Clinical Efficacy of Intravitreal Injection of Dobesilate for Reversing Choroidal Angiogenesis in Age-Related Macular Degeneration

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Abstract: Wet age-related macular degeneration is associated with chronic ischemia and inflammation that upregulate several inflammatory cytokines and growth factors, particularly vascular endothelial growth factor and fibroblast growth factor which promote the growth of choroidal neovascularization. Only with the introduction of drugs that directly inhibit the actions of vascular endothelial growth factor have ophthalmologists been able to offer patients with wet age-related macular degeneration reasonable hope for improvement of vision. However, intravitreal administration of anti-vascular endothelial growth factor drugs could be associated with unexpected ocular and systemic side effects. We present consecutive case series of 64 eyes of 64 patients with wet age-related macular degeneration treated with a single intravitreal injection of Dobesilate, a synthetic fibroblast growth factor inhibitor. The end points were the improvement from baseline visual acuity and normalization of retinal histology at 1 month. Intravitreal Dobesilate injection results in a significant improvement in functional and anatomic outcomes from the first month after injection. There were no cases of treatment-associated complications.

Keywords: Age-related macular degeneration, Intravitreal Dobesilate, Fibroblast growth factor inhibition.

INTRODUCTION

Among the age-related diseases that affect vision, age-related macular degeneration (AMD) is the most frequent cause of blindness in patients older than 60 years [1]. AMD presents two distinct forms: a) a slow progression non-neovascular (dry or avascular) atrophic form, which is characterized by drusen and retinal pigment epithelium (RPE) degeneration followed by photoreceptor degeneration, and eventually neural retinal ganglion cell degradation, and b) a rapidly progressive blinding vascular form. Vascular, wet or exudative AMD is characterized by the growth of new choroid blood vessels (CNV) [2]. Wet AMD results from repeated cycles of shedding, degradation and resynthesis of photoreceptor outer segment, which induce metabolic stress within the outer retina and RPE. The resultant chronic ischemia and inflammation upregulate several inflammatory cytokines and growth factors, particularly vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), which promote the growth of new permeable capillaries from the choriocapillaries into the sub-RPE space (occult, Type I CNV), the subretinal space (classic, Type 2CNV), or the inner retina as a retinal angiomatous proliferation (Type 3CNV). FGF has been implicated as contributing factor in CNV associated to AMD [3, 4].

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Intravitreal injection of VEGF inhibitors is the standard of care for patients with exudative AMD. However, VEGF is essential for normal homeostasis of endothelial cells, RPE and photoreceptors [5-7]. Because intravitreal administration of anti-VEGF drugs could be associated with unexpected ocular and systemic side effects [8], safe and effective therapy for wet AMD is needed. Recently we have reported the beneficial effects of intravitreal Dobesilate, a synthetic inhibitor of FGF and its receptors (FGF/FGFR) in patients with several retinopathies [9-13]. The aim of this study is to evaluate the effectiveness of intravitreal Dobesilate in a larger number of patients with wet AMD.

METHODS

Study Population

In this consecutive study, more than 200 patients with AMD who visited the Clínica Oftalmológica Hospital Pío XII of Madrid (Spain) between January and October 2012, were screened, and 64 eyes from 64 patients with wet age-related macular degeneration were selected for the study. The study was approved by the local institutional review board and informed consent was obtained from every patient for the intravitreal injection. The subjects received information about the off-label use of the drug (Dobesilate) for the study. Baseline data for all patients enrolled in the study are included in Table **1**.

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Table 1: Baseline Data for all Patients who Participated in this Consecutive Observational Study

Sex	
Male	25
Female	39
Age	
Mean	75±7
VA (Snellen chart)	
Mean	0.33±0.02
CNV	
Classic	51
Occult	13
Serous PED	12
Macular SD-OCT thickness (microns)	
Mean	342,97±4.02

CNV: choroidal neovascularization; PED: pigment epithelial detachment; SD-OCT: spectral domain optical coherence tomography. VA: visual acuity. The determination of whether the neovascularization was predominantly classic or occult was made using previously reported criteria [14].

Inclusion criteria in the study included any neovascular lesion type of AMD with evidence of persistent exudation on OCT and total area of subretinal haemorrhage and fibrosis comprising less than 50% of the total lesion. Persistent leakage in OCT was defined as any of the following: intraretinal cysts, subretinal fluid, or serous RPE detachment [15]. Specific exclusion criteria in the study included: a) visual acuity less than 0.20; b) history of vitrectomy surgery, submacular surgery or other surgical intervention for AMD in the studied eye; c) previous subfoveal focal laser photocoagulation in the studied eye; d) diabetic retinopathy in either eyes; e) history of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that might affect interpretation of the results, and f) previous treatment with intravitreal anti-VEGF compounds within 3 months preceding Dobesilate intravitreal injection.

