 90% of patients with newly diagnosed multiple myeloma.¹⁰ Common adverse effects of lenalidomide include neutropenia and thrombocytopenia.^{10,18}

Although the dermatologic adverse effects of lenalidomide and thalidomide have been described,^{10,17} the effects have not been compared when using similar criteria. To our knowledge, no published data report the incidence of dermatologic adverse effects in patients with amyloidosis who were receiving lenalidomide. Clinical anecdotal evidence suggests that these patients experience rashes.

The purpose of our study was to examine more closely the frequency, type, severity, and time of onset of dermatologic adverse effects of lenalidomide in 23 patients with amyloidosis and in 75 patients with multiple myeloma. We also wanted to examine the dermatologic adverse effect profile when lenalidomide is used alone and in combination with dexamethasone.

METHODS

The medical records of patients involved in 6 clinical trials of lenalidomide that have been ongoing at Mayo Clinic in Rochester, Minn, since 2002 were reviewed for dermatologic adverse effects. The study was approved by the institutional review board of Mayo Foundation. Two trials included patients with relapsed multiple myeloma who received lenalidomide alone. For the purposes of this study, the 24 patients in both trials were grouped together. Two trials included patients with newly diagnosed multiple myeloma who received lenalidomide plus dexamethasone, and 1 trial included patients with relapsed myeloma who received lenalidomide plus dexamethasone. For the purposes of this study, the 51 patients in these 3 trials were grouped together. The final trial consisted of 23 patients with amyloidosis who received lenalidomide alone.

In the 24 patients who received lenalidomide as monotherapy for multiple myeloma, the dosage was 25 to 30 mg/d for the first 21 days of a 28-day cycle, and dose adjustments were based on toxic effects. In the 51 patients who received a combination of lenalidomide and dexamethasone for multiple myeloma, the scheduled dosages were based on 1-month cycles. They received 25 mg/d of lenalidomide on days 1 through 21 of a 28-day cycle, and dosage adjustments were based on toxic effects.¹⁰ For the 23 patients who received lenalidomide for amyloidosis, the starting dosage was 25 mg/d for the first 21 days of a 28-day cycle. The dosage was not changed provided that adverse effects of the treatment were tolerable and there was no disease progression. If adverse effects were not tolerable, treatment was discontinued and then restarted at a lower dosage, or treatment was discontinued permanently, depending on the severity of the adverse effects. Evidence of disease progression also was cause for permanent discontinuation of the therapy.

The dermatologic adverse effects were grouped according to the characterization of the rashes. These characterizations

Table 1. Frequency and Characterization of Rashes in 75 Patients With Multiple Myeloma Receiving Lenalidomide Alone or in Combination With Dexamethasone

Rash Type	Therapy, No. (%) of Patients*	
	Lenalidomide Alone (n = 24)	Lenalidomide and Dexamethasone (n = 51)
Morbilloform	5 (21)	10 (20)
Urticarial	2 (8)	1 (2)
Dermatitic	0	2 (4)
Acneiform	0	1 (2)
Undefined	0	1 (2)
Total	7 (29)	15 (29)

*Percentages have been rounded and may not sum to the totals.

Table 2. Severity of Rashes in Patients Receiving Lenalidomide Alone or in Combination With Dexamethasone

Rash Severity	Therapy, No. (%) of Patients*		
	Lenalidomide Alone		Lenalidomide and Dexamethasone for Multiple Myeloma (n = 51)
	For Amyloidosis (n = 23)	For Multiple Myeloma (n = 24)	
Minor	5 (22)	5 (21)	11 (22)
Moderate	5 (22)	1 (4)	3 (6)
Severe	0	1 (4)	1 (2)
Total	10 (43)	7 (29)	15 (29)

*Percentages have been rounded and may not sum to the totals.

were made by 1 of us (M.D.P.D.) according to the descriptions of the rashes in the patients' clinical charts. The rashes were characterized as morbilliform, urticarial, dermatitic, acneiform, or undefined. The rashes were also divided into the following 3 categories of severity: minor, moderate, and severe. Minor rashes were defined as those not necessitating an alteration in the scheduled dosing of lenalidomide. Moderate rashes were defined as those not resulting in a permanent discontinuation of treatment, but their occurrence resulted in an alteration of the scheduled dosing protocol. These alterations included decreasing the dosage of lenalidomide or withholding the treatment temporarily before restarting therapy at the same dosage or at a lower dosage. Severe rashes were defined as those resulting in permanent discontinuation of lenalidomide treatment.

RESULTS

The frequency and characterization of rashes in the study patients, by disease and type of therapy, are given in **Table 1** and **Table 2**. The time of onset of the rashes after the initiation of treatment is given in **Table 3**.

