

炎症性肠病生物治疗的进展

牛小娟, 许静涌, 宋京海

■背景资料

炎症性肠病(inflammatory bowel disease, IBD)主要包括克罗恩病(Crohn's disease, CD)和溃疡性结肠炎(ulcerative colitis, UC), 以慢性肠道炎症为主要特征. 其发病机制与机体的适应性和固有免疫系统发生的病理反应密切相关. 其发生发展是遗传易感性、外部环境、感染介质、肠道共生菌及免疫系统的功能障碍等多种因素相互作用所致. 如此复杂的机制为临床和实验研究提供了许多相应的治疗靶点.

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Biological therapies for inflammatory bowel diseases

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Abstract

The inflammatory bowel diseases (IBDs) are a group of diseases characterized by chronic intestinal inflammation. Complex mechanisms underlying intestinal inflammation in IBD make it difficult to cure this disease. Pathological response to IBD involves both the adaptive and innate immune systems. Advances in the understanding of the immune mechanisms have resulted in the development of multiple monoclonal antibodies and small molecules that represent an alternative to the use of current therapies for patients with refractory IBD. This article systematically reviews the mechanisms of action, efficacy and safety of different biological therapies and discusses future directions for the treatment of IBD.

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Key Words: Biological therapy; Inflammatory bowel disease

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摘要

炎症性肠病(inflammatory bowel disease, IBD)是以慢性肠道炎症为主要表现的一组症候群, 其复杂的免疫机制始终困扰着临床治疗. IBD病理反应通常与适应性和固有免疫系统的变化紧密相关. 随着对IBD免疫机制的深入了解, 多种生物制剂及小分子得以研发, 为难治性IBD的治疗提供了新思路和方法. 本文综述了不同生物治疗方法在IBD治疗中的作用机制、临床应用的有效性及其安全性, 探讨了IBD未来治疗可能的方向.

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关键词: 生物治疗; 炎症性肠病

核心提示: 近年, 多种生物治疗方法应用于炎症性肠病(inflammatory bowel disease)的临床治疗, 但其仍处于探索阶段. 即便是抗肿瘤坏死因子(tumor necrosis factor α)药物这种目前看来最有效的治疗方法, 其疗效也差强人意. 在疾病的不同阶段选择正确的细胞因子靶向可能成为生物治疗成功的关键.

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0 引言

炎症性肠病(inflammatory bowel disease, IBD)主要包括克罗恩病(Crohn's disease, CD)和溃疡性结肠炎(ulcerative colitis, UC), 以慢性肠道炎症为主要特征. 其发病机制与机体的适应性和固有免疫系统发生的病理反应密切相关. 其发生

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发展是遗传易感性、外部环境、感染介质、肠道共生菌及免疫系统的功能障碍等多种因素相互作用所致^[1,2]。如此复杂的机制为临床和实验研究提供了许多相应的治疗靶点。我们回顾分析了近年不同生物治疗方法在IBD治疗中的作用机制、有效性和安全性,以为临床治疗提供新的可行思路。

1 针对适应性免疫系统的治疗

T细胞多态性在IBD的发病机制中占有重要地位,是目前研究的重点。以胃肠道斑片的透壁炎症为特征的CD与1型及17型辅助T细胞(Th1、Th17)的活化相关联,他们的活化有赖于抗原提呈细胞及巨噬细胞产生的白介素(interleukin, IL)-12、IL-18、IL-23及转化生长因子 β 的参与^[3-6]。而以结肠连续性的黏膜炎症为特征的UC则与IL-4、IL-5、IL-13介导的Th2免疫反应相关,导致了IL-13水平的增加^[7,8]。大多数具有治疗作用的新的生物分子是通过抑制促炎因子、增加抗炎因子、阻断T细胞抗原受体或共刺激分子等来减少病理性T细胞活化及其效应的。

1.1 阻断促炎因子

1.1.1 抗TNF- α : 抗肿瘤坏死因子(tumor necrosis factor α , TNF- α)治疗是目前治疗IBD最主要的生物治疗方法。目前临床应用的抗TNF- α 的单克隆抗体如infliximab、adalimumab以及certolizumab pegol等药物可以明显改善患者的健康相关生活质量,但在初期的治疗有效的患者中,只有1/3在1年之后维持缓解,仍有许多需要接受其他相关治疗^[9,10]。新的药物如golimumab、darsalazine、HMPL-004及ozoralizumab(ATN-103)仍在各期临床试验研究中。而最新的抗TNF疫苗的针对中重度CD患者的II期临床试验显示,这种药物的耐受性好,没有严重的不良反应,诱导机体产生的抗体与临床缓解相关^[11]。

