Efficacy of topical dexamethasone-cyclodextrin microparticle eye drops compared with ranizumab in diabetic macular edema: a phase II, multicenter, randomized controlled non-inferiority trial

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Abstract:

Background and Aim: *Diabetic macular edema (DME) is one of the leading causes of visual impairment among working-aged people responsible for more than 10,000 new cases of blindness per year. Although there are some therapeutical options for this disease, most of them are invasive, expensive, subject to a range of side effects, and may not be accessible to the entire population. In addition, conventional eye drops are not able to adequately deliver the drug to the posterior chamber of the eye, where DME develops. In this setting, it has been suggested that topical dexamethasone-cyclodextrin microparticle eye drop (TDCME) formulation may be effective in treating DME. The aim of this manuscript is to describe a study protocol for evaluating the efficacy of this formulation (new treatment), compared with intravitreal injection of ranibizumab (standard of care group).*

Design: *Phase II, randomized, double-dummy, multicenter, controlled, non-inferiority clinical trial.*

Participants: Adults aged ≥ 18 year-old, diagnosed with controlled diabetes (type I or II), and refractory moderate to severe DME in at least one eye at the beginning of study.

Measurements and procedures: *Participants will be allocated to either the new treatment or standard of care group using block randomization, through a centralized off-site computer interactive response system. The standard of care group will receive sham intravitreal injections plus TDCME, whereas the new treatment group will receive intravitreal injection of ranibizumab (0.5 mg) plus EnduraTM (artificial tears eye drops emulsion, used as placebo). While injections will be performed every month, eye drops will be given three times a day (every 8 hours). The primary efficacy outcome will be the change in best corrected visual acuity (BCVA) between baseline and at the end of the 12-month-follow-up time.*

Ethical aspects: *This trial will be carried out according to the tenants of the Declaration of Helsinki and other international guidelines. Participants will be required to provide informed written consent prior to enrolling in the study. A Data Safety Monitoring Board will be established to follow the study.*

INTRODUCTION

Diabetes mellitus affects nearly 347 million people worldwide. Globally, it is the primary cause of vision loss in individuals aged between 20 and 74 years (Varma, 2014). The condition leads to several complications, including diabetic macular edema (DME) and blindness (Mathew, 2015). DME is an increasingly prevalent condition that accounts for more than 10,000 new cases per year, and complications related to visual impairment lead to a significant reduction in quality of life (Gundogan, 2016).

The exact mechanism responsible for DME is not clear. What it is known is that macular edema reduces central visual acuity and impairs VEGF expression and signaling pathway. Some evidence suggests that the development of retinal vascular endothelial dysfunction is crucial and DME results from disruption of the blood-retinal barrier (Tarantola, 2013), leading to structural changes in the endothelium of the retinal vasculature that increases their vascular permeability (Das, 2015; De Benedetto, 2014). Regardless of the type of diabetes (i.e. Type I or II), ischemia is caused by inner capillary changes attributed to the exudation and accumulation of extracellular fluid and proteins in the macula (Tarantola, 2013).

Available therapeutic options for DME are scarce, invasive, and for many individuals, cost prohibitive. The Early Treatment Diabetic Retinopathy Study (ETDRS) first showed that focal laser photocoagulation delayed vision loss in patients with DME (Early Treatment Diabetic Retinopathy Study Research Group, 1987). Unfortunately, in patients with advanced disease, it only decreased the rate of progression in 50% of patients (Krispel, 2013). Moreover, this therapy has significant side effects, including visual field loss, laser burns and expansion of the scar over the fovea (Chen, 2011).

In response to a need for more effective treatments, inhibitors of Vascular Endothelial Growth Factor (anti-VEGF), such as ranibizumab, have been developed and evaluated in a number of randomized multicenter trials (Mitchell, 2011; Brown, 2013). Ranibizumab was found to significantly improve the visual acuity either as a monotherapy or combined with laser photocoagulation, when compared with sham injections or with laser therapy alone in several previous studies (Brown, 2013; Nguyen, 2010; Mitchell, 2011).

