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Thalidomide in Gastrointestinal Disorders

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Abstract

Thalidomide was originally marketed as a sedative, but was removed from the market in 1961 after it was associated with an epidemic of severe birth defects. Subsequently, it has been shown to have therapeutic efficacy in a number of the gastrointestinal tract conditions characterised by immune dysregulation. The exact mechanism of the immunosuppressive effects of thalidomide is unknown; proposed mechanisms include inhibition of tumour necrosis factor alpha release and inhibition of angiogenesis.

In chronic graft versus host disease, use of high dose thalidomide (1200 mg/day) may bring about a response in 20% of patients with refractory disease. Thalidomide 200 mg/day helps eradicate ulcers in 50% of patients with HIV-associated oral aphthous ulceration. In Behçet's disease, thalidomide 100 to 300 mg/day can decrease the number of mucocutaneous ulcers, although full remission occurs in less than 20% of patients. In Crohn's disease, thalidomide 50 to 300 mg/day may decrease the severity of mucosal disease and prompt closure of fistulae.

Patients to be placed on thalidomide therapy must practice either abstinence or strict birth control; women must undergo regular pregnancy testing and utilise 2 forms of contraception. Other adverse effects include sedation (present in nearly all patients), symptomatic neuropathy (present in approximately 20%), and skin rashes. Given the potential toxicity, thalidomide use should generally be limited to clinical protocols with institutional review board oversight.

From 1956 until 1961, in what may be one of the foremost tragedies of modern medicine, the drug thalidomide (α-phthalimidoglutarimide) was marketed as a sedative throughout Western Europe. In 1960, a definitive association between thalidomide and infants with hypoplastic arms and legs (phocomelia or amelia) was established, leading to the drug's prompt withdrawal from the market. Subsequently, however, the drug has been found to have potential efficacy in a number of conditions, including erythema nodosum leprosum, discoid lupus erythematosus, HIV-induced aphthous stomatitis, Behçet's syndrome, and graft versus host disease (GVHD).[1] Two non-blind pilot studies published in late 1999 also suggest potential efficacy in the treatment of refractory Crohn's disease.[2,3] In 1998, thalidomide was approved by the United States Food and Drug Administration (FDA) to treat cutaneous manifestations of leprosy (erythema nodosum leprosum). Given the concern that indiscriminate use of thalidomide could once again lead to an epidemic of birth defects, the Celgene Corporation (Warren, New Jersey) developed a patient and physician education programme designed to minimise this risk.[4]

This article provides an overview on the numerous biological effects of thalidomide, the data supporting efficacy in certain gastrointestinal diseases, and the current protocols in place to prevent the birth of babies with severe deformities.

1. Mechanisms of Action

1.1 Immunomodulatory effects

A number of *in vitro* immunomodulatory effects of thalidomide have been described. These effects have been reviewed in detail by other publications, and are summarised in table I.[1,5-15] Although thalidomide has both immunosuppressive and immunostimulatory properties, it is generally utilised as an immunosuppressive agent. The best studied immunological effect of thalidomide is inhibition of tumour necrosis factor (TNF)-α release by activated monocytes.[7] Thalidomide inhibits synthesis of the TNFα protein by promoting degradation of TNF messenger RNA.[16] In *in vitro* studies, thalidomide inhibits lymphocyte proliferation at a concentration of 1000 μg/L, but at higher or lower concentrations it may enhance lymphocyte proliferation.[15] Of particular relevance to patients with Crohn's disease, the immunomodulatory effects of thalidomide [inhibition of TNFα and interleukin (IL)-12 production] may promote a shift from a T_H1 predominant pattern of lymphocyte cytokine production to a T_H2 pattern.[7,9,15] Since Crohn's disease is characterised by increased mucosal production of TNFα, IL-12, and increased levels of T_H1-type cytokines [IL-2 and interferon (INF)-γ],

