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**Thalidomide-associated thromboembolism in off-label clinical settings: An analysis of pharmacovigilance efforts of the manufacturer and the Food and Drug Administration (FDA)**

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## **ABSTRACT:**

**Purpose:** Although thalidomide was granted Food and Drug Administration (FDA) approval in 1998 for erythema nodosum leprosum, its use has been exclusively “off-label” for cancer. Thromboembolic toxicity concerns arose during a clinical trial where deep vein thrombosis (DVT)/pulmonary embolism (PE) occurred in 28% of multiple myeloma patients who received concomitant chemotherapy and thalidomide. Herein, we investigated the clinical characteristics and completeness of all adverse event (AE) reports for thalidomide-associated thromboembolism among oncology patients and discuss patient safety implications of adverse events associated with “off label” usage of this agent.

**Methods:** Investigators from the Research on Adverse Drug Events and Reports project (RADAR) reviewed AE reports obtained from the FDA and a literature review. Clinical information and reporting quality assessments were made for thalidomide-associated DVT/PE in the clinical trial setting (n=49) and the clinical practice setting (n=141). Incidence rates were estimated from 39 clinical trials with 1,784 thalidomide-treated patients.

**Results:** One-hundred eighty thalidomide-associated thromboembolism AE reports were reported directly to the manufacturer (49 from clinical trials and 131 from non-clinical trial setting), and 10 cases reported to the FDA. DVT/PE occurred after a median duration of 52 days thalidomide (range, 6 to 469 days). Thromboembolism was most likely to occur with thalidomide-chemotherapy co-administration (17% versus 13% with thalidomide-corticosteroids and 5% with thalidomide;  $p < 0.0001$  for each comparison).

**Conclusions:** AE information identified high rates of thalidomide-associated thromboembolism among cancer patients receiving concomitant chemotherapy. Dissemination of safety information to physicians via revisions in the package insert was delayed by two years and currently does not include prophylaxis recommendations. Improvements in safety-related dissemination efforts are needed to assist physicians who prescribe thalidomide as an “off-label” cancer therapy.

## **PURPOSE:**

More than half of the serious adverse effects of drugs are discovered seven or more years after Food and Drug Administration (FDA) approval.<sup>1,2</sup> Delayed identification of serious adverse drug event signals is especially important for cancer drugs because their low therapeutic index makes it difficult to distinguish adverse events from cancer-related illness. A recent example of such a delay occurred among cancer patients who received thalidomide-containing chemotherapeutic regimens. The sole FDA-approved clinical indication for thalidomide, based primarily on decades of observational experiences, is treatment of erythema nodosum leprosum, a cutaneous complication of leprosy.<sup>3,4</sup>

Shortly after receiving FDA approval in 1998, a phase II clinical trial identified significant clinical activity for thalidomide as treatment for relapsed/ refractory multiple myeloma.<sup>5</sup> Although previous clinical trials of thalidomide as a cancer agent in the 1960s had not identified significant antineoplastic activity, this phase II trial had been initiated with a focus on anti-angiogenesis rather than on cytotoxicity.<sup>6,7</sup> Based in large part on the findings from the Arkansas study and subsequent phase II clinical trials, almost all of the 77,000 patients who received thalidomide between 1998 and 2003 had a diagnosis of cancer, making thalidomide the only FDA approved drug whose use is almost exclusively in “off-label” clinical settings.<sup>8</sup>

Pharmacovigilance for thalidomide is among the most intensive for any drug used today. In 1961, identification of thalidomide-induced teratogenicity led to its withdrawal from clinical use worldwide and was the impetus for a reorganization of the FDA.<sup>3,9,10</sup> A condition of the 1998 FDA approval of thalidomide was the requirement that all health care personnel and patients involved with thalidomide treatments participate in a teratogenicity-prevention education effort, the System for Thalidomide Education and Prescribing Safety (STEPS).<sup>3,11</sup> In 2001, reports from two clinical trials with cancer patients unexpectedly identified rates of 28% and 43% for the development of deep venous thrombosis (DVT) and pulmonary embolism (PE) when thalidomide-containing chemotherapy regimens were administered, raising concern that severe toxicities other than teratogenicity might be associated with thalidomide treatment.<sup>12,13</sup> However, only 27 reports of this toxicity (all but one associated with cancer patients) were identified with prospective monitoring of patient data recorded in the first 18 months of the STEPS program, raising concern that many of the large number of oncologists who prescribe thalidomide in non-clinical trial settings might be unaware of this potentially fatal adverse drug event.<sup>8</sup> FDA restrictions limit vendor-originated marketing and physician education regarding off-label use of thalidomide.<sup>14</sup> This restriction applies to both efficacy and toxicity information.

