引文格式:肖昂,周琼. Aflibercept 治疗湿性 AMD 和黄斑水肿的相关研究现状[J]. 眼科新进展,2014,34(6):598-600. doi:10.13389/j.cnki.rao.2014.0165

【文献综述】

Aflibercept 治疗湿性 AMD 和黄斑水肿的相关研究现状

肖昂 周琼

作者简介:肖昂,男,1986 年 12 月出生,湖北咸宁人,硕士。主要研究方向为眼底病。联系电话:15870647395;E-mail:xiao2818161@126.com

About XIAO Ang: Male, born in December, 1986. Master degree. Tel: 15870647395; E-mail: xiao2818161@126.com

收稿日期:2013-04-26
修回日期:2013-06-03
本文编辑:方红玲

作者单位:330006 江西省南昌市,南昌大学研究生院医学部第一临床(肖昂);南昌大学第一附属医院眼科(周琼)
通讯作者:周琼,E-mail:qiong-ms@126.com
Received date: Apr 26, 2013
Accepted date: Jun 3, 2013
From the *Graduate School of Medicine in Nachang University*, *First Clinical* (XIAO Ang); *Department of Ophthalmology*, *the First Affiliated Hospital of Nanchang University* (ZHOU Qiong), *Nanchang* 330006, *Jiangxi Province*, *China*
Responsible author: ZHOU Qiong, E-mail: qiong-ms@126.com

Related studies on Aflibercept for wet AMD and macular edema

XIAO Ang, ZHOU Qiong

【Key words】 Aflibercept; wet age-related macular degeneration; macular edema

【Abstract】 Aflibercept is a soluble induced receptor, which can be combined with vascular endothelial growth factor-A and placental growth factor to block the binding and activation of these homologous vascular endothelial growth factor receptor. It also inhibits retinal angiogenesis and leads to degradation of the new blood vessels. As a new anti-vascular drug in ophthalmology, Aflibercept had been gained clinical basis of pharmacokinetics, safety and tolerability, used for the treatment of wet age-related macular degeneration and macular edema. This article reviews the related studies on Aflibercept for wet age-related macular degeneration and macular edema.
[Rec Adv Ophthalmol, 2014, 34(6): 598-600]

【关键词】 Aflibercept;湿性年龄相关性黄斑变性;黄斑水肿

【摘要】 Aflibercept 是一种可溶性诱导受体,可结合血管内皮生长因子-A 和胎盘生长因子,从而阻止同源血管内皮生长因子受体的结合和激活,抑制视网膜血管增生,导致新生血管退化。作为眼科一种新的抗血管生成物,其药代动力学、安全性和耐受性等获得了临床研究依据,目前主要用于湿性年龄相关性黄斑变性和黄斑水肿的治疗,现将 Aflibercept 在湿性年龄相关性黄斑变性和黄斑水肿治疗中的相关研究作一综述。
[眼科新进展,2014,34(6):598-600]

在发达国家,糖尿病视网膜病变和年龄相关性黄斑变性(age-related macular degeneration, AMD)分别是导致中年人和老年人失明的主要原因[1-3],它们都具有一个共同特点,即病理性新生血管。血管内皮生长因子(vascular endothelial growth factor, VEGF)在视网膜新生血管生成中是必不可少的诱导因子,可导致视网膜新生血管异常增生[4-6],早期抑制 VEGF 能够阻止疾病的进展[7]。随着贝伐单抗和雷珠单抗的成功研发以及疗效的局限性、不良反应和经济问题的出现,研究者随之对 Aflibercept 进行了研究,现综述如下。

