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雷珠单抗联合复方血栓通与单独雷珠单抗治疗渗出老年性黄斑变性的前瞻性随机对照试验研究 *

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摘要 目的:探讨复方血栓通(cFXST)对玻璃体腔注射雷珠单抗(IVR)治疗湿性老年性黄斑变性(wet-AMD)的辅助治疗作用。**方法:**纳入湿性老年性黄斑变性患者 38 例,以 1:1 的比例随机纳入 Lucentis 组(单独玻璃体腔注射雷珠单抗,19 例)和 cFXST 组(玻璃体腔注射雷珠单抗联合复方血栓通,19 例)。Lucentis 组患者每月行玻璃体腔注射雷珠单抗(IVR),共计 3 次;cFXST 组患者除 IVR 外,每日口服 cFXST。分别在基线、玻璃体腔注射 Lucentis 后 1 个月、3 个月记录最佳矫正视力(BCVA)和光学相干断层扫描(OCT)影像上视网膜新生血干至色素上皮下厚度(CNV-PED)。**结果:**cFXST 组 CNV-PED 厚度在 1 月和 3 月分别降低 31.7%和 36.1%,高于 Lucentis 组的 19.7% (P=0.021)、24.2% (P=0.018)。3 个月后,cFXST 组 BCVA 变化 (P=0.045) 及视力提高显著的患者比例(16/16 vs 8/17,P=0.001)明显高于 Lucentis 组。**结论:**每日口服 cFXST 治疗可提高抗 VEGF 治疗老年 wet-AMD 的短期疗效。

关键词:复方血栓通;雷珠单抗;老年性黄斑变性

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Combined Ranibizumab with Fufang Xueshuantong Capsule Vesus Ranibizumab Alone for the Treatment of Exudative Age-related Macular Degeneration: a Prospective Randomized Controlled Pilot Study*

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ABSTRACT Objective: To determine the complementary therapeutic effect of cFXST to intravitreal injection of ranibizumab (IVR) in the treatment of wet-AMD. **Methods:** A total of 38 patients with wet age-related macular degeneration were included and randomly included in the Lucentis group (19 cases) and the cFXST group (19 cases) at a ratio of 1:1. Patients in Lucentis group received three monthly IVR while patients in cFXST also received daily oral supplementation of cFXST in addition to IVR. Best corrected visual acuity (BCVA) and total centerpoint thickness CNV-pigment epithelial detachment (CNV-PED) complex by optical coherence tomography (OCT) were recorded at baseline and 1 month, and 3 months after first intravitreal injection of Lucentis. **Results:** Nineteen patients with wet-AMD were allocated in cFXST group and 19 in Lucentis group. In cFXST group, the thickness of CNV-PED reduced by 31.7% and 36.1% at Month 1 and Month 3, respectively, higher than 19.7% (P=0.021), 24.2% (P=0.018) in Lucentis group. The BCVA increase of cFXST group after 3 months was significantly higher than that of Lucentis group (P=0.045) and the proportion of patients with functional response was also higher in cFXST group after 3 months (16/16 vs 8/17, P=0.001). **Conclusions:** Adjunctive daily oral cFXST might be capable to increase the short-time effectiveness of anti-VEGF therapy.

Key words: Fufang Xueshuantong; Ranibizumab (Lucentis); Age-related macular degeneration

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前言

渗出性年龄相关性黄斑变性(wet-AMD)是全世界老年人失明的主要原因[1]。血管内皮生长因子 (Vascular endothelial growth factor,VEGF)是 AMD 发病的主要致病因子[2],靶向抗 VEGF 药物用于湿性 AMD 具有显著效果[2,3],但仍然有 10-15%

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的患者接受抗 VEGF 治疗后视力丧失,一些渗出性病变在随访期间仍有活动迹象。因此,开发抗 VEGF 药物的替代或辅助治疗方法仍为 AMD 治疗的研究热点。

湿性 AMD 的病理特点是脉络膜新生血管(CNV)和视网膜内或视网膜下液体。CNV 渗漏引起的视网膜内或视网膜下液体破坏了视网膜层的完整性,导致视力丢失。同时,在光学相干断层扫描(OCT)中,中心黄斑厚度(CMT)相应增加[4]。在中医理论中,wet-AMD 又称血瘀证,正如清代唐荣川所著《血证论》中的 " 血流异常 "。血瘀与日语中的 "Oketsu"、韩语中的 "Eohyul" 相似,指机体微循环障碍、血液流变学异常或血液动力学异常所导致的疾病[5]。此外,wet-AMD 与某些血液流变学因素(如血管性血友病因子(vWF)、血浆纤维蛋白原、血浆黏度[6-8])相关性也被现代医学所证实。

