

难治性克罗恩病的联合治疗的研究进展

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摘 要

难治性克罗恩病(CD)是指对现有生物制剂及小分子药物反应不足或无效的疾病亚型, 其发生与多重炎症通路激活、免疫细胞异常(如AQP9 + 巨噬细胞扩增)及信号通路失调(如gp130-STAT3轴)密切相关。联合治疗通过协同靶向不同机制(如双生物制剂、生物制剂联合小分子药物)突破单一疗法的疗效瓶颈, 在难治性患者中展现出显著临床潜力。研究显示, 联合方案(如upadacitinib联合infliximab)可使多数患者获得短期临床应答, 部分实现无激素缓解。然而, 其临床应用仍面临个体疗效差异、安全性风险(如感染、输液反应)及缺乏精准生物标志物等挑战。未来需聚焦机制探索、个体化策略优化及多模态整合(如干细胞疗法、营养干预), 以提升难治性CD的治疗效果与生存质量。

关键词

难治性克罗恩病, 联合治疗, 双靶向治疗

Research Progress on Combined Therapy for Refractory Crohn's Disease

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Abstract

Refractory Crohn's disease (CD) refers to a disease subtype that shows insufficient or no response to existing biologics and small molecule drugs. Its occurrence is closely related to the activation of multiple inflammatory pathways, abnormal immune cells (such as the expansion of AQP9 + macrophages), and dysregulation of signaling pathways (such as the gp130-STAT3 axis). Combination therapy, by synergistically targeting different mechanisms (such as dual biologics or biologics combined with small molecule drugs), has broken through the efficacy bottleneck of single therapy and

demonstrated significant clinical potential in refractory patients. Studies have shown that combination regimens (such as upadacitinib combined with infliximab) can lead to short-term clinical responses in most patients and achieve steroid-free remission in some. However, its clinical application still faces challenges such as individual efficacy differences, safety risks (such as infections and infusion reactions), and the lack of precise biomarkers. In the future, efforts should focus on mechanism exploration, optimization of individualized strategies, and multi-modal integration (such as stem cell therapy and nutritional intervention) to improve the treatment outcomes and quality of life for refractory CD patients.

Keywords

Refractory Crohn's Disease, Combined Therapy, Dual-Target Therapy

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1. 引言

难治性克罗恩病(CD)是指对现有治疗策略(包括针对多种炎症通路的生物制剂和小分子药物)无应答或反应不足的疾病状态。尽管 CD 的治疗管理已取得显著进展,但一部分患者仍对现有疗法表现出顽固性不良响应,发展为多重耐药或疾病持续活动[1]。这种难治性状态在临床中较为常见,许多治疗方案虽能抑制特定炎症通路,但部分患者治疗反应差,凸显了对新治疗策略的迫切需求[2]。例如,高达 26%的 CD 患者会出现肛周瘘管问题,且这些瘘管常因药物治疗难治,最终需手术干预[3] [4]。难治性的发生与特定病理生理机制密切相关:AQP9 + 巨噬细胞的扩增可能通过增强炎症反应导致抗肿瘤坏死因子(TNF)治疗失败[5]; gp130-STAT3 信号通路的异常激活也被认为是难治性表型的重要驱动因素[6]。此外,难治性 CD 常伴随严重的肠外表现或共存免疫介导疾病,进一步增加了疾病管理的复杂性[7]。