Given the results from the aforementioned clinical studies, intravitreal injections with anti-VEGF have increasingly become the standard treatment option for severe DME. However, drug delivery by injection can lead to sight threatening complications such as endophthalmitis and retinal detachment, as well as systemic side effects like hypertension, proteinuria and ischemic cardiovascular disease (Simó, 2014). Furthermore, this treatment option is not widely available in developing countries due to high costs associated with the medication and surgical procedure.

Although less effective than anti-VEGF, intravitreal injections of steroids such as triamcinolone and dexamethasone have also shown to be effective in the treatment of DME (Gundogan, 2016) and can be used as a less costly treatment. However, this treatment is associated with elevated intraocular pressure (IOP) and cataract formation (Gundogan, 2016). Moreover, its benefit is only temporary (Fong, 2004).

In this scenario, there has been a premium to develop a topical eye drop solution as non-invasive and potentially more cost-effective alternative. A long-standing concern with drug delivery using topical eye drops relates to the fact that pharmacological biodistribution is unpredictable. Thus, the development of a topical treatment with a good pharmacokinetic profile is crucial in order to have effective clinical utility. Water-soluble polymers have been shown to enhance the stability of dexamethasone-cyclodextrin complexes (Kristinsson, 1996). These complexes increase the permeability and adherence of the corneal surface without altering its barrier function. A pilot study tested a new formulation of Topical Dexamethasone-Cyclodextrin Microparticle Eye drops (TDCME) (Tanito, 2011). They found that this medication was well tolerated, decreased central macular thickness, and improved visual acuity (Tanito, 2011), thus suggesting that this formulation would be able to treat DME by topically delivered dexamethasone.

The development of a widely accessible medication would decrease the incidence of blindness in working-age population. Therefore, we have designed the protocol of a Phase II, randomized, multi-center, double-dummy, non-inferiority trial, to evaluate the change in visual acuity of patients with DME at one year of treatment with TDCME, compared with intravitreal ranibizumab. A non-inferiority design was selected considering the scenario in which there is already an effective well-established treatment for DME. However, due to potential severe side effects and a limited availability especially in developing countries there is the need to establish a cost-effective alternative treatment option with reduced side effects.

METHODS

This study will be registered in www.clinicaltrials.com and in the countries involved under the following name: DME VITRANI study (Diabetic Macular Edema and

Dexamethasone Microparticles Eyedrops VITreal RANIbizumab Study).

Eligibility Criteria

Patients will be eligible if they are ≥ 18 years old, have type I or type II diabetes, and have refractory moderate to severe DME with impaired vision in at least one eye, defined as an ETDRS score of 24 - 72 letters (Early Treatment Diabetic Retinopathy Study Research Group, 1987) with central fovea thickness greater than 250 μm, measured by Optical Coherence Tomography (OCT). In case of bilateral disease, the eye with worst measured visual acuity will be chosen. Participants should also be on regular treatment for diabetes within 3 months prior to randomization, and have a glycosylated hemoglobin concentration (HbA1c) less than 10%.

Exclusion criteria include: uncontrolled diabetes (defined as HbA1c greater than 10%), current treatment of anti-VEGF within 3 months before the trial, current or anticipated use of systemic steroids, history of glaucoma, ocular hypertension (intraocular pressure > 23 mmHg without any treatment or > 21 mmHg on glaucoma treatment), aphakia or anterior chamber intraocular lens, history of intraocular laser or incisional surgery within 90 days before study entry, active intraocular swelling or infection, retinal vein occlusion, uveitis, pregnant or lactating women, uncontrolled hypertension, or any recent neurological or cardiac unstable disease.

Trial design

This is a phase II randomized, active controlled, multicenter, double-dummy, non-inferiority trial, with two armed parallel groups.

Recruitment

Patients will be recruited from ophthalmology outpatient clinics in five centers located in four countries within South America: Brazil (Sao Paulo and Rio de Janeiro), Mexico (Mexico City), Peru (Lima) and Colombia (Bogota). Patients will be offered the opportunity to participate in the trial if eligibility criteria are fulfilled. We will also distribute brochures with information on the trial in the pertinent waiting rooms. If recruitment rate is low, diabetes self-help groups and general practitioners will be contacted to refer additional patients.

