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# **Is Lenalidomide, in Combination with Dexamethasone, a Safe and Effective Treatment for Relapsed Multiple Myeloma?**

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A SELECTIVE EVIDENCE BASED REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

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Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
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## ABSTRACT

**OBJECTIVE:** The objective of this systematic review is to determine whether or not lenalidomide, in combination with dexamethasone, is a safe and effective treatment for relapsed multiple myeloma.

**STUDY DESIGN:** Review of three English language primary trials published in 2007 and 2009.

**DATA SOURCES:** Double blind, placebo-controlled, randomized clinical trials in which lenalidomide paired with dexamethasone was compared to placebo paired with dexamethasone were found utilizing Ovid MEDLINE and Cochrane databases

**OUTCOMES MEASURED:** Time to progression, complete response, overall response, venous thromboembolism, and fatigue. Time to progression, complete response, and overall response were all evaluated via the European Group for Blood and Marrow Transplant response criteria. Incidence of venous thromboembolism and fatigue were evaluated via the National Cancer Institute's Common Toxicity Criteria, version 2.

**RESULTS:** In two of the studies, lenalidomide with dexamethasone was found to increase the time to progression of disease, complete response, and the overall response in comparison to the placebo plus dexamethasone in patients with relapsed multiple myeloma. In the third study examined, lenalidomide with dexamethasone used in patients with only one prior therapy was found to increase the time to progression of disease, complete response, and the overall response in comparison to patients who had lenalidomide with dexamethasone with two or greater previous therapies. In two of the studies, an increase in incidence of venous thromboembolism was noted in the lenalidomide with dexamethasone group in comparison to the placebo group. There was no association to be made between fatigue and lenalidomide with dexamethasone therapy.

**CONCLUSION:** Lenalidomide with dexamethasone is an effective treatment to induce longer remissions for relapsed multiple myeloma patients. The safety of lenalidomide with dexamethasone is jeopardized by increased incidence of venous thromboembolism, neutropenia and thrombocytopenia. The combination therapy is not safe in respect to the patient's overall health, but these dangers must be balanced against the more toxic drugs like thalidomide and the outcome of no treatment, which is quicker disease progression and death. Future studies should evaluate lenalidomide with dexamethasone in patients who are newly diagnosed with no prior treatments.

**KEY WORDS:** Lenalidomide, Dexamethasone, Relapsed Multiple Myeloma, Treatment, Safety

## INTRODUCTION

Multiple myeloma is a malignancy of plasma cells that manifests as abnormalities and failure of the bone marrow, excessive production of monoclonal immunoglobulin (paraproteins), and bone destruction. The bone marrow failure results in patients becoming immunocompromised, while the bone tumors (plasmacytomas) and subsequent bone destruction cause severe pain. High levels of paraproteins circulating commonly result in renal failure in multiple myeloma patients.<sup>1,2,3</sup> Yearly incidence in the United States is about 4 people per 100,000 and the median age at diagnosis is 68 years for multiple myeloma.<sup>3</sup>

Diagnosis is made using the classic triad of bone marrow plasmacytosis > 10%, osteolytic lesions, and a serum and/or urine M (paraprotein) component that is determined via protein electrophoresis.<sup>1,2,3</sup> Patients with multiple myeloma are treated first with induction therapy consisting of dexamethasone and either thalidomide or bortezomib or some combination of the two; after induction, patients under the age of 76 will usually undergo autologous hematopoietic stem cell transplantation for consolidation therapy.<sup>1,2,3</sup> This two part treatment regimen is the gold standard. Since the exact etiology of multiple myeloma is unknown, a definitive cure for multiple myeloma has remained elusive; throughout this past decade, researchers and pharmaceutical companies have tried to find newer and possibly more effective and safer drugs, such as lenalidomide, which is a derivative of the parent compound, thalidomide.<sup>4,5,6</sup> As of an article published in 2009, the cost to treat multiple myeloma patients with bortezomib was \$3,504 after one year of treatment, while lenalidomide was \$4,766 and thalidomide was \$4,443.<sup>7</sup> Other treatments than multiple myeloma-specific drugs were adjusted to cost around \$3,907 for one year after diagnosis.<sup>7</sup>

With cancer being the second most common cause of death in the United States, the treatment of multiple myeloma is relevant to a PA's scope of practice, especially PAs employed in the hematology/oncology subspecialty, as well as primary care PAs.

## OBJECTIVE

The objective of this systematic review is to determine whether or not lenalidomide, in combination with dexamethasone, is a safe and effective treatment for relapsed multiple myeloma.

