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EDITOR: STUART MADDIN

Thalidomide

On Friday, September 19, 1997 the FDA indicated to the Celgene Corporation that thalidomide, Thalomid[®] has been designated as **approvable** (see explanation below) for the treatment of cutaneous manifestations of erythema nodosum leprosum (ENL). In this condition there are no good alternative treatments to thalidomide. ENL is a severe and painful complication for approximately half of all leprosy patients, affecting about two million people worldwide.

The Thalidomide Chronology

Introduced in the late 1950's

- First marketed as a sedative & for morning sickness. Never marketed in the US.

Worldwide ban in 1961

- Associated with phocomelia & other congenital abnormalities.

Sheskin, 1965¹

- Found thalidomide effective in erythema nodosum leprosum. Dose of 100 mg three to four times daily.

From the ban until now

- Unapproved, illegal use. Bootleg/blackmarket supply.
- Compassionate use approval available in the US and Canada. Supplies from Carville, La. in the past, Celgene now.

1988 – WHO recommend

- WHO's treatment of choice for severe ENL. Based on the results of a double-blind, multi-centered trial.

Late 1997 – first US approval nears

- FDA Advisory Panel September 5, 1997 *recommends the approval* of thalidomide for ENL.
- FDA, September 19, 1997 *designates thalidomide as approvable* for the treatment of cutaneous manifestations of ENL.

Future indications

- Candidates are AIDS-related cachexia or aphthous ulcers,² graft versus host disease, and recalcitrant discoid lupus erythematosus.

Future developments

- Celgene and Andrulis are involved in on-going clinical trails with thalidomide. Celgene are working on developing related compounds with useful activity and fewer side effects.

Use of thalidomide for ENL

The WHO has stated that thalidomide is a treatment of choice for severe ENL and now the FDA has decided that the benefits of treatment with thalidomide outweigh the risks involved. ENL can be life threatening and may cause permanent nerve paralysis and disfigurement. Previously available treatments for severe ENL, corticosteroids and clofazimine are not very effective. Mild ENL has been successfully treated with aspirin, indomethacin, chloroquine or colchicine.

If Celgene's claim that at least 90% of ENL patients respond to thalidomide proves correct, does this raise the possibility of thalidomide being used for all cases of ENL?

Dr. Stuart Maddin, Editor

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Other uses of thalidomide

More than 20 clinical trials are underway and the drug is also supplied on an emergency use basis or investigator IND basis for over 30 conditions. Currently the dermatologic conditions include Behcet's disease, prurigo nodularis, discoid lupus erythematosus, pyoderma gangrenosum, erythema multiforme, Jessner's lymphatic infiltration, pompholyx, scleroderma, urticaria, bullous pemphigoid and cutaneous sarcoidosis.³

Mechanism of action

The mechanism by which thalidomide reduces the elevated levels of tumor necrosis factor-alpha (TNF- α) associated with ENL is yet to be understood.⁴ Thalidomide has other immunopharmacologic actions which are under investigation.⁴

Thalidomide prevents the immune system from overreacting to disease and harming the body. Among its known modes of action is the inhibition of production of cytokine TNF- α .

Dr Kaplan, Rockefeller University.⁵

Precautions

Restricted distribution Celgene designed and has submitted a restricted distribution proposal (System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) to the FDA. The objective of the S.T.E.P.S. program is to help insure that fetal exposure to thalidomide occurs with the lowest possible incidence. This comprehensive program will be directed to physicians, pharmacists, and patients, both male and female. It will require all physicians and pharmacies to register in order to prescribe or dispense Thalomid™ (thalidomide) and all patients to complete an informed consent process and participate in a **mandatory and confidential** surveillance registry.

There are precedents for restricted distribution of a drug, isotretinoin, clozapine and fentanyl oralet have all been marketed successfully this way, and thalidomide when approved, will have more restrictions on it than any drug ever sold in the U.S.

M. Lumpkin, FDA's Centre for Drug Evaluation⁶

Off-label use Some members of the FDA's Advisory panel have suggested that off-label use for other illnesses be prohibited; however the distribution system is designed to cover any use of the drug.

"We need to make this system as leak-proof as possible."

Dr. J. McGuire, Stanford
(Advisory Committee Chairman)⁷

Informed consent waivers Patients and physicians will have to sign detailed informed consent waivers.

