The Early Treatment Diabetic Retinopathy Study historical review and relevance to today's management of diabetic macular edema

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Purpose of review
To provide an historical review of the Early Treatment Diabetic Retinopathy Study (ETDRS) in the management of diabetic macular edema (DME), and to discuss its relevance to the management of DME.

Recent findings
The ETDRS reported that argon laser treatment is beneficial in the management of 'clinically significant' DME. The study provided guidelines for the treatment with focal and/or grid laser based on fluorescein angiographic patterns. In today's world, with the advent of optical coherence tomography, 'clinically significant' DME is now classified into center-involved DME (CI DME) and noncenter-involved DME (non-CI DME). Modified ETDRS focal/grid laser photocoagulation has been utilized in more recent clinical trials [diabetic retinopathy clinical research (DRCR) Protocols I and T] in combination with intravitreal injections.

Summary
The ETDRS provided outcomes data for DME, both untreated and following laser therapy. In the management of patients with DME today, the modified ETDRS focal/grid laser photocoagulation treatments remain relevant in combination with anti-vascular endothelial growth factor (anti-VEGF) therapy as ophthalmologists and their patients choose how best to treat DME. Ongoing studies in eyes with DME, nonproliferative diabetic retinopathy, and good visual acuity will help further define the place of modified ETDRS focal/grid laser in the treatment of DME.

Keywords
diabetic macular edema, Early Treatment Diabetic Retinopathy Study, focal laser photocoagulation

INTRODUCTION

Diabetic macular edema (DME) is an important cause of central vision impairment among people with diabetic retinopathy, which can have a significant adverse effect on daily activities and quality of life. The Early Treatment Diabetic Retinopathy Study (ETDRS) [1] was a National Eye Institute-sponsored, multicenter randomized clinical trial organized in 1979 and results were first published in 1985, which indicated that ETDRS style argon laser treatment is beneficial for many people who have 'clinically significant' DME. From April 1980 to August 1985 the ETDRS research group enrolled 3711 patients with nonproliferative diabetic retinopathy, early proliferative retinopathy, and/or DME in each eye. The ETDRS reported visual acuity outcomes comparing immediate versus deferred (control) treatment group in multiple different patient subgroups, looking at both the timing of scatter photocoagulation and the effect of modified focal/grid laser photocoagulation on DME.

THE EARLY TREATMENT DIABETIC RETINOPATHY STUDY: HISTORICAL REVIEW (ADAPTED FROM THE EARLY TREATMENT DIABETIC RETINOPATHY STUDY PUBLICATIONS)

The Early Treatment Diabetic Retinopathy Study methodology

In the ETDRS, 'clinically significant macular edema' (CSME) was defined as retinal thickening involving or threatening the center of the macula (even if visual acuity was not reduced) and was

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Curr Opin Ophthalmol 2017, 28:205–212
DOI:10.1097/ICU.0000000000000362

KEY POINTS

- The ETDRS demonstrated the benefit of laser treatment for clinically significant DME compared to the untreated clinical course.
- Modified ETDRS focal/grid laser photocoagulation for non-CI DME is still a reasonable option for many patients in today's world.
- Subretinal fibrosis observed after focal/grid laser photocoagulation is related to the presence of severe hard exudates prior to laser photocoagulation.
- DRCR clinical trials (protocols I and T) for DME showed that the intravitreal anti-VEGF with or without laser is beneficial.
- In protocol I, pseudophakic eyes with DME treated with intravitreal steroids and prompt laser has similar visual acuity outcomes compared to intravitreal ranibizumab with prompt/deferred laser.

assessed by stereo contact lens biomicroscopy or stereophotography. The ETDRS criteria for CSME (adapted from ETDRS publications) [1] included the presence of any of the following three characteristics:

(1) Thickening of the retina at or within 500 μm of the center of the macula.
(2) Hard exudates at or within 500 μm of the center of the macula, if associated with thickening of adjacent retina (not residual hard exudates remaining after disappearance of retinal thickening).
(3) 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.

