

## Review

## Thalidomide

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**Despite its history as a human teratogen, thalidomide is emerging as a treatment for cancer and inflammatory diseases. Although the evolution of its clinical application could not have been predicted from the tragedy associated with its misuse in the past, its history serves as a lesson in drug development that underscores the need to understand the molecular pharmacology of a compound's activity, including associated toxicities. Here, we summarise the applications for thalidomide with an emphasis on clinical trials published over the past 10 years, and consider our knowledge of the molecular pharmacology of the drug in the context of clinical trial data, attempting to provide a mechanism-guided understanding of its activity.**

Thalidomide (figure 1) was synthesised in 1954 by the CIBA pharmaceutical company,<sup>1</sup> and prescribed as a sedative, tranquiliser, and antiemetic for morning sickness. Chemically similar to barbiturates, the drug became a popular sedative, marketed under at least 37 names worldwide,<sup>2,3</sup> though it was never approved by the US Food and Drug Administration (FDA) due in part to concerns raised about potentially irreversible neuritis and the drug's safety.<sup>4</sup> Initial reports of limb abnormalities—phocomelia, dysmelia, amelia, bone hypoplasticity—and other congenital defects—ear, heart, internal organs—were made by women who took as little as a single dose of thalidomide during gestation.<sup>2,5</sup> The highest risk for teratogenicity arose when the drug was taken between weeks 3 and 8 after conception.<sup>5,6</sup> About 10 000 children worldwide were born with malformations related to the use of thalidomide and, as a result, it was withdrawn from the European and Canadian markets in 1961 and 1962, respectively.<sup>6</sup> The drug resurfaced in 1965 as an effective treatment for erythema nodosum leprosum lesions and, in 1998, the FDA approved it for this indication.<sup>3</sup>

In 1994, D'Amato and colleagues<sup>1</sup> postulated that thalidomide-associated malformations were the result of the drug's interference with vasculogenesis, and that a similar mechanism might prevent the growth of blood vessels recruited by solid tumours. The ability of thalidomide to inhibit angiogenesis was confirmed in a rabbit cornea micropocket assay.<sup>1,7</sup> Establishment of thalidomide as an anti-inflammatory, immunomodulatory, and antiangiogenic compound inspired researchers to define its mechanism of action and clinical range. That a drug with antivasular side-effects that was originally prescribed as a sedative is now in clinical trials for vascular diseases with sedation considered to be the side-effect is ironic. Here, we review the basic science of thalidomide and summarise the mounting clinical trial data in inflammatory disorders and neoplasms.

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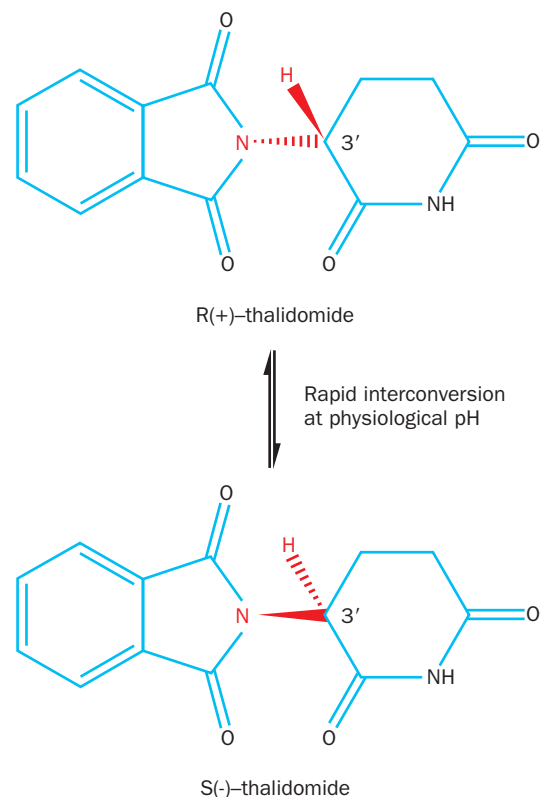


Figure 1: Structure of thalidomide enantiomers

### Structure and bioactivity

The thalidomide molecule is a racemic glutamic acid analogue, consisting of S(–) and R(+) enantiomers that interconvert under physiological conditions (figures 1 and 2).<sup>7</sup> The S(–) form potently inhibits release of tumour necrosis factor (TNF)  $\alpha$  from peripheral

### Search strategy

We searched MEDLINE and PubMed databases with the term thalidomide associated with the terms mechanism, pharmacology, analogues, and clinical trials. Historical information was taken from reviews. We restricted our search to English-language papers published between 1970 and 2003, and excluded clinical abstracts as a general rule. Articles were selected on the basis of their relevance in both basic science and clinical diseases.

