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糖尿病黄斑水肿患者抗VEGF治疗的长期疗效观察及其与视网膜前膜的关系

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摘　要

目的：观察糖尿病黄斑水肿(DME)患者行玻璃体腔内注射抗血管内皮生长因子(VEGF)药物康柏西普治疗后的长期疗效，探讨其与视网膜前膜的相互影响。方法：对2018年3月~2021年3月在青岛大学附属医院接受抗VEGF治疗的120例DME患者的166只眼的临床资料进行回顾性研究。所有患眼均行玻璃体腔注射康柏西普(0.05 ml/0.5mg)治疗，每一个月1次，连续3次，若发现视力下降或CMT ≥ 300 μm则需继续每月注射，直至视力稳定。记录患者治疗前、治疗后1月、3月、6月、12月的最佳矫正视力(BCVA)、黄斑中心视网膜厚度(CMT)及玻璃体黄斑界面异常(VMIA)发生情况。结果：治疗前DME患者logMAR BCVA为0.68 ± 0.38，CMT为(478.96 ± 140.62) μm，治疗后1月、3月、6月、12月logMAR BCVA分别为0.56 ± 0.31 ($Z = -3.207$, $P = 0.001$)、0.46 ± 0.34 ($Z = -6.635$, $P < 0.001$)、0.51 ± 0.35 ($Z = -4.208$, $P < 0.001$)、0.53 ± 0.36 ($Z = -3.980$, $P < 0.001$)，CMT分别为(349.94 ± 86.15) μm ($Z = -6.777$, $P < 0.001$)、(351.59 ± 115.86) μm ($Z = -5.901$, $P < 0.001$)、(408.77 ± 142.14) μm ($Z = -2.419$, $P = 0.032$)、(415.77 ± 118.63) μm ($Z = -2.271$, $P = 0.023$)，与基线相比，BCVA均显著提高，CMT显著下降。治疗前伴有ERM的DME患者基线logMAR BCVA为0.75 ± 0.31，CMT为(481.20 ± 102.75) μm，经抗VEGF治疗后1月、3月、6月、12月logMAR BCVA分别为0.68 ± 0.29 ($Z = -2.115$, $P = 0.034$)、0.58 ± 0.31 ($Z = -3.132$, $P = 0.002$)、0.62 ± 0.28 ($Z = -2.359$, $P = 0.018$)、0.67 ± 0.30 ($Z = -2.558$, $P = 0.011$)，CMT分别为(381.56 ± 71.28) μm ($Z = -3.245$, $P = 0.001$)、(363.19 ± 82.67) μm ($Z = -2.587$, $P = 0.010$)、(412.92 ± 118.80) μm ($Z = -2.436$, $P = 0.012$)、(418.33 ± 109.36) μm ($Z = -2.106$, $P = 0.039$)，与基线相比，BCVA均显著提高，CMT显著下降，差异均有统计学意义($P < 0.05$)。DME患者治疗前ERM发生率为25.90% (43只眼)，经抗VEGF药物治疗后1、3、6、12月时，ERM的发生率分别为31.3% (52只眼)、41.6% (69只眼)、46.4% (77只眼)、48.2% (80只眼)，差异具有统计学意义($\chi^2 = 111.352$, $P < 0.001$)。与治疗前ERM的发生率比较，除治疗后1月差异无统计学意义($P = 0.431$)，治疗后3、6、12月差异均有统计学意义($P < 0.001$)。结论：抗VEGF药物治疗可有效降低DME患者CMT，提高BCVA，治疗后3~6月视力最佳，12月时视力有所下降，但仍明显优于治疗前；抗VEGF治疗可增加ERM的发生率，可能是影响其长期疗效的原因之一。

关键词

糖尿病，黄斑水肿，抗血管内皮生长因子药物，视网膜前膜

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The Long-Term Efficacy of Anti-Vascular Endothelial Growth Factor Therapy in Diabetic Macular Edema Patients and Relationship of Epiretinal Membrane