Study inclusion/exclusion criteria

All patients had confirmed diabetes mellitus as consistent with using medication to control blood sugar and confirmation of diagnosis by primary physician. To be included in the ETDRS, patients required color and fluorescein angiographic documentation of diabetic retinopathy, no history of prior intraocular surgery, and patients who were likely to have minimum follow-up for 5 years. Patients with 'high-risk' proliferative retinopathy, pseudophakia, advanced glaucoma, macular degeneration, and visual acuity worse than 20/200 were excluded from the study. Approximately 67% of ETDRS patients had visual acuity 20/25 or better at baseline.

Where to treat

The pretreatment fluorescein angiogram was required in the determination of 'treatable lesions', which included discrete points of retinal hyperfluorescence or leakage, areas of diffuse leakage within 2 disc diameters of the macula center but at least 500 μm from the center.

How to treat

Microaneurysms and other focal leakage sites were treated with 50–100 μm 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. Microaneurysms with size greater than 40 μm in diameter were treated with variable spot sizes laser to obtain actual whitening or darkening of the microaneurysm (Fig. 1). Areas of diffuse leakage or nonperfusion within 2 disc diameters of the center of the macula were treated in a grid pattern (Figs 2–4). The goal of treatment in such cases was to produce a burn of light to moderate intensity, not more than 200 μm in diameter. To accomplish this, 50–200 μm spot sizes were utilized. A space one burn width apart was left between each lesion. The burns could be placed in the papillomacular bundle.

When to retreat

Treatment was not required for lesions closer than 500 μm to the macula initially. If the vision was decreased to 20/40 or worse and retinal edema and leakage persisted, treatment of lesions up to 300 μm from the center was recommended unless there was perifoveal capillary dropout, which could have been worsened by this central treatment. In the ETDRS, retreatment was considered at each 4-monthly follow-up examination. If 'clinically significant DME' persisted, the decision to treat was based on the extent of DME, the location of leakage, and the presence of treatable lesions as determined on fluorescein angiography. Repeat focal burns were applied based on the angiographic leakage and stereo viewing of persistent macular edema. Care was taken to avoid rupturing Bruch's membrane from intense focal laser spots.

Subretinal fibrosis, an infrequent complication seen in patients with DME, has been attributed to the presence of very severe hard exudates rather than from an excessive number of photocoagulation burns [2].

Early Treatment Diabetic Retinopathy Study treatment outcomes for diabetic macular edema

The reduction in the risk of moderate vision loss (MVL, doubling of visual angle) by focal

