Bevacizumab and Retinal Ischemia

Dear Editor:

The unselective anti–vascular endothelial growth factor (VEGF) antibody bevacizumab (Avastin, Genentech, Inc., South San Francisco, CA) has been used for the treatment of diabetic retinopathy (DR), with early promising results.[1,2] However, little is known about its effect on retinal ischemia, which is a major factor in the pathogenesis and progression of DR. We therefore investigated the longitudinal changes in central and peripheral ischemia after intravitreal bevacizumab treatment by means of fluorescein angiography using a novel high-resolution ultrawide-field scanning laser ophthalmoscopy system.

Consecutive patients who underwent intravitreal bevacuzimab at the Department of Ophthalmology, Ludwig-Maximilians University in Munich were evaluated. All had diffuse clinically significant macular edema and nonproliferative DR, had not responded to photocoagulation, and had not received any previous posterior segment surgery. All patients underwent ultrawide-field fluorescein scanning laser ophthalmoscopy angiography (Optomap 200 fa, Optos, Dunfermline, United Kingdom) and optical coherence tomography (Carl Zeiss Meditec, Jena, Germany) before and 4 weeks after the intravitreal injection of 1.25 mg of bevacizumab, as described previously.[1] Details of the scanning laser ophthalmoscopy fluorescein angiography examination technique have been described elsewhere.[3] In brief, a series of digital images was taken after the rapid intravenous injection of 5 ml of a 10% solution of fluorescein. Each image covers an area of approximately 180° on the retina with an optical resolution of 3900×3072 pixels for that angle. This results in approximately 17 to 22 pixels per degree, yielding excellent imaging characteristics of both the retinal center and the periphery. The nonconfocal setup of the machine ensures simultaneous focus of all imaged structures.

We assessed 2 pictures per patient eye at baseline and 2 at the 1-month follow-up: one from the early phase (<60 seconds) and one from the late arteriovenous phase (approximately 5 minutes). To assess central ischemia, caliper measurements of the width of the foveal avascular zone were performed. For grading peripheral retinal ischemia, we applied a special grid scheme (Fig 1 [available at http://aaojournal.org]) to the normalized images: the central field was placed in the macula's center, the diameter of 1 field adjusted to match 1 disc diameter. Peripheral retinal ischemia was quantified by counting the number of fields out of the central 48 fields of the grid that were affected by significant ischemia (>50% of the field). Nonperfusion in terms of capillary dropout was defined analogous to literature reports.[4] All measurements were performed by one experienced investigator (LC) in arbitrary sequence who was masked to the clinical data and measurements.

In 19 individuals, mean visual acuity (VA) before intravitreal bevacizumab was 0.87±0.37 logarithm of the minimum angle of resolution (logMAR) (i.e., 20/145). After 1 month, there was some improvement, of 0.13±0.28 logMAR ($P = 0.08$). Central macular thickness on optical coherence tomography was 440±146 μm, the foveal avascular zone diameter was 655±192 μm before therapy, and neither thickness nor diameter changed 4 weeks after therapy. Mean peripheral retinal ischemia decreased significantly, from 10.8±9.4 fields to 7.8±5.6 fields ($P = 0.02$), 1 month after intravitreal injection when assessed on early phase fluorescein angiography images. On late-phase images, the decrease was even more pronounced, from 14.8±10.5 to 8.6±6.3 fields ($P<0.001$). Some examples of typical changes are illustrated in Figure 2 (available at http://aaojournal.org). There was no correlation of peripheral ischemia to VA, optical coherence tomography thickness, or foveal avascular zone size.

In summary, we could show semiquantitatively in a small series of patients with DR that intravitreal unselective anti-VEGF treatment improved peripheral ischemia in the short term. We saw no evidence of increasing ischemia, as might be feared in view of the systemic anti-VEGF side effects such as thrombembolism.[5] Limitations of the study include the small number of patients and short follow-up after only one administration. Although spontaneous improvements of capillary perfusion have been described in DR,[4] those appear to be associated with changes in metabolic control—absent, as far as we are aware, from our study. On the other hand, they may occur—over a significantly longer time—mostly with a pattern of intraretinal neovascularization,[4] which was never observed in our series. In summary, the observed reduction of ischemia makes anti-VEGF therapy a promising approach in the treatment of DR, but further investigations with longer follow-up times are needed.

