

ABSTRACTS

of the International Scientific Meeting: *News in Ophthalmology*

NEW DEVELOPMENTS IN ANTERIOR KERATOPLASTY

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Anterior keratoplasty has been a surgical option for treatment of cornea diseases located to the corneal stroma, such as keratoconus, stromal corneal dystrophies and corneal scars after keratitis. Earlier, anterior keratoplasty was performed by manual dissection of the diseased corneal stroma. The interface often caused scarring and impaired visual acuity.

During the last decades improvement of surgical techniques, introduction of femtosecond lasers and new surgical approaches have expanded the surgical options and improved the outcome anterior lamellar keratoplasty.

Today, dissection can be performed at the interface between stroma and Descemet's membrane, reducing interface scarring significantly, femtosecond lasers can be used to make superficial anterior lamellar keratoplasty an easy procedure without the need for suturing, and intrastromal implantation of corneal implants can also be used to treat keratoconus. The presentation will update on current and coming techniques, including the possibilities for using synthetic tissues for anterior keratoplasty.

Keywords: anterior lamellar keratoplasty; corneal scars; keratoconus; corneal dystrophy.

REGENERATION OF THE OCULAR SURFACE USING BIOMATERIALS AND MODIFICATION OF THE CORNEA

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Background: Amniotic membranes have been used for many years for reconstruction of the ocular surface. Despite having anti-inflammatory and anti-angiogenic properties as well as being suitable as a carrier for corneal epithelial cells, amniotic membranes also have some limitations for use at the human cornea: availability is limited, there are major interindividual variations in structure and growth factor content and are not free from the risk of disease transmission. Progress in tissue engineering has been made aiming at the development and improvement of alternative biomaterials.

Objectives: This article presents new approaches for reconstruction of the corneal surface with collagen-based biomaterials and polymers.

Material and methods: Electronic databases were searched for articles which evaluated collagenous biomaterials for use at the corneal surface. In addition, the authors' own experiences with novel biomaterials are described.

Results: In vitro evaluation of the described biomaterials suggested a high biocompatibility with corneal epithelial cells in cell cultures. In vivo experiments with these materials in animal corneas demonstrated a certain variability in degradation and remodelling. Although some materials showed promising experimental results none of these are established in the clinical routine and only few clinical studies have so far been conducted with collagen-based biomaterials.

Conclusion: Although the majority of the described biomaterials are currently still in the experimental stage, a transfer into the clinical routine is conceivable and of great therapeutic interest. A range of alternatives to human donor tissue for corneal transplantation are being developed to address the shortfall of good quality tissues as well as the clinical conditions in which allografting is contraindicated. Classical keratoprotheses, more commonly referred to as artificial corneas have been around and are being used clinically to replace minimal corneal function, but only as last resorts, as they are still associated with significant in vivo complications, such as extrusion/rejection, glaucoma,

or retinal detachment. In the past few years, there have been many significant developments in technologies that are designed to replace part or the full thickness of damaged or diseased corneas that encourages regeneration to different extents. In this review, we describe selected examples from the range of these corneal substitutes that range from keratoprostheses with regenerative capabilities through tissue-engineered scaffolds pre-seeded with stem cells to cell-based regenerative strategies. It is unlikely that there will be one best corneal substitute for all indications, but taken together, the various approaches may soon be able to supplement the supply of human donor corneas for transplantation or allow restoration of diseased or damaged corneas that cannot be treated by currently available techniques.

Keywords: corneal surface reconstruction; collagen-based biomaterials; cell-based regenerative therapy.

THE EYE AND THE GUT: TWO SIDES OF THE SAME IMMUNOLOGICAL COIN

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The topic of this talk was presentation of commonalities and disparities between the eye and the intestine from an immunological point of view.

The main objective of presented research work was to show how we can translate basic research results in mucosal immunology treatments for chronic diseases, specifically inflammatory bowel disease, liver disease and cancer into a basic research in eye immunology. In particular, research results focusing in characterizing the mucosal microenvironment and how it affects host cells were presented.

In addition, during the lecture we saw results of a sample biobank management and results of immunological research in a cohort of patients with gastrointestinal disorders and cancers.

Keywords: immunology of intestine; eye immunology; immune privilege.

DEVELOPMENT OF OPHTHALMOLOGY IN REGION – BUSINESS MODELS

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Main change in the development of ophthalmology in the region was foundation of private clinics in Croatia and the region. As an example, foundation and growth of a private eye hospital Svjetlost was presented. The hospital is based on the “one-day surgery” model in which it is possible to treat all eye diseases that require surgical treatment - laser vision correction, ultrasound cataract surgery, surgery on the back of the eye due to disease caused by diabetes, diseases of macula or degenerative changes of the retina, surgical treatment of glaucoma (elevated intraocular pressure), surgical treatment of strabismus (squint), plastic and reconstructive surgery on eyelids, and corneal transplants with a shortest stay in the hospital. For almost all eye surgeries patients stay for half an hour after the surgery and are able to go home. However, there is also medical unit with hospital beds in Svjetlost, just for cases that require intensive care or for patients which underwent complex surgical procedures and thus need prolonged monitoring. Soon after its foundation, Svjetlost clinic became one of the first private university clinic in Croatia with the parent institution situated in Zagreb. Later on, Svjetlost branches were opened also in Split (Croatia) and in several in neighbouring countries: in Sarajevo and Banja Luka (Bosnia and Herzegovina), Budva (Montenegro), Novi Sad (Serbia) and in collaboration with local hospitals in Skopje (Macedonia); and soon its opening its offices in Priština (Kosovo) and Tirana (Albania).

