引文格式:梁婉玲,周怀胜,马海智,卢彦,晏世刚. 地塞米松玻璃体内植入剂 Ozurdex 治疗视网膜静脉阻塞继发黄斑水肿的短期疗效[J]. 眼科新进展,2019,39(7):666-669. doi:10.13389/j.cnki.rao.2019.0153

【应用研究】

地塞米松玻璃体内植入剂 Ozurdex 治疗视网膜静脉阻塞继发黄斑水肿的短期疗效△

梁婉玲 周怀胜 马海智 卢彦 晏世刚

作者简介:梁婉玲,女,1984 年 10 月出生,广东佛山人,硕士,主治医师。研究方向:白内障和眼底病的临床诊治。联系电话:15015893683;E-mail:wingleung_016@126.com;ORCID:0000-0002-8132-3260

About LIANG Wan-Ling: Female, born in October, 1984. Master degree. Tel: 15015893683; E-mail: wingleung_016@126.com; ORCID: 0000-0002-8132-3260

收稿日期:2018-12-31
修回日期:2019-04-22
本文编辑:付中静
△基金项目:广东省佛山市十三五医学重点专科和特色专科建设项目(编号:FSGSPZD135020)

作者单位:528000 广东省佛山市,佛山市第二人民医院眼科中心
通讯作者:晏世刚,E-mail:fsyansg@126.com;ORCID:0000-0002-6251-2912

Received date: Dec 31, 2018
Accepted date: Apr 22, 2019
Foundation item: Foshan 13th Five-year Key and Characteristic Medical Building Project (No: FSGSPZD135-020)

From the *Department of Ophthalmology, the Second People's Hospital of Foshan, Foshan* 528000, *Guangdong Province, China*
Responsible author: YAN Shi-Gang, E-mail: fsyansg@126.com; ORCID: 0000-0002-6251-2912

The short-term efficacy of Ozurdex for macular edema secondary to retinal vein occlusion

LIANG Wan-Ling, ZHOU Huai-Sheng, MA Hai-Zhi, LU Yan, YAN Shi-Gang

【Abstract】 Objective To evaluate the short-term clinical efficacy of Ozurdex by comparing intravitreal injection of Ozurdex with ranibizumab in the treatment of macular edema secondary to retinal vein occlusion (RVO-ME). **Methods** The clinical data of forty-two eyes of 42 RVO-ME patients who were admitted to the Department of Ophthalmology of the Second People's Hospital of Foshan City from January to December 2018 were retrospectively analyzed. They were divided into two groups: DEX group with 11 patients and anti-VEGF group with 31 patients. The best corrected visual acuity (BCVA), central retinal thickness (CRT), duration of drug efficacy (recurrence rate), and adverse reactions of the two groups were observed before and after treatment. **Results** The differences of BCVA at 1 month, 2 months, 3 months and 4 months after treatment in the DEX group were statistically significant than that before treatment (all $P<0.05$), while there was no statistical significance at 6 months after treatment ($P=0.054$). There were significant differences of CRT at 1 month, 2 months, 3 months, 4 months and 6 months after treatment in the DEX group than that before treatment (all $P<0.05$). There were significant differences of BCVA and CRT in the anti-VEGF group at 1 month after treatment than those before treatment (both $P<0.05$). At 1 month after treatment, there were no significant differences of BCVA and CRT between the DEX group and the anti-VEGF group (both $P>0.05$). There were no significant differences between branch retinal vein occlusion and central retinal vein occlusion in the DEX group, the anti-VEGF group and between the two groups (all $P>0.05$), except for the CRT at 1 month after treatment in the DEX group. The duration of efficacy in the DEX group was 3 to 4 months, and the duration of efficacy in the anti-VEGF group was <2 months. The incidence of high intraocular pressure in the DEX group was higher than that in the anti-VEGF group, and the difference was statistically significant ($P=0.004$). **Conclusion** Ozurdex has a significant short-term efficacy in the treatment of RVO-ME for a period of 3 to 4 months (less than 6 months). Intraocular pressure is still the main adverse reaction that needs to be closely monitored.

