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Advances in the treatment of difficult-to-treat Crohn's disease

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Abstract: Crohn's disease is a chronic, progressive, and non-specific inflammation of the gastrointestinal tract. Despite a significant increase in available therapeutic agents in recent years, a considerable proportion of patients exhibit an inadequate response or experience a loss of response to existing treatments, leading to a state of refractory disease. Furthermore, there is a lack of consensus on the understanding of difficult-to-treat Crohn's disease. The International Organization for the Study of Inflammatory Bowel Disease has defined difficult-to-treat inflammatory bowel disease, providing an important framework for clinical research and practice. This article systematically reviews the definition of difficult-to-treat Crohn's disease, associated risk factors, selection of therapeutic drugs, evolving treatment concepts, and future directions in treatment, aiming to provide a beneficial reference for the diagnosis and management of difficult-to-treat Crohn's disease.

Keywords: Crohn's disease, difficult-to-treat; Biologic therapy; Small molecule medicine; Combination therapy; Cell therapy

Crohn's disease (CD) is a chronic, relapsing inflammatory disease of the digestive tract whose etiology and pathogenesis are not yet fully understood. As the disease progresses, complications such as intestinal strictures and penetrating disease may occur. Globally, the incidence and prevalence of CD are continuously rising, especially in newly industrialized countries [1]. With a deeper understanding of the disease, the treatment of CD has undergone revolutionary changes, evolving from conventional therapies such as mesalazine, glucocorticoids, and immunosuppressants to biologics and small-molecule drugs targeting different pathways [2]. Despite the increasing number of treatment options, significant challenges remain in clinical practice: a considerable proportion of patients do not respond to initial therapy or experience loss of response during treatment. Moreover, as the number of drug classes used increases, the response rate to subsequent treatments tends to decline, reflecting a "ceiling effect" of treatment [3-4]. In addition, 50%–80% of CD patients require surgery, and the postoperative recurrence rate within 10 years was approximately 50% [5], highlighting the difficulties in clinical management. Against this background, the concept of "difficult-to-treat CD (DTT-CD)" has emerged. Previously, the lack of a unified definition led to inconsistencies across clinical studies. In 2023, an expert panel from the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) published an international consensus on difficult-to-treat inflammatory bowel disease (DTT-IBD) [6], providing an important framework for clinical research and practice. The consensus summarizes therapeutic agents targeting different pathways and proposes concepts of combination therapy and individualized treatment, offering useful evidence and references for the management of DTT-CD.

1 Definition and Epidemiology of DTT-CD

In the international consensus on DTT-IBD, which includes DTT-CD, issued by the IOIBD expert panel [6], a clear definition is proposed. DTT-CD is considered when a patient presents with any of the following: (1) failure of at least two biologics or small-molecule drugs with different mechanisms of action; (2) postoperative recurrence of CD after two or more bowel resections; (3) presence of complex perianal disease [7]; (4) psychosocial factors in the patient that significantly affect clinical disease management.

Based on this definition, Parigi *et al.* [8] conducted an epidemiological study of DTT-IBD at two Italian

tertiary referral centers. The study included 1,736 patients with moderate to severe IBD treated with biologics or small-molecule drugs and found that 24.8% (430 patients) met at least one of the difficult-to-treat criteria. Among CD patients, the proportion with difficult-to-treat disease was 26.3% (241/917). Among CD patients meeting the difficult-to-treat criteria, multidrug failure was the most common reason (77.6%), followed by recurrence after at least two surgical resections (24.2%) and complex perianal disease (9.0%). Psychosocial factors accounted for only 0.7%, possibly due to underreporting in clinical records.

2 Risk Factors for the Development of DTT-CD

Current research suggests that the development of DTT-CD is related to multiple factors, including disease behavior, severity of inflammation, treatment strategies, and individual patient factors. Disease behavior is one of the important factors affecting prognosis. The retrospective study by Parigi *et al.* [8] found that, in terms of disease behavior, both structuring (OR = 2.24, 95% CI: 1.52–3.34, P < 0.01) and penetrating (OR = 2.33, 95% CI: 1.55–3.53, P < 0.01) phenotypes significantly increased the risk of DTT-CD. Complex perianal disease was also an important risk factor (OR = 2.49, 95% CI: 1.75–3.53, P < 0.01). Regarding disease location, ileocolonic involvement and upper gastrointestinal tract involvement were significantly associated with difficult-to-treat disease (OR = 3.04, 95% CI: 1.09–8.34, P = 0.03). Delayed initiation of advanced therapy was significantly associated with difficult-to-treat disease (OR = 1.74, 95% CI: 1.27–2.41, P < 0.01) [8]. Additionally, studies have shown that factors such as age at onset <40 years, smoking, *NOD*2 mutations, and severe endoscopic inflammation are closely related to an increased risk of disease progression and surgery [9].

