Growth hormone and AIDS-related wasting

One of the most devastating effects of AIDS is body wasting. Is human growth hormone the answer?

The news about the rapid US Food and Drug Administration's (FDA) approval of the new HIV protease inhibitors at the beginning of March (see story, page 257) overshadowed another important FDA hearing held that week. A joint FDA Advisory Committee composed of members from both the Antiviral Drug Committee and the Endocrinologic and Metabolic Drugs Committee examined data and heard testimony about Serostim, a recombinant human growth hormone made by Serono Laboratories, for the treatment of AIDS-related wasting. However, after a day of conflicting and often confusing testimony and debate, the advisory committee voted eight to seven against full approval of Serostim to treat wasting. Serono officials are still working with the FDA to obtain some form of approval, but the close verdict has parties from all sides blaming each other.

AIDS wasting syndrome, defined as a loss of ten percent or more of body weight for unexplained reasons, is a common and often fatal outcome of HIV infection. There is a lack of effective treatments; the only two FDA-approved drugs, megestrol acetate (Megace) and dronabinol (Marinol, which is based on the active ingredient in marijuana), are appetite stimulants. Both were approved on the basis of weight gain, although it has subsequently been shown that the gain is an increase in fat rather than lean body mass (presumed to be the critical loss in those suffering AIDS-related wasting). Other potentially promising drugs, including anabolic steroids, are still several years away, so community representatives were hopeful that Serostim was the answer, albeit an expensive one (at US$150 per day, or approximately $55,000 a year). Although human growth hormone manufactured by other companies by different means is approved by the FDA for other uses, this is the first application for AIDS-related wasting, and Serono was trying to break into the potentially lucrative US market with this application. But the application failed, at least for now.

Despite the advisory committee vote, both the company and AIDS community representatives — and many of the FDA committee members — still believe Serostim is beneficial, at least for some AIDS-wasting patients, and should be approved as soon as possible by the FDA. But the community representatives differ from the company in that they almost unanimously believe that the advisory committee was correct in turning down full approval. They argue that the company representatives did not make the case for full approval of the drug and should first have sought some form of accelerated approval. "It was our position all along that they didn't have the data for full approval, and the FDA [committee] saw that," says Tim Horn of the Treatment Action Group. "I hate to say, 'we told you so,' but there it is." Indeed, many community representatives were angered and committee members confused by what they perceived to be the refusal of Serono officials at the meeting to accept less than full approval, a perception challenged by James Breitmeyer, vice president for clinical research at Serono Labs. "We don't know about accelerated approval: that's really an FDA decision," says Breitmeyer. "But we are actively working with the [FDA] to get this application approved; we're very agreeable to reanalyzing the data or providing additional data to clear up any misperceptions."

Other company representatives express frustration at what they say is inconsistency on the part of the FDA in defining and enforcing the regulations applicable to Serono's application, arguing that the advisory committee should not have discussed accelerated approval at all. The company, from previous work with the FDA, believed that the weight gain data served to support full rather than accelerated approval, the basis of the application. Indeed, the possibility of accelerated approval was raised by committee member and community representative William Thorne during the committee deliberations, and it was sub-

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sequently discussed at length by the whole committee. "We tried to draw this [a commitment to accelerated approval requirements] out of the company," says Thorne. "The FDA is most comfortable when the sponsor makes a commitment in an open public hearing, so everyone is on the same page." Serono officials, however, were clearly confused by the discussion.

Some of the confusion is a result of the demands that the AIDS epidemic has placed on the FDA. "In many ways, the FDA has given a lot of latitude to AIDS drug approval," says Thorne. "They're trying to take a system that wasn't set up to get drugs out speedily and adapt it to meet life-threatening situations." This is particularly difficult for newcomers to the politically tumultuous world of AIDS drug approval such as Serono, whose representatives appeared unprepared for the intense scrutiny trained on their data during the committee meeting and the behind-the-scenes intrigue after the meeting.

