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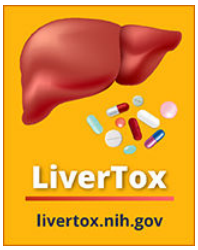

Macular Degeneration Agents

Updated: May 15, 2018.

OVERVIEW

Introduction

Macular degeneration is an age-related disease of the retina marked by progressive loss of central visual acuity that is usually due to neovascularization in the subretinal space. The vascularization is dependent, at least in part, on action of vascular endothelial growth factor (VEGF). Recently, several agents that specifically target VEGF have been developed and shown to slow the progression of neovascular or "wet" macular degeneration when given as intravitreal injections. These agents include monoclonal antibodies to VEGF (bevacizumab, ranibizumab), aptamers (small oligonucleotides that bind to VEGF: pegaptanib), and fusion VEGF receptor proteins that act as a decoy of the circulating growth factor (aflibercept). All four agents are given as intravitreal injections every 4 to 8 weeks. Most adverse events of these agents are ocular and relate to their local injection. Systemic exposure is limited and ex-ocular adverse events are rare. Some of the agents have been implicated in cardiovascular or cerebrovascular thromoembolic events but these are uncommon. None of the drugs for macular degeneration have been implicated in causing hepatotoxicity, either serum enzyme elevations during treatment or clinically apparent liver injury, at least when administered by intravitreal injection. The lack of hepatotoxicity is probably due largely to the lack of significant systemic absorption and exposure. When given intravenously as therapy of neoplastic conditions, several have been linked to instances of liver injury.

Bevacizumab

Bevacizumab is a humanized monoclonal antibody to VEGF that is approved for use intravenously for metastatic colon, renal cell and non-small cell lung cancer and for brain glioblastoma. Bevacizumab has been used off label to treat macular degeneration and, in controlled trials, was as effective as ranibizumab in improving or stabilizing vision in persons with age-related neovascular (wet) macular degeneration. Bevacizumab is available in vials of 100 and 400 mg in a concentration of 25 mg/mL under the brand name Avastin. The dosage used off label for macular degeneration is 1.25 mg (0.05 mL) once monthly by intravitreal injection.

Ranibizumab

Ranibizumab is a recombinant humanized monoclonal antibody fragment (Fab) to VEGF (similar to bevacizumab). It was approved for use in neovascular (wet) age-related macular degeneration, macular edema following retinal vein occlusion and diabetic macular edema in 2006. Ranibizumab is available in single use vials of 0.5 mg/0.05 mL under the brand name Lucentis. The recommended dose is 0.5 mg once monthly by intravitreal injection.

Pegaptanib

Pegaptanib is a pegylated aptamer, a modified oligonucleotide which binds with and inactivates extracellular VEGF. It was approved for use in neovascular (wet) age-related macular degeneration in 2004. Pegaptanib is available in single use glass syringe of 0.3 mg/90 µL under the brand name Macugen. The recommended dose is 0.3 mg by intravitreal injection once every six weeks.

Aflibercept

Aflibercept is a unique fusion protein consisting of VEGF receptors 1 and 2 fused to the Fc portion of IgG that acts as a decoy receptor competing for the binding of endogenous VEGF. It was approved for use in neovascular age related macular degeneration and for macular edema after central retinal vein occlusion in 2011. Indications have been broadened and aflibercept is also approved for use in diabeteic macular edema and retinopathy. Aflibercept is available in single use vials of 2 mg/0.05 mL under the brand name Eylea. The initial recommended dose is 2 mg once monthly by intravitreal injection.

Aflibercept is also available in a form for parenteral administration (ziv-aflibercept: Zaltrap) which is approved for use in combination with other antineoplastic agents (fluorouracil, leucovorin and irinotecan: FOLFIRI) for metastatic colon cancer. Administration of FOLFIRI is associated with fairly high rates of serum ALT and AST elevations and with occasional liver related serious adverse events. The addition of ziv-aflibercept to FOLFIRI has not been associated with higher rates of either serum enzyme elevations or clinically apparent liver injury, but experience with this combination has been limited.

Likelihood score: E (all four agents are unlikely causes of clinically apparent liver injury).

