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SPECIAL REPORT: 8TH CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS

Interleukin-2 therapy shows promise when combined with antiretroviral regimen

Variety of studies presented at retrovirus conference

What's old is becoming new again in the search for potent therapies in treating HIV disease. A well-established treatment for certain types of cancer, therapy with the T-cell growth factor Interleukin-2 (IL-2), is now showing promise as a treatment for HIV.

Researchers across the nation have been studying how HIV-infected patients respond when they are given IL-2 in combination with their antiretroviral drug regimen. Some of the investigators' findings were presented at the 8th Conference on Retroviruses and Opportunistic Infections, held Feb. 4-8 in Chicago.

"IL-2 has been around for a long time, and it's approved for use in certain types of cancer where it has been shown to have a benefit in controlling tumors," says **Ronald Mitsuyasu**, MD, a professor of medicine and the director of the University of California - Los Angeles Center for Clinical AIDS Research and Education.

The route to using IL-2 therapeutically for treating cancer and HIV-infected patients is a long and well-worn path.

"My lab first discovered the IL-2 molecule and receptor in the late 1970s," says **Kendall A. Smith**, MD, professor of medicine and immunology at the Weill Medical College of Cornell University in New York City.

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COMING IN FUTURE ISSUES

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■ **Double-edged sword:** California researchers are studying the role of IL-7, which both facilitates T-cell production and fosters HIV-1 disease progression

■ **Many HIV patients overuse ED services:** Study sheds light on which patients will bypass doctor's office for more costly ED care

■ **Will the world ever see a viable AIDS vaccine?** The author of a recently published book on the search for an AIDS vaccine answers *AIDS Alert*'s questions about the past and future of this worldwide effort

■ **New Pan-Caribbean partnership against AIDS:** With goals of reducing the AIDS threat in the Caribbean, one of the hardest-hit regions in the world, a new partnership has been launched

"We spent a decade or two working on the details of how IL-2 binds to its receptor and what happens subsequently to the cells and immune response," Smith adds.

Now, some 20-plus years after the IL-2 molecule and receptor were first discovered, researchers at Cornell, UCLA, the National Institutes of Health (NIH), and other research centers are close to determining how IL-2 therapy could best be used in treating HIV-infected patients.

NIH investigators first began looking at the possibility of using IL-2 to treat HIV-infected patients during the early 1980s, says **H. Clifford Lane**, MD, clinical director of the National Institutes of Allergy and Infectious Diseases at NIH in Bethesda, MD.

Investigators learned early on that IL-2 had some potency against the AIDS virus, but it was unknown whether the treatment would work in people as well as in the lab.

The first trials in 1983 showed that the crude natural product of IL-2 used in treating AIDS patients had no effect. A year later, researchers gave recombinant IL-2 therapy in doses of a million or more units per day to AIDS patients over a period of eight weeks, Lane says.

"The lymphocyte counts would go up over the first week or two, and then they would come back down to baseline," Lane explains. "So the effects looked quite transient."

The studies were repeated in 1986 when AZT became available, and the results were the same. So investigators decided to try something a little different. They began to administer high doses of IL-2 intravenously over a five-day period until about the time the T-cell counts started to climb again, and then they would stop IL-2 for two months. Researchers settled on a protocol that involved administering the IL-2 treatment for five days every eight weeks.

Intermittent IL-2 therapy has positive results

In the beginning of the 1990s, investigators hit the jackpot. They found that patients treated intermittently with IL-2 began to generate more T-cells than they had ever imagined possible. "Giving five days of therapy plus a rest period leads to a positive expansion of the CD4 T-cell count pool," Lane says.

Because investigators had arrived at this protocol through guesswork, they decided to test various other treatment structures to see what worked best. As it turned out, five days over eight weeks was the most effective regimen.

The next step is to prove the treatment has clinical benefit, Smith says.

"So what is the clinical benefit of an increase in CD4 cell counts?" he asks. "We need a Phase III clinical end point study."

There are two Phase III studies under way in 22 countries that are expected to enroll 5,400 patients total, Smith says.

"Within the entire study, we hope to look at the development of AIDS-surviving illnesses and mortality," Smith says. "We'll take a large sample of patients, and within that sample we will have enough patients who do show progression to show an effect from IL-2 treatment."

