

Photocoagulation for Diabetic Macular Edema

Early Treatment Diabetic Retinopathy Study Report Number 1

Early Treatment Diabetic Retinopathy Study Research Group

● Data from the Early Treatment Diabetic Retinopathy Study (ETDRS) show that focal photocoagulation of "clinically significant" diabetic macular edema substantially reduces the risk of visual loss. Focal treatment also increases the chance of visual improvement, decreases the frequency of persistent macular edema, and causes only minor visual field losses. In this randomized clinical trial, which was supported by the National Eye Institute, 754 eyes that had macular edema and mild to moderate diabetic retinopathy were randomly assigned to focal argon laser photocoagulation, while 1,490 such eyes were randomly assigned to deferral of photocoagulation. The beneficial effects of treatment demonstrated in this trial suggest that all eyes with clinically significant diabetic macular edema should be considered for focal photocoagulation. Clinically significant macular edema is defined as retinal thickening that involves or threatens the center of the macula (even if visual acuity is not yet reduced) and is assessed by stereo contact lens biomicroscopy or stereo photography. Follow-up of all ETDRS patients continues without other modifications in the study protocol.

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The Early Treatment Diabetic Retinopathy Study (ETDRS) is a National Eye Institute-supported, multicenter, randomized clinical trial designed to evaluate photocoagulation and aspirin treatment in the management of patients with nonproliferative or early proliferative diabetic retinopathy. The ETDRS was designed to address the following three major questions:

1. When in the course of diabetic retinopathy is it most effective to initiate panretinal photocoagulation?
2. Is photocoagulation effective in the treatment of diabetic macular edema?
3. Is aspirin treatment effective in altering the course of diabetic retinopathy?

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A complete listing of the participants in this research study appears at the end of this article.

Reprint requests to the Biometry & Epidemiology Program, National Eye Institutes, Bldg 31, Room 6A24, 9000 Rockville Pike, Bethesda, MD 20892.

For editorial comment see
"Photocoagulation Therapy for Diabetic Eye Disease"
JAMA, Dec 6, 1985.

This first report deals only with question number 2.

Previous studies have suggested that photocoagulation may be beneficial in the treatment of diabetic macular edema.¹⁻¹⁷ These studies did not provide conclusive evidence because of one or more of the following reasons: (1) Patients were not randomized. (2) Visual acuity was measured without prior refraction and/or was not measured by a "masked" observer. (3) There were confounding effects of advanced proliferative diabetic retinopathy and/or panretinal photocoagulation. (4) The number of patients was small. (5) Treatment techniques were incompletely described. (6) Evaluation of possible photocoagulation effects on visual function other than visual acuity was not reported. Because of these limitations, clinical guidelines for the treatment of macular edema were difficult to formulate.^{18,19}

In the ETDRS, the effects of focal photocoagulation for macular edema are being evaluated in a prospective, large-scale, randomized clinical trial involving 29 centers (including 23 clinical centers). This first ETDRS report presents the data that support the conclusion that focal photocoagulation for macular edema is beneficial.

PATIENTS AND METHODS

From April 1980 to August 1985, the ETDRS research group enrolled 3,928 diabetic patients with early proliferative retinopathy, moderate to severe nonproliferative retinopathy, and/or diabetic macular edema in each eye. Patients with "high-risk" proliferative retinopathy²⁰ (moderate or severe optic nerve neovascularization or any neovascularization with hemorrhage) were not eligible for the study, because immediate panretinal photocoagulation already has been recommended for such patients.²¹ Patients with other significant ocular disease or visual acuity worse than 20/200 were also ineligible. Prior to

entry into the ETDRS, patients were asked to give written informed consent after receiving written and verbal information concerning their disease and the study.

Study Design

The complete design of the ETDRS has been summarized previously and is described in detail in the 848-page Manual of Operations (available from the US Department of Commerce, National Technical Information Service, 5285 Port Royal Rd, Springfield, VA 22161; Accession No. PB85 223006/AS).^{22,23} The present report is limited to the subgroup of eyes in the ETDRS that were identified as having mild to moderate nonproliferative diabetic retinopathy and macular edema, as determined by the initial grading of baseline fundus photographs and fluorescein angiograms of the ETDRS Fundus Photograph Reading Center, Madison, Wis.

The treatment assignment scheme for these eyes is detailed in Fig 1. First, they were randomly assigned to immediate photocoagulation or deferral of photocoagulation until high-risk proliferative retinopathy developed. The eyes assigned to immediate photocoagulation were then randomly divided into two photocoagulation regimens. One half (754) of the eyes assigned to immediate photocoagulation received only focal treatment for macular edema initially. This report compares these focally treated eyes with those randomized to deferral of photocoagulation (1,490 eyes).

Excluded from this report are the results for the eyes with mild to moderate retinopathy and macular edema that were randomly assigned to an initial treatment of panretinal photocoagulation and follow-up focal photocoagulation if macular edema persisted (Fig 1), the eyes with moderate nonproliferative retinopathy that did not have macular edema at the time of entry into the ETDRS, and all eyes initially graded as having severe nonproliferative or early proliferative retinopathy at the time of entry into the ETDRS. Follow-up continues for these groups of eyes.

Treatment

In the ETDRS, an eye is classified by the Fundus Photograph Reading Center as having macular edema when there is retinal thickening at or within 1 disc diameter of the center of the macula or definite hard exudates in this region. Macular edema is designated as being "clinically significant" if at least one of the characteristics listed in Table 1 is present.

An example of an eye with clinically significant macular edema and mild to moderate nonproliferative diabetic retinopathy is illustrated in Fig 2. Figure 2, middle left, shows the appearance of the retina immediately after focal treatment for macular edema, as performed in the ETDRS. A pretreatment fluorescein angiogram is used during photocoagulation to identify "treatable lesions" (Table 2). Treatment is prescribed for all such lesions located within 2 disc diameters of the center of the macula but at least 500 microns from the center.