Study Medication and Treatment

The pharmacologic activity of the study drug (Dobesilate) is based in its inhibitory activity of FGF, a protein implicated in the pathogenesis of AMD. Patients received an intravitreal solution of Dobesilate (150µl) in the eye object of the study, under sterile conditions following the International Guidelines for intravitreal injections [16]. Dobesilate was administered as a 12.5% solution of diethylammonium 2.5-dihydroxybenzenesulfonate (etamsylate; Dicynone® Sanofi-Aventis. Paris. France). Antibiotic eye drops were then applied. Thereafter, the ocular fundus was examined to rule out any complications and to check the perfusion of the central artery at the optic disc. Patients returned to the outpatient clinic for routine postinjection follow-up. At day one and day three after injection, an ophthalmic examination, including slit lamp biomicroscopy and pressure measurement, was performed to rule out intraocular inflammation or elevated intraocular pressure (IOP).

Study Assessments

Clinical evaluation included a brief physical examination, an ophthalmic history assessment, measurement of best corrected visual acuity (BCVA) and intraocular pressure, dilated fundus examination and fundus photography. Spectral domain optical coherence tomography (SD-OCT) was used for retinal structural study. OCT based in low-coherence interferometry of light is the critical method for monitoring patients with AMD.

Study Objectives

The overall study objective was to evaluate the safety and effects of Dobesilate in improving function and anatomy of the retina. The primary outcome measure of the study was the change in BCVA. Other secondary outcome measures included the change in mean macular thickness and improvement of outer retinal layers as determined using SD-OCT.

Statistic Analysis

Visual acuity and SD-OCT data at baseline and after one month of treatment were compared by paired *t*'-test. Graphical representations of data are expressed as mean ± standard error of the mean (SEM).

RESULTS

Ocular and Systemic Safety of Study Drug

No ocular or systemic effects related to treatment have been observed in any patient.

Effect of Dobesilate on Visual Acuity

BCVA at baseline was evaluated and compared to BCVA after one month of Dobesilate injection. Figure **1A** shows the mean increase in visual acuity from baseline to one month after treatment. These data demonstrate that Dobesilate significantly improved visual acuity (baseline 0.33±0.02 vs postreatment 0.57±0.03; $p < 0.0001$, paired *t*'test).

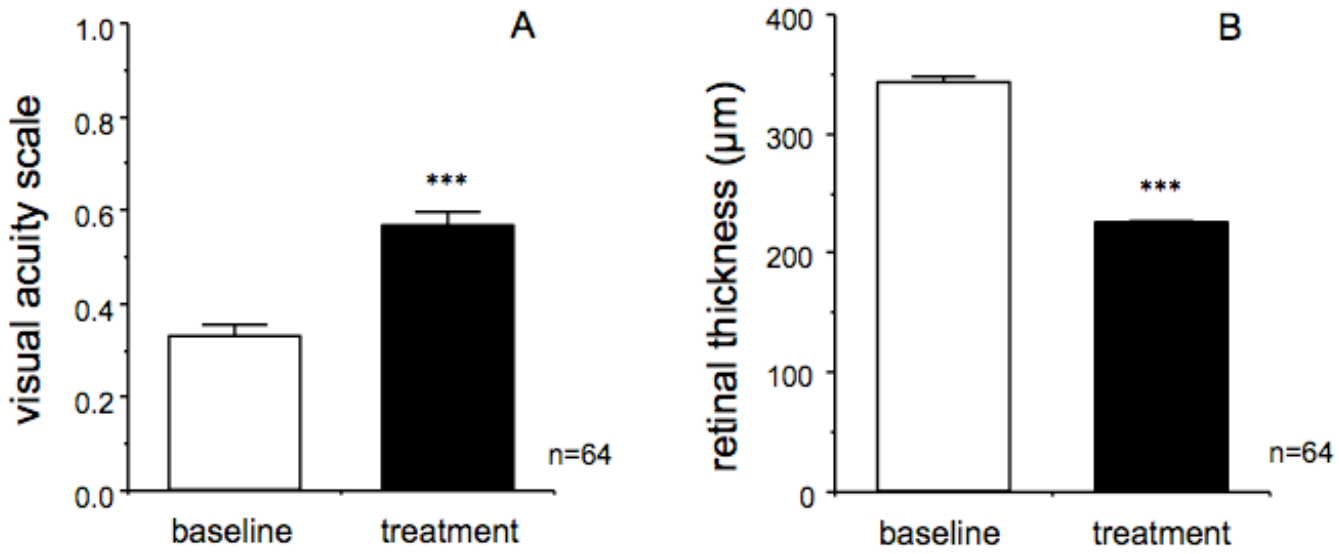

Figure 1: Improvement of visual acuity (**A**) and macular thickening (**B**) after one month of a single injection of intravitreal Dobesilate; n: 64 eyes from 64 patients were enrolled for study treatment. *** p = 0.001, paired t'test.