1.1.2 抗IL-12、IL-23: apilimod是IL-12和IL-23转录的小分子抑制剂。尽管初期的试验显示了apilimod mesylate在治疗活动期CD的临床作用及其良好的耐受性,但随后的随机对照试验并没有显示良好的疗效^[12,13]。ustekinumab和briakinumab都以IL-12和IL-23的p40亚单位为靶点。多项研究表明ustekinumab可能尤其适用于抗TNF- α 治疗失败的患者^[14,15]。SCH-900222以IL-23的特异性的p19亚单位为靶点,尚在研究的初始阶段。

1.1.3 抗IL-2: IL-2对T细胞的活化和增殖起到至关重要的作用。这使其成为一个非常具有吸引

力的靶点。IL-2R抑制剂包括basiliximab和daclizumab,这两者都是抗CD25(IL-2R α)的单克隆抗体。Creed等^[16]用basiliximab治疗激素抵抗的UC患者,90%在8 wk后获得缓解,70%在24 wk后获得完全缓解,且在basiliximab的治疗下激素敏感。随后用单剂量的basiliximab联合激素治疗激素抵抗的UC患者,结果在第24周65%的患者获得了临床缓解^[17]。两个试验均显示这种药物耐受性好,没有严重的不良反应。

1.1.4 抗 γ 干扰素: fontolizumab是唯一以 γ 干扰素(interferon- γ , IFN- γ)为靶点的生物制剂。Hommes等^[18]使用fontolizumab治疗CD患者,第56天反应率为69%,而安慰剂组为32%。Reinisch等^[19]发现,尽管在第29天,用fontolizumab治疗的CD患者与安慰剂组的反应率没有显著的区别,但是,29 d之后的时间点,接受fontolizumab治疗的患者得到显著的临床反应及改善的克罗恩病活动指数评分和CRP水平,提示fontolizumab的作用是逐渐的。其良好的试验数据有望为临床提供更有力的依据。

1.1.5 抗IL-6: 作为一个多效因子,IL-6导致了Th17分化,增加的IL-6及可溶性IL-6R的水平与IBD中增加的疾病严重程度相关^[20]。IL-6基因的多态性也与早发的CD相联系,持续的IL-6信号通路的激活在结肠癌的发展中起到了作用^[21-23]。以IL-6为靶点的生物制剂包括C326、sirukumab(CNT0136)、CDP6038、PF-04236921等。相比之下,tocilizumab是抗IL-6R的单克隆抗体。Ito等^[24]用tocilizumab治疗活动期CD患者12 wk,没有严重的不良反应,80%患者得到临床反应,而安慰剂组为31%。

1.1.6 抗IL-17: vidofludimus(4SC-101/SC12267),一个IL-17释放的小分子抑制剂。来自无对照非盲ENTRANCE研究显示vidofludimus是安全的,耐受性好,不良反应少。Herrlinger等^[25]用vidofludimus治疗激素依赖的缓解期CD或UC患者12 wk,53.9%维持了无激素下的缓解,34.6%维持了较低剂量激素下的缓解,11.5%没有反应。这些表明调节IBD中IL-17的功能的尝试值得更多的研究。

1.1.7 阻断信号传导通路: 除了抑制细胞因子及其受体,另一种减少IBD中炎症反应的手段是阻断由细胞因子介导的下游信号通路。作为与细胞因子受体作用的信号分子,Janus激酶(janus kinase, JAK)-JAK1、JAK2、JAK3,在细胞生长、存活、发育及免疫细胞的分化中起到了至

■ 研发前沿

随着对IBD免疫机制的深入了解,多种生物制剂及小分子得以研发,为难治性IBD的治疗提供了新思路和方法。

■相关报道

2008-01 FDA批准natalizumab用于诱导和维持中重度活动期CD患者的临床反应和缓解,但仅限于对传统CD治疗和抗TNF- α 反应不足及不能耐受的患者。该药说明书上有安全警告,并设置了一项针对CD患者的风险管理计划(包括强制的TOUCH处方程序),旨在告知开处方者、患者和输液中心药物的用法并将可能导致的PML及其他机会感染降到最低。