复方血栓通(cFXST)是一种临床上多年来应用于玻璃体出血和糖尿病视网膜病变(diabrtic retinopathy,DR)[9]的中药方剂,研究表明其对糖尿病视网膜病变和视网膜静脉阻塞动物模型具有较好的疗效。我们之前已经探索了 cFXST 中核心的单个生物活性成分及其在缓解循环功能障碍中的药理学作用[10-12]。这些生物活性成分已经被证实可以影响血清蛋白如 vWF、血浆纤维蛋白原和凝血酶 III,从而减弱红细胞聚集、降低血浆黏度。然而,目前尚无随机对照研究报告其在 wet-AMD 中的临床疗效。为此,我们开展了一项前瞻性随机对照研究探讨 cFXST 对玻璃体内抗 VEGF 治疗湿性 AMD 患者的辅助疗效,现将研究结果报道如下。

1 材料与方法

1.1 研究设计

本研究为南京医科大学第一附属医院内进行的单中心、随机对照临床试验。本试验已在中国临床试验注册(http://www.chictr.org/cn/ 注册号:ChiCTR-IPR-16009602),按照《赫尔辛基和东京人类宣言》的指导原则进行,经南京医科大学第一附属医院伦理委员会批准(2015-SR-190)。所有患者均获得知情同意。

本次试验中,各组样本量由前期的队列研究数据计算而得。在前期队列研究中,两个试验组在治疗 3 个月后,OCT 检查时 CNV-PED 总中心点厚度有 0.3SD 差异。按照双侧检验(80%检测力度),$P < 0.05$ 为差异有统计学意义,计算得出每组患者需 18 例。共纳入 38 例患者进行研究。

入选标准:(1) 年龄 50 岁以上;(2) 最佳矫正视力(ETDRS)小于 70 个字母;(3) 荧光血管造影 (HRA 2, and Spectralis; Heidelberg Engineering, Germany) 显示活动性脉络膜新生血管形成的渗出性 AMD;OCT (Cirrus; Carl Zeiss Meditec, Inc., Dublin, CA)检测显示视网膜下液体。排除标准包括:(1)视网膜下纤维化或萎缩;(2)吲哚菁绿血管造影证实息肉样脉络膜血管病变(PCV);(3)既往有抗 VEGF 药物治疗、光动力治疗或玻璃体切除术病史;(4)12 个月内发生过心脑血管事件。

将患者随机分为 cFXST 组和 Lucentis 组。每位患者每月进行 3 次玻璃体腔内注射雷珠单抗(1.25 mg,0.05 mL)。cFXST 组患者自首次玻璃体腔注射雷珠单抗以后还每日给予 3 次口服 cFXST (4500 mg/ 天,广东中盛药业股份有限公司,批号:150201,国家医疗许可证号:Z20030017)。Lucentis 组患者自首次玻璃体腔注射雷珠单抗以后每日服用外观与 cFXST 相同的安慰剂。cFXST 由三七、黄芪、丹参、玄参组成,比例为 25:8:8。为了保证整个试验中所有患者使用的 cFXST 的质量一致,我们采用相同的工艺制备胶囊(批号:150301)。

1.2 观测指标

主要观测指标:最大视网膜下液 (SRF) 高度和中心 CNV-PED 厚度。中心 CNV-PED 厚度包括视网膜色素上皮(RPE)厚度、RPE 脱离厚度、视网膜下中央凹处高反射信号厚度(CNV)。我们首先比较了两组患者每次就诊的 OCT 参数与基线参数。然后比较各组在每次随访中这些参数与基线值的变化情况及变化率。变化率定义为比值 = (Hbaseline - Hvisit)/Hbaseline。

次要观测指标:BCVA (字母在 4 m 时使用 ETDRS 图表);治疗应答患者数量(BCVA 较基线改善的患者)。

观测时间点:治疗前、治疗后 1 月、治疗后 3 月。

1.3 统计学分析

采用 SPSS 19.0 进行统计学分析,计量资料数据用均数± 标准差($\bar{x}\pm s$)表示,组内前后比较采用配对 t 检验,组间比较采用成组 t 检验,Fisher 精确 t 检验或 x^2 检验比较两组之间的分类数据。以双侧 P 值 <0.05 为差异有统计学意义。

