·文献综述·

ARMD 治疗的当前策略与未来方向

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摘要
年龄相关性黄斑变性(ARMD)是好发于年龄超过 55 岁人群的进行性视力损伤眼底疾病。其主要风险因素为机体衰老、长期吸烟、遗传以及人种差异等,发病机制包括视网膜色素上皮功能异常、血视网膜屏障受损及免疫功能异常等。目前,玻璃体腔注射(IVI)抗 VEGF 药物是临床治疗 ARMD 的首选方案,然而其同样面对着治疗反复、医疗费用昂贵以及患者依从性较差等问题。ARMD 治疗的困境催生出许多新的治疗方案,文章旨在对干性 ARMD 与湿性 ARMD 的治疗方式及其进展进行综述,为解决当前临床抗 VEGF 治疗的局限性提供新思路。
关键词:年龄相关性黄斑变性(ARMD);多靶向治疗;抗 VEGF 联合治疗
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Current strategies and future directions in the treatment of age - related macular degeneration

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Abstract
• Age - related macular degeneration (ARMD) is a progressive visual impairment fundus disease that frequently occurs in individuals aged >55 years. The main risk factors are aging, long-term smoking, genetics, and racial differences. Pathogenesis includes abnormal function of the retinal pigment epithelium, damaged blood - retinal barrier, and abnormal immune function. Currently, intravitreal injection (IVI) of anti - vascular endothelial growth factor (VEGF) drugs is the preferred treatment option for ARMD in clinical practice. However, it also faces challenges such as repeated treatments, high medical costs, and poor patient compliance. The predicament in the treatment of ARMD has given rise to several new treatment options. This article aims to review the treatment methods and progress of dry ARMD and wet ARMD, providing new ideas for addressing the limitations of the current clinical anti-VEGF treatment.
• KEYWORDS: age - related macular degeneration (ARMD); multi - targeted therapy; anti - vascular endothelial growth factor (VEGF) combination therapy

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0 引言

进展期渗出性年龄相关性黄斑变性(wet age-related macular degeneration,wARMD)影响着全球约 1.96 亿人,是老年人严重视力损伤的主要原因,预计到 2040 年,全球将有近 3 亿人受到此病影响[1]。ARMD 患者的数量相当于所有侵袭性癌症患者的总和,是阿尔茨海默病(Alzheimer's disease,AD)患者的两倍以上[2]。根据 GBD 数据库统计,1990-2021 年中国 ARMD 患病率不断上升[3],且女性患病负担高于男性,且预计其后 15 a 内患病率会持续增加。随着人口老龄化问题日趋严重,wARMD 严重影响着患者生活质量,且增加医疗负担。尽管通过抗血管内皮生长因子(vascular endothelial growth factor,VEGF)靶向治疗 wARMD 是临床的一线选择,但仍无一种方法可以一次性、彻底的治愈该疾病。本综述旨在参考国内外研究总结 ARMD 治疗策略,为未来临床治疗 ARMD 提供新的思路和方法。

1 ARMD 的风险因素

老龄化、遗传因素和环境因素(如吸烟)等均与 ARMD 的发生有关。一项全球荟萃分析发现,欧洲裔地图样萎缩(geographic atrophy, GA)的患病率高于非洲裔和亚洲裔,而新生血管性 ARMD 在所有地区人群中患病率接近[1]。