Smith's research group has been taking an entirely different approach to using IL-2 therapy for HIV-infected patients. The group is studying the administration of IL-2 therapy on a daily basis at about one-tenth of the dose that the NIH team has used.

"We found several things when you give IL-2 on a daily basis," Smith says. "First, the natural killer cells increased rapidly over the first couple of months or so, and then they plateaued. Secondly, the CD4 cell count gradually and progressively increased over the course of a year, with an increase of 10 cells per month."

When compared with patients who were treated with highly active antiretroviral therapy (HAART) alone, the patients treated with both IL-2 and HAART had a significantly higher number of CD4 cells.

Patients tolerate daily IL-2 treatments well

"At the same time, we found that the CD8 cell count, which was twice the normal count at the time of starting the study, still remained elevated but dropped by 25% from what it was," Smith adds. "People could tolerate IL-2 treatment on a daily basis with no side effects and no systemic side effects, and they could go to work or school and carry on normal activities."

A 1998 trial involved 40 HIV-infected people who had CD4 cell counts of less than 300 cells / mm^3 and who were given a low dose of IL-2 along with HAART for six months, Smith says.

The study confirmed data from the earlier research, Smith adds. **(See story on IL-2 research, p. 44.)**

"There was a dramatic increase over four months of naive CD4 cell subset," he explains. "The total CD4 cell count was higher than the control, but it had borderline significance."

IL-2 group had lower cholesterol

An offshoot of the therapy was that the IL-2 group had a significant decrease in cholesterol and triglyceride levels, Smith adds.

Furthermore, some patients have been receiving IL-2 therapy at the low doses for more than six years, and their CD4 cell counts remain around 1,000 cells / mm^3, which is about five times higher than it was when they started IL-2 therapy, Smith says.

Mitsuyasu's work has built on the NIH research by studying intermittent IL-2 therapy in patients who have more advanced HIV disease, such as those with CD4 cell counts below 400 cells / mm3.

"We had questions of whether patients with lower T-cell counts would be able to respond immunologically," Mitsuyasu says. "Also, if you give IL-2 subcutaneous injections, would that be as effective as IL-2 administered intravenously?"

Mitsuyasu and co-investigators began in 1997 to recruit patients who had CD4 cell counts of 50-350 cells / mm^3. The patients had not been on protease inhibitor therapy previously but may have been on other antiretrovirals. Patients were randomly assigned to three groups: those given a PI regimen plus IL-2 administered by intravenous infusion; patients given a PI regimen alone; and patients given a PI regimen with IL-2 administered by subcutaneous injection.

"What we found after a year of treatment was that those who got the IL-2 either by subcutaneous injection or intravenous infusion had a markedly higher T-cell count, almost three times higher, than those who were on HAART alone," Mitsuyasu says. "The HAART patients would have a good increase, maybe a 200 T-cell increase, but the IL-2 groups would have a 600-cell increase at the end of the period."

The study was small, involving only 200 patients, so there are limited conclusions that can

be drawn from it, Mitsuyasu adds. "What we still don't know is whether just raising the T-cell count will be of clinical benefit to patients who have more advanced disease, although we suspect from other data that it will be of clinical benefit."

High doses lead to major side effects

High-dose treatment with IL-2 has some major side effects, including flu-like symptoms, fatigue, fever, and muscle aches, Mitsuyasu says.

Smith says the smaller doses of IL-2 do not have the same problem with side effects as the intermittent, higher-dose IL-2 therapy.

Another drawback to IL-2 therapy is the expense, which is not reimbursed by many insurers. Currently, IL-2 therapy is packaged for cancer patients in vials with the equivalent of 10 doses, costing about $500 per vial, Smith says.

"We have an experimental pharmacist who works with our clinical research center and draws up IL-2 in syringes for patients," Smith says. "We send patients home with 14 syringes with which they take a shot every day, and then they throw the syringe away."

Because the use of IL-2 remains experimental and HIV clinicians have no clear protocols for how to administer it, their best strategy would be to refer patients who are interested in IL-2 therapy to some of the ongoing clinical studies, Lane suggests.

