Retina Roundup

January 2019

Rationale and Application of the Protocol S Anti-Vascular Endothelial Growth Factor Algorithm for Proliferative Diabetic Retinopathy.

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ABSTRACT

PURPOSE:

To present the rationale, guidelines, and results of ranibizumab treatment for proliferative diabetic retinopathy (PDR) in Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol S.

DESIGN:

Post hoc analyses from a randomized clinical trial.

PARTICIPANTS:

Three hundred five participants (394 study eyes) having PDR without prior panretinal photocoagulation (PRP).

METHODS:

Intravitreous ranibizumab (0.5 mg) versus PRP for PDR. Ranbizumab-assigned eyes (n = 191) received monthly injections for 6 months unless resolution was achieved after 4 injections. After 6 months, injections could be deferred if neovascularization was stable over 3 consecutive visits (sustained stability). If neovascularization worsened, monthly treatment resumed. Panretinal photocoagulation could be initiated for failure or futility criteria.

MAIN OUTCOME MEASURES:

Neovascularization status through 2 years.

RESULTS:

At 1 month, 19% (35 of 188) of ranibizumab-assigned eyes showed complete neovascularization resolution and an additional 60% (113) showed improvement. At 6 months, 52% (80 of 153) showed neovascularization resolution, 3% (4) were improved, 37% (56) were stable, and 8% (13) had worsened since the last visit. Among eyes with versus without resolved neovascularization at 6 months, the median (interquartile range) number of injections between 6 months and 2 years was 4 (1-7; n = 73) versus 7 (4-11; n = 67; P < 0.001). Injections were deferred in 68 of 73 eyes (93%) meeting sustained stability at least once during the study; 62% (42 of 68) resumed injections within 16 weeks after deferral. At 2 years, 43% (66 of 154) showed neovascularization resolution, 5% (7) showed improvement, 23% (36) were stable, and 27% (42) had worsened since the last visit. Only 3 eyes met criteria for failure or futility through 2 years.

CONCLUSIONS:

The DRCR.net treatment algorithm for PDR can provide excellent clinical outcomes through 2 years for patients initiating anti-vascular endothelial growth factor (VEGF) therapy for PDR. When choosing between anti-VEGF and PRP as first-line therapy for PDR, treatment decisions should be guided by consideration of the relative advantages of each therapeutic method and anticipated patient compliance with follow-up and treatment recommendations.

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Choroideremia Gene Therapy Phase 2 Clinical Trial: 24-Month Results.

Lam BL[1], Davis JL[2], Gregori NZ[2], MacLaren RE[3], Girach A[4], Verriotto JD[2], Rodriguez B[2], Rosa PR[2], Zhang X[2], Feuer WJ[2].

PURPOSE:

To report the final results of a phase 2 high-dose gene therapy clinical trial in choroideremia.

METHODS:

Design: Phase 2 clinical trial.

PARTICIPANTS:

Six men (aged 32-72 years) with genetically-confirmed advanced choroideremia. Patients received subfoveal injection of AAV2-REP1 (1011 genome particles in 0.1 mL) in the worse-sighted eye.

OUTCOME MEASURES:

Primary measure was best-corrected visual acuity (BCVA) change from baseline in the treated eye compared to the untreated eye. Secondary endpoints included change from baseline in microperimetry, fundus autofluorescence, and spectral-domain optical coherence tomography (OCT). Safety evaluations included adverse events, viral shedding in body fluids, and vector antibody responses.

RESULTS:

Baseline mean ETDRS BCVA was 65.3 ± 8.8 (SD, range 56-77, 20/32-20/80) letters in the treated eyes and 77.0 ± 4.2 (69-81, 20/25-20/40) letters in the untreated eyes. At 2 years, 1 treated eye improved by 10 letters and another by 5 letters, while 1 untreated eye improved by 4 letters. All other eyes were within 2 letters of baseline. Baseline microperimetry sensitivities in the treated eyes were poor (1.2 ± 2.1 (0, 5.1) dB) and showed no significant change. No serious adverse event occurred. Two patients developed an atrophic retinal hole in a nonfunctioning macular area where baseline OCT showed preexisting thinning. Intraoperative microscope-integrated OCT allowed proper subretinal injection with avoidance of excessive foveal stretching and macular hole formation.