## METHODS

The three randomized, double-blind, phase III clinical control trials studied the subpopulation of multiple myeloma patients who were over the age of 18, had received one previous therapy for multiple myeloma, and also were in need of additional treatment at the time of enrollment in the trials. The first trial evaluated, by Weber et al., had 353 participants enroll between February 23, 2003 to April 14, 2004, who met the abovementioned criteria, lived in the US or Canada, and had multiple myeloma sensitive to dexamethasone; patients had to be on greater than 200 milligrams in a previous treatment regimen without any progression of multiple myeloma during that time period to be considered dexamethasone-sensitive. Participants were clinically diagnosed by having M protein serum levels of at least 0.5 gram/deciliter or a urinary Bence Jones protein level of at least 0.2 gram per day. In addition, there were other eligibility criteria concerning patient's immune status, and renal and hepatic levels of functioning. The trial's evaluation of responses to treatment was analyzed up until the trial was unblinded in June 2005.

The second trial evaluated, by Dimopoulos et al., had 351 patients with enrollment between September 22, 2003 and September 15, 2004. The study had the exact same inclusion and exclusion criteria as the study done by Weber et al., with the one difference of only including patients who lived in Europe, Israel, or Australia. The trial's evaluation of response to the experimental treatment was analyzed up until the trial was unblinded in August 2005. The third article by Stadtmauer et al., had 353 participants pooled from the two clinical trials by Weber et al. and Dimopoulos et al. and evaluated the specific subset of patients on lenalidomide with dexamethasone who had one previous therapy versus two or more previous therapies.

The intervention evaluated in these three articles was oral lenalidomide 25 milligrams on days 1 through 21 of a 28-day cycle in combination with oral dexamethasone 40 milligrams on days 1 to 4, 9 to 12, and 17 to 20 for the first four cycles. After the fourth cycle, 40 milligrams of dexamethasone was administered only on days 1 to 4. The experimental intervention was compared to a placebo pill distributed in conjunction with 40 milligrams of dexamethasone on days 1 to 4, 9 to 12, and 17 to 20 for the first four cycles and then after the fourth cycle, 40 milligrams of dexamethasone was given on days 1 to 4.

The outcomes assessed in the clinical trials were patient oriented objectives of time to progression (TTP), overall response (OR), and complete response (CR) for the patients being treated with multiple myeloma. A detailed search by the author utilizing the search engines Ovid MEDLINE and the Cochrane database was performed with the keywords of lenalidomide, Revlimid, and multiple myeloma. All articles selected were published in peer-reviewed journals in the English language. Articles for this systematic review were chosen if they reviewed randomized clinical control trial data, the treatment included lenalidomide plus dexamethasone, and patient-oriented evidence was analyzed. Exclusion criteria included studies that only

evaluated lenalidomide alone as a treatment for multiple myeloma or studies that evaluated lenalidomide in conjunction with other drugs. Statistics utilized in the studies included hazard ratio, *p*-value and confidence interval (CI).

## OUTCOMES MEASURED

The outcomes of interest in the clinical trials were patient oriented objectives of time to progression (TTP), complete response (CR), and overall response (OR) for the patients being treated with multiple myeloma. TTP is a measure of time after a disease is diagnosed (or treated) until the disease starts to advance. The Weber et al. and Dimopoulos et al. articles delineated progression of multiple myeloma as an increase of at least 25% in M protein from lowest baseline, an absolute increase in serum M protein of greater than 500 milligrams per deciliter from lowest baseline, an absolute increase in urinary M protein of more than 200 milligrams per 24-hour period, a new bone lesion (or increase in size of such lesions), and/or serum calcium level of more than 11.5 milligrams per deciliter.<sup>4,6</sup> TTP, CR and OR were evaluated via the European Group for Blood and Marrow Transplant response criteria. The articles by Weber et al. and Dimopoulos et al. defined CR as the complete disappearance of M protein in serum and urine by immunofixation and less than 5% marrow plasma cells.<sup>4,6</sup>

Lastly, the OR takes into account patients who had a complete response in addition to patients with near-complete response and partial responses to therapy administered. The criteria for near-complete and partial responses were identical in Weber et al. and Dimopoulos et al. Near-complete response was identical to those for complete remission but without confirmation of marrow plasma cells less than 5% or confirmation of disappearance of M protein in serum or urine via repeated immunofixation.<sup>4,6</sup> Partial response was considered to be a reduction of M protein by at least 50% in serum, 90% in urine, or both.<sup>4,6</sup>