Microaneurysms and other focal leakage sites receive 50- to 100-micron argon blue-green or green-only burns of 0.1-s duration or less, with adequate power to obtain definite whitening around the microaneurysm or leakage site. For all microaneurysms greater than 40 microns in diameter, an attempt is made to obtain actual whitening or darkening of the microaneurysm itself, which is generally accomplished utilizing a 50-micron spot size. Repeated burns are sometimes needed. Care is taken to avoid rupturing Bruch's membrane.

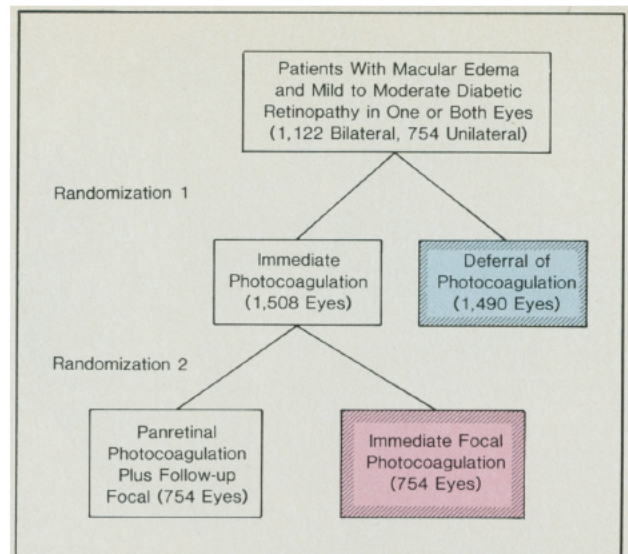


Fig 1.—Early Treatment Diabetic Retinopathy Study treatment assignment schedule for patients with macular edema and mild to moderate diabetic retinopathy in one or both eyes. Randomization 1: All study patients had one eye randomly assigned to immediate photocoagulation and other eye to deferral of photocoagulation until "high-risk" proliferative retinopathy (as described by the Diabetic Retinopathy Study²⁰) developed. Macular edema and mild to moderate retinopathy were present in both eyes of 1,122 patients (2,244 eyes), and one eye was randomly assigned to immediate photocoagulation or deferral. Seven hundred fifty-four patients had macular edema and mild to moderate retinopathy in only one eye; these eyes are about equally divided between immediate and deferral groups. Randomization 2: Eyes with macular edema and mild to moderate retinopathy assigned to immediate photocoagulation were randomized to either a combination of initial panretinal photocoagulation and follow-up focal macular photocoagulation if macular edema persisted or only focal macular photocoagulation at initial treatment with panretinal photocoagulation if retinopathy progressed to severe nonproliferative stage or beyond. Hatched boxes indicate those groups compared in this report.

Table 1.—Clinically Significant Macular Edema (Any of the Following Characteristics)

Thickening of the retina at or within 500 microns of the center of the macula
Hard exudates at or within 500 microns of the center of the macula, if associated with thickening of adjacent retina (not residual hard exudates remaining after disappearance of retinal thickening)
A zone or zones of retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the center of the macula

Treatment of lesions closer than 500 microns to the macula is not required initially. However, if vision is less than 20/40, and the retinal edema and leakage persist, treatment of lesions up to 300 microns from the center is recommended, unless there is perifoveal capillary dropout, which might be worsened by this treatment.

Areas of diffuse leakage or nonperfusion within 2 disc diameters of the center of the macula are treated in a grid

