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A Randomized Trial Comparing Intravitreal Triamcinolone and Focal/Grid Photocoagulation for Diabetic Macular Edema: Baseline Features

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Abstract

Purpose—To compare baseline demographic, systemic, and ocular characteristics within age and racial subgroups among participants in this Diabetic Retinopathy Clinical Research Network clinical trial and to compare this cohort with other cohorts enrolled in phase 3 clinical trials for diabetic retinopathy.

Methods—Thirty-six month, randomized, controlled, multicenter clinical trial of 693 participants with diabetic macular edema enrolled at 88 clinical sites in the United States. Participants were categorized into self-reported race/ethnicity subgroups and into one of three age groups: 18 to <60, 60 to <70, and 70 and older.

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*The most recently published list of the Diabetic Retinopathy Clinical Research Network investigators and staff participating in this protocol can be found in Am J Ophthalmol 2007;144: 454-6 with a current list available at www.drcr.net.

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Summary Statement: "The rationale, study design, methods and baseline characteristics of participants in this DRCR.net clinical trial designed to compare two doses of intravitreal triamcinolone acetonide and focal/grid photocoagulation for the treatment of diabetic macular edema is described."

Results—Mean age of participants was 63 years, 72% were white, and median visual acuity letter score was 62 (~20/63). No substantial difference was identified between racial subgroups for any baseline variable. Older participants were more likely to have type 2 diabetes mellitus and longer duration disease. The most frequent levels of diabetic retinopathy among 840 study eyes were moderate (level 43) to moderately severe (level 47) non-proliferative disease.

Conclusion—While the racial composition of this cohort does not differ from other cohorts in large phase 3 trials that have evaluated participants with diabetic retinopathy, the inclusion of many subjects over age 70 and a better level of glycemic control are distinguishing features.

Keywords

baseline characteristics; clinical trial; diabetic macular edema; Diabetic Retinopathy Clinical Research Network; intravitreal injection; laser photocoagulation; study design; triamcinolone

Introduction

Vision loss from diabetic macular edema (DME) remains a major cause of visual impairment in the United States despite current therapies.[1-3] Evidence from large randomized clinical trials support the following means to reduce the risk of vision loss from DME: intensive glycemic control (Diabetes Control and Complications Trial [DCCT]) and United Kingdom Prospective Diabetes Study [UKPDS])[4, 5], blood pressure control (United Kingdom Prospective Diabetes Study)[6] and focal/grid photocoagulation (Early Treatment Diabetic Retinopathy Study [ETDRS]).[7] The identification of additional treatments that are safe and effective is desirable and of public health importance.

The Diabetic Retinopathy Clinical Research Network (DRCR.net), sponsored by the National Eye Institute, is presently conducting a clinical trial designed to compare intravitreal injection (s) of triamcinolone acetonide (hereafter referred to as intravitreal triamcinolone) and focal/grid photocoagulation for the treatment of DME.[8] The two primary study objectives are: 1.) to determine whether intravitreal trimcinolone at doses of 1mg or 4mg produce greater benefit, with an acceptable safety profile, than focal/grid photocoagulation in the treatment of DME; and 2.) to compare the safety and efficacy of the 1mg and 4mg intravitreal triamcinolone doses.

The purpose of this article is to describe the demographic, systemic, and ocular characteristics of the subject population at study entry. Baseline characteristics are categorized by participant age and self-reported race/ethnicity to evaluate any noteworthy differences within these subgroups or differences that distinguish this cohort from other cohorts enrolled in phase 3 DME clinical trials.

Study Design

This study was designed as a randomized, multi-center clinical trial. The full text of the protocol and Manual of Procedures are available online at www.drcr.net. The primary efficacy analysis will be performed at 24 months although follow-up will continue through 36 months. The primary outcome variable is the change in visual acuity (VA) letter score from baseline to 24 months as assessed by protocol refraction and vision determination using the Electronic-Early Treatment Diabetic Retinopathy Study (E-ETDRS) chart. Institutional Review Board (IRB) approval, from either a central IRB (Jaeb Center for Health Research) or from institutional IRBs, was obtained before screening of subjects at any of the participating clinical sites. All subjects provided written informed consent. Subjects meeting ocular eligibility criteria in one or both eyes were eligible for the study if they were at least 18 years old and had type 1 or type 2 diabetes. Subjects could not have chronic renal failure, a kidney transplant, uncontrolled

hypertension, or systemic corticosteroids within 4 months of study participation. Table 1 reports the major study ocular inclusion and exclusion criteria.

Baseline Assessments

At baseline, demographic data collected from each participant included age, gender and race/ethnicity. A complete medical history including diabetes history and current management, current medications and other medical conditions was also elicited from each participant. Measurement of blood pressure, done within 21 days of randomization, and a glycosylated hemoglobin level, obtained within 3 months prior to randomization or no later than 3 weeks after randomization, were recorded. A complete ocular examination including slit-lamp and dilated fundus examination, intraocular pressure measurement (IOP), and lens assessment was performed. The treating physician classified the lens status in the phakic eyes relative to standard photographs illustrating specific types of lens opacity.

Imaging tests submitted to a Reading Center (RC) at the University of Wisconsin included optical coherence tomography (OCT) images obtained with Stratus OCT 3 (Carl Zeiss Meditec; Dublin, CA) and stereoscopic film based color fundus photographs (FP). Duplicate OCT scans were performed for each eye. All images were obtained in accordance with standardized protocols by study certified personnel. The trial protocol did not require fluorescein angiograms (FA); however, if digital or film based FA's were performed for clinical care, their submission to the RC was encouraged.