2 ARMD 的发病机制

ARMD 的发病机制见图 1。

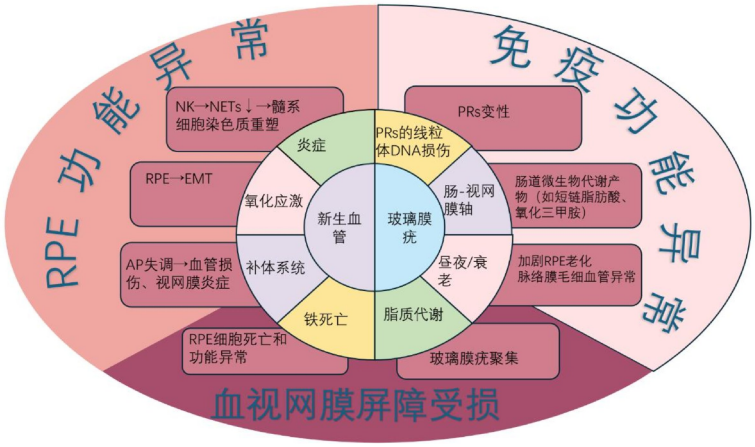

图 1 ARMD 的发病机制。

2.1 炎症与氧化应激 在外周炎症的短暂刺激下，大量免疫细胞包括视网膜小胶质细胞和吞噬细胞被吸引聚集[4-5]，并触发转录激活因子 3（activating transcription factor3，ATF3）表达，引起更强大的促血管生成反应和炎症细胞因子产生抑制[6]。视网膜光感受器高代谢需求引起线粒体 DNA 损伤和能量供应不足[7]，同时 NK 细胞诱发中性粒细胞外诱捕网（neutrophil extracellular traps，NETs）清除衰老的脉管系统能力减弱[8]，导致大量氧化代谢产物不能被内源性抗氧化机制充分平衡[9]。氧化应激诱导视网膜色素上皮（retinal pigment epithelium，RPE）细胞发生上皮间质化（epithelial-mesenchymal transition，EMT）[10]及铁离子在 RPE 中的异常积累[11]，均加剧了细胞死亡和视网膜光感受器变性。Zhao 等[12]在碘酸钠（$NaIO_3$）诱导的干性 ARMD 小鼠模型中发现敲除胰岛素样生长因子 2 mRNA 结合蛋白 2（insulin-like growth factor 2 mRNA-binding protein 2，IGF2BP2）可显著减轻视网膜结构和功能损伤。

2.2 RPE 功能异常 肠道菌群失调使其代谢产物（如短链脂肪酸、氧化三甲胺）通过“肠-视网膜轴”促进玻璃膜疣大量聚集[13]。蛋白激酶 AKT2 的上调抑制 EB 信号通路和非经典自噬途径的激活[2]，RPE 细胞自噬清除异常蛋白质（如 β-淀粉样蛋白、脂褐素）的能力下降[14]，导致毒性蛋白堆积形成恶性循环，触发溶酶体分泌型自噬。昼夜节律破坏加剧 RPE 老化[15]，衰老的 RPE 细胞分泌促炎因子（如 IL-8、MMP2、MMP9 等），破坏血视网膜屏障，促进脉络膜新生血管生成[14,16-17]。同时，RPE 细胞衰老还引起脉络膜毛细血管阻力增加和绒毛膜的密度降低[18]，Bruch 膜脂质运输和脂蛋白异常沉积，以及光感受器的密度降低[15,19]。

2.3 补体系统 补体系统过度激活可导致视网膜炎症、血管损伤及退行性改变，GA 的进展与之密切相关[20]。补体旁路途径（alternative pathway，AP）的失调被认为是 ARMD 的重要致病因素[21]。

3 ARMD 的光学相干断层扫描标志物

通过光学相干断层扫描（optical coherence tomography，OCT）检测，中心凹亚区存在视网膜下液（subretinal fluid，SRF）或视网膜内液（intraretinal fluid，IRF）是活动性病灶诊断的关键指标[22-23]，也是调整治疗方案的重要依据。2025 年一项 Meta 分析[24]发现 OCT 检查中完整视网膜外界膜（external limiting membrane，ELM）和椭圆体带（ellipsoid zone，EZ）可作为预测最佳矫正视力（best corrected visual acuity，BCVA）转归良好的标志物。

