

视网膜静脉阻塞性黄斑水肿的治疗

卢颖毅, 戴虹*

(北京医院 眼科 国家老年医学中心, 北京 100730)

【摘要】 视网膜静脉阻塞 (retinal vein occlusion, RVO) 是一种老年人群中常见的视网膜血管性疾病, 黄斑水肿是导致患者视力损伤的主要并发症。目前 RVO 黄斑水肿的主要治疗方式为玻璃体腔内注射抗血管内皮生长因子 (vascular endothelial growth factor, VEGF) 药物或者植入地塞米松玻璃体内植入剂, 二者均能显著改善患者视力, 减轻黄斑水肿。对于抗 VEGF 药物或其他治疗反应不佳的患者, 地塞米松缓释植入剂同样有效。RVO 黄斑水肿的临床预后与治疗时机有关, 早期治疗的患者视力获益更多。

【关键词】 视网膜静脉阻塞; 黄斑水肿; 地塞米松; 血管内皮生长因子

【中图分类号】 R774

【文献标志码】 A

【文章编号】 1672-3384(2019)06-0035-05

doi:10.3969/j.issn.1672-3384.2019.06.008

Treatment of macular edema to retinal vein occlusion

LU Ying-yi, DAI Hong*

(Department of Ophthalmology, Beijing Hospital, National Center of Gerontology, Beijing 100730, China)

【Abstract】 Retinal vein occlusion (RVO) is a retinal vascular disease frequently occurred in the elder population, and macular edema is the major complication associated with severe vision impairment. At present, the main treatments of RVO macular edema are intravitreal anti-VEGF agents or intravitreal implantation of dexamethasone, both of them can significantly improve visual acuity and alleviate macular edema. Additionally, dexamethasone sustained-release implants can be effectively used among patients with poor response to intravitreal anti-VEGF agents or other treatments. The clinical prognosis of RVO macular edema is related to the treatment timing, and patients with early treatment could benefit more from visual acuity.

【Key words】 retinal vein occlusion; macular edema; dexamethasone; vascular endothelial growth factor

视网膜静脉阻塞 (retinal vein occlusion, RVO) 是一种可造成严重视力损伤的常见视网膜血管性疾病, RVO 根据阻塞部位可分为: 视网膜中央静脉阻塞 (central retinal vein occlusion, CRVO)、视网膜分支静脉阻塞 (branch retinal vein occlusion, BRVO)、半侧视网膜静脉阻塞 (hemi-central retinal vein occlusion, HRVO), 根据视网膜血液循环状况, 又可分为缺血型和非缺血型 RVO^[1-2]。RVO 的总体发病率约为 0.52%, 但在不同地区和种族之间存在差异, 并且随年龄增加而增高, 亚洲人群中约为 0.57%^[3]。中国一项调查显示, 40 岁以上人群 10 年内 RVO 发病率约为 1.9%^[4]。在各种 RVO 类

型中, BRVO 的发病率约为 0.442%, CRVO 约为 0.008%, 虽然 CRVO 发病率明显低于 BRVO, 但其所造成的视力损害更为严重^[3,5]。RVO 患者视力受损的原因, 包括缺血引起的视网膜组织的直接损害、视网膜新生血管形成以及新生血管青光眼等, 但最主要、最常见的原因还是继发性黄斑水肿 (macular edema, ME)^[6-9]。

1 视网膜静脉阻塞性黄斑水肿的发病机制

RVO 的发病机制复杂, 主要是由于各种原因所致的视网膜静脉阻塞, 导致其上游的静脉血管腔内压力增高, 加之有些患者本身存在的血管病变, 从

[收稿日期] 2019-05-24

[作者简介] 卢颖毅, 女, 硕士, 主治医师; 研究方向: 玻璃体视网膜疾病及黄斑病; Tel: (010)85133322; E-mail: lu.yy@263.net

[通信作者] *戴虹, 男, 大学本科, 主任医师; 研究方向: 玻璃体视网膜疾病及黄斑病; Tel: (010)85133322; E-mail: Dai-Hong@x263.net