3 Reasons for Patients Becoming Difficult-To-Treat

(1) When patients experience failure of multiple drug therapies, first reconsider whether the diagnosis is correct; establishing an accurate diagnosis is a prerequisite for effective treatment.

(2) A comprehensive assessment of the patient's disease is required to rule out complications; patients with surgical indications should undergo timely surgery.

(3) Exclude refractory symptoms caused by *Clostridioides difficile* or cytomegalovirus infection, small intestinal bacterial overgrowth, or bile salt malabsorption.

(4) Medication-related issues, including subtherapeutic drug levels or the development of antibodies; ensure dose optimisation of the treatment and allow sufficient treatment duration before objectively assessing the response.

(5) Pay attention to patient adherence.

(6) Exclude genetically related CD-like changes, especially in children and adolescents presenting with refractory disease [9].

4 Treatment Drug Options for DTT-CD

4.1 Monotherapy with drugs of different mechanisms

The main therapeutic agents with different targets currently used for CD include anti-tumour necrosis factor (TNF) agents such as infliximab (IFX) and adalimumab, anti-interleukin (IL)-12/23 antibody (ustekinumab, UST), anti-integrin antibody (vedolizumab), and JAK inhibitors (upadacitinib). A study including 6,584 patients who failed anti-TNF therapy showed that both UST and vedolizumab (VDZ) could be subsequent treatment options [10]. Furthermore, in biologic-DTT-CD patients, upadacitinib achieved 12-week clinical response and remission rates of 53.25% and 42.86%, respectively, and endoscopic response and remission rates of 50.00% and 38.89%, respectively [11]. With the advent of novel biologics—the IL-23p19 inhibitors (risankizumab, guselkumab) —a multicenter real-world study of DTT-CD showed that at 52 weeks, 58.2% of patients treated with risankizumab achieved clinical response and the endoscopic response rate was 50%, indicating efficacy even in patients who had failed multiple lines of therapy [12]. Guselkumab also demonstrated favorable clinical and endoscopic benefits in the GALAXI-1 study [13], although its study population included patients with moderate to severe CD who were biologic-naïve or had failed only one biologic; real-world evidence for its efficacy in DTT-CD remains relatively limited. Besides the above biologics and small molecules, studies have shown that thalidomide may be effective in some refractory patients [9].

4.2 Combination of Therapeutic Agents

4.2.1 Dual-target therapy

In recent years, the concepts of dual-target therapy and the broader advanced combination therapy (ACT) have emerged, referring to the combination of two biologics with different mechanisms of action, or a biologic combined with a small-molecule drug, to simultaneously intervene in multiple inflammatory pathways. ACT is suitable for patients who have failed multiple previous drug treatments, those with complex perianal disease, extraintestinal manifestations, or concomitant immune-mediated diseases. However, prospective randomized studies are still limited [14].

A single-center retrospective study included 23 DTT-CD patients who had failed at least two biologic agents. After combination therapy, 68% achieved endoscopic response, 45% achieved endoscopic remission, 70% achieved clinical response, and 60% achieved clinical remission. Stratified analysis showed that UST combined with adalimumab was more effective than UST combined with VDZ. No serious adverse events were observed with the different combination regimens, suggesting that biologic combination therapy may have good efficacy and safety in DTT-CD [15]. Moreover, dual-target therapy is not limited to dual biologic combinations. A real-world study included nine DTT-CD

patients treated with upadacitinib combined with VDZ; 75% achieved clinical response or remission, and 69% achieved endoscopic remission [16]. Another multicenter study from China included 18 DTT-IBD patients (10 with CD) who received dual-target therapy including a JAK inhibitor. At nine months, the clinical response rate was 100% and the endoscopic response rate was 88.89%. Adverse events included two infections, but treatment was continued after management [17].

Regarding the use of dual-target therapy in CD with complex perianal disease, a prospective single-center study of 33 CD patients with difficult-to-treat perianal disease showed that intensive dose IFX combined with UST resulted in complete clinical remission in 48.5% of patients, subjective symptom improvement in 97.0%, radiographic remission in 24.2%, improvement in luminal disease and extraintestinal manifestations in approximately 46%, and good tolerability in 90.9% [18].