面对这一挑战,联合治疗(如双生物制剂联合、生物制剂结合小分子药物)已成为一种有前景的应对策略。其发展背景源于单一疗法存在的局限性:许多患者难以达到持续临床缓解,而双靶向治疗(DTT)通过协同不同作用机制的药物(如生物制剂与小分子制剂),旨在突破传统治疗的“疗效天花板”[7]。临床研究数据显示,联合治疗在难治性 CD 患者中展现出积极效果:一项病例系列研究报道,27 名难治性患者接受 upadacitinib 与 infliximab 或其他生物制剂联合治疗后,24 人在 12 周内获得临床应答,9 人实现无激素缓解[8]。更大规模分析表明,81%的联合治疗应用于医学难治性炎症性肠病(IBD)患者,尤其针对多线治疗失败者[9]。具体而言,infliximab 联合硫唑嘌呤在 CD 和溃疡性结肠炎中被证实比单药治疗更能有效诱导缓解[10]; 儿科研究也显示甲氨蝶呤联合治疗显著降低治疗失败率[11]。高级联合治疗(ACT)策略聚焦于互补作用机制,以克服耐药性和提升疗效[7]。系统评价支持双生物疗法的可行性,表明其在经 JAK 抑制剂等高级治疗失败的高度难治 IBD 患者中仍具有潜在效果[9]。然而,联合治疗也面临安全性考量。例如,ustekinumab 用药可能引发输液反应[12],但总体证据表明其风险可控[9]。此外,联合治疗的实际应用还需考虑医保政策与药品说明书更新滞后等现实问题,这些因素可能限制联合疗法的临床推广[13]。综上,尽管联合治疗在理论上能通过互补机制克服耐药,但现有证据高度依赖小样本观察性数据,缺乏大规模随机对照试验(RCT)对不同联合方案的头对头比较,且其长期安全性(如感染、恶性肿瘤风险)与停药后复发规律仍属未知[7] [9]。本文旨在系统梳理联合治疗的机制与方案,并重点剖析其临床转化中的证据缺口与争议,为未来研究提供关键方向。

2. 难治性克罗恩病的联合治疗的作用机制研究

2.1. 互补靶向机制

通过同时靶向多重通路克服耐药性联合治疗的核心机制在于采用互补作用靶点, 通过同时抑制多个炎症途径或免疫通路, 打破单一疗法失效的限制。这种策略在难治性 CD 患者中尤为重要, 因为这些患者常存在多通路炎症激活。先进联合疗法(ACT)通过结合两种生物制剂或生物制剂与小分子药物, 针对 IBD 的不同发病环节(如细胞信号转导和白细胞迁移)产生协同效应[7]。互补机制有助于克服传统治疗的耐药性, 例如, 一种药物靶向 TNF- α 信号, 另一种则靶向白细胞粘附或趋化过程, 从而全面抑制肠道炎症级联反应[14]。研究显示, 这种策略能减少免疫逃逸或适应性耐药的发生, 为临床改善提供基础[7]。

2.2. 细胞信号通路干预

调节关键炎症信号轴联合治疗通过调节特定信号通路(如 STAT 或 IL 家族)在难治性 CD 中发挥重要作用。其中, gp130-STAT3 信号轴的激活与抗 TNF 治疗耐药相关, 阻断这一通路可增强现有抗 TNF 疗法的疗效[6]。此外, IL-23 抑制剂(如 guselkumab)通过靶向 Th17 细胞介导的炎症反应, 与抗 TNF 药物形成互补, 共同逆转免疫紊乱[15]。其他通路(如 mTOR 或 MAPK)的协同抑制也被证明可减少组织损伤并延缓纤维化进展[14]。这些干预措施不仅提高治疗响应率, 还成为新靶向策略的关键组成部分[6]。

2.3. 炎症介质和细胞调控

靶向特定免疫细胞和分子联合治疗还涉及对炎症微环境中关键介质(如巨噬细胞和白细胞迁移过程)的调控。研究发现, AQP9 + 巨噬细胞的扩增与抗 TNF 耐药相关, 靶向 AQP9 可增强抗 TNF 治疗的疗效[5]。同时, 通过抑制白细胞迁移(如使用维多珠单抗靶向整合素), 联合疗法能有效阻止炎症细胞在肠黏膜的浸润, 补充其他通路靶向药物的作用[14]。此外, 间充质干细胞(MSCs)通过调节局部细胞因子环境和招募调节性 T 细胞, 促进组织愈合, 尤其在难治性肛周瘘管的治疗中显示出潜力[16][17]。这些多项调控机制共同作用于慢性炎症和免疫失衡的核心环节[5][17]。