Drug Class: Macular Degeneration Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Bevacizumab – Avastin®

Ranibizumab – Lucentis®

Pegaptanib – Macugen®

Aflibercept – Eylea®

DRUG CLASS

Macular Degeneration Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Bevacizumab	216974-75-3	Monoclonal Antibody	Not Available
Ranibizumab	347396-82-1	Monoclonal Antibody	Not Available

Table continued from previous page.

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Pegaptanib	222716-86-1	Ribonucleic Acid Aptamer	Not Available
Aflibercept	862111-32-8	Aberrant Angiogenesis Inhibitor	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 15 May 2018

Henderer JD, Rapuano CJ. Agents used to treat retinal neovascularization and macular degeneration. Ocular pharmacology. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-54.

(Textbook of pharmacology and therapeutics).

Cunningham ET Jr, Adamis AP, Altaweel M, Aiello LP, Bressler NM, D'Amico DJ, Goldbaum M, et al.; Macugen Diabetic Retinopathy Study Group. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology 2005; 112: 1747-57. PubMed PMID: 16154196.

(Among 172 patients with diabetic macular edema treated with intraocular pegaptanib or sham injections for 20 weeks, visual acuity was more likely to be improved or stable with pegaptanib, and adverse events were uncommon and largely due to the intravitreal injections).

Pegaptanib sodium (Macugen) for macular degeneration. Med Lett Drugs Ther 2005; 47 (1212): 55-6. PubMed PMID: 15988400.

(Concise review of the mechanism of action, efficacy, safety and cost of pegaptanib shortly after its approval in the US mentions that intraocular pegaptanib and bevacizumab may be associated with a higher rate of cardiovascular and cerebrovascular thromboses due to their inhibitory effects on angiogenesis).

Ranibizumab (Lucentis) for macular degeneration. Med Lett Drugs Ther 2006; 48 (1246): 85-6. PubMed PMID: 17051134.

(Concise review of the mechanism of action, efficacy, safety and costs of ranibizumab shortly after its approval for use in the US, along with comparison to other agents used in macular degeneration including bevacizumab and pegaptanib).

de Jong PT. Age-related macular degeneration. N Engl J Med 2006; 355: 1474-85. PubMed PMID: 17021323.

(Review of the clinical features, course and outcome, pathogenesis and risk factors for age related macular degeneration).

Avery RL, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, Giust MJ. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology. 2006; 113: 363-72. e5. PubMed PMID: 16458968.

(Among 79 patients with age related macular degeneration treated with bevacizumab by intravitreal injection monthly, there were no significant systemic side effects).

VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group, D'Amico DJ, Masonson HN, Patel M, Adamis AP, Cunningham ET Jr, Guyer DR, Katz B. Pegaptanib sodium for neovascular age-related macular degeneration: two-year safety results of the two prospective, multicenter, controlled clinical trials. Ophthalmology 2006; 113: 992-1001. PubMed PMID: 16647134.

(Among 147 patients with age related macular degeneration treated with varying doses of pegaptanib for 54 weeks, ocular adverse events were common, but usually mild-to-moderate, while nonocular events were uncommon and there was no evidence of systemic toxicity).

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: 1419-31. PubMed PMID: 17021318.

(Among 716 patients with neovascular age related macular degeneration, average visual acuity at 24 months improved in ranibizumab treated subjects, but decreased in controls; no mention of ALT changes or hepatotoxicity).

Kourlas H, Abrams P. Ranibizumab for the treatment of neovascular age-related macular degeneration: a review. Clin Ther 2007; 29: 1850-61. PubMed PMID: 18035187.

(Review and summary of 3 clinical trials of ranibizumab for macular degeneration mentions that nonocular adverse events were uncommon and similar in frequency in standard of care and ranibizumab treated subjects; no mention of ALT elevations or hepatotoxicity).

Macugen AMD Study Group, Apte RS, Modi M, Masonson H, Patel M, Whitfield L, Adamis AP. Pegaptanib 1-year systemic safety results from a safety-pharmacokinetic trial in patients with neovascular age-related macular degeneration. Ophthalmology 2007; 114: 1702-12. PubMed PMID: 17509689.

(Among 147 patients with neovascular age-related macular degeneration from two clinical studies receiving varying high doses of pegaptanib by intravitreal injection for up to 54 weeks, nonocular adverse events were uncommon and there was no evidence of systemic toxicity).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, none were attributed to agents used to treat macular degeneration).

