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New Drugs

S.T.E.P.S.™ : A Comprehensive Program for Controlling and Monitoring Access to Thalidomide

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ABSTRACT

In July 1998, the US Food and Drug Administration approved the marketing of thalidomide for the treatment of cutaneous manifestations of erythema nodosum leprosum. To ensure that fetal exposure to this teratogenic agent does not occur, the manufacturer has instituted a comprehensive program to control prescribing, dispensing, and use of the drug. This program, known as the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.™ [Celgene Corporation, Warren, New Jersey]), is based in part on experience gained with other drugs—specifically isotretinoin and clozapine—that offer important clinical benefits but carry the potential for serious harm. To achieve its goal of the lowest possible incidence of drug-associated teratogenicity, the S.T.E.P.S.™ program uses a three-pronged approach: (1) controlling access to the

drug; (2) educating prescribers, pharmacists, and patients; and (3) monitoring compliance. Clinicians who wish to prescribe thalidomide must be registered in the S.T.E.P.S.™ Prescriber Registry and agree to prescribe the drug in accordance with S.T.E.P.S.™ patient eligibility criteria and monitoring procedures. Pharmacies must also register and agree to comply with patient identification and monitoring criteria. Finally, patients receive visual aids, including a videotape, written material, and verbal counseling about the benefits and risks of thalidomide therapy, the importance of not becoming pregnant during therapy, and the types of contraception required (including emergency contraception) and their availability. Women of childbearing potential must agree to undergo pregnancy testing before starting therapy and on a regular schedule during therapy. All patients must agree to complete a confidential survey about their

compliance with contraception, testing, and drug therapy. The manufacturer is monitoring survey results and outcome data and is prepared to make whatever modifications to the S.T.E.P.S.[™] program are necessary to ensure its effectiveness. In addition to minimizing the potential risk for fetal harm associated with thalidomide therapy, the S.T.E.P.S.[™] program may provide a model for future cases in which a drug offers compelling benefits but poses profound risks unless its distribution is carefully controlled. **Key words:** congenital abnormalities, teratogenicity, thalidomide, patient education, prevention.

INTRODUCTION

For the first time, thalidomide is being sold commercially for clinical use in the United States. In July 1998, the US Food and Drug Administration (FDA) approved thalidomide* for the treatment of cutaneous manifestations of moderate-to-severe erythema nodosum leprosum (ENL) and as maintenance therapy for the prevention and suppression of ENL recurrence.¹

This latest development in the long history of the drug followed much debate over its benefits and risks and how, if at all, the risks can be managed.² Thalidomide is now available to those who require it, but as the FDA has stated, it is "among the most tightly restricted drugs to be marketed in the United States."¹ To reduce the risk of thalidomide-related teratogenicity to the absolute minimum, Celgene has developed a comprehensive program to control and monitor the drug's prescribing, dispensing, and use.

*Trademark: THALOMID[™] (Celgene Corporation, Warren, New Jersey).

The System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.[™] [Celgene Corporation, Warren, New Jersey]) is based partly on 2 existing models—the safety programs developed for isotretinoin and clozapine. However, the scope of the S.T.E.P.S.[™] program exceeds that of these earlier programs by incorporating additional mandatory controls and ongoing compliance monitoring and by establishing a set of interrelated databases and standard operating procedures that provide mechanisms for improving the program if deficiencies in its operation are detected. This article describes the organization of the S.T.E.P.S.[™] program; the roles of prescribers, pharmacists, and patients; and the structures and procedures in place for monitoring both participant compliance and the program's effectiveness in preventing fetal exposure to thalidomide.

A BRIEF HISTORY OF THALIDOMIDE

First marketed in 1956 in West Germany, thalidomide was widely sold outside the United States, most commonly as a sedative; it had a benign safety profile compared with that of barbiturates.³ By 1961, it was clear that use of thalidomide during pregnancy was associated with major congenital abnormalities. Withdrawal of the drug from markets followed, but approximately 12,000 infants worldwide were born with severe birth defects.⁴ Because the FDA had not yet approved the drug, in part out of concern about reported cases of peripheral neuropathy, thalidomide never reached the US market, and this country was largely spared the tragedy.²

In 1965, Sheskin⁵ reported use of thalidomide as a sedative in leprosy pa-

tients with ENL and in drug caused rapid improvement in type II. Subsequent controlled studies confirmed the efficacy of the drug of ENL.^{6,7} In addition, thalidomide was used widely in the treatment of ENL. Thalidomide has been and continues to be investigated for the treatment of other conditions.⁸