Special Hospital for Ophthalmology Svjetlost believes in the education and training of young people and every year employees several new doctors who get a possibility to specialize in ophthalmology. In addition to having their costs of specialization fully covered, these doctors have the option of going to a prestigious global conference and to visit most famous ophthalmological centres, where they can acquire new knowledge and always be in step with the latest developments in the profession. Mainly due to its well-designed business model, Special Eye Hospital Svjetlost became the leading ophthalmic institution in the region that provides a comprehensive service. It is known for the highest stan-

dards of technical support and knowledge and constantly proves to be a representative of the latest technology in ophthalmologic practice.

Keywords: ophthalmology business model; private clinic; one-day surgery.

TRANSPLANTATION OF CORNEAL LIMBAL STEM CELLS CULTIVATED *IN VITRO*

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Transplantation of corneal limbal stem cells is a successful treatment for patients with partial or total limbal stem cell deficiency caused by ocular combustion. This method of treatment is known since 1970-ies and is currently performed at only a few European ophthalmological centres. Namely, in case of corneal burn, limbal stem cells are destroyed and corneal conjunctivalisation and opacification occurs. In such cases conventional corneal transplantation cannot succeed since normal epithelialization of the grafted corneas is impossible without limbal stem cells. Current and best available treatment for such patients is to take a small (2 mm) sample of limbal stem cells from the contralateral healthy eye, cultivate them *in vitro* on the amniotic membrane (or some other scaffold) in a tissue bank and then, once the sufficient number of limbal stem cells is cultivated, transplantation of these cells onto a diseases eye. In some cases, transplantation of limbal stem cells alone is sufficient treatment and no further action is needed. In cases where visual improvement is not adequate, corneal transplantation may be performed several months after limbal stem cell transplantation, and in such cases corneal graft will survive since limbal stem cells are provided previously. In the Special Eye Hospital "Svjetlost" we have started with this method of treatment in 2016, as first regional hospital providing this sophisticated treatment to patients with previously untreatable corneal diseases. We have presented results of first cases, young patients with corneal combustion caused by lime, tear gas and explosive burn, which were blind to an eye for a previous at least 5-10 years. All three cases recovered their vision

significantly and did not need corneal transplantation as a second step procedure at all.

Keywords: limbal stem-cell transplantation; corneal combustion; *in vitro* cultivation of limbal stem cells; amniotic membrane scaffold.

SYNTHETIC VS NATURAL SCAFFOLDS FOR HUMAN LIMBAL STEM CELLS

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Aim: To investigate the impact of synthetic electrospun polyurethane (PU) and polycaprolactone (PCL) nano-scaffolds, before and after hydrolytic surface modification, on viability and differentiation of cultured human eye epithelial cells, in comparison with natural scaffolds: fibrin and human amniotic membrane.

Methods: Human placenta was taken at elective caesarean delivery. Fibrin scaffolds were prepared from commercial fibrin glue kits. Nano scaffolds were fabricated by electrospinning. Limbal cells were isolated from surpluses of human cadaveric cornea and seeded on feeder 3T3 cells. The scaffolds used for viability testing and immunofluorescence analysis were amniotic membrane, fibrin, PU, and PCL nano-scaffolds, with or without prior NaOH treatment.

Results: Scanning electron microscope photographs of all tested scaffolds showed good colony spreading of seeded limbal cells. There was a significant difference in viability performance between cells with highest viability cultured on tissue culture plastic and cells cultured on all other scaffolds. On the other hand, electrospun PU, PCL, and electrospun PCL treated with NaOH had more than 80% of limbal cells positive for stem cell marker p63 compared to only 27% of p63 positive cells on fibrin.

Conclusion: Natural scaffolds, fibrin and amniotic membrane, showed better cell viability than electrospun scaffolds. On the contrary, high percentages of

p63 positive cells obtained on these scaffolds still makes them good candidates for efficient delivery systems for therapeutic purposes.

Keywords: natural scaffolds; electrospun polyurethane; nan-scaffolds; p63 positive cells; limbal stem cells.