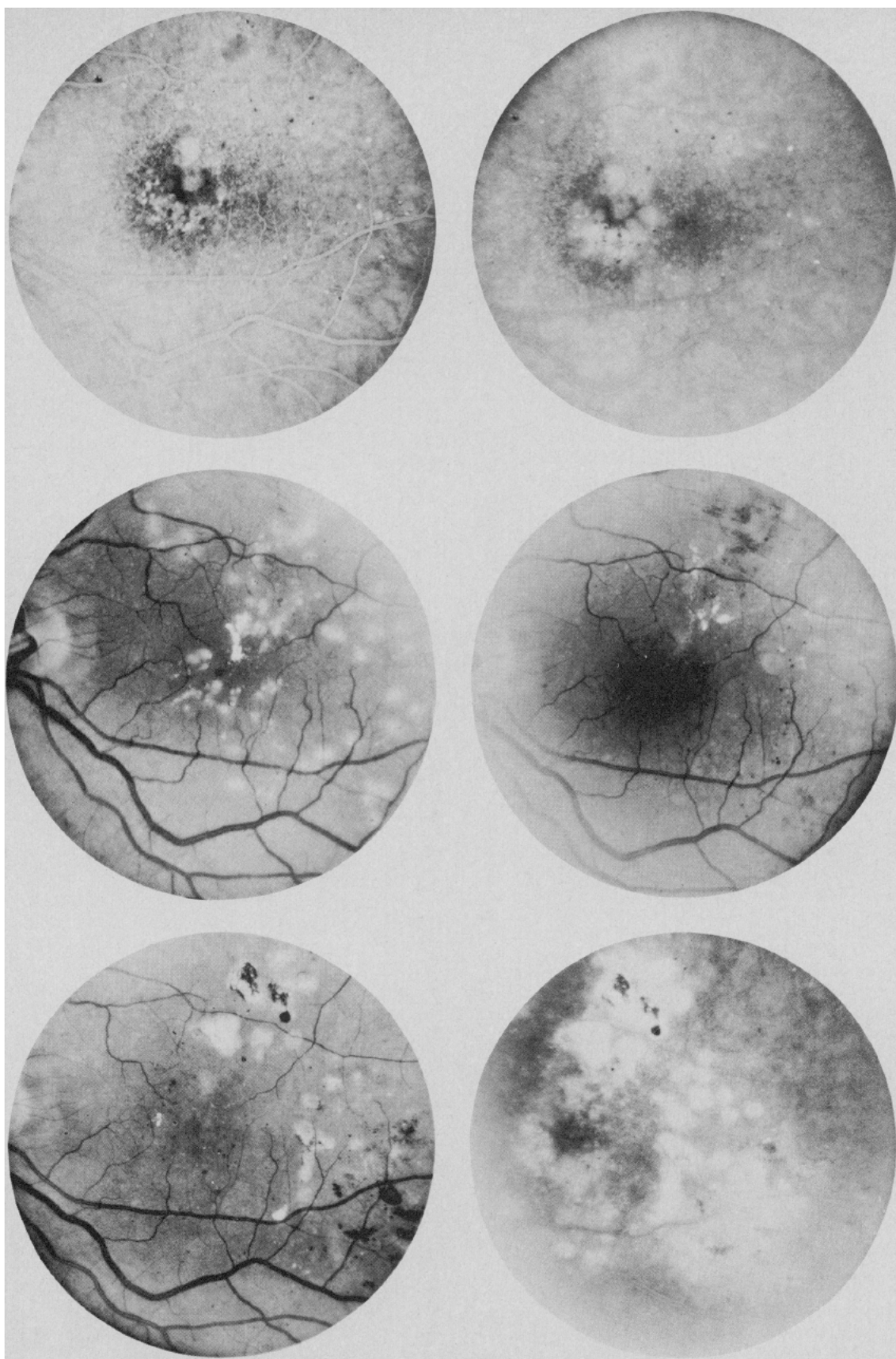


Fig 2.—Left eye with retinal thickening involving center of macula, small amount of hard exudate, and focal fluorescein leakage. Top left, Pretreatment fluorescein angiogram, mid-phase. Some microaneurysms have filled, others have not. Top right, Pretreatment angiogram, late phase (at seven to ten minutes). Fluorescein leakage in macular area is extensive and involves center. Middle left, Immediately following initial treatment, essentially all microaneurysms have been treated focally and many have lost original red color. Small hemorrhage just nasal to center of macula has been avoided. Middle right, At one-year follow-up visit, area of retinal thickening with adjacent hard exudate is present superotemporally, extending to within 500 to 1,000 microns of center of macula. Additional focal treatment was carried out. Bottom left, At three-year follow-up visit, note scars of additional focal treatment. Microaneurysms are present below and nasal to center of macula and there is small amount of hard exudate, but no retinal thickening was detected on contact lens examination or in stereo photographs. Additional focal treatment was therefore not required by protocol but was allowed. Bottom right, At three-year follow-up visit, late-phase fluorescein angiogram shows that some of microaneurysms below and nasal to center of macula do not fill with fluorescein, as was also case at baseline. Retinal thickening and fluorescein leakage no longer involves center of macula.

pattern. The goal of treatment in such cases is to produce a burn of light to moderate intensity, not more than 200 microns in diameter. To accomplish this, a 50- to 200-micron spot size is utilized. A space one burn wide is left between each lesion. The burns can be placed in the papillomacular bundle but not closer than 500 microns from the center of the macula.

A comparison of the results of focal photocoagulation for eyes with macular edema in patients who were randomly assigned to treatment with aspirin (650 mg/day) with the results of focal photocoagulation for eyes with macular edema in patients who were assigned to treatment with placebo shows that aspirin usage did not modify the effect of focal photocoagulation. Therefore, results are presented without regard to the aspirin treatment assignment.

Outcome Assessment

Visual acuity, the primary means of gauging treatment effects in this study, was measured at each visit by an examiner who did not know the treatment assignment (masked) and who followed a detailed protocol using a specially developed visual acuity chart (Fig 3).²⁴ The test results are used to calculate a visual acuity score by totaling the number of letters correctly read.²⁴ Changes in visual acuity are calculated by subtracting the visual acuity score measured during a follow-up visit from the baseline visual acuity score (taken not more than 72 hours before the initial treatment). A loss of 15 letters is equivalent to a three-line visual acuity decrease on this chart or a doubling of the initial visual angle (eg, 20/20 to 20/40 or 20/100 to 20/200). Changes in visual acuity, such as a doubling of the visual angle, are used to assess treatment effects. If visual acuity scores were missing for up to two consecutive follow-up visits, but scores were available from the visits immediately preceding and following the missing scores, then the arithmetic mean of the two bracketing scores replaced the missing score. This interpolation was done for less than 3% of the scores; more than 98% of patients have been seen within the last year.

Other visual function tests include the Farnsworth-

Table 2.—Characteristics of Treatable Lesions

Discrete points of retinal hyperfluorescence or leakage (most of these are microaneurysms)
Areas of diffuse leakage within the retina
Microaneurysms
Intraretinal microvascular abnormalities
Diffusely leaking retinal capillary bed
Retinal avascular zones

Munsell 100-hue test scored in standard fashion²⁵ and Goldmann perimetry with the I-2 and I-4 test objects from which visual field scores are calculated by summing the peripheral extent of the field in 12 meridians, excluding areas of scotomas.

Each patient was scheduled for a follow-up visit six weeks after initial treatment and at four-month intervals. Follow-up focal photocoagulation is required for all eyes assigned to immediate treatment that have persistent clinically significant macular edema and treatable lesions.

Fundus photographs and fluorescein angiograms are taken at prescribed intervals and as needed for follow-up treatment. These photographs and angiograms are graded in a masked and standard fashion at the Fundus Photograph Reading Center. These assessments of the presence and extent of macular edema and retinopathy level are used in this report.

The effects of focal photocoagulation were assessed by comparing eyes in the immediate focal treatment group with eyes in the deferral of treatment group, using the two-sample test of proportions with unequal variances.²⁶ The usual critical Z value of ± 1.96 corresponding to a .05 level of significance for a two-sided test of one comparison of one end point was not appropriate because multiple end points in several subgroups were compared at frequent intervals during the course of the study. For monitoring purposes, an observed Z value of ± 1.96 to ± 2.57 was considered suggestive of a treatment difference, and an observed Z value of ± 2.58 or greater (corresponding to a .01 level for a single test of significance) was considered a statistically significant difference. Observed Z values of ± 3.29 or greater (corresponding to .001 level) are also identified below.