THALIDOMIDE-ASSOCIATED TERATOGENICITY

Fetal abnormalities related to thalidomide therapy include amelia (absence of limbs), phocomelia (shortened limbs), hypoplasticity (absence of bones, external abnormalities, facial palsies, heart defects.⁹ A German study suggested that the teratogenicity occurs when thalidomide is ingested during the 34th pregnancy.¹⁰ However, data derived from the historical use of thalidomide administered during pregnancy suggest that there is no level of exposure at which the drug is safe. For example, a single 100-mg dose was detected in malformed fetuses.¹¹

EXPERIENCE IN MANAGING SPECIAL DRUG-ASSOCIATED RISKS

Isotretinoin

In the past 2 decades, the pharmaceutical industry has gained experience in the use of drugs with important clinical benefits

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THALIDOMIDE-ASSOCIATED TERATOGENICITY

Fetal abnormalities related to thalidomide therapy include amelia (congenital ab- sence of limbs), phocomelia (shortened limbs), hypoplasticity of the bones, ab- sence of bones, external ear and eye ab- normalities, facial palsy, and congenital heart defects.⁹ A German retrospective study suggested that the greatest risk of teratogenicity occurs when thalidomide is ingested during the 34th to 50th day of pregnancy.¹⁰ However, it cannot be in- ferred from the historical data that there is any period of pregnancy during which thalidomide administration is safe, nor is there any level of exposure during preg- nancy at which the drug is known to be safe. For example, a single exposure to a 100-mg dose was determined to cause malformations.¹¹

EXPERIENCE IN MANAGING SPECIAL DRUG-ASSOCIATED RISKS

Isotretinoin

In the past 2 decades, clinicians and the pharmaceutical industry have gained ex- perience in the use of drugs that offer im- portant clinical benefits but carry poten-

tially serious risks. Teratogenicity has been addressed in the case of isotretinoin,* an oral drug capable of producing pro- longed remissions in patients with severe, recalcitrant cystic acne.¹² In 1988, after receiving reports of retinoic acid-induced embryopathy, the manufacturer of iso- tretinoin implemented a program de- signed to allow female patients access to the drug while minimizing the teratogenic hazard.¹³

In contrast to the case of thalidomide, retinoic acid's teratogenic effect was known before marketing; the initial label- ing of isotretinoin included a warning against use during pregnancy. Nonethe- less, reports of birth defects and sponta- neous abortions appeared in women ex- posed to isotretinoin during the first trimester of pregnancy.¹² The reports mounted despite warnings to physicians through direct mailings, advertisements, and the package insert; by 1989, 78 mal- formed infants had been born to women taking isotretinoin.¹¹

The FDA and the manufacturer of isotretinoin redoubled their efforts to alert physicians and patients to the teratogenic effects of the drug. In addition, the man- ufacturer implemented a variety of educa- tional programs and made changes in la- beling and packaging.¹² In 1988 the labeling was revised to state that iso- tretinoin therapy is contraindicated in women capable of becoming pregnant, with the exception of those with severe, disfiguring nodular acne that is unrespon- sive to standard therapies. In addition, women who are candidates for isotretinoin therapy must be judged capable of com- plying with therapy and taking contracep-

*Trademark: Accutane® (Roche Pharmaceuticals, Nutley, New Jersey).

tive measures, must be given verbal and written warnings of the teratogenic hazard, and must have a negative result on a serum or urine pregnancy test within 14 days of starting therapy.

The manufacturer also instituted the Pregnancy Prevention Program to encourage attention to the above requirements.¹³ This program comprises a kit containing educational material for patients, a standard patient consent form, and checklists for both the patient and physician to verify that the patient meets the criteria for therapy with isotretinoin. Awareness of the program has been reinforced by periodic communications to prescribers and pharmacists. The elements of the program that depart from usual medical practice include: (1) a formalized process for ensuring informed patient consent, (2) a provision by the manufacturer to reimburse patients for the cost of contraceptive counseling, and (3) the requirement that women use the drug solely for its labeled indication. Later the manufacturer repackaged isotretinoin in a 10-capsule blister pack containing information directed specifically at women: a warning about the risks of becoming pregnant while taking isotretinoin or during the month after treatment, an "avoid pregnancy" icon on each capsule, and line drawings of malformations associated with the drug.

In 1995, Mitchell and coworkers,¹³ from the Slone Epidemiologic Unit (SEU) at the Boston University School of Medicine School of Public Health, reported that women receiving isotretinoin under the Pregnancy Prevention Program had a substantially lower pregnancy rate than the general population: 8.8 versus 109 per 1000 person-years. In addition, 24,258 (99%) of 24,503 women interviewed within 1 month of enrollment in the pro-

gram said that they had been told to avoid pregnancy. Further, posttherapy tracking showed that pregnancy rates increased in the 4 months after cessation of isotretinoin therapy, which is consistent with avoidance of pregnancy during the period of teratogenic risk.