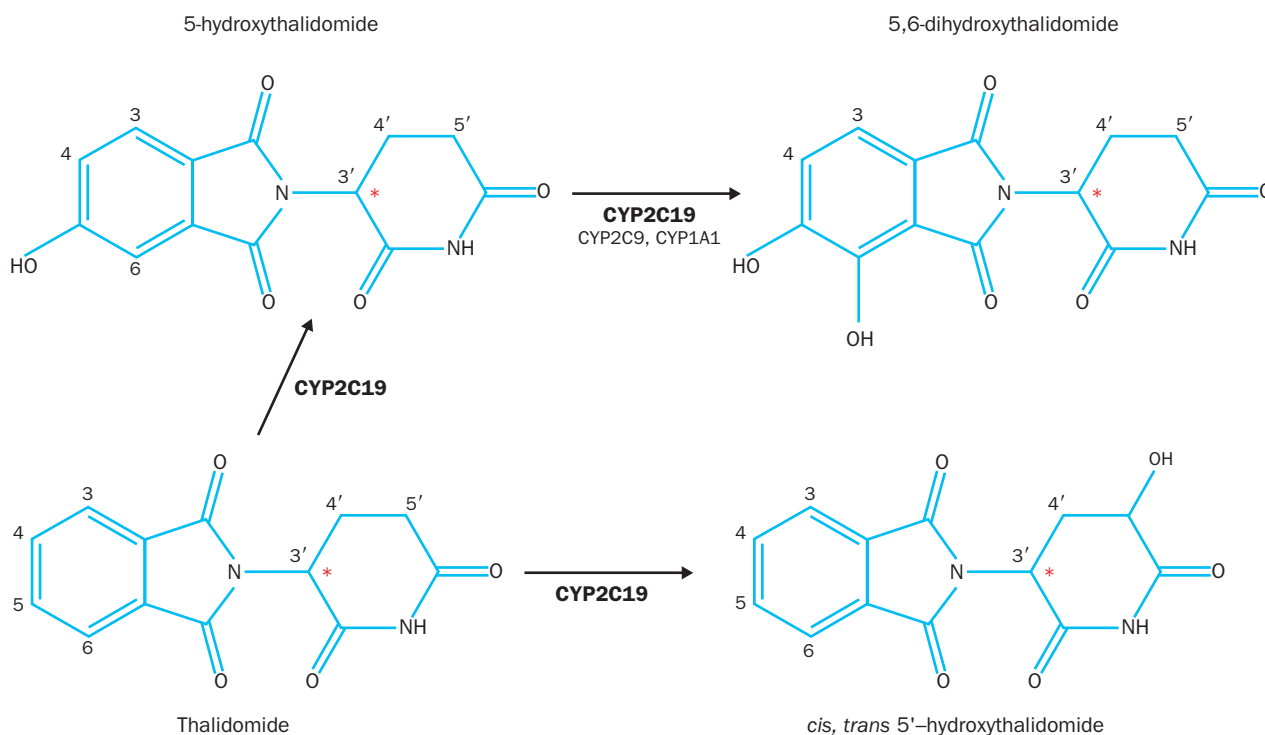


Figure 2: **Thalidomide metabolism by cytochrome P450 enzymes**  
\*3' chiral centre.

mononuclear blood cells,<sup>8</sup> whereas the R(+) form seems to act as a sedative, probably mediated by sleep receptors in the forebrain.<sup>9</sup>

One of the unique chemical aspects of thalidomide is that the parent compound undergoes spontaneous hydrolysis in aqueous solution at pH 7.0. Thalidomide

degradation results in more than 20 products, and its activity—eg, inhibition of microvessel formation or reduction of aortic endothelial cell proliferation—seems to depend on its metabolism.<sup>10</sup> The active metabolite seems to be generated by cytochrome P450 2C19 (CYP2C19) isozyme-mediated oxidation of thalidomide (figures 2 and 3).<sup>10</sup> However, there are some preliminary data from a human placental arterial model, indicating antiangiogenic activity without the addition of microsomes (Stirling D, Celgene, personal communication). Whether the metabolism of thalidomide contributes specifically to its immunomodulatory activity, therefore, remains unclear.

### Mechanism of action

The mechanisms that underlie the immunomodulatory, anti-inflammatory, and antiangiogenic properties of thalidomide are also unclear, although modulation of inflammatory cytokines such as TNF $\alpha$ ,  $\gamma$  interferon, interleukin 10, interleukin 12, cyclooxygenase 2 (COX-2), and possibly the nuclear factor  $\kappa$  B (NF- $\kappa$ B) transcription factor, are involved.

TNF $\alpha$  regulates inflammatory cascades and represents a therapeutic target in inflammatory diseases, some of which have been associated with raised concentrations of the cytokine in patients' tissues.<sup>11</sup> Thalidomide inhibits production of TNF $\alpha$  in lipopolysaccharide-induced human monocytes and mouse macrophages by enhancing degradation of its mRNA.<sup>12,13</sup> It also inhibits the production of tumour-

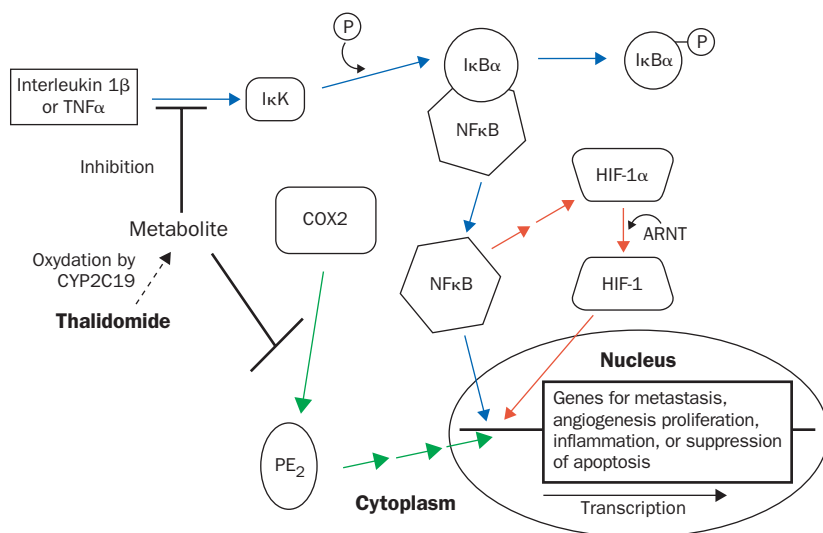


Figure 3: **Mechanisms by which thalidomide modulates immune responses and angiogenesis**