For information regarding these studies, contact the NIH at (800) TRIALS-A or on the web at www.espritstudy.org. ■

Benefits of IL-2 therapy in treating HIV disease

Researchers at conference report latest findings

A quick look at the many recently published studies about Interleukin-2 (IL-2) therapy among HIV-infected patients clearly shows the popularity of this new approach to treatment.

Investigators from universities, government agencies, pharmaceutical companies, and other research centers around the world are studying IL-2 treatment.

Here is a brief summary of some of the more recently published studies:

• The National Institutes of Health (NIH) in Bethesda, MD, and Italian researchers evenly divided a group of 12 HIV-infected people between those who received IL-2 treatment with antiretroviral therapy and those who received antiretroviral therapy alone. The groups were matched for CD4 cell counts, viral load, and duration of antiretroviral therapy. After 30 days, the IL-2 treatment reduced viral isolation despite increasing CCR5 expression, suggesting that the combination of IL-2 and antiretroviral therapy may improve host defenses against HIV in patients receiving antiretroviral therapy.[1]

• A study of 115 patients showed a dramatic effect of daily, subcutaneous, low-dose IL-2 on the natural killer cell population, with increases significantly greater than a control group that did not receive IL-2 therapy. IL-2-treated patients also experienced a 3.52% increase in the mean percentage of CD4 T-cells, compared with a 1.33% increase among the control group. HIV-infected subjects receiving the daily, low-dose IL-2 therapy had substantially fewer adverse events than what is commonly experienced by patients on intermittent, high-dose IL-2 therapy.[2]

Using antiviral reactivity to monitor efficacy

• Researchers at Weill Medical College at Cornell University in New York studied in vivo antiviral activity before and after treatment interruption among patients who received low-dose IL-2 therapy. They found that plasma viral relapse occurred in all participants, reaching peak concentration at 2.5 weeks, but over the subsequent two weeks viremia was reduced. The study concluded that in vivo antiviral reactivity after antiviral interruption can be useful in monitoring the efficacy of different therapies.[3]

• California and Boston investigators conducted a randomized trial of IL-2 added to highly active antiretroviral therapy (HAART) and found that HIV-infected patients achieved higher CD4 cell counts when IL-2 was added to HAART.[4]

• Paris investigators found that treatment with intermediate doses of IL-2 combined with HAART resulted in a greater increase of CD4 cells than treatment with HAART alone.[5]

• Another NIH study of IL-2 plus HAART vs. HAART alone concluded that treatment with IL-2 added to HAART results in a significant enhancement of CD4 T-cells in the periphery, while there is no change in replication-competent HIV in resting CD4 T-cells compared with patients treated with HAART alone over a 12-month period of follow-up.[6]

• A large prospective randomized study of IL-2 in advanced HIV patients found significant increases in CD4 cell counts associated with both continuous intravenous and subcutaneous IL-2 compared to HAART alone after 60 weeks of therapy. The CD4 cell count continued to increase to week 84.[7]

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Researchers seek solutions for HIV treatment failures

Cavalry's a few years away from the rescue

Among the more sobering news presented at the 8th Conference on Retroviruses and Opportunistic Infections, held February 2001 in Chicago, was the evidence that HIV patients are having numerous side effects from antiretroviral medications.

Hyperlipidemia, fat redistribution, bone disease, metabolic problems, and the threat of heart disease are among the more prominent concerns of clinicians and researchers working in the field of HIV disease. These adverse effects, coupled with increasing evidence of drug-resistant virus, have brought attention to new classes of drugs that could fight HIV on different battlefields and therefore avoid the risk of the same types of drug resistance or side effects.

"We particularly need new drugs that will treat resistant virus," says **Charles F. Farthing**, MD, medical director of AIDS Healthcare Foundation (AHF) Healthcare Center in Los Angeles.

Farthing says the new class of drugs called the entry inhibitors could be one solution to the problem. Three different entry inhibitor classes are being studied: fusion inhibitors, attachment inhibitors, and coreceptor antagonists.

Toxicity concerns make new drugs necessary

HIV clinicians need new drugs because while protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) are potent, there is increasing concern about toxicity, says John Moore, PhD, professor of microbiology and immunology at Weill Medical College of Cornell University in New York.

"That's why the treatment guidelines are being changed," Moore says, referring to an announcement made at the retroviruses conference. "The reason for the change is because the PIs and RTIs accumulate toxicities, so people who have to take them have to minimize the amount of drugs they have to take. This highlights the need for new drugs with hopefully negligible or limited toxicity.