Table I. Immunomodulatory effects of thalidomide from human studies

Effect	Reference
Inhibits TNFα production by monocytes	7,8
Inhibits IL-12 production by monocytes	9
Costimulator (with anti-CD3) of T cell proliferation (especially CD8+ T cells)	10
Increases IL-2 synthesis in stimulated mononuclear cells	11
Enhances random migration of leukocytes	12
Decreases generation of superoxide and free radicals	13
Downregulates β_2 integrin expression in mononuclear cells	14
Increases IL-4 and IL-5 (T_H2) cytokine production in stimulated PBMC	15
Decreases IL-2 and INFγ (T_H1) cytokine production in stimulated PBMC	15

IL = interleukin; **INF** = interferon; **PBMC** = peripheral blood mononuclear cells; **TNF** = tumour necrosis factor.

thalidomide may correct some of the mucosal immunological abnormalities present in Crohn's disease.[17]

1.2 Inhibition of Angiogenesis

Angiogenesis is defined as the formation of capillaries from pre-existing blood vessels. Certain cytokines [e.g. basic fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF) and hepatocyte growth factor] released from endothelial and mononuclear cells are potent stimulators of angiogenesis.[18,19] These cytokines bind to specific receptors and stimulate signal transduction leading to endothelial cell proliferation.[20] Thalidomide potently inhibits FGF-mediated angiogenesis in rabbit cornea, and the inhibition of angiogenesis may be the mechanism by which embryonal limb bud growth is suppressed in humans.[21] The antiangiogenic effects of thalidomide are not secondary to TNFα inhibition. Since submucosal vascular proliferation may occur in Crohn's disease tissues, and since serum levels of angiogenesis promoting cytokines are elevated in patients with Crohn's disease, inhibition of angiogenesis may be another mechanism of thalidomide's beneficial therapeutic effect in gastrointestinal diseases.[22-25]

1.3 Interference With Cell Adhesion

Cell-cell contact is essential for both embryonic development and immune system activation. Such cellular contact is mediated by proteins on the cell surface termed adhesion molecules. Adhesion molecules include members of the integrin superfamily [e.g. lymphocyte function-associated antigen (LFA)-1, very late antigen (VLA)-4], immunoglobulin superfamily [e.g. intercellular adhesion molecule (ICAM)-1], and addressin superfamily (e.g. Leu8). Neubert et al.[26] have demonstrated that treatment of marmoset embryos with thalidomide results in a decrease in adhesion molecule expression on developing limb bud cells. While the investigators propose this as a potential mechanism of teratogenicity, it is also possible some of the immunosuppressive effects of thalidomide may be secondary to interference with adhesion molecule expression on lymphocytes.[26]

2. Clinical Pharmacology

There is a paucity of modern pharmacokinetic data on thalidomide. A dose of 100 to 200mg administered orally results in peak blood concentrations of 0.9 to 1.5 mg/L; such a single dose is capable of producing human limb deformities.[27] Chen et al.,[28] in a study of thalidomide pharmacokinetics in 8 healthy human volunteers, calculated an elimination half-life of 8.7 hours, and an apparent volume of distribution of 120.6L. In a group of patients with HIV infection, Piscitelli et al.[29] calculated an elimination half-life of 6 hours and a volume of distribution of 85L. Both these studies utilised low doses (<300 mg/day) of thalidomide. In a study of 21 elderly men with prostate cancer, Figg et al.[30] compared pharmacokinetics of low dose (200mg) *vs* high dose (800mg) thalidomide. The group of men receiving the high dose thalidomide had longer elimination half-lives (18.3 *vs* 6.5 hours) and higher volume of distribution (165.8 *vs* 66.9L), possibly related to changes in absorption or protein binding.[30]

The exact pathways of thalidomide metabolism and the principal route of excretion are unknown. Thalidomide is most probably hydrolysed in the plasma to a number of metabolites. Studies in patients with hepatic and renal insufficiency have not been performed. One study suggests the hydrolysed metabolites have decreased immunomodulatory effects (i.e. hydrolysed thalidomide may not inhibit TNFα release).[31] However, whereas native thalidomide inhibits TNFα production, metabolites may be responsible for the antiangiogenic properties.[32]

3. Clinical Use

In 1965, Sheshkin[33] noted that thalidomide healed cutaneous lesions in patients with erythema nodosum leprosum. Since then, a number of (mostly non-blind, uncontrolled) studies have reported efficacy in a number of autoimmune and dermatological conditions (reviewed in references[1,5,34]).