CYP2C19 oxidises thalidomide to active metabolite, which interferes with TNF $\alpha$  or interleukin 1 $\beta$ -induced activation of I $\kappa$ K. Inhibition of I $\kappa$ K prevents dissociation of I $\kappa$ B $\alpha$  from NF $\kappa$ B, precluding its nuclear translocation and induction of genes that function in cellular proliferation, inflammation, angiogenesis, and protection from apoptosis. Inactivation of NF $\kappa$ B also prevents induction of hypoxia inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ) accumulation, association with aryl hydrocarbon receptor nuclear translocator, nuclear translocation, and activation of inflammatory and angiogenic genes. Blue arrows=TNF $\alpha$ -mediated or interleukin 1 $\beta$ -mediated induction of inflammatory and angiogenic genes via NF- $\kappa$ B. Red arrows=TNF $\alpha$ -mediated or interleukin 1 $\beta$ -mediated induction of HIF-1 via NF- $\kappa$ B. Green arrows=COX2-mediated induction of prostaglandin E<sub>2</sub> (PE<sub>2</sub>) biosynthesis and up-regulation of angiogenic growth factor production. Multiple arrows=poorly understood pathways. Dotted arrow=unclear whether thalidomide's immunomodulatory activity depends on its metabolism to an active compound.

	Number of treated patients	Daily thalidomide dose (mg)	Response rate*	Reference
<b>Refractory myeloma</b>				
Thalidomide monotherapy	84	200–800	25%	73
	169	200–800	30%	74
	16	200–800	25%	77
	20	200–800	43%	78
	17	200–800	59%	85
	17	100–400	29%	79
	53	200–400	36%	81
	60	100–800	28%	82
	83	50–800	48%	84
	75	200–800	28%	86
	51	100–400	18%	25
	23	200–800	13%	87
Thalidomide and steroids	38	100+dexamethasone	52%	90
	47	200–800+dexamethasone	47%	92
	21	Unknown+dexamethasone	57%	89
	37	100+dexamethasone	51%	91
Thalidomide, steroids, and chemotherapy	135	400+dexamethasone+PACE	54%	75
	38	400+DCEP	36%	75
	42	400+CED	78%	93
	24	50–200+clarithromycin+dexamethasone	93%	94
	4	50+VAD	100%†	95
<b>Newly diagnosed or untreated myeloma</b>				
Thalidomide monotherapy	16	200–800	38%	97
	28	200–600	36%	98
Thalidomide and steroids	26	200–800+dexamethasone	77%	97
	16	200–600+dexamethasone	72%	98

PACE=cisplatin/doxorubicin/cyclophosphamide/etoposide. DCEP=dexamethasone/cyclophosphamide/etoposide/cisplatin. CED=cyclophosphamide/etoposide/dexamethasone. VAD=vincristine/doxorubicin/dexamethasone. \*>50% reduction in urine or serum concentrations of paraprotein. Responses included ability to undergo peripheral blood stem cell transplant.

Table 1: Results of studies of thalidomide in refractory and newly diagnosed multiple myeloma

associated macrophages in rats with MAT-Lu tumours. The immunomodulatory and antiangiogenic effects of the drug probably produce an additive antitumour response. Thalidomide-mediated inhibition of immune responses and angiogenesis are probably interrelated because affected cytokines, such as TNF $\alpha$ , function in both processes. However, by contrast with the suppressive effect of thalidomide on TNF $\alpha$  production by monocytes and macrophages, interleukin-2-dependent superinduction of TNF $\alpha$  takes place in CD4<sup>+</sup> and CD8<sup>+</sup> T cells treated with thalidomide, indicating an elaborate pharmacology during an inflammatory response that is not yet understood.<sup>14</sup>

A dose-dependent inhibition of the cancer-associated growth factor interleukin 6 has been noted after treatment with thalidomide.<sup>15</sup> Likewise, the drug inhibits production of interferon  $\gamma$  in mitogen-stimulated peripheral blood mononuclear cells<sup>16</sup> and the stimulating effects of insulin-like growth factor 1 on chondrogenesis and limb-bud development;<sup>17</sup> thalidomide might inhibit growth factor-mediated activation of  $\alpha_v\beta_3$ -integrin genes,<sup>17</sup> thus preventing stimulation of angiogenesis in developing limb buds. Interference with integrin and growth-factor gene expression may contribute to immunomodulatory responses via NF- $\kappa$ B.<sup>18</sup> A similar effect of thalidomide on cancer cells would result in decreased production of integrins needed for angiogenesis. Results of molecular studies have resulted in the identification of several mechanisms whereby thalidomide is active in multiple myeloma.<sup>19</sup> These include: reduction of cell adhesion in multiple myelomas and related drug resistance;<sup>20</sup> induction of apoptosis;<sup>21</sup> inhibition of angiogenesis in the bone marrow;<sup>1</sup> and augmentation of immunity of multiple myelomas through stimulation of natural killer cells (with subsequent increase of interleukin-2-mediated T-cell proliferation and  $\gamma$ -interferon production) and increase in cytotoxicity of natural killer cells.<sup>22,23</sup>