RESULTS

This report is based on data available at the Coordinating Center, Baltimore, as of June 14, 1985. At the time of this analysis, 12 months had elapsed since the time of initial treatment for 80% of the enrolled patients, and 36 months had elapsed since initial treatment for 35% of the patients. In the following sections, analyses are presented according to the outcome variable used to assess treatment effect (visual acuity, retinal thickening, or visual function tests that measure factors other than visual acuity).

Visual Acuity Results

Visual Acuity Results in All Eyes.—Eyes assigned to immediate focal photocoagulation were about half as likely to lose 15 or more letters on the ETDRS eye chart compared with eyes assigned to deferral of photocoagulation: 5% vs 8% at one year, 7% vs 16% at two years, and 12% vs 24% at three years (Fig 4).

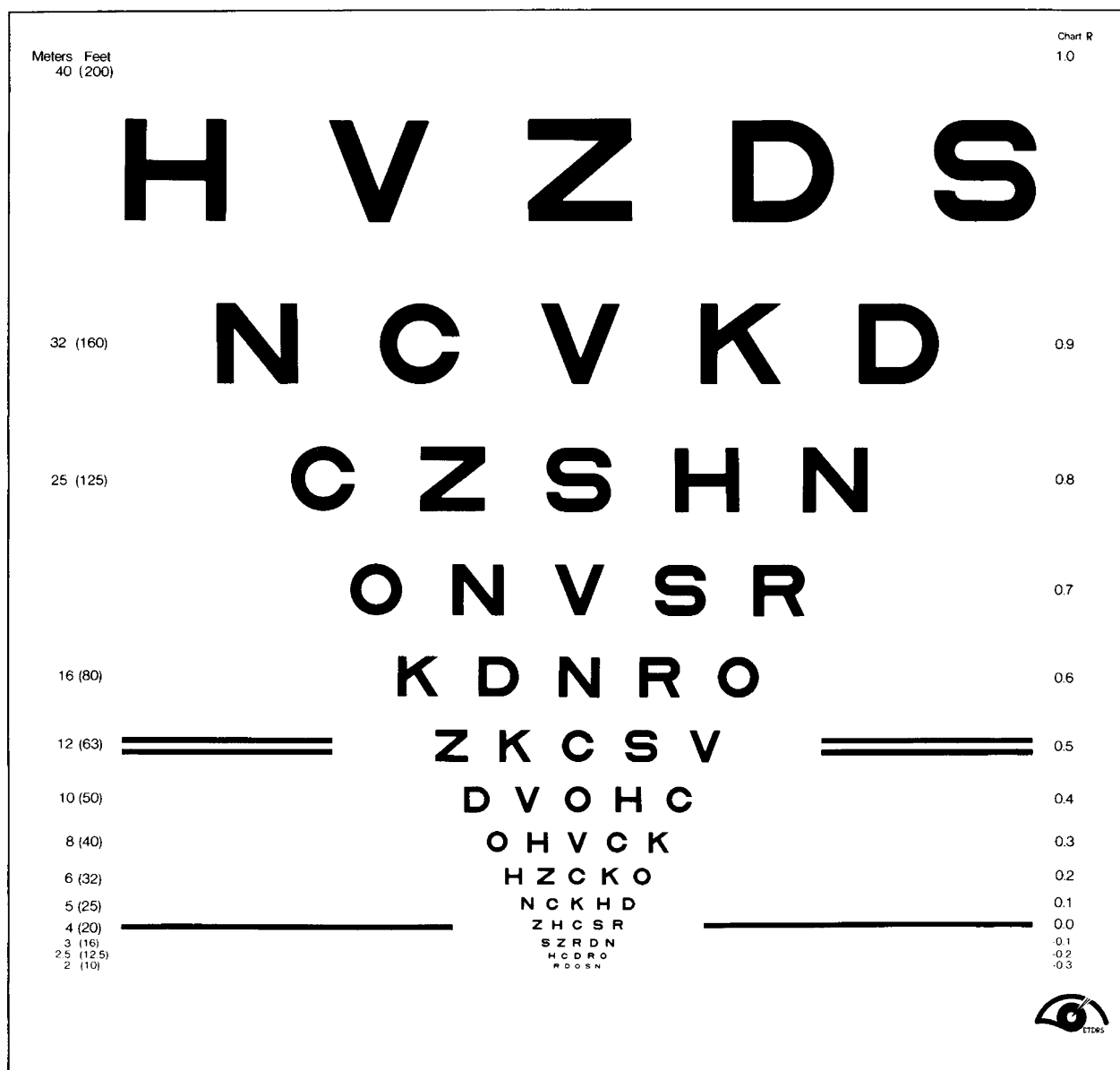


Fig 3.—One of three Early Treatment Diabetic Retinopathy Study visual acuity charts. Four-meter testing distance with this chart yields the following Snellen equivalent lines: 20/10, 20/12.5, 20/16, 20/20, 20/25, 20/31.5, 20/40, 20/50, 20/63, 20/80, 20/100, 20/125, 20/160, and 20/200. At 1 m, the following additional Snellen equivalent lines of visual acuity could be measured: 20/250, 20/315, 20/400, 20/500, 20/630, and 20/800. Note that every three lines is a doubling of the visual angle and that there are five letters on each line.

The comparison of the two groups yielded Z values of 2.58 or more from the end of the first year of follow-up through the third year of follow-up. This analysis includes all eyes with macular edema and nonproliferative retinopathy, as determined in the initial evaluation by the Fundus Photograph Reading Center. Of the 754 eyes assigned to immediate focal photocoagulation, 574 were from patients with bilateral macular edema and nonproliferative retinopathy. A separate analysis based on these paired eyes showed similar results.

