Regression of Sight-Threatening Macular Edema in Type 2 Diabetes Following Treatment With the Anti–Tumor Necrosis Factor Monoclonal Antibody Infliximab

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Diabetic retinopathy and diabetic macular edema (DME) are leading causes of blindness in an increasing number of patients with diabetes (1). Reduction of visual aquity in DME results from accumulation of fluid produced from a rupture of the blood-retinal barrier into the inner nuclear layer of the retina (1,2). Although the etiology of DME is unclear, an altered local expression of the pleiotropic cytokine tumor necrosis factor (TNF) may play an important pathogenetic role (2–5). Standard treatment of clinically significant DME consisting of laser photocoagulation reduces the risk of vision loss in 60% of cases, but recurrences are common, even among those patients who achieve an initial response (1). Various pharmacological therapies are currently under study, including intavitreal triamcinolone injections (6) or high doses of nonsteroidal anti-inflammatory agents that lower retinal expression of TNF (7).

The monoclonal anti-TNF antibody Infliximab neutralizes TNF actions and has been used for inflammatory arthritic conditions and Crohn's disease since 1998 with a favorable safety profile (8). Because of the limitations of current treatments for DME, and based on our recent findings indicating that Infliximab is an effective therapy for cystoid macular edema associated with uveitis (9–11), we decided to give Infliximab for sight-threatening refractory DME.

RESEARCH DESIGN AND METHODS

— Four women, aged 52–76 years, with type 2 diabetes in danger of vision loss due to severe DME are included in this prospective, interventional, noncomparative case series. They used oral antidiabetic agents for 14–20 years, while one patient required exogenous insulin therapy for the last 4 years. Patients were free of other major medical disorders and had no evidence of infection. Following full discussion and informed consent, two infusions of Infliximab (5 mg/kg; Remicade, Sherring-Plough, Greece) in 1-month intervals were given intravenously over 3 h in an outpatient setting on a compassionate basis. Concomitant medications remained unchanged, and one patient with previous tuberculosis history received Isoniazide according to standard guidelines.

Systemic and ophthalmic examination, as well as ocular coherence tomography (OCT) (Model 3000; Zeiss, Humphrey Systems), were performed immediately before each Infliximab infusion and 2 months after the last infusion. The main outcome measurements were best corrected visual acuity (BCVA) measured in Snellen charts and the OCT-derived maximum height of DME, recorded as described (11).

RESULTS

— DME of >12 months duration was present in seven eyes, six of which were refractory to previous treatment with laser photocoagulation (two sessions for each eye, performed at least 12 months before baseline). DME was classified (1) as severe in six eyes (range of macular thickness 420–720 μm) or mild in one eye (macular thickness of 290 μm, following laser photocoagulation plus vitrectomy). Of those eyes with severe DME, a dense epiretinal membrane was present in two. Baseline BCVA was profoundly impaired, ranging from 0.0125 to 0.1 decimal notation.

As soon as at the 1st month postbaseline, macular thickness had decreased in the five eyes without coexisting epiretinal membranes from 503 ± 171 μm (range 290–720) to 426 ± 165 μm (265–690). The other two eyes did not improve. Two months after the second Infliximab infusion, the macular thickness had further regressed to 330 ± 134 μm (170–515). BCVA increased from 0.0125 to 0.1 (n = 2), 0.05 to 0.1, 0.05 to 0.4, and 0.1 to 0.2, respectively, in each of the five eyes.

At 3 months postbaseline, we decided to offer an additional Infliximab infusion to the three patients who had the least improvement of DME. Repeated OCT after 2 months revealed a further decrease of macular thickness in three of five eyes by a mean of 15%. At this point the patient who still had the most severe condition received a fourth Infliximab infusion. Repeated OCT after 2 months revealed further improvement of DME (Fig. 1), while BCVA increased from 0.0125 at baseline to 0.2.

Infliximab therapy was well tolerated,

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Abbreviations: BCVA, best corrected visual acuity; DME, diabetic macular edema; OCT, ocular coherence tomography; TNF, tumor necrosis factor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

