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# THALIDOMIDE: Emerging Role in Cancer Medicine

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■ **Abstract** Thalidomide—removed from widespread clinical use by 1962 because of severe teratogenicity—has antiangiogenic and immunomodulatory effects, including the inhibition of tumor necrosis alpha factor. It has now returned to practice as an effective oral agent in the management of various disease states including erythema nodosum leprosum, for which it was approved by the U.S. Food and Drug Administration in 1998, and more recently certain malignancies, including multiple myeloma. Although thalidomide's mechanism of action remains incompletely understood, considerable insight has been generated by extensive preclinical studies in multiple myeloma. Moreover, clinical trials have confirmed benefit in relapsed disease, and the role of thalidomide in treating newly diagnosed patients is currently under study. Its use in other tumors is under evaluation, with promise in renal cell carcinoma, prostate cancer, glioma, and Kaposi's sarcoma. Activity has also been demonstrated in chronic graft-versus-host disease and in symptom relief as part of palliative care.

## INTRODUCTION

A tragic event in the history of drug development occurred with the over-the-counter marketing of thalidomide in Europe during the late 1950s for the treatment of pregnancy-associated morning sickness. As early as 1961, reports of teratogenicity and dysmyelia (stunted limb growth) associated with thalidomide use prompted its subsequent withdrawal (1, 2). The return of thalidomide as a therapy in certain conditions stems from its broad array of pharmacoimmunologic effects (3). This rehabilitation was reflected by its approval in 1998 by the U.S. Food and Drug Administration for the short-term treatment of cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL), along with its use as maintenance therapy to prevent and suppress the cutaneous manifestations of ENL recurrence (3). Thalidomide has since became a treatment of choice for ENL, and its wide spectrum of activity has fostered its application in a variety of disease states (Table 1) (3–5). Because of its teratogenic effects, thalidomide is now used under strict guidelines to prevent fetal exposure to the drug (4).

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**TABLE 1** Potential therapeutic uses of thalidomide currently under investigation

| | |
|---|---|
| Cancer and related conditions | Solid tumors (e.g., brain, breast, renal cell carcinoma); hematologic malignancies (e.g., multiple myeloma) |
| Infectious diseases | HIV/AIDS and related conditions; aphthous ulcerations; wasting syndrome; mycobacterial infections (e.g., tuberculosis) |
| Autoimmune diseases | Discoid and systemic lupus erythematosus; chronic graft-versus-host disease; inflammatory bowel disease; rheumatoid arthritis; multiple sclerosis |
| Dermatologic diseases | Behcet's syndrome; prurigo nodularis; pyoderma gangrenosum |
| Other disorders | Sarcoidosis; diabetic retinopathy; macular degeneration |



In the field of medical oncology, the discovery of thalidomide's antiangiogenic properties has coincided with the emerging importance of angiogenesis in tumor growth and progression. Thalidomide has been shown to inhibit angiogenesis induced by basic fibroblast growth factor ($\beta$-FGF) in a rabbit cornea micropocket assay and by vascular endothelial growth factor (VEGF) in a murine model of corneal vascularization (6, 7). In human studies, the drug appears to undergo activation to metabolites with antiangiogenic activity (8). Because of these antiangiogenic properties, thalidomide is currently undergoing evaluation in the treatment of various solid tumors, multiple myeloma, and other hematologic malignancies (9–13). Results in multiple myeloma are particularly promising, although thalidomide's antiangiogenic effects are believed to be only part of its antimyeloma activity. Its other potential actions include modulation of adhesion molecules, inhibition of tumor necrosis alpha factor (TNF-$\alpha$), downregulation of lymphocyte surface molecules, lowering of CD4:CD8 peripheral lymphocyte ratios, and direct effects on myeloma cells themselves (10, 14–18).

This chapter presents a comprehensive review of the pharmacology of thalidomide, a description of preclinical studies in multiple myeloma to illustrate the drug's complex putative mechanisms of action, and a description of clinical studies in multiple myeloma. Studies in other hematologic malignancies are also addressed, as is the status of research in solid tumors and in other cancer-related applications.