【Key words】 dexamethasone intravitreal implant; retinal vein occlusion; macular edema; ranibizumab

【摘要】 目的 通过比较地塞米松玻璃体内植入剂 Ozurdex 与雷珠单抗治疗视网膜静脉阻塞继发黄斑水肿(macular edema secondary to retinal vein occlusion,RVO-ME)的情况,评估 Ozurdex 的短期临床疗效。**方法** 回顾性分析 2018 年 1 月至 12 月就诊于佛山市第二人民医院眼科中心的 RVO-ME 患者(42 例 42 眼)的临床资料。将其分为 DEX 组(11 例)和抗 VEGF 组(31 例)。观察两组患者治疗前后的最佳矫正视力(best corrected visual acuity,BCVA)、中央视网膜厚度(central retinal thickness,CRT)、药效持续时间(复发率)、不良反应等。**结果** DEX 组治疗后 1 个月、2 个月、3 个月和 4 个月的 BCVA 与治疗前比较差异均有统计学意义(均为 $P<0.05$),治疗后 6 个月与治疗前比较差异无统计学意义($P=0.054$);DEX 组治疗后 1 个月、2 个月、3 个月、4 个月和 6 个月 CRT 与治疗前比较差异均有统计学意义(均为 $P<0.05$)。抗 VEGF 组治疗后 1 个月 BCVA、CRT 与治疗前比较差异均有统计学意义(均为 $P<0.05$)。治疗后 1 个月,DEX 组与抗 VEGF 组间 BCVA、CRT 比较差异均无统计学意义(均为 $P>0.05$)。DEX 组内、抗 VEGF 组内及两者间视网膜分支静脉阻塞与视网膜中央静脉阻塞的 BCVA、CRT 比较除 DXE 组治疗后 1 个月CRT 外,差异均无统计学意义(均为 $P>0.05$)。DEX 组的药效持续时间为 3~4 个月,抗 VEGF 组的药效持续时间 <2 个月。DEX 组的高眼压发生率较抗 VEGF 组高,差异有统计学意义($P=0.004$)。**结论** Ozurdex 在治疗 RVO-ME 上有明显的短期疗效,维持时间为 3~4 个月(少于 6 个月)。眼压仍是其需密切监控的主要不良反应。

【关键词】 地塞米松玻璃体内植入剂;视网膜静脉阻塞;黄斑水肿;雷珠单抗
【中图分类号】 R774

视网膜静脉阻塞(retinal vein occlusion,RVO)是常见的视网膜血管疾病[1-2]。RVO导致视网膜缺血缺氧,血-视网膜屏障或(及)视网膜色素上皮(retinal pigment epithelium,RPE)层功能受损,血管通透性增加和血管内皮生长因子浓度的上调,使视网膜厚度增加,累及黄斑时,可致黄斑水肿(macular edema,ME)[3]。视网膜静脉阻塞继发黄斑水肿(macular edema secondary to retinal vein occlusion,RVO-ME)是导致视力下降的最主要原因[4]。目前,玻璃体内注射激素[5]或抗血管内皮生长因子(vascular endothelial growth factor,VEGF)药[6-7]是治疗RVO-ME的有效手段。地塞米松(dexamethasone,DEX)玻璃体内植入剂Ozurdex,是一种治疗RVO-ME的缓慢释放的水溶性眼内制剂[8]。本研究通过玻璃体内注射新药物Ozurdex与雷珠单抗治疗RVO-ME的疗效比较,评估Ozurdex的临床有效性。

1 资料与方法

1.1 一般资料 选择2018年1月至12月就诊于佛山市第二人民医院的RVO-ME患者(42例42眼)的资料进行回顾性分析,其中男19例,女23例。将其分为两组:DEX组(注射Ozurdex)11例和抗VEGF组(注射雷珠单抗)31例。DEX组中3例单纯行玻璃体内注药术,其余8例均为玻璃体内注药联合视网膜激光光凝。抗VEGF组中6例为单纯玻璃体内注药术,其余25例为玻璃体内注药联合视网膜激光光凝。入选标准:(1)年龄>18岁;(2)结合眼底照相、眼底荧光素血管造影(fundus fluorescein angiography,FFA)与光学相干断层扫描(optical coherence tomography,OCT)仪检查,明确诊断为RVO-ME,包括视网膜中央静脉阻塞(central retinal vein occlusion,CRVO)和视网膜分支静脉阻塞(branch retinal vein occlusion,BRVO);(3)中央视网膜厚度(central retinal thickness,CRT)>250 μm。排除标准:(1)近期有心脑血管意外或者症状的患者;(2)有青光眼病史或者高危房角的患者。