关重要的作用。JAK1和JAK2是广泛表达的,但是JAK3仅在造血细胞中存在,是信号通路的一部分,被IL-2、IL-4、IL-7、IL-9、IL-15、IL-21激活^[26]。tofacitinib(CP-690, 550)是一种新型的JAK3的小分子抑制剂,目前在II期临床试验中。药物作用的体外研究显示他干扰Th2及Th17细胞的分化,阻断IL-17及IL-22的产生,为有效地抑制IBD中存在的病理性免疫反应提供了可能性^[27]。

1.2 应用抗炎因子 治疗IBD的抗炎因子包括IL-10、IL-11及IFN- β 等,通过增加抗炎因子的数量,有助于维持IBD中炎症反应的平衡。研究显示IL-10基因的变异与UC的易感性明显相关^[28],基因敲除IL-10的小鼠自发地发生结肠炎^[29]。van Deventer等^[30]用IL-10治疗激素抵抗的CD患者,缓解率为50%,而安慰剂组是23%。但是,因为皮下注射给药的方式不能使炎症局部达到足够的药物浓度,所以不能防止术后的复发^[31]。目前应用基因修饰的能产生IL-10的乳酸乳球菌,可通过口服使IL-10直接到达肠黏膜。这项研究已经进入II期临床试验。

1.3 阻断T细胞激活及诱导T细胞凋亡 在生理性炎症的过程中,被病原体活化的T细胞数保持着增殖与凋亡的动态平衡。而在慢性病理性炎症中,T细胞增殖远远多于凋亡^[1,2]。因此,增加T细胞的凋亡可能是合理控制病理性炎症的手段之一。

1.3.1 visilizumab: visilizumab是抗T细胞抗原受体CD3链的单克隆抗体,阻断CD3导致T细胞凋亡。Plevy等^[32]使用visilizumab治疗严重激素难治性的UC患者,84%得到临床缓解。但过度的T细胞靶向控制会导致严重不良反应,近乎所有患者均发生了相关的不良反应,包括腹腔脓肿、房颤、巨细胞病毒感染及带状疱疹等。

1.3.2 abatacept: abatacept是2个细胞毒性T淋巴细胞相关抗原4(cytotoxic T lymphocyte-associated antigen-4, CTLA-4)分子的细胞外功能区与人IgG1的Fc段结合而成的可溶性重组融合蛋白。CTLA-4可以干扰T细胞表达的CD28与抗原提呈细胞上的配体CD80和CD86相互作用,诱导T细胞无能及凋亡。其对中重度IBD治疗有待进一步研究。

2 加强固有免疫系统的治疗

CD发病的一种假说是减弱的急性炎症反应导致了渗透到肠壁的细菌的清除延迟^[33,34]。其免疫学基础即为先天性免疫系统的缺陷。刺激机体固

有免疫系统增加固有免疫细胞(如中性粒细胞、单核细胞等)或生成相应的抗菌蛋白质成分(如防御素等),可能对治疗IBD是有效的。

filgrastim和lenograstim是重组人型G-CSF。Dejaco等^[35]发现G-CSF与CD的黏膜愈合是相关的,愈合时间3-9 mo,且没有不良反应。Korzenik等^[36]用filgrastim治疗活动期CD患者,55%得到临床反应,25%获得缓解,唯一的值得注意的不良反应是轻微的骨痛。目前关于G-CSF的疗效还有待进一步证实。sargramostin是重组人型GM-CSF。I、II期临床试验显示sargramostin耐受性好,没有严重的不良反应,与安慰剂组相比,有较高的反应率和缓解率,可降低疾病严重程度、提高生活质量^[37-40]。

3 阻止内皮的白细胞浸润

一旦机体中的T细胞和中性粒细胞被激活,他们就会从体循环中迁移到小肠黏膜。白细胞浸润的过程是由白细胞上的整合素和趋化因子受体以及内皮细胞上的黏附分子所控制的,这些分子在炎症性肠病中是上调的^[41]。其中,整合素 $\alpha 4\beta 1$ 、 $\alpha 4\beta 7$ 、 $\alpha 2\beta 2$,分别与黏附分子VCAM-1、MAdCAM-1、ICAM-1相互作用^[42,43]。