4 ARMD 的治疗

4.1 干性 ARMD 的治疗 干性 ARMD 治疗途径及机制见图 2。

4.1.1 靶向治疗 补体系统异常激活是干性 ARMD 的核心病理机制之一，尤其是 C3 和 C5 补体成分的过度活化。在 2023 年，美国 FAD 先后批准 Pegcetacoplan（Syfovre）和 Avacincaptad pegol（ACP）玻璃体内注射治疗 GA 方案。Syfovre 在 30 mo 内降低 GA 生长率高达 45%[25]。当 GA 距中心凹中心距离≥250 μm 时，患者视力丧失和生活质量下降趋势均减慢[25]。GATHER1 和 GATHER2 试验事后分析发现 2 mg ACP 可减少 GA 扩张[26]。而对于已存在 CNV 的 GA 患者，接受 ACP 玻璃体腔注射（IVI）治疗者视觉和解剖结果更差[27]。一项网络 Meta 分析发现，Syfovre 和 ACP 对减缓 GA 进展具有临床显著作用，但贝叶斯 NMA 表明，2 mg ACP 是最有效的补体抑制剂[28]。2025 年的一项回顾性药物警戒分析发现：Syfovre 的不良事件（AE）谱比 ACP 更广，如虹膜出血、虹膜新生血管、脉络膜新生血管、眼内注射并发症、出血性闭塞性视网膜血管炎、视网膜闭塞性血管炎和细菌性眼内炎[29]。这提示临床使用补体抑制剂治疗干性 ARMD 应更加谨慎。Elamipretide 作为线粒体靶向剂可减轻进行性 EZ 衰减，甚至可能逆转干性 ARMD 的进行性视力下降[30]。但当超过 EZ 衰减的阈值，就无法改变潜在的 RPE 丢失和 GA 形成。多波长光生物调节（photobiomodulation，PBM）疗法同样靶向线粒体系统，可改善早中期 ARMD 临床和解剖学结果[31]。一项荟萃分析中提出，样本量不足限制了 PBM 对干性 ARMD 疗效的评估，同时视力和玻璃膜疣体积的变化不能作为干性 ARMD 治疗有效结果的测量指标，容易造成高风险偏倚[32]。另一项荟萃分析同样指出，PBM 可能会在短期内改善患者的生活质量，不良反应的结果好坏参半[33]。在 RPE 衰老的小鼠模型中：抗衰老化合物 Nutlin-3a 通过靶向清除衰老的 RPE 细胞能够高效延缓神经视网膜退化[34]。而 Risuteganib 通过整合同时抑制 αVβ3、αVβ5、α5β1 和 αMβ2 结合位点影响血管生成、炎症和血管通透性，在Ⅱ期试验两次玻璃体腔内给药中48%患者获得显著