This review focuses on studies of diseases with prominent gastrointestinal manifestations (i.e. those diseases which may involve any part of the alimentary tract from mouth to anus, the liver, or the pancreas).

3.1 Graft versus Host Disease

Severe chronic GVHD may occur in bone marrow transplant (BMT) patients who have received a marrow from an unrelated donor or from a human leucocyte antigen (HLA)-nonidentical relative. In this condition, severe inflammation and scarring of skin and mucous membranes result in sclerodermalike symptoms. Gastrointestinal complications include chronic diarrhoea, colitis and cholestasis. Chronic GVHD may affect up to 40% of BMT patients who survive for longer than 3 months, and may result in mortality rate of up to 30%.[35]

Non-blind trials suggest that high dose thalidomide (up to 1200 mg/day) can promote either a partial response or a complete remission in approximately 20% of patients with GVHD unresponsive to conventional therapy (cyclosporin, azathioprine and prednisone).[36,37] Patients who respond may have resolution of painful oral ulcers, decreased skin dryness and sclerosis, decline in serum bilirubin levels, and resolution of bloody diarrhoea.[38,39] The high doses of thalidomide in these studies have significant toxicity; in 1 study, up to 36% of patients discontinued therapy because of adverse effects (sedation, constipation, neuropathy, skin rashes or neutropenia).[37]

3.2 Human Immunodeficiency Virus Infection

Recently, thalidomide was found to be effective in the treatment of a variety of symptoms associated with HIV-1 infection, including aphthous ulcers, wasting syndrome and HIV-related diarrhoea.[27,40-46]

In one double-blind, placebo-controlled study, 29 patients with HIV infection and oral aphthous ulcers received a 4-week course of either thalidomide 200mg or placebo orally once daily. 16 of 29 (55%) of patients in the thalidomide group had complete healing of their aphthous ulcers after 4 weeks, compared with only 2 of 28 (7%) of patients in the placebo group ($p < 0.001$).[41] Six of the 29 patients discontinued treatment because of toxicity. The same authors evaluated the use of thalidomide in a multicentre, double-blind, randomised, placebo-controlled clinical trial for the treatment of oesophageal aphthous ulceration.[42] Patients with HIV infection and biopsy-confirmed aphthous ulceration of the oesophagus were randomly assigned to receive either oral thalidomide 200 mg/day or placebo for 4 weeks. Endoscopically confirmed complete healing of aphthous ulcers after 4 weeks was demonstrated in 8 of 11 (73%) patients randomised to receive thalidomide compared with 3 of 13 (23%) patients on placebo ($p = 0.03$).[42]

The efficacy of thalidomide in treating the wasting syndrome in patients with advanced HIV infection was demonstrated in a randomised, double-blind, placebo-controlled trial in Mexico City.[44] 28 patients were treated for 12 weeks with oral thalidomide 100mg 4 times daily or a matching placebo. Weight gain occurred in only 1 patient on placebo compared with 8 patients who received thalidomide, and after 12 weeks the Karnofsky index was significantly higher in the thalidomide group ($p = 0.003$).[44]

Other interesting clinical observations include the increase of plasma levels of soluble IL-2 receptor, soluble CD8 antigen and IL-12, as well as increased cutaneous delayed-type hypersensitivity reactions to recall antigens in thalidomide-treated HIV-positive patients, suggesting an immunomodulatory effect of thalidomide.[47] Thalidomide also produces a dose-dependent inhibition of lipopolysaccharide-induced up-regulation of CXCR4 and CCR5, the chemokines that facilitate the entry of HIV into cells.[48]

