·老年人眼部疾病专栏·

新生血管性眼病的治疗进展

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【摘 要】随着人口老龄化和生活质量的提高，以年龄相关性黄斑变性及糖尿病性视网膜病变为主的新生血管性眼病正日益成为影响患者生活质量的主要因素。新生血管性眼病以新生血管形成为主要病理表现，病因复杂、机制多样、预后不佳是其主要特征。近年来激光、抗VEGF药物及手术等多种药物和治疗方法的不断涌现与改进，为该类疾病的治疗带来更多更好的疗法。本文就这一系列新生血管性眼病的治疗进展予以综述。

【关键词】新生血管性眼病；抗VEGF；激光；光动力疗法

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Progress in the treatment of ocular neovascular diseases

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【Abstract】 With population ageing and improvement of life quality, ocular neovascular disease, mainly manifesting as age-related macular degeneration and diabetic retinopathy, gradually becomes a major factor affecting the quality of life in the patients. Neovascularization is its main pathological manifestation. What's more, the disease is characterized by its complicated causes, various mechanisms, and poor prognosis. In recent years, there are a variety of drugs and treatment methods emerged and improved, such as laser therapy, anti-VEGF drugs, and surgical treatment, which have provided more and better therapies to treat such diseases. This article reviewed the advances in the treatment of the ocular neovascular diseases.

【Key words】 ocular diseases, neovascular; anti-VEGF; laser; photodynamic therapy

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新生血管性眼病以新生血管形成为主要病理表现，病理性新生血管不同于正常血管，其内皮不完整导致易渗出、出血，进而出现多种并发症，严重影响患者的视觉质量[1]。常见的新生血管性眼病包括新生血管性年龄相关性黄斑变性（neovascular age-related macular degeneration，nAMD）、增殖性糖尿病性视网膜病变（proliferative diabetic retinopathy，PDR）、早产儿视网膜病变（retinopathy of premature children，ROP）、视网膜静脉阻塞（retinal vein occlusion，RVO）、新生血管性青光眼（neovascular glaucoma，NVG）、新生血管性角膜病（corneal neovascularization）等。随着人口老龄化的日益加剧，年龄相关性黄斑变性及糖尿病性视网膜病变已成为致盲性眼疾的重要组成部分[2,3]。近年来激光、抗血管内皮生长因子（vascular endothelial growth factors，VEGF）药物及手术等多种方法的不断涌现与改进，为该类疾病的治疗带来更多更好的疗法。本文就这一系列新生血管性眼病的治疗进展予以综述。

1 目前对于新生血管性眼病的主要治疗方法

1.1 激光光凝

激光治疗应用于眼科疾病始于上世纪40年代[4]，

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其封闭血管、减少氧耗的功能可达到减少新生血管及渗漏的作用[5]。早期糖尿病视网膜病变治疗研究(Early Treatment Diabetic Retinopathy Study，ETDRS）证明，对于有临床意义的黄斑水肿局部光凝可治疗微血管瘤引起的局部渗漏，而格栅样光凝则用于弥漫性或囊样黄斑水肿。光凝对轻中度黄斑水肿的患者效果明显，可延缓其视功能的损害，并且黄斑水肿早治疗的疗效要好于延期激光治疗[6]。而ETDRS视力表成为了评价糖尿病性黄斑水肿疗效中视力指标的金标准。尽管抗VEGF药物已逐渐成为治疗新生血管性眼病的主流[7]，现如今导航激光用于全视网膜光凝（panretinal photocoagulation，PRP）[4]较传统光凝术定位更加准确，具有治疗时间缩短、治疗疼痛减轻以及光斑更为规则等优势，还可与其他方法伍用[8,9]，是治疗新生血管性眼病不可或缺的方法之一。

1.2 光动力疗法

光动力疗法（photodynamic therapy，PDT）最初用于治疗肿瘤。第二代光敏剂维替泊芬问世后，采用冷激光照射破坏异常的新生血管内皮细胞[10]的疗法于2000年获批用于典型性脉络膜新生血管（choroidal neovascularization，CNV），曾作为AMD的一线治疗方法。而随着培加他尼钠（pegaptanib，Macugen）、雷尼珠单抗（诺适得，ranibizumab Lucentis）等抗VEGF药物的相继问世，这种单一疗法在稳定视力、保护视野等方面不如抗VEGF治疗[11,12]，而且实验证实，PDT治疗AMD可产生急性网膜下积液[12]。采用光学相干断层扫描（optical coherence tomography，OCT）评估视网膜厚度及网膜下积液，是评估眼底新生血管性疾病病情的又一重要指标。因维替泊芬组织特异性不高，常需多次注射，其高昂的费用使得冷激光照射破坏异常的新生血管内皮细胞技术的推广受限。现在更多的是采取PDT伍用抗VEGF药物治疗新生血管性眼病[13,14]，两者的结合能减少急性血管反应，更为有效地封闭新生血管，减少复发以及治疗次数。