3.1 natalizumab natalizumab是以 $\alpha 4$ 为靶点的单克隆抗体,已经被批准用于CD的二线治疗^[44],是唯一可用于临床治疗CD的非以TNF- α 为靶点的生物制剂。10年前的第一个研究显示,接受natalizumab治疗的患者,39%获得缓解,而安慰剂组仅有8%^[45]。批准上市前最后一期试验显示,应用natalizumab的患者,12 wk持续反应率为48%,持续缓解率为26%,而安慰剂组是32%和16%^[46]。另外,最近的Meta分析得出结论,这种治疗在诱导CD缓解方面是优于安慰剂的^[47]。尽管natalizumab的成功,他仍然是二线治疗,仅用于难治性CD患者。因为其增加了机会性人多瘤JC病毒感染的风险,这种病毒会导致进行性多灶性白质脑病(progressive multifocal leukoencephalopathy, PML)。患者应用natalizumab治疗需要定期监测以保证与PML相关的风险最小化^[44]。

3.2 vedolizumab vedolizumab(MLN-02)是以 $\alpha 4\beta 7$ 为靶点的单克隆抗体。Feagan等^[48]用vedolizumab治疗活动期UC患者,缓解率为32%,而安慰剂组为14%,没有与vedolizumab相关的严重的不良反应发生。另外,一项实验性自身免疫性脑脊髓炎的恒河猴的研究显示,natalizumab在减少中枢系统炎症上有效,而vedolizumab则没有。这提示

vedolizumab不损伤中枢神经系统的免疫监视, 因此可能比natalizumab在诱发IBD患者PML方面有相对低的风险^[49].

4 以细胞为基础的治疗

目前以细胞为基础的治疗目的是刺激或替代异常的免疫细胞. 治疗药物包括干细胞及自体免疫细胞, 如以间质/造血干细胞为基础的remestemcel-L(Prochymal)和multistem、采用了胎盘来源干细胞的PDA-001以及自体T细胞药物OvaSave. 这些药物均在各期的临床试验研究中.

已完成的小样本研究结果显示了以细胞为基础治疗的有效性. Burt等^[50]发现, 自体造血干细胞移植后的重度CD患者, 缓解率达到100%, 5年的随访显示保持缓解患者的比例为1年91%, 3年57%, 5年19%.

尽管以细胞为基础的治疗取得了成功, 但收集、扩增、移植这些细胞所需要的技术、消耗的时间及费用都成为推广该治疗方法的瓶颈. 目前仅作为其他治疗无效时的选择.

5 结论

近年, 多种生物治疗方法应用于IBD的临床治疗, 但其仍处于探索阶段. 即便是抗TNF- α 药物这种目前看来最有效的治疗方法, 其疗效也差强人意, 远期的预后并没有明显改善. 究其原因, 我们的转化医学研究仍需解决以下问题: (1)动物模型如何能够更好地再现人的发病过程. IBD的动物模型已经广泛地用于新药的研发. 但一些对实验性结肠炎有显著疗效的药物对人并不起作用; (2)在众多上调或下调的分子中, 如何挖掘真正有效的治疗靶点; (3)如何能更深入地研究患者所携带的易感基因与疾病发生发展的相关性, 从而可调控这些致病的易感基因. 相信随着对IBD发病机制的深入研究, 在疾病的不同阶段选择正确的细胞因子靶向可能成为生物治疗成功的关键.

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■创新盘点

本文从针对适应性免疫系统的治疗、加强固有免疫系统的治疗、阻止内皮的白细胞浸润以及以细胞为基础的治疗4个方面分述了不同作用机制的生物治疗方法的有效性及其安全性.

■应用要点

本文综述了不同生物治疗方法在IBD治疗中的作用机制、临床应用的有效性 & 安全性, 探讨了IBD未来治疗可能的方向。

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■同行评价

本文总结了不同生物治疗方法在IBD治疗中的作用机制、临床应用的有效性及其安全性,探讨了IBD未来治疗可能的方向,这对临床治疗及科研指导都有一定的意义。

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