2 结果

2.1 两组基线资料比较

本研究入组的 38 例患者,cFXST 组 19 例,Lucentis 组 19 例。两组年龄(59.17± 4.03 vs 63.35± 3.65, P=0.445),女性比例(9/19 vs 8/19, P=0.840), 病程 (4.13± 1.60 vs 3.99± 0.98, P=0.939),术前 BCVA (47.56± 5.52 vs 59.11± 3.84, P=0.351),SRF 高度 (176.93± 28.82 vs 164.79± 28.00, P=0.766),CNV-PED 总厚度 (197.93± 13.68 vs 188.35± 14.91, P=0.764),PED 高度 (200.68± 53.89 vs 224.81± 65.54),发生 PED、或视网膜间积液(SRF)或视网膜内液体(IRF)的比例比较差异无统计学意义(P 均 >0.05,表 1)。

2.2 两组 OCT 的改变比较

与基线相比,两组患者随访中 CNV-PED 复合物厚度均显著降低 (图 1A)。cFXST 组患者在治疗一月后和三月后中心 CNV-PED 复合物厚度较基线分别降低 62.71± 10.53 和 71.50 ± 10.55;Luentis 组降低两分别为 27.12± 8.50 (P=0.064) 和 45.56± 9.01(P=0.072)(图 1B)。虽然各组间 CNV-PED 厚度变化无统计学差异,但两组变化比例存在显著差异。cFXST 组 CNV-PED 厚度在治疗后 1 月和 3 月分别下降 31.7%和 36.1%,高于 Lucentis 组的 19.7% (P=0.021)、24.2% (P=0.018)(图 1C)。两组的视网膜下液也明显减轻(图 2A)。cFXST 组 SRF 高度变化及变化比 Lucentis 组稍高,但差异无统计学意义(图 2B、2C)。图 3 为 cFXST 和 Lucentis 组的两个代表性案例。联合治疗的患者 CNV-PED 厚度明显减少(图 3A, C, E, G),而单独使用雷珠单抗对另一患者疗效较差(图 3B, D, F, H)。

2.3 两组 BCVA 的改变比较

cFXST 组 BCVA 均值在基线时为 47.56± 5.52,治疗一月后为 59.68± 5.92(P=0.001),治疗三月后为 62.25± 6.03($P<0.001$)。

表 1 cFXST 和 Lucentis 组患者基线资料的比较

Table 1 Comparison of the baseline Parameters between cFXST group and Lucentis group

Parameters	cFXST group	Lucentis group	*P* value
Number	19	19	-
No. female	9	8	0.840
Age (years)	59.17 ± 4.03	63.35 ± 3.65	0.445
Duration since diagnosis	4.13 ± 1.60	3.99 ± 0.98	0.939
BCVA	47.56 ± 5.52	59.11 ± 3.84	0.351
PED (n)	11	8	0.421
SRF (n)	12	11	0.740
IRF (n)	4	7	0.476
SRF (μm)	176.93 ± 28.82	164.79 ± 28.00	0.766
CNV-PED complex (μm)	197.93 ± 13.68	188.35 ± 14.91	0.764
PED (μm)	200.68 ± 53.89	224.81 ± 65.54	0.780

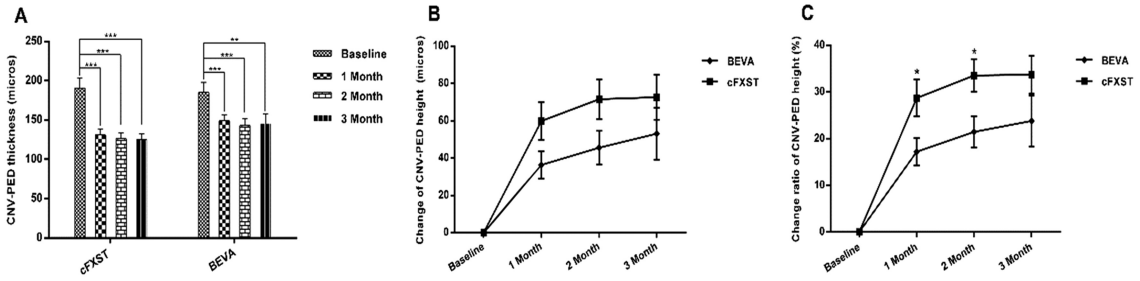

图 1 两组患者治疗后黄斑中心 CNV-PED 的厚度变化比较

Fig.1 Change of centerpoint thickness of CNV-PED complex

(A) The thickness of CNV-PED complex was significantly reduced after treatment in either cFXST group or BEVA group; Paired t test. (B) and (C) Changes and change ratios of thickness of CNV-PED complex in each visit of the two groups; Independent t test. Change: Hbaseline - Hvisit. Change ratio = (Hbaseline - Hvisit)/ Hbaseline.* *P < 0.05*; ** *P < 0.01*; *** *P < 0.001*. Abbreviations: CNV-PED: Choroidal neovascularization-pigment epithelial detachment; cFXST: Combined therapy group of Fufang Xueshuantong Capsule with bevacizumab; BEVA: Bevacizumab alone group.