1 Aflibercept 概述

Aflibercept 是一种融合蛋白,它的配体结合域融合了来自 VEGF 受体 1、2 及 IgG1 的 Fc 部分[8-9]。Aflibercept 作为眼科一种新的抗血管生成物,是人 VEGF 受体 Flt-1、KDR 的细胞外区域部分与人 IgG 的 Fe 片段的结合体,阻止 VEGF 与 Flt-1、KDR 的结合,也作为一种可溶性诱导受体来结合 VEGF-A 和胎盘生长因子(placental growth factor, PIGF),抑制同源 VEGF 受体的结合和激活,且 Aflibercept 与血液中 VEGF 的亲合力比单克隆抗体高 100 ~ 1000 倍[10]。与雷珠单抗(Kd 46 pmol · L^{-1})和贝伐单抗(Kd 58 pmol · L^{-1})相比,Aflibercept 与 VEGF165 具有高亲和力(Kd 0.49 pmol · L^{-1})[11],是目前为止唯一抑制 VEGF-B 和 PIGF 的重组 VEGF 受体蛋白[12]。Papadopoulos 等[13]指出,Aflibercept 与人 VEGF-A 具有高结合率,中和 VEGF-A 的效能强于雷珠单抗或贝伐单抗。这可能有利于减缓湿性 AMD 和黄斑水肿(macular edema, ME)的进展速度,使患者中央视觉维持较长时间,并减少给药频率。

2 Aflibercept 的临床研究

2.1 药代动力学 眼部 Aflibercept 药代动力学的基础研究较少,多基于临床试验数据。Stewart 等[14-16]研究发现,人眼每 2 周玻璃体内注射 Afliber-

cept 2 mg 在波峰和波谷阶段结合 VEGF 的水平均很高,由于 Aflibercept 的相对分子质量达115 000,Aflibercept 在血清中的半衰期约 18 d,高于贝伐单抗(8.25 d)和雷珠单抗(4.75 d);玻璃体内注射 Aflibercept 的半衰期达到7.1 d,高于雷珠单抗(4.75 d)和贝伐单抗(3.34 d)[15,17]。这使2个月一次的给药剂量成为可能,改变湿性 AMD 每个月一次注射的治疗方案,有利于定期复诊困难的湿性 AMD 患者。

2.2 安全性、耐受性 有研究发现,单眼玻璃体内注射 Aflibercept 2.0 mg 或4.0 mg,眼部耐受性良好,安全且无眼部毒性作用及眼部不良反应(0/51眼)[18-22]。Heier 等[23]研究指出,Aflibercept 单眼玻璃体内注射2.0 mg 的眼部不良反应(包括眼内炎、视力下降、后囊膜混浊和视网膜出血)与雷珠单抗每个月给药的结果类似(Ranibizumab 组 1.83%、Aflibercept 组1.17%)。

2.3 用药方法和范围 目前,Aflibercept 眼部用药多为经验性的用药。在两项临床试验中,玻璃体内注射 Aflibercept 2.0 mg 组最佳矫正视力和视网膜厚度稳定改善[22,24]。Nguyen 等[22]和 Heier 等[23,25]研究发现,玻璃体内 Aflibercept 2.0 mg/4 周(每4周注射2.0 mg)组视网膜厚度平均减少量(170.9 μm)高于0.5 mg/4 周 Aflibercept 组(149.5 μm)、0.5 mg 组(129.8 μm)和 Ranibizumab 组(138.5 μm)。Aflibercept 推荐治疗方案为初始3个月注射2.0 mg/4 周,而后2.0 mg/8 周[12,26]。更频繁地给药并不有利于患者[16]。Aflibercept 主要适用于湿性 AMD 和 ME 的治疗。

2.4 Aflibercept 疗效 目前治疗湿性 AMD 和 ME 的疗法中,除了激光光凝、贝伐单抗和雷珠单抗治疗,Aflibercept 治疗也是研究热点,其光学相干断层扫描(optical coherence tomography,OCT)和视力改善指标(ETDRS 字母表)成为评价疗效的重点。