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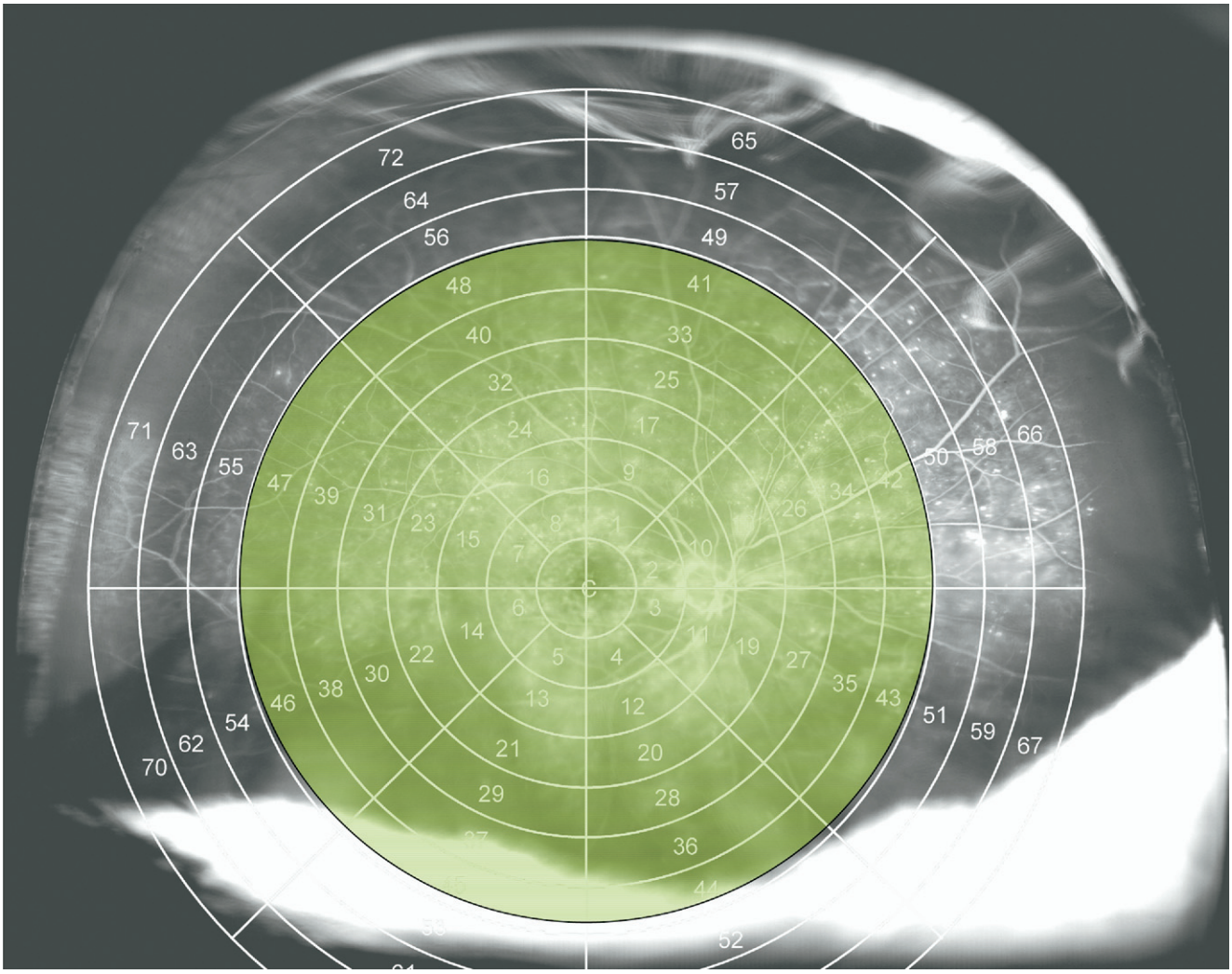

Figure 1. Example of ultrawide-field fluorescein angiography (early phase) of a patient with diabetic retinopathy. The grid is shown overlain to assess the number of ischemic peripheral fields. The central 48 fields were graded in the study (shaded yellow), as the far peripheral fields were often obscured by artifacts such as lashes (top half of the image) or the lid margin (bottom half).