## PHARMACOLOGY

Thalidomide is a derivative of glutamic acid and is pharmacologically classified as an immunomodulatory agent (19). Structurally, thalidomide contains two amide rings and a single chiral center (Figure 1); its full chemical name is alpha-N{phthalimido}glutarimide [C*13* O*4* N*2* H*9*] and its gram molecular weight is 258.2 (19).

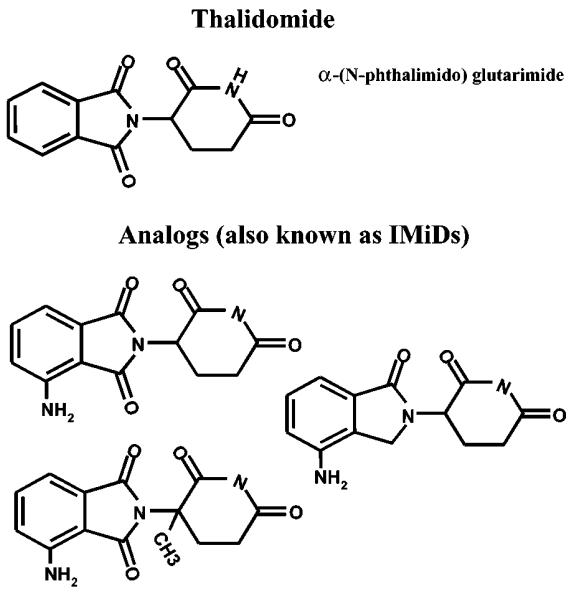


**Figure 1** Structures of thalidomide and its potent analogues, immunomodulatory drugs (IMiDs).

The currently available formulation is a nonpolar racemic mixture present as the optically active S and R isomers at physiologic pH, which can effectively cross cell membranes (19, 20). The S isomer has been linked to thalidomide's teratogenic effects, whereas the R isomer appears to be primarily responsible for its sedative properties (7, 20, 21). The isomers rapidly interconvert at physiologic pH in vivo, and thus efforts at formulating only the R isomer have failed to obviate the teratogenic potential of thalidomide (20, 22).

## Pharmacokinetics

Pharmacokinetic analysis of thalidomide in humans has been limited by the absence of a suitable intravenous formulation, owing to the drug's instability and poor solubility in water. The pharmacokinetics of thalidomide have therefore been determined only from animal studies and in humans receiving the oral therapy. Single-dose thalidomide trials have been conducted in healthy volunteers, patients with HIV infection, and patients with hormone-refractory prostate cancer (23–27).

As Table 2 shows, the pharmacokinetics appear highly variable. Moreover, in patients with HIV infection, dose adjustments based on both ideal body weight and body surface did not affect this variability (23, 24). As a result of this variability, the pharmacokinetic properties of thalidomide in humans have not been well characterized, and this has confounded the definition of a dose-response effect against human cancer.

**TABLE 2** Single dose pharmacokinetic parameters of thalidomide in humans (27)

| Population | Dose | Mean apparent pharmacokinetic parameters | | |
|---|---|---|---|---|
| | | $t_{max}$ | $t_{1/2}$ (L) | $V_d$ (L) |
| Elderly patients with hormone-refractory prostate cancer | 200 mg | 3.3* | 6.5 | 66.9 |
| | 800 mg | 4.4* | 18.3 | 165.8 |
| Patients with HIV infection | 300 mg | 3.4 | 5.7 | 78.2 |
| Healthy female volunteers | 200 mg | 5.8 | 4.1 | 53.0 |
| Healthy male volunteers | 200 mg | 4.4 | 8.7 | 120.7 |

Abbreviations: $t_{max}$, time to reach maximum concentrations; $t_{1/2}$, elimination half-life; $V_d$, volume of distribution; HIV, human immunodeficiency virus.

*Median value.