The recently initiated Research on Adverse Drug Events and Reports (RADAR) project reviews in detail adverse drug reaction (ADR) reports for many pharmaceutical agents.<sup>15,16,17</sup> By reviewing all reported thalidomide-associated thromboembolism cases, RADAR investigators had the opportunity to provide a comprehensive update on the clinical characteristics and occurrence rates of thalidomide-associated thromboembolism

and to evaluate the completeness of adverse event reporting from the clinical trial versus observational setting.

## **METHODS:**

### Case identification and data collection-

The RADAR project is a National Cancer Institute (NCI) funded collaboration of oncologists, clinical pharmacologists, pharmacists, and statisticians affiliated with The Robert H. Lurie Comprehensive Cancer Center of Northwestern University; an NCI-designated comprehensive cancer center. The program is designed to identify and report on potentially fatal adverse reactions with cancer drugs that occur either during clinical trials or as part of cancer care in a non-clinical trial setting. RADAR investigators obtained case descriptions of thalidomide-associated thromboembolic events reported to the FDA's Adverse Event Reporting System (AERS) or in the published literature between January 1, 1998 and December 31, 2003.

AERS data were reviewed for the following information: date of adverse event report, pharmacovigilance program to which the case was initially reported (drug manufacturer or MedWatch), clinical trial (yes/no), and patient characteristics including socio-demographics, clinical and laboratory findings, use of prophylactic warfarin and/or low molecular weight heparin, diagnosis of DVT and/or PE, types and dates of use of chemotherapeutic drugs and/or corticosteroids, and participation in a clinical trial, treatment, and outcome. Information was collected through the use of a case report form validated in our initial study of thalidomide-associated thromboembolism. The case definition included use of thalidomide as an anti-cancer agent and clinical and/or laboratory evidence of thromboembolism. Diagnostic methods included Doppler vascular flow studies, vascular ultrasound, computerized tomography (CT) scans of the chest, and/or ventilation-perfusion (V/Q) scans. Clinical trial reports from the published literature were reviewed for information on thalidomide-associated thromboembolism incidence rates. Published clinical reports were carefully assessed for "double-counting" of patients. Medline search terms used for the literature review were thalidomide, thromboembolism, DVT, and PE.

### Data analysis

Based on our prior RADAR findings for other cancer drugs, we hypothesized that data reporting would be best for adverse events that occurred in the clinical trial setting.<sup>18,19</sup> We compared the completeness and diagnostic certainty of adverse event reports for cancer patients enrolled in clinical trials with those reports from patients treated outside of a clinical trial. Completeness was based on analysis of the presence or absence of information on the case report form for individual clinical elements, primarily patient age and gender, dose of drug, date of diagnosis of thromboembolism, and tests used to confirm the diagnosis. Diagnostic certainty was assessed by independent review of each case history by two study investigators and was characterized as probable (positive finding on ultrasound, CT, Doppler studies, or V/Q scans) or incompletely reported (no

mention of findings from each of the various diagnostic tests). Thalidomide was considered a possible cause of the thromboembolic event if at least one dose of thalidomide had been prescribed before the onset of symptoms of a thromboembolic event. Comparisons were made between the completeness of the cases reported to the drug manufacturer from both clinical and non-clinical trial settings and the cases reported directly to the FDA's MedWatch program using univariate optimal discriminate analysis.<sup>20,21</sup> Additional completeness comparisons generally focused on cases reported from the clinical trial versus non-clinical trial settings. We also compared rates of thromboembolic events for thalidomide as monotherapy, or when used in conjunction with other chemotherapeutic agents, corticosteroids or immunologic therapies statistically using pairwise Fisher's exact tests.

## RESULTS

A total of 190 case reports of thromboembolic adverse events in thalidomide-treated patients were identified in the AERS database: 180 cases were reported initially to the drug manufacturer (26% from the clinical trial setting and 69% from the non-clinical trial setting including STEPS), and 5% were reported directly to MedWatch. The annual number of reports of thalidomide-associated thromboembolism cases among cancer patients was greatest for events reported directly to the manufacturer from the non-clinical trial setting, reaching its maximum of 46 annual reports in 2002, while annually fewer than three such cases were reported directly to MedWatch (Figure 1).