NOVEL ANTIFIBROTICS IN CORNEAL WOUND HEALING

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Corneal wound healing is often affected by TGF- β -mediated fibrosis and scar formation. Guided fibrosis with IGF-1 and antifibrotic substances might maintain corneal transparency. Primary human corneal keratocytes under serum-free conditions were used as a model of corneal stromal wounding, with markers of corneal fibrosis and opacity studied under TGF- β 2 stimulation. Single-cell imaging flow cytometry was used to determine nuclearization of Smad3, and intracellular fluorescence intensity of Smad7 and the corneal crystallin aldehyde dehydrogenase 3A1. Extracellular matrix proteoglycans keratan and biglycan were quantified using ELISAs. On the TGF- β 2 background, the keratocytes were treated with IGF-1, and suberoylanilidehydroxamic acid (SAHA) or halofuginone \pm IGF-1. IGF-1 alone decreased Smad3 nuclearization and increased aldehyde dehydrogenase 3A1 expression, with favourable extracellular matrix proteoglycan composition. SAHA induced higher Smad7 levels and inhibited translocation of Smad3 to the nucleus, also when combined with IGF-1. Immunofluorescence showed that myofibroblast trans-differentiation is attenuated and appearance of fibroblasts is favoured by IGF-1 alone and in combination with the antifibrotic substances. The TGF- β /Smad pathway of fibrosis and opacity was inhibited by IGF-1, and further with SAHA in particular, and with halofuginone. IGF-1 is thus a valid aid to antifibrotic treatment, with potential for effective and transparent corneal wound healing.

Keywords: corneal wound healing; TGF- β , IGF-1; antifibrotic treatment.

THE ROLE OF PROANGIOGENIC CYTOKINES AND THEIR RECEPTORS IN NEOVASCULARIZATION OF CORNEAL GRAFT

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Purpose: To evaluate correlation of vascular endothelial growth factor (VEGF) and its soluble receptors quantity in the recipient cornea at the time of penetrating keratoplasty (PK) and its potential influence on graft rejection.

Methods: Study included 60 eyes scheduled for PK, equally distributed by corneal pathology into 3 risks groups: low, medium, high and controls. Quantity of VEGF-A and C, sVEGFR-1, R2 and R3 was analysed in total cornea and its layers using an enzyme-linked immunosorbent assay; correlated and compared with neovascularization rate and frequency of graft reaction/rejection in 2 post-operative years.

Results: Highest concentrations of VEGF-A and C in total cornea were in high risk cases (599 pg/ml; 8.49 ng/ml) and the lowest in controls (102 pg/ml; 5.23ng/ml). Soluble VEGFR-1 and sVEGFR-3 were significantly higher in low risk patients (2.11 ng/ml; 1.62 ng/ml) as compared to high risk group in total cornea (1.8 ng/ml; 0.63 ng/ml). There were 2 graft rejections, both in high risk group. Eyes with graft reaction had significantly higher VEGF-A (477 pg/ml) and VEGF-C (6.06 ng/ml) and lower sVEGFR-1 (2.23 ng/ml) and R3 (0.49 ng/ml) as compared to clear grafts. Statistical analysis was done by Kruskal-Wallis ANOVA non-parametric test and difference between groups was analysed by Mann-Whitney U-test.

Conclusion: Our data implicate that graft reaction occurs more often in corneas with increased VEGF-A and C and decreased sVEGFR-1 and R3. Novelty is that soluble VEGF receptors in human corneas may suppress rejection acting as a VEGF-sink, and potentially serve as anti-rejection therapy.

Keywords: penetrating keratoplasty; vascular endothelial growth factor; soluble VEGF receptors; human corneas; corneal neovascularization; graft survival rate.

PREMIUM CATARACT AND REFRACTIVE LENS EXCHANGE SURGERY WITH EXTENDED DEPTH OF FOCUS INTRAOCULAR LENSES

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Cataract surgery is more and more becoming refractive surgery. Patients demand excellent vision at all distances without wearing glasses or contact lenses. Modern technology and lens designs are enabling ophthalmologists fulfilling of increased patient's expectations.

In Eye Hospital Svjetlost, Zagreb, Croatia in last two years around one third of patients who had PHACO surgery got presbyopia correcting intraocular lenses in their eyes. Multifocal intraocular lenses (MFIOL) enable high level of spectacle independence but have high rate of halo and glare in night driving.

The newest generation of presbyopia correcting intraocular lenses (IOL) is so called Extended Depth of Focus (EDOF) lenses. EDOF IOLs represent a new category of intraocular lenses, combining benefits of different technologies. They have a wider range of clear vision than monofocal IOLs and fewer side effects than multifocal IOLs.

There are a few different designs of EDOF IOLs.

AT LARA (Carl Zeiss Meditec AG) is aspheric, diffractive intraocular lens with extended depth of focus. It gives spectacle independence for intermediate and far distances and less visual side effects than multifocal IOL. It has an aberration-neutral aspheric design and advanced chromatic correction for better contrast sensitivity. Patients have to wear glasses for reading a small print.

Mini Well Ready IOL (Sifi Medtech) is the first progressive multifocal aspheric IOL for the presbyopia correction. It has three optical zones with different spherical aberrations. Among the optical zones there are smooth transition areas, thanks to which a good vision at all distances is achieved without halos.

Small aperture IC-8 IOL (AcuFocus) is a one-piece hydrophobic acrylic IOL with an embedded black circular mask. The mask blocks unfocused rays of light, extending depth of focus and providing patients with good visual acuity across a range of distances. The lens is implanted in the nondominant eye but does not create monovision.

