

References - Combined Treatment

1. Schmidt-Erfurth UM, Richard G, Augustin A, Aylward WG, Bandello F, Corcostegui B, Cunha-Vaz J, Gaudric A, Leys A, Schlingemann RO. Guidance for the treatment of neovascular age-related macular degeneration. *Acta Ophthalmol Scand.* 2007;85(5):486-494.
2. Zuluaga MF, Mailhos C, Robinson G, Shima DT, Gurny R, Lange N. Synergies of VEGF inhibition and photodynamic therapy in the treatment of age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2007;48(4):1767-1772.
3. Markabi S. Combination therapy from the regulatory perspective. *Retina.* 2009;29(6Suppl):S12-S14.
4. Karel I. Možnosti a ekonomické ukazatele léčby exsudativní vekem podmíněné makulární degenerace s choroidální neovaskulární membránou. *Cesk Slov Oftalmol.* 2007;63(5):311-319.
5. Smiddy WE. Relative cost of a line of vision in age-related macular degeneration. *Ophthalmology.* 2007;114(5):847-854.
6. Smiddy WE. Economic implications of current age-related macular degeneration treatments. *Ophthalmology.* 2009;116(3):481-487.
7. Dugel PU. Anti-Platelet Derived Growth Factor: Where Do We Stand? Paper presented at: American Academy of Ophthalmology Annual Meeting; November 10, 2012; Chicago.
8. Dugel PU. Anti-PDGF Combination Therapy in Neovascular Age-related Macular Degeneration: Results of a Phase 2b Study. *RetinaToday* March 2013. Available at: <http://retinatoday.com/2013/03/anti-pdgf-combination-therapy-in-neovascular-age-related-macular-degeneration-results-of-a-phase-2b-study/>. Accessed April 30, 2017.
9. Potter MJ, Claudio CC, Szabo SM. A randomised trial of bevacizumab and reduced light dose photodynamic therapy in age-related macular degeneration: the VIA study. *Br J Ophthalmol.* 2010;94(2):174-179.
10. Olk RJ, Peralta E, Gierhart DL, Brown GC, Brown MM. Triple combination therapy and zeaxanthin for the treatment of neovascular age-related macular degeneration: an interventional comparative study and cost-effectiveness analysis. *Int J Retina*

11. Ambati J, Fowler BJ. Mechanisms of age-related macular degeneration. *Neuron*. 2012;75(1):26-39.
12. Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, Toth C, Redford M, Ferris FL 3rd. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration. *Ophthalmology*. 2012;119(7):1388-1398.
13. Silva R, Axer-Siegel R, Eldem B, Guymer R, Kirchhof B, Papp A, Seres A, Gekkieva M, Nieweg A, Pilz S; SECURE Study Group. The SECURE Study: Long-Term Safety of Ranibizumab 0.5 mg in Neovascular Age-related Macular Degeneration. *Ophthalmology*. 2013;120(1):130-139.
14. Singer MA, Awh CC, Sadda S, Freeman WR, Antoszyk AN, Wong P, Tuomi L. HORIZON: an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology*. 2012;119(6):1175-1183.
15. Bhisitkul RB, Rofaghaet S, Boyer DS, Sadda S, Zhang K. Year 7 outcomes for ranibizumab-treated subjects in ANCHOR/MARINA: a multicenter, prospective cohort study. Paper presented at: ARVO Annual Meeting; May 8, 2012; Fort Lauderdale, FL. *Invest Ophthalmol Vis Sci*. 2012; 53(14):3679.
16. Gerhardt H, Golding M, Fruttiger M, Ruhrberg C, Lundkvist A, Abramsson A, Jeltsch M, Mitchell C, Alitalo K, Shima D, Betsholtz C. VEGF guides angiogenic sprouting utilizing endothelial tip cell filopodia. *J Cell Biol*. 2003;161(6):1163-77.
17. De Smet F, Segura I, De Bock K, Hohensinner PJ, Carmeliet P. Mechanisms of Vessel Branching Filopodia on Endothelial Tip Cells Lead the Way. *Arterioscler Thromb Vasc Biol*. 2009;29:639-649.
18. Larrivée B, Freitas C, Suchting S, Brunet I, Eichmann A. Guidance of vascular development: lessons from the nervous system. *Circ Res*. 2009; 104(4):428-41.
19. Wang Y, Wang VM, Chan CC. The role of anti-inflammatory agents in age-related macular degeneration (AMD) treatment. *Eye (Lond)*. 2011 Feb;25(2):127-139.
20. Funatsu H, Yamashita H, Sakata K, Noma H, Mimura T, Suzuki M, Eguchi S, Hori S. Vitreous levels of vascular endothelial growth factor and intercellular adhesion molecule 1 are related to diabetic macular edema. *Ophthalmology*. 2005 May;112(5):806-16.