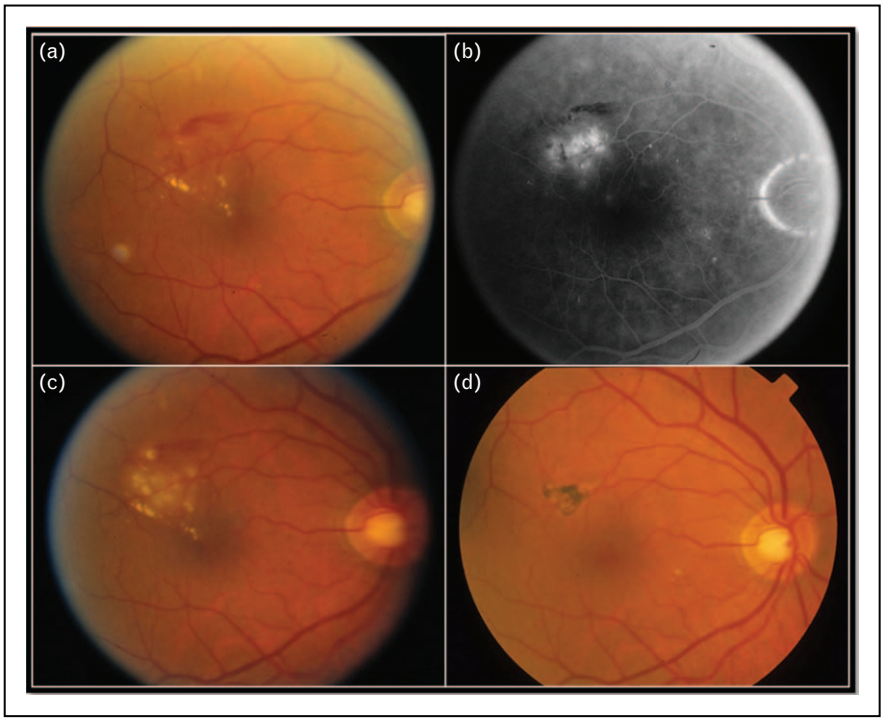

FIGURE 1. Early Treatment Diabetic Retinopathy Study (ETDRS) focal laser photocoagulation: (a) 62-year-old diabetic man with localized retinal edema supero-temporal to fovea in left eye, (b) fluorescein angiography illustrates a cluster of leaks supero-temporal to fovea. The visual acuity was 20/20. (c) ETDRS style focal laser photocoagulation was performed to areas of retinal edema demonstrated by stereo fundus photography and fluorescein angiography. (d) One-year follow-up shows laser scar supero-temporally and resolution of retinal hemorrhages, hard exudates and macular edema.

photocoagulation for DME was the primary outcome of the study. At 3-year follow-up among the eyes with macular edema and nonproliferative retinopathy, the rates of MVL (defined as a loss of 15 or more letters on ETDRS visual acuity charts) was noted in 12% (91/754) of eyes that received immediate treatment compared with 24% (358/1490) of eyes assigned to the deferred treatment group [1,3].

Among ETDRS patients with initial visual acuity 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 more frequent in the treated eyes than in eyes assigned to deferral of treatment based on stereo fundus photography. It increases the chance of moderate vision gain (halving of the initial visual angle) in eyes with baseline visual acuity worse than 20/40. These beneficial effects of laser treatment, compared with no treatment, demonstrated in this trial, suggest that eyes with CSME should be considered for focal/grid laser photocoagulation. Based on the fundus stereophotography, focal/grid laser photocoagulation treatment reduced the retinal thickening.

The treatment effect was reported to be similar in eyes irrespective of the severity of the nonproliferative retinopathy (mild/moderate/severe). There were no significant differences among treatment groups for visual field scores, proportions of patients with scotomas, and color vision (Farnsworth-Munsell 100-hue test). Adverse effects of the treatment were also assessed by patients' impressions of change in visual function. At 3-year follow-up, more improvement and less worsening from baseline was reported by patients who received immediate treatment compared to patients assigned to deferred treatment group. Various advantages and disadvantages of focal photocoagulation have been reported.

RELEVANCE OF THE EARLY TREATMENT DIABETIC RETINOPATHY STUDY IN TODAY'S MANAGEMENT OF DIABETIC MACULAR EDEMA

The information on treatment of DME provided by ETDRS is still relevant today. In today's world, intravitreal injections of anti-VEGFs and steroids are increasingly used and recommended for initial and follow-up management of DME; however, laser photocoagulation treatment for DME continues to have an important role (Table 1). It is important to understand that in the ETDRS, the diagnosis of CSME was made based on the fundus photography