1.2 方法

1.2.1 手术方法 (1)所有患者均知情同意。(2)术前3 d开始局部滴5 g·L^{-1}左氧氟沙星滴眼液,每天4次,每次1滴。(3)患者术前给予复方托吡卡胺滴眼液充分散瞳(即对光反射消失),分别给予50 g·L^{-1}聚维酮碘溶液1 mL浸泡消毒结膜囊约2 min和生理盐水20 mL冲洗结膜囊,盐酸丙美卡因滴眼液行表面麻醉。(4)Zeiss S88显微镜下操作:采用30G注射针头在距离角膜缘3.5~4.0 mm的巩膜处穿刺至眼球中心,注入雷珠单抗0.05 mL(10 g·L^{-1});或采用DEX自带的22G无菌专用给药器,在距离角膜缘3.5~4.0 mm的巩膜处穿刺,注入DEX 0.7 mg。(5)按压穿刺口,再次给予50 g·L^{-1}聚维酮碘溶液1 mL消毒穿刺口和生理盐水20 mL冲洗结膜囊。(6)予3 g·L^{-1}氧氟沙星眼膏包眼。

1.2.2 观察指标 所有患者治疗前后均需接受视力、眼压、角膜曲率、裂隙灯与OCT等检查。术后观察指标:两组患者注射一针药物(Ozurdex或雷珠单抗)后的最佳矫正视力(best corrected visual acuity,BCVA)、眼压、CRT、药效持续时间和不良反应等。其中通过黄斑区水平位及垂直位的CRT的平均值为CRT,治疗前后的BCVA以最小分辨角对数(logMAR)表示。DEX组随诊时间为4.1~12.7(8.45±3.18)个月;抗VEGF组随诊时间为2.0~10.0(4.42±2.05)个月。

1.3 统计学方法 采用SPSS 20.0统计学软件对数据进行分析。计量资料用均数±标准差表示,采用t检验;计数资料采用卡方检验。检验水准:$\alpha=0.05$。

2 结果

2.1 两组间基本资料比较 治疗前两组基本资料比较见表1,差异均无统计学意义(均为$P>0.05$),具有可比性。

表1 两组患者的一般资料比较

指标	DEX组	抗VEGF组	χ^2值/t值	P值
人数/例	11	31	-	-
性别(男/女)	6/5	13/18	0.521*	0.470
年龄/岁	61.40±6.86	64.61±9.90	0.434**	0.667
BRVO/CRVO	5/6	22/9	2.302*	0.129
术前BCVA(logMAR)	0.901±0.459	1.001±0.465	-0.618**	0.540
术前CRT/μm	677.50±174.93	632.69±269.31	0.626**	0.536
治疗方式(IVJ/+Laser)	3/8	6/25	0.302*	0.582