Randomization—Subjects were randomly assigned to receive: focal/grid photocoagulation, 1mg intravitreal triamcinolone, or 4mg intravitreal triamcinolone. Patients were stratified by visual acuity letter score (20/40-20/63, <20/63 ->20/200, and 20/200 to 20/320) and history of prior or no prior macular photocoagulation. Subjects and physicians were masked to the intravitreal triamcinolone dose (1mg vs. 4mg), but not to the treatment assignment of focal/grid photocoaulation vs. intravitreal triamcinolone. Subjects with two study eyes had the right eye randomly assigned to one of these three treatment strategies, with the left eye assigned to the alternate strategy. If the right eye was assigned to focal/grid photocoagulation then the left eye was randomly assigned to one of the two intravitreal triamcinolone doses. The study drug, micronized triamcinolone acetonide, was formulated and manufactured as a sterile intravitreal, preservative free injectable by Allergan Inc. (Irvine, CA) of 1mg or 4mg per 0.05cc. Randomization was completed on a website maintained by the Data Coordinating Center (Jaeb Center for Health Research, Tampa, FL) using a permuted-blocks design. The technique for Modified- Early Treatment Diabetic Retinopathy Study (m-ETDRS) focal laser, as employed in the first DRCR.net protocol, has been published previously[9], and the injection protocol for intravitreal steroid administration may be found online at www.drcr.net.

Patients were retreated with the randomly assigned treatment at 4 month intervals except when the criteria to defer additional treatment were met or when the criteria to employ the alternate treatment regimen were satisfied. Detailed criteria for re-treatment and application of the alternate treatment regimen will be reported in the primary outcomes report, but are available for review at www.drcr.net.

Assessment of retinopathy severity and macular edema—The RC followed standardized protocols to grade retinopathy level and macular edema using 7 field stereoscopic film based FP and were masked to treatment assignment and subject clinical data.[10, 11] Graders classified the proportion of fluorescein leakage derived from microaneurysms, categorically, in an attempt to differentiate eyes with focal vs. diffuse leakage patterns. Areas of fluorescein leakage were assessed quantitatively as continuous variables for the ETDRS macular grid (a circle 2 disc diameters [DD] in radius centered on the fovea) as a whole and for its inner zone

(1 DD radius) and its central subfield (1/3 DD radius). Retinal thickening was quantified from OCT images and morphologic features of DME were reported using a standardized protocol developed at the RC. Quantitative data (e.g. central subfield thickness [CST]) were extracted from the fast macular map scan consisting of 6mm radially oriented scans; whereas qualitative data (e.g. presence or absence of vitreomacular traction or cystoid spaces) were obtained from the higher resolution vertical and horizontal crosshair images centered on the fovea.

All OCT images were graded independent of FP or FA. For 18% of the scans, the automated thickness measurements were judged by the RC to be inaccurate and CST was imputed from the center point thickness (usually manually measured) using a regression equation.[9] Continuous measures from the OCT were taken as the mean of the two scans for each eye. Categorical measures (e.g. cystoid abnormalities) were taken from the first scan.

Results

Between July 2004 and May 2006, 693 subjects were enrolled at 88 sites in 34 states. Approximately one-fifth of the participants (147) had both eyes randomly assigned to treatment for a total of 840 study eyes. Table 2 and Table 3 report demographic and systemic characteristics of the cohort by participant; while Tables 4, 5, 6, 7 and 8 describe select ocular characteristics of the cohort by eye.

Baseline Description

Demographic and Systemic Characteristics—Participants ranged from age 30 to 86 with a median (25th, 75th percentiles) age of 63 (57, 69) years and 49% were women. The median CST for men was 419 microns and the median CST for women was 383 microns. No other gender differences were observed for any of the baseline demographic, systemic or ocular characteristics reported here (data not shown). The majority (72%) of participants identified themselves as white; 13% as Hispanic, 10% African-American and 3% Asian (Table 2). No substantial differences were identified between any of the racial subgroups for any of the baseline variables reported in Table 2.

Participants were categorized into 1 of 3 age groups: 18 to <60, 60 to <70, and 70 and older (Table 3). Baseline characteristics in the 70 and older age group were of specific interest because this group was excluded from the ETDRS. The two other age strata were chosen to divide the remaining cohort into equivalent size subgroups. The two older age subgroups had fewer persons with type 1 diabetes than the youngest subgroup. Nearly all (95%) participants had Type 2 diabetes mellitus (DM) (Table 3). Median duration of DM was 15 (10, 22) years, mean (± standard deviation) glycosylated hemoglobin was 7.9 ± 1.8, and 564 (81%) reported a past or present history of hypertension among whom 550 (98%) were receiving medical treatment. Self report of hypercholesterolemia was noted in 461 (67%) and hypertriglyceridemia in 167 (24%) with reported active medical treatment for their lipid disorder in 88% and 61% of these participants, respectively (Table 3). Duration of diabetes and prevalence of hypertension progressively increased with advancing age among the 3 age subgroups. Thiazolidinedione (TZD) use was assessed because of the possible effects of this class of drug on DME. Thirty-one percent of patients reported using a TZD within 6 months of randomization.

Ocular Characteristics—Nearly all (98%) study eyes had no prior history of ocular hypertension by patient history; 10 eyes (1%) were receiving treatment for ocular hypertension with a single topical medication (Table 4). At study entry, median (25^{th}, 75^{th} percentiles) IOP was 16 (14, 18) mm Hg. No age-related differences were observed for any of these variables. Cataract surgery had been performed prior to study entry in 178 (21%) eyes. Older participants were more likely to be pseudophakic at study entry (48% pseudophakic in the age 70 and older

group vs. 7% in the under 60 age group). Among phakic eyes, some degree of nuclear sclerosis was present in 92%, cortical cataract in 49%, and posterior subcapsular cataract in 21%. Each type of lens opacity and a more advanced degree of lens opacity were more prevalent at baseline in the oldest age group.