Tecnis Symphony extended range of vision IOL is a diffractive IOL with elongated focus and achromatic technology which enhances contrast sensitivity. This lens enables continuous vision from far to near, less halos compared to MFIOLs, better contrast sensitivity and high level of spectacle independence. Still, some patients have to wear glasses for small print. Tecnis Symphony can be viable option for post LASIK patients, amblyopes, patients with mild macular pathology and patients with monofocal IOL in first eye.

EDOF IOLs represent a new generation of presbyopia correcting lenses with better quality of vision and fewer visual disturbances but poorer uncorrected near visual acuity compared to MFIOLs. The choice of the IOL must be made according to patient's lifestyle, job and everyday activities.

Keywords: extended range of vision lens; multifocal lens; refractive lens exchange.

EXCIMER LASER TREATMENT OF IRREGULAR CORNEAS

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Purpose: To evaluate efficacy and safety of ocular or corneal wavefront guided transepithelial photorefractive keratectomy (transPRK), alone or in combination with corneal collagen crosslinking (CXL), in treatment of irregular astigmatism.

Patients and methods: 10 cases (10 patients) with iatrogenic cause of irregular astigmatism (e.g corneal scars caused by previous infection or injury) and 17 cases (14 eyes) of corneal ectasia (either keratoconus or post LASIK ectasia) were treated. Follow up was from 3 months up to 3 years. Corneal or ocular wave-front guided treatment was used depending on ablation plan and amount of tissue needed for excimer laser ablation. For ectatic cases CXL was performed simultaneously with either 3 or 10 mW/cm² lamp.

Results: In both groups there was no statistically significant improvement in uncorrected distance visual acuity (group I p=0.06, group II p= 45). Corrected

distance visual acuity significantly improved ($p < 0.001$), together with all high order aberrations ($p < 0.001$). There were no complications with corneal epithelialization which lasted in average for 5 days. Transient mild haze was noticed in all cases, 5 cases from group II have permanent mild haze without influence on visual acuity. 2 cases (1 eye post LASIK ectasia and 1 eye keratoconus) are experiencing progressive flattening for up to 3 years after the treatment.

Conclusion: Wavefront guided treatments are efficient in regularizing anterior corneal surface. Additional caution and more patients with longer follow up are needed to prove its safety in treatment of ectatic corneas.

Keywords: excimer laser; irregular corneas; transPRK; corneal crosslinking.

OVERVIEW OF MULTIFOCAL IOLS USED IN SVJETLOST HOSPITAL

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Purpose: To make systematic review of the numbers and types of multifocal intraocular lenses implanted in our clinic, importance of good patient's selection, preoperative assessment and selection of the proper intraocular lens along with the limitations of the lens design.

Methods: Prospective, consecutive, interventional case series. The study analysed different types of multifocal intraocular lenses implanted in patients underwent surgeries in Special eye hospital „Svjetlost“ in period 2005-2017. All surgeries were done by experienced surgeons and on the same phaco machine. Patient selection based on their needs, professions, demands as well as type of refraction has been included in the study. We follow-up patients up to 5 years, visual acuity, postoperative change in refraction and adverse events were recorded.

Results. In period of 2005-2012 we implanted: „ReSTORE +4“ intraocular lenses in 344 eyes, Tecnis ZM900 & ZMA00 & ZB00 in 610 eyes, „ReZoom“ in 160 eyes, „AcryLisa & AT LISA 809 MP“ in 536 eyes and Mix and Match has been used in 440 eyes.

In period of 2013 till 2017 we implanted „new“ MF for refractive lens exchange. In total we included 1844 eyes, out of that number „Symfony lens has been implanted in 632 eyes, „Technis low-add“ lenses in 396 eyes, „Acryva Reviol Tri-Focal lenses in 130 eyes, „PanOptix“ in 44 eyes and other MF in 60 eyes. During 12 years follow-up time we made learned about advantages and insufficiencies of different lens type and design.

Conclusion. There is no important difference in visual acuity between Restor and Tecnis IOL apart from low-light conditions where Tecnis acrylic do better. Patients with ReZoom lenses have better intermediate vision then Restor and Tecnis but lack good near vision. Patient with bilateral ReZoom lenses have more night-time driving difficulties then Restor and Tecnis patients. Mix and Match group: highly satisfied (75%) or highly unsatisfied (25%). There is no significant differences in visual acuity between „new“ MF intraocular lenses, though „Symfony“ can be used in patients with amblyopia.

Keywords: intraocular lens; multifocal; phaco; patient selection.