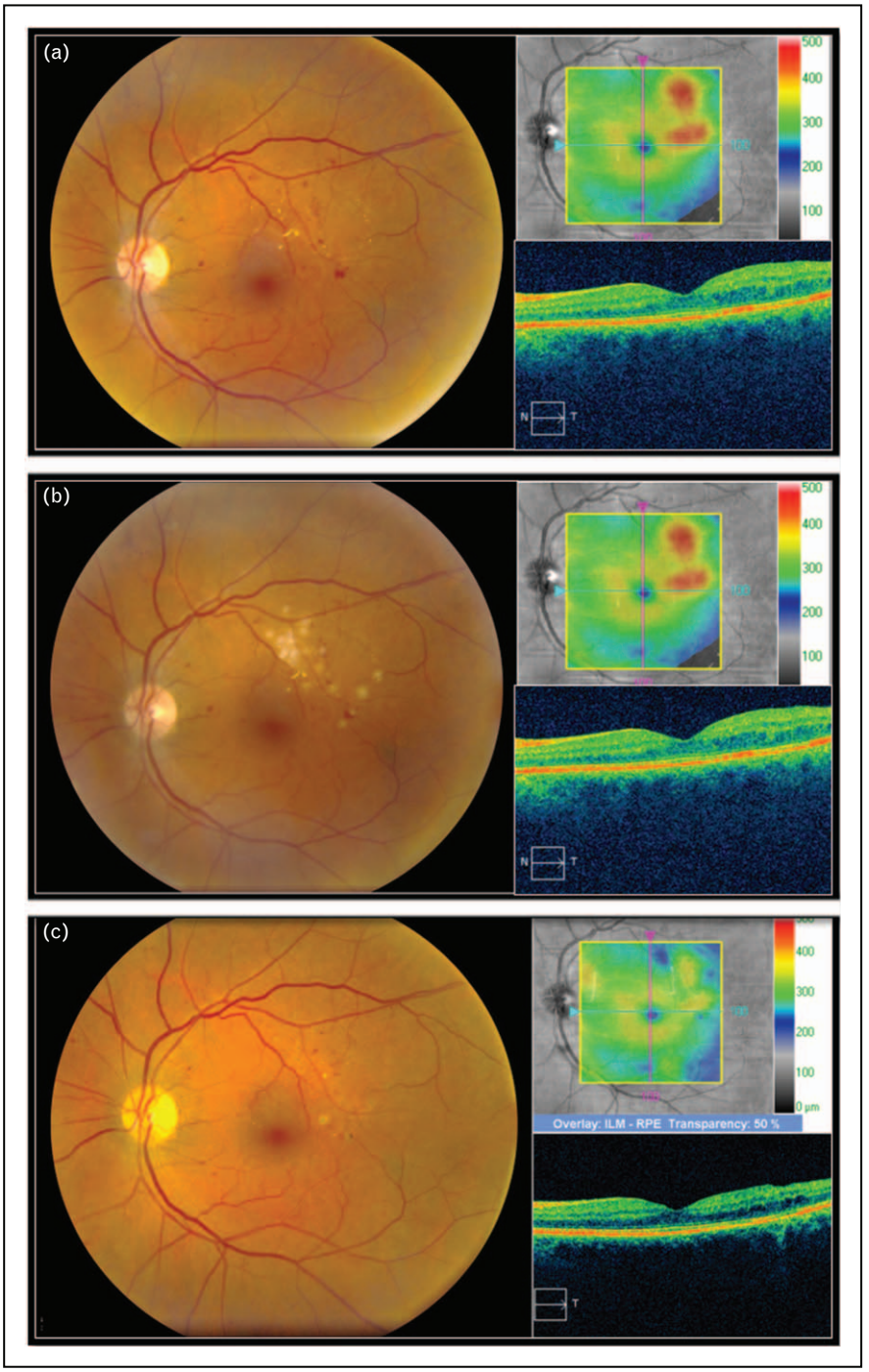

FIGURE 2. Early Treatment Diabetic Retinopathy Study (ETDRS) focal/grid laser photocoagulation: (a) 60-year-old man with localized retinal edema supero-temporal to fovea in left eye. (b) focal/grid laser photocoagulation performed to areas of retinal edema demonstrated by optical coherence tomography (OCT). (c) One-year follow-up shows resolution of retinal hemorrhages, hard exudates, and macular edema.

and stereophotography evaluated by a reading center. Optical coherence tomography (OCT) was not available at that time. However, OCT is a very important tool in assessing the severity of DME in recent clinical trials, including those carried out by the Diabetic Retinopathy Clinical Research Network (DRCR.net). Most trials have divided DME into center-involved DME (CI DME) and noncenter-involved DME (non-CI DME). The DRCR.net is a collaborative network conducting multicenter clinical research of diabetic retinopathy, DME, and associated conditions. The DRCR.net funded by the National Eye Institute was formed in September 2002 includes over 115 participating sites