LENALIDOMIDE MONOTHERAPY IN AMYLOIDOSIS

Of the 23 patients with amyloidosis who received lenalidomide monotherapy, 10 (43%) experienced dermato-

Table 3. Time of Onset of Rashes After Initiation of Therapy

Time of Onset	Therapy, No. of Patients		
	Lenalidomide Alone		Lenalidomide and Dexamethasone for Multiple Myeloma (n = 51)
	For Amyloidosis (n = 23)	For Multiple Myeloma (n = 24)	
First month	10	6	7
Second to fourth month	0	1	4
After fourth month	0	0	4

logic adverse effects. These rashes were characterized as having a morbilliform pattern (7 patients) or as urticarial (3 patients). The rashes were minor in half of these patients and moderate in the other half (Table 2). All of the rashes developed within the first month of lenalidomide therapy; there were no late-onset rashes (Table 3).

A typical moderate-severity rash was noted in a 66-year-old man with amyloidosis. Two weeks after treatment was begun with lenalidomide at a dosage of 25 mg/d, an extensive rash developed that involved more than 50% of his body surface. The rash consisted of large pruritic urticarial plaques, mainly involving the trunk and upper extremities. Therapy with lenalidomide was discontinued, and the rash resolved within 2 weeks. Therapy was then started at a lower dosage (15 mg/d), but the rash recurred after 5 days of treatment. Use of the medication was again discontinued, and the rash resolved during the next week. Therapy at a lower dosage (10 mg/d) was begun, but the rash subsequently recurred. The rash again involved more than 50% of his body surface, but it affected the limbs more than the trunk. The rash resolved within 6 days after discontinuation of therapy. The dosage of lenalidomide was decreased to 5 mg/d. The patient continued to have a manageable rash on the dorsum of his hands and the bottoms of his feet while receiving the 5-mg/d dosage of lenalidomide.

LENALIDOMIDE MONOTHERAPY IN MULTIPLE MYELOMA

Of the 24 patients with multiple myeloma who received lenalidomide monotherapy, 7 (29%) experienced dermatologic adverse effects. In most of these patients (n=5), the rash was characterized as morbilliform. In the other 2 cases, the rash was characterized as urticarial (Table 1). The rashes were of minor severity in 5 patients, moderate in 1, and severe in 1 (Table 2). All of the rashes but 1 occurred within the first month of therapy (Table 3).

A severe skin reaction was noted in a 76-year-old man with relapsed myeloma. After he had taken lenalidomide at a dosage of 25 mg/d for 2 weeks, pruritus without rash developed on his back. Shortly thereafter, pruritic urticarial papules developed on his chest and abdomen. Lenalidomide therapy was discontinued and, during the ensuing week, the pruritus and rash almost completely resolved. After the rash completely resolved, lenalidomide therapy was restarted at a lower dos-

age (15 mg/d). During the third treatment cycle at the new dosage, a widespread morbilliform eruption involving the trunk, extremities, and head and neck developed. Lenalidomide therapy was again discontinued. The rash resolved in 2 weeks; because the patient had been responding well to the lenalidomide, therapy was restarted at a lower dosage (10 mg/d). Five days later, the rash and pruritus recurred. The lenalidomide treatment subsequently had to be discontinued. At follow-up appointments, the patient had no subsequent reported problems with rashes.

LENALIDOMIDE AND DEXAMETHASONE COMBINATION THERAPY IN MULTIPLE MYELOMA

Of the 51 patients with multiple myeloma who received lenalidomide and dexamethasone combination therapy, 15 (29%) experienced dermatologic adverse effects. Most of the patients (n=10) had rashes characterized as morbilliform. In the remaining patients, the rashes were characterized as dermatitic in 2 and urticarial, acneiform, and undefined in 1 each (Table 1). The severity of the rashes was minor in 11 patients, moderate in 3, and severe in 1 (Table 2). This group had the highest rate of delayed-onset rashes (Table 3).

A severe skin reaction leading to cessation of therapy was noted in a 60-year-old man receiving combination therapy for newly diagnosed multiple myeloma. During the fourth cycle of treatment, a diffuse, maculopapular, erythematous rash developed involving his lower extremities, inner elbow region, and waist area. The rash was associated with pruritus and discomfort and involved more than 50% of his body surface. The lenalidomide therapy was discontinued. Two weeks later the rash was of the same extent but was associated with decreased pruritus and discomfort. The rash had resolved by 1 month after discontinuation of combination therapy, but combination therapy was not restarted.

COMMENT

Lenalidomide, an immunomodulatory drug belonging to a class of thalidomide analogues, is gaining popularity as an agent for treating multiple myeloma and other hematologic diseases. Lenalidomide is currently undergoing clinical trials and awaiting approval by the US Food and Drug Administration. In this retrospective study, lenalidomide therapy was associated with skin eruptions more often in patients with amyloidosis than in those with multiple myeloma. Skin eruptions developed in 10 (43%) of 23 patients receiving lenalidomide for systemic amyloidosis and in 7 (29%) of 24 patients receiving lenalidomide alone for multiple myeloma. The addition of dexamethasone to lenalidomide therapy for multiple myeloma did not decrease the incidence of skin eruption (15 [29%] of 51 patients).