Photocoagulation prior to study entry had been performed for macular edema in 61%; whereas 16% had undergone panretinal photocoagulation (PRP) presumably for severe non-proliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR). A greater number of participants in the oldest age group had received treatment for DME when compared with the younger age group (65% vs 54%), but fewer older subjects had received PRP (12% vs 19%

No age related differences were noted in baseline visual acuity letter score between any of the subgroups (Table 4). There were 487 (58%), 315 (38%) and 38 (5%) study eyes within the three VA strata used for randomization (20/40-20/63, <20/63->20/200, and 20/200-20/320).

Nearly all study eyes (829, 99%) had FP available for review. All levels of diabetic retinopathy ranging from microaneurysms only to high risk proliferative retinopathy were represented (Table 4). The most common levels of retinopathy were moderate (level 43) to moderately severe (level 47) non-proliferative disease (53% of cohort). Clinically significant macular edema (CSME) was confirmed on FP in 762 (92%) of these eyes, typically involving the foveal center. Overall, the distribution of diabetic retinopathy severity level favored milder stages among the oldest participants and fewer eyes with foveal center involved CSME. The RC confirmed the presence of prior focal laser photocoagulation in 57% and PRP in 17% approximating the same fractions of the cohort that self-reported prior focal laser photocoagulation or PRP treatment as described in Table 4. Lipid exudates were found within 2 DD of the foveal center in 82%, although the amount of lipid was generally minimal in these cases with a median (25^{th}, 75^{th} percentiles) value of 0.07 (0.02, 0.17) disc areas (DA) (data not shown). The maximum potential areas of thickening within the inner zone and within the grid are 4 DA and 16 DA, respectively. The median areas of thickening within the inner zone and within the grid were 3.38 (2.13, 4.00) DA and 6.69 (3.59, 10.69) DA, respectively. The area of retinal thickening within the inner zone or within the grid was largest in the youngest subgroup and progressively decreased among the 2 older age groups.

Fast macular thickness maps documented median (25^{th}, 75^{th} percentiles) CST of 401 (326, 500) microns and median retinal volume of 9.0 (7.9, 10.4) mm^3 (Table 4). Retinal volume decreased with advancing age among the 3 age subgroups. In the qualitative evaluation of OCT images (Table 5) nearly all (96%) study eyes had at least questionable or mild cystoid abnormalities on OCT with one-third graded at the moderate or severe level. Subretinal fluid was absent in the majority of study eyes; however, 19% had subretinal fluid directly under the foveal center. Thirty three percent of eyes were interpreted as manifesting questionable or definite vitreomacular interface abnormalities on the OCT images. Vitreomacular interface abnormalities included vitreomacular traction, epiretinal membranes or pre-macular hole lesions.

Fluorescein angiograms were available for review in 350 (51%) participants (Table 6). Participants who had baseline FA's reviewed at the RC did not differ from participants who did not have FA's reviewed at the RC with respect to age, race, gender, type and duration of DM, glycosylated hemoglobin, study eye VA and OCT measured CST. Fluorescein angiograms captured with digital (80%) and film (20%) based systems had fair or better quality in 71% of the submissions. There was no predominant pattern or relationship with age for the source of leakage on FA. Leakage occupying the entire central subfield (total area of the central subfield is 0.44 DA) was documented to be present in 53% of the eyes. Median (25^{th}, 75^{th}

percentiles) values for total leakage within the inner zone and within the grid as a whole were 2.50 (1.34, 3.73) DA and 5.45 (2.86, 9.49) DA respectively, values that are fairly similar to the area of thickened retina identified on the FP. As previously demonstrated for area of retinal thickening on FP, the area occupied by FA leakage was age related (6.16 DA among the <60 year old group vs 4.31 DA among the ≥70 year olds). For participants who contributed both eyes to random treatment assignment, assessment of capillary closure was difficult for both eyes since only one eye could be viewed during the fluorescein dye transit phase. Identification of capillary closure remained problematic even among the eyes imaged during the dye transit as only approximately 75% of FA's were of sufficient quality to assess this characteristic. Among the studies with sufficient quality to make this assessment (N=264) relatively few participants in each age group had areas of capillary closure, and when this occurred the size of the area involved was likely inconsequential (median value for capillary closure within the grid: 0 [0, 0.13 DA]).

Baseline Characteristics by Race—Table 7 shows the baseline ocular characteristics by race/ethnicity. No substantial difference was identified between racial/ethnic subgroups for any of the baseline ocular variables. Compared with other groups the Asian participants appeared to be slightly older, have a shorter duration of DM, and a slightly lower level of VA. However, considering there were only 19 participants in this racial subgroup, these estimates are likely imprecise and no definite conclusions can be made.

Baseline Characteristics of Non-study Fellow Eyes—Among the 693 participants, 546 contributed one eye to random treatment assignment within the protocol. The contralateral non-study eye in these 546 individuals had a median VA letter score of 75 (Snellen equivalent 20/32 [range: 20/12, 20/400] (Table 8). Comparison of VA in the study eye and non-study eye within these participants identified 358 (66%) in which the study eye had a VA letter score that was ≥10 letters lower than that of the non-study eye. Only 39 participants (7%) had study eyes with a VA letter score that was 10 or more letters higher than the non-study eye; whereas the remaining individuals (27%) had VA letter scores from each eye that were within 2 lines of each other. The median CST was thinner in the contralateral non-study eyes at 259 microns (219, 328) when compared with the paired study eyes of these individuals with median of 392 microns (322, 480). The CST was at least 40 microns greater in 415 (77%) of the study eyes relative to the non-study fellow eye; whereas only 47 (9%) had measurements that were at least 40 microns thinner in the study eye relative to the non-study fellow eye. The distribution of diabetic retinopathy severity was similar in the non-study fellow eyes to the study eyes (none/microaneursyms only/mild NPDR: 12%, moderate/moderately severe NPDR: 53%, severe NPDR: 5%, proliferative diabetic retinopathy: 27%).