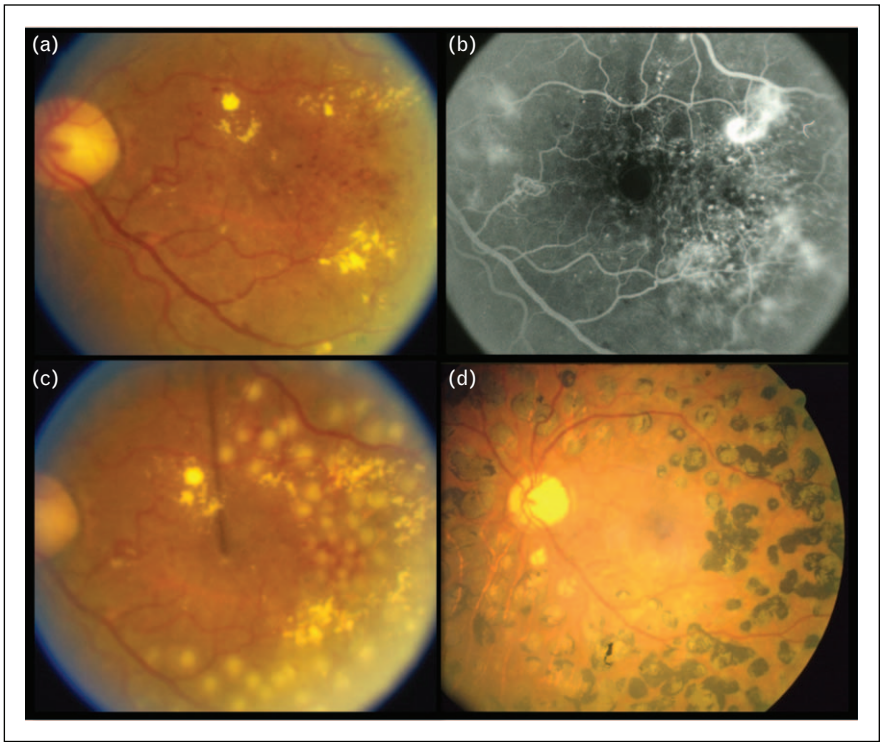

FIGURE 3. Early Treatment Diabetic Retinopathy Study (ETDRS) focal/grid laser photocoagulation: (a) 73-year-old diabetic man with diffuse retinal edema, neovascularization elsewhere, superficial retinal hemorrhages, and hard exudates in left eye. (b) Fluorescein angiography illustrates enlarged foveal avascular zone, multiple microaneurysms over posterior pole, neovascular fronds, and leaking neovessels arising from supero-temporal arcade. The visual acuity was 20/60. (c) ETDRS style focal and grid laser photocoagulation was performed to areas of retinal edema demonstrated by stereo fundus photography and fluorescein angiography. Scatter panretinal photocoagulation (PRP) was subsequently performed in this eye. (d) One-year follow-up shows laser scar supero-temporally and resolution of retinal hemorrhages, hard exudates, and macular edema. The visual acuity improved to 20/40.

(private offices and academic centers) with over 400 physicians throughout the United States.

As per evidence-based guidelines in treating non-CI DME, the focal/grid laser treatment is supported by level 1 evidence when compared with no treatment (ETDRS). For patients with CI DME [4–6], level 1 evidence supports the use of focal/grid laser treatment for the management and other treatment strategies which include intravitreal ranibizumab with prompt or deferred laser. Many retina specialists prefer to now use a modified ETDRS treatment approach [7] for treating noncenter involving DME. This modified focal/grid treatment includes a less intense laser, greater spacing, directly targeting microaneurysms, and avoiding perifoveal vasculature within at least 500 μm of the center of the macula.

A prospective, multicenter, observational, focal/grid photocoagulation DRCR study of 122 eyes with CI DME [time domain OCT central subfield thickness (CST) ≥250 μm] showed continued improvements in OCT thickness (10% further reduction in CST from 16 to 32 weeks in 42%) and visual acuity (by at least five letters in 36%) at 4 or more months after laser treatment [8]. In 23–63% of patients, continued improvement was observed without additional treatment (protocol K). This study highlights the beneficial effects of laser photocoagulation over the long term.