Approximately 60% of the reported cancer patients with thalidomide-associated thromboembolism were male, with a median age of 60 years (range, 15 to 89 years). The median duration of thalidomide prior to thromboembolism was 52 days (range, 6 to 469 days). Thalidomide was used for the treatment of multiple myeloma (100 patients), glioblastoma multiforme/glioma (25 patients), renal cell carcinoma (10 patients), colorectal carcinoma (6 patients), myelodysplastic syndrome (7 patients), melanoma (5 patients), prostate cancer (5 patients), and miscellaneous cancer diagnoses (27 patients). Fewer than 5% of the case reports included information indicating that patients had received prophylaxis with warfarin or low molecular weight heparin. Seventy-eight percent of the case reports described patients who had developed DVT, 21% had developed both a DVT and a PE, and 1% had developed a PE alone. While 13% of the case reports described patients who died shortly after the onset of thalidomide-associated thromboembolic complications, only 4% of the case reports included text indicating that the fatality was directly related to a DVT or PE. Compared to patients who had received thalidomide through a clinical trial, patients in the non-clinical trial setting were three times less likely to have received concomitant chemotherapy (24% versus 70%,  $p < 0.0001$ ), and 45% less likely to receive concomitant corticosteroids (45% versus 81%,  $p < 0.0001$ ).

Thirty-nine prospectively monitored clinical trials with 1,784 thalidomide-treated patients provided detailed information on thromboembolism among thalidomide-treated patients (Table 1). The most common clinical diagnosis was multiple myeloma. Incidence rates varied according to diagnosis, stage, and other concurrent therapy. When thalidomide

was used as a single agent, the incidence of thromboembolism was 5%,<sup>22-27</sup> versus 13% among patients who received concomitant corticosteroids<sup>28,29</sup> and 17% among patients who received concomitant chemotherapy ( $p < 0.0001$  for each comparison).<sup>30,31</sup> Additionally, in one phase II and one phase III clinical trial, both of which closely compared combination chemotherapy regimens with and without thalidomide, those patients treated with the non-thalidomide containing regimens had 3% and 4% rate of thromboembolic complications versus 43% and 28%, respectively, when thalidomide was added to the treatment regimen.<sup>13,30</sup> Among thalidomide-treated patients with multiple myeloma, the most common thalidomide-treated malignancy in the United States, thromboembolism rates ranged from a low of 1 in 30 individuals treated with concomitant administration cyclophosphamide, etoposide, and cisplatin to a high of about 1 in 3 individuals treated with concomitant administrations of doxorubicin containing regimens. Of note, in several clinical trials with concomitant corticosteroids or chemotherapy, identification of high rates of thromboembolism among initial patients in the study often prompted investigators to include prophylactic warfarin or low molecular weight heparin among subsequent patients.<sup>28,32-33</sup>

Data completeness varied according to clinical trial participation and whether the report was submitted directly to the FDA or the manufacturer (Table 2). Between 59% and 90% of the adverse event reports describing cancer patients enrolled in clinical trials and reported directly to the manufacturer, included information on the dates of administration of thalidomide, date of onset of thromboembolism, number of days after thalidomide initiation prior to the occurrence of the thromboembolism, and the diagnostic tests used to confirm the diagnosis of a DVT or PE. In contrast, these data were included in only 17% to 28% of adverse event reports submitted directly to the manufacturer for patients not enrolled in clinical trials, and in 10% to 40% of the adverse event reports submitted directly to the FDA ( $p < 0.0001$  for each comparison). The three sources of adverse event reports had similar rates of recording of information on patient age, gender, dose of thalidomide, and outcome (survival versus death as a result of the DVT or PE).

## DISCUSSION

This study describes the clinical characteristics of thalidomide-associated thromboembolic complications. Thalidomide-associated DVT/PE were reported for persons with all types of cancer, occurring at a median of 52 days after treatment initiation. In 5% of the cases, thromboembolism occurred within two weeks of thalidomide initiation. The mean incidence rates of these adverse events were 1.5 and 3-fold greater when chemotherapy was also administered in comparison to regimens with concurrent corticosteroids or single-agent thalidomide, respectively. In interpreting our findings several factors should be considered.