Eyes Randomized within the Study Failing to Meet the Inclusion Criteria—Only 4 (<1%) study eyes deviated from the inclusion criteria at time of enrollment. Deviations included CST of less than 250 microns (n=2), prior steroid injection in the non-study fellow eye (n=1), and presence of open angle glaucoma (n=1). Following post-randomization review of baseline OCT scans at the RC, some eyes originally submitted with CST of at least 250 microns required a manual re-grade due to inaccurate OCT instrument generated boundary lines; this resulted in the reclassification of 25 study eyes as having CST measurements of less than 250 microns.

Discussion

Baseline characteristics of a cohort within a clinical trial are shaped by the eligibility criteria. Nevertheless, many of the baseline demographic characteristics of this DRCR.net cohort, who were specifically enrolled in a treatment trial of DME, are similar to those reported for other cohorts enrolled in large phase 3 studies evaluating diabetic retinopathy (though not

specifically DME) including the ETDRS, (N=3711) and the PKC-DRS2 (a recent trial which evaluated ruboxistaurin for diabetic retinopathy, N=685).[12, 13] Similarities include the duration of diabetes and the racial/ethnic profile of the participants.[12, 13] However, the age of participants in this DRCR.net cohort is slightly older than the ETDRS (48% of study participants were under age 50) and the PKC-DRS2 cohort (mean age 59 years, range 23 – 87 years). The ETDRS specifically excluded individuals who were age 70 and older; whereas nearly one quarter of this DRCR.net cohort is in this age group. Therefore, when the results from this study are available, they will reflect a population of diabetic patients that is older compared with the cohorts recruited for the ETDRS and the PKC-DRS2.[12, 13] The PKC-DRS2 did not have a ceiling on the maximum age of participants during their recruitment period of 2001 and 2005, yet the PKC-DRS2 cohort was younger than our cohort. This DRCR.net trial required the presence of center involving DME confirmed by OCT whereas the PKC-DRS2 did not have this requirement. One-half of the PKC-DRS2 subjects had either no DME or retinal thickening that was more than 500 microns from the foveal center implying an earlier stage in the disease process and therefore a greater probability of a younger subject age.

This DRCR.net cohort was recruited between 2004 and 2006 from a geographically diverse and large number of clinical centers, therefore, the characteristics of this group may be more indicative of the type of individuals expected to enroll in contemporary clinical trials that focus on center-involved DME. Furthermore, participants in this current DRCR.net trial were enrolled without contemporaneous eligibility review from the RC and all but 29 (3%) of the participants met the inclusion criteria following the RC review of baseline images. Therefore, the results of this trial may be generalized to similar patient populations at large identified to have DME by a retina specialist.

Another important distinguishing baseline characteristic of this cohort relative to other trials is the level of glycemic control as reflected in glycosylated hemoglobin levels. The mean HbA1C is 7.9 in this DRCR.net study with 10% of subjects having a value of 10.0 or higher. In contrast, the mean level of HbA1C was 8.1 in the PKC-DRS2 and in the ETDRS 42% of participants had a HbA1C $\geq$10.0. While unknown confounding factors could account for these differences, we presume that improved systemic control of the DM will result in a cohort at lower risk and slower rate of progression of their retinopathy which may indicate a more benign natural course of their DME and potentially a different treatment response.[14, 15] The lower glycosylated hemoglobin levels in this DRCR.net cohort relative to the ETDRS cohort may also be an indicator of more optimal management of other systemic factors that relate to severity of diabetes complications such as hypertension and lipid levels. In this regard, the majority of our participants also reported receiving treatment for hypertension and hypercholesterolemia. Since systemic control of DM may affect DME, the importance of using concurrent controls rather than historical controls from other clinical trials, is highlighted.

Individuals could only participate in this DRCR.net study if their VA was between 20/40 and 20/320 Snellen equivalent. Participants and investigators were willing to randomize eyes at the better end of this VA spectrum to either focal/grid photocoagulation or intravitreal triamcinolone as 19% of the study eyes had a VA letter score between 69 and 73 inclusive (Snellen equivalent of 20/40) and 43% had a VA letter score between 59 and 68 inclusive (Snellen equivalent of 20/50 to 20/63). In comparison with other large phase 3 studies for diabetic retinopathy, the baseline VA of this DRCR.net cohort is lower (median letter score of 62 letters, 20/63). However, this may be the result of different inclusion criteria for VA between studies. Subjects were permitted in this trial with VA letter scores between 24 and 74 inclusive. In contrast, the range of permissible VA letter scores was $\geq$34 in the ETDRS and >45 in the PKC-DRS2 which were associated with mean baseline VA letter scores of approximately 80 in the ETDRS and 77 in the PKC-DRS2. The lower initial VA in this DRCR.net cohort may allow a better opportunity to determine if either treatment intervention (intravitreal

triamcinolone or focal/grid photocoagulation) provides for an increase in VA letter score of 15 or more although this may be tempered by the possibility that subjects with lower initial VA letter scores may be refractory to treatment due to factors such as ischemia or chronic macular edema.