2.4. 其他相关机制

干细胞移植和营养干预的辅助作用非药理学策略(如干细胞移植和营养疗法)也为联合治疗提供扩展机制。自体造血干细胞移植(SCT)可能通过重置免疫系统, 消除自身反应性 T 细胞并重建免疫稳态, 为药物联合提供深度治疗支持[2]。而排他性肠内营养(EEN)作为辅助手段, 通过调节肠道微生物组和改善黏膜屏障, 与生物制剂产生协同效应。这些机制虽为次要, 但丰富了联合治疗的多模态作用概念, 为难治患者提供额外维度的干预[2]。

总之, 难治性 CD 联合治疗的作用机制研究集中于互补靶向、信号通路干预和炎症介质调控等领域, 旨在通过协同抑制多重炎症通路克服耐药性。这些机制不仅解释了联合治疗在临床中提高响应率的基础[7][8], 也为新靶点开发提供理论支持[5][6]。未来需进一步明确干细胞治疗等机制的具体作用[16], 推动该领域向精准医疗转化。

3. 难治性克罗恩病联合治疗的类型和方案

难治性克罗恩病的联合治疗以多机制协同调控炎症通路为核心, 形成了靶向药物组合、传统免疫联合及非药物干预等多元化方案体系, 各类方案的适用场景、具体策略与疗效数据如下。

双靶向治疗(Dual-Targeted Therapy, DTT)是当前主流方案之一, 其核心是同时使用两种不同机制的高级药物(生物制剂或小分子药物)以覆盖多个炎症通路[7]。该方案的常见组合包括两类: 一是生物制剂联

合生物制剂,如维多珠单抗联合乌司奴单抗、英夫利昔单抗联合利生奇珠单抗[8];二是生物制剂联合小分子药物,如乌帕替尼分别与英夫利昔单抗、维多珠单抗或乌司奴单抗联用[7][8]。临床数据显示,此方案在难治性患者中疗效显著,12周时临床缓解率达89%(24/27例),52周时部分患者可实现无激素缓解[8]。

针对高度难治或对常规方案无效的病例,三联靶向治疗提供了进阶选择,其定义为同时使用三种靶向药物(如两种生物制剂联合一种小分子药物)[18],目前已明确的具体方案为维多珠单抗+阿达木单抗+甲氨蝶呤[18]。

生物制剂与传统免疫抑制剂的联合则是临床中更易普及的策略,常用组合包括英夫利昔单抗或阿达木单抗,分别与硫唑嘌呤或甲氨蝶呤联用。其中,英夫利昔单抗联合硫唑嘌呤或甲氨蝶呤可降低治疗失败风险(如避免手术或更换生物制剂)[19];甲氨蝶呤联合阿达木单抗在儿童克罗恩病中更展现出优势,能使治疗失败风险降低2倍,且安全性可控[11][20]。需特别注意的是,若停用英夫利昔单抗后仅维持免疫抑制剂单药治疗,可能会增加疾病复发风险[13]。此外,甲氨蝶呤还可单独与抗TNF药物联用,既适用于激素难治性克罗恩病,也能通过降低抗TNF药物的免疫原性,实现疾病缓解的诱导与维持,同时减少抗TNF抗体产生[20]。

在药物治疗效果有限或存在特定并发症时,非药物联合策略可发挥补充作用。自体造血干细胞移植(Autologous Hematopoietic Stem Cell Transplantation, SCT)通过重置患者免疫系统实现治疗目的[8],其潜在机制可能与改变免疫病理生理过程以达成长期缓解相关,但具体作用路径仍需进一步研究[2]。高压氧治疗则聚焦于药物难治性肛瘘,短期(16周)治疗可改善肛瘘的临床症状、影像学表现及生化指标[21],长期(60周)应用不仅疗效稳定,且安全性良好,尤其适用于复杂肛瘘患者[21][22]。对于难治性肛瘘克罗恩病,粪菌移植与间充质干细胞治疗可作为替代方案,若生物制剂无效,粪流改道术(如造口术)或间充质干细胞注射也可纳入选择[4]。此外,克罗恩病排除饮食(Crohn's Disease Exclusion Diet, CDED)作为部分肠内营养疗法,适用于轻中度疾病,有望诱导临床缓解及内镜应答[23]。

