Thalidomide’s tightly controlled “comeback”

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■ ABSTRACT

Thalidomide has anti-inflammatory properties and shows promise for treating a variety of infectious and autoimmune diseases, but it must be used with strict precautions.

Thalidomide, removed from the worldwide market 40 years ago because it caused birth defects, is making a comeback as an anti-inflammatory agent. Long a symbol of the danger of unanticipated and undetected side effects in new pharmaceuticals, thalidomide is now being tested for a variety of different indications, but only with very strict safeguards.

■ THE THALIDOMIDE TRAGERY

Thalidomide was thought to be safe when it was introduced in Canada and Europe as a sedative hypnotic in the mid-1950s, although it was not approved for use in the United States. It was often prescribed to treat morning sickness. But by the early 1960s, reports were becoming more common that women who had taken thalidomide during pregnancy had given birth to infants with profound birth defects. Thalidomide was quickly removed from most of the worldwide market, but not before an estimated 10,000 to 12,000 children had been born with serious birth defects. The ensuing controversy strengthened the power of the US Food and Drug Administration (FDA) to regulate pharmaceuticals. Today, about 5,000 thalidomide victims survive.

■ WHY THALIDOMIDE IS MAKING A COMEBACK

We have learned much about thalidomide in the 40 years since its original introduction. Although its role as a sedative hypnotic has been assumed by better drugs, carefully controlled experiments have shown that thalidomide has a unique spectrum of useful anti-inflammatory, immunomodulatory, and anti-angiogenic properties. Specifically, thalidomide:

- Inhibits production of tumor necrosis factor alpha (TNF-alpha), a proinflammatory cytokine
- Inhibits leukocyte chemotaxis at the site of inflammation
- Decreases helper T cells and increases suppressor T cells
- Inhibits angiogenesis

It is not yet clear which of these mechanisms predominates in the treatment of a particular disease. However, the inhibition of TNF-alpha is attracting particular interest. There is no known “normal” level of TNF-alpha, but we do know that TNF-alpha levels rise markedly in many diseases such as autoimmune diseases and infections, particularly human immunodeficiency virus (HIV) infection.

■ APPROVED USE OF THALIDOMIDE: ERYTHEMA NODOSUM LEPROSUM

On September 19, 1997, thalidomide received FDA approval for treating the debilitating and disfiguring lesions associated with erythema nodosum leprosum, which occurs in approximately 40% to 50% of patients with lepromatous leprosy. This disease is the only currently approved indication for thalido-
mide. In fact, thalidomide is the drug of choice in uncomplicated cases.

**EXPERIMENTAL USES OF THALIDOMIDE**

In preliminary studies in relatively small numbers of patients, thalidomide has shown some promise as a treatment for a number of infectious and autoimmune diseases, including the following.

**Complications of HIV infection**

TNF-alpha levels rise with HIV infection and rise as viral load increases.

**HIV-associated aphthous ulcers.** We have used thalidomide extensively in our HIV patients at the Cleveland Clinic, and some patients whose aphthae have been refractory to other agents have healed within a matter of days after the introduction of thalidomide. One small study found significant healing of aphthous ulcers using thalidomide 200 mg/day for 4 weeks vs placebo (55% complete healing with thalidomide vs 7% for placebo).\(^7\)

**HIV-associated wasting syndrome.** TNF-alpha appears to have a role in the wasting syndrome of HIV. One study using two dosages of thalidomide, 100 mg/day and 200 mg/day for 8 weeks, found steady and progressive weight gain, 60% of it in lean body mass.\(^8\) The 100-mg/day dosage appeared as effective as the 200-mg/day dosage.

**HIV-associated diarrhea.** Several small, controlled trials have found that thalidomide decreases the number of stools.\(^9\)-\(^11\)

**Autoimmune diseases**

**Rheumatoid arthritis.** The data to support the use of thalidomide in rheumatoid arthritis are not robust. Several uncontrolled trials suggested that thalidomide in moderately high doses of 300 to 600 mg/day may be effective, but many patients find these amounts difficult to tolerate.\(^12\) A study of low-dose thalidomide (100 mg/day) in combination with low-dose methotrexate, which was reported during the 1998 annual meeting of the American College of Rheumatology last year, was more promising.\(^13\)

**Discoid lupus erythematosus and Behçet disease.** Several studies have found thalidomide effective in treating discoid lupus erythematosus\(^14\) (FIGURE 1) and Behçet disease,\(^15\) a multisystem syndrome of oral, genital, and ocular inflammation.

**Other diseases**

Thalidomide is currently being tested for use in other diseases, including graft-versus-host disease,\(^16\) HIV infection itself, tuberculosis, sepsis, inflammatory bowel disease, autoimmune neurologic disease, bacterial meningitis, cancer cachexia, and Kaposi’s sarcoma. Because thalidomide may also have antiangiogenic properties, it is also being investigated as a treatment for some solid tumors.

![FIGURE 1. Top, oral ulcer in a male patient with lupus erythematosus. The ulcer failed to respond to cyclosporine and corticosteroid therapy. Bottom, lesion resolution after 4 weeks of 200 mg/day thalidomide therapy.](image-url)
PREVENTING NEW BIRTH DEFECTS

Even a single dose of thalidomide taken in early pregnancy can cause birth defects such as phocomelia (absence of the arms and legs, with the hands and feet attached to the shoulders and hips, respectively). Therefore, all physicians, pharmacists, and patients who prescribe, dispense, or take thalidomide must register with thalidomide's manufacturer (Celgene; Warren, NJ; 1-888-423-5436) and agree to follow a rigorous protocol devised jointly by the FDA and Celgene, called STEPS (System for Thalidomide Education and Prescribing Safety).

Women of childbearing potential must understand the risks and agree to use a reliable form of contraception. Moreover, the physician must warrant that the patient is competent and willing to do so, and the patient must undergo pregnancy testing before starting thalidomide, at 2 weeks, and every month thereafter.

The drug should not be stored in a shared medicine cabinet where it may be taken inadvertently by anyone other than its intended recipient.

OTHER SIDE EFFECTS AND COST

Side effects

Neuropathy is the other major complication of thalidomide therapy, although its prevalence is difficult to ascertain. Neuropathy is reversible in most patients if the drug is promptly stopped at the first signs of dysesthesia. Whether electromyelographic monitoring is helpful is still a subject of debate.

Somnolence. Thalidomide's remaining side effects are rather modest. In the study of Kaplan et al in HIV-associated wasting, the most frequently reported adverse effect was somnolence, which is in keeping with thalidomide's original indication as a sedative hypnotic. Other common adverse effects are mucous membrane dryness and constipation.

Cost

Thalidomide is expensive. At approximately $7.50 per 50-mg tablet, a 100-mg/day dosage costs $450 per month. This expense precludes its use as a first-line drug, except for erythema nodosum leprosum.

REFERENCES


CME ANSWERS

Answers to the CREDIT TEST on page 191 of this issue

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