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长期随访雷珠单抗联合康柏西普治疗年龄相关性黄斑变性 1 例

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[摘　要]　报告雷珠单抗联合康柏西普玻璃体腔注射治疗难治性年龄相关性黄斑变性(age-related macular degeneration，AMD)1例，患者经15次抗血管内皮生长因子(vascular endothelial growth factor，VEGF)治疗55个月后，视力从0.25提高维持至1.0，黄斑光学相干断层扫描成像(optical coherence tomography，OCT)提示病灶逐渐缩小并趋于稳定。抗VEGF是治疗AMD的首选有效方法，其个性化治疗非常重要，在治疗过程中还需考虑药物的延迟应答，且OCT在观察AMD的病情变化中具有良好的应用价值。

[关键词]　雷珠单抗；康柏西普；年龄相关性黄斑变性；延迟应答

Long-term outcome with intravitreal injections of lucentis and conbercept in age-related macular degeneration: A case report

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Abstract　This paper reports 1 case of refractory age-related macular degeneration (AMD) treated with combined intravitreal injections of lucentis and conbercept 15 times. After 15 combined injections of lucentis and conbercept, the patient got a gradually increased best corrected visual acuity (BCVA) and a diminishing maculopathy on optical coherence tomography (OCT), both keeping stable at the end of visit. It reveals that intravitreal lucentis combined with conbercept appeared to be an effective treatment for refractory AMD. The management of AMD should be individualized or personalized according diagnosis time and delayed response of drugs. OCT has a good application value in observing the changes of macular anatomical changes in AMD.

Keywords　lucentis; conbercept; age-related macular degeneration; delayed response

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年龄相关性黄斑变性(age-related macular degeneration，AMD)是导致55岁及以上人群视力严重丧失以至致盲的最常见原因[1]，它是发生在黄斑区退行性眼底疾病，伴发脉络膜新生血管(choroidal neovascularization，CNV)从而导致视网膜渗出、出血及纤维瘢痕形成[2]。

AMD发病机制尚不完全明确，常考虑与炎性反应和氧化应激有关。血管内皮生长因子(vascular endothelial growth factor，VEGF)在CNV形成及发展过程中扮演重要角色。临床上治疗AMD以玻璃体内注射抗血管内皮生长因子药物(简称抗VEGF治疗)为首选的一线治疗方法，目前临床常用的药物有雷珠单抗、贝伐单抗、阿柏西普、康柏西普等。雷珠单抗和康柏西普均为通过阻断血管内皮生长因子(vascular endothelial growth factor，VEGF)及其受体(VEGFR)的结合发挥治疗作用，因结构不同，作用机制略有不同。雷珠单抗是一种人源化的重组单克隆抗体片段，只包含抗体的Fab，不含Fc片段，能特异性结合所有VEGF-A，不与VEGF-B和胎盘生长因子结合。康柏西普是一种VEGF受体与人免疫球蛋白Fc段基因重组的融合蛋白，结合所有VEGF-A，VEGF-B和胎盘生长因子，由VEGFR-1中的免疫球蛋白样区域2和VEGFR-2中的免疫球蛋白样区域3和4，与人免疫球蛋白Fc片段经过融合而成。现报告1例使用雷珠单抗联合康柏西普治疗AMD患者，对其随访55个月，途中经历转换抗VEGF药物，经过多疗程治疗后，患者的CNV得到控制。经相关检索，这是目前国内首例随访时间最长、抗VEGF治疗最多次的AMD病例。

1 临床资料

患者，女，63岁，因“右眼视力下降2月余”就诊。既往体健，否认高血压糖尿病冠心病等，无传染病史，无药物实物过敏史，个人无烟酒嗜好，家族无类似疾病史，无遗传病史。首次就诊查体：右眼视力(VOD) 0.25，眼压14 mmHg(1 mmHg=0.133 kPa)，右前节(–)，眼底可见渗出灶。完善眼底荧光血管造影(fluorescence fundus angiography，FFA)及光学相干断层扫描成像(optical coherence tomography，OCT)后诊断：右眼年龄相关性黄斑病变(图1)。按照抗VEGF的3+PRN方案治疗，治疗过程中无全身并发症，无眼红眼痛，眼部感染合并眼内压升高、晶状体进行性混浊等并发症。详细治疗过程及用药详见表1。第1，2次行雷珠单抗治疗后，患者最佳矫正视力(best corrected visual acuity，BCVA)提高不满意，结合OCT的变化，给予中途更换药物，于第3次、第4次行玻璃体腔内注射康柏西普注射液。术后患者BCVA几乎无提高，OCT提示黄斑区病灶改善欠佳，此时考虑康柏西普对患者的药物应答延迟，再次更改用药方案，转雷珠单抗继续治疗，治疗后，药物应答好，患者BCVA及CNV同步改善明显，病情稳定后，考虑到CNV仍有小部分未控制，仍需定期行抗VEGF治疗，患者由于经济原因，提出更换康柏西普治疗，于第12，13，14，15次治疗再次使用康柏西普，患者BCVA及CNV得到很好控制。治疗过程的BCVA及OCT变化见图2，图3。