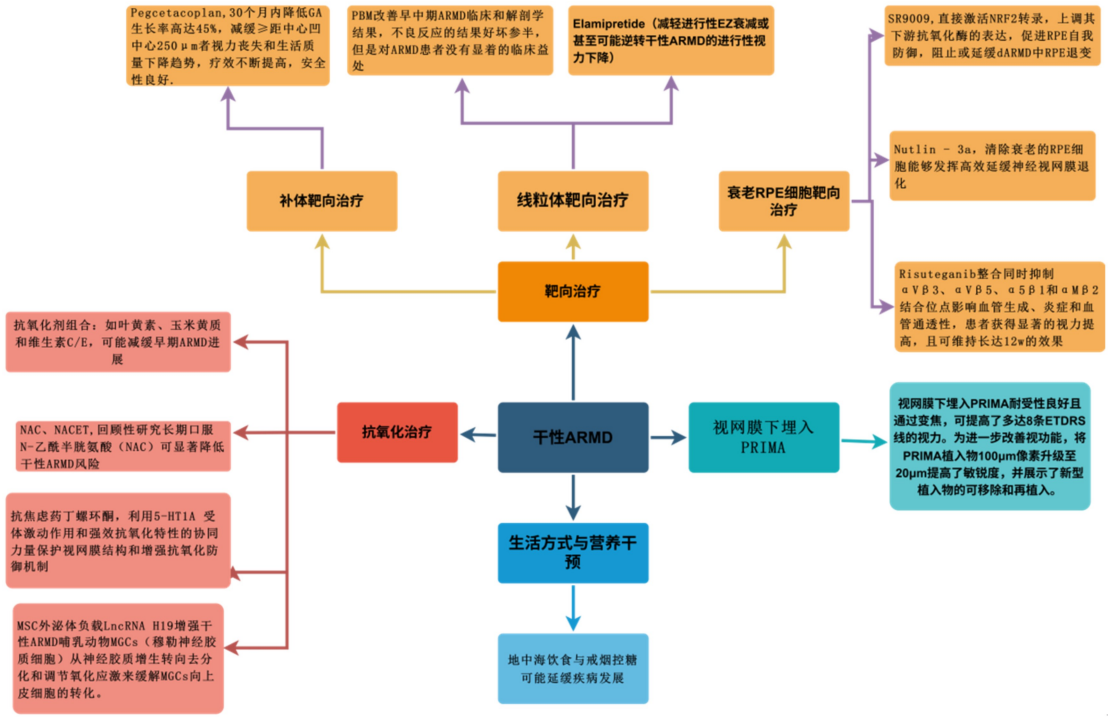

图 2　干性 ARMD 治疗途径及机制。

的视力提高,并可维持长达 12 wk 的效果[35]。

4.1.2 抗氧化治疗　抗氧化剂食物如叶黄素、玉米黄质和维生素 C/E,可能减缓早期 ARMD 进展,但效果有限[36]。一项研究发现长期口服 N-乙酰半胱氨酸(NAC)可显著降低干性 ARMD 风险[37]。而另一项大鼠模型中指出,N-乙酰基-L-半胱氨酸乙酯作为 NAC 四种酯衍生物之一,与 NAC 发挥相同的抗氧化作用,反应更快且效率更高[38]。且在此模型中还指出 NAC 并不能阻止氧化损伤。抗焦虑药丁螺环酮利用 5-HT1A 受体激动作用和强效抗氧化特性的协同力量可以保护视网膜结构,增强抗氧化防御机制[39]。在 1% $NaIO_3$ 诱导的小鼠干性 ARMD 中[40],健脾补肾益视方同样通过 PGC-1α/SIRT1 信号通路发挥抗氧化应激作用。口服抗氧化剂治疗在未来或许会成为视网膜疗法辅助方案。

核受体 REV-ERBα 作为一种氧化还原敏感的转录因子[41],可被 SR9009 和 SR9011 通过激活 REV-ERBα 直接激活核因子相关因子 2 转录,阻止或延缓干性 ARMD 中 RPE 退变[41]。在诱导 ARPE-19 细胞衰老模型中,SR9009 可增强正常 ARPE-19 细胞的吞噬活性,并增加了昼夜节律控制吞噬相关基因的表达[42]。间充质干细胞外泌体负载 LncRNA H19 可增强干性 ARMD 哺乳动物穆勒神经胶质细胞(Müller glial cells,MGCs)从神经胶质增生转向去分化和调节氧化应激,来缓解 MGCs 向上皮细胞的转化[43]。

4.1.3 生活方式与营养干预　地中海饮食包括鱼类、坚果和抗氧化剂(如叶黄素)的高摄入与 ARMD 进展减缓相关,可能与抗炎和抗氧化作用有关[36]。吸烟和高血糖均为 ARMD 风险因素,对其进行干预可能延缓疾病发展[19,36]。

4.1.4 视网膜下光伏植入物　将视网膜下光伏植入物(PRIMA)植入视网膜地理萎缩区曾在首次人体临床试验中验证了此法的可行性和稳定性[44]。之后 4 a 的随访研究进一步验证了视网膜下植入 PRIMA 耐受性良好,且通过变焦可提高多达 8 条 ETDRS 线的视力[45]。随后在大鼠试验中,以 22 μm 像素的新设备将 PRIMA 植入物的光栅精度从 100 μm 提升至 28 μm,并展示了新型植入物的可移除和再植入[46]。然而,前植入物位置的视网膜下纤维化和升级后的植入物后面是否仍会形成纤维化膜还需要进一步的研究。