CONCLUSIONS:

Sustained improvement or maintenance of BCVA is achievable in choroideremia with high-dose AAV2-REP1, indicating BCVA is a viable primary outcome in advanced choroideremia. Choroideremia gene therapy delivered with intraoperative OCT has a good safety profile.

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Retinal Vasculometry Associations with Cardiometabolic Risk Factors in the European Prospective Investigation of Cancer-Norfolk Study.

Owen CG[1], Rudnicka AR[2], Welikala RA[3], Fraz MM[4], Barman SA[3], Luben R[5], Hayat SA[5], Khaw KT[5], Strachan DP[2], Whincup PH[2], Foster PJ[6].

PURPOSE:

To examine associations between retinal vessel morphometry and cardiometabolic risk factors in older British men and women.

DESIGN:

Retinal imaging examination as part of the European Prospective Investigation into Cancer-Norfolk Eye Study.

PARTICIPANTS:

Retinal imaging and clinical assessments were carried out in 7411 participants. Retinal images were analyzed using a fully automated validated computerized system that provides novel measures of vessel morphometry.

METHODS:

Associations between cardiometabolic risk factors, chronic disease, and retinal markers were analyzed using multilevel linear regression, adjusted for age, gender, and within-person clustering, to provide percentage differences in tortuosity and absolute differences in width.

MAIN OUTCOMES MEASURES:

Retinal arteriolar and venular tortuosity and width.

RESULTS:

In all, 279 802 arterioles and 285 791 venules from 5947 participants (mean age, 67.6 years; standard deviation [SD], 7.6 years; 57% female) were analyzed. Increased venular tortuosity was associated with higher body mass index (BMI; 2.5%; 95% confidence interval [CI], 1.7%-3.3% per 5 kg/m2), hemoglobin A1c (HbA1c) level (2.2%; 95% CI, 1.0%-3.5% per 1%), and prevalent type 2 diabetes (6.5%; 95% CI, 2.8%-10.4%); wider venules were associated with older age (2.6 µm; 95% CI, 2.2-2.9 µm per decade), higher triglyceride levels (0.6 µm; 95% CI, 0.3-0.9 µm per 1 mmol/l), BMI (0.7 µm; 95% CI, 0.4-1.0 per 5 kg/m2), HbA1c level (0.4 µm; 95% CI, -0.1 to 0.9 per 1%), and being a current smoker (3.0 µm; 95% CI, 1.7-4.3 µm); smoking also was associated with wider arterioles (2.1 µm; 95% CI, 1.3-2.9 µm). Thinner venules were associated with high-density lipoprotein (HDL) (1.4 µm; 95% CI, 0.7-2.2 per 1 mmol/l). Arteriolar tortuosity increased with age (5.4%; 95% CI, 3.8%-7.1% per decade), higher systolic blood pressure (1.2%; 95% CI, 0.5%-1.9% per 10 mmHg), in females (3.8%; 95% CI, 1.4%-6.4%), and in those with prevalent stroke (8.3%; 95% CI, -0.6% to 18%); no association was observed with prevalent myocardial infarction. Narrower arterioles were associated with age (0.8 µm; 95% CI, 0.6-1.0 µm per decade), higher systolic blood pressure (0.5 µm; 95% CI, 0.4-0.6 µm per 10 mmHg), total cholesterol level (0.2 µm; 95% CI, 0.0-0.3 µm per 1 mmol/l), and HDL (1.2 µm; 95% CI, 0.7-1.6 µm per 1 mmol/l).

CONCLUSIONS:

Metabolic risk factors showed a graded association with both tortuosity and width of retinal venules, even among people without clinical diabetes, whereas atherosclerotic risk factors correlated more closely with arteriolar width, even excluding those with hypertension and cardiovascular disease. These noninvasive

microvasculature measures should be evaluated further as predictors of future cardiometabolic disease.

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DEXAMETHASONE IMPLANT FOR DIABETIC MACULAR EDEMA IN NAIVE COMPARED WITH REFRACTORY EYES: The International Retina Group Real-Life 24-Month Multicenter Study. The IRGREL-DEX Study.

