Interferon May Offer First Drug Therapy for Diabetic Retinopathy

New Research Showing That α-Interferon Blocks New Blood Vessel Formation in the Iris of Monkeys May Point the Way to New Treatment for Diabetes Retinopathy.

Eye researchers are looking to the immune system for new ways to prevent, treat, or reverse proliferative retinopathy, the most serious form of diabetic retinopathy.

Proliferative retinopathy is marked by the development of new blood vessels, or neovascularization, in the retina. Joan Miller, William G. Stinson, and Judah Folkman, all of Harvard Medical School and the Massachusetts Ear and Eye Infirmary in Boston, have found that the lymphokine α-interferon delivered systemically can slow or stop the growth of new small vessels in the irises of monkeys.

So far the work has been performed only in animals, and α-interferon's effects have not been shown directly on blood vessels in the retina. However, controlled clinical trials on one form of neovascularization in the eye are being planned. The work could lead to a new mode of treatment for proliferative retinopathy, a major factor behind the 12,000 new cases of blindness attributable to diabetes in the United States each year.

In proliferative retinopathy, new blood vessels grow on the retina or on or near the optic disk. These blood vessels are fragile and rupture easily, and a major hemorrhage can cause a sudden loss of vision. The scarring that accompanies recurrent hemorrhaging can lead to permanent loss of vision.

Approximately 700,000 people in the United States have proliferative retinopathy, with ~65,000 new cases being diagnosed each year. Proliferative retinopathy rarely develops within the first 5 yr of diagnosis of insulin-dependent diabetes mellitus, although ~26% of people diagnosed with insulin dependent diabetes mellitus will develop proliferative retinopathy within 10 yr. Less than 4% of people with non-insulin-dependent diabetes develop proliferative retinopathy within the first 4 yr of their diabetes diagnosis. After 15 yr with the disease, from 5 to 20% of those diagnosed with non-insulin-dependent diabetes will develop proliferative retinopathy.

The new research is the by-product of research into the formation of new blood vessels, or angiogenesis. New blood vessel formation occurs naturally during development, but can also signal the progression of disease. At the International Diabetes Federation Congress and ADA Scientific Sessions held last June in Washington, DC, Folkman noted that angiogenesis research started some 20 yr ago "as an inquiry into how tumors stimulate new vessels." Today, he says, "studies of angiogenesis have led to a new understanding of some of the vascular complications of diabetes."

Angiogenesis was first linked to interferon ~10 yr ago. Until then, interferon has been known mainly for its ability to stimulate the production of T lymphocytes. Then studies showed that the protein could slow the migration of endothelial cells during the growth of new blood vessels. Soon after, other researchers showed that α-interferon slows down blood vessel growth in mice.

In 1989, Carl W. White and colleagues at the University of Colorado Health Sciences Center in Denver used α-interferon to treat a child with a hemangioma, a mass resulting from the proliferation of capillaries. Hemangiomas can occur anywhere in the body, and can be fatal when they occur in certain organs. White's patient had a hemangioma in the lung, a rare and usually fatal condition. Treatment with interferon, however, caused the hemangioma to regress.

In 1990, Folkman and several colleagues began a clinical trial of α-interferon treatment for hemangioma. Their results validated White's results; the mortality rate fell from 60 to 5% for those treated with α-interferon.

The positive results led Folkman and colleagues to consider applying the treatment to neovascularization in the eye. "It turns out," he says, "that the new capillary blood vessels in hemangioma grow at very similar rates and by similar rules as do new vessels in the eye." The same angiogenic molecules appear in the same sequence to induce capillaries to grow.

Folkman, Miller, and their colleagues blocked branch retinal veins in the eyes of monkeys, a procedure that induces intense capillary growth and neovascularization in the iris. A total of 11 eyes were studied.

After the new blood vessels appeared, eight were treated with α-interferon, while three were left untreated.

The α-interferon was given twice a day at twice the normal human dose. After 14 days, new blood vessel growth began to slow in the eyes treated with α-interferon. Within 3 wk, the disease regressed in all of the treated eyes. Among the eyes that had not been treated, however, the disease progressed steadily.

Although the researchers speculate that α-interferon may have a similar effect on the retina as on the iris, that remains difficult to prove. Currently, there is no good animal model of diabetic retinopthy, says Miller. "It's hard to get new vessels to grow from the retina of animals," she says. "There are other models in other parts of the eye—the cornea, for example—but it's a bigger leap from treating that to treating diabetic retinopathy."

Still, on the strength of the studies on irises, Miller, along with Tony Adamis, David Guyer, Evangelos Gragoudas of the Massachusetts Eye and Ear Infirmary, and Larry Yanuzzi of the Manhattan Eye, Ear, and Throat Hospital in New York are now planning a pilot study involving people with choroidal neovascularization, in which new blood vessels grow in the vascular later between the retina and the sclera of the eye.

The researchers hope to uncover the mechanism by which α-interferon reverses neovascularization. Miller speculates that α-interferon may work both by inhibiting the growth of endothelial cells and by suppressing their migration; both processes are necessary for the growth of blood vessels. "But in terms of what α-interferon is doing in an animal system, it's probably much more complicated than that," she says.

A more immediate question is whether α-interferon treatment for some forms of diabetic retinopathy will represent an improvement over treatment now available. Currently, patients with proliferative retinopathy are treated with scatter laser photocoagulation. In this treatment, laser burns on the retina are used to arrest neovascularization, possibly by stopping the production of angiogenic factors. Laser photocoagulation can reduce the risk of severe vision loss by as much as 60%

Matthew Davis, professor of ophthalmology at the University of Wisconsin at Madison School of Medicine, points out that laser treatment is a very satisfactory therapy for diabetic retinopathy. "I doubt that any pharmacologic treatment that presumably would have to be kept up for a year or two . . . might be useful in eyes that failed photocoagulation."

Miller counters that although photocoagulation is effective, it has side effects that may make drug therapy attractive. "You end up having to destroy tissue that, if not totally normal, is functional," she says. "If you had a treatment that could stop the vessels from growing without having to destroy the tissue, it would be a preferred treatment."

Davis argues that α-interferon could actually have greater clinical usefulness in the treatment of age-related degeneration of the macula, the central area of the retina responsible for final vision. "In the age-related macular degeneration area, the current treatment is substantially less satisfactory," he notes, and a new drug potentially more important.

Indeed, at the meeting of the American Academy of Ophthalmology last October, Wayne Fung, a San Francisco ophthalmologist, reported some positive, but preliminary, findings on treating macular degeneration with interferon. "In general, I'm seeing visual improvement in at least half the patients and stabilization of the condition in all the patients."

Another important question to be answered concerns α-interferon's toxicity. In this area, α-interferon has a track record. The Food and Drug Administration has approved its use for hairy cell leukemia and AIDS-related Kaposi's sarcoma. In general, α-interferon produces a flulike response, including fatigue, muscle aches and pains, and low-grade fevers. But Miller added that it can also decrease the number of lymphocytes and affect liver enzymes

Although those side effects are controllable for many people, "the more medical problems people have, the more difficult the drug is to use," Miller says. It may prove difficult to treat the sickest people with diabetes who could benefit most. Other inhibitors of angiogenesis that are more effective and less toxic than α-interferon, may be developed, she says.

—Joe Wakelee-Lynch, *Associate Editor for Diabetes Forecast* and Peter Banks, *Editorial Director*