Randomization and blinding

After the recruitment process, eligible participants who consented to take part in the study will be assigned to either standard of care or new treatment group using block randomization with varying block sizes. We will use a centralized off-site computer Interactive Voice Response System (IVRS) to carry out the randomization.

Investigators will be blinded to the study design, whereas participants, data collectors and outcome assessors will be blinded to the treatment and the randomization sequence through the allocation concealment. In order to protect the blinding, commercially available artificial eye drops (EnduraTM) will be acquired and all labels will be removed. TDCME drops will be packed in identical EnduraTM bottles, so it is not possible to distinguish between them. This procedure will be performed by an independent pharmacist from Rio de Janeiro, who will be responsible to deliver the eye drops to the other centers. Since the clinicians responsible for injections will not be blinded, the appearance of intravitreal injections will not be modified. In order to avoid unblinding due to the potential side effects in the standard of care group, there will be two independent groups of statisticians assessing efficacy and safety outcomes. Furthermore, we will use placebo artificial eye drops resembling the microparticle formulation and identical procedures will be performed before and after injections for both groups (Glassman, 2012).

Treatment allocation will only be revealed in the case of medical emergency. The site coordinators will contact the principal investigator and the official medical advisor in order to evaluate the indication for unblinding and report the details to the Data Monitoring Committee. The allocation will be revealed through a 24-hour emergency line available from the off-site center. Participants will not be able to continue the trial and the actual allocation will be disclosed to them.

Intervention

Participants will be divided in two randomized groups. The standard care group will receive intravitreal ranibizumab (0.5 mg) plus artificial eye drops emulsion (EnduraTM). The new intervention group will receive TDCME plus sham intravitreal injection. Injections will be administered at predetermined monthly intervals while eye drops will be given every 8 hours. For the intravitreal injection procedure (standard of care group), ranibizumab will be injected following skin asepsis and topical subconjunctival anesthesia. For the new treatment group the same pre-application procedure will be followed but the hub of a syringe without a needle will be pressed against the conjunctival surface to mimic an actual injection (Glassman, 2012).

The TDCME formulation employed has been described in detail previously (Tanito et al., 2011). Briefly, an aqueous dexamethasone microsuspension is

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produced by suspending 1.50 g dexamethasone and 14 g of γ- cyclodextrin in 100 mL of an aqueous solution containing benzalkonium chloride (20 mg), EDTA (100 mg), poloxamer 407 (2.5 g), and sodium chloride (570 mg). The suspension is sterilized by autoclave (121°C for 20 minutes) and then, cooled at room temperature under constant agitation.

Outcomes

The primary outcome will be the change in BCVA after 12 months of intervention (Massin, 2010; Brown, 2013; Callanan, 2016) measured by ETDRS chart scores (Massin, 2010; Mitchell, 2011; Nguyen, 2010). As a secondary efficacy outcome, mean retinal thickness in the center of the fovea and the total macular volume will be measured by OCT. The follow-up time of 12 months was chosen in accordance with previous studies (Massin, 2010; Brown 2013; Callanan 2016) and to allow to monitor immediate as well as mid-term effects of the treatment of DME as a chronic condition.

Quality of life will be evaluated using the Visual Function Questionnaire (VFQ-25) (Ware, 1992) and the 36-item Short Form Health Survey (SF-36) at baseline and after 12 months of intervention (Mangione, 2001).

Safety measures will include comparison of serious local and systemic effects between groups, which will be reported by patients and clinicians (Lang, 2013). Side effects will be considered serious in cases of death or a life- threatening event, hospitalization, persistent or significant disability, or incapacity, and any other side effects requiring intervention to prevent further complications. The definition of these effects will be determined by the clinical staff. Screenings for IOP elevation (intraocular pressure > 23 mmHg), mean change in OCT retinal nerve fiber layer average thickness, cataracts, and potential development of endophthalmitis will also be performed as part of the comprehensive ophthalmological assessment.