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Abstract

Objective: To investigate the long-term efficacy of intravitreal injections of anti-vascular endothelial growth factor drug conbercept in diabetic macular edema patients and interaction with epiretinal membrane. Method: The present study was a retrospective observational case series, including 166 eyes from 120 patients with DME, who were diagnosed and treated at Ophthalmology, the Affiliated Hospital of Qingdao University, between April 2018 and March 2021. All patients completed three consecutive monthly intravitreal injections of conbercept 0.5 mg. Monthly injections have to be continued if a decrease in BCVA due to DME or CMT ≥ 300 μm were observed investigator's opinion and were continued until stable visual acuity was reached. Morphological characteristics potentially associated with prognosis were assessed at baseline, month 1, month 3, month 6 and years 1 of follow-up. Results: The BCVA (log MAR) at baseline was 0.68 ± 0.38 and 0.56 ± 0.31 (Z = −3.207, *P* = 0.001), 0.46 ± 0.34 (Z = −6.635, *P* < 0.001), 0.51 ± 0.35 (Z = −4.208, *P* < 0.001)、0.53 ± 0.36 (Z = −3.980, *P* < 0.001) at 1, 3, 6, 12 months, respectively. Similarly, CMT reduced from (478.96 ± 140.62) μm to (349.94 ± 86.15) μm (Z = −6.777, *P* < 0.001), (351.59 ± 115.86) μm (Z = −5.901, *P* < 0.001)、(408.77 ± 142.14) μm (Z = −2.419, *P* = 0.032), (415.77 ± 118.63) μm (Z = −2.271, *P* = 0.023) at 1, 3, 6, 12 months, respectively. The BCVA (log MAR) at baseline in DME patients with ERM was 0.75 ± 0.31 and 0.68 ± 0.29 (Z = −2.115, *P* = 0.034)、0.58 ± 0.31 (Z = −3.132, *P* = 0.002), 0.62 ± 0.28 (Z = −2.359, *P* = 0.018), 0.67 ± 0.30 (Z = −2.558, *P* = 0.011) at 1, 3, 6, 12 months, respectively. Similarly, CMT reduced from (481.20 ± 102.75) μm to (381.56 ± 71.28) μm (Z = −3.245, *P* = 0.001), (363.19 ± 82.67) μm (Z = −2.587, *P* = 0.010), (412.92 ± 118.80) μm (Z = −2.436, *P* = 0.012), (418.33 ± 109.36) μm (Z = −2.106, *P* = 0.039) at 1, 3, 6, 12 months, respectively. Significant differences all could be found after treatment, while the visual prognosis was poorer in DME patients with ERM at baseline. ERM was identified in 43 (25.90%) eyes at baseline, 52 (31.3%, *P* = 0.431) eyes at 1 month, 69 (41.6%, *P* < 0.001) eyes at 3 months, 77 (46.4%, *P* < 0.001) eyes at 6 months and 80 (48.2%, *P* < 0.001) eyes at 12 months. Significant probabilities for differences were considered after Bonferroni correction (alpha = 0.05/10 = 0.005). The study showed that the incidence of ERM increased with an increasing number of injections (χ^2 = 111.352, *P* < 0.001). Conclusion: Anti-VEGF therapy is effective in the DME treatment, as demonstrated by BCVA improvement and CMT decrease. Better visual prognosis could be obtained at 3 to 6 months after treatment, followed by 12 months. Intravitreal anti-VEGF therapy was associated with ERM development and progression, that it may be one of the reasons affecting long-term efficacy.

Keywords

Diabetic, Macular Edema, Anti-Vascular Endothelial Growth Factor Agents, Epiretinal Membrane

1. 前言

糖尿病视网膜病变(Diabetic retinopathy, DR)是糖尿病的重要并发症，是全球成人获得性视力丧失的主要原因之一。糖尿病黄斑水肿(Diabetic macular edema, DME)是糖尿病相关黄斑病变的严重和特征性并发症[1]。近年来，血管内皮生长因子(Vascular endothelial growth factor, VEGF)的发现使 DME 靶向治疗成为可能[2] [3]。目前，在“亚洲人群糖尿病黄斑水肿管理专家小组共识”[4]及英国皇家眼科医师学会 2020 年 DR 指南[5]中，均认为玻璃体腔内注射抗 VEGF 药物是 DME 的一线治疗方法。