Although, the ETDRS demonstrated a definite benefit in favor of laser photocoagulation in both CI DME and non-CI DME, approximately two thirds of patients with DME in the ETDRS had 20/25 or better pretreatment visual acuity. These patients with good visual acuity would not have been eligible for DRCR protocols I or T, as these protocols included only CI DME with baseline visual acuity of 20/32 to 20/320 [5,9,10▪▪–12▪▪]. Because OCT was not available in the ETDRS, the determination of CI DME versus non-CI DME was not possible for many of the patients with relatively mild DME. Although intravitreal injections of anti-VEGFs and steroids are increasingly used and recommended for the management of DME, laser photocoagulation treatment for DME continues to have an important role in current management. The role of combination

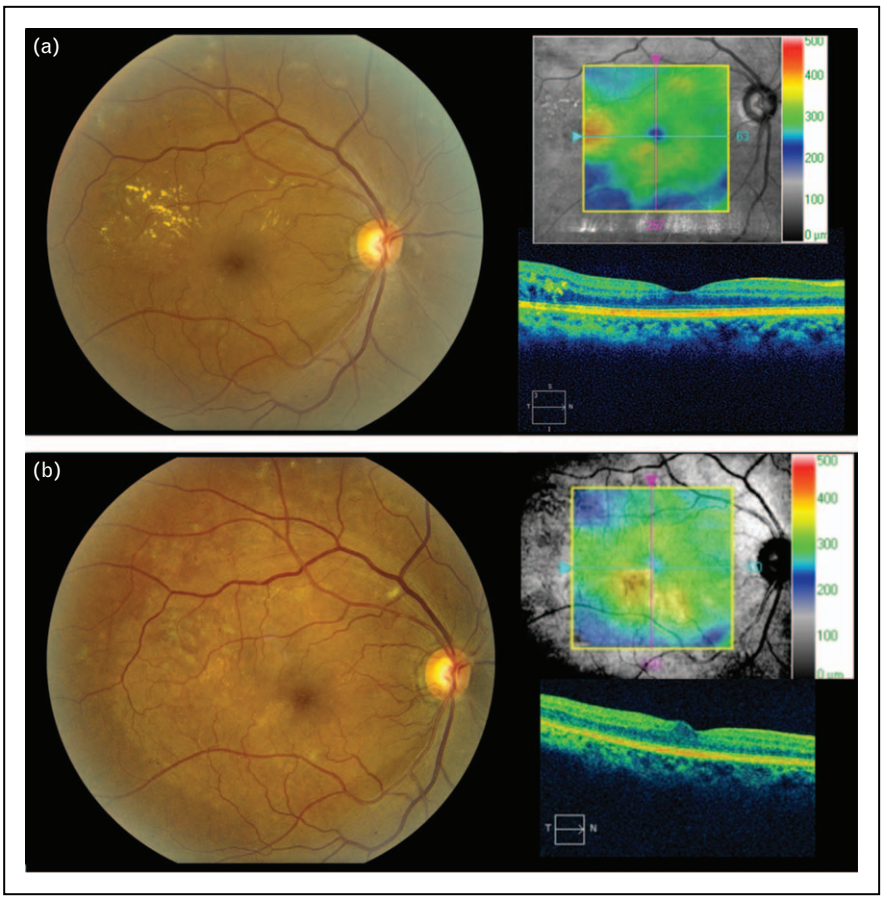

FIGURE 4. Early Treatment Diabetic Retinopathy Study (ETDRS) grid laser photocoagulation: (a) 60-year-old man with visual acuity 20/20 and localized diabetic macular edema (DME) temporal to the fovea in right eye. The right eye was treated with a light grid pattern within the area of retinal edema. (b) One-year follow-up shows resolution of hard exudates and retinal edema temporal to fovea. Faint laser scars in a grid pattern can be seen temporal to the macula. New macular edema by optical coherence tomography (OCT) has formed inferior to the fovea. The visual acuity remains 20/20.

therapy of intravitreal injections (anti-VEGF/steroids) and laser photocoagulation have been and continue to be evaluated in recent clinical trials.