"The entry inhibitors have a completely different mechanism of action, which is one reason why this area of research has become so attractive," Moore notes, who has been researching fusion inhibitor compounds in recent years.

Variety of fusion inhibitors under study

Researchers presented a variety of data from studies of entry inhibitors at the recent retrovirus conference. A number of studies assessed the regulation of chemokine receptors CCR5 and CXCR4, while others showed evidence that a T-20 fusion inhibitor could be an effective addition to antiretroviral treatment. **(See story about abstracts of fusion inhibitors presented at the conference, p. 47.)**

"The whole idea behind this newest area of anti-HIV drug development is to look at blocking virus entry," says **Gregory Reyes**, MD, PhD, vice president of biological research, infectious diseases, and oncology at Schering-Plough Research Institute in Kenilworth, NJ.

Reyes, whose company is developing co-receptor antagonist compounds that target CCR5, spoke at the conference about the development of CCR5 antagonists as a new class of anti-HIV medications.

"The current set of inhibitors for HIV are directed to viral product, while the newer set of compounds targeting CCR5 would actually block the virus from attaching to the cell and entering the cell," Reyes explains. "What is critical for the virus to enter the cell is to first bind to CD4 and then utilize the co-receptors, and the two principal co-receptors are CCR5 and CXCR4."

HIV uses the CCR5 co-receptor early in the course of HIV infection. About 40% of the time, after the virus evolves and mutates and the disease progresses, the virus gains entry to the CXCR4 co-receptor, Reyes says.

"So the idea is if you can block virus entry with CCR5 and CXCR4 antagonists, then you are indeed blocking the viral life cycle," he says.

As an interesting side note, CCR5 is the major co-receptor for transmitted viruses, and the absence of CCR5 in humans has no negative effect on their health, Moore says.

"About 1% of Caucasians naturally lack CCR5, and that doesn't impact their health," Moore notes. "But that is strongly protective against HIV transmission, so if you have a complete absence of CCR5, it is strongly protective against getting HIV in the first place."

Schering-Plough currently has two co-receptor antagonist compounds under study. One called SCH-C is a CCR5 antagonist that has undergone Phase I clinical trials but has been put on clinical hold because of potential cardiac problems at very high doses, Reyes says.

"I think that some of the data I presented indicated that we are getting tremendous exposures in individuals and could easily achieve viral inhibitory levels at much lower doses than the doses where we saw the problem," Reyes says. "So now we're taking a close look at the data, and we're in the process of investigating preclinical models."

The second compound is Schering-Plough's SCH-D, which is a second-generation compound that has demonstrated very high potency in preclinical data. Research into this compound is still in its early stages, he says.

Drugs would be available in oral doses

Schering-Plough's two compounds would have the additional advantage of being taken orally, if they are successful in future clinical studies and make it to market. Reyes points out that such fusion inhibitors could be used in combination with current antiretroviral treatment, potentially boosting potency without increasing resistance to the current classes of antiretrovirals.

SCH-C has shown some resistance to the compound, but the other CCR5 antagonists appear to be active to this resistance, so there is no data suggesting a broad cross-resistance to the CCR5 antagonists, Reyes says.

A prototypic fusion inhibitor called T-20, developed by Trimeris Inc. of Durham, NC, is among the first of its kind to be tested in Phase II and Phase III clinical trials. T-20 has demonstrated some efficacy, Moore says.

"The problem with T-20 is it is an injectable and can't be taken orally, so it's not easy to take," Moore says. "This is a limiting factor, an inconvenience, but the drug still is useful to have, and T-20 does give you proof of concept, saying that a fusion inhibitor can have an effect in vivo."

Investigators also are looking at the use of fusion inhibitors as a preventive strategy, such

as using them in microbicides as a prophylactic measure, Moore says.

"In absence of a vaccine, and the world does not have an effective vaccine, how do we prevent sexual transmission of HIV?" Moore asks. "One possible way of doing that is to use this kind of compound to apply topically as a vaginal or rectal cream and see if it prevents virus from taking hold."

Moore predicts such studies are likely to take place with various fusion inhibitors, particularly because federal grant money is being directed to this area of research. "This is a credible area of research," he adds.