注:*表示采用χ^2检验;**表示采用独立样本t检验;IVJ表示玻璃体内注射;+Laser表示玻璃体内注射联合激光治疗

2.2 BCVA与CRT 玻璃体内注射第一针药物后1个月,DEX组与抗VEGF组两组间BCVA、CRT比较差异均无统计学意义($t=-0.471$,$P=0.640$;$t=-0.625$,$P=0.536$)。两组间CRVO的BCVA及CRT比较差异均无统计学意义($t=-0.911$,$P=0.379$;$t=-1.769$,$P=0.111$),BRVO的BCVA及CRT比较差异均无统计学意义($t=0.286$,$P=0.778$;$t=1.095$,$P=0.284$)。DEX组在治疗后1个月、2个月、3个月和4个月BCVA与治疗前比较差异均有统计学意义($t_1=4.213$,$P_1=0.002$;$t_2=4.308$,$P_2=0.002$;$t_3=3.011$,$P_3=0.013$;$t_4=2.454$,$P_4=0.034$),治疗后6个月与治疗前比较差异无统计学意义($t=2.307$,$P=0.054$);DEX组治疗后1个月、2个月、3个月、4个月和6个月CRT与治疗前比较差异均有统计学意义($t_1=6.554$,$P_1<0.001$;$t_2=7.434$,$P_2<0.001$;$t_3=4.449$,$P_3=0.001$;$t_4=2.673$,$P_4=0.023$;$t_6=3.198$,$P_6=0.015$),见表2。DEX组中BRVO与CRVO在对应时间点比较(除1个月CRT外),差异均无统计学意义(均为$P>0.05$),见表3。抗VEGF组在治疗后1个月BCVA为(0.642±0.444)logMAR与治疗前(1.001±0.465)

logMAR 比较差异有统计学意义(t = 3.805, P = 0.01);CRT 为(324.82 ± 197.65)μm,与治疗前(632.69 ± 269.31)μm 比较差异有统计学意义(t = 5.912, P < 0.001)。抗 VEGF 组中 BRVO 与 CRVO 在各时间点比较,差异均无统计学意义(均为 P > 0.05),见表 4。玻璃体内注射 Ozurdex 的典型患者治疗前后眼底的变化见图 1。

表 2 DEX 组患者治疗前后 BCVA、CRT 的比较

指标	治疗前	治疗后				
		1 个月(n = 11)	2 个月(n = 11)	3 个月(n = 11)	4 个月(n = 11)	6 个月(n = 8)
BCVA/logMAR	0.901 ± 0.459	0.571 ± 0.364 *	0.458 ± 0.315 *	0.558 ± 0.373 *	0.652 ± 0.468 *	0.621 ± 0.330
CRT/μm	677.50 ± 174.93	286.09 ± 86.91 *	238.95 ± 43.46 *	350.23 ± 163.95 *	481.19 ± 212.65 *	484.50 ± 224.18 *

注:* 表示与治疗前比较,P < 0.05

表 3 DEX 组患者 BRVO 与 CRVO 治疗前后 BCVA、CRT 的比较 ($\bar{x} \pm s$)

指标	治疗前		治疗后									
			1 个月		2 个月		3 个月		4 个月		6 个月	
	BRVO(n = 5)	CRVO(n = 6)	BRVO(n = 5)	CRVO(n = 6)	BRVO(n = 5)	CRVO(n = 6)	BRVO(n = 5)	CRVO(n = 6)	BRVO(n = 5)	CRVO(n = 6)	BRVO(n = 3)	CRVO(n = 5)
BCVA/logMAR	0.918 ± 0.502	0.886 ± 0.467	0.648 ± 0.454	0.508 ± 0.299	0.524 ± 0.333	0.404 ± 0.319	0.708 ± 0.400	0.433 ± 0.330	0.740 ± 0.610	0.579 ± 0.355	0.540 ± 0.408	0.669 ± 0.315
CRT/μm	592.60 ± 209.70	748.25 ± 113.19	341.90 ± 87.08	239.58 ± 57.71	258.10 ± 28.69	223.00 ± 49.46	385.20 ± 177.66	321.08 ± 162.07	396.80 ± 224.60	551.50 ± 192.44	332.17 ± 218.20	575.90 ± 190.52
$t_{BCVA值}$	0.109		0.616		0.610		1.251		0.548		-0.508	
$P_{BCVA值}$	0.916		0.553		0.557		0.242		0.597		0.630	
$t_{CRT值}$	-1.574		2.339		1.396		0.626		-1.232		-1.667	
$P_{CRT值}$	0.150		0.044		0.196		0.547		0.249		0.147	

表 4 抗 VEGF 组患者 BRVO 与 CRVO 治疗前后 BCVA、CRT 的比较 ($\bar{x} \pm s$)