Effect of Dobesilate on Macular Thickness and Outer Retinal Layers

Macular structural retinal disturbances were evaluated using SD-OCT. At baseline SD-OCT outer retinal structural findings showed in all patients irregular foveal loss with disturbance and focal loss of retinal layers. Mean retinal thickness in the central subfield of the fovea and structural findings of the macula were evaluated using SD-OCT scans at baseline and 1 month thereafter. Mean central subfield retinal thickness decreased after treatment (baseline 342.97±4.02µm vs postreatment 224.81±2.77µm; paired *t*-test, p<0.001), (Figure **1B**). The presumed external limiting membrane, the presumed photoreceptor inner segment-outer segment junction and the presumed interdigitation between photoreceptor outer segments and RPE appeared normalized along the horizontal meridian in SD-OCT scans. Inflammatory microenvironment is responsible for tissue disturbances in wet AMD, mainly due to retinal edema and neovascularization. These disturbances led to increase macular thickness. Available data suggest that retinal structure improvement by intravitreal Dobesilate in AMD patients is related to its anti-inflammatory and anti-angiogenic activities. RPE detachment represents a serious complication in wet AMD and effective treatment of vascularized RPE detachment is still lacking. As an example of effectiveness of Dobesilate, we show a SD-OCT scan of a patient with serous RPE detachment, secondary to wet AMD that improved after treatment with Dobesilate (Figure **2**).

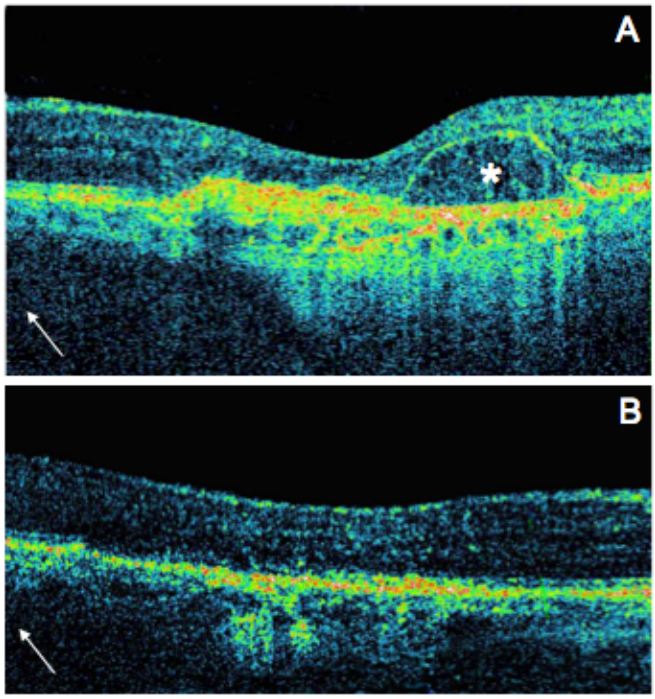

Figure 2: Clinical course and spectral coherence tomography images of a patient with neovascular macular degeneration with serous retinal pigment epithelial detachment (asterisk) (**A**). At baseline, visual acuity was 0.30. The detachment is resolved one month after a single intravitreal injection of Dobesilate (**B**) and visual acuity measures 0.60.

DISCUSSION

Previously we have reported the efficacy of intravitreal Dobesilate in neovascular AMD patients with poor visual acuity (less than 0.20) [12]. In this current study, we have enrolled 64 eyes from 64 patients with neovascular AMD with a visual acuity more than 0.20 (mean and SD: 0.33±0.02). This study

shows that a single administration of intravitreal Dobesilate is associated with visual acuity and retinal anatomy improvements in patients with wet AMD. There were no related ocular and systemic adverse events in any patients treated with intravitreal Dobesilate. The effectiveness and safety data in the current study corroborated those obtained in previous studies with this same drug in other retinopathies [9-13].

Numerous molecular pathways affect different facets of angiogenesis, and may therefore be involved in promoting neovascularization in human patients with AMD [17]. VEGF-signalling is the best characterized of these, and the recent development of anti-VEGF therapy to treat patients with advanced AMD has been proposed and widely used [18]. Current antibody-based therapies target advanced forms of AMD by inhibiting the bioactivity of VEGF. However, anti-VEGF therapy also suppresses vital physiological functions mediated by VEGF like its vasodilatory effect or the stimulated expression of plasminogen activators, resulting in arterial thromboembolic events [19,20]. Ultrastructural analyses showed the reduction of choriocapillaries, endothelial cell fenestration and emerging thrombosis after anti-VEGF therapy [21-23]. Evidence for vasoconstriction of retinal vessels has been also reported, altogether raising concerns about retinal vascular events [24-26]. In addition, anti-VEGF therapy could produce cone photoreceptors destruction [27]. Furthermore, VEGF may be a survival factor for RPE cells under oxidative stress [28]. Thus, anti-VEGF drugs could potentially contribute to the development of RPE loss [29]. Although intravitreal anti-VEGF therapy target pathologic hyperpermeable vessels, there is a latent risk inherent with this therapy for normal photoreceptors and choriocapillaries. Furthermore, the repetitive injection of anti-VEGF agents carries substantial risks for the patient such as retinal detachment, endophthalmitis, cataract formation, ocular hypertension, submacular haemorrhage [30, 31] as well the possibility that intravitreal injected VEGF-inhibitors may diffuse systemically and cause unexpected events [8]. All these findings suggest that therapeutic approaches to blocking VEGF signalling in retinal diseases might have unexpected side effects and that the development of alternative strategies is necessary.

