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Preparing for Thalidomide's Comeback

Thalidomide is on the verge of being introduced—with great care—into the U.S. marketplace. The news provokes polarized reactions: disbelief that such a potent teratogen could be made available after the lessons of almost 40 years ago, and impatience for a drug that can lead to exceptional improvements in some rare debilitating immune diseases.

In early September, an advisory committee to the U.S. Food and Drug Administration (FDA) recommended that the FDA approve marketing of thalidomide for erythema nodosum leprosum, an inflammatory manifestation of leprosy that results in painful cutaneous lesions on the arms, legs, and face. The committee also strongly recommended limiting distribution of thalidomide, with stringent safety measures put in place to avoid birth defects and other side effects.

The renewed interest in thalidomide comes from studies showing a complete response in 90% of patients with erythema nodosum leprosum who used thalidomide, according to Janet Woodcock, MD, chief of the FDA's Center for Drug Evaluation and Research. The drug is also under investigation to determine its effectiveness against graft-versus-host disease, the AIDS wasting syndrome, some solid tumors, certain serious primary dermatologic conditions, tuberculosis, aphthous ulcers, and macular degeneration. Woodcock said that evidence is most compelling for the drug's effect on aphthous ulcers in patients with HIV infection (N Engl J Med. 1997;335: 1487-93) and with Behçet disease. She considers the data on the AIDS wasting syndrome "promising" but preliminary.

The committee's recommendation was preceded by a year of intensive debate and planning because of the drug's potentially severe side effects. Even one dose of thalidomide, when taken during the early stages of pregnancy, can cause fetal deformities. The drug can also cause peripheral neuropathy, sometimes resulting in permanent nerve damage.

A Brief History

Thalidomide was originally marketed as a sedative and was often used for morning sickness outside of the United States in the 1950s and early 1960s. Although thalidomide was the third largest-selling drug in Europe—considered so safe it was sold over-the-counter in many places—it never passed FDA scrutiny. At least 8000 of the babies born to women who took the drug during pregnancy had phocomelia, which is characterized by missing digits, arms and legs, and internal organ deformities. In the United States, 17 babies were born with the rare birth defect; their mothers had received the drug from overseas sources or received premarketing samples distributed by drug company representatives. The thalidomide episode resulted in stricter review requirements for drug approval by the FDA, including proof of safety and efficacy plus informed consent by all participants in clinical trials.

Today, the FDA has in hand new data that indicate thalidomide's promise in fighting several serious diseases for which no effective alternate therapy exists, but the risks, of course, remain. Because many of the diseases in which thalidomide is potentially beneficial afflict young women (Behçet disease, the Sjögren syndrome, Crohn disease, and rheumatoid arthritis), issues of teratogenicity are critical. Because of a recent study showing thalidomide in rabbit semen and uncertainty about its presence in human semen, both women and men receiving the drug will be required to use contraception.

Concerns about birth defects have been so great that investigational use of thalidomide for erythema nodosum leprosum has been limited to men and postmenopausal or surgically sterilized women. The FDA is unlikely to limit general use of the drug to that extent, but if it is approved as proposed, thalidomide will be the most restricted drug in the United States, Woodcock confirmed. Every physician, pharmacist, and patient involved with thalidomide will be required to adhere to a tightly controlled protocol, according to Bruce J. Williams, from Celgene Corporation of Warren, New Jersey, the drug's marketer.

To gain access to the drug, patients will be required to receive risk–benefit counseling, sign an informed-consent agreement, use two forms of birth control, and participate in frequent surveys; monthly prescriptions will only be filled after pregnancy testing. Compliance and fetal exposures will be tracked. Only pharmacists registered to participate will be permitted to dispense the drug. By registering, they commit to dispense thalidomide in 28-day supplies in original packaging (special blister-packs with pregnancy warnings encasing each pill) only after seeing the signed informed-consent document. The drug cannot be dispensed as a simple refill, and patients will be advised to return unused doses.