而导致不同程度的视网膜低灌注、缺血缺氧^[8,10-11]。临床研究表明 RVO 患者眼内血管内皮生长因子 (vascular endothelial growth factor, VEGF) 水平升高。VEGF 可增加血管的通透性、破坏血-视网膜屏障, 导致血管渗漏增加, 从而导致黄斑水肿的产生^[6]。VEGF 水平升高还会诱发眼球前后段产生新生血管, 从而继发玻璃体积血、牵拉性视网膜脱离及新生血管性青光眼等并发症^[9,12-13]。

近年来越来越多的证据表明, 炎症在 RVO 黄斑水肿的发生发展中发挥着重要作用, 一方面, 视网膜静脉阻塞后, 视网膜缺血缺氧, 会诱发炎症介质上调, 进而小胶质细胞活化、Müller 细胞功能异常、血管通透性增加, 从而导致神经细胞损伤, 视网膜液体积聚, 进而形成黄斑水肿^[14-15]。另一方面, 在一些年轻患者中, 炎症还可能是导致 RVO 以及黄斑水肿的原发病因^[16-17]。

2 视网膜静脉阻塞性黄斑水肿的治疗现状

RVO 黄斑水肿的治疗经历了从传统的视网膜激光光凝治疗到抗 VEGF 治疗、抗炎治疗 (糖皮质激素玻璃体内植入剂) 的转变。视网膜激光光凝主要对 BRVO 有效, 但临床研究发现激光光凝早期可使黄斑水肿一过性加重, 且长期观察黄斑水肿虽然能消退, 但患者视力改善情况与对照组无显著差异^[18-19], 加之对视野的损害和其他弊端, 激光已不作为治疗 RVO 黄斑水肿的首选方法^[5,20-21]。而随着对 RVO 黄斑水肿发病机制认识的不断深入, 目前已经基本明确了抗 VEGF 和抗炎治疗在改善 RVO 患者视力、缓解黄斑水肿等方面的显著作用, 因此玻璃体腔内注射抗 VEGF 药物或者植入糖皮质激素玻璃体内植入剂是国际指南推荐的 RVO 黄斑水肿一线治疗措施, 也是临床首选的治疗方式^[5,22]。

3 视网膜静脉阻塞性黄斑水肿的抗 VEGF 治疗

抗 VEGF 药物玻璃体腔内注射可降低患者眼内 VEGF 水平, 减轻血管渗漏, 从而促进黄斑水肿消退, 视力提高。目前应用于 RVO 黄斑水肿治疗的抗 VEGF 药物包括单克隆抗体类药物 (如雷珠单抗) 和融合蛋白类药物 (如阿柏西普等), 临床试验结果显示几种抗 VEGF 药均能显著提高患者视力, 减轻黄斑水肿^[5]。

BRAVO 研究和 CRUISE 研究分别评估了 0.5

mg 雷珠单抗治疗继发于 BRVO 以及 CRVO 的黄斑水肿的效果, 患者均予以 6 + PRN (确诊后起始每月注射 1 次, 连续 6 次, 随后每月随访, 根据每次随访情况决定是否予以再次注射) 的治疗方案, 6 个月随访疗效显著, 患者视力提高, 黄斑水肿改善 (BRVO: 治疗组视力提高 18.3 个字母, 对照组视力提高 7.3 个字母; CRVO: 治疗组视力提高 14.9 个字母, 对照组视力提高 0.8 个字母^[23-25]。

完成长达 4 年随访的临床研究 (RETAIN 研究) 也发现, 53.1% 的患者抗 VEGF 治疗后视力提高 ≥ 15 个字母, 43.8% 的患者随访终末视力 $\geq 20/40$ ^[26]。同样, 用阿柏西普治疗 CRVO 黄斑水肿的研究 (COPERNICUS, GALILEO) 也获得相似的结果^[27-28]。

此外, 这些研究的随访结果也显示, 从每月注药改为每月随访、按需注药后, 不管是每 3 个月或 2 个月的间隔随访, 均发现患者视力逐渐下降, 且视网膜内无积液的比例也逐渐降低, 表明 RVO 黄斑水肿的抗 VEGF 治疗需要反复多次频繁注射, 由此必然会伴随治疗费用增加以及多次有创操作的安全隐患, RVO 黄斑水肿的抗 VEGF 治疗需要探索更加合理的治疗模式。此外, 并非所有患者对抗 VEGF 治疗反应良好, 对于此类患者, 目前推荐的治疗方法包括换用其他抗 VEGF 药物或者植入地塞米松缓释植入剂等^[12,22,29-30]。