特殊临床场景下,联合治疗策略需针对性调整。对于合并肠外表现或风湿性疾病的患者,双靶向治疗(如生物制剂联用小分子药物)应用率较高,此类患者占比约12%[9];当抗TNF治疗失败后,乌司奴单抗与维多珠单抗的联合应用显示出潜在疗效[24]。在治疗管理中,需重点关注两方面问题:一是安全性,联合治疗可能增加感染、输液反应等不良事件(AEs)风险,但严重不良事件(SAEs)风险未发现显著升高[11][12];二是停药风险,停用生物制剂后需谨慎评估,因疾病复发风险与特定血液蛋白谱密切相关[25]。

总之,难治性克罗恩病的联合方案以双靶向治疗为核心,覆盖生物制剂/小分子药物组合(如抗整合素+抗IL12/23[8][24])、三联靶向治疗、生物制剂联合免疫抑制剂(如甲氨蝶呤[20])及非药物疗法(如自体造血干细胞移植[2]、高压氧治疗[22]、CDED饮食[23])等类型。未来需进一步探索个性化联合方案的安全性及长期疗效,以优化难治性患者的治疗结局[7]。

4. 难治性克罗恩病联合治疗的临床实践中的考量

4.1. 基于临床表型与治疗史的个体化方案选择

联合治疗的选择需优先评估疾病表型与既往治疗反应。对于高炎症负荷或急性重度患者,强化联合方案如双重生物制剂(如英夫利昔单抗联合乌司奴单抗)或生物制剂与小分子药物(如乌帕替尼)联用可能快速控制症状[8][26]。研究显示,此类方案在12周内可使约89%的难治患者获得临床应答,但需密切监测感染风险[27]。针对肛周瘘管型CD,传统生物制剂疗效有限,需整合多模式治疗:高压氧疗法可改善60%患者的瘘管愈合[21][22],而间充质干细胞移植在成本效益上优于粪流改道手术[4]。若患者存在抗TNF治疗失败史,转向不同机制药物(如维多珠单抗或古塞奇尤单抗)的联合或能突破耐药瓶颈[15][24]。

此外，肠外表现突出者(如关节或皮肤受累)可能受益于免疫调节剂(甲氨蝶呤)与生物制剂的协同作用[11] [18]。

4.2. 难治性 CD 的阶梯式治疗路径

- 基于疾病严重度与治疗响应动态调整的阶梯路径可优化临床决策(图 1):
- 1) 一线强化: 对传统生物制剂失效者, 优先选择双靶向治疗(DTT), 如抗-TNF 药物联合整合素抑制剂[7] [14];
 - 2) 二线救援: 若 DTT 应答不佳, 引入小分子药物(如 JAK 抑制剂)或探索干细胞移植[2] [17], 后者通过免疫重建修复肠黏膜[28];
 - 3) 特殊表型管理: 肛周瘻管型 CD 需早期联合外科清创、局部干细胞注射与生物制剂[3] [29];
 - 4) 维持与降阶: 达到深度缓解(内镜愈合)后, 可参考生物标志物(如血清蛋白谱[25])逐步撤停免疫抑制剂, 但英夫利昔单抗停药后复发风险达 40%, 需谨慎权衡[13]。