Iglicki M[1], Busch C[2], Zur D[3,4], Okada M[5], Mariussi M[6], Chhablani JK[7], Cebeci Z[8], Fraser-Bell S[9], Chaikitmongkol V[10], Couturier A[11], Giancipoli E[12], Lupidi M[13], Rodríguez-Valdés PJ[14], Rehak M[2], Fung AT[15,16,17], Goldstein M[3,4], Loewenstein A[3,4,17].

ABSTRACT

PURPOSE:

To investigate efficacy and safety of repeated dexamethasone (DEX) implants over 24 months, in diabetic macular edema (DME) eyes that were treatment naive compared with eyes refractory to anti-vascular endothelial growth factor treatment, in a real-life environment.

METHODS:

This multicenter international retrospective study assessed best-corrected visual acuity and central subfield thickness (CST) of naive and refractory eyes to anti-vascular endothelial growth factor injections treated with dexamethasone implants. Safety data (intraocular pressure rise and cataract surgery) were recorded.

RESULTS:

A total of 130 eyes from 125 patients were included. Baseline best-corrected visual acuity and CST were similar for naive (n = 71) and refractory eyes (n = 59). Both groups improved significantly in vision after 24 months (P < 0.001). However, naive eyes gained statistically significantly more vision than refractory eyes (+11.3 ± 10.0 vs. 7.3 ± 2.7 letters, P = 0.01) and were more likely to gain ≥10 letters (OR 3.31, 95% CI 1.19-9.24, P = 0.02). At 6, 12, and 24 months, CST was significantly decreased compared with baseline in both naive and refractory eyes; however, CST was higher in refractory eyes than in naive eyes (CST 279 ± 61 vs. 313 ± 125 µm, P = 0.10).

CONCLUSION:

Over a follow-up of 24 months, vision improved in diabetic macular edema eyes after treatment with dexamethasone implants, both in eyes that were treatment naive and eyes refractory to anti-vascular endothelial growth factor treatment; however, improvement was greater in naive eyes.

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Optical coherence tomography angiography findings in cystoid macular degeneration associated with central serous chorioretinopathy.

Sahoo NK[1], Mishra SB[1], Iovino C[2], Singh SR[1], Munk MR[3,4], Berger L[3], Peiretti E[2], Chhablani J[5].

ABSTRACT

AIM:

To describe the optical coherence tomography (OCT) characteristics and to identify and analyse the incidence of choroidal neovascular (CNV) network seen on optical coherence tomography angiography (OCTA) in eyes with cystoid macular degeneration (CMD) associated with central serous chorioretinopathy (CSCR).

METHODS:

This was a retrospective, observational study of 29 eyes of 25 patients who were previously diagnosed as CSCR with CMD. Baseline patient characteristics, best-corrected visual acuity (BCVA), evidence of CNV network and its pattern on OCTA, distribution of CMD changes and OCT parameters, such as height of the neurosensory retinal detachment (NSD), presence of double layer sign, central macular thickness, were analysed. The eyes were classified into two groups depending on the presence or absence of CNV network on OCTA. BCVA, OCT parameters and CMD distribution were compared in the two groups at baseline using independent t-test.

RESULT:

A total of 13 (44.8 %) eyes had a CNV network, while only 9 out of the 13 eyes had pattern-I CNV. Among the eyes with CNV network (13 eyes), mean height of NSD was of 65.2±22.7 µ, whereas, among the eyes without CNV (16 eyes), it was 134.6±77.4 µ. The difference was statistically significant (p=0.013). There was no statistically significant difference between eye having a CNV and eyes without CNV in terms of other parameters.

CONCLUSION:

A CNV network is seen in a large subset of patients with CMD in CSCR. A shallower subretinal fluid may point towards the presence of an underlying CNV network.

KEYWORDS:

CSCR; OCT angiography; central serous chorioretinopathy; choroidal neovascularisation; cystoid macular degeneration

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Fully automated detection of retinal disorders by image-based deep learning.

Li F[1], Chen H[2], Liu Z[1], Zhang X[1], Wu Z[3].

