Effects of Ruboxistaurin on Visual Loss in Patients With Diabetic Retinopathy

PKC-DRS2 Group, Ophthalmology 2006; 113; 2221-2230

Patients with diabetes mellitus have an increased risk of vision loss despite current therapies. Severe loss of vision from PDR and moderate loss of vision from Diabetic macular oedema (DME) can be reduced by laser photocoagulation, however the main goal of therapy is to prevent further visual loss, and it is associated with many complications.

Hyperglycemia induced synthesis of diacylglycerol results in the activation of protein-kinase C beta (PKC), which plays a central role in mediating the ocular complications of diabetes. VEGF also activates PKC beta. Diabetes-induced activation of PKC increases both retinal vascular permeablilty and neovascularization in animal models.

Ruboxistaurin, an orally administered PKC beta isozyme selective inhibitor, ameliorates the adverse effect of high glucose and diabetes induced blood flow abnormalities in patients.

PKC DRS2 was a 36-month multicentre double masked parallel placebo controlled study. Patients were randomized to either a placebo or ruboxistaurin (32 mg) administered orally once daily. 685 patients participated in this study which was conducted in 70 centers, under the supervision of Dr. Lloyd Paul Aiello, Beetham Eye Institute, Joslin Diabetes Center, Boston. Patients were eligible if they had Best corrected visual acuity score of >45 letters(20/125) measured by Early treatment diabetic retinopathy study visual acuity (ETDRS VA) protocol, retinopathy level > 47A and < 53E,(ETDRS retinopathy severity scale) and no prior pan retinal photocoagulation in at least one eye.

Ophthalmologic examination and VA assessment were performed at screening and at each 3-month visit. Retinopathy status was assessed every 6 months with (ETDRS) standard 7-field 30° colour stereoscopic fundus photography.

Effect of oral ruboxisaturin (32mg/day) on reduction of sustained moderate visual loss (SMVL) (>15-letter decrease in ETDRS VA score maintained > 6 months or VA sustained from month 30 to 36) in patients with moderately severe to very severe non proliferative diabetic retinopathy was taken as the main criteria for success.

Sustained moderate visual loss occurred in 9.1% of placebo-treated patients versus 5.5% ruboxistaurin-treated patients(40% risk reduction, P=0.034). Mean VA was better in the ruboxistaurin-treated patients after 12 months. Baseline-to-end point visual improvement of >15 letters was more frequent (4.9% vs. 2.4%) and >15-letter worsening was less frequent (6.7% vs. 9.9%) in ruboxistaurin-treated patients relative to placebo (P=0.005). When clinically significant macular edema was > 100 micrometer from the center of the macula at baseline, ruboxistaurin treatment was associated with less frequent progression of edema to within 100 micrometre (68% vs. 50%, P=0.003.) Initial laser treatment for macular edema was 26% less frequent in eyes of ruboxistaurin treated patients (P=0.008).

To put in a nutshell, according to the study, oral ruboxistaurin treatment reduced vision loss, need for laser treatment and macular edema progression, while
increasing occurrence of visual improvement in patients with nonproliferative retinopathy. It is the first pharmacological agent demonstrated to reduce vision loss from diabetes over an extended period. Given that it is well tolerated, nondestructive, and beneficial even after prior laser treatment, ruboxistaurin represents a novel therapeutic approach that might be used along with optimal metabolic control and current ophthalmic therapies to reduce the likelihood of vision loss in patients with diabetes.

The International Clasificaiton of Retinoblastoma Predicts Chemoreduction Success