Safety

Treatment will be stopped in the case of suspected allergic reactions to the medication or the occurrence of any side effects. These adverse events will be recorded as secondary safety outcomes. Treatment will also be stopped in patients with significant reduction of BCVA (> 5 ETDRS letters compared with baseline). In these cases, the patients will be excluded from the study and receive the standard treatment (e.g., anti-VEGF and/or laser photocoagulation) as determined appropriate by the attending ophthalmologist. Unblinding will not be performed until the end of the study, unless it required (see blinding section above).

Adherence and follow-up

Every participant will be reminded by phone to confirm attendance two days prior to the scheduled appointment. During the first year, there will be monthly visits followed by a final control visit two years afterwards. During the first visit, trained staff will explain the use of medications, identification of side effects, follow-up protocol, and planned schedules (Dziura, 2013).

Subsequent sessions will occur during follow-up visits. At each visit, intravitreal medication will be administered and eye drops (active medication or placebo) will be provided for the entire month. Efforts will be made to improve adherence clarifying issues and answering questions as necessary. Each month patients will be asked to bring back the empty bottle of eye drops. Patients that return with more than half of the content of the eye drop bottle for three consecutive months will be excluded from further follow-up. At the end of the study, we will compare the number of patients that were excluded in both groups. In addition, we will conduct semi-structured phone interviews with the subjects that dropped out including questions on side effects and reasons for dropping out.

Patients will be monitored on a monthly basis with a standard ophthalmic examination (Figure 1). Blood samples will be taken at baseline and every three months (up to 12 months) and will include tests for glycaemia, HbA1c concentration, hepatic and renal function. An OCT will be also performed at baseline, 6, and 12 months (Lang, 2013).

Logistical support will be provided to minimize waiting times and compensation will be offered to cover transportation expenses (including free parking) and time from missed work. Occasionally, e-mails will also be sent as well as phone calls to promote communication between the research team and patients, with motivational messages and greetings on special dates (e.g. birthdays) (Dziura, 2013).

Data management

Researchers responsible for enrollment will collect and transcribe the data. After verification for accuracy and completeness, the data will be locked. Patients will be de-identified using a predetermined and unique number sequence code.