AVELLINO DNA TEST FOR REFRACTIVE SURGERY SAFETY

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Nowadays with high patient expectations and tremendous technology improvements, refractive surgery stands for one of the most safe and predictable surgical procedures. The biggest fear for most surgeons is postoperative corneal ectasia. The prevalence of this condition is about 1 in 2000 eyes, comparable with prevalence of keratoconus in the general population. Advanced corneal topography systems make it easier for clinicians to identify patients at increased risk of postsurgical ectasia, but the condition can still go undetected preoperatively. On the other hand, there is another possible complication that doesn't come in mind so often or can easily be overlooked. Another potential complication after laser vision correction is the exacerbation of some types of corneal dystrophy like granular (GCD) type 1 (GCD1) or type 2 (GCD2). Currently, when we gener-

ally speak about dystrophies, their classification is based on the affected layer of the cornea, with differing phenotypic presentations that affect different corneal layers, there is obviously a question about the genetic background of those disorders. The specific genetic mutation in combination with some sort of tissue damage will produce the classic phenotypic appearance of each of the dystrophies. Dystrophies are caused by genetic mutations of transforming growth factor beta (TGF- β)–induced gene, which is associated with the wound-healing process of the cornea. TGFBIp is one of the most common proteins in the human cornea. While it is not fully understood, it is believed that it plays a critical role in important functions such as regulating cellular adhesions and migration within the cornea and binding with other macromolecules in the extracellular matrix, especially collagen. One of its most important functions is thought to be during wound healing. After corneal injury the expression of TGFBI protein is upregulated in keratocytes near the wound. Dystrophies are autosomal dominant. Those who carry the gene for the condition will exhibit the phenotype, though the age. While homozygous patients start to lose visual acuity at a young age, those with the heterozygous condition may develop visual acuity loss later in life. Since the global prevalence of heterozygous TGFBI- dystrophies appears to be greater than that of keratoconus, therefore patients undergoing laser vision correction may be at higher risk of developing TGFBI- dystrophies than corneal ectasia. There have been cases reported across the globe, with first larger study launched in Korea, published as high prevalence of GCD2, genetic testing has quickly become the standard of care. Today, there has been performed more than 500 000 refractive surgery safety DNA tests with Avellino genetic test and identified more than 550 patients with inherited corneal dystrophies, protecting them from accelerated vision loss. Twice as prevalent as keratoconus, it has become evident that testing for Corneal Dystrophies is becoming the standard of care in the many countries. Testing for 5 corneal dystrophy gene mutations identifies LASIK candidates at risk of post-surgery complications so that refractive surgeons can offer non-surgical alternatives for those patients.

Materials and methods: We tested two different families with Avellino genetic test, one family with previous family history of keratoplasty with suspect GCD1, and one with previous history of refractive surgery with suspect GCD2. Within all family members, buccal swab was taken and specimens were sent to Avellino Labs. For genetic testing.

Results: In GCD1 family only one member was negative to genetic testing, and two members with worst clinical appearance were tested as homozygous. In GCD2 family all members were tested as heterozygous.

Conclusion: In many cases, the identification of a specific mutation will provide more accurate information about the course or progression of the condition and patients' response to surgical intervention. Genetic testing such as Avellino genetic test for refractive safety should provide information that will help clinicians to correctly diagnose dystrophy and molecular genetics will ensure the possibility of therapeutic intervention with drugs or gene therapy to prevent or delay the need for more invasive surgical treatment.

Keywords: Avellino test; corneal dystrophy; TGFB1-dystrophies; corneal ectasia; refractive surgery; genetic testing.

NEW TREATMENTS FOR DIABETIC RETINOPATHY TESTED IN CLINICAL STUDIES

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Numerous clinical studies have confirmed the significance of antiVEGF treatment for diabetic retinopathy (DR) and diabetic macular oedema (DME). Other than antiVEGF, laser photocoagulation, corticosteroids such as triamcinolone or Ozurdex are used in treatment or pars plana vitrectomy (PPV) in more severe cases. The Diabetic Retinopathy Clinical Research Network (DRCR.net) have confirmed that patient who received ranibizumab + differed laser had the most significant results gaining most letters in ETDRS chart, followed by ranibizumab +prompt laser, sham + laser, and triamcinolone +laser at the primary outcome point at 52nd week of the study. Mean change in central foveolar thickness (CFT) from the baseline was followed by the same pattern: with group of ranibizumab + differed laser being the best and triamcinolone and laser being the last group with even increase of CFT at week 104 of the study. VISTA-DME and VIVID-DME studies were 2 multicentric randomised studies which showed

in Phase III of the study the superiority of aflibercept (Eylea) as compared to laser therapy, which led Eylea to be approved for DME in 2014. DRCR.net has recently published protocol T study about the relative efficacy and safety of intravitreal aflibercept, bevacizumab, and ranibizumab for treating eyes with DME and concluded that aflibercept, bevacizumab, or ranibizumab improved vision in eyes with DME, but the relative effect depended on baseline visual acuity. When the initial visual-acuity loss was mild, there were no apparent differences, on average, among study groups. At worse levels of initial visual acuity, aflibercept was more effective at improving vision. Other factors that have been studied and published in research are placental growth factor (PGF) which was showed in blocked PGF mice to prevent loss of pericytes, capillary permeability and degeneration (Huang H et al. Diabetes, 2014). The RISE and RIDE studies has expanded the approved use for ranibizumab injection to treat DR in patients with DME which gave approval to patients with DR and DME the first significant therapy to treat this vision-impairing complication. Other novel agents and studies which are currently ongoing include: antiVEGF+squalamine, antiVEGF+Tie2, CRaf inhibitors and anti-integrins. We can conclude that pharmacotherapy in DME treatment will be eventually combined of different agents with antiVEGF being so far the main approach and must not be given in low dosage. The laser will always have its place in combined pharmacotherapy treatment with PPV reserved for the most severe cases of proliferative DR.

