Interferon alfa–associated retinopathy

ROBERT B. CHAMBERS, DO; ALAN DOWNIE, MD;
BRITTAIN FOOTE, BS; FREDERICK H. DAVIDORF, MD

Interferon alfa and its related compounds have been used for more than 10 years in the treatment of a number of conditions including viral illnesses, childhood hemangiomas, various cancers, and leukemia. The potential applications for this class of medication continue to grow. The use of interferon alfa in experimental protocols has also increased, thus making it more likely that new indications will be discovered. It is probable that primary care physicians will be called on to initiate therapy or will see patients being treated with interferon in their practice. We report the development of interferon-related retinopathy in a 43-year-old man while he was receiving experimental treatment with interferon alfa for hepatitis B virus and hepatitis C virus infection. The vision loss was acute and only partially reversible. Interferon, its mechanism of action, and the past literature are briefly discussed.

(Key words: Interferon, interferon alfa, retinopathy, angiogenesis antagonists)

Use of the interferons has increased dramatically since their introduction more than 10 years ago. A review of the literature since 1985 finds more than 3000 articles in which interferon alfa (IFN-α) was investigated in some way. The studies of the larger family of interferons have been reported in nearly 20,000 articles during that time. Interferon is an endogenous glycoprotein that can be derived from human leukocytes and fibroblasts; and it is now available in a recombinant form.

Early reports concentrated on the antiviral effects. Currently, the interferons have been used to treat leukemia.[1] childhood hemangiomas,[2] Kaposi's sarcoma,[3] age-related macular degeneration,[4] lymphoproliferative disorders,[5] melanomas,[6] metastatic cancers,[6] and chronic non-A, non-B hepatitis. Numerous experimental protocols exist including at least one for IFN-α in the treatment of hepatitis C.

The reported side effects of interferon therapy include general systemic symptoms, such as malaise, weakness, nausea, and fever. Other systemic complaints reported are depression, chest pain, arrhythmias, paresthesia, and diarrhea.[7-9] Laboratory abnormalities noted were elevated levels of liver enzymes and proteinuria. Additional side effects include rash, pruritus, alopecia, and weight loss.

We describe interferon-associated retinopathy in a patient with diabetes mellitus, hypertension, and hepatitis.

From the William H. Havener Eye Center, The Ohio State University,Columbus, Ohio.
Correspondence to Robert B. Chambers, DO, 456 W Tenth Ave, Columbus, OH 43210.

Report of case

A 43-year-old man with a 5-year history of diabetes mellitus and a 10-year history of hypertension and no previous eye complaints came to our attention because of a 5-week history of blurred vision in both eyes (OU). The patient's blood sugar level had been under good control (range, 110 mg/dL to 130 mg/dL). The patient went to his optometrist, who was unable to correct the blurred vision with glasses. At that time, it was noted that the patient had "retinal hemorrhages OU." The patient was referred to an ophthalmologist for further evaluation. He was next referred to the Retina Service at the Ohio State University Medical Center.

On review of the patient's history, we noticed that he was being treated with IFN-α for hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. The patient had serologic test findings consistent with chronic HBV infection as evidenced by serum positive hepatitis B surface antigen, hepatitis B_e antigen, and hepatitis B core antibody (anti-HB_c). The patient was also noted to have HCV positivity by both the enzyme-linked immunosorbant assay (ELISA) and radioimmunoassay. At the time of our examination, the patient had been receiving IFN-α, 5×10^6 U/d for 6 months. Other medications included insulin, fluoxetine hydrochloride (Prozac), nifedipine (Procardia), and lorazepam (Ativan).

The patient's best corrected visual acuities were 20/200 right eye and 20/60 left eye. Ophthalmoscopy revealed numerous "cotton-wool spots" (infarcts) and intraretinal hemorrhages OU. The right eye also had marked macular edema and a large infarct involving the macula (*Figure 1*). A fluorescein angio-gram demonstrated marked hypoperfusion of the macula of the right eye as well as multiple arteriolar occlusions (*Figure 2*). The angiogram of the left eye was similar. Blood pressure was 170/85 mm Hg. A systemic evaluation revealed normal blood cell counts, negative human immunodeficiency virus status, serum anti-HB_c positivity, and elevated erythrocyte sedimentation rate and complement levels. In consultation with the patient's internist, it was agreed to stop the interferon therapy but have the patient continue taking all other medications. The IFN-α therapy was discontinued 3 days after the initial ophthalmologic examination.