Table 1- Demographics &amp; Characteristics of Included Studies

| Study  | Type  | Number of Patients | Age (years)   | Inclusion criteria   | Exclusion criteria  | W/D Due to Toxicity   | Interventions   |
|--|---|--------------------|---|--|---|---|---|
| Weber, USA and Canada, 2007                    | Double-blind, placebo-controlled, phase III RCT | 353                | 36-86<br>Median: 64 for experimental group and 62 for placebo group           | Measurable disease using standardized serum and/or urinary markers                   | Disease that was considered resistant to dexamethasone; patients under 18 yo    | 53  | Patients randomized to receive either lenalidomide plus dexamethasone or placebo plus dexamethasone |
| Dimopoulos, Europe, Israel and Australia, 2007 | Double-blind, placebo-controlled, phase III RCT | 351                | 33-82<br>Median: 63 for experimental group and 64 for placebo group           | Measurable disease according to clinical criteria using serum and/or urinary markers | Disease that was considered resistant to dexamethasone; patients under 18 yo    | 31  | Patients randomized to receive either lenalidomide plus dexamethasone or placebo plus dexamethasone |
| Stadtmauer, international, 2009                | Double-blind, placebo-controlled, RCT           | 353                | Median for 1 therapy group was 62.1 and for $\geq 2$ therapies group was 63.1 | Measurable disease according to clinical criteria using serum and/or urinary markers | Patients that had never been treated for multiple myeloma; patients under 18 yo | 14.3% with 1 therapy; 14.5% in patients with $\geq 2$ therapies | Patients randomized to receive either lenalidomide plus dexamethasone or placebo plus dexamethasone |

Secondary outcomes that were evaluated include side effects experienced by patients

during the active treatment phase of the studies. The incidence of venous thromboembolism and fatigue in both the experimental and control groups was noted out of the other adverse events reported because they were patient-oriented conditions. Adverse side effects experienced during treatment were graded using the National Cancer Institute's Common Toxicity Criteria, version



2. In this systematic review, grade three (out of four) toxic effects for venous thromboembolism and fatigue were analyzed.

## RESULTS

In the three articles, the primary outcome of time to progression was presented as continuous data, while the rest of the primary and secondary outcomes analyzed in this review were presented in a dichotomous manner. The studies employed an intention to treat analysis on all patients. Sixty-eight patients in the lenalidomide group and 126 patients in the placebo group from the Weber et al. study were automatically discontinued from the study due to progression of their disease, while 35 patients in the lenalidomide group and 18 in the placebo group discontinued the study due to toxic effects from treatment. Dimopoulos et al. article disclosed that patients were automatically discontinued from both the experimental and control groups due to progression of their disease. Out of both the experimental and control groups, 31 patients stopped the study due to toxic effects from treatment.

In Weber et al., median time to progression, measured in months, was 11.1 in the lenalidomide plus dexamethasone (L&D) group and 4.7 in the placebo plus dexamethasone (P&D) group with a hazard ratio of 0.35 and a p-value  $< 0.001$ ; hence, around one-third as many patients in the L&D group had disease progression at any point in time in the study compared to the placebo group. In the Dimopoulos et al. article, the median time to progression, measured in months, was 11.3 and 4.7 in the L&D and P&D groups, respectively, with a hazard ratio of 2.85 and a p-value  $< 0.001$ . Therefore, patients in the P&D group had 2.85 times the likelihood of disease progression at any point in time in the study when compared to the L&D group. The Stadtmauer et al. study published a median time to progression, measured in months, of 17.1 in the lenalidomide with one previous therapy experimental group and 10.6 in the lenalidomide

with greater than or equal to two previous therapies comparison group and a hazard ratio of 0.68 with a p-value = 0.026. Hence, the Stadtmauer et al. study had around two-thirds as many patients in the lenalidomide with one previous therapy experimental group who experienced disease progression in comparison to the lenalidomide with two or greater previous therapies group.

Other primary results analyzed across all the three studies were complete response and overall response to treatment. In the Weber et al. and Dimopoulos et al. studies, the L&D groups had 14.1% and 15.9% complete responses to the therapy, respectively. The absolute benefit increase (ABI) for the lenalidomide plus dexamethasone treatment calculated from the Weber et al. study was 13.5% and the Dimopoulos et al. study had a similar computed ABI of 12.5%. Both studies evaluated would need to treat 8 patients with lenalidomide plus dexamethasone to achieve one complete response.