Statistical considerations

All statistical analyses will be performed using Stata 14 (Stata Corp, College Station, TX, USA). The primary and secondary outcomes (mean differences in ETDRS Scores and macular thickness) will be evaluated with a Mann
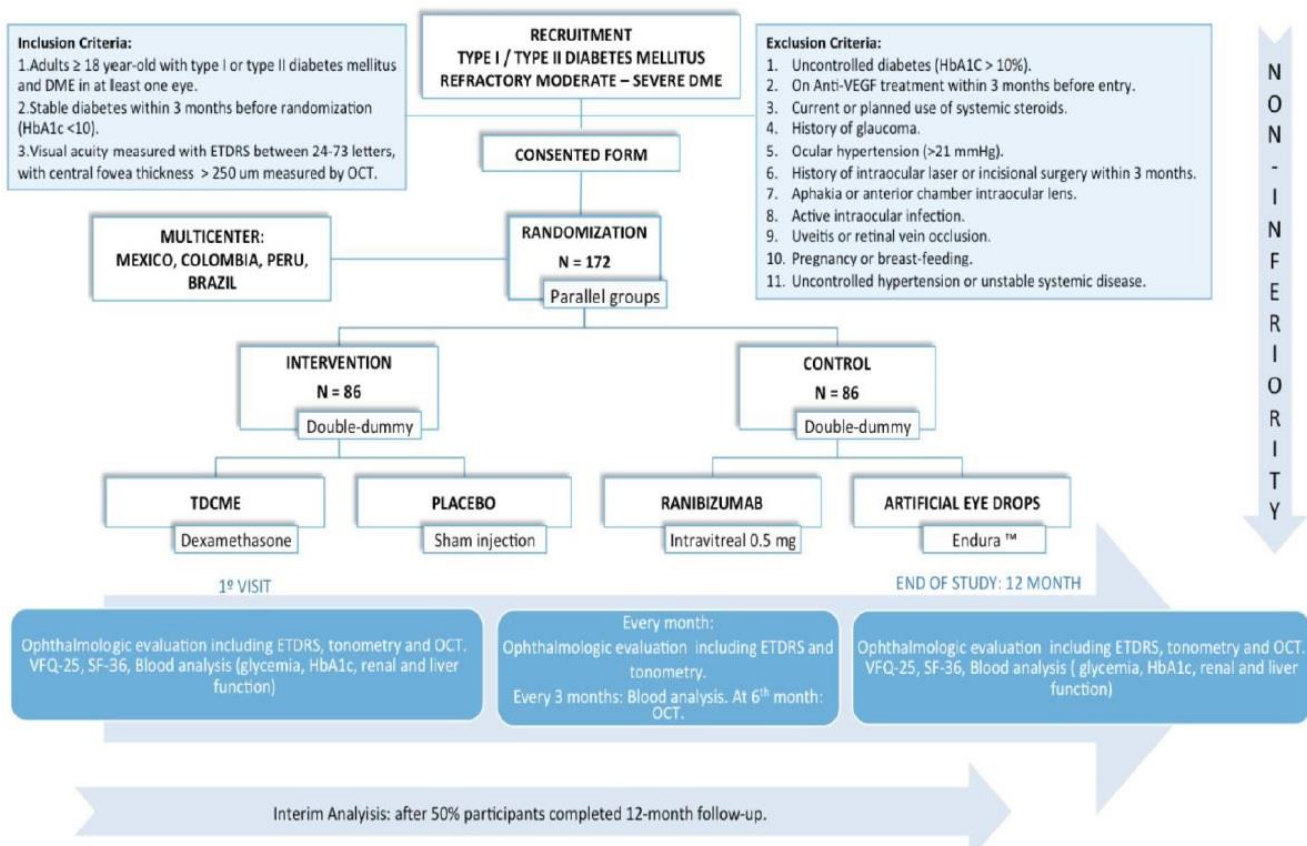
Figure 1. Study timeline. DME: Diabetic Macular Edema. HbA1c: Glycosylated hemoglobin. ETDRS: Early Treatment Diabetic Retinopathy Study Score. VEGF: Vascular Endothelial Growth Factor. OCT: Optical Coherence Tomography. VFQ-25: Visual Function Questionnaire. SF-36: Short Form health survev.

Whitney U test. The incidence of serious side effects and IOP elevation will be compared between groups with a Chi square test or Fisher's exact test. Change in quality of life outcomes will be compared with t-test or Wilcoxon test, according to the distribution of data. Longitudinal data will be analyzed using a two-way repeated ANOVA including treatment group, time and the interaction term of treatment group and time. Subgroup analyses will examine the effects of type and severity of diabetes and site centers on the main continuous outcome BCVA (Massin, 2010; Mitchell, 2011; Nguyen, 2010). Two-sided tests will be performed for all analyses, except for the primary outcome of interests (non- inferiority).

Power and sample size calculation

A total of 172 participants will be enrolled (86 patients per group). The calculation was based on alpha error of 0.025, power of 85%, one-sided 97.5% confidence interval, non-inferiority margin of 5 letters (ETDRS Score), and dropout rate of 20% (Flight, 2016).

Interim analysis and monitoring

An interim analysis will be performed on the primary outcome of efficacy (change in ETDRS score) after 50% of the patients have completed the 12 months follow-up period. A cut-off p-value of 0.005 will be considered significant to stop the trial for efficacy, according to the O'Brien Fleming spending function (O'Brien, 1979). The interim analysis will be performed by independent statisticians, blinded to the treatment allocation, and report the results to a Data Monitoring Committee (DMC) (Lang, 2013).

Missing data

Missing data are expected to be less than 20% for the primary efficacy analysis. Multiple imputation analyses will be performed to impute missing data. We will use both intention-to-treat (primary) and per-protocol (secondary) approaches to perform a sensitivity analysis (Dziura, 2013).