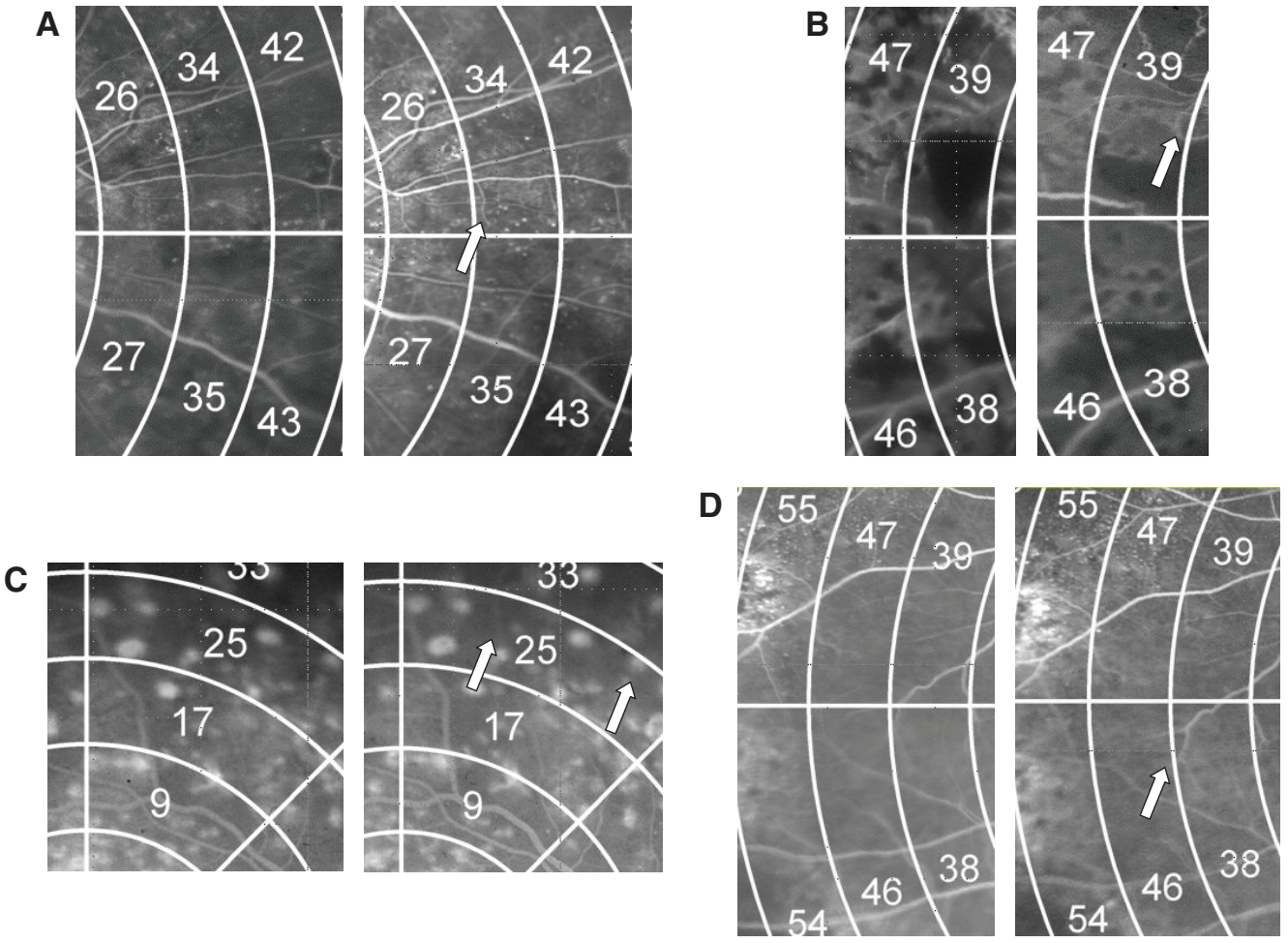

Figure 2. Typical examples of changes occurring 1 month after a single injection of bevacizumab. The left image gives the baseline fluorescein angiogram, and the right image the follow-up examination. **A**, Vasculature can be assessed better with small vessels better visible or reperfused (arrow). **B**, Reperfusion of capillaries causes ischemic areas to be reperfused (arrow). **C**, Even where no specific vessels can be identified, overall less ischemia exists—indicated by capillary dropout (darkness in normalized image; arrows). **D**, Vasculature can be assessed better with small vessels better visible or reperfused (arrow).