Contraception Female patients will have to agree to use two forms of birth control, to undergo ongoing pregnancy tests and to participate in monthly surveys. Patients who have irregular menstrual periods, vaginal bleeding or missed periods may need more frequent pregnancy tests. Males will have to agree to use condoms and to complete surveys every three months. They must abstain from sexual intercourse or use a condom during intercourse while, and for one month after, taking thalidomide. It is not known if thalidomide is present in semen.⁸

A female patient must immediately stop taking thalidomide if she:



- Has a late or irregular period.
- Stops practicing abstinence.
- Stops using birth control.
- Thinks that she is pregnant.
- Does become pregnant.⁹

Supply of thalidomide

Thalomid™ will possibly be available commercially in the first half of this year. The projected cost of a 50 mg capsule is US\$6, meaning that daily treatment of ENL (100–200 mg per day) will cost approximately US\$12–24. Patients will only get a 28 day supply; subsequent supply requires a new prescription.³

Adverse effects

The most common adverse effects are drowsiness, rash and constipation.

Continued on page 5

Rosacea

Clinical rosacea is not a single disease *but rather a combination of cutaneous stigmata which include flushing, erythema, telangiectasia, facial edema, papules, pustules, ocular lesions, and rhinophyma.* Most patients, of course, have less than the full set of these stigmata.¹ The stigmata of rosacea are treatable. It is unpredictably, but potentially, progressive and relapsing.¹

Incidence

There are no accurate figures for the overall prevalence and incidence, which vary with the racial mix of the population. Clinical variants including ocular rosacea or rosacea fulminans should not be forgotten.² The highest prevalence is in countries with a predominantly fair skinned Caucasian population, many with Celtic ancestry,^{3,4} but rosacea does occur in other groups including blacks⁵ and east asians.⁶

Rosacea is frequently missed or misdiagnosed

The most common wrong diagnosis is acne,⁷ and often patients who actually have rosacea, have already seen many doctors and dermatologists with their so-called acne.⁷ Ocular rosacea generally goes unrecognized (see later section).²

Trigger factors for rosacea

The most frequent trigger factors identified by patients are sunlight, heat, spicy foods and alcohol.⁸ The sun and other climatic influences are important *pathogenetically*, but less important as precipitants of attacks.³ Dietary factors are only important with regard to flushing,³ but these factors play no other role in causing or maintaining rosacea lesions. Everything else is folklore.⁷ Keep in mind that undue intake of pro-inflammatory substances (e.g. halogens, including iodides and bromides) from fad diets or medications (e.g. cold remedies, sedatives, radio-opaque contrast media) can sometimes precipitate a devastating outbreak of rosacea.⁷

Treatment of rosacea

General

The regular use of an effective, cosmetically acceptable sunscreen with good substantivity is very important.⁷ Sunscreens should be used throughout the day.^{7,8}

Topical

The topical therapy of choice for rosacea is metronidazole. Sodium sulfacetamide, with or without sulfur,

is also used,⁹ and more recently azelaic acid 20% has been found to be of some benefit.^{3,10} In general, it is not necessary to complicate *topical* application of metronidazole, by adding other so-called active agents such as sulphur, corticosteroids or tretinoin.^{3,7}

The use of topical tretinoin may provoke and worsen the inflammatory process.¹ In most patients the inflammatory process can be controlled with systemic and topical antibiotics *without* exacerbating the underlying vascular process. Since rosacea appears to be in its most fundamental elements a vascular disorder, it would be wise to first do no harm.¹

Systemic

Antibiotics Tetracycline (or erythromycin) in full dosage for up to six months.³ Tetracycline one g/day initially and then reduce the dose (500mg–250 mg/day) for a total period of 3–6 months. Alternatively, minocycline 100 mg/day (reducing to 50 mg/day) can be given. Erythromycin can also be used and clarithromycin compared well with doxycycline in a recent study.¹¹

Isotretinoin With recalcitrant rosacea, isotretinoin has proved to be a worthwhile option.⁸ In some instances low doses of isotretinoin, say 5–10 mg per day, often provide excellent results in *mild to moderate rosacea* when given once a day initially, later reducing to 3–5 days a week.⁷ Higher doses of 0.5 mg/kg bodyweight, usually combined with systemic steroids, are given to patients with rosacea conglobata or rosacea fulminans.⁷ *In recalcitrant rosacea*, particularly in some cases resistant to systemic tetracycline and in patients with rhinophyma, isotretinoin 0.5–1 mg/kg/day for 20 weeks can be administered orally.⁸ Treatment may have to be continued for several months. Isotretinoin used to treat rosacea is often less effective than when used to treat acne.¹²