During an examination 6 weeks later, the patient noticed a small subjective improvement in his visual symptoms, but best corrected visual acuity remained 20/200 in the right eye and 20/60 in the left eye. In the interim, atenolol (Tenormin) was added to the regimen for blood pressure control. Ophthalmoscopy revealed pronounced improvement in the macular edema of the left eye with substantial resolution of the cotton-wool spots and intraretinal hemorrhages.

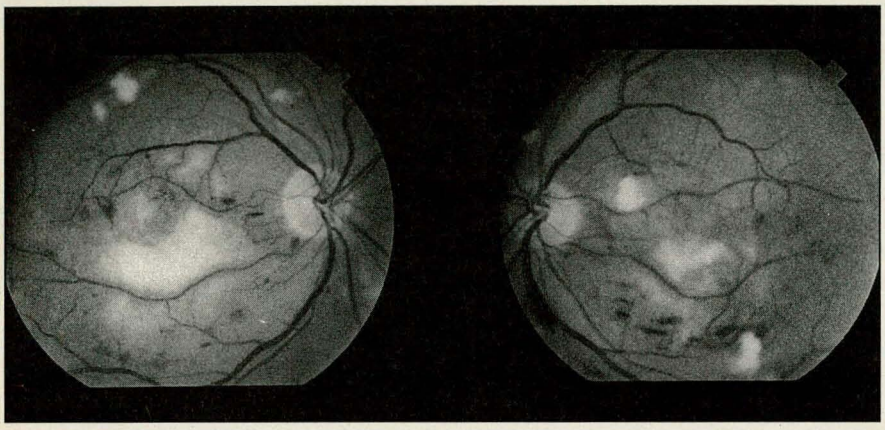

Figure 1. *Bilateral fundus photographs show intraretinal hemorrhages, nerve fiber infarcts (cotton-wool spots), and massive macular edema in left eye 6 months after start of treatment with interferon alfa.*

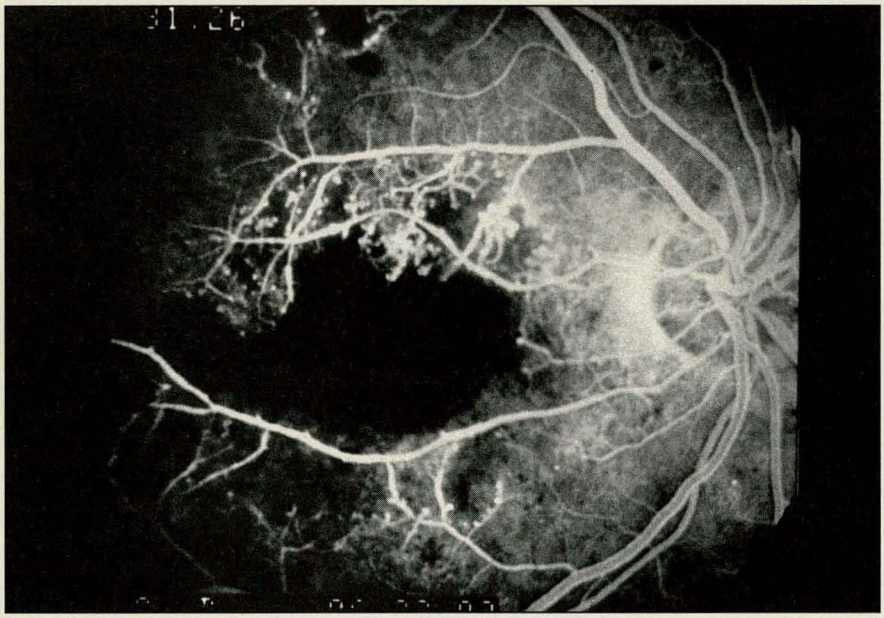

Figure 2. *Fluorescein angiogram of right eye. Notice large region of nonperfusion of the macula with multiple apparent microvascular occlusions.*

Further follow-up occurred at 4 months after the initial presentation. Visual acuity in the right eye remained unchanged at 20/200, but the acuity of the left eye improved to 20/25. The intraretinal hemorrhages, cotton-wool spots, and the macular edema of the left eye had almost completely resolved (*Figure 3*). The fluorescein angiogram revealed resolution of the macular edema, but the macular nonperfusion was unchanged (*Figure 4*). Note in *Figure 3* that the patient retains findings consistent with moderate nonproliferative diabetic retinopathy, but most of the findings have resolved after discontinuing the IFN-α therapy.