The pathophysiology of thalidomide-associated thromboembolism in cancer patients is not fully understood. The risk of thromboembolism is increased among cancer patients, many of whom have activated protein C resistance or elevated levels of Factor VIII and von Willebrand factor.<sup>34,35</sup> Development of thromboembolism early in the course of thalidomide-therapy for cancer patients who are receiving concomitant chemotherapy

regimens suggests that increased activation of tissue factor in the plasma membrane of apoptotic tumor cells may be important.<sup>31,36,37</sup> Among persons with multiple myeloma, the risk of DVT or PE has been reported to be 2.5 fold greater among newly diagnosed patients in comparison to those who had received prior therapy.<sup>38</sup> Chemotherapy-induced endothelial cell damage may be aggravated by a thalidomide-induced increase in integrin levels, which in turn can enhance tumor cell adhesion.<sup>39</sup> Rates of endothelial cell damage and subsequent development of DVT or PE will undoubtedly vary according to chemotherapeutic regimen, with especially high rates of thalidomide-associated thromboembolism being noted among multiple myeloma patients who received concomitant doxorubicin-containing regimens, brain cancer patients who received concomitant carmustine, and renal cell cancer patients who receive concomitant gemcitabine and 5-fluoruracil.<sup>30,31,40</sup> Several clinical trials reported that after identifying high rates of thalidomide-associated thromboembolism among early participants, addition of prophylaxis with warfarin or low molecular weight heparin decreased the rate of thromboembolic complications among subsequent patients in the studies.<sup>28,32,36,41,42</sup>

Our findings have practical implications related to patient safety efforts for thalidomide, the cornerstone of which in the United States and foreign countries are based on controlling access to the drug; educating physicians, pharmacists, and patients; and monitoring compliance with precautions designed to ensure that fetal exposure to the drug does not occur.<sup>45-47</sup> Prior to filling new thalidomide prescriptions, providers are queried about factors related to teratogenicity, and educational material that emphasizes teratogenicity-related precautions is provided to patients. The STEPS program requests basic demographic and clinical information on all thalidomide-treated patients, including dose and schedule of drug, and indication for use. Despite extensive communications between health professionals and STEPS program representatives in the United States, only six thromboembolism cases were reported by health care providers directly to STEPS program representatives. In 2002, the pharmaceutical manufacturer for thalidomide indicated that the STEPS program might be modified after reviewing the first four-year experience with the program. One potential modification would be to include queries related to diagnosis, treatment, and prophylaxis of thromboembolism, a clinical event that, is probably the most common serious adverse event associated with thalidomide use in cancer patients. Because of the comprehensive nature of the STEPS program, these queries could provide information on exposure-adjusted incidence rates for thalidomide-associated thromboembolism according to patient-, disease-, prophylaxis regimen-, and treatment-related clinical considerations. However, even without this modification, concern exists that patient safety efforts are compromised as, for cost reason alone, a steadily increasing number of cancer patients in the United States are purchasing thalidomide from non-United States countries, thereby circumventing both STEPS and routine patient education efforts.<sup>48</sup>

Other mechanisms for disseminating safety-related clinical information are via package insert materials and pharmaceutical representatives, sources that are routinely used for dissemination of clinical information for all pharmaceutical agents. In October 2003, two years after the initial reports of thromboembolic events were reported in the medical literature, the pharmaceutical manufacturer revised the package insert to indicate that

thalidomide-treated cancer patients may have an increased incidence of pulmonary embolism, deep vein thrombophlebitis, thrombophlebitis, or thrombosis, and that it was not known if concomitant therapy with other medications including anticancer agents, were a contributing factor.<sup>70</sup> In contrast, our analysis, as well as the phase III clinical trial from Zangari et al, highlight the likelihood that concomitant administration of thalidomide and doxorubicin is associated with a marked increase in the rates of venous thromboembolism. The revised package insert does not include information on the potential benefits of coumadin or low molecular weight heparin prophylaxis, although several studies report marked decrements in venous thromboembolism rates when antineoplastic chemotherapy/thalidomide-containing regimens are accompanied by administration of these agents.<sup>28,32,33,73</sup> In contrast, pharmaceutical sales representatives are prohibited by FDA regulation from disseminating information on thalidomide-associated venous thromboembolism to physicians who prescribe thalidomide primarily in off-label settings such as for multiple myeloma and other malignancies.