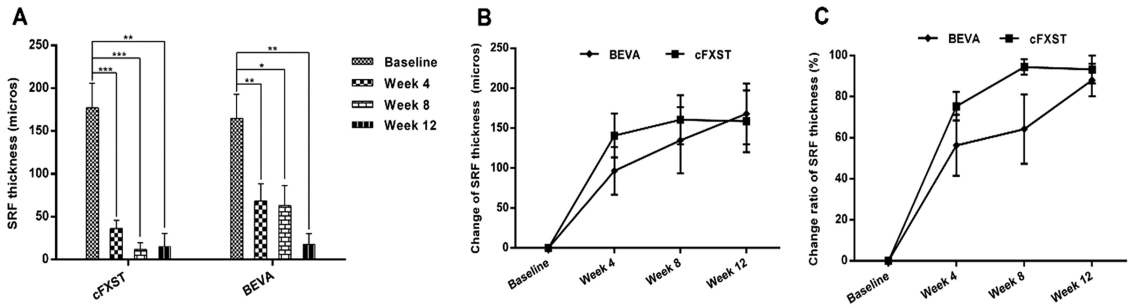

图 2 两组患者治疗后视网膜下液的高度变化

Fig. 2 Change of height of SRF

(A) The thickness of SRF was significantly allivated after treatment in either cFXST group or BEVA group; Paired t test. (B) and (C) Changes and change ratios of height of SRF in each visit of the two groups; Independent t test. Change = Hbaseline - Hvisit. Change ratio = (Hbaseline - Hvisit)/ Hbaseline. * *P < 0.05*; ** *P < 0.01*; *** *P < 0.001*. Abbreviations: SRF: subretinal fluid; cFXST: Combined therapy group of Fufang Xueshuantong Capsule with bevacizumab; BEVA: Bevacizumab alone group.

Lucentis 组的 BCVA 均值在基线时为 59.11± 3.84，治疗一月后为 65.94± 3.29 (*P<0.001*)，治疗三月后为 64.94± 3.57 (*P<0.05*)(图 4A)。cFXST 组 3 个月后 BCVA 改变明显高于 Lucentis 组 (14.68± 2.83 vs 5.82± 3.12, *P*=0.045)(图 4B)。cFXST 组 3 个月后功能反应患者比例也高于 Lucentis 组 (16/16 vs 8/17，*P* = 0.001)。

3 讨论

以往治疗 wet-AMD 患者的脉络膜新生血管有非药物方法，包括激光光凝 [13]、黄斑下手术 [14] 和椎体光动力疗法 (PDT)[15,16]，这些方法均取得了不同程度的成功。自 2006 年雷珠单抗获得批准以来[17,18]，抗 VEGF 治疗的时代到来。到目前为

止，有 4 种眼内 VEGF 抑制剂可用于治疗渗出性 AMD[19,20]，其中 3 种是食品和药物管理局(FDA)批准的，1 种是标签外使用的。就雷珠单抗而言，MARINA 和 ANCHOR 试验已经证明了其治疗上的突破，该试验的观察结果是大约 90%的患者在接受每月一次的雷珠单抗治疗 2 年后，视力丢失少于 15 个字母[21]。虽然抗 VEGF 治疗在渗出性 AMD 方面取得了突破性进展，但仍有部分患者对抗 VEGF 药物反应不佳或无反应，经常规治疗后仍有持续性积液[22-25]。

目前，研究者也在努力寻找新的更有效的治疗策略，包括 PDT 联合治疗[16]、玻璃体切除术[26]、放射疗法[27,28]、低剂量经瞳孔温热疗法[29]、两周一次的抗 VEGF 治疗[30]或辅以玻璃体内皮质类固醇激素[31,32]、补充 ω - 3[33]和外用盐酸多佐胺 - 噻吗洛尔滴眼液[34]进行辅助药理学治疗。然而，这些策略的报告存在不一致性，结果变异性较大。在本研究中，我们将 cFXST 联合玻璃体内雷珠单抗治疗 wet-AMD。我们主要关注的是在 OCT 中看到的中心点 CNV-PED 复合物和视网膜下液，因为这两个指标是与 wet-AMD 进展过程中功能变化相关的最重要的参数。如预期，单独玻璃体腔内注射雷珠单抗可以诱导功能和形态学的显著改善，这与之前的文献一致。但与联合治疗相比，3 个月后 cFXST 组 CNV-PED 复合物厚度平均减少 36.1%，而 Lucentis 组仅减少 24.2%。此外，我们未能检测每次来访时 SRF 变化的组间差异，可能有两个方面的原因。一方面，两组都显著降低了 SRF 的最大高度。另一方面，我们考虑 cFXST 的有效性可能被雷珠单抗所覆盖。值得注意的是，第 3 个月 cFXST 组 BCVA 改善优于 Lucentis 组，这与 OCT 的结果一致。