This DRCR.net study will provide an opportunity to evaluate several ocular characteristics that have not been fully evaluated in any other phase 3 studies for DME, namely retinal thickness and retinal thickening as measured by OCT. This cohort had a median CST of 401 microns, representing a moderate degree of retinal thickening. A very wide range of retinal thickness is represented with nearly equal fractions of mild, moderate, and severe thickening measurements. Similar to results from a DRCR.net study of diabetic patients with little or no retinopathy and no clinical evidence of center involved DME[16], men in this study had larger CST values than women (median 419 vs. 383 microns). Qualitative assessment of the OCT images at the RC also demonstrated anatomical abnormalities such as moderate to severe cystoid abnormalities present in 34% and subfoveal subretinal fluid in 19% of participants. Notably, 33% of participants were assessed by the RC as having questionable or definite vitreoretinal interface abnormalities at baseline. The frequency with which the RC identified these changes is important since investigators were asked to exclude potential participants who had macular edema from any cause other than DME which may have included clinically apparent vitreo-retinal interface abnormalities. Outcomes of the treatment interventions will be explored in each of these OCT based subgroups to determine their influence on treatment effect.

Baseline demographic, systemic and ocular characteristics by self-reported race were evaluated. This DRCR.net cohort (72% white) is similar to the ETDRS (76% white) and the PKC-DRS2 (78% white) in racial demographic. No substantial differences were identified between any of the racial subgroups for any of the baseline variables; however, this analysis is limited by the small number of participants in this DRCR.net cohort who are categorized as non-white.

Comparison of several demographic, systemic and ocular characteristics by participant age led to the following observations: older participants were more likely to have type 2 diabetes, have a longer duration of DM and were more likely to be pseudophakic. The distribution of retinopathy severity level favored milder stages of retinopathy and lesser degrees of macular edema among the oldest participants. In particular, subjects 70 years or older were less likely than younger participants to have severe NPDR or PDR, and less likely to have extensive areas of macular retinal thickening or angiographic macular leakage despite having a longer median duration of DM (Table 4 and 6). A larger proportion of participants in the older subgroup had received laser treatment for DME prior to enrollment when compared with the other age groups and this may explain, in part, the differences in areas of retinal thickening and leakage. However, there also appears to be a difference in retinopathy level between the older subgroup and the other subgroups which would not be explained by differential rates of PRP. These potential relationships between age and retinopathy levels could possibly be explained by a long-term survival hypothesis: individuals with more severe diabetes, as reflected by the severity of diabetic retinopathy, may be more likely to die at an early age such that only those with milder levels of retinopathy live to an older age. In support of this hypothesis, a long term follow-up study of ETDRS participants at one center found that more severe degrees of retinopathy and poorer levels of VA at study entry and close out of the ETDRS increased the odds of subsequent mortality.[17]

Baseline characteristics of the non-study fellow eye indicate that the majority of participants had their more severely effected eye enrolled into this trial. The reason for this phenomenon is unclear, but may reflect a hesitancy of participating ophthalmologists to enroll the “better

seeing" eye and may reflect a referral pattern in which participating ophthalmologists treat mainly patients with asymmetric disease.

Summary

The rationale, study design, methods and baseline characteristics of participants in this DRCR.net clinical trial designed to compare two doses of intravitreal triamcinolone and focal/grid photocoagulation for the treatment of DME are described. Evaluation of demographic, systemic and ocular characteristics show that this is an older group of diabetic persons that is primarily white and likely to have type 2 diabetes. Systemic control of diabetes appears to be good as evidenced by the median glycosylated hemoglobin level. As a cohort, substantial thickening of the retina was documented by OCT and a significant area of retinal thickening was documented by evaluation of FP. Despite this, the baseline level of VA of many of the enrolled participants was good. Older participants were more likely to have type 2 diabetes, have a longer duration of DM and were more likely to have milder retinopathy and milder DME levels as assessed on FP. No substantial differences were identified between any of the racial subgroups for any of the baseline variables. The inclusion criteria for this clinical trial were broad and participants were recruited from a large number of settings ranging from private practices to university-based settings. As such, the results forthcoming from the main outcomes reports are likely to be generalizable to a contemporary and broad population of patients with DM.

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Table 1
Study eye major inclusion and exclusion criteria

Inclusion criteria

- Best corrected E-ETDRS visual acuity letter score of ≤73 (approximate Snellen equivalent of 20/40 or worse) and ≥24 (approximate Snellen equivalent of 20/320 or better). [*Note: the original upper limit of visual acuity letter score was expanded from ≤68 letters to ≤73 letters eight months after accrual began*]
- Center-involved diabetic macular edema present on clinical examination
- Central subfield mean thickness (CST) of two OCT fast macular scans ≥250 microns
- Media clarity, pupillary dilation, and subject cooperation sufficient for adequate fundus photographs

Exclusion criteria

- Presence of macular edema due to a cause other than diabetic macular edema
- Presence of an ocular condition such that visual acuity would not improve from resolution of the edema (e.g. foveal atrophy)
- Substantial cataract estimated to have reduced visual acuity by 3 lines or more
- Prior treatment with intravitreal corticosteroids at any time or peribulbar steroid injection within 6 months prior to randomization
- History of focal/grid macular photocoagulation within 15 weeks (3.5 months) *or* panretinal photocoagulation (PRP) within 4 months prior to randomization *or* anticipated need for PRP within the 4 months following randomization
- Prior pars plana vitrectomy
- Major ocular surgery (including cataract extraction) within prior 6 months or anticipated within the next 6 months following randomization
- YAG capsulotomy performed within 2 months prior to randomization
- Intraocular pressure (IOP) ≥25 mmHg, open-angle glaucoma (either primary open-angle glaucoma or other cause of open-angle glaucoma), steroid-induced IOP elevation that required IOP-lowering treatment or pseudoexfoliation
- Aphakia

Table 2

Baseline Demographic and Systemic Characteristics by Self-Reported Race/Ethnicity (N=676[a] subjects)