4 视网膜静脉阻塞性黄斑水肿的抗炎治疗

炎症是 RVO 黄斑水肿形成和发展的重要原因, 糖皮质激素因具有强大的抗炎作用, 可显著下调 RVO 患者眼内炎症因子水平、稳定血管通透性, 并间接抑制 VEGF 促进黄斑水肿消退^[20,31-32]。同时, 糖皮质激素还能抑制小胶质细胞的激活和迁移, 减轻炎症反应所造成的组织损伤^[14]。

曲安奈德是临床上最早应用于玻璃体腔注射治疗 RVO 黄斑水肿的糖皮质激素, Ip 等^[33] 观察发现, 与假注射组和激光治疗组相比, 玻璃体腔内注射曲安奈德能够改善 RVO 患者视力。但因剂型问题, 常伴随显著的不良事件如眼压升高、晶状体混浊等, 临床应用受到限制。

近年来上市的地塞米松玻璃体内植入剂 (傲迪适[®]) 是一种缓释、可降解的地塞米松缓释植入剂, 由 0.7 mg 地塞米松和生物可降解基质构成^[34-35], 植

入玻璃体腔后依靠其缓释装置可持续释放地塞米松长达3~6月。缓释剂型不仅可以维持稳定的眼内药物水平、延长有效药物作用时间, 还有效减少眼内注药等有创操作的次数以及既往糖皮质激素相关的不良反应, 因而药物的有效性和安全性大大提高, 在RVO黄斑水肿临床治疗中的应用日益广泛。地塞米松玻璃体内植入剂(傲迪适[®])是目前唯一获得美国FDA和欧盟批准用于RVO黄斑水肿的治疗的糖皮质激素类药物, 2017年获得我国食品药品监督管理总局批准应用于RVO黄斑水肿的临床治疗。

4.1 地塞米松玻璃体内植入剂用于视网膜静脉阻塞黄斑水肿的初始治疗

糖皮质激素类玻璃体内植入剂被欧美多个国家推荐为RVO黄斑水肿一线治疗方案, 大型多中心临床试验表明, 相比假注射组, 地塞米松玻璃体内植入剂(傲迪适[®])可显著提高RVO患者视力, 减轻黄斑水肿^[5,12,21,36-39]。

全球Ⅲ期随机对照临床试验(GENEVA)评估了0.7 mg地塞米松玻璃体内植入剂(傲迪适[®])玻璃体腔内植入治疗RVO黄斑水肿的有效性和安全性。随访发现, 植入1周后患者视力即有显著改善(较基线提高5.3个字母)并可有效维持长达6个月。视力提高的峰值在注药后2个月, 视力较基线提升高达9.8个字母。此外, 患者的黄斑水肿也显著缓解并可长期维持^[34]。黎晓新等^[39]在我国进行的多中心随机对照临床试验也表明地塞米松玻璃体内植入剂(傲迪适[®])用于RVO黄斑水肿安全有效, 药效峰值同样出现在植入后第2个月, 患者视力较基线提高10.6个字母, CRT降低406.9 μm。

4.2 地塞米松玻璃体内植入剂用于难治性视网膜静脉阻塞黄斑水肿的转换治疗

RVO黄斑水肿的抗VEGF治疗推荐起始至少连续注射3针, 而对于其中反应不佳、黄斑水肿持续存在的患者, 则推荐换用其他抗VEGF药物或者植入糖皮质激素缓释剂。多个研究^[5,12,22,29-30]表明, 地塞米松玻璃体内植入剂(傲迪适[®])对于此类难治性RVO黄斑水肿同样有效。一项回顾性研究观察了地塞米松玻璃体内植入剂(傲迪适[®])用于难治性RVO黄斑水肿患者的疗效(纳入患者既往抗VEGF治疗次数的中位数为6), 平均随访4.3个

月, 患者BCVA提高4个字母, CRT从植入前455 μm降至285 μm^[40]。Hussain等^[41]纳入了既往平均接受过7次治疗(包括激光、抗VEGF或者曲安奈德)、黄斑水肿持续时间至少为4个月[平均(0.8±17.6)月]的患者, 也观察到类似结果。