However, most entry inhibitor research is still years away from producing marketable products; therefore, other short-term solutions will need to be found to prevent patients from failing current therapy.

A solution might be advanced-generation antiretrovirals, such as the protease inhibitor lopinavir/ritonavir (Kaletra), which has not encountered resistance in PI-naive patients according to 48-week data. **(See story on Kaletra, p. 48.)**

"Kaletra is a well-studied drug, and I think it's fair to say it's more potent than anything else we have at the present time, and certainly within the protease inhibitor class, it's definitely the most tolerable," Farthing says. ■

Fusion inhibitors intercept virus at cell entry point

Researchers at the 8th Conference on Retroviruses and Opportunistic Infections, held in February 2001 in Chicago, presented a variety of studies on the use of fusion inhibitors as possible HIV treatment.

This new class of drugs is expected to fight HIV at its entry point into a cell and has the potential of being a well-tolerated and potent treatment that could be used in combination with antiretroviral medications.

Here is a brief summary of some of the fusion inhibitor research presented:

• A 36-amino-acid synthetic peptide called T-20 demonstrated the greatest plasma drug exposure in a cohort receiving subcutaneous doses of 60 mg/m^2 when compared with two lower-dose intravenous cohorts. Also, people receiving the subcutaneous dose achieved 12-hour troughs above the target level of 1,000 ng/mL.[1]

• Fusion inhibitors T-20 and T-1249, currently in Phase III and Phase I/II clinical trials, respectively, target a structural transition in the viral envelope glycoprotein gp41 required for membrane fusion and virus entry. This study found that virus coreceptor usage does not modulate sensitivity to the fusion inhibitors investigated, despite recent reports suggesting such a result.[2]

• Separate research involving fusion inhibitors T-20 and T-649 found that sensitivity to both of the synthetic peptides is strongly influenced by coreceptor specificity defined by the V3 loop of gp120.[3]

• A combination of CCR5 and CXCR4 inhibitors completely blocked infection with CCR5 HIV-1 infection, while each inhibitor alone was only partially effective in blocking CCR5 or CXCR4 HIV-1 infection. The research suggests that combinations of the inhibitors may prevent coreceptor switch variants and provide increased safety.[4]

• One abstract built upon previous research showing that double- and triple-drug cocktails of attachment inhibitors, coreceptor inhibitors, and fusion inhibitors potently and synergistically block HIV-1 entry over a wide range of experimental conditions in vitro. Investigators found that the data suggested a model in which the drugs act cooperatively to delay the recruitment of a critical number of fusion-active HIV-1 envelope glycoproteins to the site of the fusion pore.[5]

• A Phase II trial assessing various doses of T-20 used in combination with a protease inhibitor regimen found that patients who were failing therapy with at least one PI and who were naive to non-nucleoside reverse transcriptase inhibitors fared better with the addition of T-20 to their antiretroviral regimens. T-20 was well-tolerated and provided additional virologic and immunologic activity in addition to that provided by the oral antiretroviral regimen alone.[6]

• A pediatric study of T-20 indicated that short-term subcutaneous administration of T-20 is safe and well-tolerated in children, and the compound rapidly suppresses HIV.[7]

• Based on a promoter single nucleotide polymorphism (59029) differences in CCR5 expression on monocytes correlate with genotype (59029 G / G = low; G / A = medium; A / A = high CCR5 expression on monocytes). There's a logical increase in viral propagation of R5 viruses in cells that have higher levels of CCR5 expression.[8]

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Kaletra is potent addition to antiretroviral therapy

48-week data found no PI resistance

Clinicians and patients who are disenchanted with protease inhibitors (PIs) typically have two major concerns: The drugs cause side effects that make life uncomfortable for patients, and clinicians are finding more PI resistance among their HIV patients, possibly because side effects of PIs are discouraging patient adherence to PI regimens.

"A lot of doctors, including myself, have been avoiding protease inhibitors because of the gastrointestinal side effects of nausea, bloating, gas, and diarrhea, which made patients very uncomfortable," says **Charles F. Farthing**, MD, medical director of AIDS Healthcare Foundation (AHF) Healthcare Center in Los Angeles. The community-based provider of HIV medical care serves 4,500 patients in nine clinics.