Because it has been reported that other growth factors potentially involved in neovascular AMD may include both acidic and basic isoforms of FGF (FGF1 and FGF2 respectively) [32-34], FGF inhibitors seem may constitute an alternative approach.

Chronic local inflammatory components are associated with the formation of drusen, the age-related extracellular deposits that are often linked with AMD [35]. Inflammatory related molecules, amyloid-beta oligomers deposition, complement activation, recruitment of macrophages and microglial activation are directly or indirectly suggested as key contributors to RPE atrophy, drusen biogenesis and the pathogenesis of AMD [36-45].

Drusen as the hallmark of AMD has been reported to contain nonfibrillar amyloid oligomers [46]. New evidence suggests that amyloid oligomers act as a potential activator of the complement cascade in the context of drusen formation [36]. The inflammatory properties of the oligomers, precursors of the formation of the amyloid fibrils, are widely accepted as a cause of AMD [47]. Today it is widely accepted that amyloid tangles are some sort inert waste that, except for some mechanical alteration of tissue homeostasis, do not show neither toxic nor inflammatory properties [48]. Consequently, improvement of wet AMD symptoms probably do not require removal of the amyloid plaques but merely to counteract the inflammatory features of the amyloid-precursor oligomers, by blunting the activity of one of the main responsible cytokines of the intraocular inflammation. Also, amyloid oligomers in drusen enhanced the release of VEGF and pigment epithelium-derived factor from RPE cells promoting angiogenesis [49], that could lead to accumulation of plasma and occasionally blood in the retina of AMD patients. Inhibition of microglia-mediated chemotactic activity may serve as a strategy to protect retinal cells in environment of chronic inflammation. Furthermore, it has been reported that retinal inflammation was associated with the presence of reactive microglia [50].

FGF in spite of being an angiogenesis promoter [51] is involved also in inflammation [8, 52-57] and seems to play key roles in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases as well in AMD, through activation of microglial cells [58]. Microglial cells are the resident macrophages of the central nervous system that synthesize FGF when they become activated. Since they also express FGF receptors, these growth factors should autocrinally contribute to sustain a chronic neuroinflammation [58-60]. Although the implication of FGF in microglial cell migration from the inner retina to the outer retina, and its activation site in AMD has not been specifically studied, the general antimigratory [61] and anti-inflammatory [62] activities of Dobesilate could explain its efficacy in wet AMD.

FGF as a proinflammatory molecule may participate in the retinal inflammatory process by upregulation of complement receptors [63, 64]. Furthermore, FGF receptor activation promotes macrophage recruitment at the site of inflammation *via* induction of CS3CL1 chemokine [65], the same molecule that appears to be crucial in the drusen microglia and macrophage accumulation observed in AMD [66].

We have spent important efforts in the development of synthetic inhibitors of FGF. These studies led to the identification of a family of small-size chemical inhibitors. The most active of the group was a compound known in pharmacology as Dobesilate, the active principle of Doxium, a drug orally administered for more than 35 years for the treatment of diabetic retinopathy with a good safety profile, but dubious outcomes [67, 68]. Our results may seem in contradiction with those of Haritoglou *et al*., [68]. who did not find statistically significant clinical benefits for treating diabetic retinopathy with Dobesilate. Dobesilate is a quite unstable chemical, clearly not too appropriate for both oral administration and systemic transportation to its biological targets. So, as we discussed in detail in previous articles, the different administration procedures employed in the Haritoglou *et al*. study and in our treatments, respectively, could be the reason of the outcome differences [12]. A detailed discussion about the apparent paradox that constitutes that the administration of a FGF inhibitor does not cause considerable distortion in adult tissues of mesodermal and neuroectodermal origin, being FGF involved in their homeostasis, was also pointed in previous articles [12]. Clear positive results were obtained in other retinal inflammatory conditions [9-13] when Dobesilate, a compound rediscovered as inhibitor of the FGF/FGFR system in our laboratories [61] was administered by intraocular injection. The therapeutic effects observed in this study are consistent with the anti-inflammatory and anti-angiogenic activities of Dobesilate, which have been observed in other disease conditions.

As a future perspective, the evaluation of intravitreal Dobesilate efficacy after longer observation periods should be mandatory. In addition, determination of retinal growth factor signalling in wet AMD and the influence of Dobesilate represent another important issue for future investigational approaches.

In conclusion, we demonstrated that local inhibition of retinal overexpressed FGF with a single intravitreal administration of Dobesilate improved retinal function and anatomy in wet AMD patients. These results, supported by considerable evidence from other studies, suggest that intervention/suppressors of inflammation/angiogenesis related to FGF overexpression should be considered as a potential therapy in the treatment of degenerative retinopathies.

COMPETING INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Conceived and designed the study: PC, GGG, LO. Performed the study LO, CA. Analyzed the data: LO, CA, JA, GGG, PC. PC, GGG, wrote the paper. All authors read and approved the final manuscript.