Do DV, Nguyen QD, Shah SM, Browning DJ, Haller JA, Chu K, Yang K, et al. An exploratory study of the safety, tolerability and bioactivity of a single intravitreal injection of vascular endothelial growth factor Trap-Eye in patients with diabetic macular oedema. Br J Ophthalmol 2009; 93: 144-9. PubMed PMID: 19174400.

(Pilot study of a single intravitreal injection of aflibercept in 5 patients with diabetes and macular degeneration showed clinical improvements in 4 patients and no systemic effects).

Wroblewski JJ, Wells JA 3rd, Adamis AP, Buggage RR, Cunningham ET Jr, Goldbaum M, Guyer DR, et al.; Pegaptanib in Central Retinal Vein Occlusion Study Group. Pegaptanib sodium for macular edema secondary to central retinal vein occlusion. Arch Ophthalmol 2009; 127: 374-80. PubMed PMID: 19365011.

(Among 98 patients with macular edema from central retinal vein occlusion treated with pegaptanib or sham intravitreal injections, visual acuity tended to be better among the pegaptanib treated patients and there was "no evidence of an increased risk of systemic adverse events").

Tufail A, Patel PJ, Egan C, Hykin P, da Cruz L, Gregor Z, Dowler J, et al.; ABC Trial Investigators. Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study. BMJ 2010; 340: c2459. PubMed PMID: 20538634.

(Among 131 patients with neovascular macular degeneration, improved vision at one year occurred in 32% of bevacizumab vs 3% of standard therapy treated subjects and side effects were largely related to the intravitreal injections).

Sultan MB, Zhou D, Loftus J, Dombi T, Ice KS; Macugen 1013 Study Group. A phase 2/3, multicenter, randomized, double-masked, 2-year trial of pegaptanib sodium for the treatment of diabetic macular edema. Ophthalmology 2011; 118 1107-18. PubMed PMID: 21529957.

(Among 282 patients with diabetic macular edema treated with pegaptanib or placebo for up to 2 years, there were no differences in nonocular adverse events between the two groups).

CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011; 364: 1897-908. PubMed PMID: 21526923.

(Among 1208 patients with neovascular age related macular degeneration, ranibizumab and bevacizumab had similar effects on visual acuity and systemic adverse effects were uncommon; no mention of ALT elevations or hepatotoxicity).

Comparison of Age-related Macular Degeneration Treatments Trials(CATT) Research Group, Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, Toth C, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 2012; 119: 1388-98. PubMed PMID: 22555112.

(Among 1107 patients who were followed during year 2 of ranibizumab or bevacizumab therapy for neovascular age related macular degeneration, systemic adverse events could not be definitely linked to the intravitreal injections of anti-VEGF therapy; no mention of ALT elevations or hepatotoxicity).

Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, Kirchhof B, et al.; VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology 2012; 119: 2537-48. PubMed PMID: 23084240.

(Among 2419 patients with neovascular age related macular degeneration treated with intravitreal injections of aflibercept or ranibizumab, response rates were similar with the two drugs and the incidence of systemic adverse events was similar; no mention of ALT elevations or hepatotoxicity).

Tang PA, Cohen SJ, Kollmannsberger C, Bjarnason G, Virik K, MacKenzie MJ, Lourenco L, et al. Phase II clinical and pharmacokinetic study of aflibercept in patients with previously treated metastatic colorectal cancer. Clin Cancer Res 2012; 18: 6023-31. PubMed PMID: 22977191.

(Among 75 patients with metastatic colorectal cancer treated with aflibercept, few had an objective response and adverse events included fatigue, hypertension and proteinuria; no mention of ALT elevations or hepatotoxicity).

Ho AC, Scott IU, Kim SJ, Brown GC, Brown MM, Ip MS, Recchia FM. Anti-vascular endothelial growth factor pharmacotherapy for diabetic macular edema: a report by the American Academy of Ophthalmology. Ophthalmology 2012; 119: 2179-88. PubMed PMID: 22917890.

(Systematic review of safety and efficacy of anti-VEGF therapies of diabetic macular edema mentions that there is no greater risk of systemic adverse events from intravitreal infusions of anti-VEGF therapies including bevacizumab, ranibizumab, pegaptanib and aflibercept).