21. Butler JM, Guthrie SM, Koc M, Afzal A, Caballero S, Brooks HL, Mames RN, Segal MS, Grant MB, Scott EW. SDF-1 is both necessary and sufficient to promote proliferative retinopathy. *J Clin Invest.* 2005 Jan;115(1):86-93.
22. Penfold PL, Wong JG, Gyory J, Billson FA. Effects of triamcinolone acetonide on microglial morphology and quantitative expression of MHC-II in exudative age-related macular degeneration. *Clin Experiment Ophthalmol.* 2001;29(3):188-192.
23. Schmidt-Erfurth U, Hasan T. Mechanisms of action of photodynamic therapy with verteporfin for the treatment of age-related macular degeneration. *Surv Ophthalmol.* 2000 Nov-Dec;45(3):195-214.
24. Schmidt-Erfurth U, Kiss C, Sacu S. The role of choroidal hypoperfusion associated with photodynamic therapy in neovascular age-related macular degeneration and the consequences for combination strategies. *Prog Retin Eye Res.* 2009;28(2):145-154.
25. Tatar O, Adam A, Shinoda K, Stalmans P, Eckardt C, Lüke M, Bartz-Schmidt KU, Grisanti S. Expression of VEGF and PEDF in choroidal neovascular membranes following verteporfin photodynamic therapy. *Am J Ophthalmol.* 2006 Jul;142(1):95-104.
26. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med.* 2006;355(14):1419-1431.
27. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP, Schneider S; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med.* 2006;355(14):1432-1444.
28. QLT announces final results from its radical study evaluating verteporfin PDT (Visudyne®) combination therapy in exudative AMD. Press Release, June 22, 2010. Available at: <https://globenewswire.com/news-release/2010/06/22/423627/194795/en/QLT-Announces-Final-Results-From-Its-RADICAL-Study-Evaluating-Verteporfin-PDT-Visudyne-R-Combination-Therapy-in-Exudative-AMD.html> . Accessed April 30, 2017.
29. Augustin AJ, Puls S, Offermann I. Triple therapy for choroidal neovascularization due to age-related macular degeneration: verteporfin PDT, bevacizumab, and dexamethasone. *Retina.* 2007;27:133-140.
30. Larsen M, Schmidt-Erfurth U, Lanzetta P, Wolf S, Simader C, Tokaji E, Pilz S, Weisberger A; MONT BLANC Study Group. Verteporfin plus ranibizumab for

choroidal neovascularization in age-related macular degeneration: twelve-month MONT BLANC study results. *Ophthalmology*. 2012 May;119(5):992-1000.