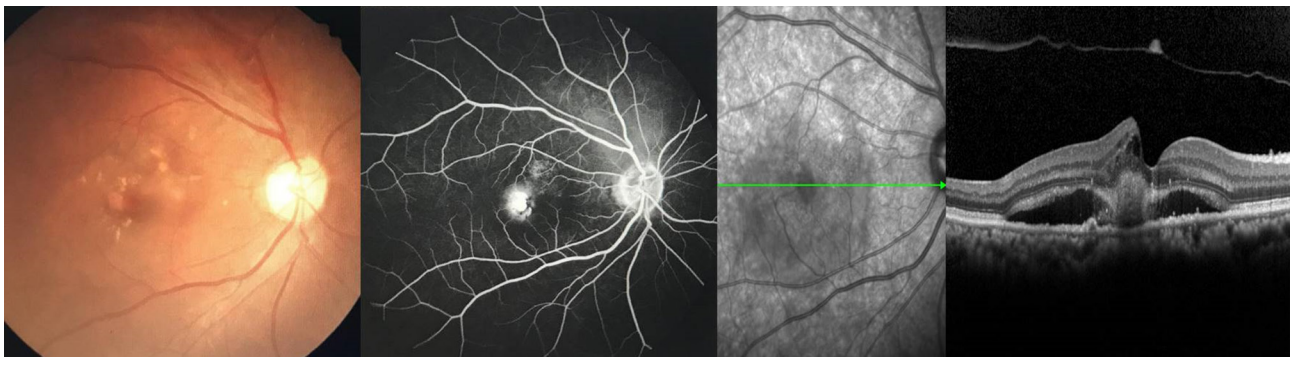

图1 患者治疗前的眼底彩照、FFA及OCT图像

Figure 1 Fundus color image, FFA and OCT images of patient before treatment

眼底彩照可见右眼黄斑区渗出及出血灶。FFA提示黄斑区团片状高荧光。OCT提示黄斑区团块隆起，黄斑水肿。

The fundus color showed blood and the exudation accumulated over the macular region in the right eye. The result of FFA showed high fluorescence signs of dyeing with agglomerate or flake. The OCT showed macular edema and macular damage.

表1 治疗过程一览表

Table 1 List of treatment procedures

抗VEGF次数	发病月数	术前BCVA	术后BCVA	术前CNV高度/μm	术后CNV高度/μm	注射药物
1	1	0.25	0.4	336	315	Lucentis
2	2	0.40	0.6	300	220	Lucentis
3	6	0.50	0.5	340	330	Conbercept
4	9	0.30	0.4	338	335	Conbercept
5	12	0.50	1.0	320	240	Lucentis
6	16	0.50	1.0	252	171	Lucentis
7	19	0.60	1.0	224	183	Lucentis
8	22	0.60	1.0	183	144	Lucentis
9	26	0.60	1.0	176	142	Lucentis
10	30	0.60	1.0	183	163	Lucentis
11	35	0.50	1.0	186	144	Lucentis
12	39	0.60	1.2	135	100	Conbercept
13	43	0.50	0.8	115	105	Conbercept
14	50	0.80	1.0	106	92	Conbercept
15	55	0.80	1.0	110	95	Conbercept