	White N (%)	Hispanic N (%)	African American N (%)	Asian N (%)
# Subjects	500	88	69	19
Age (yrs)				
median (25th, 75th percentiles)	63 (57, 69)	63 (56, 68)	63 (58, 70)	68 (65, 76)
18-<60	191 (38)	37 (42)	25 (36)	2 (11)
60-<70	196 (39)	34 (39)	26 (38)	8 (42)
≥70	113 (23)	17 (19)	18 (26)	9 (47)
Gender				
Women	230 (46)	43 (49)	46 (67)	9 (47)
Men	270 (54)	45 (51)	23 (33)	10 (53)
Diabetes Type				
Type 1	26 (5)	6 (7)	1 (1)	0
Type 2	474 (95)	82 (93)	68 (99)	19 (100)
Duration of DM[b] (yrs)				
median (25th, 75th percentiles)	16 (10, 22)	17 (11, 23)	14 (11, 20)	11 (8, 19)
< 10 yrs	125 (25)	17 (19)	10 (14)	8 (42)
10-<20 yrs	190 (38)	39 (44)	38 (55)	8 (42)
≥20 yrs	185 (37)	32 (36)	21 (30)	3 (16)
HbA1c[c] %				
Mean ± standard deviation	7.7 ± 1.6	8.6 ± 2.3	8.5 ± 2.1	7.6 ± 1.2
<7%	142 (34)	16 (27)	11 (19)	6 (32)
7-<9%	207 (50)	25 (42)	31 (53)	10 (53)
≥9%	66 (16)	18 (31)	17 (29)	3 (16)
Hypertension: *n (%)*	397 (79)	73 (83)	64 (93)	16 (84)
Hypercholesterolemia: *n (%)*	327 (65)	60 (68)	48 (70)	16 (84)
Hypertriglyceridemia: *n (%)*	123 (25)	18 (20)	17 (25)	4 (21)

[a] Excludes N=17 subjects of other (5 American Indian/Alaskan Native, 1 Pacific Islander, 1 mixed race) or unknown (10) race/ethnicity.

[b] DM = Diabetes Mellitus

[c] HbA1c missing for N=124 of these subjects.

Table 3
Baseline Demographic and Systemic Characteristics of Cohort by Age (yrs) (N=693 subjects)

	18-<60 N (%)	60-<70 N (%)	≥70 N (%)	All N (%)
# Subjects	263	269	161	693
Gender				
Women	117 (44)	138 (51)	82 (51)	337 (49)
Men	146 (56)	131 (49)	79 (49)	356 (51)
Diabetes Type				
Type 1	24 (9)	6 (2)	4 (2)	34 (5)
Type 2	239 (91)	263 (98)	157 (98)	659 (95)
Duration of DM[a] (yrs)				
median (25^{th}, 75^{th} percentiles)	14 (8, 20)	16 (10, 22)	18 (11, 26)	15 (10, 22)
<10 yrs	78 (30)	58 (22)	28 (17)	164 (24)
10-<20 yrs	109 (41)	115 (43)	57 (35)	281 (41)
≥20 yrs	76 (29)	96 (36)	76 (47)	248 (36)
HbA1c[b] (%)				
Mean ± standard deviation	8.3 ± 2.3	7.6 ± 1.4	7.5 ± 1.2	7.9 ± 1.8
<7%	62 (30)	70 (31)	47 (35)	179 (32)
7-<9%	84 (41)	125 (56)	72 (53)	281 (50)
≥9%	60 (29)	28 (13)	17 (13)	105 (19)
Hypertension: n (%)	203 (77)	223 (83)	138 (86)	564 (81)
Hypercholesterolemia: n (%)	170 (65)	183 (68)	108 (67)	461 (67)
Hypertriglyceridemia: n (%)	60 (23)	67 (25)	40 (25)	167 (24)
TDZ[c] usage within 6 months	80 (30)	92 (34)	43 (27)	215 (31)

[a] DM = Diabetes Mellitus

[b] HbA1c missing for 128 subjects

[c] TDZ- thiazolidinedione

Table 4
Baseline Ocular Characteristics of the Study Eye by Age (N=840 study eyes)

	18-<60 N (%)	60-<70 N (%)	≥70 N (%)	All N (%)
# Study Eyes	318	327	195	840
Ocular Hypertension	7 (2)	6 (2)	2 (1)	15 (2)
No medications	3 (<1)	2 (<1)	0	5 (<1)
Single Topical agent	4 (1)	4 (1)	2 (1)	10 (1)
Intraocular Pressure (mmHg)				
median (25^{th}, 75^{th} percentiles)	16 (13, 18)	16 (14, 18)	15 (13, 17)	16 (14, 18)
Lens Status (clinical exam): n *(%)*				
Pseudophakic	23 (7)	62 (19)	93 (48)	178 (21)
Phakic	295 (93)	265 (81)	102 (52)	662 (79)
Nuclear Sclerosis[a]				
Absent	47 (16)	8 (3)	1 (<1)	56 (8)
Present, < standard	219 (74)	206 (78)	76 (75)	501 (76)
Present, ≥ standard	29 (10)	51 (19)	25 (25)	105 (16)
Cortical Cataract[a]				
Absent	173 (59)	130 (49)	33 (32)	336 (51)
Present, < standard	102 (35)	106 (40)	52 (51)	260 (39)
Present, ≥ standard	20 (7)	29 (11)	17 (17)	66 (10)
Posterior Subcapsular[a]				
Absent	240 (81)	213 (80)	72 (71)	525 (79)
Present, < standard	46 (16)	44 (17)	26 (25)	116 (18)
Present, ≥ standard	9 (3)	8 (3)	4 (4)	21 (3)
Prior Photocoagulation[b]				
Focal only	134 (42)	170 (52)	112 (57)	416 (50)
PRP only	24 (8)	8 (2)	9 (5)	41 (5)
Focal and PRP	37 (12)	43 (13)	14 (7)	94 (11)
Visual Acuity Letter Score (Snellen Equivalent)				
median (25^{th}, 75^{th} percentiles)	63 (53, 68)	61 (52, 67)	61 (53, 67)	62 (53, 67)
73-60 (20/40 – 20/63)	198 (62)	183 (56)	106 (54)	487 (58)
59-36 (<20/63 – >20/200)	108 (34)	127 (39)	80 (41)	315 (38)
35-24 (20/200 – 20/320)	12 (4)	17 (5)	9 (5)	38 (5)
Central Subfield[c] (OCT, microns)				
median (25^{th}, 75^{th} percentiles)	399 (333, 523)	404 (324, 490)	397 (318, 468)	401 (326, 500)
<400 microns	159 (50)	160 (49)	98 (51)	417 (50)
400-<500 microns	64 (20)	89 (27)	57 (30)	210 (25)
≥500 microns	93 (29)	78 (24)	38 (20)	209 (25)
Retinal Volume[d] (mm^3)				