2.4.1 OCT 指标 Heier 等[23,25]和 Zampros 等[27]研究发现,玻璃体内注射 Aflibercept 治疗组视网膜厚度在第12周开始减少,并在第12-52周内继续减少,脉络膜新生血管范围在52周内平均退化了2.21 mm,脉络膜新生血管面积减少了6.0 mm^2,高于雷珠单抗组(4.2 mm^2),中央视网膜厚度减少了170.9 μm,高于雷珠单抗组(138.5 μm)。Do 等[28-29]发现 Aflibercept 治疗组中央黄斑厚度减少范围(127.3~194.5 μm)高于激光组(58.4~67.9 μm)($P \leqslant 0.001$)。在另一项研究中,Alfibercept 治疗组视网膜厚度减少了457.2 μm,高于假性注射组(144.8 μm)($P < 0.001$)[30]。在3个月的疗程中,浆液性色素上皮脱离和视网膜渗出几乎完全消退[31];在6个月随访中,中央视网膜中央凹厚度平均减少了168 μm($P = 0.004$),色素上皮脱离最大高度和直径分别平均降低了56 μm($P < 0.001$)和316 μm($P = 0.040$)[32]。

2.4.2 视力改善指标 Do 等[28-29]和 Boyer 等[30]研究发现,玻璃体内注射 Aflibercept 2.0 mg 组视力平均提高13.6个字母,高于激光治疗组(2.5个字母)和假性注射组(4.0个字母)($P < 0.001$)。在 III 期临床试验中,观察组1结果显示初始3个月后每2个月玻璃体内注射 Aflibercept 2.0 mg 组提高了7.9个字母,观察组2结果中提高了8.9个字母,且比雷珠单抗或贝伐单抗的用药次数少[33]。Tyagi 等[34]指出 Aflibercept 在 ME 治疗中有一定的疗效和临床意义。OCT 和视力改善指标表明,Aflibercept 在治疗 AMD 中疗效较好[35],这使得 Aflibercept 在治疗脉络膜新生血管和 ME 中成为一个新的治疗方法[8]。

2.5 不良反应 众多研究结果显示[19,21,25,27,36],眼部对 Aflibercept 的一般耐受性良好,无严重不良反应,最常见不良反应包括结膜出血、一过性眼压升高、屈光不正、视网膜出血、主观性视力下降、玻璃体脱离、眼痛,发生率均很低。Heier 等[23]研究发现玻璃体内注射 Aflibercept 2.0 mg,眼部一般耐受性良好;少数患者在52周内出现眼压一过性升高,且玻璃体内注射雷珠单抗0.5 mg/4 周组、0.5 mg/4 周 Aflibercept 组、2.0 mg/4 周 Aflibercept 组、2.0 mg/8 周 Aflibercept 组不良反应(包括眼部异常、眼内炎、手术并发症、眼压升高)发生的概率分别是1.1/1000、0.1/1000、0.8/1000、0.2/1000,与雷珠单抗类似,且无注射剂量性不良反应的证据。

3 展望

Aflibercept 的药代动力学、安全性、耐受性和疗效等在研究中获得了临床依据。美国 FDA 已经于2011年9月批准 Aflibercept 应用于新生血管性 AMD 和 ME 的治疗[33,35]。Aflibercept 的疗效、给药周期延长和给药次数减少等潜在优势可能能够稳定提高患者视力、降低患者复诊次数和经济负担[37-39],其眼科应用前景比较理想。但该药的临床试验基于小样本、短期的研究,我们需对 Aflibercept 的远期效果和大样本试验结果进行分析研究,今后需继续探索该药物的疗效、安全和价值的相关性,从而帮助和指导患者选择最佳治疗方案。

参考文献

1 Bressler NM, Bressler SB. Preventative ophthalmology. Age-related macular degeneration[J]. *Ophthalmology*, 1995, 102(8): 1206-1211.
2 Rahmani B, Tielsch JM, Katz J. The cause-specific prevalence of visual impairment in an urban population. The Baltimore Eye Survey[J]. *Ophthalmology*, 1996, 103(11): 1721-1726.
3 Anderson OA, Bainbridge JW, Shima DT. Delivery of anti-angiogenic molecular therapies for retinal disease[J]. *Drug Discov Today*, 2010, 15(7-8): 272-282.
4 Shibuya M. Angiogenesis regulated by VEGF and its receptors and its clinical application[J]. *Rinsho Ketsueki*, 2009, 50(5): 404-412.
5 Adamis AP. Pathological Retinal Angiogenesis[M]//Immunology, Inflammation And Disease Of The Eye. Amsterdam: Elserler Ltd, 2010: 280-289.