3.3 Behçet's Disease

Behçet's disease is a complex multisystem disease characterised by aphthous stomatitis, genital ulceration, nonerosive synovitis, uveitis, meningoencephalitis, and a cutaneous leukocytoclastic vas-

culitis.[49] The disease is most prevalent in Eastern Mediterranean countries (especially Turkey) and the Far East (especially Japan). It most commonly involves young adults, although it has been reported in infants.[49,50] Severe colitis with intestinal ulceration and perforation complicates this illness, particularly in Japanese patients. Although there is no diagnostic test for Behcet's disease, formal diagnostic criteria have been proposed by the Behcet's International Study Group. To meet study group criteria, a patient must have recurrent oral ulceration plus any 2 of the following:

- recurrent genital ulceration
- eye lesions (uveitis or retinal vasculatis)
- skin lesions (e.g. erythema nodosum) or
- a positive pathergy test.[51]

Of the many features of this disorder, the recurrent oral and genital ulcers are typically the most painful and debilitating.

Many uncontrolled studies suggested thalidomide may be effective in healing urogenital ulcers, with response rates as high as 80%.[50,52-54] In the only published randomised trial, Hamuryudan et al.[55] randomised 96 male patients with oral and/or genital ulceration to placebo, thalidomide 100 mg/day, or thalidomide 300 mg/day for 24 weeks. A complete response (defined as ulcer resolution and no recurrence during therapy) occurred in 5 of 31 (16%) patients treated with 300 mg/day, 2 of 32 (6%) patients treated with 100 mg/day, and 0% of patients treated with placebo ($p = 0.03$). Oral ulcers resolved faster than genital ulcers (4 weeks *vs* 8 weeks). Even in patients who did not attain a complete remission, the mean number of oral and genital ulcers in both thalidomide groups was significantly less than in the placebo group ($p < 0.001$). In addition, patients treated with thalidomide had significantly fewer decreases in visual acuity than the placebo group ($p = 0.045$). However, treatment was associated with a rise in the number of erythema nodosum lesions during the first 8 weeks of therapy ($p = 0.03$). Seven patients in the thalidomide treatment groups withdrew because of adverse effects (3 for severe sedation and 1 for polyneuropathy).[55]

3.4 Idiopathic Recurrent Aphthous Stomatitis

The efficacy of thalidomide in oral ulceration complicating HIV and Behçet's disease has prompted its use in individuals with recurrent aphthous stomatitis unresponsive to corticosteroid treatment. Bonnetblanc et al.[56] treated 25 patients with thalidomide up to 100 mg/day for a period ranging from 1 to 55 months. 16 patients achieved clinical remission after thalidomide was added to the medical regimen; of these, 10 patients required thalidomide to maintain remission and 6 were able to discontinue therapy without recurrence of symptoms.[56] The group that stopped therapy was followed for a mean of 2.6 years after thalidomide withdrawal without recurrence.

3.5 Crohn's Disease and Ulcerative Colitis

Crohn's disease is a chronic relapsing illness which may cause transmural inflammation in any portion of the gastrointestinal tract from mouth to anus; noncaseating granulomas may be seen in intestinal biopsies. Complications include mucosal inflammation (especially ileocolitis), perianal and intestinal fistulae, strictures, and oral ulceration. Because of the high likelihood of postoperative recurrence of Crohn's disease, treatment is primarily medical, with surgery reserved for medical failures. Conventional medical therapy involves a combination of elemental diet, corticosteroids, aminosalicylates, and antibacterials; patients who are refractory to treatment are often treated with 6-mercaptopurine (mercaptopurine), azathioprine or methotrexate.