When asked whether a patient using thalidomide can decline the use of birth control for religious or other reasons, Williams responded: "Women can make informed choices about whether or not to take the drug. But if they are of childbearing age and want the drug, they must use contraception." Boston University researchers will maintain a thalidomide users registry modeled after the registry that tracks use and pregnancy outcomes for users of isotretinoin, which is marketed by Hoffman-La Roche in Nutley, New Jersey, under the trade name Accutane (Box).

Zero Risk Impossible

Even with these unprecedented safety measures, experts admit that zero risk is an impossible goal. Babies will be born with birth defects if thalidomide is made available. But based on the isotretinoin experience, 20 years of testing in erythema nodosum leprosum, and limited use of thalidomide by 72 women with the AIDS wasting syndrome or aphthous ulcers, the FDA is prepared to move ahead.

Implications of this regulatory action go beyond U.S. borders. It sends a message to other countries, said Colin Crawford, MB, ChB, DPH&H, from London's Imperial

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College of Science, Technology, and Medicine. If the U.S. government makes thalidomide available, developing countries may do the same, he predicted, most likely without the comprehensive safety and tracking program being planned for the United States.

Thalidomide is already available in 8 of 10 South American countries. Thirty-four cases of thalidomide embryopathy have been reported since 1965. Most have occurred in Brazil, where the prevalence of leprosy is high and where, until recently, thalidomide was available without a prescription.

In the United States, the communications challenges are twofold. A population of patients vividly remembers the first thalidomide tragedy. But an informal FDA poll found that most people under age 35 have never heard of thalidomide and are unaware of its potential harmful effects. "When communicating about risks of any disease to a patient, we have to be aware of the cohort experience that patient brings," said Gail J. Povar, MD, clinical professor of medicine and health care sciences at George Washington University School of Medicine in Washington, D.C. Recalling her own reaction to the thalidomide news in the 1960s, Povar stated that nothing could have convinced her to take the drug if she had any chance of becoming pregnant. But she predicts that 25-year-olds will be furious if their physicians refuse to prescribe it for them. She has seen this happen with isotretinoin. "Every week I have a teenager ask for Accutane inappropriately. We have to accept the fact that this will happen with thalidomide and be prepared."

Advocates for survivors of thalidomide defects are calling for efforts to develop analogues of thalidomide without the harmful side effects. But analogue development may take some time because researchers are not sure exactly how thalidomide works. Its immunomodulatory effects may occur through selective inhibition of tumor necrosis factor, the inflammatory cytokine involved in many diseases. It may also block angiogenesis, the most likely reason for its reported effectiveness against some solid tumors and perhaps the method by which it blocks fetal limb and organ development.

"Thalidomide will likely spark disagreements both within the medical community and between medicine and the public about what limits, if any, to impose on use in fertile women. In addition, because of its exciting potential in the amelioration of serious illnesses, thalidomide may tempt clinicians to go beyond well-documented indications to more experimental applications," said Povar. "Informed consent becomes much more important here. Our obligation goes way up. We need to be very clear that use is experimental.

"For the most part, thalidomide poses no more—and no less—a challenge to the practitioner than any other drug with substantial promise and potential toxic effects," she continued. "It would be unfortunate if thalidomide was considered too risky because of its past. Physicians just need to work closely with patients."

—Cori Vanchieri

Will Pregnancy Prevention Work?

A program to reduce pregnancies in women who use isotretinoin, a known teratogen, for severe, cystic acne is being considered as a model for thalidomide. In 1988, "an unprecedented and novel" pregnancy prevention program was developed for isotretinoin users, according to Allen A. Mitchell, MD, professor of epidemiology and pediatrics at the Boston University School of Public Health. Rates of oral contraceptive use and abstinence were higher in the isotretinoin users than in the general public. The pregnancy rate was 7% that of the U.S. population. Of the 210 009 women with complete follow-up, 623 became pregnant. Two thirds of the pregnancies resulted from contraceptive failure; 68% were electively aborted, 16% were spontaneously aborted, 3% were ectopic, and 11% resulted in live births. As expected, 25% to 30% of the babies had birth defects. Mitchell, who implemented the isotretinoin registry, has suggested that a more stringent program may be required for thalidomide users.