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The international classification of retinoblastoma (ICBR) was finalized by a group of retinoblastoma experts in April 2003 at Paris. The primary goal for development of this new classification was to create a simpler, more user-friendly classification that would be quick to recall and more applicable to current therapies such as chemoreduction (CRD). The previously used Reese-Ellsworth classification was created in the 1960s when external beam radiotherapy (EBRT) was the most popular conservative (non enucleation) treatment. In fact, it became apparent that tumor location, multifocality, and size were not of major concern because CRD was effective despite these variables. The aim of the study was to evaluate the reliability of the International Classification of Retinoblastoma (ICRB) for predicting treatment success with chemoreduction. The study was designed as a non-comparative interventional study. 249 patients participated in this study which was done at ocular oncology service Wills Eye Hospital. The eligibility criteria for treatment with CRD were children with RB in whom either eye ordinarily would require enucleation or EBRT for cure of disease based on published indications. All eyes were treated with CRD and were classified according to ICRB; group A included those eyes with retinoblastoma \( \leq 3 \text{mm} \); group B included those eyes with retinoblastoma \( >3 \text{mm} \), macular location or minor subretinal fluid; group C included those eyes with retinoblastoma with localized seed; group D included those eyes with retinoblastoma with diffuse seeds; group E included those eyes with massive retinoblastoma necessitating enucleation. The CRD regimen included vincristine, etoposide and carboplatin for 6 cycles plus local consolidation with thermotherapy or cryotherapy. Each case was classified according to Reese-Ellsworth classification also. Chemoreduction success, was defined as avoidance of external beam radiotherapy or enucleation. Of the 249 eyes 23 (9\%) were in-group A, 96 (39\%) were in-group B, 21 (8\%) were in-group C and 109 (44\%) in-group D. In this series, group E were managed with enucleation. Treatment success was achieved in 100\% group A, 93\% of group B, 90\% of group C and 47\% of group D eyes. ICBR showed consistent predictability for CRD success with in major categories. The authors claim that ICRB can be of assistance in predicting CRD success for retinoblastoma. Additional treatment methods are necessary to salvage more group D eyes.
Keratoconus is a degenerative non-inflammatory disease of the corneas with onset generally at puberty. It is progressive in 20% of cases and can be treated by lamellar or penetrating keratoplasty. Changes in corneal collagen structure organization and intercellular matrix as well as apoptosis and necrosis of keratinocytes prevalently or exclusively involving the central anterior stroma and the Bowman's lamina, are documented in the literature.

The technique of corneal collagen cross-linking consists of photo polymerization of stromal fibers by the combined action of a photosentizing substance (riboflavin or vitamin B2) and ultraviolet type A rays (UVA) from a solid-state UVA source. Photopolymerization increases the rigidity of corneal collagen and its resistance to keratectasia.

The method of corneal cross-linking using riboflavin and UV light is technically simple and less invasive than all other therapies proposed for keratoconus, Unlike other mini-invasive methods, such as intrastromal rings (INTACS) and excimer laser surgery, that do not block keratectasia but merely treat the refractive effects of the disease, Riboflavin UV Type A rays treats and prevents for underlying pathophysiological mechanism.

The main aim of this study was to assess the effectiveness and safety of riboflavin-UV induced cross-linking of corneal collagen in reducing the progression of keratoconus and in improving visual acuity. This was a prospective nonrandomized open study. Staring in September 2004, 10 eyes of 10 patients (mean amen 31.4 years) with bilateral keratoconus were treated by combined riboflavin-ultraviolet type- A rays (UVA) collagen cross-linking. Radiant energy was 3mW/cm² or 5.4 joule/cm² for a 30-minute exposure at 1 cm form the corneal apex. A complete ophthalmologic examination (uncorrected visual acuity (IUCA), sphere spectacles corrected visual acuity (SSCVA), best corrected visual acuity (SSCVA) best spectacle-corrected visual acuity (BSCVA) was performed. Patients had corneal computerized topographic examination, linear scan optical tomography, endothelial cell count, ultrasound pachemetry, intraocular pressure (IOP) evaluation, and HRT II system confocal microscopy at 1, 2, 3 and 6 months. After treatment, eyes were medicated and dressed with a soft contact lens.

Comparative preoperative and postoperative results showed increases of 3.6 lines for UCVA (P=.0000112), 1.85 lines for SSCVA (P=.00065), and 1.66 lines for BSCVA (P=.00071), Topographic analysis showed a mean K reduction of 2.1 ± 0.13 diopters (D) in the central 3.0 mm. Statistical analysis of IOP and endothelial cell count did not show significant differences. Topo-aberrometric analysis findings of corneal symmetry showed a trend toward increasing corneal symmetry with major reduction in asymmetry between vertical hemi meridians. Refractive results showed a reduction of about 2.5D in the mean spherical equivalent, topographically confirmed by the reduction in mean K. Result of surface aberrometeric analysis showed improvement in morphologic symmetry with significant reductions in comaic aberrations. Although this study was limited in terms of follow up and number of patients, it confirms that UV rays emitted by Light Emitting Diodes is perfectly calibrated in energy density to produce apoptosis, hence, necrosis of unhealthy activated keratocytes in addition to being completely absorbed by riboflavin beyond the programmed dose and necessary thickness. The results of the pilot study of riboflavin UV induced corneal collagen cross linking were encouraging as far as safety and effectiveness are concerned.