"So patients would stop taking the drugs and didn't adhere well to them, and of course, if you don't do that, you are lost," Farthing adds. He has been involved in research into a new drug that seems to answer some of these concerns: the next-generation PI lopinavir / ritonavir (Kaletra), produced by Abbott Laboratories of Abbott Park, IL.

"Kaletra came out as an approved drug last September, and it was available in expanded access for a good 18 months before that, so we have good clinical trial experience with the drug," Farthing says. "It's a well-studied drug, and I think it's fair to say that it's more potent than anything else we have at the present time, and certainly within the PI class, it's definitely the most tolerable."

A 48-week study of treatment-naive patients showed that of those who experienced viral rebound while being treated with lopinavir, none were found to have PI-resistant HIV by genotypic analysis. By comparison, 32% of the patients treated with a nelfinavir-based regimen had PI-resistant HIV, according to data presented at the 8th Conference on Retroviruses and Opportunistic Infections, held Feb. 4-8 in Chicago.

In fact, none of the patients in a two-year lopinavir clinical trial of naive patients have become resistant to the drug, Farthing notes. "But a few people who previously were resistant to other PIs and then were introduced to Kaletra became resistant to it," he adds.

In a separate study presented at the conference, investigators showed that at 48 weeks of treatment with lopinavir and other antiretrovirals, 84% of children who were treatment-naive and 75% of children who had treatment experience had undetectable levels of HIV. Only 2% of the 100 children were forced to discontinue treatment because of side effects. Unlike other PIs, lopinavir is indicated for children as young as six months.

Lopinavir research also may address some clinicians' concerns about cross-resistance, Farthing says.

A study of viral isolates from 56 patients who already were resistant to a single protease inhibitor but had not taken lopinavir prior to the study were treated with lopinavir for rescue. Four of these patients subsequently developed resistance to lopinavir, but those viruses still showed susceptibility to amprenavir and saquinavir.

"Some doctors have been concerned about using this protease inhibitor first because if a virus becomes resistant to it, they thought it would become resistant to all other PIs," Farthing explains. "This research demonstrates that that certainly is not always the case."

Lopinavir associated with increased fat levels

Lopinavir's main drawbacks are the same ones found with other protease inhibitors. While lopinavir apparently produces fewer gastrointestinal side effects, it is associated with elevated levels of cholesterol, triglycerides, and plasma glucose, similar to the effects seen in patients taking other PIs, Farthing says.

Also, the drug may be associated with a similar amount of fat redistribution, although it's too early to know for certain.

"Like other PIs, Kaletra can cause raised fat levels, and that's something the doctor has to watch for and either treat or take the patient off of Kaletra," Farthing says. "It's not a big enough concern when putting a patient on the drug in the first place, but it might be a reason to switch away from the drug if it becomes a problem."

The drug is taken as three pills twice a day, and there are no food restrictions.

"The most useful thing is Kaletra can salvage some patients because it can treat some resistant viruses, and I suppose that's what impresses me the most about the drug," Farthing adds. ■

Clinical study examines HIV-related lipodystrophy

Fat redistribution syndrome still poorly understood

[Editor's note: ***Donald Kotler****, MD, a professor of medicine at Columbia University and chief of GI at St. Luke's Roosevelt Hospital Center in New York City, answers questions about the problem of lipodystrophy, a potential treatment for it, and other issues related to the long-term adverse effects now associated with HIV disease and antiretroviral therapy. Kotler is involved with research into the use of somatropin (Serostim), a recombinant human growth hormone that appears to be of benefit to patients who have lipodystrophy, also called HIV-Associated Adipose Redistribution Syndrome. A Serostim clinical trial currently is recruiting 200 patients at trial sites across the United States.]*

AIDS Alert: Are lipodystrophy and other adverse effects of antiretroviral medications, including heart disease, the biggest challenges that physicians face in treating HIV patients these days?

Kotler: The relationship to heart disease is not yet established. My own personal feeling is that that link will be made; it has not yet been made, and in my own mind that is perhaps the most significant downside of therapy. It is not the only one, and perhaps the other major downside of therapy would be osteopenia, bone loss, which has also come up over the past few years as being an important consideration. Both of these problems are serious enough in the adult HIV population but maybe even more problematic in the pediatric population.