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REFERENCES

[1] Clemons TE, Milton RC, Klein R, Seddon JM, Ferris FL 3rd; Age-Related Eye Disease Study Research Group Risk factors for the incidence of Advanced Age-Related Macular Degeneration in the Age-Related Eye Disease Study (AREDS) AREDS report no. 19. Ophthalmology 2005; 112: 533-9. http://dx.doi.org/10.1016/j.ophtha.2004.10.047

[2] Ferris FL 3rd, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. Arch Ophthalmol 1984; 102: 1640-2. http://dx.doi.org/10.1001/archopht.1984.01040031330019

[3] Frank RN. Growth factors in age-related macular degeneration: pathogenic and therapeutic implications. Ophthalmic Res 1997; 29: 341-53. http://dx.doi.org/10.1159/000268032

[4] Amin R, Puklin JE, Frank RN. Growth factor localization in choroidal neovascular membranes of age-related macular degeneration. Invest Ophthalmol Vis Sci 1994; 35: 3178-88.

[5] Marneros AG, Fan J, Yokoyama Y, Gerber HP, Ferrara N, Crouch RK, *et al.* Vascular endothelial growth factor expression in the retinal pigment epithelium is essential for choriocapillaris development and visual function. Am J Pathol 2005; 167: 1451-9. http://dx.doi.org/10.1016/S0002-9440(10)61231-X

[6] Brar VS, Sharma RK, Murthy RK, Chalam KV. Bevacizumab neutralizes the protective effect of vascular endothelial growth factor on retinal ganglion cells. Mol Vis. 2010; 16: 1848-53.

[7] Kurihara T, Westenskow PD, Bravo S, Aguilar E, Friedlander M. Targeted deletion of Vegfa in adult mice induces vision loss. J Clin Invest 2012; 122: 4213-7. http://dx.doi.org/10.1172/JCI65157

[8] Stewart MW. The expanding role of vascular endothelial growth factor inhibitors in ophthalmology. Mayo Clin Proc 2012; 87: 77-88. http://dx.doi.org/10.1016/j.mayocp.2011.10.001

[9] Cuevas P, Outeiriño LA, Angulo J, Giménez-Gallego G. Treatment of dry age-related macular degeneration with Dobesilate. BMJ Case Rep 2012; pii: bcr0220125942.

[10] Cuevas P, Outeiriño LA, Angulo J, Giménez-Gallego G. Chronic cystoid macular edema treated with intravitreal Dobesilate. BMJ Case Rep 2012; pii: bcr2012006376.

[11] Cuevas P, Outeiriño La, Azanza C, Angulo J, Giménez-Gallego G. Short-term efficacy of intravitreal Dobesilate in central serous chorioretinopathy. Eur J Med Res 2012; 17: 22. [Epub ahead of print]. http://dx.doi.org/10.1186/2047-783X-17-22

[12] Cuevas P, Outeiriño LA, Azanza C, Giménez-Gallego G. Intravitreal Dobesilate in the treatment of choroidal neovascularization associated with age-related macular degeneration. Report of two cases. BMJ Case Rep 2012; pii: bcr2012006619.

[13] Cuevas P, Outeiriño La, Angulo J, Giménez-Gallego G. Treatment of Stargardt disease with Dobesilate. BMJ Case Rep 2012; pii: bcr2012007128.

[14] Voelker M, Gelisken F, Ziemssen F, Wachtlin J, Grisanti S. Verteporfin photodynamic therapy for extrafoveal choroidal neovascularisation secondary to age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 2005; 243: 1241-6. http://dx.doi.org/10.1007/s00417-005-0021-8

[15] Brown DM, Regillo CD. Anti-VEGF agents in the treatment of neovascular age-related macular degeneration: applying clinical trial results to the treatment of everyday patients. Am J Ophthalmol 2007; 144: 627-37. http://dx.doi.org/10.1016/j.ajo.2007.06.039

[16] Aiello LP, Brucker AJ, Chang S, Cunningham ET Jr, D'Amico DJ, Flynn HW Jr, *et al*. Evolving guidelines for intravitreous injections. Retina 2004; 24(5Suppl): S3-S19.

[17] Bressler SB. Introduction: Understanding the role of angiogenesis and antiangiogenic agents in age-related macular degeneration. Ophthalmology 2009; 116(10 Suppl): S1-7.