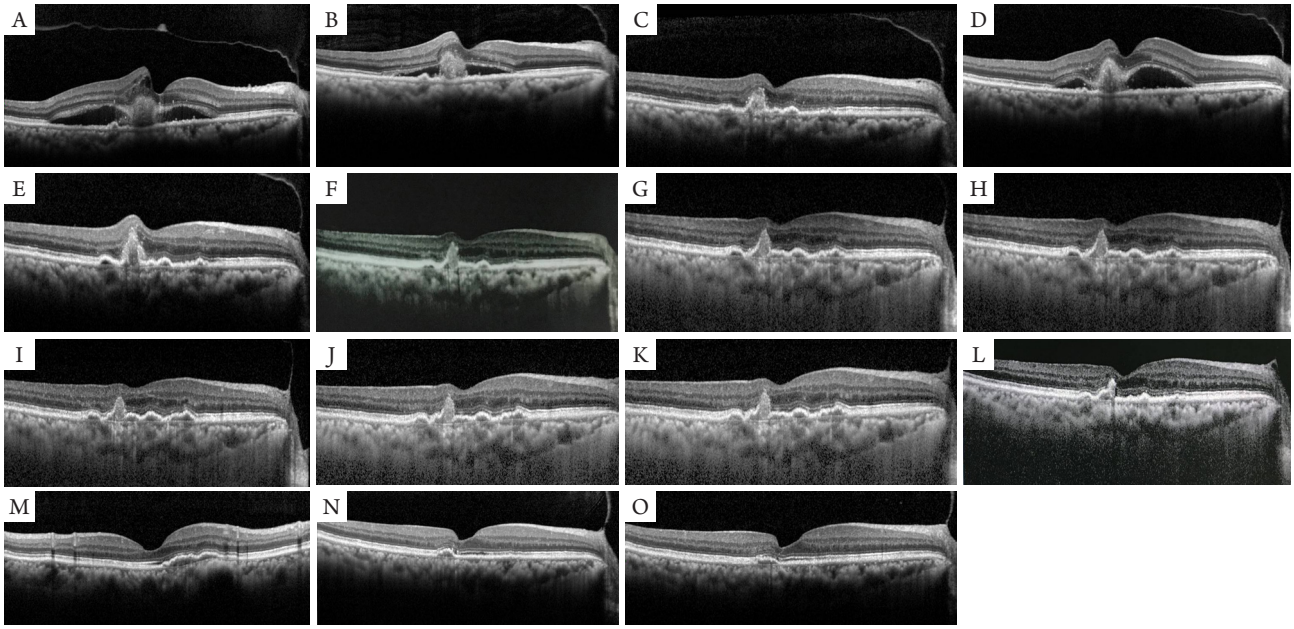

图2 抗VEGF治疗后黄斑区OCT结构变化图

Figure 2 Diagram of OCT structure in macular area after VEGF treatment

(A)术前；(B)抗VEGF × 1；(C)抗VEGF × 2；(D)抗VEGF × 3；(E)抗VEGF × 4；(F)抗VEGF × 5；(G)抗VEGF × 6；(H)抗VEGF × 7；(I)抗VEGF × 8；(J)抗VEGF × 9；(K)抗VEGF × 10；(L)抗VEGF × 11；(M)抗VEGF × 12；(N)抗VEGF × 13；(O)抗VEGF × 14。抗VEGF × 15与注药14次后差别不大。在第6次治疗后，黄斑区病灶稳定，第12次治疗后病灶再一次缩小。

(A) Before operation; (B) anti-VEGF × 1; (C) anti-VEGF × 2; (D) anti-VEGF × 3; (E) anti-VEGF × 4; (F) anti-VEGF × 5; (G) anti-VEGF × 6; (H) anti-VEGF × 7; (I) anti-VEGF × 8; (J) anti-VEGF × 9; (K) anti-VEGF × 10; (L) anti-VEGF × 11; (M) anti-VEGF × 12; (N) anti-VEGF × 13; (O) anti-VEGF × 14. There is little difference at Anti-VEGF × 15. After the 6th treatment, the macular lesion was stable and the lesion shrank again after the 12th treatment.