DRCR protocol I evaluated the efficacy and safety of 0.5-mg intravitreal ranibizumab plus prompt (within 1 week) or deferred laser (≥24 weeks), or 4-mg intravitreal triamcinolone plus prompt (within

Table 1. Advantages and disadvantages of focal/grid laser photocoagulation used for treating diabetic macular edema in today's world

Advantages	Disadvantages
Proven favorable results in noncenter-involving diabetic macular edema (non-CI DME)	Less effective in diffuse center-involving diabetic macular edema (CI DME)
May be completed in one session	Possible initial transient decrease in central vision
Reduced number of clinic visits	Accidental/inadvertent foveal burn
Saves time (convenient for the patient)	Paracentral scotomas
Decreased risk of cataract	Rupture of Bruch's membrane
No risk of endophthalmitis	Laser induced CNVM
Lower one-time treatment cost compared to intravitreal injectionsa	Expansion of laser scar area (over many years)
	No impact on retinopathy severity scale when compared to anti-VEGF agents
	Cost in purchase and maintenance of laser equipment

CI DME, center-involved diabetic macular edema.

Table 2. Frequency of modified Early Treatment Diabetic Retinopathy Study laser treatment among various treatment arms in the trial of involving intravitreal injections in protocols I and T

DRCR protocol	Treatment groups	Frequency (%) of modified ETDRS laser treatment
Protocol I (3-year follow-up)	Intravitreal ranibizumab + prompt laser	100
	Intravitreal ranibizumab + deferred laser	48
	Intravitreal triamcinolone + prompt laser	100
Protocol T (2-year follow-up)	Intravitreal aflibercept + deferred laser	41
	Intravitreal bevacizumab + deferred laser	64
	Intravitreal ranibizumab + deferred laser	52

Protocol I: Refs. [5,9,10▪▪].
Protocol T: Refs. [11▪▪,12▪▪].
ETDRS, Early Treatment Diabetic Retinopathy Study.

1 week) laser, in comparison with sham plus prompt laser for treatment of DME [5,9,10▪▪]. In protocol I, patients assigned to sham plus prompt laser using modified ETDRS focal/grid laser, a modest mean visual acuity improvement from baseline was noted compared to the group with combination therapy (three letters in sham plus prompt laser group versus nine letters in ranibizumab plus prompt or deferred laser groups). At 2 years, improvement of at least 10 letters visual acuity occurred in 25% of sham plus prompt laser group, 35% of triamcinolone plus prompt laser group and 45–50% in the ranibizumab plus prompt or deferred laser groups. At 2 years, worsening of at least 10 letters visual acuity occurred in 12% of sham plus prompt laser group, 18% of triamcinolone plus prompt laser group, and 4–5% in the ranibizumab plus prompt or deferred laser groups. In eyes that were pseudophakic at baseline, the mean visual acuity letter score improvement was four letters of sham plus prompt laser group compared to eight letters in the ranibizumab plus prompt or deferred laser groups. Five-year results of DRCR protocol I reported that visual outcomes in eyes with DME involving the fovea were no better and possibly worse for group receiving focal/grid laser treatment at the initiation of intravitreal ranibizumab injection compared to group deferring laser treatment for 24 weeks or more.

DRCR protocol T [12▪▪] compared efficacy and safety of intravitreous drugs (aflibercept –EYLEA, bevacizumab – Avastin, and ranibizumab – Lucentis). In all the study groups, focal/grid laser was initiated at or after 6 months if DME was either persistent or not improving after at least 2 injections. In part, because of the relative efficacy of aflibercept in improving retinal thickening and visual acuity, laser treatment was indicated per protocol less frequently in the aflibercept-treated eyes. An additional efficacy post-hoc analysis of DRCR protocol T (2016) [13] showed that focal/grid laser treatment substantially reduced the mean central subfield thickness between 1 and 2 years for patients with DME with baseline visual acuity of 20/50 or worse who received bevacizumab and laser treatment. Significant number of patients received modified ETDRS laser treatment during the course of follow-up in DRCR Protocols I and T (Table 2).