Keywords: diabetic retinopathy; diabetic macular oedema; antiVEGF; pharmacotherapy; pars plana vitrectomy.

RANIBIZUMAB FOR NAMD: NEW EVIDENCE TO IMPROVE PATIENT CARE

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Purpose: To report results of TREND and Rival study results.

Design: TREND Study is a 12-month phase 3b visual acuity (VA) assessor-masked, multicenter, randomized, interventional study which evaluate the ef-

ficacy and safety of ranibizumab 0.5 mg treat-and-extend (T&E) versus monthly regimens in patients with neovascular age-related macular degeneration (nAMD). RIVAL Study is a 24-month, randomised, multi-centre Phase IV study which compare the rate of development of geographic atrophy after 24 months in nAMD patients treated with 0.5 mg ranibizumab and 2.0 mg aflibercept using a 'Treat and Extend' regimen (T&E). Results from a 12-month interim analysis of pre-specified key secondary endpoints (number of injections and change in Best Corrected Visual Acuity (BCVA) from baseline to Month 12), are presented here

Methods: In TREND study treatment-naïve nAMD patients (age, ≥ 50 years) were randomized 1:1 to receive either a ranibizumab 0.5 mg T&E (n = 323) or monthly (n = 327) regimen while in RIVAL Study eyes were randomised (1:1) to receive intravitreal injections of either 0.5 mg ranibizumab (RBZ) or 2.0 mg aflibercept (AFL). After receiving three initial monthly injections, patients entered the T&E phase which allowed for extension up to 12-weekly injections by 2 weekly increments if the CNV was considered inactive as per protocol. The pre-planned 12-month interim analysis was done.

Results: TREND Study showed noninferiority of T&E regimen ($P < 0.001$) to the monthly regimen, with a mean BCVA change from baseline of 6.2 versus 8.1 letters to the end of study, respectively. The mean change in CSFT from baseline to the end of study was $-169.2 \mu\text{m}$ and $-173.3 \mu\text{m}$ in the T&E and monthly groups, respectively. Fewer injections were required in patients receiving the T&E (8.7) versus monthly (11.1) regimen with comparable rates of adverse events between the treatment groups. RIVAL Study included 278 patients. The mean BCVA at month 12 was 72.9 letters in the RBZ arm (n=127, SD=15.5 [5-95]), and 70.5 letters in the AFL arm (n=121, SD=14.6 [36-91]). The change from baseline at Month 12 was +6.93 (95% CI: 5.20 to 8.65) for RBZ and +4.41 (95% CI: 2.64 to 6.18) for AFL. In patients who withdrew from the study before Month 12, the mean BCVA at the time of withdrawal [mean change from baseline] was 66.1 letters [+7.1] for RBZ (n=14; 9.9%) and 64.8 letters [+2.0] for AFL (n=16; 11.7%). The mean number of injections from baseline to Month 12 was 9.7 injections in both the RBZ (n=141; SD=2.77 [1-13]) and AFL arms (n=137; SD=2.55 [3-13]).

Conclusions: In TREND Study ranibizumab 0.5 mg administered according to a T&E regimen was comparable with a monthly regimen in improving VA from baseline to the end results. RIVAL study for the first time in T&E dosing regimen in nAMD patients showed significant visual acuity improvements by month 12 with both ranibizumab (+6.93 letters) and aflibercept (+4.41 letters) and similar mean number of injections received over the first 12 months.

Keywords: TREND study; RIVAL study; ranibizumab; neovascular age-related macular degeneration.

SYSTEMIC INFLAMMATION IN DIABETES IS ASSOCIATED WITH RETINOPATHY DEVELOPMENT IN TYPE 2 BUT NOT IN TYPE 1 DIABETES

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Purpose. Diabetic retinopathy (DR), a microvascular and visually devastating diabetic complication, is the leading cause of new blindness among working-age adults in developed countries. Its pathogenesis is insufficiently understood and presumed to possibly involve chronic, low-grade inflammation. The aim of this study was to investigate risk factors and role of systemic inflammation and obesity in development of retinopathy in type 1 and type 2 diabetes and determine the differences in these two types of disease, with possible impact on future research and treatment guidelines.

Methods. This cross-sectional study included 84 patients with type 1 and 107 patients with type 2 diabetes. Basic and anthropometric parameters assessed were sex, age, diabetes duration, body mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR). C-reactive protein (CRP), fibrinogen (FIB), glycated haemoglobin (HbA_{1c}), fasting and postprandial blood glucose (fBG, ppBG), total cholesterol, HDL and LDL cholesterol, triglycerides (TG) and serum creatinine were determined using routine laboratory methods. HbA_{1c}_{median} was obtained by statistical analysis of data from the National Diabetes Registry. Glomerular filtration rate was estimated using CKD-EPI formula. Albumin excretion rate (AER) was measured from a 24-hr urine sample. Blood pressure was measured with a mercury sphygmomanometer after a 10-min resting period. Ophthalmologic examination included indirect slit lamp funduscopy and colour fundus photography after mydriasis of two fields of both eyes according to the EURODIAB retinal photography methodology.