However, it is clear that the data presented by the company to the advisory committee did not support full approval. The data were from two clinical trials of Serostim that used a gain in body weight (predominantly lean body mass) to determine efficacy. The first study showed an average gain of 1.6 kilograms in the study group over the control group, although there was some question as to the composition of that weight gain (which could be the result of intracellular water, protein or some other factor). The second study, however, failed to replicate the results of the first, although a secondary, "supportive" end point (a "quality-of-life" evaluation of the participants) demonstrated some benefit of Serostim treatment in this group.

This subjective "quality-of-life" benefit of Serostim treatment was emphasized during the open public discussion section of the hearings. "It was like Lourdes on a good day in there," one committee member said of the public testimony. "Everyone threw down their crutches, saying this [drug] was the best thing that has happened in AIDS treatment." Indeed, the only negative testimony at the open public discussion came from Paul Davis, a member of ACT-UP, Philadelphia, who took Serono to task for its "astronomical and obvious greed" in seeking approval for a drug many feel is overpriced, an issue not under consideration by the committee.

Despite the positive spin placed on the slender data by Serono representatives and the glowing testimony of most of the public participants, the FDA analysis of the data raised substantial questions. Besides the obvious fact that the second clinical trial did not clearly replicate the results of the first trial (thus failing to meet one of the conditions required by the FDA for any kind of approval), it was clear that the subset of patients who benefitted from the treatment was not adequately identified, which could make it difficult for physicians to decide who to treat with the drug. Committee members also raised concern about data that indicated that Serostim could increase HIV replication (although this could be controlled by antiviral treatment). Especially telling, in light of cost concerns and the hormonal side effects of the drug (such as raised levels of insulin-like growth factor) was the lack of studies to determine minimal effective dose or duration of dose.

Meanwhile, activists are trying to encourage other growth hormone manufacturers to seek approval for their products for treatment of wasting. "We are going to cooperate with anyone who wants to help people with wasting syndrome have a longer and better life," says Thorne. "For example, if Genentech wants to get their act together and show a short-term benefit to their growth hormone, we are more than willing to work with them." Matthew Sharp of Healing Alternatives in San Francisco, a group that helps test experimental treatments for wasting and has worked with Serono for five years to get Serostim approved, says that his group is frustrated enough to seek out other possibilities. "If we can find an as-effective [as Serostim] therapy for people, we'll go that route," he says. "We're not going to keep handing everything over to Serono."

Committee members who voted against approval were uncomfortable about the decision they were asked to make, but in the end it was clear only that Serostim likely offers some benefit to some people suffering from AIDS-related wasting. But just who those people are and how much Serostim can help them are questions still to be answered satisfactorily, according to the FDA and to most activists. In the meantime, the latter say the company should do what it takes to get accelerated approval, and work out the details for the studies necessary for full approval later.

FINTAN R. STEELE

Genentech sheds gp120 vaccine

Having already sunk an estimated US$50 million into the development of recombinant gp120, a candidate vaccine for the prevention of HIV infection, Genentech, Inc., of South San Francisco announced in late February plans to spin off the project to form the basis of a new company whose sole focus will be HIV vaccine development, and in which Genentech has the right to retain a 25 percent stake. Genevax, as the new company will be called, will initially concentrate on kick-starting stalled efforts to conduct a pivotal phase III efficacy trial of gp120 in the United States and in Thailand where the AIDS epidemic is still raging despite an intensive public health campaign. The new, largely venture-backed company will be headed by Donald Francis, who was formerly in charge of the gp120 clinical trial program at Genentech.

Genentech's gp120 program in particular, and the AIDS vaccine business as a whole, suffered a serious setback in June, 1994, when the US National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) pulled the plug on plans to back a large-scale efficacy trial in the United States of the two leading candidate gp120 vaccines (Genentech's and that of rival Chiron Corporation) on the grounds that these first-generation vaccines showed too little promise in preliminary safety and efficacy trials. Although NIAID, through its recently published strategy for HIV vaccine development, is now attempting to clarify the situation in the hopes of re-establishing links with industry, the scientific community is still divided over the relative merits of gp120 vaccines and over the logistical complexities of staging large-scale efficacy trials (*Nature Medicine* 1, 1105; 1995).

Whether or not NIAID's strategic plan has teeth, Genentech's decision to refocus its portfolio serves as a reminder that even an established company with relatively deep pockets must continually make value judgments about its product development pipeline. Development of