指标	治疗前		治疗后 1 个月	
	BRVO(n = 22)	CRVO(n = 9)	BRVO(n = 22)	CRVO(n = 9)
BCVA/logMAR	0.973 ± 0.444	1.071 ± 0.536	0.595 ± 0.359	0.756 ± 0.617
CRT/μm	597.14 ± 235.80	719.61 ± 337.72	282.82 ± 112.56	427.50 ± 310.67
$t_{BCVA值}$	-0.525		-0.737	
$P_{BCVA值}$	0.604		0.478	
$t_{CRT值}$	-0.993		-1.361	
$P_{CRT值}$	0.341		0.207	

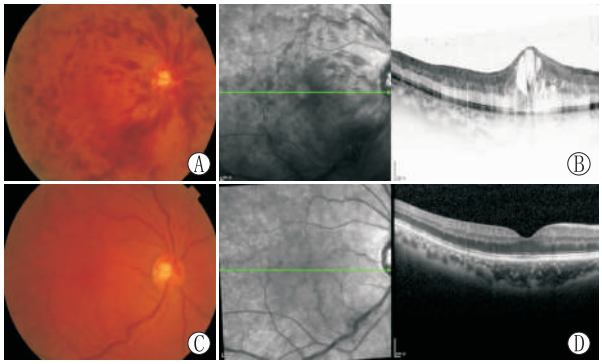

图 1 一例典型的 CRVO 患者注射 Ozurdex 前后的眼底照片及 OCT 对比情况。 A:治疗前眼底照相;B:治疗前黄斑区 OCT 情况;C:治疗后 6 个月眼底照相;D:治疗后 3 个月黄斑区 OCT 情况,水肿消除,黄斑中心凹形态恢复

2.3 疗效观察 在随诊时间内,DEX 组中 63.64%(7/11)患者在注射后 3 ~ 4 个月出现复发情况,其中 5 眼为 CRVO(5/6, 83.33%),2 眼为 BRVO(2/5, 40.00%)。抗 VEGF 组中 74.19%(23/31)患者在注射后 2 个月内出现复发或者水肿未完全消退,其中 7 眼为 CRVO(7/9, 77.78%),16 眼为 BRVO(16/22, 77.73%)。

2.4 不良反应 DEX 组中有 4 眼(36.36%)出现高眼压,其中 25 ~ 35 mmHg(1 kPa = 7.5 mmHg)者 3 眼,>35 mmHg 者 1 眼,使用 2 ~ 3 种降眼压滴眼液局部滴用后眼压恢复正常;抗 VEGF 组中 1 眼出现高眼压(25.5 mmHg, 3.23%)。两组间高眼压的发生率差异有统计学意义(χ^2 = 8.501, P = 0.004)。两组患者均无白内障加重、玻璃体积血、眼内炎、视网膜脱离、晶状体损伤等不良反应发生。

3 讨论

RVO 的病因非常复杂,发病机制目前仍未完全明确。过去视网膜激光光凝封闭无灌注区作为治疗 RVO 的一种手段[9-10]。后来大量研究表明,玻璃体内注射抗 VEGF 药或激素可使 RVO-ME 得到缓解[11]。本研究采用 Ozurdex 与雷珠单抗分组对照治疗,发现 Ozurdex 对 RVO-ME 可产生类似于雷珠单抗的短期疗效(BCVA 提高,CRT 改善),这与以往研究一致[12-13]。Ozurdex 注射后 1 个月开始,RVO-ME 患者就在解剖及功能上产生效果。疗效在注射后 1 ~ 2 个月达到最高峰。解剖上疗效可持续至治疗后 6 个月,但 6 个月时 BCVA 与术前比较差异无统计学意义。本研究还统计了 Ozurdex 对 BRVO 和 CRVO 的治疗效果,差异无统计学意义。本研究探讨的是治疗 RVO-ME 的短期疗效,由于雷珠单抗的药效持续时间一般为 1 个月。故本研究对两组间的疗效比较时间选取注射后 1 个月,差异均无统计学意义(均为 P > 0.05)。两组间 BRVO、CRVO 比较,差异均无统计学意义(均为 P > 0.05)。