1.3 抗VEGF

相对于激光治疗，抗VEGF药物针对新生血管的关键因子——VEGF，具有抗新生血管内皮细胞增生、减少血管渗漏等作用，因此倍受青睐。VEGF是1989年Ferrara等[15]从牛垂体滤泡星状细胞体外培养液中首先提纯出来的，根据其具有促血管内皮细胞有丝分裂的作用而命名。它是一种可溶性二聚体糖蛋白，其家族包含有VEGF-A、VEGF-B、VEGF-C、VEGF-D、VEGF-E和胎盘诱发生长因子（placenta-induced growth factor，PIGF）[2]，目前研究的靶点主要是VEGF-A，在未做特殊说明的情况下通常将VEGF视作VEGF-A。由于外显子剪切的不同，VEGF（-A）有VEGF121，VEGF165，VEGF189，VEGF206四个同分异构体形式[1,16]。

1.3.1 培加他尼钠 由美国Eyetech和Pfizer公司联合开发的人工合成寡核苷酸序列，对VEGF165异构体具有高亲和力，2004年12月美国食品药物管理局（Food and Drug Administration，FDA）批准用于AMD[17]。有学者[18]对PDR患者行培加他尼钠与全视网膜光凝术治疗进行比较，发现培加他尼钠能迅速有效地消退糖尿病性视网膜病变的新生血管。Rinaldi等[17]对20名病理性近视患者行玻璃体腔内注射培加他尼钠后，随访最佳矫正视力、中心网膜厚度、微视野，结果证实培加他尼钠能有效地改善上述指标。在儿童眼疾研究中，培加他尼钠在ROP中的应用同样获得了良好的疗效[19]。但由于其只能结合完整的VEGF165，而不会与其他VEGF异构体或仍有生物活性的VEGF165裂解片段结合，且贝伐珠单抗（bevacizumab，Avastin）和雷尼珠单抗相继问世，治斑剂已逐渐淡出眼科的应用。

1.3.2 贝伐珠单抗 由Genentech公司研制的全长人源化单克隆抗体，可与所有VEGF异构体结合并使其失活，美国FDA批准其用于治疗结肠癌，然而许多临床经验表明，贝伐珠单抗能有效地应对眼部新生血管、减轻黄斑水肿、减少出血、稳定甚至提高视力[11,20,21]。相对于雷尼珠单抗，其价格低廉且疗效显著，但未获准用于眼病，目前在眼科使用仍属于标签外用药[22,23]。

1.3.3 雷尼珠单抗 同样由美国Genentech公司研发，是第二代人源化重组抗VEGF单克隆抗体，由于其不含Fc段，相对分子质量约为贝伐珠单抗的1/3，能结合所有检测到的VEGF异构体及其降解产物，是专用于眼内的药物[22]。年龄相关性黄斑变性治疗比较试验（Comparison of Age-related Macular Degeneration Treatment Trial，CATT）、LUCIDATE、BRAVO、CRUISE等前瞻性随机临床试验均证实，雷尼珠单抗在新生血管性眼病中起到减少渗漏、改善视力、抑制新生血管生长的作用[3,24,25]。同贝伐珠单抗一样，重复注射仍然是新生血管性眼病患者所面临的负担[22,26]，而相伴注射次数增多所带来的白内障、眼压升高、出血、眼内炎、医源性视网膜脱离、视网膜色素上皮层撕裂等并发症[27]也是对眼科医师的一种挑战。

1.3.4 阿柏西普（aflibercept，Eylea，VEGF-Trap-eye） 此药是由Regeneron Pharmaceuticals公司生产的一种包含

有VEGFR-1和VEGFR-2细胞外区的融合蛋白，与单克隆抗体相比，对VEGF有更强的亲和力，还能结合PIGF和VEGF-B，此外在眼内半衰期为18d，是雷尼珠单抗的两倍，但短于贝伐单抗（21d）[28]。同贝伐珠单抗一样，此药最初是为治疗结肠癌研发，COPERNICUS和VIEW两项临床Ⅲ期随机双盲研究[29,30]证实了其在新生血管性眼病中的疗效与安全性。美国FDA已批准其用于治疗nAMD和视网膜中央静脉阻塞（central retinal vein occlusion，CRVO）[16,28]。