4.2 湿性 ARMD 的治疗　湿性 ARMD 的治疗方案见图 3。

4.2.1 抗 VEGF 疗法的优化与扩展

4.2.1.1 广谱抗 VEGF 策略　尽管抑制 CNV 的药物日益更迭,现有的抗 VEGF 药物治疗中仍出现对湿性 ARMD 者疗效不足甚至无反应,部分学者将研究焦点指向抗VEGF-C/D 的治疗。OPT-302 在临床试验中联合雷珠单抗治疗湿性 ARMD 显示出了增强抗新生血管的效果[47]。但其两项关键的 3 期临床试验(COAST 和 ShORe)在今年先后终止,美国临床试验数据库资料表明这两项试验记录分析终止的原因均是未达到研究的预期结果。对于补体系统的异常激活促发了 CNV 的形成,中国科学家研发 IBI302 系靶向 C3b / C4b 和 VEGF 的双特异性融合蛋白[48],一项随机对照Ⅱ期临床试验中评估 IBI302 治疗湿性 ARMD 在 BCVA 改善方面不劣于阿柏西普,并伴有相似的安全性[49]。但对于 IBI302 不同剂量之间疗效的差异并未阐述。而在剂量浓度探究中,有试验发现 8 mg 阿柏西普在解剖恢复和视觉改善均优于 2 mg 阿柏西普,并且安全性相似[50]。PULSAR 试验[51]中指出 8 mg 阿柏西普在第 96 wk随机分配到 8q12(每 12 wk 1 次,每次 8 mg)组和 8q16(每 16 wk 一次,每次 8mg)组的患者中给药间隔≥12 wk和≥16 wk 的比例分别为 87% 和 78%,甚至最长给药间隔为 24 wk。而对于治疗浓度的调整研究中,Jackson 等[52]发现黄斑上近距离放射治疗(24-Gy,EMB)

图 3 湿性 ARMD 的治疗。

不会减少按需注射雷珠单抗的次数,并且比单药治疗视力结果更差。Creer 等[53]发现当降低放射剂量至 16-Gy 立体定向放射治疗(SRT)时,SRT 作为辅助抗 VEGF 治疗可以减少注药次数,但这可能与此临床研究中大部分患者采用的治疗和延长方案(T&E)有关。一项研究中采用按需给药(PRN)SRT 联合雷珠单抗与单药组比较,进一步验证了 SRT 辅助疗效不劣于单药组[54]。蒙药明目十一味丸联合康柏西普[55]促进黄斑出血的吸收和减轻水肿,但本次研究只针对联合蒙药治疗湿性 ARMD 的疗效,缺少对其作用机制的解释。

4.2.1.2 长效递送系统 针对频繁 IVI,雷珠单抗缓释植入系统(PDS)通过持续释放药物可达到非劣效性效果,显著减少注射频率[56]。Archway 3 期试验显示 PDS 在每 24 wk 一次(Q24W)给药的 2 a 内显示出不劣于每月 1 次雷珠单抗的疗效[57],并且黄斑萎缩(macular atrophy,MA)区域进展明显少于 IVI[58]。而 Portal 试验中期结果显示 PDS 存在部分眼部不良事件(AESI),如白内障(11.4%)、玻璃体出血(6.1%)、结膜滤泡相关事件(6.3%),且多发生于 1 a内[59]。

4.2.2 联合药物传递系统与多靶点干预 纳米颗粒的递送平台(如 SAC4A 与舒尼替尼复合物)可增强药物穿透眼后段的能力,使视网膜-脉络膜药物浓度提高 2.47 倍[60]。细胞穿透肽(CPP)结合康柏西普的滴眼液[61]和带正电荷的细胞穿透肽衍生物(bxyWP)结合阿柏西普的滴眼液[62]均能有效减少 CNV 病灶大小和渗漏。另有研究开发水凝胶缓释系统(如雷珠单抗和雷帕霉素),通过持续地共同递送到视网膜并序贯给药破坏了"自噬功能障碍-氧化应激-血管生成"环路,增强抗湿性 ARMD 的疗效,解决了单靶点抗 VEGF 抗体的局限性[63]。

4.2.3 CNV 其他通路抑制剂 为防治晚期视网膜纤维化,RO 作为 γ-分泌酶抑制剂,即可抑制 Notch 和 TGFβ 信号通路中的 Müller 细胞胶质化和 RPE 细胞上皮间质转化[64],又可间接抑制 ERK1/2 信号传导,以发挥其抗纤维化作用[65]。EB3 变构抑制剂激活 CNV 中内皮细胞再生[66],截至目前尚未检索到已完成临床试验的公开数据,但其机制创新和给药方式优势使其成为湿性 ARMD 领域值得关注的研究方向。Zhang 等[67]设计了一种以核酸适配体 AS1411 为靶向基团,外泌体-脂质体杂化纳米颗粒为载体的 CRISPR/Cas9 运输系统,可靶向谷氨酰胺合成酶,减少眼部新生血管。