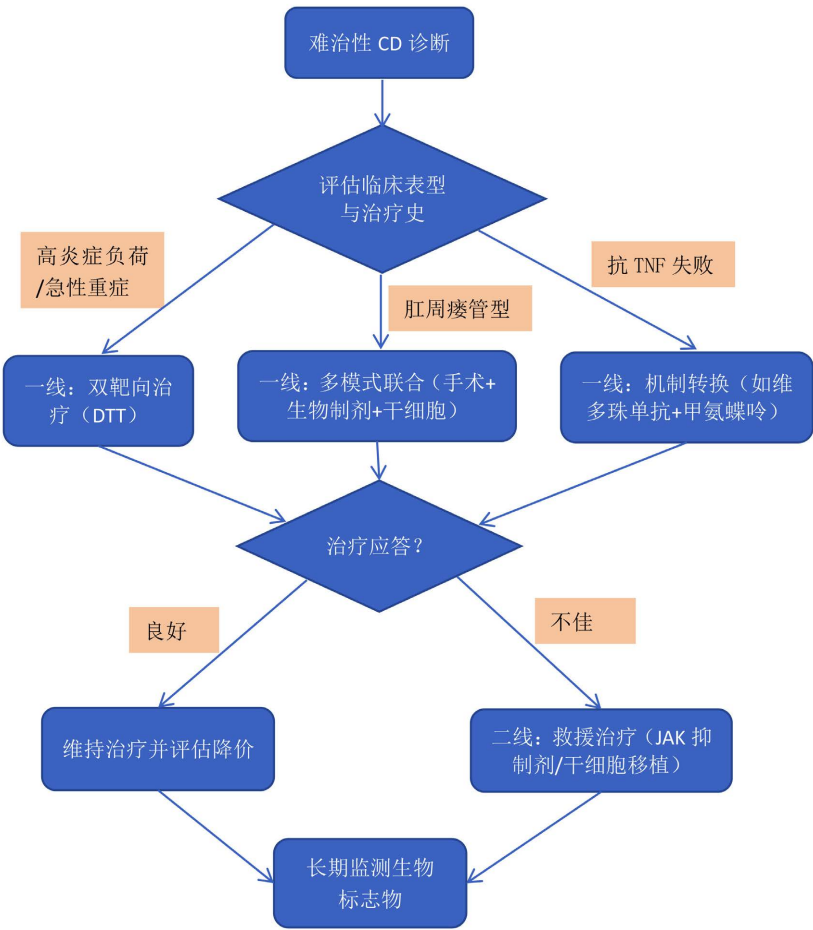


Figure 1. Combined treatment pathway for refractory Crohn's disease
图 1. 难治性克罗恩病的联合治疗路径图

4.3. 现实实践中的关键挑战

- 1) 超说明书用药: 双生物制剂联用等方案缺乏大规模 RCT 证据, 需充分告知患者潜在风险(如感染

率升高[27]), 并通过多学科团队审批[7];

2) 成本效益权衡: 新型联合方案费用高昂, 但部分策略如干细胞治疗对难治性瘘管更具长期经济优势[4]。需结合医疗资源与患者支付能力选择;

3) 患者沟通与共享决策: 医生需解释治疗目标(如黏膜愈合 vs. 症状控制), 并整合患者偏好(如对注射剂型的接受度)。血清药物浓度监测[30]和微生物标志物[31]可辅助个性化方案制定。

5. 总结与展望

本综述系统阐述了难治性克罗恩病联合治疗的研究进展, 涵盖其作用机制、方案类型及临床挑战。当前证据表明, 联合治疗通过互补靶向(如抑制 TNF- α 与 IL-23 通路)、调控关键信号轴(如 STAT3)及干预免疫细胞(如巨噬细胞迁移)等多途径协同作用, 为多重耐药患者提供了新希望。双靶向治疗(DTT)及三联疗法等方案已初步验证其可行性, 尤其在肛周瘘管型 CD 及合并肠外表现患者中潜力显著。然而, 联合治疗的推广仍受限于疗效异质性、长期安全性数据缺乏及个体化预测工具不足等问题。难治性 CD 的联合治疗需从当前“经验性组合”迈向“证据驱动的精准策略”。未来研究应优先突破以下方向: 1) 开展前瞻性 RCT: 直接比较不同联合方案(如双生物制剂、生物制剂 + 小分子药物)的疗效与安全性, 并明确其优势亚群; 2) 构建预测模型: 整合多组学数据(基因组、微生物组、血清蛋白谱), 建立个体化疗效与停药复发风险的预测工具; 3) 明确长期安全性: 设立注册登记系统, 长期追踪联合治疗的感染、恶性肿瘤等风险, 尤其关注特殊人群; 4) 深化机制研究: 探索干细胞移植、营养干预等非药物手段的作用路径, 为多模态联合提供理论基石。唯有填补这些关键空白, 联合治疗才能真正实现从“突破瓶颈”到“精准可持续”的跨越。

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