Our results have policy implications. Following the presentation of the preliminary findings of this study at the American Society of Hematology conference in December 2004, the Office of the Attorney General of Connecticut requested that the RADAR research team provide their Office with a complete copy of the presentation as well as suggested recommendations for improvement. [Personal communication from Robert Deichert, February 3, 2005] This correspondence highlighted particular concern with thalidomide as it is the only FDA-approved drug whose use is almost exclusively in off-label clinical settings. As noted earlier, information on this toxicity is not included in materials distributed by pharmaceutical sales representatives or distributed via the STEPS program to physicians, pharmacists, and patients. The currently available, but incomplete description of clinical information on this toxicity was added to the FDA approved package insert two years after the toxicity was initially identified. Despite safety concerns, thalidomide is the only drug recommended as an off label therapy in the 2004 Medicare Demonstration Project of a comprehensive pharmaceutical reimbursement program.<sup>44</sup> Policy makers should consider direct dissemination of comprehensive information on thromboembolism as well as recommendations for prophylaxis for Medicare patients with cancer who receive thalidomide concomitantly with antineoplastic agents. Concerns over problems with dissemination of safety-related information with off-label use of cancer agents of thalidomide mirror those reported previously for veno-occlusive disease associated with off-label use of gemtuzumab ozogamycin with traditional anti-neoplastic agents for younger persons with acute myeloid leukemia.<sup>71</sup> More broadly, there is a need to improve both the timeliness and completeness of safety related information provided to cancer patients who receive chemotherapy in off-label clinical settings, a scenario that accounts for over half of all oncology drug use today.

There are several limitations to our study. First, thromboembolism is known to occur at high rates among persons with many different types of cancer, regardless of the type of treatment used. However, the finding of a 14-fold and three-fold increase in the rate of thromboembolism events among multiple myeloma patients and renal cell cancer patients, respectively, who received thalidomide and chemotherapy in comparison to similar patients who received identical chemotherapy regimens without thalidomide

suggests that thalidomide use can increase the risk of thrombosis among cancer patients. Second, more information is needed on the importance of other thrombosis-related clinical factors such as concomitant medications, thromboembolism prophylaxis, and tumor type and burden. Third, adverse events varied in their completeness, with reports from clinical trials being more complete than those obtained from clinical observation settings. While only 3% of all cancer patients participate in clinical trials, their participation facilitates rapid identification of serious adverse drug reactions for cancer drugs. Fourth, the number of reported thalidomide-associated thromboembolic complications peaked in 2002 following the first publications of case reports and case series of this previously unreported toxicity. It is not known if this decline is due to a decreased incidence of thromboembolic complications with thalidomide-chemotherapy regimens as a result of increasing frequency of use of prophylaxis regimens, or decreasing frequency of reporting of thromboembolic complications to the manufacturer or the FDA. Broadening the scope of the STEPS data collection effort to include clinical information related to thromboembolism could provide empirical support for one of the two alternative hypotheses.

Thromboembolism has emerged as one of the most serious adverse events associated with the use of thalidomide as a cancer drug, especially when concurrent chemotherapy is administered. The manufacturer should revise the package insert to highlight the high rates of thromboembolism reported when cancer patients are treated concomitantly with thalidomide and standard anti-neoplastic agents and the need to consider coumadin or low molecular weight heparin prophylaxis in these settings. If a thalidomide-associated thromboembolic complication occurs, physicians and/or pharmacists should report a comprehensive summary of the clinical details of this adverse event to the pharmaceutical manufacturer, the STEPS program, or to the FDA's MedWatch program.