TNF $\alpha$  (or interleukin 1 $\beta$ ) induces normoxic accumulation of the inflammatory and angiogenic factor hypoxia-inducible-factor 1 $\alpha$  in kidney cells by way of an unknown pathway via NF- $\kappa$ B.<sup>24</sup> Maybe, thalidomide abrogates hypoxia-inducible-factor 1 $\alpha$ -mediated activity by way of its anti-TNF $\alpha$  activity (figure 3)? Our knowledge of the mechanism of action of thalidomide thus indicates a primary role for cytokine modulation. In one report,<sup>25</sup> however, no decrease in TNF $\alpha$ , vascular endothelial growth factor (VEGF), or interleukin 6 concentrations were noted in patients who responded to thalidomide, suggesting that other mechanisms could be responsible for the drug's clinical activity.

The anti-inflammatory and antiangiogenic functions of thalidomide are controlled in part through the transcription factor NF- $\kappa$ B. This factor is located in the cytoplasm and is bound by inhibitory proteins—eg, I $\kappa$ -B $\alpha$  or other I $\kappa$ -B-like proteins. Once stimulated by inducers such as interleukin 1 $\beta$  or TNF $\alpha$ , a phosphorylation cascade results in dissociation of the inhibitory proteins from NF- $\kappa$ B, freeing it to activate the expression of genes involved in cell growth, suppression of apoptosis, metastasis, and immune and inflammatory responses.<sup>26–29</sup> Thalidomide-mediated inactivation of NF- $\kappa$ B takes place in various cells, including endothelial and epithelial cells, T cells, and myeloid cells (figure 3).<sup>26,30</sup> A thalidomide metabolite, such as 5-hydroxythalidomide, could possibly induce its immunomodulatory effects as well as its antiangiogenic effects. We propose that a metabolite of thalidomide needed for activity in our angiogenesis assays also inactivates NF- $\kappa$ B by interacting with a factor upstream of I $\kappa$ B $\alpha$  phosphorylation (figure 3). Studies are needed to elucidate the elaborate molecular pharmacology of thalidomide with emphasis on endpoints upstream of NF- $\kappa$ B, including the identification of a specific thalidomide-binding factor.

The discovery that thalidomide inhibits lipopoly-saccharide-mediated induction of COX-2 by destabilising

	Number of participants	Therapy	Daily thalidomide dose (mg)	Objective response*	Reference
<b>Cancer</b>					
Prostate	63	Thalidomide	200, 1200	18%†	113
	20	Thalidomide	100	15%†	115
	75	Thalidomide/docetaxel	200	51%‡, 35%†	116§
Renal cell	18	Thalidomide	100	17%	121
	26	Thalidomide	200–800	0%	122
	25	Thalidomide	600	9%	123
	40	Thalidomide	400–1200	5%	124
	19	Thalidomide	200–1200	10%	125
	29	Thalidomide	400–1200	4%	126
	21	Thalidomide+fluorouracil+gemcitabine	200–400	10%	127
Glioma	39	Thalidomide	800–1200	6%	129
	42	Thalidomide	100–500	5%	131
	18	Thalidomide	100	6%	130
Colorectal	18	Thalidomide+irinotecan	400	29%	132
Melanoma	17	Thalidomide	100	0%	121
	12	Thalidomide+temozolamide	100–400	50%	135
Breast	12	Thalidomide	100	0%	121
	28	Thalidomide	200–1200	0%	140
Ovarian	19	Thalidomide	100	0%	121
Head and neck	21	Thalidomide	200–1200	0%	142
Kaposi's sarcoma	17	Thalidomide	100	35%	62
	20	Thalidomide	200–1000	40%	63

\*Complete or partial response. †PSA reduction >50%. ‡Soft tissue response. §Includes data from Dahut WL, personal communication.

Table 2: Results of studies of thalidomide in non-haematological cancers

its mRNA and subsequent prostaglandin-E<sub>2</sub> biosynthesis might explain in part its antiangiogenic activity (figure 3).<sup>31</sup> COX-2 is highly expressed in various human cancers and is needed for angiogenesis in a rat corneal model.<sup>32,33</sup>

## Clinical applications

### Inflammatory and infectious conditions

#### Dermatological

Interest in thalidomide resurfaced in 1965 after, by chance discovery,<sup>3</sup> it was found to be beneficial in erythema nodosum leprosum, a vasculitic complication of leprosy characterised by painful subcutaneous nodules, fever, and other constitutional symptoms. Short-term improvement was seen in 52% of patients who received 100 mg four times daily in a double-blind, randomised trial against aspirin.<sup>34</sup> Responses were seen in 70–80% of patients on thalidomide versus 25% in other placebo-controlled trials, and maintenance doses of 25–100 mg per day have proved equally efficacious after controlling initial symptoms.<sup>3</sup> Results of a review of 15 years' experience and more than 4000 patients with the condition and treated with thalidomide showed that 99% of individuals responded to treatment with thalidomide within 24–48 h.<sup>35</sup> Thalidomide is first-line therapy for symptomatic, moderate-to-severe erythema nodosum leprosum, and can be used for the suppression and prevention of cutaneous disease.<sup>3</sup>

The granulomatous skin lesions of sarcoidosis, similar to those of erythema nodosum leprosum, were also effectively controlled with single-agent thalidomide in three small studies,<sup>36–38</sup> and the best responses, either partial or complete, were noted in seven of ten patients.<sup>38</sup> Raised concentrations of angiotensin converting enzyme were reduced with thalidomide in another report.<sup>36</sup> Activity in the visceral manifestations of sarcoidosis is less clear.