Ethical aspects

Apart from applying local regulations (Bhuiyan, 2001), this study follows the tenants outlined in the Declaration of Helsinki (seventh revision; 2013) and other international guidelines, including the guidelines issued by the Council for International Organizations of Medical Sciences (CIOMS, 2002) and the International Conference

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on Harmonisation of technical requirements for registration of pharmaceuticals for human use (Bhuiyan, 2001). The study protocol and procedures for obtaining informed consent will be approved by the Institutional Review Boards of the participating centers and an independent ethics committee prior to commencement of the trial.

DISCUSSION

This is a study protocol for a Phase II, randomized, multi-center, double-dummy, non-inferiority trial to evaluate the change in visual acuity of patients with DME at one year of treatment with TDCME, compared with intravitreal ranibizumab. Ranibizumab has been selected among VEGF inhibitors as the standard of care treatment, based on the existing trials that proved its efficacy and safety.

The proposed study has several strengths. Using a double-dummy design, issues related to blinding and the use of a placebo control can be addressed (Marušić, 2013). Blinding will be ensured using two different routes of administration, reducing the possibility of biases. The use of placebo will also be avoided using a non-inferiority design, since all the participants will receive an active medication. A factorial design could have been an interesting alternative for exploring potential interaction effects. However, ethical concerns related with the use of a placebo would remain unaddressed. This trial will also evaluate potential advantages of TDCME over ranibizumab, such as better safety profile, convenience for the patient, and changes in quality of life.

In non-inferiority designs, the interpretation of type II error is different when compared with superiority trials. Therefore, in order to enhance the reliability of the results, most non-inferiority studies are designed to account more conservatively for a type II error. The study was powered at a threshold of 0.85, which is in accordance to similar studies (Callanan, 2016; Writing Committee for the Diabetic Retinopathy Clinical Research Network, 2015). Likewise, a sensitivity analysis will be performed to evaluate the type I error. To ensure the assumption of constancy, eligibility criteria, parameters for the administration of ranibizumab and outcomes were chosen in accordance to similar trials (Callanan, 2016; Writing Committee for the Diabetic Retinopathy Clinical Research Network, 2015).

The non-inferiority margin was based on the findings of the active-controlled RESOLVE Study (BVCA 10.3 +/- 9.1 letters), which included similar populations and outcomes (Massin, 2010). Following these results, the non-inferiority margin was fixed at 5 letters, which represents nearly 50% of the estimated effect size. This is also in agreement with other non-inferiority trials evaluating ranibizumab for the treatment of DME (Callanan, 2016; Writing Committee for the Diabetic Retinopathy Clinical Research Network, 2015).

The definition of the non-inferiority margin remains challenging and debatable (Flight, 2016). For example, a narrower margin could have been chosen in order to enhance the assay sensitivity. However, since the non-inferiority margin has an inverse quadratic relationship with the sample size, lowering the margin would have enormously increased the number of patients required, making the trial unfeasible. Although the small sample size could be a disadvantage in this trial, keeping the margin at 50 % of the effect size in line with previous placebo- controlled trials is likely a reasonable approach because any positive results would rely on the assay sensitivity and thus diminishing the risk of bio-creep phenomenon.

As a multicenter trial, there could be potential issues regarding the uniformity of procedures. Therefore, training in each site will be important to avoid site specific effects and differences. In addition, a logistic regression analysis will be performed to examine this issue.

Stratification by severity or type of diabetes will not be carried out as it could result in a large range of effect sizes. However, the pathological differences in the macular edema between the types of diabetes, if any, are not supported by the current evidence. Moreover, it has been established that hyperglycemia, regardless of its cause, is the main mechanism responsible for the development of DME. To adequately address these issues, the study population of this study will be limited to moderate to severe diabetes, and the severity of visual impairment and type of diabetes will be included as an independent variable in a logistic regression model.

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Conflict of interest and financial disclosure

The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors concur with the submission of the manuscript, the final version has been approved by all authors. The authors have no financial or personal conflicts of interest.

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