1.3.5 康柏西普（conbercept，KH902） 由我国康弘生物公司研制，也是VEGFR1和VEGFR2的融合蛋白[31]，同时也能与PIGF1、PIGF2和VEGF-B结合，除了阿柏西普包含的结构域外，KH902还含有VEGFR-2的第4结构域，这有助于减少药物与细胞外基质的黏附[2]。我国的随机双盲多中心2期临床AURORA试验[32]证实了康柏西普对nAMD有效，并且1次/月，每次2mg，连续12次的治疗在视力提高和中央网膜厚度减少程度均好于其他剂量。实验亦证实其在角膜、脉络膜、视网膜新生血管性疾病中均有良好的抗新生血管的作用[2,31]。我国FDA已批准其用于nAMD的治疗，糖尿病性黄斑水肿的Ⅲ期临床试验也正在进行中。

1.4 玻璃体切除术

自1970年首次应用玻璃体切除术（pars plana vitrectomy，PPV）治疗糖尿病玻璃体出血以来[33]，已成为治疗眼底新生血管引起的难治性黄斑水肿、玻璃体积血、黄斑前膜和视网膜脱离等并发症的有效手段。研究显示，对于难治性黄斑水肿PPV能有效减轻黄斑水肿[34]。Sakamoto等[35]回顾性地分析了58例DME患者采用PPV治疗的69只眼，发现黄斑部没有完整的IS/OS结构的患眼术后视力较差。此外，虹膜新生血管引起的继发性青光眼除了采用抗新生血管的治疗外，还可行小梁切除术、Ahmed Express引流阀植入术等方式控制眼压[21]。

2 难治性新生血管性眼病的治疗措施

2.1 增加治疗剂量

目前贝伐珠单抗常用剂量为1.25mg/次，雷尼珠单抗通常使用0.5mg/次的剂量。但是对于难治性新生血管性眼病，有研究表示可采用提高剂量的疗法。Waisbourd等[36]局部应用2.5mg贝伐珠单抗治疗各种继发性角膜新生血管形成，结果显示，17例患眼中有11例眼角膜新生血管减退，甚至角膜乳化作用减退。但有研究表明，大剂量的贝伐单抗眼内注射治疗nAMD病变会产生速效对药反应[37]。而Fung等[38]和Wykoff等[39]报道了使用雷尼珠单抗2.0mg治疗nAMD可获得长期的视力稳定的效果。

2.2 改变药物

从生物效应上看，培加他尼钠只能阻断VEGF165，贝伐珠单抗和雷珠单抗可有效地阻断所有VEGF-A异构体，新近出现的融合蛋白阿柏西普除了能有效地与VEGFR-1和VEGFR-2结合外，还能阻断PIGF，似乎更有优势。研究表明培加他尼纳可以稳定保持患者的现有视力，雷尼珠单抗和贝伐珠单抗可以使一定比例的患者视力得到提高[22]。新生血管往往退而复现，这可能与药物耐受有关，更换药物常可解决这一问题。如研究显示，26名雷尼珠单抗和（或）贝伐珠单抗治疗后仍活动性渗出的AMD患者改用阿柏西普治疗，6个月后中央网膜厚度下降平均38.6μm，最佳矫正视力平均增加了5.9个ETDRS视力表字母[28]。Bakall等[40]和Heussen等[41]的研究同样显示了换用阿柏西普对雷尼珠单抗和（或）贝伐珠单抗耐药的AMD患者更为有益。病例报道中也显示了阿柏西普对于雷珠单抗眼内注射后并发症治疗的优势[42]。而Lazic等[43]对15名贝伐珠单抗耐药的糖尿病性黄斑水肿患者改为地塞米松眼玻璃体植入剂Ozurdex治疗，随访4个月的研究结果证明了激素的有效性。