In non-randomised studies, thalidomide was moderately effective for the treatment of refractory, cutaneous lesions of lupus. Overall, clinical response rates ranged from 84% to 100% at daily doses of 50–400 mg, with the possibility of subsequent maintenance therapy

after initial response, mostly in patients refractory to other therapies.<sup>39,40</sup> In one study of thalidomide 300 mg daily,<sup>41</sup> erythrocyte sedimentation rates and  $\gamma$ -globulin concentrations improved, and steroid use was reduced by more than 50%. Results of studies conflict with respect to thalidomide's effect on visceral and articular lupus.<sup>41,42</sup> Thalidomide is considered second-line therapy in cutaneous lupus, based primarily on several reports of neurotoxicity and extent of relapse after discontinuation of therapy.<sup>39,40</sup>

Oral and genital lesions of Behçet's disease improved after treatment with thalidomide (100 mg or 300 mg) versus placebo in a randomised, controlled trial in 96 patients,<sup>43</sup> with complete responses reported in seven of 63 participants. Typically, oral lesions healed in 3–4 weeks, but recurrences were common after cessation of therapy. Findings of additional small series support mucocutaneous improvement with thalidomide monotherapy,<sup>44</sup> although its effects on uveitis are inconsistent.<sup>45</sup>

Graft-versus-host disease generally targets the skin, and can be quite debilitating after bone marrow transplantation. Results of a randomised, controlled study<sup>46</sup> of thalidomide 200 mg per day in 59 transplant patients, showed worsening of chronic graft-versus-host disease associated with reduced survival. Thalidomide prophylaxis is, therefore, not recommended. Overall response rates to the drug in high-risk or refractory, chronic graft-versus-host disease range from 20% to 88%, however, with acceptable toxicity.<sup>47</sup> In this setting, thalidomide seems useful as an adjunct to standard immunosuppressive therapy, rather than as first-line or single-agent treatment, where its role is limited at best.<sup>48,49</sup>

Case reports indicate that thalidomide monotherapy might also be useful in the following dermatoses: pyoderma granulorum, prurigo nodularis, porphyria cutanea tarda, and lichen planus.<sup>50</sup> The dermatological manifestation toxic epidermal necrosis, mediated in part by TNF $\alpha$ ,<sup>51</sup> was judged a good target for thalidomide. Unfortunately, in one study,<sup>51</sup> the drug exacerbated the disease, with greater mortality noted in the thalidomide-



	Proportion of patients affected		
	Thalidomide 200 mg <sup>73,90</sup>	Thalidomide 800 mg <sup>73,90</sup>	Placebo
<b>Side-effect</b>			
Constipation	2–35%	59%	0%
Fatigue	0–29%	48%	0%
Somnolence	34–38%	43%	11%
Neuropathy	8–12%	28%	0%
Dizziness	4–19%	28%	0%
Rash	16–25%	26%	31%
Mood alterations	5–22%	22%	3%
Oedema	3–8%	22%	0%
Tremor	0–10%	22%	0%
Nausea	4–13%	11%	3%
Headache	12–19%	11%	11%
Xerostomia	0–9%	–	6%
Leukopenia	0–25%	–	9%
Fever	0–22%	–	17%

Table 3: Reported toxicity of thalidomide in selected trials and according to revised thalidomide package insert (July, 1998; Celgene)

treated group than in controls. Thalidomide is, therefore, contraindicated in patients with toxic epidermal necrosis.

#### Rheumatological

The effect of thalidomide is variable in joint pain associated with refractory rheumatoid arthritis, a disease mediated in part by TNF $\alpha$ . Durable responses (80% complete or partial response), with therapeutic reductions in rheumatoid factor, were described in one report.<sup>52</sup> Combination treatment with thalidomide and methotrexate or pentoxifylline seems to have a beneficial effect.<sup>53,54</sup> However, large, controlled trials are necessary to further define thalidomide's use in rheumatoid arthritis in view of the efficacy of other anti-TNF $\alpha$  therapies in the disease. Ankylosing spondylitis, Still's disease, systemic sclerosis, Sjögren's syndrome, and other rheumatological disorders have also been treated with thalidomide, but only in a limited number of patients.<sup>55</sup>

#### Gastrointestinal

Crohn's disease, thought to be in part mediated by TNF $\alpha$  and interleukin 12, has been effectively controlled with thalidomide for short periods in steroid-dependent patients.<sup>56–58</sup> Clinical improvement was shown in stool frequency,<sup>57</sup> fistulae,<sup>58</sup> and the Crohn's disease activity index. Additionally, steroid requirements were reduced by more than half in all thalidomide-treated patients in one study.<sup>56</sup> Overall, clinical response rates ranged from 50% to 72%. Serum marker responses to thalidomide in this setting are of questionable importance (erythrocyte sedimentation rate, interleukin 12, C-reactive protein, TNF $\alpha$ ).<sup>57,59</sup> Thalidomide might also be beneficial in patients refractory to infliximab,<sup>60</sup> or as a maintenance adjunct to this drug.<sup>61</sup> Controlled, multicentre studies are underway to assess the drug's efficacy, since inflammatory bowel disease can have a variable clinical course.