Although there have been sporadic case reports describing efficacy of thalidomide in children and adults with Crohn's disease,[57-60] increased interest in thalidomide was stimulated by controlled trials demonstrating efficacy of infliximab in Crohn's disease. Infliximab, an antibody to TNFα, may induce remission and prompt closure of fistulae in patients with Crohn's disease refractory to other therapies.[61,62] Two non-blind pilot studies have now been published in patients with Crohn's disease resistant to conventional medical therapy.

Vasilauskas et al.[2] treated 12 adult males with active Crohn's disease [defined as Crohn's Disease Activity Index (CDAI) score of >250 despite at least 1 months' treatment with at least 20mg of prednisone] with thalidomide 50 to 100mg nightly. Two patients withdrew from the study after 4 weeks to pursue other therapies. Of the 10 patients who completed 3 months of treatment, 7 experienced clinical response (defined as reduction in CDAI of 100 points and lowering of corticosteroid dose by 50%), and 2 experienced clinical remission (CDAI <150 points, complete withdrawal of corticosteroids). Four of 6 patients treated with 50 mg/day responded and 2 of these entered remission; 3 of 6 patients treated with 100 mg/day responded, with none entering a complete remission. Of the 4 of 6 patients with fistulae who completed 3 months of therapy, 3 noted improvement in pain and/or drainage, and 1 experienced closure of his fistula.[2]

In a second study, Ehrenpreis et al.[3] treated 22 patients with active Crohn's disease (9 with corticosteroid refractory luminal disease and CDAI of over 200, and 13 with draining perianal fistulae) with thalidomide 200 to 300mg nightly for up to 3 months. In the first month of treatment, 6 of 22 patients withdrew from the trial (4 because of adverse effects and 2 who required surgery for their Crohn's disease). Two other patients withdrew from the trial between 1 and 3 months because of a perceived lack of clinical improvement. The 14 patients who completed 3 months of treatment all had clinical improvement, and 41% were in clinical remission. Of note, 5 of the 6 patients with fistulas who took the drug for 12 weeks had complete closure of all fistulas.[3] Adverse effects reported in these 2 trials included sedation (present in almost all participants), constipation, dermatitis, and peripheral neuropathy.

3.5.1 Ulcerative Colitis

Ulcerative colitis is another inflammatory bowel disease with certain clinical similarities to Crohn's disease. However inflammation in ulcerative colitis is limited to the large intestine and to the mucosal layer of the bowel wall; granulomas are not present. Although Crohn's disease and ulcerative colitis are considered separate illnesses, they may share a common genetic predisposition, because relatives of probands with one disease are also at increased risk of contracting the other disease.[63] Experience with thalidomide in patients with ulcerative colitits is limited, with one 1979 case report suggesting efficacy.[64] Given the reported efficacy of thalidomide in colitis complicating Crohn's and Behcet's disease, further studies are warranted.

4. Adverse Effects

Although the adverse effects of thalidomide are significant, many of the patients considered for thalidomide treatment have debilitating chronic illnesses and many have already been exposed to a multitude of toxic drugs (e.g. cyclophosphamide, azathioprine, cyclosporin and corticosteroids). In published clinical trials, adverse events necessitated stopping of thalidomide in 10 to 20% of patients, most commonly because of sedation, skin rashes or peripheral neuropathy.[2,3,36,55] The 2 most clinically important adverse effects of thalidomide, teratogenicity and peripheral neuropathy, are discussed separately in sections 4.1 and 4.2, respectively.

In the 1950s, thalidomide was marketed as a sedative; it is therefore not surprising that the most commonly reported adverse effect is sedation. In high dose thalidomide protocols (such as those in patients with GVHD), sedation and somnolence may occur in almost all patients.[36] In some patients, this can be managed by giving the drug at bedtime or lowering the dose. In addition, patients should be counselled about avoiding the concurrent use of other sedating agents (antihistamines, barbiturates, alcohol, etc.). In a small subset of patients, intractable somnolence mandates discontinuation of the drug.[55]