Results. Patients were divided into three groups: group 1 (no retinopathy), group 2 (mild/moderate NPDR) and group 3 (severe NPDR/PDR). In both types of diabetes group 3 had longer diabetes duration than group 1 (type 1 $p=0.002$; type 2 $p<0.001$). Group 3 in type 1 had higher $HbA_{1c_{median}}$ ($p<0.001$) and AER ($p=0.002$), while in type 2 had higher BMI, WC, WHR, SBP, CRP, FIB, ppBG and TG than group 1. DR was positively associated with diabetes duration ($p<0.001$), $HbA_{1c_{median}}$ ($p<0.001$) and AER (0.008) in type 1, and diabetes duration ($p<0.001$), $HbA_{1c_{median}}$ ($p=0.018$), AER (0.001), CRP ($p=0.048$) and TG ($p=0.041$) in type 2 diabetes. Logistic regression analyses showed that diabetes duration (OR=1.22, CI 1.04-1.45, $p=0.011$) and prolonged poor glycaemic control ($HbA_{1c_{median}}$) (OR=1.73, CI 1.25-2.34, $p=0.022$) were the main predictors of DR in type 1 diabetes. Diabetes duration (OR=1.25, CI 1.12-1.39, $p<0.001$), fBG (OR=1.45, CI 1.04-2.00, $p=0.024$) and TG (OR=2.08, CI 1.09-3.98, $p=0.025$) were the main predictors of DR in type 2 diabetes.

Conclusion. Diabetes duration, poor glycaemic control and nephropathy are the main risk factors for DR in both types of diabetes. Systemic inflammation and visceral obesity were found to be related to the development of DR in type 2 but not in type 1 diabetes. These findings could purpose different pathogenesis of retinopathy in these two different types of diabetes and might therefore suggest different treatment approaches.

Keywords: diabetic retinopathy; glycaemic control; type 2 diabetes; type 1 diabetes.

PARS PLANA VITRECTOMY AND INNER RETINAL FENESTRATION FOR OPTIC DISC MACULOPATHY-A CASE REPORT

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Optic disc pits (ODPs) are congenital cavitory anomalies with a pathological communication between subarachnoidal and intraretinal and subretinal spaces.

When complicated by maculopathy it may cause significant visual deterioration. So far multiple approaches for management of ODPs have been used including laser photocoagulation, pars plana vitrectomy, macular buckling and intravitreal gas injection. We present a novel approach of retinal retinotomy combined by pars plana vitrectomy (PPV) and gas instillation. 51 yr old patient presented with best corrected visual acuity (BCVA) of 0.10 and ODP maculopathy with visible communication between subarachnoidal and intraretinal and subretinal spaces confirmed by optical coherent tomography (OCT). We performed partial thickness retinal hole radial to the optic disc and PPV with SF6 gas tamponade. Macular oedema decreased and communication was closed 3 weeks postoperatively. BCVA, accordingly, increased to 0,25. 2 months postop BCVA was still 0,25, even though we noticed slightly increased macular oedema with still closed communication of ODP. Inner retinal fenestration enabled to redirect flow from subarachnoidal space to vitreous cavity thus closing communication and decreasing macular oedema and increasing BCVA of the patient. However, even though ODP was closed, we still noticed fluid in macula on 2 months control not affecting the BCVA. In literature, patients have been described for 6 months or even a year of resolving fluid in macula after surgery. This could suggest that there is still occasionally microcommunication between these spaces or increased permeability of vessels under the macula.

Keywords: optic disc maculopathy; retinotomy; pars plana vitrectomy.

SURGICAL TREATMENT OF NYSTAGMUS

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Nystagmus is an involuntary, periodic eye movement caused by slow drift of fixation which is followed by fast refixation. Although the pathologic movement is the slow drift, the direction of nystagmus is defined by the more obvious direction of jerk. There are three forms of nystagmus: 1. physiologic nystagmus, 2. acquired nystagmus caused by some neurological diseases and are not in the field of ophthalmologists and 3. Idiopathic infantile nystagmus and ocular nys-

tagmus caused by some eyes disorders. The nystagmus can be socially embarrassing and can be obstacle to good visual acuity.

Although there is no cure for nystagmus in some cases when the patients have null-zone achieved with the obvious head turn which is bigger than 10° surgery can be done. The aim of the surgery is to shift the null zone of nystagmus into primary position. There are several ways to achieve that. One of the most popular is Anderson procedure that consists of recession of horizontal recti. If the wanted position is not possible to achieve only with recessions Kestenbaum method is a good choice. In that surgery we combine recessions with resections of desired muscles to put the eyes in the best position. In other cases, were the patients preferred head position is head tilt the Kestenbaum method can be used on oblique muscles. In the cases where the null zone is in convergence the most useful surgery is Y-splitting where we enable the patient to use these position for distant vision without head turn. Y-splitting is a method where we split the muscle along the 15 mm length and by shortening of affective lever arm reduce action of the medial muscle. By performing this surgery, we enable the patient to use desired position for distant vision without head turn.