—Cori Vanchieri

Heart Disease: Women's Unique Risks Demand Attention

Responding to what it calls a "silent epidemic," the American Heart Association (AHA) has released new guidelines to help physicians prevent, diagnose, and treat heart disease in women (Circulation. 1997;96:2468-99). The AHA also unveiled a national survey of 1000 women ages 25 and older in which fewer than one third said they had discussed heart disease with a physician. Only 8% considered heart disease their biggest health threat. In reality, heart disease kills half a million women each year—more than all types of cancer combined (Box).

"Much of heart disease [in women] gets missed or misdiagnosed," said Martha Hill, RN, PhD, president of the Dallas-based AHA. "Now, we're learning a lot about the prevalence of heart disease and the benefits of treatment. This statement shares what we've learned."

Age and Coexisting Conditions

Differences in coronary heart disease (CHD) between men and women contribute to a disparity in the mortality rate. Women tend to develop CHD 7 to 10 years later than men—after menopause, when the cardiovascular benefit of estrogen is apparently lost. Because they present with heart disease at later ages, women are also more likely to have coexisting conditions that can reduce survival.

Women often present cardiac symptoms late, when the disease has progressed. And although women frequently experience the same kind of chest pain as men during a myocardial infarction (MI), they are also more likely to have confusing symptoms of upper abdominal pain, nausea, or fatigue. Finally, basic physiologic differences, such as smaller body size—hence smaller coronary arteries—make bypass surgery more difficult and lead to a higher operative mortality rate.

"All this means that physicians need to recognize that there are unique aspects of heart disease in women," said Lori Mosca, MD, PhD, a preventive cardiologist at the University of Michigan in Ann Arbor and lead author of the AHA statement. "You need to screen for the disease and then

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aggressively treat women who are at risk."

Prevention, of course, is the best approach. Educating all patients—even young ones—about the major risk factors, including smoking, diet, and lack of exercise, remains the essential first step. These factors affect both men and women at roughly the same rate.

Other risk factors disproportionately affect women. Diabetes, for example, raises a woman's risk for CHD three to seven times above normal while causing only a two- to threefold increased risk for men. The reasons for this difference are not known. As with diabetes, a decreased level of high-density lipoprotein is a stronger predictor of CHD in women than in men, and an elevated level of triglycerides may have a more serious consequence for women as well.

Routine Screening

The AHA guidelines recommend routine blood pressure screening every year or two and measurement of both total cholesterol and high-density lipoproteins beginning in a patient's twenties. Risk factor awareness and an ability to recognize warning signs are the keys to prevention and early diagnosis for women, according to the AHA.

Diagnosing heart disease may require different tests for men and women. For example, ordinary treadmill testing may be more likely to yield false-positive results in women than in men (Am J Cardiol. 1995;75:52D-60D). Instead, the AHA recommends considering the use of stress echocardiography to evaluate possible symptoms of CHD. New imaging techniques, like magnetic resonance imaging or positron emission tomography, are still experimental but may be useful in the future.

Aggressive Treatment

Within 2 years of an MI, 36% of women die, compared with 21% of men. The mortality rate is particularly high in African-American women. Severity of illness, increased age, and more comorbid conditions may all contribute to the higher mortality rate in women. But considerable evidence, including a recent Canadian study, suggests that women receive far fewer tests and less medication after an MI than men do, even when they see a physician just as often (Arch Intern Med. 1997;157:1545-51).

The AHA recommends that physicians manage heart disease as aggressively in women as in men. "There's no such thing as a touch of high blood pressure," emphasized Kelly Spratt, MD, a cardiologist at the University of Pennsylvania in Philadelphia. "If you find it, you've got to treat it." For men and women alike, the medications most commonly used to treat CHD are aspirin, angiotensin-converting enzyme inhibitors, ß-blockers, and lipid-lowering drugs.