Aflibercept (eylea) for age-related macular degeneration. Med Lett Drugs Ther 2012; 54 (1383): 9-10. PubMed PMID: 22354219.

(Concise review of the mechanism of action, efficacy, safety and costs of aflibercept shortly after its approval in the US mentions that adverse events were virtually identical to ranibizumab and largely ophthalmologic).

Gotlieb WH, Amant F, Advani S, Goswami C, Hirte H, Provencher D, Somani N, et al. Intravenous aflibercept for treatment of recurrent symptomatic malignant ascites in patients with advanced ovarian cancer: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Oncol 2012; 13: 154-62. PubMed PMID: 22192729.

(Among 55 women with advanced ovarian cancer and ascites treated with intravenous aflibercept or placebo, side effects included fatigue and dehydration; ALT elevations occurred in 10% of aflibercept, but no placebo recipient and one patient developed both ALT and bilirubin elevations during first 30 days of therapy).

Mackay HJ, Buckanovich RJ, Hirte H, Correa R, Hoskins P, Biagi J, Martin LP, et al. A phase II study single agent of aflibercept (VEGF Trap) in patients with recurrent or metastatic gynecologic carcinosarcomas and uterine leiomyosarcoma. A trial of the Princess Margaret Hospital, Chicago and California Cancer Phase II Consortia. Gynecol Oncol 2012; 125: 136-40. PubMed PMID: 22138373.

(Among 63 women with gynecologic soft tissue sarcomas who were treated with intravenous aflibercept, no objective responses occurred and side effects were common; 6 [10%] patients had mild Alk P elevations, but there was no mention of ALT elevations or hepatotoxicity).

Heier JS, Clark WL, Boyer DS, Brown DM, Vitti R, Berliner AJ, Kazmi H, et al. Intravitreal aflibercept injection for macular edema due to central retinal vein occlusion: two-year results from the COPERNICUS Study. Ophthalmology 2014; 121: 1414-20. e1. PubMed PMID: 24679444.

(Among 188 patients with macular edema due to central retinal vein occlusion for up to 2 years, improvement in visual acuity was greater with aflibercept than sham intravitreal injections, and rates of nonocular adverse events were similar; ALT elevations and hepatotoxicity were not mentioned).

Semeraro F, Morescalchi F, Duse S, Gambicorti E, Romano MR, Costagliola C. Systemic thromboembolic adverse events in patients treated with intravitreal anti-VEGF drugs for neovascular age-related macular degeneration: an overview. Expert Opin Drug Saf 2014; 13: 785-802. PubMed PMID: 24809388.

(Review of the evidence for systemic absorption of anti-VEGF agents used in ophthalmology and their possible adverse effects, focusing upon thromboembolic cardiovascular and cerebrovascular events).

Perkins SL, Cole SW. Ziv-aflibercept (Zaltrap) for the treatment of metastatic colorectal cancer. Ann Pharmacother 2014; 48: 93-8. PubMed PMID: 24259608.

(Review of efficacy and safety of aflibercept as therapy of metastatic colorectal cancer does not include ALT elevations or hepatotoxicity in list of adverse events occurring in more than 10% of patients).

Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, Brown DM, Chong V, Nguyen QD, Ho AC, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. Ophthalmology 2014; 121: 193-201. PubMed PMID: 24084500.

(Among 2457 patients with neovascular age related macular degeneration, improvement and stability of visual acuity was similar with intravitreal injections of aflibercept and ranibizumab, and nonocular adverse events were similar).

Korobelnik JF, Holz FG, Roider J, Ogura Y, Simader C, Schmidt-Erfurth U, Lorenz K, et al.; GALILEO Study Group. Intravitreal aflibercept injection for macular edema resulting from central retinal vein occlusion: one-year results of the phase 3 GALILEO study. Ophthalmology 2014; 121: 202-8. PubMed PMID: 24084497.

(Among 177 patients with macular edema due to central retinal vein occlusion, visual acuity improved with aflibercept and nonocular adverse events were similar in the sham and aflibercept treated subjects; no mention of hepatotoxicity).