Clozapine

A different challenge was posed by the antipsychotic agent clozapine.* The drug benefited patients with schizophrenia who did not respond to other medications by improving negative as well as positive symptoms of the disease.^{14,15} Unfortunately, clinical research findings and foreign postmarketing experience indicated that 1% to 2% of patients developed agranulocytosis, which is potentially fatal.¹⁶ At the same time, however, the data showed that none of the patients whose agranulocytosis was detected through laboratory tests died before they developed infections. This suggested that patient surveillance could help prevent agranulocytosis.¹⁶

The FDA's approval of the drug in 1989 was contingent on such surveillance, and the manufacturer created the Clozaril National Registry, a program designed to register treating physicians and patients, ensure patient monitoring (regular blood testing), and limit distribution of the drug to compliant individuals. All patients who received clozapine were required to have a white blood cell count at baseline and weekly thereafter until 4 weeks after the end of treatment. Patients could receive medication only when data on their white blood cell count were current. The registry system also provided guidelines for

*Trademark: Clozaril™ (Sandoz Pharmaceuticals, Hanover, New Jersey).

physicians, pharmacies, manufacturer, and distributors' use of the medication. Clozapine is distributed only by registrars that agreed to follow the "avoid pregnancy" guideline of the registrars.

A review of 5 years' experience with more than 99,000 patients in the registry showed that the incidence of agranulocytosis was significantly lower than expected, 0.5% vs the expected 1% to 2%. The success of the program was due to the recently approved a modified blood cell count-monitoring protocol. All patients must undergo weekly blood testing for the first 6 months of clozapine therapy (when the incidence of agranulocytosis is highest), followed by weekly blood tests for patients with a history of hematologic abnormality.

OBJECTIVES AND ORGANIZATION OF STUDY

Celgene Corporation has implemented both these success factors into the S.T.E.P.S.™ program, which is designed to regulate the distribution of the drug, provide educational materials for patients and physicians, and label warnings to

Table I. Methods of access control and Prescribing :

Maintenance of electronic data base and access control for patients to control access to data

Education of prescribers, pharmacists, and patients about therapy and the requirement for monitoring of childbearing potential

Continuous compliance monitoring and a patient management committee, and regulatory

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physicians, pharmacies, patients, the manufacturer, and distributors to ensure proper use of the medication. Clozapine could be distributed only by registered pharmacies that agreed to follow the "no blood-no drug" guideline of the registry.¹⁷

A review of 5 years' data from more than 99,000 patients in the registry showed that the incidence of agranulocytosis was significantly lower than expected (0.38% vs the expected 1% to 2%). As a result of the success of the program, the FDA recently approved a modification of the white blood cell count-monitoring regimen: Now patients must undergo weekly blood monitoring for the first 6 months of continuous clozapine therapy (when the risk for agranulocytosis is highest), followed by bi-weekly blood tests for patients with no evidence of hematologic abnormalities.

OBJECTIVES AND ORGANIZATION OF S.T.E.P.S.™

Celgene Corporation has incorporated elements of both these successful programs into the S.T.E.P.S.™ program for controlling the distribution of thalidomide. Educational materials for patients and physicians and label warnings similar to those

used in the isotretinoin program are coupled with clinician and patient registration and testing similar to those used in the clozapine program.

The S.T.E.P.S.™ program is multifocal—directed at prescribers, pharmacists, and both male and female patients. Its goal is straightforward: to ensure that fetal exposure to thalidomide does not occur. The methods that are being used to accomplish this goal are outlined in Table I.

A team approach is necessary. Program implementation and oversight are performed by Celgene, the SEU, and the Celgene S.T.E.P.S.™ Management Committee. The management committee has overall responsibility for monitoring and auditing the program. The committee is composed of at least 7 persons, including senior Celgene personnel in the medical affairs, regulatory, and drug safety departments, and industry experts with expertise in computerized databases, warehousing and distribution, manufacturing procedures, compliance auditing, and other areas. The SEU has a separate advisory board composed of representatives of various interest groups (eg, the Thalidomide Victims Association of Canada and the March of Dimes), experts in the use of thalidomide

Table I. Methods of accomplishing the goal of the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.™).

Maintenance of electronic databases of registered and compliant prescribers, pharmacists, and patients to control access to drug.

Education of prescribers, pharmacists, and patients about the risks associated with thalidomide therapy and the requirement for adequate contraceptive measures and pregnancy testing for women of childbearing potential.

Continuous compliance monitoring through mandatory patient surveys, reports to a central management committee, and regular system-wide audits.

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