然而，临床上仍存在难治性的黄斑水肿，其中一大原因即为玻璃体黄斑界面异常(vitreomacular interface abnormality, VMIA)，其单纯行抗 VEGF 药物治疗效果不佳[6]。根据国际玻璃体黄斑牵拉学组(The International Vitreomacular Traction Study, IVTS)分类的简化版本对玻璃体黄斑关系进行分类：不完全性玻璃体后脱离(incomplete posterior vitreous detachment, IVD)、完全性玻璃体后脱离(complete posterior vitreous detachment, PVD)、玻璃体黄斑牵引(vitreomacular traction, VMT)、视网膜前膜(epiretinal membrane, ERM) [7]。有研究发现存在 ERM 的 DME 患者对抗 VEGF 药物敏感性显著下降[8]，然而具体机制尚不明确，相关报道较少，因此本研究拟对行抗 VEGF 治疗的 DME 患者进行回顾性分析，观察治疗后的长期疗效、ERM 发生率以及二者可能存在的关系，希望为临床治疗更优方案提供数据支持。

2. 对象与方法

2.1. 研究对象

本研究最初纳入于 2018 年 3 月~2021 年 3 月在我院接受玻璃体腔注射抗 VEGF 药物治疗的 260 例 DME 患者 342 只眼作为研究对象，由于失访等原因，有 140 位患者 176 只眼被排除在外，最终选取 120 例 DME 患者的 166 只眼，纳入标准：① 符合世界卫生组织制定的 2 型糖尿病的诊断标准[9]；② 经裂隙灯、光学相干断层成像(optical coherence tomography, OCT)确诊为 DME；③ OCT 示 CMT > 250 μm。排除标准：① 既往玻璃体视网膜手术史的患者或因黄斑前膜需行 PPV 手术者；② 患有眼内疾病如青光眼、肿瘤、先天性眼部疾病等；③ 高度近视患者(≥6D)；④ 屈光间质不清眼底检查困难者。

2.2. 研究方法

收集所有研究对象的年龄、性别、糖尿病病程、PRP 病史、术前白内障手术史、抗 VEGF 药物注射次数以及 OCT 检查结果。所有患眼均行玻璃体腔注射 10 mg/ml 的康柏西普 0.05 ml (含康柏西普 0.5 mg)治疗，每一个月 1 次，连续 3 次，其后每月复查，若出现 BCVA 下降或 CMT ≥ 300 μm，则再次给予抗 VEGF 治疗。所有手术由同一名眼底病医师完成。所有患者随访周期均为 12 个月。本研究已获得所有研究对象的知情同意。

2.3. 疗效与不良反应指标

主要观察指标是在 12 个月随访期内 BCVA、CMT 及 ERM。次要观察指标包括注射次数及任何记录的不良反应。

2.4. 统计学方法

通过 SPSS26.0 统计软件处理数据，BCVA、CMT、注射次数以均数 ± 标准差($\bar{x} \pm s$)表示。常规数据采用 Shapiro-Wilk 检验进行正态性检验。Wilcoxon 符号秩检验和 Cochran's Q 检验用于对比治疗前后的数据，Bonferroni 法校正 P 值，所有检验的显著性在 $P \leq 0.05$ 被认为有统计学意义。

3. 结果

3.1. 纳入患者基本情况

总共 166 只眼纳入研究，表 1 概述基线特征。

Table 1. Clinical baseline characteristics of patients
表 1. 患者基线特征

基线特征(166 只眼)	
年龄(岁，$\bar{x} \pm s$)	60.72 ± 9.97
性别(例)	
男	47
女	73
糖尿病病程(年，$\bar{x} \pm s$)	12.61 ± 7.39
PRP 病史(例)	
是	93
否	73
白内障手术史(例)	
是	44
否	122
注射次数(次)	6.24 ± 2.52
HbA1c (%，$\bar{x} \pm s$)	7.43 ± 2.25
基线 BCVA (logMAR，$\bar{x} \pm s$)	0.68 ± 0.38
基线 CMT (μm，$\bar{x} \pm s$)	478.96 ± 140.62

3.2. 患者治疗前后的 BCVA、CMT 比较

治疗后 1、3、6、12 月的 BCVA 均有提高，CMT 显著下降，以术后 3 月、6 月效果最为显著，差异均有统计学意义。见表 2 及表 3。伴 ERM 的 DME 患者和全部 DME 患者行抗 VEGF 治疗后效果比较见图 1。