[18] Stone EM. A very effective treatment for neovascular macular degeneration. N Engl J Med 2006; 355: 1493-5. http://dx.doi.org/10.1056/NEJMe068191

[19] Eremina V, Jefferson JA, Kowalewska J, Hochster H, Haas M, Weisstuch J, *et al*. VEGF inhibition and renal thrombotic microangiopathy. N Engl J Med 2008; 358: 1129-36. http://dx.doi.org/10.1056/NEJMoa0707330

[20] Prager GW, Breuss JM, Steurer S, Mihaly J, Binder BR. Vascular endothelial growth factor (VEGF) induces rapid prourokinase (pro-uPA) activation on the surface of endothelial cells. Blood 2004; 103: 955-62. http://dx.doi.org/10.1182/blood-2003-07-2214

[21] Peters S, Heiduschka P, Julien S, Ziemssen F, Fietz H, Bartz-Schmidt KU, Tübingen Bevacizumab Study Group, Schraermeyer U. Ultrastructural findings in the primate eye after intravitreal injection of bevacizumab. Am J Ophthalmol 2007; 143: 995-1002. http://dx.doi.org/10.1016/j.ajo.2007.03.007

[22] Meyer T, Robles-Carrillo L, Robson T, Langer F, Desai H, Davila M, *et al*. Bevacizumab immune complexes activate platelets and induce thrombosis in FCGR2A transgenic mice. J Thromb Haemost 2009; 7: 171-81. http://dx.doi.org/10.1111/j.1538-7836.2008.03212.x

[23] Vidinova C, Vidinov N. [The effect of bevacizumab on the ultrastructure of choroidal neovascular membranes in patients with age-related macular degeneration (AMD)]. Klin Monbl Augenheilkd 2009; 226: 491-5. http://dx.doi.org/10.1055/s-0028-1109429

[24] Papadopoulou DN, Mendrinos E, Mangioris G, Donati G, Pournaras CJ. Intravitreal ranibizumab may induce retinal arteriolar vasoconstriction in patients with neovascular age-related macular degeneration. Ophthalmology 2009; 116: 1755-61. http://dx.doi.org/10.1016/j.ophtha.2009.03.017

[25] Sacu S, Pemp B, Weigert G, Matt G, Garhofer G, Pruente C, *et al*. Response of retinal vessels and retrobulbar hemodynamics to intravitreal anti-VEGF treatment in eyes with branch retinal vein occlusion. Invest Ophthalmol Vis Sci 2011; 52: 3046-50. http://dx.doi.org/10.1167/iovs.10-5842

[26] Soliman W, Vinten M, Sander B, Soliman KA, Yehya S, Rahman MS, *et al*. Optical coherence tomography and vessel diameter changes after intravitreal bevacizumab in diabetic macular oedema. Acta Ophthalmol 2008; 86: 365-71. http://dx.doi.org/10.1111/j.1600-0420.2007.01057.x

[27] Quaggin SE. Turning a blind eye to anti-VEGF toxicities. J Clin Invest 2012; 122: 3849-51. http://dx.doi.org/10.1172/JCI65509

[28] Byeon SH, Lee SC, Choi SH, Lee HK, Lee JH, Chu YK. Kwon OW/ Vascular endothelial growth factor as an autocrine survival factor for retinal pigment epithelial cells under oxidative stress *via* the VEGF-R2/PI3K/Akt. Invest Ophthalmol Vis Sci 2010; 51: 1190-7. http://dx.doi.org/10.1167/iovs.09-4144

[29] Ridwan S, Bauer H, Frauenknecht K, von Pein H, Sommer CJ. Distribution of granulocyte-monocyte colony-stimulating factor and its receptor α-subunit in the adult human brain with specific reference to Alzheimer's disease. J Neural Transm 2012; 119: 1389-406. http://dx.doi.org/10.1007/s00702-012-0794-y

[30] Adelman RA, Zheng Q, Mayer HR. Persistent ocular hypertension following intravitreal bevacizumab and ranibizumab injections. J Ocul Pharmacol Ther 2010; 26: 105-10. http://dx.doi.org/10.1089/jop.2009.0076

[31] Krishnan R, Goverdhan S, Lochhead J. Submacular haemorrhage after intravitreal bevacizumab compared with intravitreal ranibizumab in large occult choroidal neovascularization. Clin Exper Ophthalmol 2009; 37: 384-8. http://dx.doi.org/10.1111/j.1442-9071.2009.02043.x

[32] Schultz GS, Grant MB. Neovascular growth factors. Eye (Lond) 1991; 5: 170-80. http://dx.doi.org/10.1038/eye.1991.31

[33] Amin R, Puklin JE, Frank RN. Growth factor localization in choroidal neovascular membranes of age-related macular degeneration. Invest Ophthalmol Vis Sci 1994; 35: 3178-88.

[34] Frank RN, Amin RH, Eliott D, Puklin JE, Abrams GW. Basic fibroblast growth factor and vascular endothelial growth factor are present in epiretinal and choroidal neovascular membranes. Am J Ophthalmol 1996; 122: 393-403.