4.3 地塞米松玻璃体内植入剂用于视网膜静脉阻塞黄斑水肿治疗的安全性

眼压升高是糖皮质激素类药物眼内应用最常见的不良反应, 临床研究显示地塞米松玻璃体内植入剂(傲迪适[®])玻璃体内植入引起的眼压升高均为一过性, 且多数可通过单药控制, 再次植入眼压并无累积效应^[38]。

5 干预时机影响视网膜静脉阻塞黄斑水肿患者的预后

干预时机指从RVO黄斑水肿发病至第1次接受治疗的时间。多个研究表明, 干预时机影响RVO黄斑水肿患者的预后, 早期治疗的患者获益更多。抗VEGF药物治疗RVO黄斑水肿的临床研究发现, 早期治疗的患者与延迟治疗组相比, 视力提高与黄斑水肿缓解率均有显著差异, 延迟治疗组患者获益减少, 且治疗时机对于临床预后的影响更大于注药次数^[42-44]。

地塞米松玻璃体内植入剂(傲迪适[®])治疗RVO黄斑水肿的临床研究也表明早期干预患者获益更大。全球Ⅲ期临床试验(GENEVA)事后亚组分析发现, 黄斑水肿持续时间≤90 d的患者视力提高程度远大于黄斑水肿持续>90 d的患者。而GENEVA研究的第2阶段显示, 延迟治疗组(入组6个月后再接受治疗)视力改善≥15个字母的患者比例显著低于起始治疗组(起始治疗组为21.8%, 延迟治疗组为8.1%; $P < 0.001$)^[34]。德国一项前瞻性多中心临床试验也得出类似结论^[45]。此外, 地塞米松玻璃体内植入剂(傲迪适[®])用于难治性RVO黄斑水肿治疗的相关研究结果也表明, 虽然患者视力以及黄斑水肿均有一定程度的改善, 但幅度均不如既往报道的确诊后即接受治疗的患者。

因此, RVO黄斑水肿患者确诊后及时干预能获得更好的治疗效果, 长期存在的黄斑水肿可能造成视网膜组织不可逆性损伤, 限制患者视力提高幅度^[46]。

综上, 黄斑水肿是RVO患者视力损伤的主要

原因,炎症因素在黄斑水肿形成过程中发挥关键作用。玻璃体内注射抗 VEGF 药物或者植入地塞米松玻璃体内植入剂均能显著改善患者视力、减轻黄斑水肿。此外,对于抗 VEGF 药物反应不佳的患者,地塞米松玻璃体内植入剂同样有效。RVO 黄斑水肿患者的临床预后与治疗时机密切相关,早期干预的患者视力获益更多。