Figure 5 shows the percentages of eyes with visual acuity scores less than 50 (equivalent to visual acuity worse than 20/100) at each visit, including baseline. The pattern of differences between the immediate photocoagulation group and the deferral of photocoagulation group is similar to that seen for a loss of 15 letters (Fig 4).

Visual Acuity Results in Eyes Classified by Baseline Visual Acuity Score.—Figure 6 shows the results when eyes are categorized according to baseline visual acuity score (see also Table 3). In each of the

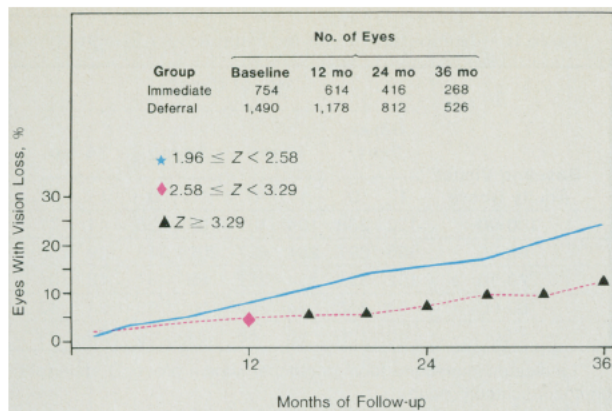


Fig 4.—Comparison of percentage of eyes that experienced visual loss of 15 or more letters (equivalent to at least doubling of initial visual angle or loss of three or more lines) in eyes with macular edema and mild to moderate diabetic retinopathy assigned to either immediate focal photocoagulation (broken line) or deferral of photocoagulation (solid line).

subgroups, immediate focal photocoagulation reduced the proportion of eyes that lost 15 or more letters compared with deferral of photocoagulation. Visual prognosis appears worse for those eyes with decreased visual acuity at baseline.

In eyes with a pretreatment visual acuity of 20/40 or worse, an improvement in visual acuity of six or more letters (more than one line on the ETDRS visual acuity chart) was much more frequent in treated eyes than in eyes assigned to deferral of treatment (Fig 7). This improvement in visual acuity was uncommon in eyes with good initial visual acuities, as might be expected. Improvement of visual acuity by 15 letters (three lines or one half of the initial visual angle) was uncommon (<3%).

Visual Acuity Results in Eyes Classified by the Presence or Absence of Clinically Significant Macular Edema.—Figure 8, top, demonstrates the clear beneficial effect of immediate focal treatment in eyes with clinically significant macular edema (see also Table 4). In those eyes, the differences in rates of visual loss between the immediate focal photocoagulation and deferral of photocoagulation groups were statistically significant at the eight-month follow-up visit and thereafter.

Eyes in which macular edema was not clinically significant at baseline had low rates of visual loss, especially during the first year of follow-up, in both the immediate and deferral of photocoagulation groups (Fig 8, bottom). At baseline, these eyes had only limited areas of retinal thickening or hard exudates and had none of the characteristics of clinically significant macular edema. Clinically significant macular edema developed in both the immediate and deferral of photocoagulation groups during follow-up. When clinically significant macular edema developed during follow-up, the eyes assigned to immediate treatment received additional focal photocoagulation, but the eyes assigned to deferral of treatment did not receive photocoagulation. Differ-

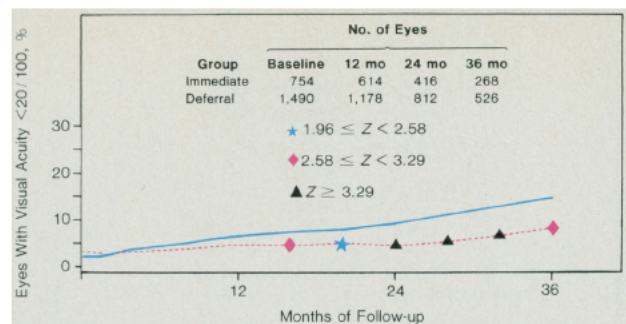


Fig 5.—Comparison of percentage of eyes with visual acuity score less than 50 (equivalent to a visual acuity of less than 20/100) in eyes with macular edema and mild to moderate diabetic retinopathy assigned to either immediate focal photocoagulation (broken line) or deferral of photocoagulation (solid line).

ences in visual loss between the immediate photocoagulation and deferral of photocoagulation groups are small in the first two years of follow-up. After this time, the differences become somewhat larger. These larger differences can be explained, at least in part, by the demonstrated beneficial effect of focal photocoagulation for eyes in which clinically significant macular edema developed during follow-up.

Visual Acuity Results in Eyes Classified by Severity of Retinopathy.—Figure 9 shows the results when eyes are categorized according to the severity of retinopathy, as determined by detailed grading of baseline fundus photographs (see also Table 5). Eyes classified as having “mild nonproliferative diabetic retinopathy” were free of soft exudates, intraretinal microvascular abnormalities, and venous beading, and they had no more than moderate intraretinal hemorrhages or microaneurysms. Eyes designated as having “moderate nonproliferative diabetic retinopathy” were subdivided into levels 1 and 2. In level 1, at least one of the above lesions was present, while in level 2 there was increased severity of one or more of these lesions but less than that in those eyes designated as having “severe nonproliferative retinopathy.” Eyes in the latter category had at least three of these lesions present (the same definition of severe nonproliferative diabetic retinopathy was used in the Diabetic Retinopathy Study).^{27,28}

The ETDRS was not designed to assess the effect of initial focal treatment without panretinal photocoagulation in eyes with severe nonproliferative or early proliferative retinopathy. However, a subgroup of eyes with this severity of retinopathy were initially graded as having only mild to moderate nonproliferative retinopathy and were treated, according to the study protocol, with only focal photocoagulation. When more detailed fundus photograph evaluation was completed, it was determined that these eyes, which had already received focal treatment, actually had severe nonproliferative or early proliferative diabetic retinopathy. The results of focal photocoagulation in this small subgroup of eyes are shown in Fig 9, bottom.