Table 2- Efficacy of Lenalidomide in Terms of Time to Progression of Multiple Myeloma Disease Process in Experimental and Control/Comparison Groups

| Study           | Therapy | Time to Progression | Hazard Ratio (95% CI) | p-value   |
|-----------------|---------|---------------------|-----------------------|-----------|
| Weber 2007      | L&D     | 11.1                | 0.35<br>(0.27-0.47)   | P < 0.001 |
|                 | P&D     | 4.7                 |                       |           |
| Dimopoulos 2007 | L&D     | 11.3                | 2.85<br>(2.16-3.76)   | P < 0.001 |
|                 | P&D     | 4.7                 |                       |           |
| Stadtmauer 2009 | L1      | 17.1                | 0.68<br>(0.48-0.97)   | P = 0.026 |
|                 | L2+     | 10.6                |                       |           |

For tables 2-5: L&D=lenalidomide plus dexamethasone; P&D=placebo plus dexamethasone; L1=lenalidomide plus dexamethasone in patients with one prior therapy; L2+=lenalidomide plus dexamethasone in patients with two or greater prior therapies; CI= confidence interval

In the Stadtmauer et al. article, the reported complete responses for the lenalidomide one previous therapy group and the lenalidomide two or greater previous therapies group were 20.3% and 11.8%, accordingly. A relative benefit increase (RBI) in complete response of 72% was

found, as well as an ABI of 8.5%, in the lenalidomide one previous therapy group in comparison to the lenalidomide two or greater previous therapies group. A NNT of 12 was calculated meaning that 12 patients with one previous therapy would need to receive lenalidomide plus dexamethasone for one complete response to occur.

The study by Weber et al. reported a statistically significant 61.0% overall response in the L&D group and 19.9% in the P&D group. In the article by Dimopoulos et al., a statistically significant overall response of 60.2% was disclosed in the L&D group and 24.0% in the P&D group. An ABI of 41.1% for the L&D group was determined in the Weber et al., while the ABI calculated for the Dimopoulos et al. L&D group was 36.2%. Both of the studies had to treat three patients for one of them to achieve an overall response. With the study by Stadtmauer et al., the lenalidomide with one previous therapy experimental group revealed a 66.9% overall response, while the comparison group had an overall response of 56.8%. The reported p-value of 0.060 is not considered statistically significant, but is in the range between 0.05 and 0.10, which indicates likelihood toward association of a higher effectiveness of lenalidomide in patients who have only had one previous therapy for multiple myeloma.

Secondary outcomes focused on adverse events experienced during treatment by patients and the possible association between the events and lenalidomide with dexamethasone treatment. The first adverse outcome to be analyzed was the incidence of venous thromboembolism (VTE) in participants of the studies. The Weber et al. clinical trial had a statistically significant calculated absolute risk increase (ARI) of 11.3% for VTE in the L&D group. The Dimopoulos et al. study had a computed statistically significant ARI of 4.0% for VTE in the L&D group. The Stadtmauer et al. clinical trial did not have a statistically significant relationship between incidence of venous thromboembolism and the experimental one previous therapy group versus

the comparison two or greater previous therapies group. The other adverse event evaluated across all three trials was fatigue. A direct relationship between the study drugs of lenalidomide with dexamethasone and fatigue during the clinical trials cannot be drawn as is evident by the data in Table 5.

Table 3- Efficacy of Lenalidomide in Terms of Complete Response in Experimental and Control/Comparison Groups

| Study           | Therapy | Complete Response | RBI   | ABI   | NNT | p-value   |
|-----------------|---------|-------------------|-------|-------|-----|-----------|
| Weber 2007      | L&D     | 25/177<br>(14.1%) | 2250% | 13.5% | 8   | P < 0.001 |
|                 | P&D     | 1/176<br>(0.6%)   |       |       |     |           |
| Dimopoulos 2007 | L&D     | 28/176<br>(15.9%) | 367%  | 12.5% | 8   | P < 0.001 |
|                 | P&D     | 6/175<br>(3.4%)   |       |       |     |           |
| Stadtmauer 2009 | L1      | 27/133<br>(20.3%) | 72%   | 8.5%  | 12  | P=0.028   |
|                 | L2+     | 26/220<br>(11.8%) |       |       |     |           |

For tables 3 & 4: RBI=relative benefit increase; ABI=absolute benefit increase; NNT=numbers needed to treat