#### HIV-1

Thalidomide has shown moderate activity in HIV-1-associated Kaposi's sarcoma. A phase II trial<sup>62</sup> of 17 patients given thalidomide 100 mg daily resulted in a 35% partial response rate; serum titres of human herpesvirus 8 were reduced in all assessable responders. In another trial,<sup>63</sup> with doses ranging from 200 mg to 1000 mg, treatment with thalidomide resulted in partial responses and stable disease in 40% and 10% of individuals, respectively. Haematological complications were rare.

Results of randomised, placebo controlled trials<sup>64,65</sup> of patients with painful oral aphthous ulcers associated with HIV-1 show overall response rates greater than 50%, and improvement in refractory, severe lesions with a 100–200 mg daily dose.<sup>66</sup> Responses to pain and burning sensations were prompt—usually less than 2 weeks—but relapses were frequent after discontinuation of therapy. Thalidomide is also effective for the treatment of gastrointestinal lesions.<sup>67</sup>

Cachexia and weight loss are common in the late stages of HIV/AIDS. Results of several studies have shown improved weight gain with thalidomide over a short period.<sup>68,69</sup> In this setting, treatment with thalidomide seems beneficial, and outweighs the unproven risk of immune-function compromise.<sup>64,70</sup>

#### Congestive heart failure

Advanced congestive heart failure is characterised by raised inflammatory mediators, including TNF $\alpha$ . In a preclinical model,<sup>71</sup> thalidomide and its analogues blocked cardiac myocyte synthesis of TNF $\alpha$  in response to lipopolysaccharide stimulation. Findings of a small study<sup>72</sup> indicated improvement in clinical variables—eg, functional capacity, ejection fraction—with thalidomide therapy. We await validation of this use of thalidomide.

#### Malignant disease

##### Haematological cancers

Multiple myeloma is an incurable disease despite aggressive treatment with high-dose chemotherapy with stem-cell rescue. Novel therapies are needed. The rationale for the use of thalidomide therapy was based primarily on the observation of enhanced neovascularisation in the bone marrow of patients with progressive disease, and the potential antiangiogenic effects of the drug via TNF $\alpha$ , basic fibroblast growth factor, and VEGF in preclinical studies.<sup>1,13</sup> The University of Arkansas group first reported on the efficacy and safety of single-agent thalidomide in refractory multiple myeloma;<sup>73</sup> in 84 evaluable patients given 200 mg of thalidomide, escalated to 800 mg, serum paraprotein concentrations were reduced by more than half in 25% of patients and by more than 90% in eight patients. Two complete responses were seen, which were durable, since median time to disease progression was not reached at 14 months' follow-up. Although more than three-quarters of those who responded had concordant reductions in marrow plasma cell infiltrates, microvascular density was not affected by therapy.<sup>73</sup> Findings of further follow-up of 169 patients by this group<sup>74</sup> showed 2-year event-free and overall survival rates of 20% and 48%, respectively. Moreover, higher doses of thalidomide were associated with improved survival in high-risk patients, lending support to a dose-dependent effect.<sup>75</sup> Response to thalidomide in patients with myeloma typically arises after 1–2 months of treatment with a 200–400 mg daily dose, and a dose of 50 mg per day can be an adequate maintenance dose for clinical response in selected cases.<sup>76</sup> Early single-agent clinical data have been supported by more robust results,<sup>77–88</sup> and, based on early favourable results in refractory myeloma, thalidomide has been given orphan drug status, which provides for 7 years of protected research and development.

Since then, results of phase I and phase II studies of combination therapies of thalidomide with dexamethasone<sup>89–92</sup> or cytotoxic chemotherapy<sup>75,93</sup> have shown improved activity compared with thalidomide alone in patients with refractory myeloma. Combination therapy with thalidomide, steroids, and clarithromycin was also

effective in one study,<sup>94</sup> and thalidomide treatment in patients with chemotherapy-refractory multiple myeloma seems to permit subsequent stem-cell transplantation in the salvage setting.<sup>95</sup> Addition of dexamethasone to treatment of thalidomide-refractory patients is also useful, even with prior steroid failure.<sup>96</sup> Additionally, a phase II dose-escalation study of thalidomide 200–800 mg in newly diagnosed patients demonstrated a 2 year progression-free survival rate of 63%.<sup>97</sup> Clinical responses in individuals with newly diagnosed disease have also been reported by others,<sup>98</sup> but use of thalidomide in this setting to delay progression to symptomatic disease remains controversial.

CC-5013, an immunomodulatory derivative of thalidomide with a favourable side-effect profile, has shown promise in relapsed and refractory myeloma, with 71% of 24 patients treated showing a reduction of paraprotein concentrations of 25%. Responders included those who had received previous treatment with thalidomide. CC-5013 alone or in combination with other therapies is under further assessment.<sup>99</sup>

Larger, prospective, randomised studies are underway, which will further define the role of thalidomide in the treatment of advanced, refractory multiple myeloma and its potential use in newly diagnosed myeloma or as a maintenance therapy. Table 1 shows results of trials published for thalidomide single-agent and combination strategies in multiple myeloma.