cFXST 在我国临床应用已有多年，但目前尚无标准的随机对照试验对其疗效进行分析。据我们所知，本研究可能是第一个为中医药治疗渗出性 AMD 提供证据的随机对照临床试验。本临床试验也是基于我们实验室对 cFXST 中核心个体生物活性成分及其在缓解循环功能障碍中的药理学研究结果[11,12]。毫无疑问，抗 VEGF 是治疗渗出性 AMD 的关键。同时，我们认为 cFXST 可以作为一种有效的辅助手段，进一步缓解视网膜微循环障碍，尤其是对于抗 VEGF 治疗反应差或无反应的患者。

当然，我们的研究也有一些局限性，包括样本量不足，随访

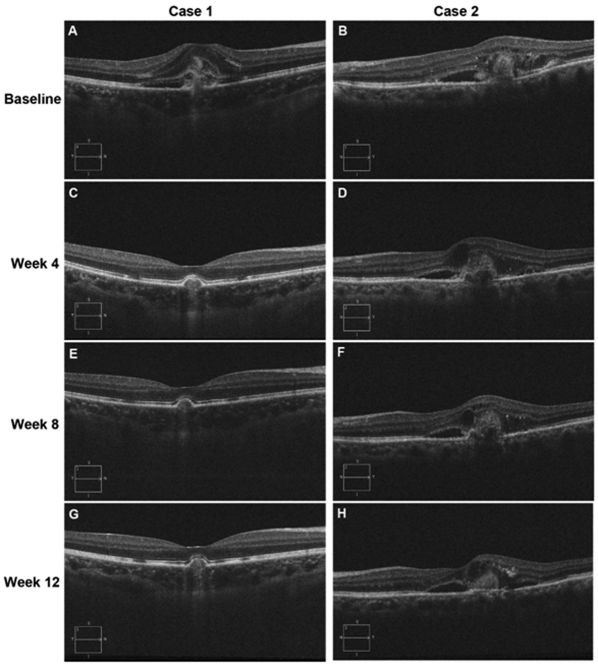

图 3 cFXST 组和 Lucentis 组治疗前后 SD-OCT 图像上黄斑影像学变化

Fig. 3 Macular images obtained by SD-OCT before and after the treatment from one case of cFXST group (A, C, E, G) and Lucentis group (B, D, F, H). After combined therapy, the subretinal fluid (*) was quickly alleviated and the thickness of CNV-PED complex (white arrows) was reduced with a localized PED (△). While subretinal fluid (*) and CNV-PED complex (white arrows) did not remarkably changed after treatment of bevacizumab alone. Abbreviations: SD-OCT: Spectral-domain optical coherence tomography; cFXST: Combined therapy group of Fufang Xueshuantong Capsule with bevacizumab; BEVA: Bevacizumab alone group; CNV-PED: Choroidal neovascularization-pigment epithelial detachment.

时间有限。此外，我们无法区分 cFXST 中哪些成分对本研究中所见的有益效果起作用。在以后的研究中，我们将前瞻性研究不同的给药方法(口服、局部或玻璃体内注射)，鉴定药物中有效的成分在治疗 wet-AMD 的有效性。另外，患者对使用 cFXST 的依从性依赖于自我报告。最后，我们依靠人工测量 CNV-PED 的厚度和 SRF 的高度，而不是自动化的计算机算法，这也可能