Other reported reactions include erythroderma, exfoliative dermatitis, nausea, mood changes, oedema, headache, dizziness, constipation, brittle fingernails, and decreased thyroid secretory activity.[1,55] In 1 study of patients with GVHD, 14 of 80 patients developed a significant neutropenia

(median white blood count $<0.9 \times 10^9$/L); other studies have not reported this adverse reaction.[37]

4.1 Teratogenicity

Although thalidomide may be the world's most notorious teratogen, the exact mechanism by which thalidomide causes birth defects is unknown. Three potential mechanisms for the teratogenicity of thalidomide have been proposed. Firstly, thalidomide is a potent inhibitor of angiogenesis (new blood vessel formation); by inhibiting growth of the blood supply essential for growth of long bones, thalidomide may predispose to absent or shortened extremities.[21] Secondly, thalidomide downregulates the expression of adhesion molecules (including CD11a/Cd18, Cd49d/Cd29, and CD61) on limb bud cells in marmosets; therefore, thalidomide may interfere with organogenesis by affecting cell-cell interactions during critical periods.[26] Thirdly, thalidomide seems to cause limb abnormalities in concordance with sclerotomes (patterns of sensory nerve innervation to extremities); this has led McCredie and Willert[65] to postulate that thalidomide may damage sensory nerves during critical periods of development, leading to a secondary effect on bone and muscle growth.[65]

Whatever the mechanism, even a single dose of thalidomide taken by a pregnant woman from 34 to 50 days after the last menstrual period may have severe consequences. The exact type of malformation appears to be greatly dependent on the timing of the ingestion. For example, amelia of the arms occurs in the infants of women taking thalidomide on postmenstrual days 38 to 43; gastrointestinal malformations (including pyloric stenosis and duodenal atresia) occur if thalidomide is taken between days 40 and 45; and phocomelia of the legs occurs if thalidomide is taken between days 42 and 47.[27] Survivors of the thalidomide embryopathy epidemic of the early 1960s characteristically have severe limb deformities (including absent thumbs, hypoplastic or absent radii, hypoplastic or absent humerii, absent or hypoplastic femur, and hypoplastic tibia).[65] Intelligence in victims of thalidomide embryopathy is normal.

The US manufacturer of thalidomide has implemented a programme [the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S. program), reviewed in section 5] designed to aggressively educate patients and physicians about the risks of teratogenicity, and to promote aggressive contraception in individuals of reproductive age engaging in sexual intercourse.

4.2 Peripheral Neuropathy

Although embryopathy is the most feared adverse effect of thalidomide use, it is also preventable by contraception or abstinence. In contrast, peripheral neuropathy has been reported in 20 to 50% of patients receiving thalidomide for chronic conditions.[2,27,37,52,55,66] Thalidomide polyneuritis occurs as a result of axonal degeneration without demyelination; sensory nerves are predominantly affected.[67] Commonly reported symptoms include numbness, paraesthesias, hyperaesthesia, 'pins and needles' sensation, and leg cramps. The lower extremities (especially the toes) are more commonly involved than the upper extremities. Objective findings detectable on neurological examination include diminished ankle jerks and decreased sensation to vibration and position.[66] The likelihood of developing neuropathy increases with cumulative dosage but neuropathy has been reported in patients taking as little as a 2.8g cumulative dose.[52]

Monitoring for neurotoxicity in clinical trials has not been well standardised. Some investigators have monitored the development of neurotoxicity through questionnaires of symptoms and careful physical examination.[2] Other investigators recommend the performance of sensory nerve action potential or electromyography studies, to detect the development of neuropathy before clinical symptoms develop.[52,66]

Although thalidomide is sometimes continued in the face of electrophysiological abnormalities, if a patient develops clinical neuropathy (numbness, paraesthesias or pain), the clinician should

Table II. S.T.E.P.S.© program. Informed consent for women (Reference: Thalomid (thalidomide) package insert, Celgene Corporation.)

