

# Thalidomide— and lenalidomide— associated thromboembolism

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With no clinical trials in the offing that could help determine the best way to prevent thromboembolism, and no requirement for drug suppliers to more vigorously inform patients, it's up to clinicians to warn those under their care that VTE is a potentially life-threatening complication of thalidomide and lenalidomide treatment.

The package insert for thalidomide (Thalomid) reports that the rate of venous thromboembolism (VTE) among multiple myeloma patients who receive thalidomide and dexamethasone is 23% compared with 5% in patients receiving dexamethasone alone.<sup>1</sup> The package insert for lenalidomide (Revlimid) states that the risk of VTE is significantly higher for multiple myeloma patients treated with lenalidomide combination therapy. However, it does not give specific details.<sup>2</sup>

VTE—defined as deep vein thrombosis or pulmonary embolism—is a serious complication. The risk increases significantly when thalidomide or lenalidomide is co-administered with standard chemotherapeutic agents (such as doxorubicin, dexamethasone, melphalan [Alkeran], and/or prednisone).<sup>3</sup>

**Symptoms of deep vein thrombosis include** pain, redness, swelling, and dilation of surface veins. **Symptoms of pulmonary embolism include** sudden-onset dyspnea; rapid breathing; chest pain worsened by breathing, cough, and coughing up blood. **In severe cases, symptoms may include** cyanosis, rapid heart rate, hypotension, shock, loss

of consciousness, and even death.

The RADAR project (Research on Adverse Drug Events And Reports) of Northwestern University conducted a review of the literature published from 1998 to 2006 for reports of thalidomide- or lenalidomide-treated patients with VTE.<sup>3</sup> Overall, VTE occurred in 12% of thalidomide-treated cancer patients (585 reports among 4,862 patients) and 8% of lenalidomide-treated cancer patients (110 reports among 1,474 patients).

Most VTE reports were among multiple myeloma patients and ranged from 0% to 40%. When prophylaxis was not administered, VTE rates in individual clinical trials were a median of 9% with thalidomide-dexamethasone and 14% with lenalidomide-dexamethasone. However, VTE rates were often (although not always) less than 10% when prophylaxis was administered. **Prophylactic options include** low-molecular-weight heparin, full-dose warfarin, or aspirin.

## Actions taken

Connecticut Attorney General Richard Blumenthal addressed safety concerns with thalidomide in a Citizen's Petition filed with the US Food and Drug Administration (FDA) in May 2005.<sup>4</sup> **The petition recommended that the FDA:**

## Fast Facts

Thalidomide (Thalomid) and its analogue lenalidomide (Revlimid) are immunomodulatory agents. Thalidomide in combination with dexamethasone has been approved by the US Food and Drug Administration (FDA) for the treatment of newly diagnosed multiple myeloma and for certain conditions associated with erythema nodosum leprosum—leprosy. Lenalidomide is FDA approved for certain types of low- or intermediate-risk myelodysplastic syndromes associated with the deletion 5q cytogenetic abnormality. Lenalidomide in combination with dexamethasone is also approved for the treatment of multiple myeloma in patients who have received at least one prior therapy.

**Side effects occur in more than 20% of multiple myeloma patients treated with thalidomide. They include** peripheral neuropathy, constipation, sensory neuropathy, confusion, hypocalcemia, edema, dyspnea, thrombosis/embolism, and rash/desquamation.<sup>1</sup>

**Side effects also occur in more than 20% of multiple myeloma patients treated with lenalidomide/dexamethasone. They include** constipation, fatigue, insomnia, muscle cramp, diarrhea, neutropenia, anemia, asthenia, pyrexia, nausea, headache, peripheral edema, dizziness, and dyspnea.

- require the supplier of thalidomide to strengthen the drug's "black-box" warning statement;
- supplement the labeling with additional bolded warnings;
- conduct a phase IV clinical trial that addresses prospectively the risks and benefits of alternative efforts to reduce the development of blood clots;
- mail a "Dear Healthcare Professional" letter notifying prescribers of increased potential for serious blood

## Resources

Both thalidomide and lenalidomide are only available through Celgene's restricted distribution programs—STEPS ([www.thalomid.com/steps\\_program.aspx](http://www.thalomid.com/steps_program.aspx)), and RevAssist ([www.revlimid.com/mm\\_ra.aspx](http://www.revlimid.com/mm_ra.aspx)), respectively—which aim to prevent severe, life-threatening birth defects. The use of both drugs is mostly for the treatment of multiple myeloma.

clots when thalidomide is used in combination with other therapies;

- expand the risk-management program to ensure the drug's safe use and take all other actions necessary to protect the integrity of that risk-management program.

By May 2006, the FDA had granted some requests outlined in the Citizen's Petition.<sup>5</sup> However, the FDA indicated that while it had considered requiring a phase IV trial of alternative an-

tithrombotic prophylactic agents, the agency had decided against supporting the recommendation. Instead, the FDA requested, and the sponsor, Celgene, agreed, to conduct an epidemiologic study of selected patients in the STEPS program to provide information on thromboembolism prophylaxis and treatment. (STEPS is a Celgene-restricted distribution program for thalidomide. See resources box at left.)

The FDA also decided against requiring expansion of the STEPS program to include information on VTE for all thalidomide-treated patients because it would be too burdensome. The expansion of the STEPS program would require only two additional questions: "What agents are you taking for prevention of a blood clot?" and "Have you experienced a blood clot?"

## Recommendations

Patients taking thalidomide or lenalidomide combination therapy for cancer treatment may benefit from prophylactic anticoagulation or aspirin. Unfortunately, the best method of prophylaxis for individual patients is unknown. **Clinical trials are needed to determine this, but for now, none is planned. As a result, we strongly recommend that:**

- patients and physicians watch for the signs and symptoms of VTE;
- patients seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or swelling of the extremities.

## Editor's Note:

For a related article on this topic, see our November 2006 issue, page 719, "Low-molecular-weight heparins in the prevention and management of malignancy-related venous thromboembolism," by Casey L. O'Connell, MD, Ilene C. Weitz, MD, and Howard A. Liebman, MD. You can read it online at [www.CommunityOncology.net/journal/articles/0311719.pdf](http://www.CommunityOncology.net/journal/articles/0311719.pdf).

## References

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