**Table 1. Incidence of Thalidomide-associated Thromboembolism from Phase II and Phase III Clinical Trials.**

Author (Reference)	Cancer Type	# Patients	Medication	DV T	PE	DVT+ PE	%
			Thalidomide Alone				
Steurer <sup>49</sup>	Myelodysplastic Syndrome	7	None^	2	1	0	43
Escudier <sup>50</sup>	Renal Cell	40	None	6	0	3	23
Dallani <sup>51</sup>	Renal cell	19	None	1	2	N/A	16
Novik <sup>52</sup>	Renal Cell	27	None	2	0	0	7
Strupp <sup>26*</sup>	Myelodysplastic Syn	29	None	2	0	0	7
Mileshkin <sup>53</sup>	Myeloma	56	None	3	0	0	5
Motzer <sup>54</sup>	Renal Cell	26	None	1	0	0	4
Weber <sup>55</sup>	Myeloma	28	None	1	N/A	N/A	4
Kumar <sup>22</sup>	Myeloma	32	None	1	0	0	3
Rajkumar <sup>23</sup>	Myeloma	31	None	1	0	0	3
Li <sup>56</sup>	Renal Cell	34	None	0	1	0	3
Tosi <sup>27</sup>	Myeloma	65	None	1	0	0	2
Barlogie <sup>57</sup>	Myeloma	169	None	3	0	0	2
Abramson <sup>24</sup>	Ovarian	8	None	0	0	0	0
Drake <sup>25</sup>	Prostate	20	None	0	0	0	0
Kong <sup>58</sup>	Hepatocellular	23	None	0	0	0	0
Nathan <sup>59</sup>	Renal Cell	13	None^^	0	0	0	0
<b>Total for Thalidomide Alone</b>		<b>627</b>		<b>24</b>	<b>4</b>	<b>3</b>	<b>5</b>
			<b>With Chemotherapy</b>				
Desai <sup>30</sup>	Renal Cell	21	Gemcitabine and 5-Fluorouracil	5	4	0	43
Fine <sup>41</sup>	Glioma	40	Carmustine	5	4	3	30

Zangari <sup>12</sup>	Myeloma	50	VAD	13	0	1	28
Osman <sup>60</sup>	Myeloma	15	Dexamethasone, Doxorubicin	4	0	0	27
Schutt <sup>72</sup>	Myeloma	31	Dexamethasone, Vincristine	6	0	0	26
Urbauer <sup>41</sup>	Myeloma	14	CDEP	2	0	1	21
Figg <sup>13</sup>	Prostate	39	Docetaxel	8	0	0	21
Urbauer <sup>41</sup>	Mantle Cell Lymphoma	10	Rituximab	1	1	0	20
Horne <sup>61</sup>	Prostate	47	Docetaxel	9	N/A	N/A	19
Lee <sup>331</sup>	Myeloma	236	D-PACE	34	0	3	15
Zervas <sup>62</sup>	Myeloma	39	VAD	4	0	0	10
Minemma <sup>73</sup>	Myeloma	211	Dexamethasone, doxorubicin, low molecular weight heparin	15	3	1	19
Kroff <sup>63</sup>	Myeloma	60	Cyclophosphamide, Dexamethasone	4	1	0	8
Hwu <sup>64</sup>	Melanoma	12	Temozolomide	0	0	1	8
Zangari <sup>31</sup>	Myeloma	40	CDEP	1	0	0	3
Hwu <sup>65</sup>	Melanoma	38	Temozolomide	1	0	0	3
<b>Total with Chemotherapy</b>		<b>803</b>		<b>112</b>	<b>13</b>	<b>10</b>	<b>17</b>
			<b>With Corticosteroids</b>				
Cavo <sup>281</sup>	Myeloma	19	Dexamethasone	4	0	1	26
Weber <sup>55</sup>	Myeloma	40	Dexamethasone	8	1	0	15
Rajkumar <sup>66</sup>	Myeloma	50	Dexamethasone	6	1	0	14
Dimopoulos <sup>67</sup>	Waldenstrom's Macroglobulinemia	20	Clarithromycin, Dexamethasone	2	N/A	N/A	10
Coleman <sup>68</sup>	Waldenstrom's Macroglobulinemia	12	Clarithromycin, Dexamethasone	1	N/A	N/A	8
Anagnostopoulos <sup>32</sup>	Myeloma	47	Dexamethasone	3	0	1	8
Osman <sup>60</sup>	Myeloma	45	Dexamethasone	2	1	0	7

Alexanian <sup>29</sup>	Myeloma	21	Dexamethasone	0	0	0	0
Rajkumar <sup>69</sup>	Myeloma	100	Dexamethasone	14	N/A	N/A	14
<b>Total with Corticosteroids</b>		<b>354</b>		<b>40</b>	<b>3</b>	<b>2</b>	<b>13</b>
		<b>1784</b>		176	<b>20</b>	15	<b>35</b>

Abbreviations: DVT, deep venous thrombosis; PE, pulmonary embolism; Syn, syndrome; W, Waldenstroms. CDEP = cyclophosphamide, dexamethasone, etoposide, and cisplatin; D-PACE = dexamethasone, cisplatin, doxorubicin, and etoposide; VAD = vincristine, doxorubicin, and dexamethasone; CAD = cyclophosphamide, doxorubicin, and dexamethasone; N/A, not available.