[35] Johnson LV, Leitner WP, Staples MK, Anderson DH. Complement activation and inflammatory processes in drusen formation and age related macular degeneration. Exp Eye Res 2001; 73: 887-96. http://dx.doi.org/10.1006/exer.2001.1094

[36] Johnson LV, Leitner WP, Rivest AJ, Staples MK, Radeke MJ, Anderson DH. The Alzheimer's A beta -peptide is deposited at sites of complement activation in pathologic deposits associated with aging and age-related macular degeneration. Proc Natl Acad Sci USA 2002; 99: 11830-5. http://dx.doi.org/10.1073/pnas.192203399

[37] Klein RJ, Zeiss C, Chew EY, Tsai JY, Sackler RS, Haynes C, *et al*. Complement factor H polymorphism in age-related macular degeneration. Science 2005; 308: 385-9. http://dx.doi.org/10.1126/science.1109557

[38] Combadière C, Feumi C, Raoul W, Keller N, Rodéro M, Pézard A, *et al*. CX3CR1-dependent subretinal microglia cell accumulation is associated with cardinal features of age-related macular degeneration. J Clin Invest 2007; 117: 2920-8. http://dx.doi.org/10.1172/JCI31692

[39] Lommatzsch A, Hermans P, Müller KD, Bornfeld N, Bird AC, Pauleikhoff D. Are low inflammatory reactions involved in

exudative age-related macular degeneration? Morphological and immunhistochemical analysis of AMD associated with basal deposits. Graefes Arch Clin Exp Ophthalmol 2008; 246: 803-10.
http://dx.doi.org/10.1007/s00417-007-0749-4

[40] Anderson DH, Radeke MJ, Gallo NB, Chapin EA, Johnson PT, Curletti CR, *et al*. The pivotal role of the complement system in aging and age-related macular degeneration: hypothesis re-visited. Prog Retin Eye Res 2010; 29: 95-112.
http://dx.doi.org/10.1016/j.preteyeres.2009.11.003

[41] Tuo J, Grob S, Zhang K, Chan CC. Genetics of immunological and inflammatory components in age-related macular degeneration. Ocul Immunol Inflamm 2012; 20: 27-36.
http://dx.doi.org/10.3109/09273948.2011.628432

[42] de Oliveira Dias JR, Rodrigues EB, Maia M, Magalhães O Jr, Penha FM, Farah ME. Cytokines in neovascular age-related macular degeneration: fundamentals of targeted combination therapy. Br J Ophthalmol 2011; 95: 1631-7.
http://dx.doi.org/10.1136/bjo.2010.186361

[43] Parmeggiani F, Romano MR, Costagliola C, Semeraro F, Incorvaia C, D'Angelo S, *et al*. Mechanism of inflammation in age-related macular degeneration. Mediators Inflamm 2012; 2012: 546786.
http://dx.doi.org/10.1155/2012/546786

[44] Buschini E, Piras A, Nuzzi R, Vercelli A. Age-related macular degeneration and drusen: neurinflammation in the retina. Prog Neurobiol 2011; 95: 14-25.
http://dx.doi.org/10.1016/j.pneurobio.2011.05.011

[45] Raoul W, Feumi C, Keller N, Lavalette S, Houssier M, Behar-Cohen F, *et al*. Lipid-bloated subretinal microglial cells are at the origin of drusen appearance in CX3CR1-deficient mice. Ophthalmic Res 2008; 40: 115-9.
http://dx.doi.org/10.1159/000119860

[46] Luibl V, Isas JM, Kayed R, Glabe CG, Langen R, Chen J. Drusen deposits associated with aging and age-related macular degeneration contain nonfibrillar amyloid oligomers. J Clin Invest 2006; 116: 378-85.
http://dx.doi.org/10.1172/JCI25843

[47] Liu RT, Gao J, Cao S, Sandhu N, Cui JZ, Chou CL, *et al*. Inflammatory mediators induced by amyloid-beta in the retina and RPE *in vivo*: Implications for inflammasome activation in age-related macular degeneration. Invest Ophthalmol Vis Sci 2013; 54: 2225-37.
http://dx.doi.org/10.1167/iovs.12-10849

[48] Yankner BA, Lu T. Amyloid beta-protein toxicity and the pathogenesis of Alzheimer disease. J Biol Chem 2009; 284: 4755-9.
http://dx.doi.org/10.1074/jbc.R800018200

[49] Yoshida T, Ohno-Matsui K, Ichinose S, Sato T, Iwata N, Saido TC, *et al*. The potential role of amyloid beta in the pathogenesis of age-related macular degeneration. J Clin Invest 2005; 115: 2793-800.
http://dx.doi.org/10.1172/JCI24635

[50] Rutar M, Natoli R, Provis JM. Small interfering RNA-mediated suppression of Ccl2 in Müller cells attenuates microglial recruitment and photoreceptor death following retinal degeneration. J Neuroinflammation 2012; 9.
http://dx.doi.org/10.1186/1742-2094-9-221

[51] Giménez-Gallego G, Rodkey J, Bennett C, Rios-Candelore M, DiSalvo J, Thomas K. Brain-derived acidic fibroblast growth factor: complete amino acid sequence and homologies. Science 1985; 230: 1385-8.
http://dx.doi.org/10.1126/science.4071057

[52] Byrd VM, Ballard DW, Miller GG, Thomas JW. Fibroblast growth factor-1 (FGF-1) enhances IL-2 production and nuclear translocation of NF-kappaB in FGF receptor-bearing Jurkat T cells. J Immunol 1999; 162: 5853-9.