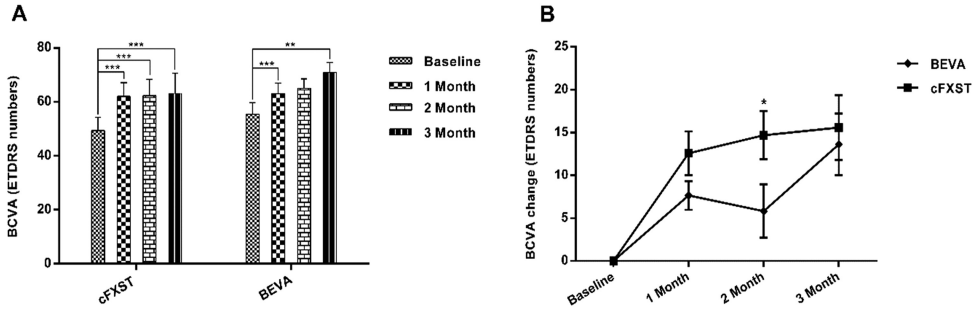

图 4 两组患者治疗后视力的变化

Fig. 4 Comparison of the changes of visual acuity between two groups

(A) BCVA ETDRS letters were was significantly incresed after treatment in either cFXST group or BEVA group; Paired t test. (B) Changes and change ratios of thickness of BCVA ETDRS letters in each visit of the two groups; Independent t test. * *P<0.05*. Change: VAvisit - VAbaseline; Change ratio = (VAvisit - VAbaseline)/ VAbaseline. Abbreviations: BCVA: Best corrected visual acuity; ETDRS: Early treatment diabetic retinopathy study. cFXST: Combined therapy group of Fufang Xueshuantong Capsule with bevacizumab; BEVA: Bevacizumab alone group; VA: Visual acuity.

会引入偏差。

综上所述，每日口服 cFXST 辅助治疗可提高抗 VEGF 治疗湿性 AMD 的短期疗效。然而，需要更大的样本量和更长的随访时间来证实其远期疗效。

参 考 文 献(References)

[1] Wong CW, Yanagi Y, Lee W-K, et al. Age-related macular degeneration and polypoidal choroidal vasculopathy in Asians [J]. Progress in retinal and eye research, 2016, 53: 107-139

[2] Villegas VM, Aranguren LA, Kovach JL, et al. Current advances in the treatment of neovascular age-related macular degeneration[J]. Expert opinion on drug delivery, 2017, 14(2): 273-282

[3] Fan X, Gao N, Li J, et al. Effects of VEGF levels on anti-VEGF therapy for patients with idiopathic choroidal neovascularization [J]. Molecular and cellular biochemistry, 2018, 441(1-2): 173-179

[4] Fragiotta S, Carnevale C, Cutini A, et al. Correlation between retinal function and microstructural foveal changes in intermediate age related macular degeneration [J]. International journal of retina and vitreous, 2017, 3: 8

[5] Chen KJ. Blood stasis syndrome and its treatment with activating blood circulation to remove blood stasis therapy [J]. Chinese journal of integrative medicine, 2012, 18(12): 891-896

[6] Bohni SC, Howell JP, Bittner M, et al. Blood flow velocity measured using the Retinal Function Imager predicts successful ranibizumab treatment in neovascular age-related macular degeneration: early prospective cohort study [J]. Eye (London, England), 2015, 29 (5): 630-636

[7] Lip PL, Blann AD, Hope-Ross M, et al. Age-related macular degeneration is associated with increased vascular endothelial growth factor, hemorheology and endothelial dysfunction[J]. Ophthalmology, 2001, 108(4): 705-710

[8] Yi Z, Chen C, Su Y, et al. Changes in Clotting Time, Plasma Fibrinogen Levels, and Blood Viscosity After Administration of Ranibizumab for Treatment of Choroidal Neovascularization [J]. Current eye research, 2015, 40(11): 1166-1171

[9] XU J-j, MEI B-y, ZHANG N. Clinical observation on early diabetic retinopathy with Compound Xueshuantong Capsule [J]. China Journal of Traditional Chinese Medicine and Pharmacy, 2012, 12

[10] Liu H, Liang JP, Li PB, et al. Core bioactive components promoting blood circulation in the traditional Chinese medicine compound xueshuantong capsule (CXC) based on the relevance analysis between chemical HPLC fingerprint and in vivo biological effects [J]. PloS one, 2014, 9(11): e112675

[11] Sheng S, Wang Y, Long C, et al. Chinese medicinal formula Fufang Xueshuantong capsule could inhibit the activity of angiotensin converting enzyme [J]. Biotechnology, biotechnological equipment, 2014, 28(2): 322-326

[12] Sheng S, Wang J, Wang L, et al. Network pharmacology analyses of the antithrombotic pharmacological mechanism of Fufang Xueshuantong Capsule with experimental support using disseminated intravascular coagulation rats[J]. Journal of ethnopharmacology, 2014, 154(3): 735-744

[13] Chhablani J, Roh YJ, Jobling AI, et al. Restorative retinal laser therapy: Present state and future directions [J]. Survey of ophthalmology, 2018, 63(3): 307-328

[14] Oshima H, Iwase T, Ishikawa K, et al. Long-term results after limited macular translocation surgery for wet age-related macular degeneration [J]. PloS one, 2017, 12(5): e0177241

[15] Gao Y, Yu T, Zhang Y, et al. Anti-VEGF Monotherapy Versus Photodynamic Therapy and Anti-VEGF Combination Treatment for Neovascular Age-Related Macular Degeneration: A Meta-Analysis[J]. Investigative ophthalmology & visual science, 2018, 59(10): 4307-4317