Laser treatment of rosacea

Be careful not to promise too much.⁷ The background diffuse erythema responds poorly to laser treatment, however discrete fine telangiectasia respond well. Large ropey vessels often require more than one treatment.¹⁴

Argon, copper vapor, krypton and KTP lasers can improve the larger telangiectasia.^{9,13}

CO2 Laser (often used with the CO2 resurfacing laser and the Shaw scalpel) Has proven very helpful for treating rhinophyma.^{8,9,13}

Pulsed Dye Laser (PDL) Can produce pleasing results for telangiectasia and sometimes erythema.⁹ The PDL is probably the best laser for small vessels,¹⁴ but patients don't like the resulting purpura which can last 10 days.^{13,14} In some cases, after treatment patients may also notice a reduction in inflammatory rosacea lesions.¹³ Repeat treatment is sometimes necessary due to recurrence caused by ongoing disease.¹³

Ocular Rosacea

Most patients with cutaneous rosacea have some degree of ocular involvement.¹⁵ Ocular rosacea generally goes unrecognized, undiagnosed, undertreated, and under-reported.¹⁶

"The most common tip-off of ocular rosacea is dry eye, a history of styes or an inability to tolerate contact lenses. Another common complaint is discharge, especially in the morning."

Guy Webster²

The easily overlooked subjective symptoms include nonspecific rather common complaints such as stinging, burning, tearing, photophobia, scratchiness, and feelings of foreign material in the eye. The objective signs are also non-specific and include blepharitis, conjunctivitis, chalazia, styes, punctate corneal erosions, corneal vascularization, and chronic keratitis, which in rare cases may even lead to blindness.^{16, 17} Tear break-up time is abnormal in patients with rosacea. Ocular erythema and telangiectasia, meibomian gland dysfunction, and short tear break-up time in patients with cutaneous rosacea are indicators of ocular rosacea.¹⁷ Often patients don't seem to be aware that they have had eye problems but most studies have found that about 50% of rosacea patients develop eye problems.²

Doxycycline is the recommended treatment and will increase the tear break-up time.¹⁷ The initial dose is 200 mg per day but often after several months patients can reduce the dose and remain controlled.² Low-dose isotretinoin can be prescribed for persistent, severe, antibiotic resistant ocular rosacea.

Helicobacter pylori and rosacea

Recent reports suggest a role for *Helicobacter pylori* in the etiology of rosacea. The disease does respond well to tetracycline, erythromycin, metronidazole and other antibacterials used in the eradication of this organism but "it is difficult to decide whether *Helicobacter pylori* is a passenger or driver of rosacea."⁸ However, if a rosacea patient has a history of dyspepsia / peptic ulcer disease, consider referral to a gastroenterologist for a ¹³C urea breath test.⁹

Summary

- Sun protection is very important.⁸
- For female patients, recommend the use of a green tinted foundation which works well at camouflaging the erythema of rosacea.⁹
- The single best topical treatment is the one that works best for your patient.⁹ Start with topical metronidazole and switch to sodium sulfacetamide if a desired response is not obtained.⁹ For severe and persistent rosacea, stress avoidance of provocative factors, and use oral antibiotics such as tetracycline, doxycycline, minocycline or erythromycin.⁹ in full dosage for up to six months.³
- The pulsed dye laser can be very effective for telangiectasia and as it becomes more available is being recommended more often.⁹
- Avoid topical corticosteroids as they make rosacea worse by adding to the dermal dystrophy that characterizes the disorder.³
- *Counsel patients with particularly intense erythema, that with successful treatment, posterythema-revealed telangiectasia (PERT) may become apparent. This preempts subsequent worries that the antibiotic therapy "produced" the telangiectasia.¹*
- When evaluating patients with cutaneous rosacea, inquire about ocular symptoms and examine the eyelids. This is especially important in patients with mild disease who are more likely to be treated with topical treatment alone.¹⁷ 🔄

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Adverse effects continued...