Table 2. Comparison of BCVA and CMT in DME patients before and after treatment ($\bar{x} \pm s$)
表 2. DME 患者治疗前后 BCVA、CMT 比较($\bar{x} \pm s$)

	基线	术后 1 月	*P*	术后 3 月	*P*	术后 6 月	*P*	术后 1 年	*P*
BCVA (logMAR)	0.68 ± 0.38	0.56 ± 0.31	0.001	0.46 ± 0.34	<0.001	0.51 ± 0.35	<0.001	0.53 ± 0.36	<0.001
CMT (μm)	478.96 ± 140.62	349.94 ± 86.15	<0.001	351.59 ± 115.86	<0.001	408.77 ± 142.14	0.032	415.77 ± 118.63	0.023

Table 3. Comparison of BCVA and CMT in DME patients with ERM before and after treatment ($\bar{x} \pm s$)
表 3. 伴 ERM 的 DME 患者治疗前后 BCVA、CMT 比较($\bar{x} \pm s$)

	基线	术后 1 月	*P*	术后 3 月	*P*	术后 6 月	*P*	术后 1 年	*P*
BCVA (logMAR)	0.75 ± 0.31	0.68 ± 0.29	0.034	0.58 ± 0.31	0.002	0.62 ± 0.28	0.018	0.67 ± 0.30	0.011
CMT (μm)	481.20 ± 102.75	381.56 ± 71.28	0.001	363.19 ± 82.67	0.010	412.92 ± 118.80	0.012	418.33 ± 109.36	0.039

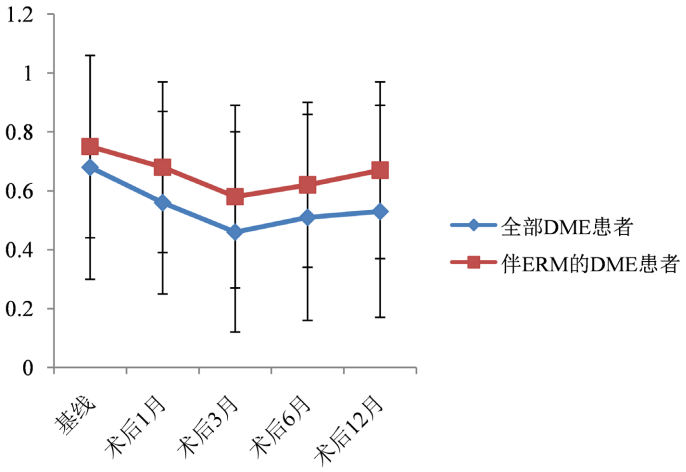

Figure 1. Comparison of therapeutic effects between DME patients and DME patients with ERM
图 1. 伴 ERM 的 DME 患者和全部 DME 患者治疗效果的比较

3.3. 治疗前后 ERM 的发生率

DME 患者治疗前 ERM 发生率为 25.90% (43 只眼)，经抗 VEGF 药物治疗后 1、3、6、12 月时，ERM 的发生率分别为 31.3%、41.6%、46.4%、48.2%，差异有统计学意义，$\chi^2 = 111.352$，$P < 0.001$。见图 2。经 Bonferroni 法校正，进行事后的两两比较，见表 4。

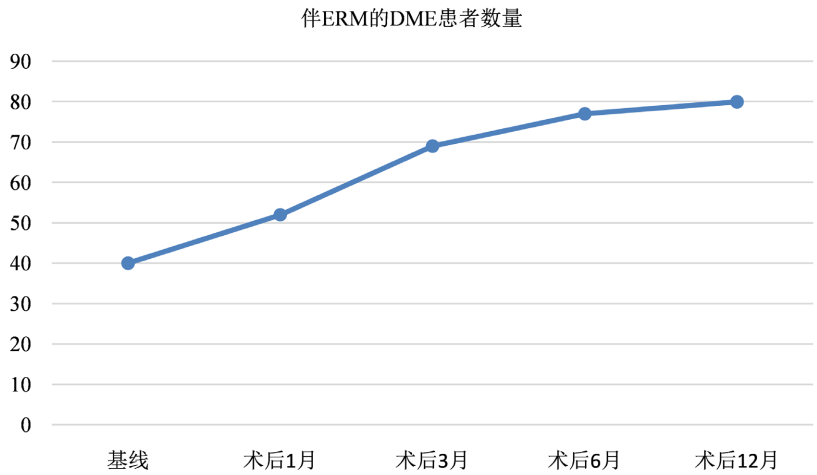

Figure 2. Incidence trend of ERM in DME patients
图 2. DME 患者 ERM 的发生率趋势

Table 4. Comparison of the incidence of ERM before and after treatment
表 4. 患者治疗前后 ERM 的发生率比较