[16] Su Y, Wu J, Gu Y. Photodynamic therapy in combination with ranibizumab versus ranibizumab monotherapy for wet age-related macular degeneration: A systematic review and meta-analysis [J]. Photodiagnosis and photodynamic therapy, 2018, 22: 263-273

[17] Cheung GCM, Lai TYY, Gomi F, et al. Anti-VEGF Therapy for Neovascular AMD and Polypoidal Choroidal Vasculopathy [J]. Asia-Pacific journal of ophthalmology (Philadelphia, Pa), 2017, 6(6): 527-534

[18] Mehta H, Tufail A, Daien V, et al. Real-world outcomes in patients with neovascular age-related macular degeneration treated with intravitreal vascular endothelial growth factor inhibitors[J].Progress in retinal and eye research, 2018, 65: 127-146

[19] Wang L, Zhang C, Hua R. Clinical effectiveness of ranibizumab and conbercept for neovascular age-related macular degeneration: a meta-analysis [J]. Drug design, development and therapy, 2018, 12: 3625-3633

[20] Zhang Y, Chioreso C, Schweizer ML, et al. Effects of Aflibercept for Neovascular Age-Related Macular Degeneration: A Systematic Review and Meta-Analysis of Observational Comparative Studies[J]. Investigative ophthalmology & visual science, 2017, 58(13): 5616-5627

[21] Mitchell P, Liew G, Gopinath B, et al. Age-related macular degeneration[J]. Lancet (London, England), 2018, 392(10153): 1147-1159

[22] Amoaku WM, Chakravarthy U, Gale R, et al. Defining response to anti-VEGF therapies in neovascular AMD[J]. Eye (London, England), 2015, 29(6): 721-731

[23] van Asten F, Rovers MM, Lechanteur YT, et al. Predicting non-response to ranibizumab in patients with neovascular age-related macular degeneration [J]. Ophthalmic epidemiology, 2014, 21 (6): 347-355

[24] Ersoy L, Ristau T, Kirchhof B, et al. Response to anti-VEGF therapy in patients with subretinal fluid and pigment epithelial detachment on spectral-domain optical coherence tomography [J]. Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie, 2014, 252(6): 889-897

[25] Zhang M. Attention to the non-responders to anti-VEGF treatment of wet age-related macular disease[J]. Chinese journal of ophthalmology, 2014, 50(6): 406-410

[26] Schramm K, Mueller M, Koch FH, et al. Effects of core vitrectomy in the treatment of age-related macular degeneration [J]. Acta ophthalmologica, 2014, 92(5): 465-472

[27] Casaroli-Marano RP, Alforja S, Giralt J, et al. Epimacular brachytherapy for wet AMD: current perspectives [J]. Clinical ophthalmology (Auckland, NZ), 2014, 8: 1661-1670

(下转第 3992 页)

mediated by antiphospholipid antibody-induced extracellular vesicles [J]. J Thromb Haemost, 2015, 13(10): 1928-1940

[42] Chaturvedi S, Cockrell E, Espinola R, et al. Circulating microparticles in patients with antiphospholipid antibodies: characterization and associations[J]. Thromb Res, 2015, 135(1): 102-108

[43] Betapudi V, Lominadze G, Hsi L, et al. Anti-beta2GPI antibodies stimulate endothelial cell microparticle release via a nonmuscle myosin II motor protein-dependent pathway[J]. Blood, 2013, 122(23): 3808-3817

[44] Giannakopoulos B, Krilis SA. The pathogenesis of the antiphospholipid syndrome[J]. N Engl J Med, 2013, 368(11): 1033-1044

[45] Arad A, Proulle V, Furie RA, et al. beta (2)-Glycoprotein-1 autoantibodies from patients with antiphospholipid syndrome are sufficient to potentiate arterial thrombus formation in a mouse model [J]. Blood, 2011, 117(12): 3453-3459

[46] Mann KG, Butenas S, Brummel K. The dynamics of thrombin formation[J]. Arterioscler Thromb Vasc Biol, 2003, 23(1): 17-25

[47] Meroni PL, Raschi E, Testoni C, et al. Statins prevent endothelial cell activation induced by antiphospholipid (anti-beta2-glycoprotein I) antibodies: effect on the proadhesive and proinflammatory phenotype [J]. Arthritis Rheum, 2001, 44(12): 2870-2878

[48] Romay-Penabad Z, Aguilar-Valenzuela R, Urbanus RT, et al. Apolipoprotein E receptor 2 is involved in the thrombotic complications in a murine model of the antiphospholipid syndrome [J]. Blood, 2011, 117(4): 1408-1414