6 Campa C, Harding SP. Anti-VEGF compounds in the treatment of neovascular age related macular degeneration[J]. *Curr Drug Targets*, 2011, 12(2): 173-181.
7 Chen E, Kaiser RS, Vander JF. Intravitreal bevacizumab for refractory pigment epithelial detachment with occult choroidal neovascularization in age-related macular degeneration[J]. *Retina*, 2007, 27(4): 445-450.
8 Saishin Y, Takahashi K, Limae SR. VEGF-TRAP(R1R2) suppresses choroidal neovascularization and VEGF-induced breakdown of the blood-retinal barrier[J]. *J Cell Physiol*, 2003, 195(2): 241-248.
9 Do DV. Retinal Pharmacotherapy, CHAPTER 37 - Fusion proteins: VEGF-Trap [M]. Edinburgh, W. B. Saunders, 2010: 259-264.
10 陈丹,樊映川,李丽英. 抗VEGF药物治疗新生血管性眼病的研究进展[J]. 国际眼科杂志, 2008, 8(1): 3-6.
11 Christoforidis JB, Williams MM, Kothandaraman S. Pharmacokinetic properties of intravitreal I-124-aflibercept in a rabbit model using PET/CT[J]. *Curr Eye Res*, 2012, 37(12): 1171-1174.
12 Thomas M, Mousa SS, Mousa SA. Comparative effectiveness of aflibercept for the treatment of patients with neovascular age-related macular degeneration[J]. *Clin Ophthalmol*, 2013, 7(4): 495-501.
13 Papadopoulos N, Martin J, Ruan Q. Binding and neutralization of vascular endothelial growth factor(VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab[J]. *Angiogenesis*, 2012, 15(2): 171-185.
14 Stewart MW. Clinical and differential utility of VEGF inhibitors in wet age-related macular degeneration: focus on aflibercept [J]. *Clin Ophthalmol*, 2012, 6(11): 1175-1186.
15 Stewart MW, Grippon S, Kirkpatrick P. Aflibercept[J]. *Nat Rev Drug Discov*, 2012, 11(4): 269-270.
16 Stewart MW, Rosenfeld PJ, Penha FM, Wang F, Yehoshua I, Bueno-Lopez E, *et al*. Pharmacokinetic rationale for dosing every 2 weeks versus 4 weeks with intravitreal ranibizumab, bevacizumab, and aflibercept (vascular endothelial growth factor Trap-eye)[J]. *Retina*, 2012, 32(3): 434-457.
17 Stewart MW. What are the half-lives of ranibizumab and aflibercept (VEGF Trap-eye) in human eyes? Calculations with a mathematical model[J]. *Eye Reports*, 2011, 1: 1.
18 Nguyen QD, Shah SM, Hafiz G, Quinlan E, Sung J, Chu K, *et al*. A phase I trial of an IV-administered vascular endothelial growth factor trap for treatment in patients with choroidal neovascularization due to age-related macular degeneration[J]. *Ophthalmology*, 2006, 113(9): 1522-1532.
19 Dixon JA, Oliver SC, Olson JL, Manclava N. VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration [J]. *Expert Opin Investig Drugs*, 2009, 18(10): 1573-1580.
20 Do DV, Nguyen QD, Shah SM, Browning DJ, Haller JA, Chu 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[J]. *Br J Ophthalmol*, 2009, 93(2): 144-149.
21 Nguyen Q, Hariprasad S, Browning D. Interim results of a phase I, dose-escalation, safety, tolerability, and bioactivity study of intravitreal VEGF Trap in patients with neovascular AMD: The CLEAR-IT 1 Study[C]. Meeting of the Club Jules Gonin and the Retina Society, 2009: 2868.
22 Nguyen QD. Shah SM, Browning DJ, Hudson H, Sonkin P, Hariprasad SM, *et al*. A phase I study of intravitreal vascular endothelial growth factor trap-eye in patients with neovascular age-related macular degeneration [J]. *Ophthalmology*, 2009, 116(11): 2141-2148.