	ERM		χ^2	P^a
	有	无		
基线	43	123		
术后 1 月	52	114		0.431
术后 3 月	69	97	111.352	<0.001
术后 6 月	77	89		<0.001
术后 1 年	80	86		<0.001

注：a：Cochran's Q 检验，经 Bonferroni 法校正后，与基线进行两两比较，调整后 $\alpha = 0.005$。

4. 讨论

糖尿病是一种临床常见的代谢性疾病，DR 可出现在糖尿病各个时期，血管内皮生长因子被认为是 DR 发病的关键因素[10]。血管内皮生长因子可引起血－视网膜屏障的破坏，诱导细胞外液体在黄斑区积聚，进而引起视力下降，严重影响患者生活质量。视力丧失是多种病理生理机制的结果，包括玻璃体出血、视网膜脱离或出现新生血管。视网膜病变发生于大多数病程较长的糖尿病患者，但通过积极控制血糖可降低其发病率[11]。目前，玻璃体腔内注射抗 VEGF 药物被认为是 DME 的一线治疗方法[12] [13] [14]。国内外研究均有报道抗 VEGF 药物的有效性和安全性[15] [16] [17] [18] [19]。本研究的结果与以往的研究结果一致，术后 BCVA 提高，CMT 降低，差异有统计学意义。

随着年龄增长，玻璃体逐渐液化，液化的玻璃体穿过玻璃体后皮质进入视网膜前可形成 PVD，PVD 的形成与玻璃体液化及玻璃体视网膜粘连减弱紧密相关[20]。一种被广泛接受的理论认为，ERM 是由异常的 PVD 引起的，部分玻璃体后皮质牵拉黄斑区，引起黄斑水肿，部分残留的玻璃体后皮质可参与形成视网膜前膜[21] [22]。视网膜前膜中的胶质细胞和肌成纤维细胞等促进视网膜上细胞黏附和增殖，加强了玻璃体后皮质与黄斑之间的粘连[23]。此外有研究认为多次玻璃体腔内注射也会增加 PVD 发生的可能性[24] [25]，本研究中随着 DME 患者注射次数的增加，ERM 的发生率也增加，更加印证了这一观点。

虽然术后 BCVA、CMT 均优于治疗前，但从结果可观察到术后 3 月、6 月药物治疗效果最为显著，另外，由图 1 可看出治疗前便合并有 ERM 的 DME 患者经过抗 VEGF 治疗后虽有显著效果，但视力获益差于不伴 ERM 的患者，且随着抗 VEGF 治疗次数的增加，伴有 ERM 的 DME 患者增加，综上考虑这可能是因为患者对抗 VEGF 药物的敏感性有所下降。合并 ERM 的 DME 患者伴有玻璃体的持续牵引，加重血－视网膜屏障的损害，引发慢性炎症反应[26] [27]，另外由于 ERM 的粘附和牵引力，使得通过 ERM 的抗体通透性的抵抗力增加[28]。这就决定了抗 VEGF 药物单一治疗的局限性，因此联合玻璃体切除术以解除牵引可更有效治疗 DME 合并 ERM [29] [30]。

抗血管内皮生长因子方案是治疗 DME 的重要方法，通过给予抗血管内皮生长因子药物有助于改善患者视力，缓解黄斑水肿症状。抗 VEGF 药物最初可以预防 DME 进展，但同时可诱导 PVD 的形成，对于合并玻璃体黄斑界面异常的 DME，有效解除牵拉因素，是治疗关键所在。本研究为回顾性临床对照研究，具有无前瞻性研究、随机性较大、样本量偏小等不足之处，因此有待更大样本的 RCT 试验能够进一步证实。

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