Preliminary studies suggest that hormone replacement therapy in postmenopausal women lowers the risk for both CHD and stroke. Accordingly, many physicians prescribe estrogen supplements for their female patients, depending on the patient's comfort level with hormone replacement and relative risk for endometrial and breast cancers. The AHA statement, like those from a number of other organizations, supports an approach that weighs the pros and cons of hormone replacement therapy for each woman, considering her health, disease risks, and family history.

The AHA contends that, by applying the most up-to-date knowledge about prevention, diagnosis, and treatment of heart disease, physicians can revolutionize health care for women. "There is more information available than ever before, and physicians are more aware of heart disease's challenges," Hill said. "That's a step in the right direction."

—Kathryn S. Brown

Numbers Tell the Story

- Coronary heart disease (CHD) kills half a million U.S. women every year
- CHD accounts for 45% of all deaths in women, more than all forms of cancer combined
- The mortality rate from CHD is 69% higher in African-American women than in white women
- 1 in 2 women die of heart disease or stroke; 1 in 25 die of breast cancer
- In the Framingham Heart Study, 63% of women who died suddenly of CHD had no previous symptoms

Source: American Heart Association

Resolution Due in Medical Software Regulation

The U.S. Food and Drug Administration (FDA) has been trying for more than a decade to determine the best regulatory approach to the burgeoning "stand-alone" medical software industry. With the FDA's decision due soon, manufacturers of stand-alone software and members of the medical informatics community alike are optimistic that the agency will follow the path of least regulation.

Since it began regulating medical devices under a 1976 statute, the FDA has required stringent review of software that is "embedded" inside such devices as pacemakers and ventilators. Likewise, it has regulated "accessory" software that can be run on general-purpose computers to operate systems, such as radiation-planning systems or brain-mapping software.

But stand-alone software, which runs on conventional computers to process words and data, has been in a gray zone. Its applications range from computerized patient record systems and off-line archives to data analysis programs that aid in determining therapy, and such expert systems as decision and diagnostic support programs.

With renewed momentum, the FDA is moving to adopt its first formal regulation of the $6 billion stand-alone software industry. Harvey Rudolph, PhD, acting director of the FDA's Office of Science and Technology in the Center for Devices and Radiological Health, said the agency's position is likely to be "deregulatory" or mainly "hands-off." Rudolph said the policy options will be discussed soon with the staff of the secretary of Health and Human Services, Donna Shalala. Rudolph expects final regulations to be in place in another year.

Exempting Low Risk

Rudolph said the FDA will propose a "risk-based approach" that focuses its regulatory efforts on software with the greatest potential to harm patients, while exempting most software that poses minimal risk. For some moderate-risk products, manufacturers would be required to submit a standard premarket notification or make self-declarations that their products meet certain standards. The FDA is still defining risk categories.

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Some medical catastrophes have assured that software-controlled devices will receive high-level scrutiny. In 1986, several patients received massive overexposure to electron beam radiation from a linear accelerator because of a software problem. Two patients died and another was severely burned, recalled Rudolph.

He said that about 500 device recalls occur annually, 100 of which involve products with software. Of those 100 products, the malfunctions in 40 are related to the software itself.

Problems have included software malfunctions that resulted in improperly labeled radiographs and infusion pumps with incorrect timing that resulted in overdoses of medication.

But the FDA has trod lightly on the stand-alone medical software industry. And developers of such software, unlike the makers of traditional medical devices with embedded software, such as pacemakers and ventilators, are unaccustomed to regulation. They are worried about the implications of the new rules. Some software developers have feared, for example, that even stand-alone programs that run with widely used spreadsheet programs, such as software for billing systems or patient appointment reminders, would have to undergo the same scrutiny as a new pacemaker or infusion pump.