[53] Meij JT, Sheikh F, Jimenez SK, Nickerson PW, Kardami E, Cattini PA. Exacerbation of myocardial injury in transgenic mice overexpressing FGF-2 is T cell dependent. Am J Physiol Heart Circ Physiol 2002; 282: H547-55.

[54] Rossini M, Cheunsuchon B, Donnert E, Ma LJ, Thomas JW, Neilson EG, Fogo AB. Immunolocalization of fibroblast growth factor-1 (FGF-1), its receptor (FGFR-1), and fibroblast-specific protein-1 (FSP-1) in inflammatory renal disease. Kidney Int 2005; 68: 2621-8.
http://dx.doi.org/10.1111/j.1523-1755.2005.00734.x

[55] Zittermann SI, Issekutz AC. Basic fibroblast growth factor (bFGF, FGF-2) potentiates leukocyte recruitment to inflammation by enhancing endothelial adhesion molecule expression. Am J Pathol 2006; 168: 835-46.
http://dx.doi.org/10.2353/ajpath.2006.050479

[56] Andrés G, Leali D, Mitola S, Coltrini D, Camozzi M, Corsini M, *et al*. A pro-inflammatory signature mediates FGF2-induced angiogenesis. J Cell Mol Med 2009; 13: 2083-108.
http://dx.doi.org/10.1111/j.1582-4934.2008.00415.x

[57] Strowig T, Henao-Mejia J, Elinav E, Flavell R. Inflammasomes in health and disease. Nature 2012; 481: 278-86.
http://dx.doi.org/10.1038/nature10759

[58] Lee M, Kang Y, Suk K, Schwab C, Yu S, McGeer PL. Acidic fibroblast growth factor (FGF) potentiates glial-mediated neurotoxicity by activating FGFR2 IIIb protein. J Biol Chem 2011; 286: 41230-45.
http://dx.doi.org/10.1074/jbc.M111.270470

[59] Araujo DM, Cotman CW. Basic FGF in astroglial, microglial, and neuronal cultures: characterization of binding sites and modulation of release by lymphokines and trophic factors. J Neurosci 1992; 12: 1668-78.

[60] Liu X, Mashour GA, Webster HF, Kurtz A. Basic FGF and FGF receptor 1 are expressed in microglia during experimental autoimmune encephalomyelitis: temporally distinct expression of midkine and pleiotrophin. Glia 1998; 24: 390-7.
http://dx.doi.org/10.1002/(SICI)1098-1136(199812)24:4<390::AID-GLIA4>3.0.CO;2-1

[61] Fernández IS, Cuevas P, Angulo J, López-Navajas P, Canales-Mayordomo A, González-Corrochano R, *et al*. Gentisic acid, a compound associated with plant defense and a metabolite of aspirin, heads a new class of *in vivo* fibroblast growth factor inhibitors. J Biol Chem 2010; 285: 11714-29.
http://dx.doi.org/10.1074/jbc.M109.064618

[62] Cuevas P, Angulo J, Giménez-Gallego G. Topical treatment of contact dermatitis by pine processionary caterpillar. BMJ Case Rep 2011; 2011.
http://dx.doi.org/10.1136/bcr.06.2011.4351

[63] Takagi S, Takahashi K, Katsura Y, Matsuoka T, Ohsaka A. Basic fibroblast growth factor modulates the surface expression of effector cell molecules and primes respiratory burst activity in human neutrophils. Acta Haematol 2000; 103: 78-83.
http://dx.doi.org/10.1159/000041024

[64] Ohsaka A, Takagi S, Takeda A, Katsura Y, Takahashi K, Matsuoka T. Basic fibroblast growth factor up-regulates the surface expression of complement receptors on human monocytes. Inflamm Res 2001; 50: 270-4.
http://dx.doi.org/10.1007/s000110050753

[65] Reed JR, Stone MD, Beadnell TC, Ryu Y, Griffin TJ, Schwertfeger KL. Fibroblast growth factor receptor 1 activation in mammary tumor cells promotes macrophage recruitment in a CX3CL1-dependent manner. PLoS One 2012; 7: e45877.
http://dx.doi.org/10.1371/journal.pone.0045877

[66] Raoul W, Auvynet C, Camelo S, Guillonneau X, Feumi C, Combadière C, *et al*. CCL2/CCR2 and CX3CL1/CX3CR1 chemokine axes and their possible involvement in age-related macular degeneration. J Neuroinflammation 2010; 7: 87.
http://dx.doi.org/10.1186/1742-2094-7-87

[67] Allain H, Ramelet AA, Polard E, Bentué-Ferrer D. Safety of calcium Dobesilate in chronic venous disease, diabetic retinopathy and haemorrhoids. Drug Saf 2004; 27: 649-60. http://dx.doi.org/10.2165/00002018-200427090-00003

[68] Haritoglou C, Gerss J, Sauerland C, Kampik A, Ulbig MW, CALDIRET study group. Effect of calcium Dobesilate on occurrence of diabetic macular oedema (CALDIRET study): randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2009; 373: 1364-71. http://dx.doi.org/10.1016/S0140-6736(09)60218-X

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