To our knowledge, there are no previously published data on the dermatologic adverse effects of lenalidomide in patients with amyloidosis. A rash developed in 43% of the patients studied, and in half of them the rash

was of moderate severity. Although the lenalidomide treatment was discontinued in a few of the patients because of toxic effects, the rash was not classified as severe because there were other confounding toxic effects. The rash could not be pinpointed as the sole reason for discontinuing treatment, and therefore it could not be classified as severe according to our guidelines. Of the 3 groups of patients studied, those with amyloidosis had the highest frequency of rash and also the highest proportion of rashes of moderate severity.

The frequency of rashes in patients with multiple myeloma receiving lenalidomide seems to be less than that in patients receiving thalidomide, and the rashes are also less severe. In patients with myeloma, Hall et al¹⁷ found that a rash developed in 46% of those receiving thalidomide alone and in 43% of those receiving thalidomide and dexamethasone. In patients receiving lenalidomide instead of thalidomide, we found that these frequencies were 29% with lenalidomide alone and 29% with lenalidomide and dexamethasone. In the study by Hall et al,¹⁷ which used the same criteria for rash severity as used in this study, thalidomide treatment resulted in a higher proportion of moderate and severe rashes when given as monotherapy and also when given in combination with dexamethasone. Hall et al¹⁷ found that the rashes that developed during thalidomide therapy in 39 patients with myeloma were moderate or severe in 20 (51%). In our study, the rashes that developed during lenalidomide therapy in 22 patients with myeloma were moderate or severe in 6 (27%). Thus, the dermatologic adverse effects that occur with lenalidomide treatment appear to be less severe than the rashes associated with thalidomide treatment.

This study did not find major differences in the frequencies of rashes between groups receiving lenalidomide alone or lenalidomide and dexamethasone. The 2 groups had similar frequencies of rash (29% and 29%) and similar patterns of severity (Table 2). The larger number of patients in the combination therapy group (more than twice as many) may render the small differences statistically insignificant.

Acneiform and dermatitic eruptions were noted in the patients receiving combination therapy, a finding that raises the possibility that these eruptions could have been due to dexamethasone and not lenalidomide therapy.

The timing of rash occurrence was slightly different in the 3 groups of patients (Table 3). There were no delayed-onset rashes in patients with amyloidosis; rash developed in all 10 patients in the first month of treatment. In contrast, in the patients with myeloma treated with lenalidomide and dexamethasone combination therapy, more than half (8/15) had delayed-onset rashes (morbilliform in 5, dermatitic in 2, and acneiform in 1). In the patients with myeloma treated with lenalidomide alone, only 1 (14%) of 7 had a late-onset rash (morbilliform). These results raise the possibility that dexamethasone may have delayed the onset of rash in these patients.

In most cases, the rashes that developed after initiation of lenalidomide therapy were of minor severity and spontaneously resolved after a few days without changes in the scheduled protocol. Of the 32 cases of rash reported in this study, 9 were classified as being of moderate severity. These rashes resulted in a change in the scheduled protocol. Most

often, the lenalidomide therapy was discontinued until the rash dissipated and then therapy was restarted at a lower dosage. In some cases, the rashes were treated with antihistamines or topical corticosteroid creams, but often no treatment was pursued. Two severe cases necessitated discontinuation of treatment.

This retrospective study has limitations. Few of the rashes described in this study were evaluated clinically by a dermatologist. Amyloidosis has been associated with skin lesions due to amyloid deposition in the skin or other aspects of the disease.¹⁹ Multiple myeloma also has been associated with many dermatologic disorders. Some are a direct result of the process itself and others are non-specific conditions that may result from decreased immunity or renal failure.¹⁷ In addition, rashes are relatively common in all people. Dexamethasone occasionally is associated with skin eruptions such as acneiform eruptions. Although we cannot definitely attribute the rashes in our patients to lenalidomide treatment, we can state that most of these rashes were evaluated by the treating hematologists (including S.V.R. and A.D.), who believed them to be temporally related to the lenalidomide treatment and not to the disease processes themselves.

In summary, clinicians should be aware that lenalidomide may be associated with rashes. Lenalidomide has shown efficacy for delaying the progression of myeloma^{10,11} and is being considered as a treatment for amyloidosis. Physicians who prescribe lenalidomide should be certain to monitor their patients for possible dermatologic adverse effects, which in this study occurred in approximately one third to almost half of our patients. In most cases, these effects do not necessitate complete discontinuation of the therapy, but they may call for a reduction in drug dosage and close scrutiny. Incorporating lenalidomide as a treatment early in the disease courses of amyloidosis and myeloma may prove to be beneficial but may be associated with skin eruptions that are, for the most part, mild.

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