23 Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, *et al*. Intravitreal aflibercept(VEGF trap-eye) in wet age-related macular degeneration [J]. *Ophthalmology*, 2012, 119(12): 2537-2548.
24 Boyer DS, Vittr R, Berliner AJ. Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 copernicus study [J]. *Am J Ophthalmol*, 2013, 155(3): 429-437.
25 Heier JS, Boyer D, Nguyen QD. The 1-year results of CLEAR-IT 2, a phase 2 study of vascular endothelial growth factor trap-eye dosed as-needed after 12-week fixed dosing[J]. *Ophthalmology*, 2011, 118(6): 1098-1106.
26 Nguyen QD, Campochiaro PA, Shah SM, Browning DJ, Hudson HL, Sonkin PL, *et al*. Evaluation of very high- and very low-dose intravitreal aflibercept in patients with neovascular age-related macular degeneration[J]. *J Ocul Pharmacol Ther*, 2012, 28(6): 581-588.
27 Zampros I, Praidou A, Brazitikos P, Ekonomidis P, Androudi S. Antivascular endothelial growth factor agents for neovascular age-related macular degeneration [J]. *J Ophthalmol*, 2012, 2012: 319728.
28 Do DV, Schmidt-Erfurth U, Gonzalez VH. The DA VINCI Study: Phase 2 primary results of VEGF trap-eye in patients with diabetic macular edema [J]. *Ophthalmology*, 2011, 118(9): 1819-1826.
29 Do DV, Nguyen QD, Boyer D, Schmidt-Erfurth U, Brown DM, Vitti R, *et al*. One-year outcomes of the Da Vinci Study of VEGF Trap-Eye in eyes with diabetic macular edema[J]. *Ophthalmology*, 2012, 119(8): 1658-1665.
30 Boyer D, Heier J, Brown DM, Clark WL, Vitti R, Berliner AJ, *et al*. Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 copernicus study[J]. *Ophthalmology*, 2012, 119(5): 1024-1032.
31 Patel KH, Chow CC, Rathod R, Mieler WF, Lim JI, Ulanski LJ 2nd, *et al*. Rapid response of retinal pigment epithelial detachments to intravitreal aflibercept in neovascular age-related macular degeneration refractory to bevacizumab and ranibizumab [J]. *Eye*, 2013, 27(5): 663-667.
32 Kumar N, Marsiglia M, Mrejen S. Visual and anatomical outcomes of Intravitreal aflibercept in eyes with persistent subfoveal fluid despite previous treatments with Ranibizumab in patients with neovascular age-related macular degeneration[J]. *Retina*, 2013, 2013: 23549101.
33 Ohr M, Kaiser PK. Intravitreal aflibercept injection for neovascular(wet) age-related macular degeneration[J]. *Expert Opin Pharmacother*, 2012, 13(4): 585-591.
34 Tyagi M, Mathai A. VEGF trap for macular edema[J]. *Ophthalmology*, 2012, 119(9): 1943-1944.
35 Verner-Cole EA, Davis SJ, Lauer AK. Aflibercept for the treatment of neovascular age-related macular degeneration [J]. *Drugs Today*, 2012, 48(5): 317-329.
36 Brown DM, Heier JS, Ciulla T, Benz M, Abraham P, Yancopoulos G, *et al*. Primary endpoint results of a phase II study of vascular endothelial growth factor trap-eye in wet age-related macular degeneration[J]. *Ophthalmology*, 2011, 118(6): 1089-1097.
37 Ehlers JP. The MANTA 1-year results: the anti-VEGF debate continues[J]. *Br J Ophthalmol*, 2013, 97(3): 248-250.
38 Scott AW, Bressler SB. Long-term follow-up of vascular endothelial growth factor inhibitor therapy for neovascular age-related macular degeneration[J]. *Curr Opin Ophthalmol*, 2013, 24(3): 190-196.
39 Xu D, Kaiser PK. Intravitreal aflibercept for neovascular age-related macular degeneration[J]. *Immunotherapy*, 2013, 5(2): 121-130.