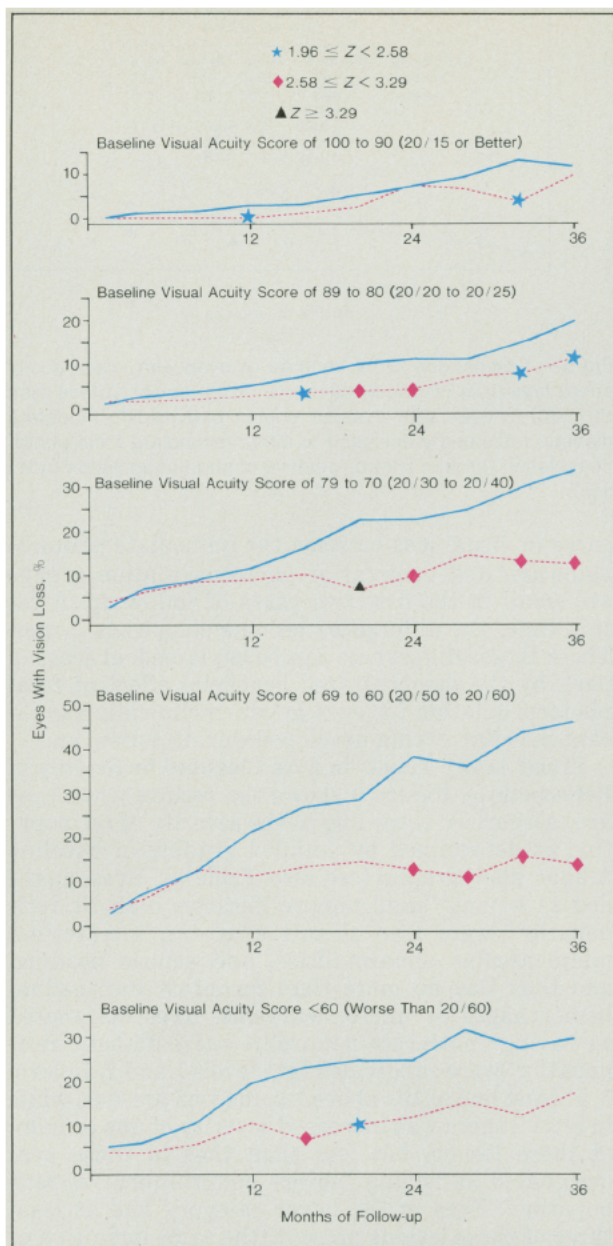


Fig 6.—Comparison of percentage of eyes that experienced visual loss of 15 or more letters (equivalent to at least doubling of initial visual angle or loss of three or more lines) in eyes with macular edema and mild to moderate diabetic retinopathy classified by baseline visual acuity score and assigned to either immediate focal photocoagulation (broken line) or deferral of photocoagulation (solid line).

The treatment effect appears similar in all four subgroups but is statistically significant only in the two moderate nonproliferative retinopathy groups, evidently because of the larger sample sizes of these two groups.

Results Based on Retinal Thickening Involving the Center of the Macula

Reading Center grading of baseline photographs identified 74% of all the eyes with clinically signifi-

Table 3.—Numbers of Eyes in Visual Acuity Subgroups

Baseline Visual Acuity Score	No. of Eyes*							
	Base-line†		12 mo		24 mo		36 mo	
	I	D	I	D	I	D	I	D
100-90	122	238	104	187	67	128	41	77
89-80	356	697	284	557	202	398	129	258
79-70	162	328	134	252	82	161	48	104
69-60	54	118	44	94	31	60	21	43
<60	60	108	48	88	34	65	29	44

*I indicates immediate focal photocoagulation group; D, deferral of photocoagulation group.

†One baseline visual acuity score was missing at the time this analysis was performed.

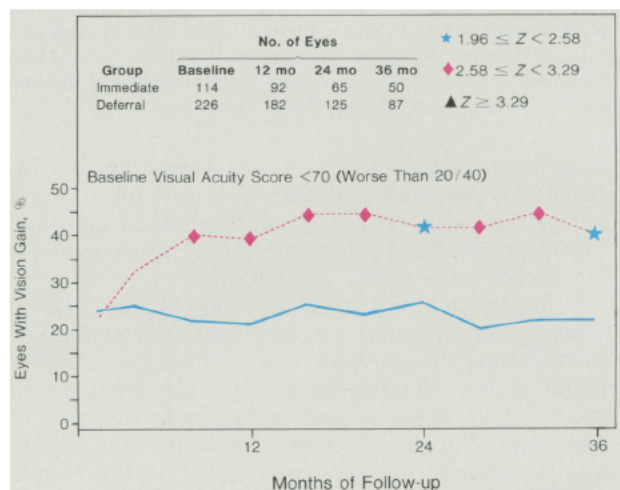


Fig 7.—Comparison of percentage of eyes that experienced visual gain of six or more letters (equivalent to more than one-line gain) in eyes with macular edema and mild to moderate diabetic retinopathy assigned to either immediate focal photocoagulation (broken line) or deferral of photocoagulation (solid line).

cant macular edema as having retinal thickening, with the center of the macula involved (Table 6). At one year, 35% of these eyes assigned to immediate focal treatment had retinal thickening with the center of the macula involved compared with 63% of eyes assigned to deferred photocoagulation. This difference was statistically significant, as it also was at three years. None of the eyes without clinically significant macular edema had retinal thickening with the center of the macula involved before entry into the study. Small differences in the occurrence of retinal thickening with the center of the macula involved were noted during follow-up in this latter group.