\* Unspecified prophylaxis regimen administered from the beginning of study.

† Unspecified prophylaxis regimen administered after the thromboembolic event.

‡ Low molecular weight heparin with or without warfarin administered after thromboembolic event.

Low-dose aspirin administered after thromboembolic event.

Coumadin 1 mg/dl or aspirin administered after thromboembolic event.

^ Darbepoietin-alpha was administered concomitantly.

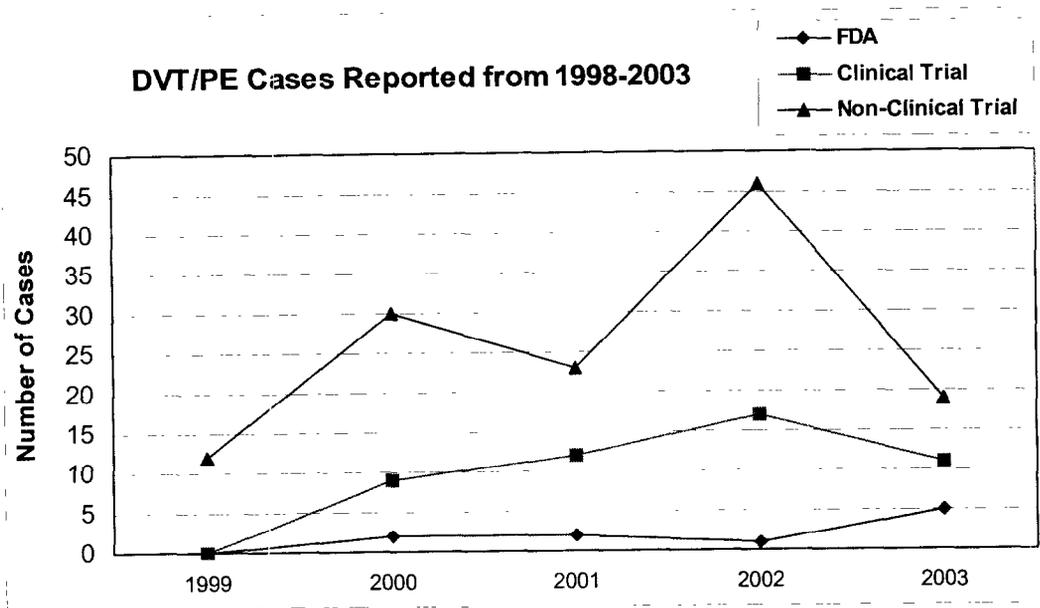
^^ Interferon was administered concomitantly.

**Table 2. Comparison of demographic, treatment, clinical and diagnostic completeness of thromboembolic complications amongst thalidomide-treated cancer patients in the FDA's Adverse Event Reporting System database.**

	<b>Clinical Trial Report to Manufacturer N=49 (%)</b>	<b>Non-Clinical Trial Report to Manufacturer N=131 (%)</b>	<b>Report to FDA N=10 (%)</b>	<b>p-value</b>
<b>Age</b>	98%	94%	90%	0.39
<b>Gender</b>	100%	96%	100%	0.29
<b>Indication</b>	100%	96%	100%	0.30
<b>Thalidomide-dosage</b>	92%	94%	100%	0.78
<b>Dates of administration</b>	76%	28%	10%	0.0001
<b>DVT/PE onset-Date(s)</b>	88%	28%	40%	0.0001
<b>Number of days until DVT/PE</b>	69%	23%	10%	0.0001
<b>Diagnostic-method</b>	59%	17%	40%	0.0001

Abbreviations: DVT, deep venous thrombosis; PE, pulmonary embolism; FDA, Food and Drug Administration.

**Figure 1. Thromboembolism Cases Reported to the FDA and Pharmaceutical Company [Clinical Trial versus Non-Clinical Trial] From 1998-2003.**



Abbreviations: DVT, deep venous thrombosis; PE, pulmonary embolism; FDA, food and drug administration.

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