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ORIGINAL ARTICLE

Combined therapy in diabetic macular edema

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KEYWORDS
Diabetic macular edema;
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Summary
Purpose: To determine the effectiveness of three different combinations for the ''loading phase'' in the treatment of diabetic macular edema (DME), using bevacizumab (BVZ), triamcinolone (TCL) and subthreshold macular photocoagulation (SMPC).
Methods: Experimental, longitudinal, prospective, comparative and blind. Patients were randomly assigned to three treatment branches: Group 1: BVZ + SMPC (12 eyes), Group 2: SMPC + BVZ + TCL (7 eyes), Group 3: BVZ + TCL (11 eyes). Treatment with BVZ and TCL was given every 4 weeks for 3 months, SMPC was applied once at the beginning of treatment. Initial and final measurements of best corrected visual acuity (BCVA), central macular thickness (CMT) and intraocular pressure (IOP) were tested.
Results: The improvement in BCVA and the reduction in CMT was statistically superior in group of BVZ + SMPCwhen compared to the other groups. There were no differences in IOP.
Conclusions: Combined therapies in the ''loading phase''are a good option when treating DME. Although the group with BVZ + SMPC obtained the best results, further studies with longer follow-up and a higher number of participants to establish this combined therapy as the first treatment option are required.

Introduction

Diabetic macular edema (DME) is the main cause of visual loss in patients with diabetic retinopathy (DR). It is considered to be the number one cause of blindness at a productive age in developed countries.[1–6] DME is the result of alterations of the inner and outer blood-retinal barriers (BRB) due to the imbalance between the inflammatory and angiogenic factors of the retinal pigment epithelium (PE) and the vitreoretinal interface. Among these, there is the vascular endothelial growth factor (VEGF), the hepatocyte growth factor and the interleukin 1B. The reduction in the pigment epithelium-derived anti-angiogenic factor, a potent anti-inflammatory, antioxidant and anti-angiogenic

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which regulates, among other things, VEGF levels, also plays an important role in DME pathophysiology.[7–9] The treatment focuses on reestablishing BRB, modulating inflammatory and angiogenic factors. Among the current options to accomplish said effect, there are the thermal laser and intravitreal drug therapies (corticosteroids and anti-angiogenics).

The laser stimulates the PE, acting as a substance modulator for PEDF and VEGF. Moreover, the thermal destruction of the outer layers of the retina reduces the metabolic demand and oxygen expenditure with the consequent VEGF reduction.[10–18] Triamcinolone is the main intraocular corticosteroid in the treatment of RD, DME and other neovascular and inflammatory diseases because it inhibits overregulation of inflammatory molecules and VEGF. Part of this regulation was completed through the reduction of vascular permeability in the retina by reducing the liberation of arachidonic acid derivatives, such as prostaglandins.[19–22] Bevacizumab is a recombinant humanized monoclonal antibody (lgG1) which unifies all isoforms of VEGF-A. It was approved by the FDA in 2004 for metastatic colon cancer treatment. Since then, it has been successfully used in an unofficial manner to treat different ocular neovascular illnesses, such as age-associated macular degeneration, proliferative DR, neovascular glaucoma, premature retinopathy, macular edema secondary to retinal venous obstruction and DME, among others. Even though, to this day, it has not been approved by the FDA nor the COFEPRIS for its ophthalmologic use, the injection of 1.25–2.5 mg in the vitreous cavity has been performed in a safe and effective manner.[23–29] Different regimes in DME treatment have been described. The laser is recommended for its application in a selective manner and on a single occasion, and, if necessary, reapply it in intervals of no less than 12 weeks apart.[18,30,31] Intravitreal pharmacological therapy has been proposed for the different ocular neovascular pathologies, from having one dose and repeating treatment as deemed appropriate by the examiner *pro re nata* (PRN), up to a monthly dose for 24 months, without regard to visual and anatomic changes.[32–41] This study showed that the maximum visual and anatomical effect occurs during the first three doses, and those following them only helped to maintain the inactivity of the pathology; thus, the decision in the selection of the scheme during this ''loading stage'' is fundamental. The ''treat and observe'' regime is currently being proposed. This is to apply three doses in a row with an interval of 4 weeks in between these ''loading doses'' until accomplishing the maximum visual and anatomic effect, repeating the same treatment PRN.[42] Based on the possible synergy between the laser, the corticosteroids and the anti-angiogenics, the combination between these has been utilized with a dual intention; to accomplish a greater visual and anatomic effect, and to accomplish the minimum number of repetitions in long-term treatment of this chronic degenerative illness.[35,36,43–49] In spite of all of this, the question about which combination may be the best option remains unanswered.

Objective

To evaluate effectiveness with three different treatment combinations in the ''loading phase'' of diabetic macular edema (DME); using bevacizumab (BVZ), triamcinolone (TCL) and subthreshold macular photocoagulation (SMPC).

Method and materials

Controlled clinical, experimental, prospective, longitudinal, comparative and blind essay, including those patients from the Department of Ophthalmology at the ''Dr. José Eleuterio González'' University Hospital using the following inclusion criteria: male and female with diabetes (type I or II), 18 years of age or older, with a clinical and tomographic DME diagnosis, best corrected visual acuity (BCVA) higher than 20/400. Patients who did not present any of the exclusion criteria; presence of significant cataract (according to the researcher's criteria), diagnosis of glaucoma, vitreous hemorrhage, previous intraocular surgery, macular laser treatment and/or intravitreal drug therapy in the three months previous to the study. Patients who for any reason did not complete treatment or developed complications during treatment were eliminated. The protocol was evaluated and approved by our institution's Ethics Committee and registered under the code OF11-010. The study was conducted following the guidelines established in the Helsinki Declaration and the International Conference on Harmonization Guidelines for Good Clinical Practices. All patients signed an informed consent form respecting the Official Mexican Standards on the patients' right to know everything about their illness and its possible treatment options.

Clinical diagnosis was made through fundoscopy, using a magnifying glass of 90 diopters and a Goldman contact lens and DME was considered as the central thickening of at least a diameter of 1500 microns, situating the center of this circle in the umbo foveolar. Tomographic diagnosis was performed whenever there was a central macular thickness (CMT) greater than 230 microns using the ''Macular Thickness Map'' scanning modality of the optical coherence tomography (OCT) using Stratus OCT™ by Carl Zeiss.

Baseline BCVA measurements were taken by means of distant subjective refraction with a Snellen primer. IOP was taken by means of an applanation tonometry from Goldmann and clinical and OCT findings were recorded.

Later, the randomized selection of the study groups was made, using the six-sided die technique: numbers 1 or 4 to group 1 (BVZ + SMPC), numbers 2 or 5 to group 2 (BVZ + TCL + SMPC), and 3 or 6 to group 3 (BVZ + TCL). In this study, the principal investigator, who evaluated the study at the beginning and finalized the treatment regimen during the ''loading phase'', did not know which group each patient belonged to.

The laser was only applied at the beginning of treatment (week 0), with the aim of avoiding possible complications from the laser threshold. The shots were made on subthreshold (invisible) mode,[50] using VISULAS™ 532s laser equipment (Carl Zeiss Meditec AG. Jena, Germany).

The pharmacological treatment was performed on week 0, repeating at weeks 4 and 8. A dose of 1.25 mg in 0.05 ml of BVZ, commercial name Avastin™ (Genentech Inc., South San Francisco, CA, USA/Roche Mexico) was applied each session. The TCL utilized was ATLC™ (conservative-free), distributed by GRIN laboratories, Mexico, at a rate of 2 mg in 0.05 ml every injection. The procedure was performed