	18-<60 N (%)	60-<70 N (%)	≥70 N (%)	All N (%)
median (25th, 75th percentiles)	9.4 (8.2, 10.7)	8.9 (7.8, 10.4)	8.7 (7.6, 9.9)	9.0 (7.9, 10.4)
Retinopathy Severity[e] (ETDRS level)				
Microanuerysms only/ Mild NPDR (20, 35)	14 (4)	20 (6)	23 (12)	57 (7)
Moderate NPDR (43)	21 (7)	43 (13)	40 (21)	104 (13)
Moderately severe NPDR (47)	132 (42)	125 (38)	77 (40)	334 (40)
Severe NPDR (53)	36 (12)	42 (13)	17 (9)	95 (11)
PDR (60-61, 65, 71-75)	102 (33)	88 (27)	30 (16)	220 (27)
Cannot Grade (90)	7 (2)	8 (2)	4 (2)	19 (2)
CSME[e,f]				
None	5 (2)	6 (2)	9 (5)	20 (2)
Questionable/Zone of retinal thickening ≥ 1 disc area, within 1 disc diameter from center	3 (<1)	5 (2)	4 (2)	12 (1)
Retinal thickening or adjacent hard exudates ≤500μ from center				
Thickening at center				
None/Questionable	4 (1)	3 (<1)	13 (7)	20 (2)
Definite	290 (93)	290 (89)	150 (79)	730 (88)
Cannot grade	10 (3)	22 (7)	15 (8)	47 (6)
Area of Retinal Thickening (in the Inner Zone)[e,g]				
median (25th, 75th percentiles) - Disc Areas	3.56 (2.56, 4.00)	3.42 (2.18, 4.00)	2.95 (1.56, 3.73)	3.38 (2.13, 4.00)
Area of Retinal Thickening (within the Grid)[e,h]				
median (25th, 75th percentiles) - Disc Areas	8.09 (4.35, 11.98)	6.86 (4.01, 10.74)	4.60 (2.44, 7.41)	6.69 (3.59, 10.69)

[a] Phakic eyes only (N=662).

[b] Self reported by subjects at baseline exams.

[c] Central subfield value taken as the mean from the two scans performed for each eye. Value is missing for 4 eyes where both scans lost (N=2) or required manual grading that was not performed (N=2).

[d] Ungradable for 129 eyes, generally due to inaccurate algorithm placement of software.

[e] Fundus photograph unavailable for 11 eyes (not performed for 8 eyes and lost for 3 eyes).

[f] CSME = Clinically Significant Macular Edema.

[g] Center and 4 inner subfields. Ungradable for 46 eyes.

[h] Center, 4 inner and 4 outer subfields. Ungradable for 46 eyes.

Table 5
Baseline OCT Characteristics (N = 838 study eyes)[a,b]

	Quantitative Measures	
	median (25th, 75th percentiles)	***Range***
Center Subfield Thickness[c] (microns)	401 (326, 500)	[133 - 1164]
	Qualitative Measures	
Cystoid Abnormalities: N (%)		
None		27 (3)
Questionable/Mild		516 (62)
Moderate/Severe		288 (34)
Cannot Grade		7 (<1)
Subretinal Fluid on OCT: N (%)		
None		615 (73)
Questionable/Definite, spares center		58 (7)
Definite, Center involved		161 (19)
Cannot Grade		4 (<1)
Vitreoretinal Interface Abnormalities		
No Evidence		553 (66)
Questionable		160 (19)
Definite		116 (14)
Cannot Grade		9 (1)

[a] Two OCT scans performed for each eye. For continuous variables the mean value from the two scans was taken for each eye. Categorical values were taken from the first scan.

[b] Excludes 2 eyes where both scans were lost.

[c] Excludes 2 eyes where both scans required manual grading that was not performed.

Table 6

Baseline Fluorescein Angiography Characteristics by Age (yrs) (428 study eyes from 350 subjects)

