REPORTS

Challenges of thalidomide distribution in a hospital setting

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Abstract: The various physician, patient, and pharmacy requirements for participation in the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) program and procedures that institutions may implement in order to comply with these requirements are described.

In 1998, FDA approved the marketing of thalidomide (Thalomid, Celgene). Because of the drug's known teratogenic effects, FDA tightly controls the distribution of thalidomide in the United States. To comply with FDA requirements, Celgene developed the S.T.E.P.S. oversight program, which includes registration of thalidomide prescribers and pharmacies that dispense thalidomide, extensive patient education about the risks associated with thalidomide, and a registry of all patients receiving thalidomide. The S.T.E.P.S. program is considered part of the product label. The pharmacy requirements of the program were developed with a focus on a retail pharmacy practice model, which does not adequately reflect current hospital practice. The pharmacy department of the National Institutes of Health Clinical Center developed a model that adapts the S.T.E.P.S. program requirements to inpatient and outpatient institutional pharmacy practice.

Procedures for registering patients and prescribers and dispensing thalidomide in the hospital setting were developed; the procedures were designed to meet the needs of both the inpatient and outpatient pharmacies and to comply with the requirements of the S.T.E.P.S. program.

Index terms: Administration; Anti-infective agents; Dispensing; Drug distribution systems; Erythema nodosum; Patient information; Patients; Pharmacists, hospital; Pharmacy, institutional, hospital; Physicians; Prescribing; Regulations; Thalidomide

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On July 16, 1998, FDA approved the marketing of thalidomide (Thalomid, Celgene) for the acute treatment of cutaneous manifestations of moderate to severe erythema nodosum leprosum, a complication of Hansen's disease (commonly known as leprosy). Thalidomide is currently being evaluated for the treatment of life-threatening diseases such as graft-versus-host disease, AIDS wasting, and malignancies.[1] It may also be useful in treating immunologic disorders (e.g., systemic and discoid lupus, Behcet's syndrome, Sjögren's syndrome, Crohn's disease, rheumatoid arthritis), dermatological conditions, macular degeneration, tuberculosis, and aphthous ulcers.

Because of thalidomide's known teratogenic effects, FDA used authority under 21 C.F.R. 314.520, subpart H, to tightly control the marketing and distribution of the drug. To comply with FDA requirements, Celgene developed the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) program, which is considered part of the product label, to support the commercial availability of thalidomide.[2]

This article (1) summarizes the objectives of the S.T.E.P.S. program, (2) describes the physician, patient, and pharmacy requirements for participation in the program, (3) reviews the dispensing process for thalidomide, and (4) describes our experience in developing systems and procedures in the hospital setting to meet the current requirements for participation in the program.

S.T.E.P.S. program

The goal of the S.T.E.P.S. program is to ensure that there is no fetal exposure to thalidomide. This is to be

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accomplished by controlling access to the drug; educating physicians, pharmacists, and patients about the drug's risks and the requirements for adequate contraceptive measures; and ensuring ongoing independent monitoring for compliance with program requirements. Specific requirements for prescribers, patients, and pharmacies have been developed as a condition of participation in the program. Celgene coordinates the registration and drug shipping process, and Boston University's Slone Epidemiology Unit (SEU) is responsible for monitoring patient and physician compliance. Celgene and FDA are expected to monitor compliance with the S.T.E.P.S. program requirements to help ensure that fetal exposure to thalidomide does not occur.

Prescriber requirements. Any licensed authorized prescriber may register in the S.T.E.P.S. program. Prescribers need to provide their Drug Enforcement Administration (DEA) number (or state medical license number or Social Security number) for program identification purposes. Each prescriber who requests to participate in the program must agree in writing to

- Provide comprehensive patient counseling on the benefits and risks of thalidomide as outlined in the informed-consent form.
- Provide appropriate contraception counseling and pregnancy testing or refer patients to a qualified obstetrician–gynecologist for counseling.
- Verify that female patients are not pregnant before initiating therapy.
- Submit completed informed-consent forms to SEU.
- Complete the prescriber portion of the patient monitoring survey and return the document to SEU.
- Prescribe no more than 28 days of therapy and not authorize refills.
- Encourage patients to return any unused thalidomide to their pharmacy.