Thalidomide also seems to be effective in treatment of other haematological disorders. In a phase II study,<sup>100</sup> patients with refractory Waldenström's macroglobulinaemia had a 25% response rate to thalidomide given at a daily dose of 200–600 mg. Combination therapy with clarithromycin, steroids, and thalidomide has also been used with some success.<sup>101,102</sup> Responses in myelofibrosis have been shown, with improvements in anaemia, thrombocytopenia, and hepatosplenomegaly described by more than half of patients.<sup>103–107</sup> However, drug toxicity and extramedullary haemopoiesis have arisen after thalidomide therapy, and caution is indicated in this setting.<sup>103,105</sup>

Results of a phase I study<sup>108</sup> of 51 patients with early myelodysplasia who received up to 400 mg thalidomide daily, showed a response rate of 31% in evaluable patients, although criteria for response was not clearly defined. Objective responses were noted in patients with advanced and refractory myelodysplasia.<sup>109,110</sup> Thalidomide could have some adverse effect on leukaemic transformation in therapy-related myelodysplasia, which needs to be assessed further.<sup>111</sup>

#### Prostate cancer

Over the past 8 years, clinical focus has shifted to prostate cancer, the most commonly diagnosed solid organ cancer in American men.<sup>112</sup> Findings of a phase II randomised trial,<sup>113</sup> comparing low-dose (200 mg daily) and high-dose (up to 1200 mg daily) thalidomide in androgen-independent prostate cancer, showed sustainable reductions in prostate specific antigen of more than 50% in about a fifth of patients. However, dose escalation over 600 mg in this elderly cohort was rare. Improvements in measurable disease by bone scan and positron emission tomography<sup>114</sup> were also noted in some responsive patients. In another study<sup>115</sup> in men with androgen independent prostate cancer, thalidomide 100 mg per day resulted in a fall in prostate specific antigen in 15% of patients, with VEGF and basic fibroblast growth factor serum concentrations correlating with progression and favourable response, respectively.

Combination therapy with thalidomide and docetaxel has been used for androgen independent prostate cancer in a randomised phase II study.<sup>116</sup> A reduction in serum prostate-specific antigen concentrations of greater than half was shown in 51% of the combined treatment group versus 37% in patients who took docetaxel alone. Although the study was not powered to detect a difference in median overall survival, the addition of thalidomide improved survival by a median 14 months (28.9 *vs* 14.7 months; William Dahut, NCI, personal communication). The survival reported with docetaxel monotherapy was in line with other reports (12–20 months), which further substantiates this finding.<sup>117–119</sup>

Thalidomide has a therapeutic role in advanced prostate cancer, either alone or in combination with other drugs, and several trials are underway to more fully define this role. In conjunction with a cytotoxic agent, thalidomide could further act to stabilise prostate cancer growth when tumour burden is lowest, prolonging disease control with potentially reduced toxicity.

#### Renal-cell carcinoma

Renal-cell cancers secrete VEGF and TNF $\alpha$ , forming the basis for the use of thalidomide in this disease. Notably, the first oncology report of use of thalidomide was published in 1965,<sup>120</sup> and the lone clinical responder was a patient with metastatic renal cell carcinoma after nephrectomy. More recently, Eisen and colleagues<sup>121</sup> treated 18 patients with 100 mg of thalidomide with some success; three partial responders (17%), and three others with short duration stable disease. Unfortunately, partial radiographic responses were rare in several other phase II trials<sup>122–126</sup> in which higher doses (200–1200 mg) were given. Overall, an objective response rate of 0–10% with some effect on disease stability (26–32%) was shown with thalidomide monotherapy<sup>121,122–126</sup> or with combination regimens, including gemcitabine, fluorouracil, and thalidomide.<sup>127</sup> Some preliminary data,<sup>128</sup> however, suggest combination therapy with thalidomide and interleukin 2 might be clinically useful, and the progression-free and overall survival benefit of thalidomide in combination with other biological response modifiers or chemotherapy is being assessed.

#### Glioma

High-grade gliomas often have enhanced vascularity and microvessel density, and some have postulated that thalidomide could provide some benefit in this poor-prognosis group that includes anaplastic mixed glioma, anaplastic astrocytoma, and glioblastoma multiforme. In a phase II, non-randomised trial<sup>129</sup> of thalidomide 200–1200 mg in 36 patients, two partial radiographic responses were noted, with disease stability in 33%. A criticism of this report was that tumour histology was not identified at the time of treatment and, given the variable prognosis of glioma subtypes, the responses are questionable.<sup>47</sup> Partial responses to thalidomide monotherapy were rare in other studies (5–6% partial response).<sup>130,131</sup> Combination regimens are under investigation.

#### Colorectal cancer

Thalidomide nightly (400 mg), in combination with irinotecan, showed clinical utility in four of 14 (29%) evaluable patients (one complete response, three partial response) in a phase II study<sup>132</sup> in metastatic, chemotherapy-refractory colon cancer. A response rate of 12–21% was noted with irinotecan alone. Stable disease was also noted in 38% of patients after short-term follow-

up. Importantly, the dose-limiting gastrointestinal side-effects of irinotecan were also minimised with thalidomide treatment—nearly all patients completed therapy.<sup>133</sup> Preliminary data from this group<sup>134</sup> also indicate improved survival in the group treated with irinotecan and thalidomide when compared with historical data. Phase III studies of this complementary combination are in accrual, and a double-blind, placebo controlled trial of thalidomide after resection of stage IV colon cancer metastases is underway at the US National Cancer Institute, USA.