[49] McNally T, Mackie IJ, Isenberg DA, et al. beta 2 glycoprotein-I inhibits factor XII activation on triglyceride rich lipoproteins: the effect of antibodies from plasma of patients with antiphospholipid syndrome[J]. Thromb Haemost, 1996, 76(2): 220-225

[50] Schousboe I. Inositolphospholipid-accelerated activation of prekallikrein by activated factor XII and its inhibition by beta 2-glycoprotein I[J]. Eur J Biochem, 1988, 176(3): 629-636

[51] Schousboe I, Rasmussen MS. Synchronized inhibition of the phospholipid mediated autoactivation of factor XII in plasma by beta 2-glycoprotein I and anti-beta 2-glycoprotein I [J]. Thromb Haemost, 1995, 73(5): 798-804

[52] Rahgozar S, Yang Q, Giannakopoulos B, et al. Beta2-glycoprotein I binds thrombin via exosite I and exosite II: anti-beta2-glycoprotein I antibodies potentiate the inhibitory effect of beta2-glycoprotein I on thrombin-mediated factor XIa generation [J]. Arthritis Rheum, 2007, 56(2): 605-613

[53] Rau JC, Beaulieu LM, Huntington JA, et al. Serpins in thrombosis, hemostasis and fibrinolysis[J]. J Thromb Haemost, 2007, 5(Suppl 1): 102-115

[54] Goldsmith GH, Pierangeli SS, Branch DW, et al. Inhibition of prothrombin activation by antiphospholipid antibodies and beta 2-glycoprotein 1[J]. Br J Haematol, 1994, 87(3): 548-554

[55] Nimpf J, Bevers EM, Bomans PH, et al. Prothrombinase activity of human platelets is inhibited by beta 2-glycoprotein-I [J]. Biochim Biophys Acta, 1986, 884(1): 142-149

[56] Shi W, Chong BH, Hogg PJ, et al. Anticardiolipin antibodies block the inhibition by beta 2-glycoprotein I of the factor Xa generating activity of platelets[J]. Thromb Haemost, 1993, 70(2): 342-345

[57] Galli M, Bevers EM, Comfurius P, et al. Effect of antiphospholipid antibodies on procoagulant activity of activated platelets and platelet-derived microvesicles [J]. Br J Haematol, 1993, 83 (3): 466-472

[58] Ruggeri ZM, Mendolicchio GL. Adhesion mechanisms in platelet function[J]. Circ Res, 2007, 100(12): 1673-1685

[59] Hulstein JJ, Lenting PJ, de Laat B, et al. beta2-Glycoprotein I inhibits von Willebrand factor dependent platelet adhesion and aggregation[J]. Blood, 2007, 110(5): 1483-1491

(上接第 3986 页)

[28] Jackson TL, Desai R, Simpson A, et al. Epimacular Brachytherapy for Previously Treated Neovascular Age-Related Macular Degeneration (MERLOT): A Phase 3 Randomized Controlled Trial [J]. Ophthalmology, 2016, 123(6): 1287-1296

[29] Odergren A, Algvere PV, Seregard S, et al. Vision-related function after low-dose transpupillary thermotherapy versus photodynamic therapy for neovascular age-related macular degeneration [J]. Acta ophthalmologica, 2010, 88(4): 426-430

[30] Mimouni M, Meshi A, Vainer I, et al. Bevacizumab dosing every 2 weeks for neovascular age-related macular degeneration refractory to monthly dosing [J]. Japanese journal of ophthalmology, 2018, 62(6): 652-658

[31] Chaudhary V, Barbosa J, Lam WC, et al. Ozurdex in age-related macular degeneration as adjunct to ranibizumab (The OARA Study) [J]. Canadian journal of ophthalmology Journal canadien d'ophtalmologie, 2016, 51(4): 302-305

[32] Calvo P, Ferreras A, Al Adel F, et al. Dexamethasone intravitreal implant as adjunct therapy for patients with wet age-related macular degeneration with incomplete response to ranibizumab[J]. The British journal of ophthalmology, 2015, 99(6): 723-726

[33] Rezende FA, Lapalme E, Qian CX, et al. Omega-3 supplementation combined with anti-vascular endothelial growth factor lowers vitreal levels of vascular endothelial growth factor in wet age-related macular degeneration [J]. American journal of ophthalmology,2014, 158(5): 1071-1078

[34] Sridhar J, Hsu J, Shahlaee A, et al. Topical Dorzolamide-Timolol With Intravitreous Anti-Vascular Endothelial Growth Factor for Neovascular Age-Related Macular Degeneration [J]. JAMA ophthalmology, 2016, 134(4): 437-443