Celgene's customer service division maintains a prescriber registration database and activates the prescriber in the database once the signed agreement is returned. A packet of materials is mailed to each interested or registered prescriber for use with each patient undergoing thalidomide treatment. The packet contains an FDA-approved informed-consent form, an initial confidential patient survey, several patient surveys for use on subsequent visits, a form for referring patients for contraception counseling, a brochure on emergency contraception, a brochure on contraceptive choice, a brochure containing important information for the patient, a patient quiz, and a letter from the Thalidomide Victims Association of Canada. In addition, videotapes on the risks, precautions, and requirements associated with thalidomide for both men and women are distributed to each prescriber to help convey information on the risks and benefits.

Patient requirements. Patients must be active participants in the program. All patients receive prescriber-provided education on the risks and benefits of thalidomide and their responsibilities in taking the drug. They are then required to complete the informed-consent form and, for women of childbearing age, required to test negative for pregnancy before beginning drug therapy. Patients are eligible to continue to receive thalidomide if they agree to and meet the following requirements:

- For women of childbearing potential, use two reliable forms of contraception or continuous abstinence and have regular pregnancy tests as defined in the informed-consent form and labeling.
- For men, use a latex condom every time they have sex with a woman.
- Not share thalidomide with anyone.
- Participate in a mandatory and confidential patient survey every 30 days (women) or every 90 days (men).

Pharmacy requirements. Pharmacies must register with Celgene and agree in writing to comply with the requirements of the program in order to receive thalidomide. Any pharmacy may register. As a condition of registration, pharmacies must provide specific discreet information, such as their National Association of Boards of Pharmacy (NABP) number, as part of the distribution-control requirements. If the NABP number is not used, as is the case for federal facilities, the DEA number can be substituted. Pharmacies must agree in writing to

- Collect a signed informed-consent form with the initial prescription.
- Register the patient with Celgene.
- Dispense a maximum of 28 days' supply with no refills.
- Dispense thalidomide in the manufacturer's intact blister pack.
- For subsequent prescriptions, verify that the patient is registered and seek authorization to dispense the prescription by online transmission, fax, or telephone.
- Not dispense thalidomide unless there are seven or fewer days of therapy remaining from the previous prescription.
- Accept and destroy, or return to Celgene, any unused thalidomide returned by patients.
- Inform all staff pharmacists of the dispensing procedures for thalidomide.

Dispensing process. *Initial prescriptions.* When a registered pharmacy receives the initial prescription for thalidomide, the patient must present the pharmacy copy of the signed informed-consent form. If the signed form is on file at another pharmacy, the pharmacist should contact that pharmacy to obtain a copy, unless other arrangements are made with Celgene. The signed form must be kept on file in the pharmacy, because it provides assurance that the patient has been educated on the risks and benefits of the drug. It also contains information that is required in the dispensing process.

The pharmacy is responsible for registering the patient with Celgene by one of three methods: online adjudication, submission of a manual patient-registration form by fax (1-888-432-9325), or telephone (1-888-4CELGENE). This patient registration process is sepa-

rate from prescription verification or authorization. Patient registration is the process by which the patient is entered into Celgene's database. Prescription verification or authorization is the process by which Celgene authorizes the release of the medication. A pharmacist who registers a patient by telephone can provide the information required for prescription authorization at the same time. Pharmacists who use the fax process for patient registration and prescription authorization are required to fax both forms to Celgene. The pharmacist must receive approval either orally or by fax before dispensing the drug.

Subsequent prescriptions. Subsequent prescriptions are filled in accordance with many of the same requirements used in the initial prescription-filling process. The pharmacist must verify that the pharmacy requirements for length of therapy, number of days since the prescription was written, and time limits from the end of the previous prescription have been met. The pharmacist must then verify that the patient has been entered into Celgene's database. Once patient eligibility is confirmed, the prescription needs to be authorized through online adjudication, fax submission, or telephone contact with Celgene.

If all the elements of the dispensing process have not been completed, the pharmacy may be removed by Celgene from the list of registered dispensers and be unable to participate in the program.

Institutional procedures for implementing the S.T.E.P.S. program

Because the pharmacy requirements under the S.T.E.P.S. program are based on the retail pharmacy practice model, they present challenges for hospital pharmacies in the inpatient and outpatient settings. The pharmacy department of the NIH Clinical Center has developed procedures to meet the requirements of the program in the inpatient and outpatient areas. Significant modifications to usual institutional procedures were required in the inpatient area, drug monitoring systems, and database systems.