#### Melanoma

Although single-agent thalidomide is ineffective in metastatic melanoma at 100 mg,<sup>121</sup> results of a phase I trial<sup>135</sup> in 12 patients with thalidomide (up to 400 mg) and temozolamide showed some antitumour activity in six of 12 patients (one complete response, five partial responses). Previous work showed great responses in patients with melanoma brain metastases.<sup>136</sup> Combination therapy seems to be well tolerated, and phase II and phase III trials are in progress.

#### Cancer supportive care

Anorexia and cachexia are common in late stage cancers, probably associated with a TNF $\alpha$  mediated effect. Great improvement in sleep, nausea, and appetite in 72 cachectic cancer patients has been reported with thalidomide 400 mg nightly.<sup>137</sup> Other groups confirm the short-term palliative benefits of thalidomide in this setting.<sup>137–139</sup>

#### Other cancers

Thalidomide monotherapy has been fairly ineffective in breast, ovarian, head and neck, and various solid-organ cancers,<sup>121,140–142</sup> although trials of combination regimens are planned and in progress ([http://www.nci.nih.gov/search/clinical\\_trials](http://www.nci.nih.gov/search/clinical_trials); <http://www.cancer.gov>; <http://www.clinicaltrials.gov>; <http://www.controlled-trials.com>). Table 2 shows results of trials published for thalidomide treatment in non-haematological cancers.

#### Adverse effects

Aside from its well documented teratogenicity, sedation is the most frequently reported thalidomide-associated toxicity,<sup>3</sup> followed by peripheral neuropathy.<sup>143,144</sup> Calculation of a total neuropathy score helps to ascertain proper dosing so as to prevent permanent nerve damage.<sup>144</sup> Other frequent thalidomide-associated adverse effects include rash, dizziness, constipation, tremor, mood changes, and headache.<sup>73</sup> In what seems to be synergistic enhancement of toxicity, combination of thalidomide and some chemotherapies raises the risk of deep vein thrombosis.<sup>145–147</sup> Rash is also potentiated when thalidomide and steroids are combined,<sup>98</sup> and docetaxel and thalidomide use in patients with prostate cancer is associated with additional pulmonary toxicity.<sup>148</sup> Rare complications with combination treatments have also been reported, such as toxic epidermal necrosis,<sup>149,150</sup> severe hepatic toxicity,<sup>151,152</sup> hypothyroidism, bradycardia, and poor CD34+ cell mobilisation with stem-cell procurement.<sup>153</sup>

The frequency of side-effects with thalidomide monotherapy is summarised in table 3. The drug should be administered in combination with chemotherapy only in the setting of clinical trials, wherein adverse effects are closely monitored.<sup>145</sup> The STEPS program (System for Thalidomide Education and Prescribing Safety) was initiated by the manufacturer of thalidomide (Celgene,

Warren, NJ, USA) to reduce the risk of teratogenicity and, in the USA, thalidomide cannot be prescribed without first registering a patient with the programme. Included in STEPS are strategies that control drug access, provide education to patients, doctors, and pharmacists, and guide compliance.<sup>154</sup>

#### Dosing and pharmacogenetics

Clinical responses have been shown at many doses (50–1200 mg), and because of its history and development, no formal systematic dose-escalation studies have been done. Off-protocol dosing should be started at 100–200 mg daily, typically given in the evening as a single dose. Split-dosing has no additional benefit with respect to toxicity profile. The target dose varies for individual patients for various reasons, including age, co-administration with other drugs, and genetic polymorphisms in genes that alter thalidomide metabolism. For example, the polymorphic hepatic enzyme CYP2C19, involved in the conversion of thalidomide to the 5-hydroxythalidomide metabolite, could contribute to thalidomide's clinical activity, although metabolism of drugs other than thalidomide might be also affected.<sup>155</sup> Identification of patients with specific genetic polymorphisms in this gene could help to stratify the likelihood of clinical response to thalidomide. We are investigating this notion of individualised cancer therapy.<sup>156,157</sup>

#### Cancer summary

Thalidomide has shown single-agent activity. However, in almost all cases of haematological and solid malignant diseases, combination strategies seem more beneficial. Efficacy is unproven, since few phase III trials have been undertaken but its usefulness in refractory multiple myeloma is impressive and thalidomide's use in plasma cell dyscrasias has been summarised.<sup>158</sup> Future studies will yield optimum dosing and combination strategies for multiple myeloma and other cancers. Toxicity, which is variable, has occasionally limited the length and durability of responses. Thalidomide is a candidate drug for novel trial designs being considered by the National Cancer Institute and other agencies that use compounds where traditional endpoints are less appropriate—ie, angiogenesis inhibitors.

#### Thalidomide analogue development

Our laboratory has developed 118 novel thalidomide analogues. Preclinical assessment of some of these analogues has revealed their potent antiangiogenic activity in ex-vivo aortic ring, and in in-vitro endothelial cell proliferation and tube formation assays.<sup>159</sup> Furthermore, certain analogues have shown significant antitumour activity in prostate cancer xenograft preclinical models. Clinical assessment of promising lead compounds will result in the development of thalidomide-like drugs that could have an improved clinical profile relative to the parent compound. Molecular pharmacological studies are now underway to elucidate the mechanisms of action for these analogues and other products, including the immunomodulatory derivatives, two of which (CC-5013 and CC-4047) are in phase I trials, and selective cytokine inhibitory drugs. Such studies should lead to the identification of specific molecular targets of thalidomide and its analogues, structural determination of these targets, and rational design of specific small-molecule inhibitors (other than thalidomide and its analogues) with better pharmacological profiles.



## Conflict of interest statement

None declared.

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