It should be noted that high-quality evidence for dual-target therapy remains scarce, with most studies being case reports. Therefore, it is still difficult to draw firm conclusions regarding the optimal combination regimen, timing of administration, treatment duration, and long-term safety. The choice of agents for dual-target therapy is mainly based on principles of mechanistic complementarity and individualization. The most common combinations in clinical practice are anti-TNF agents plus VDZ, followed by UST plus VDZ or an anti-TNF agent [19]. For patients with extraintestinal manifestations, combination therapy can be guided by disease-specific immune pathways; for example, an anti-TNF-based combination is preferred in patients with spondylarthritis, whereas for psoriasis, IL-23/IL-17 pathway-related options may be considered [20].

4.2.2 Combination of multiple drugs

For patients who have a suboptimal response to dual-target therapy, some studies have explored combining three or more advanced therapies with different mechanisms to more fully suppress inflammation and treat complex phenotypes. The EXPLORER open-label phase 4 study evaluated a triple regimen of VDZ, adalimumab, and methotrexate, and found an endoscopic response rate of 54.4% and endoscopic remission rate of 34.5% at 26 weeks, with no new safety signals identified [21]. However, this study lacked a control group, and the true efficacy in DTT-CD needs further confirmation.

High-quality prospective studies on multiple-drug combination therapy in CD are still limited, and existing data mostly come from small-sample, short-term follow-up studies. Additionally, attention should be paid to adverse events of multiple-drug combination therapy. In the European multicenter COMBIO study, infections occurred in approximately 10% of 98 IBD patients receiving combination targeted therapy, all of whom had CD [22]. Although existing small-sample studies have not reported serious adverse events, long-term combination therapy with multiple immunosuppressants may still impose a higher immunosuppressive burden and infection risk; larger sample sizes and longer follow-up are needed to assess potential risks.

4.3 Treatment Options for DTT-CD Patients Based on Genetic Abnormalities

With the development of precision medicine, individualized treatment based on genetic and immunological characteristics is gradually becoming a research hotspot. For patients with severe disease or failure of multiple lines of therapy, single-gene screening should be considered [23]. A study of 750 patients with monogenic IBD found an overall efficacy rate of biologics of only about 25.5%, indicating limited effectiveness of conventional IBD treatments in this population. When abnormal gene mutations are identified through single-gene screening, corresponding treatments can be selected. For example, patients with LRBA or CTLA4 abnormalities may be considered for CTLA4-Ig therapy, while anti-IL-1 therapy may be considered for some autoinflammatory diseases [24]. Additionally, studies have shown that peripheral blood T-cell transcriptomic features have predictive potential for aggressive disease, which may in the future help identify high-risk patients and guide treatment selection [9].

4.4 Cell Therapy-hematopoietic Stem Cell Therapy

Autologous hematopoietic stem cell transplantation (ASCT) is considered a potentially viable cell therapy for DTT-CD. A clinical meta-analysis including 12 studies showed that ASCT can significantly reduce disease activity and also has some efficacy in complex perianal disease [25]. However, ASCT can also lead to adverse events, especially serious ones, mainly including one case of pulmonary veno-occlusive disease, three cases of histologically confirmed renal thrombotic microangiopathy, one death from respiratory failure, and one death from acute oliguric renal failure [26]. The risks of ASCT are not negligible; therefore, it is still primarily recommended for refractory patients who have failed multiple lines of therapy, have a significantly impaired quality of life, and cannot be further improved by surgery. In the future, with safer mobilization and conditioning regimens, ASCT and other cell therapies may drive treatment from mere suppression towards immune reconstitution.

5 Summary

DTT-CD is a major challenge in current clinical management. Approximately one-quarter of patients with moderate-to-severe CD meet the criteria for DTT disease. Its occurrence is closely associated with penetrating or structuring behavior, complex perianal disease, and treatment delay. Early identification of high-risk patients and seizing the therapeutic window of opportunity are crucial. As the treatment landscape shifts from conventional immunosuppression to sequential application of ACT– by simultaneously targeting multiple immune pathways – holds promise for overcoming the efficacy limitations of monotherapy. In the future, with

the advent of new target drugs, bispecific antibodies, and individualized applications guided by precision medicine, along with clarification of the timing and duration of combination therapy, the treatment of DTT-CD is expected to achieve more effective mechanism-driven interventions, thereby improving long-term patient outcomes.