31. 12-Months results from Denali Study evaluating verteporfin PDT (Visudyne®) combination therapy QLT news release, June 15, 2010. Available at: <https://globenewswire.com/news-release/2010/06/15/423254/194371/en/12-Month-Results-From-DENALI-Study-Evaluating-verteporfin-PDT-Visudyne-R-Combination-Therapy.html> . Accessed April 30, 2017.
32. Koh A, Lee WK, Chen LJ, Chen SJ, Hashad Y, Kim H, Lai TY, Pilz S, Ruamviboonsuk P, Tokaji E, Weisberger A, Lim TH. THE EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy. *Retina*. 2012 Sep;32(8):1453-64.
33. Triple Therapy - PDT Plus IVD and Intravitreal Ranibizumab Versus Lucentis Monotherapy to Treat Age-Related Macular Degeneration (PDEX). <https://clinicaltrials.gov/ct2/show/NCT00390208?term=NCT00390208&rank=1> . Accessed April 30, 2017.
34. Ranchod TM, Ray SK, Daniels SA, Leong CJ, Ting TD, Verne AZ. LUCEDEX: A Prospective Study Comparing Ranibizumab plus Dexamethasone Combination Therapy Versus Ranibizumab Monotherapy for Neovascular Age-Related Macular Degeneration. *Retina*. 2013 Sep;33(8):1600-4.
35. Buchholz P, Buchholz A, Kirchhof J, Augustin A. Combination Therapies for AMD: Latest Developments. *Retinal Physician*. 2010 Mar. Available at: <http://www.retinalphysician.com/issues/2010/march-2010/combination-therapies-for-wet-amd-latest-developm> . Accessed April 30, 2017.
36. Sheidow T, Kertes PJ et al. The role of combination therapy in AMD: the Canadian study of Avastin and Visudyne in exudative AMD (CAVE STUDY), paper presented at Retina Congress 2009;sept 30-Oct. 4, 2009; New York, NY.
37. Loewenstein A, Kuppermann BD, Weinberger D, Goldstein M, Singer M, Liu CC, Lou J, Li XY, Whitcup SM. Safety and Efficacy of OZURDEXTM (Dexamethasone Intravitreal Implant) as Adjunctive Therapy to Lucentis® in Patients With Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD). *Invest Ophthalmol Vis Sci*. 2010; 51(13):1255.
38. Flaxel C, Schain MB, Hamon SC, Francis PJ. Prospective randomized controlled trial of combination ranibizumab (Lucentis) and bromfenac (Xibrom) for neovascular age-related macular degeneration: a pilot study. *Retina*. 2012 Mar;32(3):417-23.

39. Dugel P. Angiogenesis, Exudation, and Degeneration 2012 Meeting in Miami on Februay 4th. The 2-year results of the CABERNET study.
40. Söderberg AC, Algvere PV, Hengstler JC, Söderberg P, Seregard S, Kvanta A. Combination therapy with low-dose transpupillary thermotherapy and intravitreal ranibizumab for neovascular age-related macular degeneration: a 24-month prospectiverandomised clinical study. *Br J Ophthalmol.* 2012;96(5):714-8
41. Koch F, Scholtz S, Singh P, Koss MJ. Kombinierte intravitreale Therapie zur Behandlung der altersbedingten Makuladegeneration. *Klin Monbl Augenheilkd.* 2008;225(12):1003-1008.
42. Jo N, Mailhos C, Ju M, Cheung E, Nishijima K, Robinson GS, Adamis AP, and Shima DT. Inhibition of platelet-derived growth factor B signaling enhances the efficacy of anti-vascular endothelial growth factor therapy in multiple models of ocular neovascularization. *Am J Pathol.* 2006;168(6):2036-2053.
43. Ciulla TA, Jaffe GJ, Patel S. Assessment of Retinal Pigment Epithelium (RPE) Atrophy in a Phase 2b Study of a Platelet Derived Growth Factor inhibitor (Fovista®), in combination with a Vascular Endothelial Growth Factor inhibitor (Ranibizumab) for Neovascular Age-Related Macular Degeneration (NAMD). *Invest Ophthalmol Vis Sci.* 2016; 57(12):4418.
44. Stahl A, Paschek L, Martin G, Feltgen N, Hansen LL, Agostini HT. Combinatory inhibition of VEGF and FGF2 is superior to solitary VEGF inhibition in an in vitro model of RPE-induced angiogenesis. *Graefes Arch Clin Exp Ophthalmol.* 2009;247(6):767-773.
45. Bhutto IA, McLeod DS, Hasegawa T, Kim SY, Merges C, Tong P, Lutty GA. Pigment epithelium-derived factor (PEDF) and vascular endothelial growth factor (VEGF) in aged human choroid and eyes with age-related macular degeneration. *Exp Eye Res.* 2006; 82(1):99-110.
46. Campochiaro PA, Nguyen QD, Shah SM, Klein ML, Holz E, Frank RN, Saperstein DA, Gupta A, Stout JT, Macko J, DiBartolomeo R, Wei LL. Adenoviral vector-delivered pigment epithelium-derived factor for neovascular age-related macular degeneration: results of a phase I clinical trial. *Hum Gene Ther.* 2006;17(2):167-176.
47. Diago T, Pulido JS, Molina JR, Collett LC, Link TP, Ryan EH Jr. Ranibizumab combined with low-dose sorafenib for exudative age-related macular degeneration. *Mayo Clin Proc.* 2008;83(2):231-234.