Institutional guidelines. A member of our pharmacy management team, who was designated as the project coordinator, carefully reviewed the prescriber and pharmacy requirements of the program. The project coordinator was responsible for developing institutional guidelines that would enable all the prescribing and dispensing requirements of the program to be met and for developing the necessary data systems. The guidelines were reviewed by the pharmacy administrative staff, the hospital information systems department, the nursing quality assurance board, and prescribers and were subsequently approved by the pharmacy and therapeutics committee. Key individuals in the inpatient and outpatient pharmacies were designated as associate coordinators to assist the project coordinator with registering prescribers and patients, as well as with implementing the program.

Systems for sharing information. Patients were expected to receive thalidomide primarily on an outpatient basis, although there are occasions on which a patient will start receiving therapy in the hospital and then require subsequent outpatient treatment. Two databases were developed to provide detailed information on eligible prescribers, registered patients, and thalidomide prescriptions filled and to facilitate the sharing of this information between inpatient and outpatient settings.

The first database displays all registered prescribers and the prescriber information needed in the authorization process. The database lists registered prescribers, their Celgene identification number (DEA number or state medical license number or Social Security number), the date of registration, and their affiliation (institute and branch within NIH). The project coordinator maintains the prescriber database.

A second database lists all authorized patients and their previous prescription information. Each pharmacist who dispenses thalidomide is required to enter the prescription information into the database before dispensing. The patient database provides critical patient-related information that is found on the consent form: the patient's date of birth and, for each prescription, the dispensing date, the hospital status of the patient (inpatient or outpatient), the number of days' supply dispensed, the prescriber's name, and the initials of the dispensing pharmacist. The patient database is essential in the authorization process in that it allows any pharmacy staff member to (1) determine whether a patient was previously registered and approved to receive thalidomide, (2) acknowledge that the pharmacy has received the signed consent form, and (3) provide prescription information as to the length and duration of therapy.

Prescriber registration. The NIH Clinical Center uses a computerized physician medication order entry system. Thalidomide is included as an option in the electronic medication index, but selecting the drug notifies prescribers that they must be registered and are required to use the thalidomide restricted-access screens to prescribe the drug. To gain access to these screens, physicians are instructed to contact the project coordinator, who assists them with Celgene's registration process and provides each prescriber with electronic access.

Patient registration and authorization. The methods for completing the patient-registration process and for authorizing new prescriptions, particularly during off hours, were a major point of discussion. Online adjudication permits pharmacies to dispense thalidomide on a 24-hour basis, but many hospitals (including the NIH Clinical Center) do not use this system. Celgene provides telephone and fax services for patient registration, patient approval, and prescriber

verification only on Monday through Friday from 0800 to 1900, Eastern Standard Time. Registered prescribers should be notified of this limitation. Prescribers and patients who need to initiate or continue therapy must wait until manual verification and authorization can be completed.

As a means of gaining experience with the program and preventing registration errors, the project coordinator and associate coordinators were initially responsible for patient registration when patients started receiving thalidomide. Pharmacy staff was instructed to initially contact the project coordinator or an associate coordinator when a new order for thalidomide was received for a patient who was not in the database. Once a signed consent form was received, the coordinator entered the new patient in the pharmacy department's database of patients receiving thalidomide and filled the first prescription. Once a patient was listed in the database, any pharmacist could contact Celgene to obtain authorization for the next prescription or medical order.

Dispensing issues in the inpatient setting. Under the S.T.E.P.S. program, the pharmacy cannot dispense more than a 28-day supply of medication or dispense additional supplies if there is more than a 7-day supply remaining from the previous prescription. Celgene requires pharmacies to dispense the entire blister pack; the S.T.E.P.S. program does not allow for traditional unit dose dispensing. Celgene also requires prescribers to specify the number of days of therapy as part of the patient survey process. However, prescribers rarely know exactly how long a patient will be hospitalized. Dispensing a 28-day blister-pack supply at one time presents significant risk-management issues to hospitals. Our approach was to write standard medication orders specifying that the pharmacy will dispense sufficient blister packs to provide for a seven-day course of therapy and that new orders are required every seven days. This minimized concerns about dispensed medications being mislabeled if the dosage was changed, avoided problems associated with storing up to 28 days' supply of thalidomide on patient care units, and permitted patients to have their thalidomide prescriptions filled at any registered pharmacy at the time of discharge.

Dispensing issues in the outpatient setting. Most of the prescription orders for thalidomide were generated from the outpatient or clinic setting. A new prescription is required for all discharged patients. The database provides the informed-consent information and previous prescription information that is needed to authorize a prescription.