【参考文献】

- [1] Hayreh S S, Klugman M R, Beri M, et al. Differentiation of ischemic from non-ischemic central retinal vein occlusion during the early acute phase[J]. *Graefes Arch Clin Exp Ophthalmol*, 1990, 228(3):201-217.
- [2] Hayreh S S, Zimmerman M B, Podhajsky P. Incidence of various types of retinal vein occlusion and their recurrence and demographic characteristics[J]. *Am J Ophthalmol*, 1994, 117(4):429-441.
- [3] Rogers S, McIntosh R L, Cheung N, et al. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia[J]. *Ophthalmology*, 2010, 117(2):313-347.
- [4] Liu W, Xu L, Jonas J B. Vein occlusion in Chinese subjects[J]. *Ophthalmology*, 2007, 114(9):1795-1796.
- [5] Pulido J S, Flaxel C J, Adelman R A, et al. Retinal vein occlusions preferred practice pattern[®] guidelines[J]. *Ophthalmology*, 2016, 123(1):182-208.
- [6] Campochiaro P A, Bhisitkul R B, Shapiro H, et al. Vascular endothelial growth factor promotes progressive retinal nonperfusion in patients with retinal vein occlusion[J]. *Ophthalmology*, 2013, 120(4):795-802.
- [7] Campochiaro P A, Hafiz G, Shah S M, et al. Ranibizumab for macular edema due to retinal vein occlusions: implication of VEGF as a critical stimulator[J]. *Mol Ther*, 2008, 16(4):791-799.
- [8] Hayreh S S, Podhajsky P A, Zimmerman M B. Natural history of visual outcome in central retinal vein occlusion[J]. *Ophthalmology*, 2011, 118(1):119-133.
- [9] Hayreh S S. Management of central retinal vein occlusion[J]. *Ophthalmologica*, 2003, 217(3):167-188.
- [10] Noma H, Funatsu H, Mimura T, et al. Vitreous levels of interleukin-6 and vascular endothelial growth factor in macular edema with central retinal vein occlusion[J]. *Ophthalmology*, 2009, 116(1):87-93.
- [11] Aiello L P, Avery R L, Arrigg P G, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders[J]. *N Engl J Med*, 1994, 331(22):1480-1487.
- [12] Coscas G, Loewenstein A, Augustin A, et al. Management of retinal vein occlusion: consensus document[J]. *Ophthalmologica*, 2011, 226(1):4-28.
- [13] Boyd S R, Zachary I, Chakravarthy U, et al. Correlation of increased vascular endothelial growth factor with neovascularization and permeability in ischemic central vein occlusion[J]. *Arch Ophthalmol*, 2002, 120(12):1644-1650.
- [14] Gallina D, Zelinka C P, Cebulla C M, et al. Activation of glucocorticoid receptors in Müller glia is protective to retinal neurons and suppresses microglial reactivity[J]. *Exp Neurol*, 2015, 273:114-125.
- [15] Yafai Y, Iandiev I, Wiedemann P, et al. Retinal endothelial angiogenic activity: effects of hypoxia and glial (Müller) cells[J]. *Microcirculation*, 2004, 11(7):577-586.
- [16] Fong A C O, Schatz H. Central retinal vein occlusion in young-adults[J]. *Surv Ophthalmol*, 1993, 37(6):393-417.
- [17] Fong A C O, Schatz H, McDonald H R, et al. Central retinal vein occlusion in young-adults (papillophlebitis)[J]. *Retina*, 1992, 12:3-11.
- [18] Patz A. Argon-laser photocoagulation for macular edema in branch vein occlusion[J]. *Am J Ophthalmol*, 1984, 98(3):374-375.
- [19] Clarkson J G, Chuang E, Gass D, et al. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. The Central Vein Occlusion Study Group M report[J]. *Ophthalmology*, 1995, 102(10):1425-1433.
- [20] Yeh S, Kim S J, Ho A C, et al. Therapies for macular edema associated with central retinal vein occlusion: a report by the American Academy of Ophthalmology[J]. *Ophthalmology*, 2015, 122(4):769-778.
- [21] Adelman R A, Parnes A J, Bopp S, et al. Strategy for the management of macular edema in retinal vein occlusion: the European Vitreo Retinal Society macular edema study[J]. *Biomed Res Int*, 2015, 2015:870-877.
- [22] Berger A R, Cruess A F, Altomare F, et al. Optimal treatment of retinal vein occlusion: Canadian expert consensus[J]. *Ophthalmologica*, 2015, 234(1):6-25.
- [23] Brown D M, Campochiaro P A, Bhisitkul R B, et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study[J]. *Ophthalmology*, 2011, 118(8):1594-1602.
- [24] Campochiaro P A, Brown D M, Awh C C, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study[J]. *Ophthalmology*, 2011, 118(10):2041-2049.
- [25] Campochiaro P A, Heier J S, Feiner L, et al. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study[J]. *Ophthalmology*, 2010, 117(6):1102-1112.