Discussion

Interferons are a family of glycoproteins that occur naturally but are now available in a recombinant form. They were first thought important when they were found to be secreted by human leukocytes in response to viral infections. Interferon alfa has been used since 1984 in treatment of hairy-cell leukemia.[2] Since that time, the uses for the interferons have expanded considerably. They have been shown to have an enhancing effect on the primary and secondary immune response.[10] Perhaps significantly for our patient with hepatitis, interferons have been shown to exacerbate immune-mediated diseases, such as polyarthropathy and thyroiditis.

Interferons have been found to inhibit the proliferation and migration of vascular endothelial cells and lymphocyte-induced angiogenesis.[11] Systemically administered IFN-α has caused regression of experimentally induced iris neovascularization and has been used to treat hemangiomas in infants.[2] This antiangiogenic effect has led to the investigation of IFN-α in ophthalmic diseases associated with neovascularization, such as the exudative form of age-related macular degeneration and potentially for the neovascular stage of diabetic retinopathy.

Interferon-related retinopathy was first reported by Guyer and associates.[12] They describe the development of signs of retinal nonperfusion, cotton-wool spots, hemorrhages, and capillary dropout in 10 patients being treated with systemic interferon after therapy was started. Five of the patients in their series had coexisting diabetes mellitus as a potential factor to explain the retinal findings. They state that these patients "had no other ocular signs of diabetes or hypertension." This observation was also true in our patient. Our patient had been examined elsewhere by a retinal surgeon 2 months after starting interferon therapy for HBV/HBC infection and found to have only mild nonproliferative diabetic retinopathy.

The resolution of much of the retinopathy after the discontinuance of the interferon therapy with little change in our patient's overall medical condition argues strongly for the patient's vision loss representing a case of interferon-related retinopathy. The fact that this patient and five of the patients in Guyer and coworkers' series[12] had coexistent diabetes may suggest a possible mechanism for the retinal vascular damage. The histopathologic correlate of the retinal findings in our patient and in those of the other patients described with

interferon retinopathy is an infarct of the nerve fiber layer of the retina known as a cotton-wool spot. There is nonperfusion of the retinal capillaries in the region and swelling of the superficial retina where cytoid bodies can be identified histologically.

Comment

Guyer and associates[12] suggest that IFN-α therapy may cause deposition of immune complexes in the retinal vasculature with subsequent leukocyte infiltration leading to capillary closure, retinal ischemia, and cotton-wool spot formation. Patients with chronic hepatitis are known to have circulating immune complexes and patients with diabetes and hypertension have been shown to have damage to endothelial cells, retinal ischemia, and capillary nonperfusion. It may be that in patients in whom just this combination of factors exists, interferon therapy may be most likely to cause retinopathy. All physicians—especially primary care physicians, oncologists, rheumatologists, and pediatricians—should be aware of this potential risk to patients treated with interferons. Patients with conditions predisposing to vascular nonperfusion should be followed up closely and visual complaints should be investigated thoroughly.

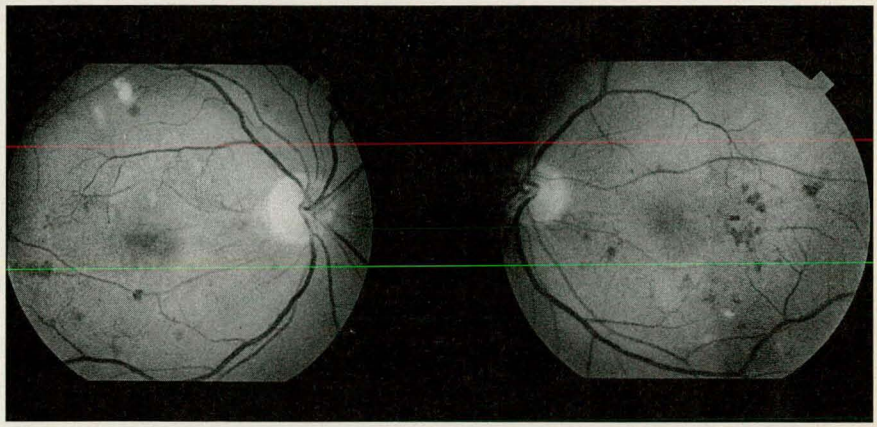

Figure 3. *Bilateral fundus photographs showing pronounced resolution of retinopathy. Notice that patient maintains what is probably a basal level of moderate nonproliferative retinopathy.*