Results Based on Other Visual Function Assessment (Visual Fields, Color Vision, and Patients' Impressions of Change in Visual Function)

Adverse effects of treatment also were assessed by considering changes from baseline to follow-up visits

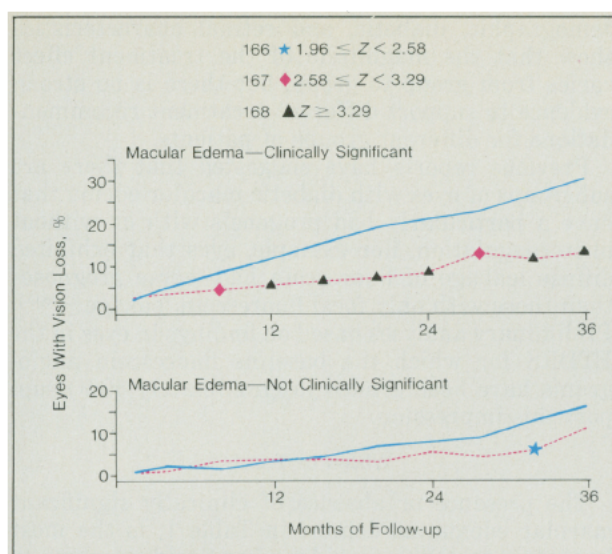


Fig 8.—Comparison of percentage of eyes that experienced visual loss of 15 or more letters (equivalent to at least doubling of initial visual angle or loss of three or more lines) in eyes classified by presence or absence of clinically significant macular edema and assigned to either immediate focal photocoagulation (broken line) or deferral of photocoagulation (solid line).

Table 4.—Numbers of Eyes in Macular Edema Subgroups

Clinically Significant Macular Edema	No. of Eyes*							
	Base-line†		12 mo		24 mo		36 mo	
	I	D	I	D	I	D	I	D
Present	434	853	375	717	249	497	168	311
Absent	277	545	235	455	164	311	100	215

*I indicates immediate focal photocoagulation group; D, deferral of photocoagulation group.

†All of the gradings for the baseline photographs were not available at the time this analysis was performed.

in visual field and color vision scores. Small, not statistically significant differences were observed in visual field scores and proportions of patients with scotomas to the I-2 test object. No treatment differences were observed in the Farnsworth-Munsell 100-hue test color vision scores.

In 16 of the 23 clinical centers, patients were asked for their impressions of change in visual function. They reported more improvement and less worsening from baseline for eyes assigned to immediate focal treatment than for eyes assigned to deferral of photocoagulation: for improvement, 36% vs 14% at 12 months, 43% vs 18% at 24 months, and 57% vs 11% at 36 months; for worsening, 18% vs 25% at 12 months, 20% vs 25% at 24 months, and 28% vs 35% at 36 months. The results for improvement were statistically significant ($Z > 2.57$).

COMMENT

These results from the ETDRS show that eyes with clinically significant macular edema (Table 1)

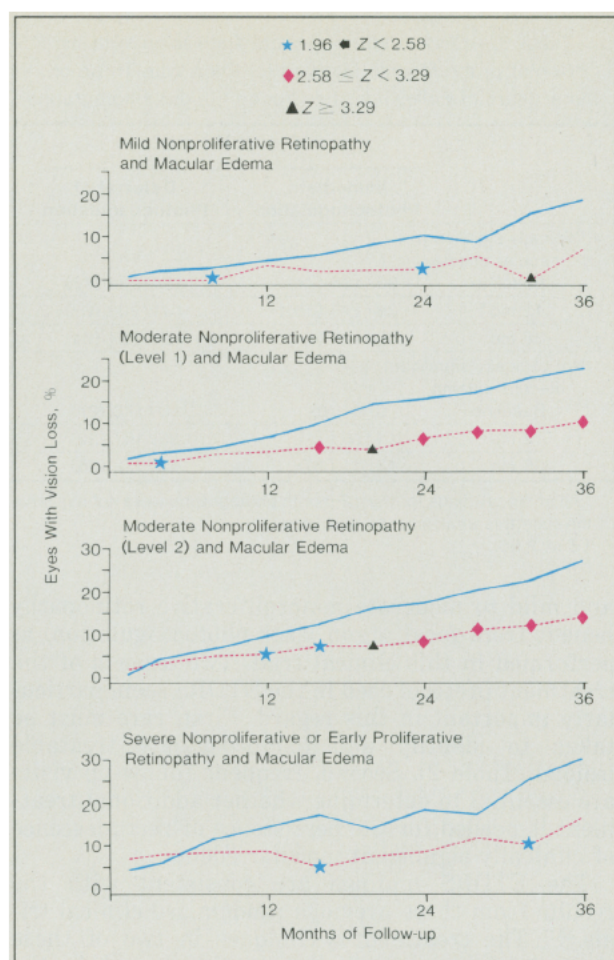


Fig 9.—Comparison of percentage of eyes that experienced visual loss of 15 or more letters (equivalent to at least doubling of initial visual angle or loss of three or more lines) in eyes with macular edema classified by severity of retinopathy at baseline and assigned to either immediate focal photocoagulation (broken line) or deferral of photocoagulation (solid line).

Table 5.—Numbers of Eyes in Retinopathy Subgroups

Severity of Retinopathy	No. of Eyes*							
	Base-line†		12 mo		24 mo		36 mo	
	I	D	I	D	I	D	I	D
Mild nonproliferative and macular edema	69	150	58	131	40	97	28	76
Moderate nonproliferative (level 1) and macular edema	273	537	231	454	151	304	97	195
Moderate nonproliferative (level 2) and macular edema	295	593	253	482	176	336	107	212
Severe nonproliferative or early proliferative and macular edema	74	119	68	105	46	71	36	43

*I indicates immediate focal photocoagulation group; D, deferral of photocoagulation group.

†All of the gradings for the baseline photographs were not available at the time this analysis was performed.

Table 6.—Occurrence of Retinal Thickening With the Center of the Macula Involved for Eyes With Three or More Years of Follow-up and Graded Fundus Photographs

	Group, No. (%)	
	Immediate Photocoagulation	Deferral of Photocoagulation
Clinically significant macular edema		
Baseline	93 / 126 (74)	164 / 224 (73)
12 mo*	38 / 110 (35)†	131 / 208 (63)
36 mo	30 / 126 (24)†	121 / 224 (54)
Not clinically significant macular edema		
Baseline	0 / 81 (0)	0 / 173 (0)
12 mo*	11 / 75 (15)	35 / 157 (22)
36 mo	13 / 81 (16)	43 / 173 (25)

*All of the gradings for the 12-month photographs were not available at the time this analysis was performed.