- [26] Campochiaro P A, Sophie R, Pearlman J, et al. Long-term outcomes in patients with retinal vein occlusion treated with ranibizumab; the RETAIN study [J]. *Ophthalmology*, 2014, 121 (1) : 209-219.
- [27] Brown D M, Heier J S, Clark W L, et al. 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.
- [28] Korobelnik J F, Holz F G, Roeder J, et al. Intravitreal aflibercept injection for macular edema resulting from central retinal vein occlusion; one-year results of the phase 3 GALILEO study [J]. *Ophthalmology*, 2014, 121 (1) : 202-208.
- [29] Bajor A, Pielen A, Danzmann L. Retinal vein occlusion. Which treatment when [J]. *Klin Monbl Augenheilkd*, 2017, 234 (10) : 1259-1265.
- [30] Feltgen N, Pielen A. Retinal vein occlusion; therapy of retinal vein occlusion [J]. *Ophthalmologie*, 2015, 112 (8) : 695-704.
- [31] Rezar-Dreindl S, Eibenberger K, Pollreisz A, et al. Effect of intravitreal dexamethasone implant on intra-ocular cytokines and chemokines in eyes with retinal vein occlusion [J]. *Acta Ophthalmol*, 2017, 95 (2) : e119-e127.
- [32] Zhao M, Bousquet E, Valamanesh F, et al. Differential regulations of AQP4 and Kir4.1 by triamcinolone acetonide and dexamethasone in the healthy and inflamed retina [J]. *Invest Ophthalmol Vis Sci*, 2011, 52 (9) : 6340-6347.
- [33] Ip M S, Scott I U, VanVeldhuisen P C, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion; the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5 [J]. *Arch Ophthalmol*, 2009, 127 (9) : 1101-1114.
- [34] Haller J A, Bandello F, Belfort R Jr, et al. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion [J]. *Ophthalmology*, 2010, 117 (6) : 1134-1146.
- [35] Haller J A, Bandello F, Belfort R Jr, et al. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results [J]. *Ophthalmology*, 2011, 118 (12) : 2453-2460.
- [36] Girmens J F, Glacet-Bernard A, Kodjikian L, et al. Management of macular edema secondary to retinal vein occlusion [J]. *J Fr Ophthalmol*, 2015, 38 (3) : 253-263.
- [37] Sivaprasad S, Amoaku W M, Hykin P, et al. The Royal College of Ophthalmologists Guidelines on retinal vein occlusions; executive summary [J]. *Eye*, 2016, 30 (4) : 642.
- [38] Yoon Y H, Kim J W, Lee J Y, et al. Dexamethasone intravitreal implant for early treatment and retreatment of macular edema related to branch retinal vein occlusion; the multicenter COBALT study [J]. *Ophthalmologica*, 2018, 240 (2) : 81-89.
- [39] Li X, Wang N, Liang X, et al. Safety and efficacy of dexamethasone intravitreal implant for treatment of macular edema secondary to retinal vein occlusion in Chinese patients; randomized, sham-controlled, multicenter study [J]. *Graefes Arch Clin Exp Ophthalmol*, 2018, 256 (1) : 59-69.
- [40] Pielen A, Bühler A D, Heinzelmann S U, et al. Switch of intravitreal therapy for macular edema secondary to retinal vein occlusion from anti-VEGF to dexamethasone implant and vice versa [J]. *J Ophthalmol*, 2017. DOI:10.1155/2017/5831682.
- [41] Hussain R M, Ciulla T A, Ciulla L M, et al. Efficacy of dexamethasone intravitreal implant for refractory macular edema caused by retinal vein occlusion [J]. *Retin Cases Brief Rep*, 2018, 12 (4) : 294-299.
- [42] Holz F G, Roeder J, Ogura Y, et al. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion; 6-month results of the phase III GALILEO study [J]. *Br J Ophthalmol*, 2013, 97 (3) : 278-284.
- [43] Pikkil J, Chassid O, Busool Y, et al. Bevacizumab for CRVO associated CME; effect of timing and frequency of injections on final visual outcome [J]. *J Ophthalmol*, 2013. DOI: 10.1155/2013/974670.
- [44] Thach A B, Yau L, Hoang C, et al. Time to clinically significant visual acuity gains after ranibizumab treatment for retinal vein occlusion; BRAVO and CRUISE trials [J]. *Ophthalmology*, 2014, 121 (5) : 1059-1066.
- [45] Eter N, Mohr A, Wachtlin J, et al. Dexamethasone intravitreal implant in retinal vein occlusion; real-life data from a prospective, multicenter clinical trial [J]. *Graefes Arch Clin Exp Ophthalmol*, 2017, 255 (1) : 77-87.
- [46] Yeh W S, Haller J A, Lanzetta P, et al. Effect of the duration of macular edema on clinical outcomes in retinal vein occlusion treated with dexamethasone intravitreal implant [J]. *Ophthalmology*, 2012, 119 (6) : 1190-1198.

(本文编辑:杨昕)