2.3 联合治疗

2.3.1 抗VEGF药物联合激光或手术 Di Lauro等[44]对68名PDR患者行术前注射1.25mg贝伐珠单抗的研究中，将患者随机分为假注射组、术前7d注药组、术前21d注药组，结果显示术前玻璃体腔内注射有助于减少视网膜和虹膜新生血管，手术更快更安全，从而使患者获得更佳的预后，并且该研究表明术前7d注药为最佳时期。Diabetic Retinopathy Clinical Research Network[45]于2012年公布一项关于雷尼珠单抗治疗联合即时激光和延期激光治疗DME随访3年的数据。结果显示，在抗VEGF药物治疗后，延期激光组在视力改善程度好于即时激光疗组，平均注药次数延期激光组多于即时激光组，但54%延期激光组患者在后续试验中并未再接受激光治疗，与之前的结果[46,47]一致。RESTORE[48]试验对随访雷尼珠单抗、激光、雷尼珠单抗伍用激光3种治疗12个月的结果分析后，得出了伍用组相对于激光组的DME患者视力改善更佳的结论。Yang等[20]对20只PDR患眼实施贝伐珠单抗2.5mg联合PRP治疗后，患眼玻璃体内出血和视网膜新生血管迅速改善，短期内视力得到明显提高。在糖

尿病性黄斑水肿的治疗中[9]，无灌注区的局部光凝对于贝伐珠单抗是一种有效的补充作用。

抗VEGF联合其他疗法在儿童新生血管性眼病中也同样适用。Autrata等[19]比较培加他尼钠伍用激光与激光联合冷冻治疗3期ROP疗效，结果显示，抗VEGF的应用能有效地稳定ROP网膜的解剖结构，相比于激光在阻止新生血管的复发上也具有明显优势。Gaillard等[49]关于玻璃体腔内注射雷尼珠单抗联合激光光凝、网膜冷冻术治疗晚期Coat病的报道结果显示，所有入组的9名患者在治疗后2周虹膜新生血管消退，视网膜也在4个月后重新发挥作用，其中4名患者恢复了一定的视力。尽管如此，抗VEGF对儿童有无毒副作用、生长发育是否有影响尚待进一步的研究，且儿童的用药剂量还需根据患儿的年龄与病情做更为深入的探讨。

2.3.2 PDT联合抗VEGF或激素治疗 DENALI研究[13]中321名AMD患者随机分为雷尼珠单抗组、雷尼珠单抗联合标准PDT治疗组以及雷尼珠单抗伍用减量PDT治疗组，结果显示抗VEGF伍用标准PDT相对于其他两种方法在视力改善、减轻中央网膜厚度等方面均有优势。在PDT伍用贝伐珠单抗治疗PCV的研究中，88.2%的入组患者避免了3年后视力降低[14]。PDT伍用曲安奈德治疗继发于CNV的AMD，可以减少PDT治疗的次数[50]。

2.3.3 激光联合激素 糖皮质激素作为减轻炎症反应的药物应用于临床各科中效果肯定。Tunc等[51]报导了Tenon囊内注射曲安奈德联合黄斑局部光凝能有效改善糖尿病性黄斑水肿患者治疗早期的视力。Gillies[52]在比较了激光前6周行ITVA和安慰剂治疗，随访6个月后，发现视力比较两组无异，激光前6周ITVA组的视网膜黄斑中心厚度较对照组低，但是该组需要降眼压治疗。Callanan等[8]以最佳矫正视力、OCT和FFA评价激素与激素联合激光治疗黄斑囊样水肿疗效，结果显示，在随访12个月时，最佳矫正视力提高10个字母的患者比例两者差异无统计学意义，但渗漏面积减少和最佳矫正视力平均提高的字母数联合治疗组均好于激素单独治疗组。Pichi等[53]比较Ozurdex联合激光治疗分支RVO Cbranch RVO，（BRVO），相比单独黄斑区格栅样光凝，联合治疗的最佳矫正视力更佳，且延长了眼内注药的时间间隔。

3 小 结

随着人均寿命的增长与生活质量的提高，老龄化所带来的疾病正日益突出，其中新生血管性眼病成为影响日常生活质量的重要因素。目前各种疗法对于新生血管性眼病的治疗各有利弊。眼底激光能减少视网膜耗氧、封闭渗漏、应对新生血管，并且经济实惠。PDT作为一种特殊的激光治疗，曾作为新生血管性眼病的一线治疗方案，但光敏剂因副作用大、治疗费用高而难以推广。抗VEGF药物虽属针对病因的治疗，但新生血管常常退而复现，须重复注射，给患者和整个社会带来经济负担。必要时可多种方法联合治疗，如手术解决并发症与反复发作的难题和激素抗炎治疗等，未来必将诞生更为经济有效的治疗方法。

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