Chang AA, Broadhead GK, Hong T, Joachim N, Syed A, Schlub TE, Toth L, et al. Intravitreal aflibercept for treatment-resistant neovascular age-related macular degeneration: 12-month safety and eficacy outcomes. Ophthalmic Res 2015; 55: 84-90. PubMed PMID: 26637166.

(Among 49 patients with macular degeneration treated with intra-vitreal aflibercept every 1 to 2 months for 1 year, there were 22 serious adverse events, but none were liver related).

Brown DM, Schmidt-Erfurth U, Do DV, Holz FG, Boyer DS, Midena E, Heier JS, et al. intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID Studies. Ophthalmology 2015; 122: 2044-52. PubMed PMID: 26198808.

(Among 872 patients treated with intra-vitreal aflibercept every 4 or 8 weeks or with laser photocoagulation for up to 2 years, adverse event rates including myocardial infarction and stroke were similar in all three groups; no mention of liver related adverse events).

Scott LJ, Chakravarthy U, Reeves BC, Rogers CA. Systemic safety of anti-VEGF drugs: a commentary. Expert Opin Drug Saf 2015; 14: 379-88. PubMed PMID: 25489638.

(Review of trials of different anti-VEGF agents for macular degeneration found no increase in rates of all-cause mortality as well as arterio-thrombotic and gastrointestinal serious adverse events; no specific mention of hepatotoxicity).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to drugs used to treat macular degeneration).

Ziemssen F, Sobolewska B, Deissler H, Deissler H. Safety of monoclonal antibodies and related therapeutic proteins for the treatment of neovascular macular degeneration: addressing outstanding issues. Expert Opin Drug Saf 2016; 15: 75-87. PubMed PMID: 26568279.

(Review of safety of monoclonal anti-VEGF therapy of macular degeneration states that systemic levels and effects are detectable after intra-vitreal injections and that extraocular serious adverse effects may include cerebrovascular events; no mention of hepatotoxicity).

Avery RL, Gordon GM. Systemic Safety of prolonged monthly anti-vascular endothelial growth factor therapy for diabetic macular edema: a systematic review and meta-analysis. JAMA Ophthalmol 2016; 134: 21-9. PubMed PMID: 26513684.

(Metaanalysis of 4 controlled trials of long term intra-vitreal anti-VEGF therapy of diabetic macular edema found increased risk for arterio-thrombotic events and death, occurring in 30 of 791 [4%] treated vs 7 of 537 [1.3%] controls; no mention of hepatotoxicity).

Kitchens JW, Do DV, Boyer DS, Thompson D, Gibson A, Saroj N, Vitti R, et al. Comprehensive review of ocular and systemic safety events with intravitreal aflibercept injection in randomized controlled trials. Ophthalmology 2016; 123: 1511-20. PubMed PMID: 27084563.

(Review of safety outcomes from more than 4000 patients enrolled in 10 controlled trials of intravitreal aflibercept therapy of macular degeneration, found no increase in systemic adverse events with aflibercept treatment compared to controls).

Mansour AM, Ashraf M, Dedhia CJ, Charbaji A, Souka AAR, Chhablani J. Long-term safety and efficacy of ziv-aflibercept in retinal diseases. Br J Ophthalmol 2017; 101: 1374-6. PubMed PMID: 28270485.

(Among 55 patients with macular degeneration treated off-label with ziv-aflibercept by intravitreal injection, visual acuity improved and "systemic adverse effects were not registered").

Bevacizumab-Ranibizumab International Trials Group. Serious adverse events with bevacizumab or ranibizumab for age-related macular degeneration: meta-analysis of individual patient data. Ophthalmol Retina 2017; 1: 375-81. PubMed PMID: 29038796.

(Independent review of pooled data from 3052 patients participating in 5 large randomized controlled trials comparing bevacizumab and ranibizumab as therapy of macular degeneration, found rates of systemic serious adverse events to be the same with the two anti-VEGF monoclonal antibodies).

Thulliez M, Angoulvant D, Pisella PJ, Bejan-Angoulvant T. Overview of systematic reviews and meta-analyses on systemic adverse events associated with intravitreal anti-vascular endothelial growth factor medication use. JAMA Ophthalmol 2018; 136 (5): 557-66. PubMed PMID: 29566105.

(Review of 21 systematic reviews suggested that intravitreal therapy of macular degeneration is not associated with a higher rate of systemic adverse events).