48. Chaudhry N. Oral VEGF receptor/PDGF receptor inhibitor X-82. Paper presented at: the American Academy of Ophthalmology Annual Meeting; November 14-17, 2015; Las Vegas, NV.
49. Jackson T. A phase 1 study of oral tyrosine kinase inhibitor (X-82) in previously treated wet age-related macular degeneration. Paper presented at: 15th Annual Euretina Congress; September 17-20, 2015; Nice, France.
50. Jackson T. A phase 1 study of oral tyrosine kinase inhibitor (X-82) in previously treated wet age-related macular degeneration. Paper presented at: 15th Annual Euretina Congress; September 17-20, 2015; Nice, France.
51. X-82 to Treat Age-related Macular Degeneration.
<https://clinicaltrials.gov/ct2/show/NCT02348359>. Accessed November 28, 2016.
52. A Safety and Efficacy Study of DE-120 Injectable Solution for Age-related Macular Degeneration (VAPOR1). <https://clinicaltrials.gov/ct2/show/NCT02401945>. Accessed November 28, 2016.
53. Hanahan D. Signaling vascular morphogenesis and maintenance. *Science*. 1997;277:48-50.
54. Maisonpierre PC, Suri C, Jones PF, Bartunkova S, Wiegand SJ, Radziejewski C, Compton D, McClain J, Aldrich TH, Papadopoulos N, Daly TJ, Davis S, Sato TN, Yancopoulos GD. Angiopoietin-2, a natural antagonist for Tie2 that disrupts in vivo angiogenesis. *Science*. 1997;277:55-60.
55. Bergers G, Song S. The role of pericytes in blood-vessel formation and maintenance. *Neuro Oncol*. 2005 Oct;7(4):452-464.
56. Slakter JS, Ciulla TA, et al. Final Results from a Phase 2 study of Squalamine Lactate Ophthalmic Solution 0.2% (OHR-102) in the treatment of neovascular age-related macular degeneration (AMD). *Invest Ophthalmol Vis Sci*. 2015;56(7):4805.
57. Brown D, Ingerman A, Shearn SP, Slakter JS. CNV lesion characteristics as a predictor of visual outcome in wet AMD patients receiving combination therapy of intravitreal anti-VEGF therapy and topical Squalamine lactate ophthalmic solution. *Invest Ophthalmol Vis Sci*. 2016; 57(12):4419.
58. A Phase 2 Study (EMERGE) Evaluating Repeated Intravitreal Administration of ICON-1 in Patients With Choroidal Neovascularization (CNV) Secondary to Age-related Macular Degeneration (AMD). <https://clinicaltrials.gov/ct2/show/NCT02358889>. Accessed November 28, 2016.

59. Christmas NJ. A Phase 2 Study (EMERGE) Evaluating Repeated Intravitreal Administration of ICON-1 in Patients With Choroidal Neovascularization (CNV) Secondary to Age-related Macular Degeneration (AMD). *Invest Ophthalmol Vis Sci.* 2016; 57(12):4434.
60. Kaiser PK. Strategies for inhibiting vascular endothelial growth factor. *Retina.* 2009;29(6Suppl):S15-S17.
61. Geltzer A, Turalba A, Vedula SS. Surgical implantation of steroids with antiangiogenic characteristics for treating neovascular age-related macular degeneration. *Cochrane Database Syst Rev.* 2007 Oct;(4):CD005022.

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