Human Intervention Loophole

The argument for exemption is based on a draft policy supported in 1989 by then FDA Commissioner Frank Young, MD, who stated that software, such as expert systems and products using artificial intelligence, should be exempted if it is "intended to involve competent human intervention before any impact on human health occurs."

Rudolph warned that some manufacturers have "purposely or inadvertently" tried to apply the "competent human intervention" standard to avoid regulation. Harold Schoolman, MD, deputy director for research at the National Library of Medicine in Bethesda, Maryland, added, "We all thought we had a simple solution: As long as a competent health professional can interpret and intervene and make the ultimate decision, then there was no need for premarket approval. But things have gotten more complicated since 1989." Computer networking has resulted in interconnections among several software devices. When data flow through a combination of programs, the chance of malfunction can increase.

Still, developers of stand-alone medical software hope that the FDA will continue its present practice of minimal regulation, according to Edward Larsen, president of Health Patterns, of LaGrange, Illinois. Larsen prepared a proposal on FDA regulation for the Center for Healthcare Information Management (CHIM) in Ann Arbor, Michigan, which represents about 100 vendors of stand-alone software and computer networking equipment. The American Medical Informatics Association has also joined with related groups to propose an approach that keeps federal regulations to a minimum (Ann Intern Med. 1997;127:842-5. J Am Med Informatics Assoc. 1997;4:442-57).

"There is no evidence of hazard in terms of death or serious injury attributable to 'stand-alone' medical software that CHIM has been able to find," according to the CHIM report. "Mandating new regulations is unwarranted in the face of the absence of data showing harm and the availability of data showing that stand-alone software reduces paperwork errors."

CHIM has submitted to the FDA an algorithm to determine whether a stand-alone product should be regulated or excluded. It would exempt software used for education and in financial and administrative systems. It calls for increased scrutiny of software used in immediate decisions that could harm or kill patients in the absence of competent human review.

The FDA has met several times with CHIM to draft regulations that would serve the public health and be acceptable to industry. Rudolph said he expects that the FDA's deregulatory proposals are "in concert" with CHIM's recommendations.

But Larsen said he is taking a wait-and-see approach: "Self-declaration about meeting standards in theory is a good thing. But who is going to write the standards? And what are they going to say? The devil is in the details."

—Howard Wolinsky

News Notes

The Shifting Landscape of AIDS

The mortality rate from HIV and AIDS declined by 26% in 1996. This substantial drop—from 15.6 deaths per 100 000 persons in 1995 to 11.6 per 100 000 in 1996—moved AIDS from the number one to the number two cause of death among 25- to 44-year-olds, according to the Centers for Disease Control and Prevention in Atlanta. The improvement is being attributed primarily to the recent availability of combination therapies for patients with HIV and AIDS.

This good news is tempered by reports that the number of U.S. women ages 13 and older diagnosed with AIDS has increased almost sixfold—from 0.9 cases per 100 000 in 1991 to 5.2 per 100 000 in 1995. The greatest increases were among women who acquired HIV through heterosexual contact rather than through use of injection drugs (JAMA. 1997;278:911-16). Women now comprise almost 20% of adult patients with AIDS.

Women Confuse Arthritis and Osteoporosis

U.S. women may mistakenly wait for symptoms of arthritis before taking action against osteoporosis, according to a recent telephone survey. Six in ten women surveyed think that osteoporosis has warning signs or symptoms. More than 70% of respondents cited pain, 50% mentioned stiffness, and 33% referred to swollen joints as symptoms of osteoporosis.

More than 40% of respondents stated that osteoporosis and osteoarthritis are related diseases. Half said that they believe the treatments for arthritis and osteoporosis are similar. The random-digit dialed telephone survey of 505 women was funded by the National Osteoporosis Foundation in Washington, D.C.

Robert Lindsay, MD, PhD, president of the foundation and chief of internal medicine at Helen Hayes Hospital in New York, expressed concern that confusion surrounding these diseases leads many women to ignore their risk for osteoporosis and fail to take steps to protect themselves from the disease.

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