DEX 组与抗 VEGF 组在随诊时间内的复发率(或 ME 未完全消除率)均偏高。注射一针后,DEX

组的复发率为63.64%。国外Lin等[14]研究发现，RVO-ME的患者注射Ozurdex后随访6个月以上，只有44.12%的患者注射一针可以缓解ME。抗VEGF组的复发率为74.19%，这与国外研究(77.5%)[15]基本一致。目前，RVO复发的机制尚未完全明确，本研究未作进一步探讨。但本研究发现，DEX组的药效持续时间为3~4个月，抗VEGF组则<2个月。在治疗时效性上Ozurdex较雷珠单抗有优势。Haller等[16]的GENEVA Ⅲ期临床研究表明，注射单针Ozurdex后其药效可维持6个月以上。Coscas等[17]研究也发现，Ozurdex治疗RVO-ME，第一针后平均间隔5.9个月后需重复注射，第二针后平均间隔8.7个月后需重复注射。但本研究的结果却不一致。本研究发现Ozurdex的药效持续时间少于6个月。这与Chang-Lin等[18]、Querques等[19]、Parravano等[20]的研究相一致。

另外，DEX组的高眼压比例(36.36%)较抗VEGF组(3.23%)高，眼压升高的程度也较明显。国外的报道却只有16%~20%患者出现高眼压情况并需要治疗[16,21]。Ozkaya等[22]发现，在2 a的随访中，注射Ozurdex的患者白内障加重的比例高达46.1%，雷珠单抗组却只有5.7%。本研究中两组患者中均未见白内障加重情况，考虑与随诊时间短有关。本研究中两组患者均未发现玻璃体积血、视网膜脱离、眼内炎、晶状体损伤等严重并发症发生，均未发现新的不良反应。

本研究通过Ozurdex与雷珠单抗的对比研究发现，Ozurdex在治疗RVO-ME(包括BRVO和CRVO)上有明显的疗效，维持时效为3~4个月(少于6个月)，较雷珠单抗长；但是眼压仍是其需密切监控的主要不良反应。本研究存在不足之处：DEX组观察的病例数少，随诊时间较短。在以后的研究中，我们将加大样本量，继续跟踪随访，对Ozurdex治疗RVO-ME患者的远期疗效进行研究。

参考文献

[1] ROGERS S, MCINTOSH R L, CHEUNG N, LIM L, WANG J J, MITCHELL P, *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): 313-319.

[2] THAPA R, BAJIMAYA S, PAUDYAL G, KHANAL S, TAN S, THAPA S S, *et al*. Prevalence, pattern and risk factors of retinal vein occlusion in an elderly population in Nepal: the Bhaktapur retina study[J]. *BMC Ophthalmol*, 2017, 17(1): 162.

[3] STANCA H T, MANEA G. Physiopathology of macular edema in central vein occlusion[J]. *Oftalmologia*, 2012, 56(2): 15-20.

[4] REHAK M, WIEDEMANN P. Retinal vein thrombosis: pathogenesis and management[J]. *J Thromb Haemost*, 2010, 8(9): 1886-1894.

[5] CHEN S D, SUNDARAM V, LOCHHEAD J, PATEL C K. Intravitreal triamcinolone for the treatment of ischemic macular edema associated with branch retinal vein occlusion[J]. *Am J Ophthalmol*, 2006, 141(5): 876-883.

[6] HUANG P, NIU W, NI Z, WANG R, SUN X. A meta-analysis of anti-vascular endothelial growth factor remedy for macular edema secondary to central retinal vein occlusion[J]. *PLoS One*, 2013, 8(12): e82454.

[7] BRAITHWAITE T, NANJI A A, GREENBERG P B. Anti-vascular endothelial growth factor for macular edema secondary to central retinal vein occlusion[J]. *Cochrane Database Syst Rev*, 2010, 10: CD007325.

[8] LONDON N J, CHIANG A, HALLER J A. The dexamethasone drug delivery system: indications and evidence[J]. *Adv Ther*, 2011, 28(5): 351-366.

[9] 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.