1. I understand that I must not take THALOMID® (thalidomide) if I am pregnant, breast-feeding a baby, or able to get pregnant and not using the required 2 methods of birth control
2. I understand that severe birth defects can occur with the use of THALOMID® (thalidomide), I have been warned by my doctor that my unborn baby will almost certainly have serious birth defects or may even die if I am pregnant or become pregnant while taking THALIDOMID® (thalidomide)
3. I understand that if I am able to become pregnant, I must use at least one highly effective method and 1 additional effective method of birth control (contraception) **at the same time**:
At least one highly effective method and 1 additional effective method
IUD — Latex condom
Hormonal (birth control pills, injections or implants) — Diaphragm
Tubal ligation — Cervical cap
Partner's vasectomy
These birth control methods must be used for at least 4 weeks before starting THALOMID® (thalidomide) therapy, and for at least 4 weeks after THALOMID® (thalidomide) therapy has stopped. I must use these methods even if I am infertile, unless I have had a hysterectomy or because I have been post-menopausal for at least 24 months (been through the changes of life). The only exception is if I completely avoid heterosexual sexual intercourse. If a hormonal (birth control pills, injections, or implants) or IUD method is not medically possible for me, I may use another highly effective method or 2 barrier methods **at the same time**
4. I know that I must have a pregnancy test done by my doctor within the 24 hours prior to starting THALOMID® (thalidomide) therapy, then every week during the first 4 weeks of THALOMID® (thalidomide) therapy. I will then have a pregnancy test every 4 weeks if I have regular menstrual cycles, or every 2 weeks if my cycles are irregular while I am taking THALOMID® (thalidomide)
5. I know that I must immediately stop taking THALOMID® (thalidomide) and inform my doctor if I become pregnant while taking the drug; if I miss my menstrual period, or experience unusual menstrual bleeding; stop using birth control; or think, **for any reason**, that I may be pregnant. If my doctor is not available, I can call 1-888-668-2528 for information on emergency contraception
6. I am not now pregnant nor will I try to become pregnant for at least 4 weeks after I have completely finished taking THALOMID® (thalidomide)
7. I understand that THALOMID® (thalidomide) will be prescribed **only** for me, I must **not** share it with **anyone**, **even** someone who has symptoms similar to mine. It must be kept out of the reach of children and should never be given to women who are able to have children
8. I have read the THALOMID® (thalidomide) patient brochure and/or viewed the videotape, 'Important Information for Men and Women Taking THALOMID® (thalidomide).' I understand the contents including other possible health problems from THALOMID® (thalidomide), so-called 'side effects'. I know that I cannot donate blood while taking THALOMID® (thalidomide)
9. My doctor has answered any questions I have asked
10. I understand that I must participate in a survey and patient registry while I am on THALOMID® (thalidomide), which will require completing additional forms

IUD = intrauterine device; **S.T.E.P.S.©** = The System for Thalidomide Education and Prescribing Safety.

stop thalidomide to decrease the likelihood of longstanding painful neuropathy.[52,66]

5. Controlling Access to Thalidomide: The S.T.E.P.S. Program

In the US, the manufacturer of thalidomide (Celgene Corporation, Warren, New Jersey) has designed a comprehensive programme designed to prevent fetal exposure to thalidomide and its potential teratogenic effects. The S.T.E.P.S. program involves 3 principal components: registration of prescribers; education of physicians, pharmacists and patients (including informed consent); and monitoring of compliance.

To register, the physician calls a toll-free number and is sent an application form. Once the form is returned to the company, the physician receives a box of educational materials. The materials include a package insert, a letter from the Thalidomide Victims Association, materials on contraception, an educational videotape, and a detailed informed consents for women and men (tables II and III). Women of reproductive age who have not had a hysterectomy must either abstain from sex or utilise 2 methods of birth control concurrently: 1 highly effective method (intrauterine device, tubal ligation, partner's vasectomy, or hormonal therapy) and one additional method (condom, diaphragm or cervical cap). Men taking thalidomide

must either abstain from sex or utilise a latex condom. The company also suggests referral for reproductive counselling if appropriate. Women must also agree to undergo routine pregnancy testing (at baseline, weekly during the first month of use, and every 2 to 4 weeks while the woman remains on the drug).