Peripheral neuropathy


Peripheral neuropathy occurs in less than 1% of ENL patients treated with thalidomide, despite long-term treatment, pre-existing neuropathies, or use in patients who are receiving other medications known to be associated with neuropathies.³ Neuropathy is more common (between 21% and 50%) in AIDS patients. The neuropathy generally occurs following chronic use over a period of months but reports following relatively short-term use also exist. In some cases, the nerve damage has proved irreversible even after treatment with the drug is discontinued. Individual susceptibilities, with possible genetic predisposition, seem to be more important than daily dose and duration of therapy.¹⁰ Patients should be examined for early signs of neuropathy at monthly intervals for the first three months.³ Symptoms of nerve damage include numbness, tingling or pain in the arms, hands, legs and feet. Patients should be warned of this side effect, and understand that they must stop thalidomide immediately if paresthesias develop.¹¹ To detect asymptomatic neuropathy, consider measuring sensory nerve action potential (SNAP) at baseline and every six months. If symptoms develop, stop thalidomide immediately and only restart therapy if the neuropathy completely resolves.³

Birth defects

At the meeting of the FDA Advisory Committee, a spokesman for the 5,000 individuals with birth defects caused by thalidomide who are still living, was saddened at the prospect of potential approval but said that the group preferred regulation to unmonitored use of black market supplies. Celgene said that there have been no birth defects reported so far among the 5,000 ENL patients who have received thalidomide, either through clinical trials or on an emergency basis.

Professor Louis Dubertret of Paris is of the opinion that the French regulatory controls for distribution and use have made thalidomide a very safe drug for the very limited number of patients receiving it.¹²

Future Possibilities

Molecular manipulation has uncovered other thalidomide-related compounds which inhibit TNF- α production more efficiently than thalidomide, and cause fewer side effects in animals.⁵ Celgene's first compound entered Phase 1 clinical study in 1997.³ *The goal, a non-teratogenic compound, with equal or greater immunomodulating potential than thalidomide, offers the exciting possibility of new and relatively safe compounds which may prove effective in treating diseases at present resistant to currently available therapies. Thalidomide itself has a range of interesting and potentially useful immunopharmacologic actions⁴ and after further study and sensible precautions as to its use, has a clear potential as a future immunomodulator.⁴ *

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Approvable Status: An approvable letter indicates that FDA is prepared to approve the application upon the satisfaction of conditions specified in the approvable letter. Such drug products may not be legally marketed until the firm has satisfied the identified deficiencies, as well as any other requirements that may be imposed by the FDA, and has been notified in writing that the application has been approved.

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Update on Drugs

Class	Name/Company	Approval Dates and Comments
<i>Antibiotic</i>	Mupirocin calcium cream 2% Bactroban Cream® <i>SmithKline Beecham</i>	Approved by the US FDA December, 1997 for the treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm ² in area) due to susceptible strains of <i>Staphylococcus aureus</i> and <i>Streptococcus pyogenes</i> .
<i>Antifungal</i>	Butenafine cream Mentax® <i>Penederm</i>	A supplemental claim of efficacy for a one week course for interdigital tinea pedis was granted by the US FDA November, 1997.
<i>Diabetic ulcers</i>	Becaplermin gel 0.01% Regranex® <i>Ortho-McNeil</i>	Approved by the US FDA December, 1997 for the treatment of diabetic foot ulcers. Becaplermin is a genetically engineered, platelet derived growth factor. It is produced by recombinant technology in yeast cells and is not derived from blood.
<i>Male-pattern hair-loss</i>	Finasteride 1mg tablets Propecia® <i>Merck</i>	Approved by the US FDA December, 1997 for the treatment of male-pattern hair-loss. It will only be available on prescription and is for use by men only. Finasteride has already been approved in New Zealand and Mexico.
	Minoxidil 5% Rogaine Extra Strength for Men® <i>Pharmacia & Upjohn</i>	Approved by the US FDA December, 1997 for the OTC treatment of male-pattern baldness.
US FDA – Recommendations		
<i>Skin - Artificial</i>	Dermagraft® <i>Advanced Tissue Science</i>	The FDA's Advisory Committee has recommended approval for the treatment of diabetic foot ulcers.
	Graftskin® (apligraf) <i>Novartis</i>	The FDA's Advisory Committee has recommended approval for the treatment of venous leg ulcers. (Reviewed in Vol. 2 No. 5)
<i>Ultraviolet light</i>	An advisory group to the FDA recommended that <i>ultraviolet light, whether from sunlight or an artificial light source such as tanning booths and tanning beds, be listed as known to be a human carcinogen</i> . Up to 10% of Americans, mostly young women, were estimated to have used artificial tanning devices. The largest occupational exposure to ultraviolet light is in the estimated half million welders using <i>electric arc welding equipment</i> .	

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