## Absorption

When oral thalidomide at a dose of 100 mg/kg has been administered in animal studies, maximum serum concentrations were reached within 4 h (28). Absorption was apparently independent of the administered doses and slower than drug elimination. Recent studies in humans show a similar pattern; thalidomide at 200 mg per dose reaches peak concentration ($t_{max}$) in a mean of ~4 h (23–25, 29).

## Distribution

Animal studies have demonstrated a wide distribution of thalidomide throughout most tissues and organs (28). It is present in semen following oral administration in rabbits, but it is not known whether the drug is present in human semen (19, 30). Human pharmacokinetic studies to date also indicate that thalidomide has a large apparent volume of distribution ($V_d$) (24–26). Further, studies in elderly prostate cancer patients suggest variability in $V_d$, possibly due to alterations in absorption and plasma protein binding (24).

## Metabolism

Thalidomide undergoes rapid and spontaneous nonenzymatic hydrolytic cleavage at physiologic pH to generate up to 50 metabolites, of which five are considered primary metabolites (8, 20, 22, 28, 31). Research efforts to better characterize the biologic properties of the specific metabolites have been complicated by their instability and rapid degradation under physiologic conditions (32). Whereas in vitro studies suggest thalidomide induces cytochrome P-450 isoenzymes in rats, recent evaluation of single- or multiple-dose pharmacokinetic parameters of oral thalidomide at 200 mg daily in healthy human volunteers has indicated that thalidomide

does not inhibit or induce its own metabolism over a 21-day period in humans, and thus very little metabolism of thalidomide is thought to occur via the hepatic cytochrome P-450 system (26, 33, 34).

## Excretion

Thalidomide appears to be rapidly excreted in urine as its metabolites, with the nonabsorbed portion of the drug excreted unchanged in feces. However, clearance is primarily nonrenal; mean terminal half-lives of the R and S isomers in healthy male human volunteers were measured at 4.6 and 4.8 h, respectively (23, 28, 29). In a study report of urinary excretion data for a single dose (200 mg daily), the elimination half-life was ~8 h, with minimal drug excretion over a 24-h period (23). Both single and multiple dosing of thalidomide in older prostate cancer patients revealed a significantly longer half-life at a higher dose (1200 mg daily) than at a lower dose (200 mg daily) (24). Conversely, no effect of increased age on elimination half-life was identified in the age range of 55–80 years (24). Thus, the effects of renal or hepatic dysfunction on the clearance of thalidomide remain unclear, and additional studies are needed to better characterize age-related or physiologic effects on drug clearance.

## Drug Interactions

The only drug that has been systematically evaluated for interaction with thalidomide is oral hormonal contraceptives, which showed no significant interaction. Animal studies suggest that thalidomide enhances the sedative effects of barbituates and alcohol as well as the catatonic effects of chlorpromazine and reserpine. Central nervous system stimulants (including methamphetamine and methylphenidate) appear to counteract the depressant effects of thalidomide (35).

## Potential Antitumor Effects

D'Amato et al., while evaluating thalidomide's mechanism of teratogenicity, found that it exhibited antiangiogenic properties (6, 7). They postulated that thalidomide inhibited angiogenesis by interrupting processes induced by $\beta$-FGF and/or VEGF (6, 7, 36). Further in vitro studies suggested that the antiangiogenic effect of thalidomide was due to specific metabolites and not the parent compound (37).

Another important property of thalidomide is that it selectively inhibits TNF-$\alpha$ production while leaving the patient's immune system otherwise intact (38). This has led to its application in various disorders characterized by abnormal TNF-$\alpha$ activity, including ENL, mycobacterium tuberculosis infection, graft-versus-host disease, rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis, Crohn's disease, cancer- and HIV-related cachexia, diabetes mellitus, and endotoxic shock.

The exact mechanism of thalidomide-induced TNF-$\alpha$ inhibition is unclear, but it does appear to differ from other TNF-$\alpha$ inhibitors such as pentoxyfylline and

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