AIDS Alert: Tell us a little more about that, please.

Kotler: One of the findings that's been made in relationship to lipodystrophy or the potential

bad outcomes that would come from lipodystrophy, such as heart disease, is that it's a time-dependent phenomenon. People have not yet demonstrated clear evidence of increased risk of heart attacks because the follow-up is so short. The data presented at the 8th Conference on Retroviruses and Opportunistic Infections in Chicago, however, suggested that we will be seeing an increased risk of heart disease, but it may take several years of follow-up before that becomes manifest.

When you consider there is a time element, who has more time for bad outcomes to develop than little children? If we're worried that adults may have a problem over the course of five to ten years, how about little children whose course of disease is a whole lifetime, maybe thirty to forty years? If there is going to be a problem, then it may be magnified in pediatric patients.

AIDS Alert: What is being done right now in the field of research and in treatments that are available to counteract this phenomenon?

Kotler: There is really one question that has to be asked, and that is: What is the phenomenon? What is lipodystrophy? There is a constellation of signs and symptoms that have developed, and they include changes in the body's metabolism. Those changes are specifically high blood lipids and insulin resistance, a pre-diabetic condition, and a change in the body shape.

'Who has more time for bad outcomes to develop than little children? If we're worried that adults may have a problem over the course of five to ten years, how about little children, whose course of disease is a whole lifetime, maybe thirty to forty years?'

The change in the body's shape includes both a loss of fat and a loss of fat especially from the fat under the skin. Much of the fat in the human body is located underneath the skin, as opposed to being deep inside. So it's the fat under the skin that seems to be disappearing. Instead, fat deep inside the belly appears to be increasing in size. That's a typical shape — the big belly, skinny arms and legs — of people who have diabetes and heart disease as an associated problem. To see that kind of shape coming up in an HIV-positive person is what originally made people worry about cardiac disease as a bad outcome.

AIDS Alert: What can be done about it now, and what do we need to do in the future?

Kotler: Nobody knows why it's occurring. No one knows for certain whether it is a single phenomenon or a group of related phenomena, whether it has a single cause or whether it comes about for a variety of reasons.

We're unsure which paradigm or model lipodystrophy really fits. Is lipodystrophy like tuberculosis, where if you are exposed to the TB bug you are bound to get it? Or is lipodystrophy more like a stroke or a heart attack, in which certain aspects will make it more likely or less likely, but nothing will determine that you absolutely will or will not get the disease?

Since we don't know what lipodystrophy really is, we can't really have a treatment for lipodystrophy, for all of it. It seems more and more that it's not a single disease, but multiple diseases, and problems of high blood fats may be different from the ones that lead to fat loss. For that reason, people are looking more and more at trying to treat the individual problems. People are looking at therapies for high blood lipids. People are looking at therapies for food resistance. People are looking at different therapies for fat loss and different therapies for fat gain.

In fact, the Serostim trial is really directed at the fat gain associated with lipodystrophy. It's to get rid of the excess fat. Most people think of the drug as an anabolic agent, a drug that puts on muscle and is a performance enhancer. But when you look at the studies that have been done, it really is quite a powerful fat burner, so that almost as much lean mass as is gained is actually lost in fat. So someone can take a drug like Serostim and have a huge change in the body's composition and yet not really change body weight much at all. They may gain four to five pounds of lean mass and lose four to five pounds of fat, and body weight doesn't change very much.

AIDS Alert: How are you and other researchers hoping Serostim will address the problem of lipodystrophy?

Kotler: One of the things that's unusual about lipodystrophy is that it's kind of familiar. It's kind of familiar in the sense that people have been seen for a long time who have a kind of lipodystrophy-type of appearance. It's a syndrome called the metabolic syndrome X, and this metabolic syndrome is one that is associated with fat accumulation in the belly, similar to where it

accumulates in lipodystrophy patients; high blood lipids, insulin resistance, and a risk of heart disease or stroke.

You may have heard of a designation of women shaped like apples or pears. The importance of trying to distinguish between women shaped like apples and women shaped like pears is the fact that apples get diabetes, apples get heart attacks, and pears do not. The body shape is related to the outcome and to the metabolic phenomenon, like diabetes, heart attacks, etc., and that's not HIV infection. That's a phenomenon of the body itself. We've seen this before.