Other randomized, multicenter, double-masked trials for patients [$N = 406$ (VIVID), $N = 466$ (VISTA)] [14] with CI DME and ETDRS BCVA 20/40 to 20/320 was a comparative study of laser photocoagulation, intravitreal aflibercept 2 mg every 4 weeks and intravitreal aflibercept 2 mg every 8 weeks (after initial 5 monthly injections). The mean number of active lasers performed in the laser photocoagulation group in VIVID/VISTA was 2.1/2.7, whereas the mean number of active injections were 12.2/11.8 in injections every 4-week group and 8.7/8.4 in injections every 8-week group. Gain of at least 15 letters visual acuity was reported in 9.1%/7.8% in the laser photocoagulation group compared with 32.4%/41.6% in the every 4-week injection group and 33.3%/31.1% in the every 8-week group. Loss of at least 15 letters visual acuity was reported in 10.6%/9.1% in the laser photocoagulation group, compared with 0.7%/0.6% in the every 4-week injection group and 0.0%/0.7% in the every 8-week group.

The RISE and RIDE phase III trials [15] showed that intravitreal ranibizumab benefited both DME and the clinical course of diabetic retinopathy. In this study, the patients were randomized into three groups: sham injections, ranibizumab 0.3 mg, and ranibizumab 0.5 mg. All patients received monthly intravitreal/sham injections; and macular laser beginning month 3 if eligible. At 2 years, gain of at least 15 letters was reported in 18.1%/12.3% of sham patients versus 44.8%/33.6% of 0.3-mg ranibizumab patients ($P < 0.0001$), and 39.2%/45.7% of 0.5-mg ranibizumab patients ($P < 0.001$). In RIDE, significantly more ranibizumab-treated patients gained 15 letters or more.

Alternative diabetic macular edema treatment options

Focal/grid laser photocoagulation [1,3], intensive glycemic control [16▪▪], and blood pressure control [17] have been demonstrated to reduce the risk of vision loss from DME. Technical advances, including subthreshold techniques [18,19], different wavelengths [20], and pattern laser generation [21] offer potentially beneficial options for treating DME. More recently, the development of navigated laser photocoagulation that combines fluorescein angiography with image stabilization and tracking may also provide more efficient, accurate, preplanned, automatic, and precise focal photocoagulation, allowing delineation of the spots/areas most appropriate for treatment [22–24]. Another DRCR network study will compare the effectiveness of modified ETDRS focal/grid laser, observation, and intravitreal ranibizumab for management of DME in eyes with very good visual acuity (20/25 or better).

CONCLUSION

Laser photocoagulation as shown historically by the ETDRS, remains an important option in the management of DME. In today's world, modified ETDRS focal/grid laser is often combined with intravitreal injections (anti-VEGF or steroid).

Acknowledgements

None

Financial support and sponsorship

None.

Conflicts of interest

H.W.F. Jr. is a member of the DRCR Data and Safety Monitoring Committee. The opinions expressed in this manuscript are the author's opinions and do not represent official statements from the DRCR. N.R. has no conflicts of interest.

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- ▪▪ of outstanding interest

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DRCR protocol I included patients with CI DME with baseline visual acuity of 20/32 to 20/320. Optical coherence tomography was used for the measurement of central subfield thickness. DRCR protocol I evaluated the efficacy and safety of intravitreal ranibizumab plus prompt/deferred laser, or intravitreal triamcinolone plus prompt laser, in comparison with sham plus prompt laser for treatment of DME. Five-year outcomes of the DRCR protocol I reported that visual outcomes in eyes with DME involving the fovea were no better and possibly worse for group receiving focal/grid laser treatment at the initiation of intravitreal ranibizumab injection compared to group deferring laser treatment for 24 weeks or more.

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