Table 4- Efficacy of Lenalidomide in Terms of Overall Response in Experimental and Control/Comparison Groups

| Study           | Therapy | Overall response   | RBI   | ABI   | NNT | p-value  |
|-----------------|---------|--------------------|-------|-------|-----|----------|
| Weber 2007      | L&D     | 108/177(61.0%)     | 207%  | 41.1% | 3   | P< 0.001 |
|                 | P&D     | 35/176 (19.9%)     |       |       |     |          |
| Dimopoulos 2007 | L&D     | 106/176<br>(60.2%) | 151%  | 36.2% | 3   | P< 0.001 |
|                 | P&D     | 42/175 (24.0%)     |       |       |     |          |
| Stadtmauer 2009 | L1      | 89/133 (66.9%)     | 17.8% | 10.1% | 10  | P=0.060  |
|                 | L2+     | 125/220<br>(56.8%) |       |       |     |          |

Table 5- Adverse Events Reported in Lenalidomide and Control/Comparison Groups

| Study           | Therapy | Incidence of VTE | NNH | p-value   | Incidence of fatigue | NNH   | p-value      |
|-----------------|---------|------------------|-----|-----------|----------------------|-------|--------------|
| Weber 2007      | L&D     | 26/177 (14.7%)   | 9   | P < 0.001 | 11/177 (6.2%)        | -1000 | P < 0.001    |
|                 | P&D     | 6/175 (3.4%)     |     |           | 11/175 (6.3%)        |       |              |
| Dimopoulos 2007 | L&D     | 13/176 (7.4%)    | 25  | P < 0.001 | 11/176 (6.2%)        | 36    | P < 0.001    |
|                 | P&D     | 6/175 (3.4%)     |     |           | 6/175 (3.4%)         |       |              |
| Stadtmauer 2009 | L1      | 14/133 (10.5%)   | -55 | P = 0.63  | 10/133 (7.5%)        | -12   | Not reported |
|                 | L2+     | 27/220 (12.3%)   |     |           | 13/220 (15.9%)       |       |              |

VTE=venous thromboembolism; NNH=numbers needed to harm; please note that the -55 means that 55 patients should be treated in the L1 group to prevent one case of VTE and -1000/-12 means that 1000/12 patients should be treated in L&D/L1, respectively, to prevent one case of fatigue

## DISCUSSION

Lenalidomide (Revlimid) plus dexamethasone is considered a treatment for multiple myeloma patients who have had at least one prior therapy regimen since the FDA approved it in mid-2006 due to the overwhelming results of the trials discussed in this systematic review.

Lenalidomide is also FDA-approved for myelodysplastic syndrome patients. Lenalidomide dosing amount and schedule is affected in patients with renal impairment. Contraindications to the use of lenalidomide include hypersensitivity to the drug or any constituents in its formulation. Boxed warnings issued by the FDA concern hematologic toxicity, thromboembolism and pregnancy. Hematologic toxicity is exhibited in the majority of patients who are on lenalidomide in the forms of neutropenia and thrombocytopenia to the severity that complete blood counts (CBC) are routinely used in treatment regimens. Lenalidomide has been correlated with a higher incidence of venous thromboembolism in patients on combination therapy with dexamethasone. Finally, since lenalidomide is derived from the parent compound thalidomide, a known teratogen, pregnancy needs to be avoided in patients taking lenalidomide.

The articles strictly studied the use of lenalidomide in combination with dexamethasone in patients who had one or more relapses of their multiple myeloma. An obvious limitation to the studies was not evaluating if lenalidomide could be as effective in patients with newly diagnosed multiple myeloma without a history of treatment or relapse. In the study of relapsed multiple myeloma, the patients averaged a greater amount of time since diagnosis than patients who are newly diagnosed. Therefore, the relapsed patients were farther along in the natural disease progression and also had been exposed to more toxic treatments than newly diagnosed patients. These factors in the study are a limitation to the overall efficacy of lenalidomide plus dexamethasone in preventing multiple myeloma disease progression and inducing complete and overall responses.

## CONCLUSION

Based on the data presented and calculated from the studies, lenalidomide with dexamethasone is an effective treatment to induce longer remissions than just dexamethasone alone in patients with relapsed multiple myeloma. The efficaciousness of lenalidomide with dexamethasone was demonstrated through statistically significant longer time to progression of the disease state and higher complete and overall responses in comparison to placebo with dexamethasone. The safety of lenalidomide with dexamethasone for patients is jeopardized by an increase in incidence of venous thromboembolism as well as other events not statistically represented in this analysis like neutropenia and thrombocytopenia. In the future, randomized control trials should evaluate lenalidomide with dexamethasone in newly diagnosed patients without prior treatment to further assess the efficacy of this combination treatment in induction of remissions for multiple myeloma patients.

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