[10] PATZ A. Argon laser photocoagulation for macular edema in branch vein occlusion[J]. *Am J Ophthalmol*, 1984, 98(3): 374-375.

[11] PIELEN A, FELTGEN N, ISSERSTEDT C, CALLIZO J, JUNKER B, SCHMUCKER C. Efficacy and safety of intravitreal therapy in macular edema due to branch and central retinal vein occlusion: a systematic review[J]. *PLoS One*, 2013, 8(10): e78538.

[12] CHIQUET C, DUPUY C, BRON A M, APTEL F, STRAUB M, ISAICO R, *et al*. Intravitreal dexamethasone implant versus anti-VEGF injection for treatment-naive patients with retinal vein occlusion and macular edema: a 12-month follow-up study[J]. *Graefes Arch Clin Exp Ophthalmol*, 2015, 253(12): 2095-2102.

[13] POMMIER S, MEYER F, GUIGOU S, BARTHELEMY T, GOBERT F, HAJJAR C, *et al*. Long-term real-life efficacy and safety of repeated Ozurdex® injections and factors associated with macular edema resolution after retinal vein occlusion: The REMIDO 2 Study[J]. *Ophthalmologica*, 2016, 236(4): 186-192.

[14] LIN C J, CHEN H S, SU C W, TIEN P T, LIN J M, CHEN W L, *et al*. The effect of age and initial central retinal thickness on earlier need of repeat Ozurdex® treatment for macular edema due to retinal vein occlusion: a retrospective case series[J]. *J Ocul Pharmacol Ther*, 2017, 33(10): 763-772.

[15] KARAGIANNIS D A, KARAMPELAS M D, SOUMPLIS V M, AMARIOTAKIS C, GEORGALAS I, KANDARAKIS A. Recurrence of macular edema in retinal vein occlusions after treatment with intravitreal ranibizumab (Lucentis)[J]. *Can J Ophthalmol*, 2011, 46(6): 486-490.

[16] HALLER J A, BANDELLO F, BELFORT R, BLUMENKRANZ M S, GILLIES M, HEIER J, *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.

[17] COSCAS G, AUGUSTIN A, BANDELLO F, DE SMET M D, LANZETTA P, STAURENGHI G, *et al*. Retreatment with Ozurdex for macular edema secondary to retinal vein occlusion[J]. *Eur J Ophthalmol*, 2014, 24(1): 1-9.

[18] CHANG-LIN J E, ATTAR M, ACHEAMPONG A A, ROBINSON M R, WHITCUP S M, KUPPERMANN B D, *et al*. Pharmacokinetics and pharmacodynamics of a sustained-release dexamethasone intravitreal implant[J]. *Invest Ophthalmol Vis Sci*, 2011, 52(1): 80-86.

[19] QUERQUES L, QUERQUES G, LATTANZIO R, GIGANTE S R, DEL TURCO C, CORRADETTI G, *et al*. Repeated intravitreal dexamethasone implant (Ozurdex(R)) for retinal vein occlusion[J]. *Ophthalmologica*, 2013, 229(1): 21-25.

[20] PARRAVANO M, ODDONE F, BOCCASSINI B, GIORNO P, CHIARAVALLOTI A, TEDESCHI M, *et al*. Exploring the morphological and functional retinal changes after dexamethasone intravitreal implant (Ozurdex(R)) in macular edema due to retinal vein occlusion[J]. *Ophthalmic Res*, 2014, 51(3): 153-160.

[21] TSERVAKIS I, KOUTSANDREA C, PAPACONSTANTINOU D, PARASKEVOPOULOS T, GEORGALAS I. Safety and efficacy of dexamethasone intravitreal implant (Ozurdex) for the treatment of persistent macular edema secondary to retinal vein occlusion in eyes previously treated with anti-vascular endothelial growth factors[J]. *Curr Drug Saf*, 2015, 10(2): 145-151.

[22] OZKAYA A, TARAKCIOGLU H N, TANIR I. Ranibizumab versus dexamethasone implant in macular edema secondary to branch retinal vein occlusion: Two-year outcomes[J]. *Optom Vis Sci*, 2018, 95(12): 1149-1154.