PURPOSE:

With the aging population and the global diabetes epidemic, the prevalence of age-related macular degeneration (AMD) and diabetic macular edema (DME) diseases which are the leading causes of blindness is further increasing. Intravitreal injections with anti-vascular endothelial growth factor (anti-VEGF) medications are the standard of care for their indications. Optical coherence tomography (OCT), as a noninvasive imaging modality, plays a major part in guiding the administration of anti-VEGF therapy by providing detailed cross-sectional scans of the retina pathology. Fully automating OCT image detection can significantly decrease the tedious clinician labor and obtain a faithful pre-diagnosis from the analysis of the structural elements of the retina. Thereby, we explore the use of deep transfer learning method based on the visual geometry group 16 (VGG-16) network for classifying AMD and DME in OCT images accurately and automatically.

METHOD:

A total of 207,130 retinal OCT images between 2013 and 2017 were selected from retrospective cohorts of 5319 adult patients from the Shiley Eye Institute of the University of California San Diego, the California Retinal Research Foundation, Medical Center Ophthalmology Associates, the Shanghai First People's Hospital, and the Beijing Tongren Eye Center, with 109,312 images (37,456 with choroidal neovascularization, 11,599 with diabetic macular edema, 8867 with drusen, and 51,390 normal) for the experiment. After images preprocessing, 1000 images (250 images from each category) from 633 patients were selected as validation dataset while the rest images from another 4686 patients were used as training dataset. We used deep transfer learning method to fine-tune the VGG-16 network pre-trained on the ImageNet dataset, and evaluated its performance on the validation dataset. Then, prediction accuracy, sensitivity, specificity, and receiver-operating characteristic (ROC) were calculated.

RESULTS:

Experimental results proved that the proposed approach had manifested superior performance in retinal OCT images detection, which achieved a prediction accuracy of 98.6%, with a sensitivity of 97.8%, a specificity of 99.4%, and introduced an area under the ROC curve of 100%.

CONCLUSION:

Deep transfer learning method based on the VGG-16 network shows significant effectiveness on classification of retinal OCT images with a relatively small dataset, which can provide assistant support for medical decision-making. Moreover, the performance of the proposed approach is comparable to that of human experts with significant clinical experience. Thereby, it will find promising applications in an automatic diagnosis and classification of common retinal diseases.

KEYWORDS:

Age-related macular degeneration; Deep transfer learning; Diabetic macular edema; Optical coherence tomography; Visual geometry group 16 network

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Comparison of clinical outcomes of intravitreal ranibizumab and aflibercept treatment for retinopathy of prematurity.

Sukgen EA[1,2], Koçluk Y[3].

PURPOSE:

To compare the results of ranibizumab and aflibercept treatment in infants with treatment-requiring retinopathy of prematurity (ROP) in the posterior zone.

METHODS:

In this single-center, retrospective study, the records of the infants, who were treated between January 2015 and June 2017 in a tertiary center for screening and treatment of ROP, were reviewed. Infants who were administered ranibizumab or aflibercept as initial treatment and completed at least 1 year of corrected age were included. The patients were evaluated in terms of regression, progression or recurrence of the disease, vascularization of the peripheral retina, and ocular complication profile in early or late period.

RESULTS:

Fifty-four eyes of 27 infants who received ranibizumab treatment (ranibizumab group) and 72 eyes of 36 infants who received aflibercept treatment (aflibercept group) were enrolled. The rate of recurrence was 48.1% in ranibizumab group and 13.9% in aflibercept group. The mean recurrence times were at 8.2 ± 0.92 weeks following the injection of ranibizumab and at 14.2 ± 1.03 weeks following the injection of aflibercept. There were significant statistical differences between the groups in the rate of ROP recurrence, the time of recurrence, and the time of vascularization of peripheral retina ($p = 0.001$, $p < 0.001$, $p < 0.001$, respectively).

CONCLUSION:

Although both ranibizumab and aflibercept are effective therapies for the treatment of ROP, more frequent and much earlier recurrences can be seen with ranibizumab treatment. Further studies are needed to obtain ideal options for the treatment of ROP.

KEYWORDS:

Aflibercept; Anti-VEGF; Intravitreal; Ranibizumab; Retinopathy of prematurity

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