† $Z \geq 2.58$.

and mild to moderate nonproliferative retinopathy benefit from focal argon laser photocoagulation, as performed in this clinical trial. Two aspects of the treatment protocol used in the ETDRS seem particularly important in this regard. First, care must be taken to identify and photocoagulate treatable lesions (Table 2). Second, frequent follow-up visits are essential to determine whether additional treatment is needed for the persistence or recrudescence of clinically significant macular edema.

The ETDRS findings are consistent with the results from three previous randomized clinical trials.^{2,3,10} The treatment techniques in two of these three trials^{2,10} were similar to those used in the ETDRS. Focally applied xenon arc photocoagulation was utilized in the British Collaborative Study,³ but these investigators suggested that argon laser might be preferable.

Some of our patients were treated with argon green laser, whereas others underwent argon blue-green photocoagulation treatment. We have no direct evidence that one is preferable to the other, but many of our investigators have switched to argon green, particularly when treating near the fovea, to avoid excessive uptake of the blue light by the xanthophyll in the inner retina. Krypton red laser was not used, because it makes direct coagulation of microaneurysms difficult.

Very few adverse effects of focal photocoagulation have been observed in this study to date. We identified only minor adverse effects (not statistically significant) on central visual fields and no adverse effects on color vision. Our patients reported that their treated eye improved more frequently and worsened less frequently than their untreated eye. Although this assessment is subjective and vulnerable to bias, the results are consistent with those of other visual function tests.

Thus far, we have not identified any subgroup of patients or eyes harmed by focal photocoagulation. Preliminary multivariate analyses investigating

demographic, diabetic, and retinal characteristics show that the magnitude of the treatment effect varies from group to group, but there is no strong evidence to support different treatment recommendations for different groups of patients.

Previous reports have suggested that there are subgroups of eyes with diabetic macular edema that have a particularly bad prognosis with or without photocoagulation. For example, eyes that exhibited diffuse leakage of fluorescein had worse prognoses than those with only focal fluorescein leakage.^{2,3,10,15,17} Preliminary analyses based on findings in eyes in the ETDRS for which the baseline fluorescein angiograms have been graded (approximately 50%) support this impression.

Whom to Treat

The presence or absence of clinically significant macular edema, as defined in Table 1, is the most important factor to consider when deciding whom to treat. Clinically significant macular edema is assessed by stereo contact lens biomicroscopy and stereo photography. A magnified stereo examination of the macula is necessary to detect retinal thickening. Fluorescein leakage without retinal thickening does *not* meet our definition of macular edema. However, once clinically significant macular edema is identified, an angiogram is required to determine the presence of treatable lesions located within 2 disc diameters of the center of the macula. In follow-up visits at four-month intervals after initial focal treatment, the same investigative techniques and criteria are used to identify persistent clinically significant macular edema and treatable lesions, which together indicate that additional treatment is needed.

Patients who show early signs of diabetic macular edema but who do not yet have clinically significant macular edema should be seen at four- to six-month intervals.

When to Treat

The time of onset of clinically significant macular edema is an appropriate time to consider focal photocoagulation for macular edema. Prior to the development of clinically significant macular edema, the risk of visual loss is very low, and we have no evidence of added benefit from this earlier treatment. Once clinically significant macular edema develops, focal photocoagulation is clearly beneficial. We have not identified any subgroup of eyes with mild to moderate nonproliferative diabetic retinopathy and clinically significant macular edema for which there was no benefit from focal treatment. Of particular note is benefit of treatment regardless of the level of acuity at baseline (Fig 6). This suggests that even patients with excellent visual acuity should be considered for photocoagulation, if they have clinically significant macular edema. Stabilizing visual acuity in this range may be particularly valuable.

Eyes that had already lost vision were more likely

to regain some vision following treatment (Fig 7), and loss of vision sufficient to reach the legal blindness range was substantially reduced by treatment (Fig 5). Focal treatment also was associated with a significant decrease in the occurrence of retinal thickening involving the center of the macula at follow-up examinations (Table 6). Although these results show that treatment is effective when visual acuity is reduced, they should not be used to justify deferral of treatment until visual loss has already occurred.

In our study, eyes with more advanced diabetic retinopathy and clinically significant macular edema received both focal and panretinal photocoagulation. The design of the ETDRS does not permit a definitive answer to the question of the effects of focal treatment in the absence of panretinal photocoagulation for this group. However, as previously discussed, there was a small group of eyes graded as having mild to moderate nonproliferative retinopathy at the preliminary grading but found to have either severe nonproliferative or early proliferative diabetic retinopathy at the time of detailed fundus photograph grading. Although the number of eyes is small, it appears that they, too, benefited from focal treatment of macular edema, responding in much the same way as eyes with less severe retinopathy. This apparent benefit of treatment in the absence of significant side effects suggests that focal photocoagulation might well be appropriate for eyes with clinically significant macular edema, even when they are in the more advanced stages of diabetic retinopathy.

Recommendations

The data presented in this report support the following: (1) Focal photocoagulation is recommended for all eyes with clinically significant macular edema and mild or moderate nonproliferative diabetic retinopathy. (2) Focal photocoagulation should be considered for all eyes with clinically significant macular edema and more severe nonproliferative or proliferative retinopathy.

No recommendations can yet be made concerning (1) panretinal photocoagulation for moderate to severe nonproliferative retinopathy or early proliferative retinopathy (stages of retinopathy less severe than the high-risk proliferative retinopathy for which the Diabetic Retinopathy Study has previously recommended treatment¹) or (2) aspirin treatment for diabetic retinopathy. Evaluation of these treatments continues in the ETDRS.

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