Interestingly enough, studies have been done that have suggested that people who have fat accumulation in the belly, of a kind that you would see similar to the HIV-positive people, appear to have some impairment in the secretion of growth hormone. In addition, people who are growth-hormone deficient have increased fat in the belly, and the metabolic profile is beginning to look more and more over time like someone is getting set to have a heart attack. If that's not enough, treatment of such people with growth hormone therapy actually makes the fat in the belly less, and that's all in non-HIV-infected people. Now, most recently, studies in HIV-infected people have shown essentially the same thing: that HIV-infected people with excess fat in the belly also have a decrease in the secretion of growth hormone. So perhaps it's a similar phenomenon.

So the thought of replacing growth hormone in an attempt to decrease fat in the belly — and maybe, at the same time, to decrease cardiac risk — becomes a logical extension of what's known in the non-HIV infected field.

There are other things to be studied for treatment of lipodystrophy. There are no real data for testosterone, but testosterone can burn fat just as it increases lean mass like Serostim.

AIDS Alert: Tell us a little about what the studies to this point have shown with regard to treatment of lipodystrophy.

Kotler: My lab, along with a community research group called Community Research Initiative on AIDS in New York City, performed a pilot study initially looking at 30 HIV-infected subjects, mostly men but some women as well, who were given the standard dose of Serostim, the same dose we would use for someone who was malnourished, wasting. We found a very positive effect in increasing lean mass and burning fat. We actually saw a stronger response than we've seen when Serostim was used just for wasting. In fact, associated with that was a decrease in the accumulated fat in the belly, but the amount of fat in the belly appeared to fall disproportionately. Whereas the total fat in the body fell by about 20%, the amount of fat under the skin fell by less than 10%, and the amount of fat in the belly fell by more than 40%. So it appeared to be there was a preferential loss of fat from the abdomen. The

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effect that was seen in the HIV-positive people with lipodystrophy was actually greater than the effect when it was studied for wasting.

It was not all good news. When the drug was stopped, the fat began to reaccumulate. So this was not a cure; it was a treatment. When you think about it, it was much the same as any hormonal treatment. As I mentioned, there is some data from another lab that suggests that there is a suppression of growth hormone secretion in patients with lipodystrophy. What this would suggest is that when the drug was given, a new steady state was set up, and when the drug was taken away, the drug reverts back to its prior steady state. It is not a cure, it's just the physiology, the steady-state phenomenon.

We realized that we didn't have a cure and that we were just altering a steady state. The drug appeared to be moderately toxic; there were a fair number of side effects to using the drug. So after the first study was finished, we had a second part of the study in which we gave a much lower dose of therapy. This showed that the lower dose of therapy had fewer side effects, and it still had some efficacy — less, but some.

Maybe the amount of growth hormone that's given could be a much smaller amount than what we have been using for wasting, and that could be a great benefit, because one of the downsides to Serostim therapy is cost. If it's true that it might even need a fraction of the doses that have been given, then perhaps that might be given at a fraction of the cost.

One of the aims of a new study is to reduce the amount of growth hormone used for treatment. In this study, we're using much lower doses than what we were using before, based upon what we found in the pilot.

AIDS Alert: Would you please describe the study?

Kotler: It's a double-blind, placebo-controlled trial looking at two doses, both lower than the dosage currently being used. After the initial 12 weeks, there is a prolonged open-label phase. It's a re-randomization so people who were given no drug will be given a drug to take, and the opportunity for evaluating lower doses of drugs for much longer periods of time will be available.

AIDS Alert: Where can clinicians and HIV patients find more information about the study?

Kotler: For more information about the Serostim clinical trial, call (888) 566-5593 or visit Serono Inc.'s web site at www.seronostudies.com. ■

CE objectives

After reading this issue of *AIDS Alert*, CE participants should be able to:

- identify the particular clinical, legal, or scientific issues related to AIDS patient care;
- describe how those issues affect nurses, physicians, hospitals, clinics, or the health care industry in general;
- cite practical solutions to the problems associated with those issues, based on overall expert guidelines from the Centers for Disease Control and Prevention or other authorities and/or based on independent recommendations from specific clinicians at individual institutions. ■