Conflict of Interest None

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·学术前沿·

难治性克罗恩病的治疗进展

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摘要：克罗恩病是一种慢性、进展性、非特异性的消化道炎症性疾病，尽管近年来治疗药物显著增多，但仍有相当比例的患者对现有治疗反应不佳或失应答，使该病处于难治状态，且外界对难治性克罗恩病的理解也尚未统一。国际炎症性肠病研究组织颁布了难治性炎症性肠病的定义，为临床研究和实践提供了重要框架。本文系统综述难治性克罗恩病的定义、发生的危险因素，治疗药物的选择、治疗理念的改变及未来治疗的研发方向，旨在为难治性克罗恩病的诊治提供有益的参考。

关键词：克罗恩病，难治性；生物制剂；小分子药物；联合治疗；细胞治疗

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Advances in the treatment of difficult-to-treat Crohn's disease

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Abstract: Crohn's disease is a chronic, progressive, and non-specific inflammation of the gastrointestinal tract. Despite a significant increase in available therapeutic agents in recent years, a considerable proportion of patients exhibit an inadequate response or experience a loss of response to existing treatments, leading to a state of refractory disease. Furthermore, there is a lack of consensus on the understanding of difficult-to-treat Crohn's disease. The International Organization for the Study of Inflammatory Bowel Disease has defined difficult-to-treat inflammatory bowel disease, providing an important framework for clinical research and practice. This article systematically reviews the definition of difficult-to-treat Crohn's disease, associated risk factors, selection of therapeutic drugs, evolving treatment concepts, and future directions in treatment, aiming to provide a beneficial reference for the diagnosis and management of difficult-to-treat Crohn's disease.

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克罗恩病(Crohn's disease, CD)是一种病因及发病机制尚不完全明确的慢性、复发性消化道炎症性疾病,伴随疾病进展可发生肠狭窄及穿透等并发症。全球范围内,CD 的发病率和患病率呈持续上升趋势,尤其是新兴工业化国家[1]。随着对疾病的深入认识,CD 的治疗发生了革命性变化,从传统的美沙拉秦、糖皮质激素和免疫抑制剂发展到不同作用靶点的生物制剂和小分子药物[2]。尽管治疗选择不断增加,临床实践中仍面临严峻挑战:相当数量的患者对初始治疗无应答,或在使用过程中存在失应答,且随治疗使用的药物种类增多,患者后续治疗的应答率呈下降趋势,存在"治疗天花板"效应[3-4]。此外,50%~80%的 CD 患者需要手术治疗,而患者在 10 年内的术后复发率接近 50%[5],因此,临床治疗存在难点。在这种背景下,"难治性克罗恩病(difficult-to-treat CD, DTT-CD)"的概念应运而生,既往该概念缺乏统一的定义标准,导致临床研究结果的不一致性。2023 年国际炎症性肠病研究组织(International Organization for the Study of Inflammatory Bowel Disease, IOIBD)专家组颁布了难治性炎症性肠病(difficult-to-treat IBD, DTT-IBD)的国际共识[6],为临床研究和实践提供了重要框架,总结了不同靶点的治疗药物,提出联合治疗和个体化治疗理念,为 DTT-CD 治疗提供有益的依据和参考。

1 DTT-CD 的定义与流行病学

在 IOIBD 专家组颁布难 DTT-IBD 的国际共识中[6],对 DTT-IBD 包括 DTT-CD 提出明确的定义,当患者出现以下任何一种情况,考虑 DTT-CD,包括:(1) 经历至少两种不同作用机制的生物制剂或小分子药物治疗失败;(2) 两次或多次肠道切除术后 CD 的复发;(3) 存在复杂肛周疾病[7];(4) 患者合并的社会心理问题显著影响疾病的临床管理。

基于上述定义,Parigi 等[8]在意大利两个三级转诊中心开展了 DTT-IBD 的流行病学研究,该研究纳入 1 736 例接受生物制剂或小分子药物治疗的中重度 IBD 患者,结果显示 24.8%(430 例)的患者符合至少一项难治性标准,其中 CD 患者中难治性比例为 26.3%(241/917)。在符合难治性标准的 CD 患者中,多重药物失败是最常见的原因(77.6%),其次为至少两次手术切除后复发(24.2%)、复杂肛周疾病(9.0%),而社会心理因素仅占 0.7%,这可能与临床记录不充分有关。