To monitor outcomes, a copy of the consent form with a clinical survey is sent to the Boston University Sloane Epidemiology Unit (SEU) at the start of therapy. Follow-up survey questionnaires (monthly for female patients, every 3 months for males) submitted to the SEU include demographic data, sexual history and the results of pregnancy testing in females. Patient and provider identifiers are stored in the SEU and the company is unaware of specific patient names; however, study records are open to FDA audits.[47]

6. Conclusion

Thalidomide is being increasingly utilised as a therapeutic agent in a number of diseases characterised by immunological dysregulation leading to tissue destruction. In prospective studies of individuals with GVHD and Behcet's disease, thalidomide seems to benefit up to 20% of patients. In patients with HIV infection, thalidomide has been shown to heal both oral and oesophageal ulcers. Although the drug appears promising, thalidomide's efficacy in other gastrointestinal diseases (including Crohn's disease, ulcerative colitis, and idiopathic aphthous ulceration) has not been definitively demonstrated. Placebo-controlled trials would be highly desirable before this drug is to be widely utilised by practitioners treating inflammatory bowel disease.

Although a programme exists in the US to prevent indiscriminate prescribing of thalidomide and promote appropriate contraception, no systematic standards for monitoring of thalidomide neuropathy have been established. In addition, no guidelines for use in children exist (although the drug has been used in infants and children).[50,58] Women of childbearing age who receive thalidomide outside the US, and are not enrolled in the S.T.E.P.S. program, need to receive extensive reproductive counselling, be monitored with pregnancy tests both before the start of and during therapy, and to utilise 2 methods of birth control during therapy. Men also need to practice abstinence or barrier contraception. Any sexual activity by patients should ideally be documented in the medical record. In addition, each physician's visit should include information on signs of neuropathy, and documentation of the neurological component of the physical examination.

Given the ethical complexities of thalidomide use, we recommend that individuals planning to

Table III. S.T.E.P.S.© program informed consent for men (Reference: Thalomide package insert, Celgene Corporation.)

1. I understand that I must not take THALOMID® (thalidomide) if I cannot avoid unprotected sex with a woman, even if I have had a successful vasectomy
2. I understand that severe birth defects or death to an unborn baby have occurred when women took thalidomide during pregnancy
3. I have been told by my doctor that I must never have unprotected sex with a woman because it is not known if the drug is present in semen or sperm. My doctor has explained that I must either completely avoid heterosexual sexual intercourse or I must use a latex condom **every time I** have sexual intercourse with a female partner while I am taking THALOMID® (thalidomide) - and for 4 weeks after I have stopped taking the drug, even if I have had a successful vasectomy
4. I also know that I must inform my doctor if I have had unprotected sex with a woman, or if I think **for any reason**, that my sexual partner may be pregnant. If my doctor is not available, I can call 1-888-668-2528 for information on emergency contraception
5. I understand that THALOMID® (thalidomide) patient brochure and/or viewed the videotape, 'Important Information for Men and Women Taking THALOMID® (thalidomide).' I understand the contents, including other possible health problems from THALOMID® (thalidomide), so-called 'side-effects'. I know that I cannot donate blood or semen while taking THALOMID® (thalidomide)
6. My doctor has answered any questions I have asked
7. I understand that I must participate in a survey and patient registry while I am on THALOMID® (thalidomide), which will require completing additional forms
S.T.E.P.S.© = The System for Thalidomide Education and Prescribing Safety.

prescribe thalidomide consult with their hospital's institutional review board, and develop their own formal protocols and informed consent independent of the consent provided by the manufacturing company. Such a consent should include information about the drug's efficacy in the condition being studied, and review adverse effects of sedation, constipation, erythroderma, neuropathy and teratogenicity.

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