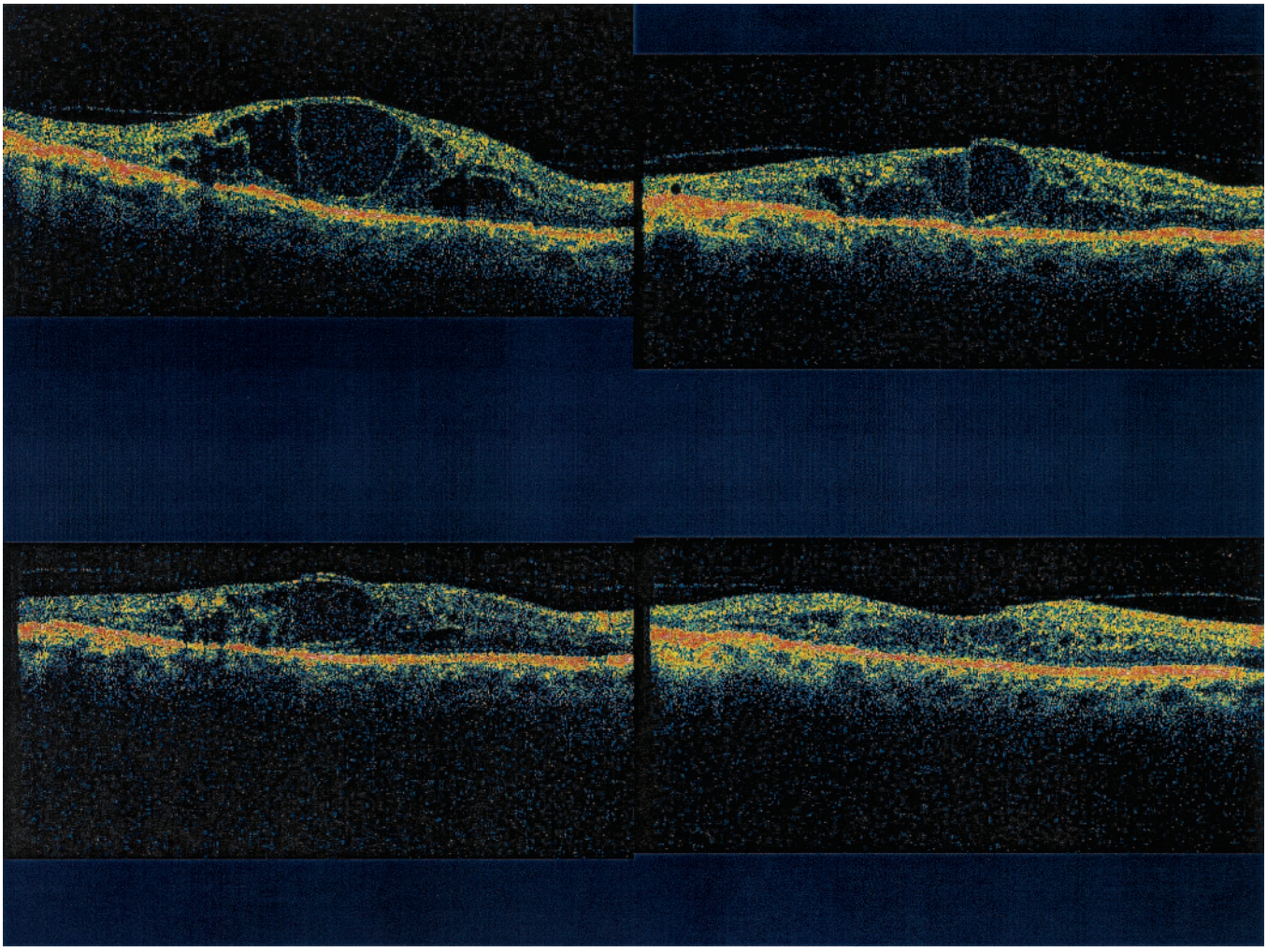

Figure 1—*Severe refractory to laser photocoagulation DME demonstrated by OCT before Infliximab administration (upper left, macular thickness 720 μm). A marked anatomic improvement was achieved within 7 months following four infusions of Infliximab at baseline, 1 month (upper right, macular thickness 550 μm), 3 months (lower left, macular thickness 515 μm), and 5 months (lower right, macular thickness 275 μm) postbaseline.*

and no ocular or extraocular side effects were noted. Available follow-up ranged from 4 to 7 months after the last infusion; a recurrence of DME was observed in two eyes at the 7th and 11th month postbaseline, albeit at a less severe level. The Infliximab-induced effect remained stable in three eyes at 8, 9, and 11 months, respectively.

CONCLUSIONS — Anatomic and functional improvement was achieved after two Infliximab infusions in four of the six eyes with severe DME. Both eyes with coexisting epiretinal membranes did not improve, suggesting that this condition might be a relative contraindication to Infliximab treatment. The observed recovery of useful vision represents an important clinical result, especially for eyes in which laser photocoagulation failed (1). Because Infliximab was given over 12 months after laser treatment, a late effect contributing to the observed improvement of DME is unlikely. Arterial pressure in these patients remained essentially unchanged during follow-up; therefore, a hypertension control–related effect is also unlikely. Comparable Infliximab-induced results have been obtained in cystoid macular edema, complicating uveitis (11). Additional treatment produced further improvement of DME, indicating that the clinical response to anti-TNF dosing regimens is individualized, as has also been observed in patients with arthritis (8) and uveitic macular edema (10,11). Thus, a sustained beneficial effect of Infliximab for DME may require repetitive treatment. Infliximab was well tolerated by our patients. However, potential adverse effects, such as infections and development of systemic autoimmunity, or diabetes type 1 in one case, have been reported (8), suggesting that anti-TNF treatment for DME in type 1 diabetic patients needs further consideration.

These preliminary findings suggest a role for TNF-mediated pathogenetic mechanisms in DME. Recent experiments indicate that low-grade inflammation is responsible for many of the signature vascular lesions of diabetic retinopathy (12). In addition, studies in patients with arthritis have shown that anti-TNF therapy negatively affects vascular permeability and angiogenesis by decreasing vascular endothelial growth factor (8,13), which has also been implicated in DME pathogenesis (14–16). While the number of

our patients is very limited, this data may suggest that a placebo-controlled long-term study on the safety and efficacy of anti-TNF treatment for refractory DME is warranted.

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