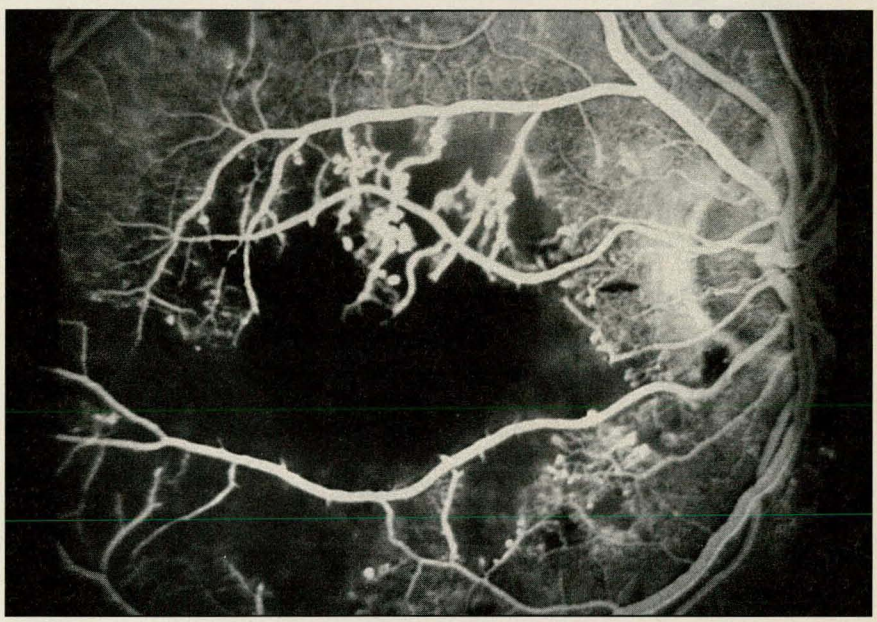

Figure 4. *Fluorescein angiogram 6 months after discontinuing interferon therapy. Notice that region of nonperfusion of right macula persists despite improved clinical appearance.*

References

1. Quesada JR, Reuben J, Manning JT, Hersh EM, Gutterman JU: Alpha interferon for induction of remission in hairy-cell leukemia. *N Engl J Med* 1984;310:15-18.

2. Rickets RR, Hatley RM, Corden BJ, et al: Interferon-alpha-2a for the treatment of complex hemangiomas of infancy and childhood. *Ann Surg* 1994;219:605-614.

3. Krown SE, Real FX, Cunningham-Rundles S, et al: Preliminary observations of the effects of recombinant leukocyte A interferon in homosexual men with Kaposi's sarcoma. *N Engl J Med* 1983;308:1071-1076.

4. Fung WE: Interferon alpha 2a for treatment of age-related macular degeneration. *Am J Ophthalmol* 1991;112:349-350.

5. Trigg ME, de Alarcon P, Runelhart S, Holida M, Giller R: Alpha-interferon therapy for lymphoproliferative disorders developing in two children following bone marrow transplants. *J Biol Response Mod* 1989;8(6):603-613.

6. Sharpe RJ, Byers HR, Scott CF, Bauer SI, Maione TE: Growth inhibition of murine melanoma and human colon carcinoma by recombinant human platelet factor 4. *J Natl Cancer Inst* 1990; 82:848-853.

7. Product Information Sheet. Nutley, NJ, Roche Laboratories, 1988.

8. Product Information Sheet. Kenilworth, NJ, Schering Corp, 1988.

9. Jones G, Itri L: Safety and tolerance of recombinant interferon alfa-a (Roferon-A) in cancer patients. *Cancer* 1986;57:1709-1715.

10. Yilma T, Owens S, Fennie EH, Anderson KP: Enhancement of primary and secondary immune responses by interferon-gamma. *Adv Exp Med Biol* 1989;251:145-152.

11. Tsuruoka N, Sugiyama M, Tawaragi Y, et al: Inhibition of in vitro angiogenesis by lymphotoxin and interferon-gamma. *Biochem Biophys Res Commun* 1988;155(1):429-435.

12. Guyer DR, Tiedman J, Yannuzzi LA, et al: Interferon-associated retinopathy. *Arch Ophthalmol* 1993;111:350-356.