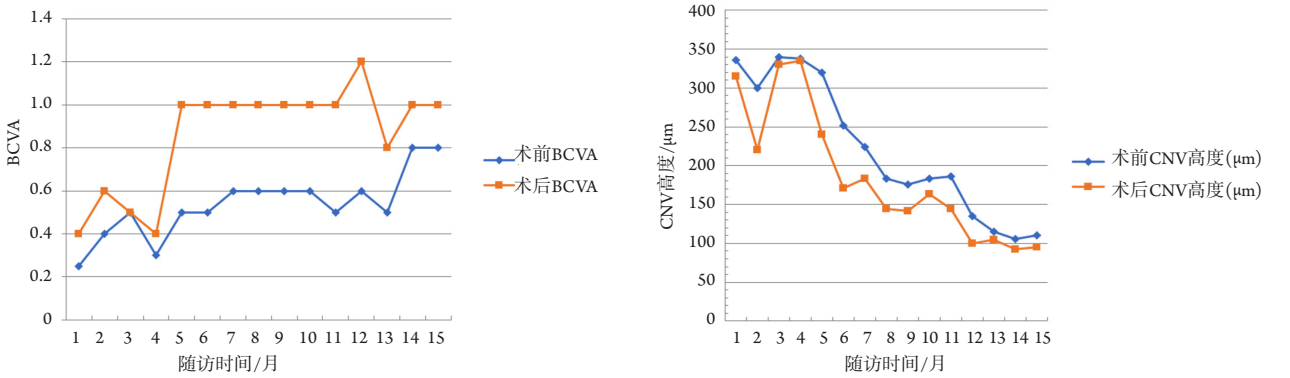

图3 抗VEGF治疗后BCVA及CNV变化

Figure 3 Changes of BCVA and CNV after anti-VEGF treatment

治疗初期BCVA及CNV高度波动较大，治疗后期基本稳定，结合BCVA与CNV高度选择再次注药时机。

Height of BCVA and CNV were fluctuated greatly in the early treatment period, and they were basically stable in the later treatment period. The timing of re-injection was selected based on the height of BCVA and CNV.

2 讨论

AMD的发病年龄一般大于55岁，其病因与环境和遗传因素有较大关系，因发病率随着年龄的增加而显著增高而得名。有学者[3-5]对AMD的全球发病率和进展方案进行了系统分析，结果显示：在55~64岁、65~74岁和75~84岁的人群中，AMD发病率分别为7.2%，13.1%和17.7%，且17.2%的患者并且会继续发展。有研究[6]指出：我国上海地区，致盲人群中约17.96%是AMD患者。临床上湿性AMD是导致视力丧失的主要类型，继发的CNV是视力严重受损的主要原因。玻璃体腔内注射抗VEGF药物能阻止眼内异常血管的生长，防止视力下降，从而达到改善视力的目的。众多研究[7-8]表明：抗VEGF治疗AMD是首选的一线有效及安全的治疗方法。

3+PRN(3：治疗前3个月每月1针，PRN：长期必要时)方案是共识，PRN的选择非常重要。有研究[9]指出AMD治疗无反应已成为眼科越来越关注的问题。本例患者在进行前3针治疗时，治疗效果不好，提示抗VEGF个体化的治疗中仍然存在很多问题，具体到个人，存在长期随访、给药方式、给药种类选择与转换以及药物延迟应答问题。Mimouni等[10]将每月抗VEGF无反应的患者改为每2周频次，治疗后约25%的AMD无反应者有效，且没有不良事件报告发生。因此，在个性化治疗中，我们需要不同的尝试方案来追求最好的效果。本例患者再治疗初期，CNV控制不理想，药物应答迟缓，笔者根据BCVA及CNV的变化来决定是否换药、换药的意义，实践证明，在考虑不同药物的应答反应后，患者的疗效较为满意。研究[11]表明：抗VEGF治疗中约18%~29%早期反应良好，视力上涨，而15%~16%的患者存在药物延迟反应；15%~16%患者的视力显著提高发生在治疗后的4~12个月。Stoller等[12]提出：约25.2%的患者在开始雷珠单抗治疗后3个月内视力较基线提高，而13.7%则需要在12个月内才提高到同一水平。而本例中患者视力的显著提高发生在治疗后12个月，药物延迟应答明显。

本例患者的特别之处在于患者治疗初期对抗VEGF治疗应答差，甚至在更换药物后出现了病情加重，存在较长期的延迟应答，此时的个性化治疗显得尤其重要，本例患者根据BCVA和OCT监测分析，个性化制订治疗方法，OCT在这个过程中扮演了重要的角色。有研究指出OCT可以很好显示视网膜色素上皮脱落、视网膜色素上皮破裂、视网膜积液[13]，起到量化病灶的作用。且在整个随访过程中，OCT能无创快捷准确监测CNV的发展，一旦发现CNV有波动，及时给予抗VEGF治疗，在后期，我们基本维持在6月左右进行1次治疗。长期随访是治疗后的一个重要方面[14]，本例患者属于目前国内随访时间最长，至今达55个月，且在随访过程中并未发现抗VEGF治疗的不良反应，至今国内未见类似报道。

有效控制持续反复的黄斑病变一直是临床治疗的一个挑战，抗VEGF治疗需考虑到患者的病情

及经济情况制订个性化治疗方案，同时也要考虑药物延迟应答等问题。OCT可作为评价AMD患者抗VEGF治疗预后的影像学手段。同时未来也仍需更大样本量或更长时间随访观察来研究验证其长远的治疗及预后。

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