	18 - <60	60 - <70	≥70	All
Leakage Source within Grid[a] *n(%)*	N=133	N=135	N=82	N=350
None	3 (2)	1 (<1)	2 (2)	6 (2)
<33% from Ma	33 (25)	36 (27)	21 (26)	90 (26)
33%-66% from Ma	29 (22)	36 (27)	26 (32)	91 (26)
≥67% from Ma	56 (42)	51 (38)	27 (33)	134 (38)
Can't grade	12 (9)	11 (8)	6 (7)	29 (8)
Fluorescein Leakage (Disc Areas)				
Central Subfield[b]	N=149	N=148	N=97	N=394
Median (25^{th}, 75^{th} percentiles)	0.44 (0.20, 0.44)	0.42 (0.18, 0.44)	0.44 (0.20, 0.44)	0.44 (0.19, 0.44)
[Range]	[0, 0.44]	[0, 0.44]	[0, 0.44]	[0, 0.44]
Inner Zone[c]	N=150	N=148	N=98	N=396
Median (25^{th}, 75^{th} percentiles)	2.71 (1.54, 3.84)	2.47 (1.15, 3.78)	2.18 (1.40, 3.42)	2.50 (1.34, 3.73)
[Range]	[0, 4.00]	[0, 4.00]	[0, 4.00]	[0, 4.00]
Grid as a whole[c]	N=150	N=148	N=98	N=396
Median (25^{th}, 75^{th} percentiles)	6.16 (3.45, 11.30)	5.49 (2.59, 9.95)	4.31 (2.37, 7.35)	5.45 (2.86, 9.49)
[Range]	[0, 16.00]	[0, 16.00]	[0, 15.54]	[0, 16.00]
Capillary Closure (Disc Areas)				
Central Subfield[a,d]	N=107	N=96	N=56	N=259
Median (25^{th}, 75^{th} percentiles)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
[Range]	[0, 0.27]	[0, 0.28]	[0, 0.18]	[0, 0.28]
Inner Zone[a,e]	N=110	N=97	N=56	N=263
Median (25^{th}, 75^{th} percentiles)	0 (0, 0.03)	0 (0, 0)	0 (0, 0)	0 (0, 0)
[Range]	[0, 0.61]	[0, 1.88]	[0, 0.28]	[0, 1.88]
Grid as a whole[a,f]	N=110	N=98	N=56	N=264
Median (25^{th}, 75^{th} percentiles)	0 (0, 0.19)	0 (0, 0.06)	0 (0, 0.04)	0 (0, 0.13)
[Range]	[0, 1.57]	[0, 4.00]	[0, 0.69]	[0, 4.00]

[a] For 78 subjects with 2 study eyes, only the eye imaged during the fluorescein dye transit was evaluated.

[b] Ungradable for 34 eyes.

[c] Ungradable for 32 eyes.

[d] Ungradable for 91 eyes.

[e] Ungradable for 87 eyes.

[f] Ungradable for 86 eyes.

Table 7

Baseline Ocular Characteristics by Self-Reported Race/Ethnicity (N=817 study eyes)[a]

	White N (%)	Hispanic N (%)	African American N (%)	Asian N (%)
# Study Eyes	612	106	79	20
Ocular Hypertension	8 (1)	2 (2)	2 (3)	1 (5)
Visual Acuity Letter Score (Snellen Equivalent)				
median (25^{th}-75^{th} percentiles)	62 (53, 68)	62 (54, 68)	63 (53, 67)	59 (53, 65)
73-60 (20/40 – 20/63)	360 (59)	60 (57)	47 (59)	8 (40)
59-36 (<20/63 – >20/200)	225 (37)	41 (39)	28 (35)	12 (60)
35-24 (20/200 – 20/320)	27 (4)	5 (5)	4 (5)	0
Retinopathy Severity[b]				
Microanuerysms only/Mild NPDR (20, 35)	42 (7)	11 (10)	4 (5)	0
Moderate NPDR (43)	81 (13)	11 (10)	9 (12)	1 (5)
Moderately severe NPDR (47)	237 (39)	44 (42)	34 (44)	13 (65)
Severe NPDR (53)	78 (13)	9 (9)	3 (4)	2 (10)
PDR (60-61, 65, 71-75)	152 (25)	28 (27)	24 (31)	4 (20)
Cannot Grade (90)	13 (2)	2 (2)	4 (5)	0
CSME[b,c]				
None	18 (3)	2 (2)	0	0
Questionable/Zone of retinal thickening ≥ 1 disc area, within 1 disc diameter from center	10 (2)	2 (2)	0	0
Retinal thickening or adjacent hard exudates ≤ 500μ from center				
Thickening at center				
None/Questionable	16 (3)	1 (<1)	1 (1)	2 (10)
Definite	525 (87)	96 (91)	72 (92)	16 (80)
Can not grade	34 (6)	4 (4)	5 (6)	2 (10)
Central Subfield[d] (OCT, microns)				
median (25^{th}-75^{th} percentiles)	406 (329, 510)	394 (323, 501)	386 (305, 450)	336 (307, 418)
<400 microns	291 (48)	55 (52)	45 (57)	15 (75)
400-<500 microns	155 (25)	24 (23)	21 (27)	4 (20)
≥500 microns	162 (27)	27 (25)	13 (16)	1 (5)

[a] Excludes N=23 eyes from 17 subjects of other (5 American Indian/Alaskan Native, 1 Pacific Islander, 1 mixed race) or unknown race/ethnicity (10).

[b] Fundus photograph unavailable for 11 eyes (not performed for 8 eyes and lost for 3 eyes).

[c] CSME = Clinically Significant Macular Edema.

[d] Central subfield value taken as the mean from the two scans performed for each eye. Value is missing for 4 eyes where both scans lost (N=2), or required manual grading that was not performed (N=2).

Table 8
Distribution of Baseline Visual Acuity: E-ETDRS Visual Acuity (letter score)

Letter Score (Approximate Snellen Equivalent)	840 Study Eyes N (%)	546 Non-Study Fellow Eyes N (%)
≥74 (>20/40)	N/A [a]	324 (59)
73 – 69 (20/40)	160 (19)	89 (16)
68 – 59 (20/50 to 20/63)	357 (43)	70 (13)
58 – 49 (20/80 to 20/100)	175 (21)	29 (5)
48 – 39 (20/125 to 20/160)	87 (10)	14 (3)
38 – 24 (20/200 to 20/320)	61 (7)	16 (3)
≤23 (<20/320)	N/A [a]	4 (<1)
Median (25^{th}, 75^{th} percentiles) Snellen equivalent	62 (53, 67) 20/63 (20/50, 20/100)	75 (69, 81) 20/32 (20/25, 20/40)
Range	[24, 73]	[21, 94]

[a] Eligibility criteria required visual acuity ≥24 letters and ≤73 letters