Communications. Routine communications are necessary to enable all staff members to focus on particular issues related to Celgene's program or internal control issues. We employed several means of communication with the medical staff, nursing staff, and pharmacy staff during the first six months of the program. Nursing personnel were made aware of the special requirements for thalidomide by pharmacy briefings in the nursing quality assurance committee. E-mail messages were sent to prescribers reminding them of the special dispensing requirements and of due dates for patient surveys. Pharmacy staff members were briefed on the special handling and registration requirements through staff seminars, written guidelines, and departmental newsletters and by e-mail. We found that one of the most effective communication methods is an information binder in each dispensing area that contains the department's thalidomide policies and procedures and other important documents. The binders also contain blank patient registration forms and prescription verification forms for use when registration and verification by telephone are not possible.

Communication with Celgene representatives also played a major role in the program's success. Celgene provided the names of registered prescribers, and communications on specific programs were directed to prescribers.

Ancillary issues. Because thalidomide has a pregnancy category X rating (i.e., is a known human teratogen), the same institutional policies that apply to handling other agents in this category were applied to thalidomide. For example, because gloves are required for handling hazardous drugs, gloves are required for handling thalidomide.

Thalidomide is currently available only as a 50-mg capsule. This poses problems for pediatric patients taking thalidomide for graft-versus-host disease, as well as for adults taking large doses (e.g., 600–1000 mg) for off-label indications.

Experience

Our experience with this program has been positive, and the program has been considered successful. During the first six months, we registered nine outpatients and two inpatients in the program. Prescribers have complied with the program requirements without many objections. We have been able to remind prescribers about the mandatory completion of the patient survey and have not had any problems when faced with a transition of drug therapy from the inpatient setting to the outpatient setting.

Prescriber feedback has been limited to the requirements concerning patient surveys. The surveys were viewed as quite intrusive for patients who are not at risk for fetal exposure. Prescribers should be made aware that there is a less intrusive survey available for patients under 13 years of age.

Registration may be problematic if a patient who is receiving thalidomide is admitted to the hospital and the hospital pharmacy is not registered. The pharmacy will need 7–10 days to become registered and receive a drug supply. If the decision is made to maintain the patient's

therapy, the patient may be required to use his or her own supply until the hospital pharmacy is registered.

Recommendations

We suggest that, if a hospital pharmacy elects to participate in the S.T.E.P.S. program, the following recommendations, at a minimum, be put in place:

1. Review the program's requirements. Extensive information on the program is available directly from Celgene and on the FDA Center for Drug Evaluation and Research Web site (http://www.fda.gov/cder/news/thalinfo/default.htm). The pharmacy registration card and the prescriber's patient brochure or folder should be extensively reviewed to enable a full appreciation of the patient's or prescriber's conditions for participation.
2. Designate a key person to facilitate and coordinate the program's requirements and communication issues.
3. Maintain a master list of prescribers who are registered in the program to facilitate patient registration. Computerize the list within a database if feasible.
4. Determine whether the computer system can identify all patient-specific thalidomide transactions in the inpatient and outpatient settings. If the computer system cannot track all activities, a profile system or database should be developed. A method for tracking the distribution of each patient's medication is needed in order to comply with the length of therapy requirements.
5. For patients who are initially treated in an inpatient setting, the pharmacy should not dispense more than a seven-day supply of medication for inpatients. Blister packs must be dispensed intact, so the number of blister packs dispensed should be as close as possible to the seven-day supply. This will allow for an easy transition of the patient to the outpatient setting.
6. Obtain and store the signed informed-consent forms in a central file.
7. Follow the hospital's standard policy for handling hazardous drugs or pregnancy category X products when handling thalidomide.
8. Formulate communication strategies for the pharmacy, medical, and nursing staff, who will most likely be unaware of the requirements of the program.

Conclusion

We developed procedures for registering patients and prescribers and dispensing thalidomide in the hospital setting. The procedures were designed to meet the needs of both the inpatient and outpatient pharmacies and to comply with the S.T.E.P.S. program requirements.

References

1. Tseng S, Pak G, Washenik K et al. Rediscovering thalidomide: a review of its mechanism of action, side effects and potential uses. *J Am Acad Dermatol*. 1996; 35:969-79.
2. Thalomid package insert. Warren, NJ: Celgene Corporation; 1998 Aug.