4.2.4 抗 VEGF 治疗给药部位 在抗 VEGF 药物给药方式中,与 IVI 相比较,脉络膜上腔给药能更直接作用于脉络膜新生血管的起源部位,在临床前和临床研究中显示出对 VEGF 靶向治疗的良好效果[68]。而视网膜下给药(subretinal injection,SRI)最初应用在黄斑出血的治疗中,目前也被广泛用于递送基因治疗载体以靶向治疗 ARMD 相关病变。腺相关病毒载体 ABBV-RGX-314 是利用雷珠单抗类抗 VEGF Fab 表达的腺相关病毒血清型 8 载体,在一项早期临床试验基因拷贝系数剂量递增研究中[22],发现 6×10^{10}剂量组中,在 106 wk 时房水蛋白仍持续表达。ABBV-RGX-314 通过脉络膜上给药递送,不同剂量水平均具有良好的耐受性,且没有药物相关的严重不良事件[69]。ADVM-022 (AAV.7m8-aflibercept,ixoberogene soroparvovec,Ixo-vec)IVI 给药的 OPTIC I 期试验中[70],第 96 wk 时阿柏西普在房水中维持稳定浓度,低剂量组的年化抗 VEGF 注射率可降低 81%,高剂量组降低 98%。

4.2.5 人工智能辅助诊疗 基于三维 OCT 的 AI 系统可预测单眼 wARMD 患者对侧眼的进展风险,实现早期干预[71]。"Scanly Home OCT"是一款首款经 FDA 批准为患者带来便捷的远程监测解决方案的一款家用成像设备,通过自我成像和 AI 驱动的自动分析,为 ARMD 患者带来便捷的远程监测,同时利用 AI 系统建立 ARMD 患者的数据

库,为治疗提供个性化方案。一项关于家用 OCT 指导治疗与 T&E 治疗湿性 ARMD 比较 104 wk 内的法瑞西单抗注射的次数及 BCVA 的随机临床试验正在进行中(ClinicalTrials.gov,NCT05904028)。

4.3 T&E 方案治疗 既往认知中 T&E 方案可以延长治疗间隔,减少注药次数。但在 COCOA 试验中发现尽管 T&E 方案可以延长注药间隔,但 PRN 方案在相似的 BCVA 改善条件下具有更少的注药次数[72]。目前抗 VEGF 需终身治疗,Airody 等[73]的研究中在 T&E 方案基础上采用了治疗-延长-固定(treat, extend and fixed,TEF)方案,即当注药间隔延长至 3 mo 时,保持 3 mo 一次固定频率给药,可维持 2 a 最佳矫正视力以及患者对治疗满意度和生活质量的提高。真实世界中对于影响再治疗的判断条件之一为 SRF 的存在与否,Siedlecki 等[74]指出仅表达 SRF 的湿性 ARMD,可以表现出相当低的长期地理萎缩率和稳定的视觉结果。Guymer 等[75]同样认为 T&E 方案治疗对于存在部分 SRF(中心凹中心 SRF > 200 μm)的患者与旨在完全清除所有 SRF 的患者拥有相当的视力,但注射次数更少。

5 结语

面对日趋严峻的人口老龄化趋势,寻找针对 ARMD 的有效治疗方法格外重要。面对庞大患病人群,能明显改善或缓解疾病的治疗方法在临床中屈指可数。长期口服抗氧化剂或多种靶向治疗能减缓早中期 ARMD 的发展速度,然而仍无法忽视不良事件的严重性。基因疗法在 ARMD 治疗中的应用还需要进一步大样本的临床试验以探究和发掘新问题。对于晚期发生大面积 GA,可通过视网膜下埋入 PRIMA 模拟人体光电信号转换,刺激附近的视网膜内神经元恢复中央视力,其具备了可移除和再植入的优势,并可升级视觉敏锐度。然而在其临床试验中除发生视网膜下植入处纤维化严重影响视力外,还有手术难度及植入物的移位等问题有待解决。此外,作为载体的 AAV 同样可通过运输编码广谱的抗 VEGF 蛋白来大大降低给药频率并减轻治疗负担。值得庆幸的是,在漫长的 ARMD 临床治疗过程中,人们越来越能接受其作为一种慢性病的长期治疗过程。随着对 ARMD 机制的深度剖析,不断研发新药物和治疗方式、在未来人工智能家用 OCT 与新颖治疗方式的配合下进一步优化治疗策略,将有效改善目前窘境。

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