Keywords: nystagmus; Anderson procedure; Kestenbaum method.

CROATIAN NATIONAL PREVENTIVE PROGRAM OF EARLY AMBLYOPIA DETECTION

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Aim: To present Croatian National Preventive Program of Early Amblyopia Detection, as Croatian contribution to global VISION 2020 initiative launched in 1999 promoting the world in which nobody is needlessly visually impaired.

Methods: Between September 2011 – June 2014 Zagreb Amblyopia Preschool Screening (ZAPS) project tested visual acuity of 15,648 children aged 48-54 months attending kindergartens in the City of Zagreb. Lea Symbols in lines

charts were used to test near and distance visual acuity setting the pass cut-off level to ≤ 0.1 logMAR. 78.04% passed the screening, affirming the age-specific normative threshold for determining abnormal monocular VA. The estimated prevalence of amblyopia in Croatia was 8.08%. Testability rate was 99.19%, with sensitivity and specificity of 100.00 % and 96.68%.

Results: Zagreb Amblyopia Preschool Screening study demonstrated amblyopia prevalence of 8.08%, which is within earlier reports on the prevalence of amblyopia ranging 0.8%-10%. Based on the ZAPS study results, Croatian Ministry of Health released National Preventive Program of Early Amblyopia Detection, mandatory for all 4-year-old children. At the age of 48 months the child is referred to an ophthalmologist who performs vision screening by testing visual acuity at near (40 cm) and distance (3 m) binocularly and monocularly using Lea Symbols in line charts. To facilitate the implementation of National Preventive Program of Early Amblyopia Detection and raise awareness among key audiences, Croatian Parliament introduced National Amblyopia Day in 2016, celebrating September 12th. Constitution of Croatian National Amblyopia Registry, released by Ministry of Health as user friendly on-line application in 2017, was of utmost importance to provide high-quality performance of the National Preventive Program of Early Amblyopia Detection.

Discussion. Comprehensive eye care strategy can be fully generated only by actively engaged governmental bodies in collaborative activities of successful eye care delivery.

Conclusion: The World Bank forecasts that the human population will reach 9.77 billion in 2050. If nothing is done, about 500 million people will be needlessly amblyopic world-wide. To rise level of prevention and treatment programs we advocate the establishment of national amblyopia registries to acknowledge impact of amblyopia more adequately.

Keywords: Croatian National Preventive Program of Early Amblyopia Detection; Vision 20/20; amblyopia.

WHEN TO OPERATE DUANE SYNDROM?

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Duane syndrome (DS), also known as Duane retraction syndrome (DRS), is a rare, congenital disorder of eye movement. Most individuals with Duane syndrome are diagnosed by age 10 years. In Duane syndrome, the sixth cranial nerve that controls the lateral rectus does not develop properly and this probably occurs around the sixth week of pregnancy. Lateral rectus muscle is irregularly innervated of a branch from the third cranial nerve, which controls the medial rectus muscle and when the eye moves toward the nose, the eyeball pulls into the socket (i.e., retraction). There are three types of Duane syndrome. Many patients with Duane syndrome develop a habit of turning their face to maintain binocular vision and thus compensate for improper turning of the eyes. The goal of surgery is the elimination or improvement of an unacceptable head turn. In case report there is 11 years old girl with no ability to move left eye outward and head is turned to the left. Surgery was performed because of abnormal head posture (AHP) with recession of MRM (-5 mm) on the left eye. Duane syndrome can be operated only to prevent AHP.

Keywords: Duane syndrome; surgery for Duane syndrome.

FYBROSIS SYNDROME IN NINE-YEAR-OLD GIRL

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Purpose: Successful late treatment results of Congenital Fibrosis of Extraocular Muscles syndrome (CFEOM1).

Methods: Our patient was 9 years old child with a variation of CFEOM1 syndrome, first presented with abnormal head position (AHP) of 30° chin up.

Horizontal movements were normal, both eyes showed no elevation and limited depression, converging on attempt to elevate and diverging on attempt to depress, absent Bell's phenomenon. She was slightly hypermetropic with no amblyopia. Ptosis was significant on both eyes with RE levator muscle function of 6 mm and no levator function on LE. MRD 1 was 1/ 0 mm. She had compensatory frontalis function on both sides. Three surgeries were performed to alleviate AHP. During the first strabismus surgery thick fibrotic inferior recti on both eyes were recessed. On second strabismus surgery, since the passive motility test showed good elevation, anteposition of hypoplastic superior recti situated at 10 mm behind the limbus was performed. Asymmetric ptosis surgery – frontalis suspension was performed on both eyes.

Results: After two strabismus surgeries AHP improved, but the patient still had slight chin up 15°. After ptosis surgery residual AHP was 5°.

Conclusion: Although the best results in treating congenital fibrosis syndromes are achieved by early treatment (e.g.1-2 years old), later treatment can also give satisfying results. If no amblyopia present, the most important goal is to treat AHP successfully. Because of highly asymmetric and irregular action of muscles CFEOM syndromes, special care should be taken for dosage.

Keywords: congenital fibrosis syndrome; abnormal head position; ptosis surgery.