2 DTT-CD 发生的危险因素

目前研究认为,DTT-CD 的发生与疾病行为、炎症程度、治疗策略及患者个体因素等多因素有关,疾病行为是影响疾病预后的重要因素之一。Parigi 等[8]的回顾性研究发现:在疾病行为方面,狭窄型(*OR*=2.24, 95%*CI*: 1.52~3.34, *P*<0.01)和穿透型(*OR*=2.33, 95%*CI*: 1.55~3.53, *P*<0.01)均显著增加 DTT-CD 发生风险;复杂肛周病变也是重要危险因素之一(*OR*=2.49, 95%*CI*: 1.75~3.53, *P*<0.01);在疾病分布方面,回结肠及上消化道受累与疾病难治性显著相关(*OR*=3.04, 95%*CI*: 1.09~8.34, *P*=0.03);延迟启动先进治疗与疾病难治性显著相关(*OR*=1.74, 95%*CI*: 1.27~2.41, *P*<0.01)[8];此外,有研究表明起病年龄小于 40 岁、吸烟、*NOD2* 基因突变以及内镜炎症的严重程度等因素与疾病进展及手术风险增加密切相关[9]。

3 患者出现难治性的原因

(1) 当患者出现多种药物治疗失败,首先反思诊断是否正确,建立正确诊断是治疗有效的前提;(2) 需对患者疾病进行全面评估,排除并发症存在,有手术适应症的患者需及时手术;(3) 排除艰难梭菌或巨细胞病毒感染以及小肠细菌过度生长或胆盐吸收障碍等所致症状难以纠正;(4) 药物治疗相关,包括血药浓度未达标或抗体产生等,须确保治疗的剂量和优化,并且在对治疗应答进行客观评估之前须有足够的治疗时间;(5) 重视患者的依从性;(6) 排除基因相关性的 CD 样改变,尤其是儿童青少年起病表现为难治性者[9]。

4 DTT-CD 患者的治疗药物选择

4.1 *不同作用机制药物的单药治疗* 目前用于 CD 治疗的主要不同作用靶点药物包括抗肿瘤坏死因子(tumor necrosis factor, TNF)制剂中的英夫利西单抗(infliximab, IFX)、阿达木单抗、抗白细胞介素(interleukin, IL)-12/23 抗体[乌司奴单抗(ustekinumab, UST)]、抗整合素抗体(维得利珠单抗)及 JAK 抑制剂(乌帕替尼)等。一项纳入 6 584 例抗 TNF 治疗失败患者的治疗研究显示 UST 和维得利珠单抗(vedolizumab, VDZ)均可作为后续治疗选择[10]。此外,乌帕替尼在生物制剂难治的 CD 患者中 12 周临床应答率和缓解率分别为 53.25%和 42.86%,内镜应答率和缓解率分别为 50.00%和 38.89%[11]。随着新型生物制剂 IL-23 p19 抑制剂(利生奇珠单抗、古塞奇尤单抗)的应用,一项

多中心DTT-CD的真实世界研究显示利生奇珠单抗治疗52周时有58.2%患者临床应答，内镜应答率达50%，提示其在多线治疗失败患者中仍具有疗效[12]。古塞奇尤单抗在GALAXI研究中同样显示出较好的临床和内镜获益[13]，但其研究人群包括未使用生物制剂或仅使用过一种生物制剂的中重度CD患者，其在真实世界DTT-CD的疗效证据仍相对有限。除上述生物制剂及小分子外，研究显示沙利度胺对部分难治患者可能有效[9]。

4.2 治疗药物的联合应用

4.2.1 双靶治疗 近年来提出了双靶治疗及更广义的先进联合治疗（advanced combination therapy，ACT）概念，即联合两种不同作用机制的生物制剂，或联合生物制剂与小分子药物，以同时干预多个炎症通路。ACT适用于既往多种药物治疗失败、伴复杂肛周病变、肠外表现或合并其他免疫介导疾病的患者，但前瞻性随机研究目前仍然有限[14]。

一项单中心回顾性研究纳入23例至少对两种生物制剂治疗失败的DTT-CD患者，联合治疗后68%的患者达到内镜应答，45%达到内镜缓解，70%达到临床应答，60%达到临床缓解。分层分析显示，UST联合阿达木单抗较UST联合VDZ疗效更佳。不同的联合应用方式均未观察到严重不良事件，提示生物制剂的联合治疗在DTT-CD中可能具有较好的有效性与安全性[15]。此外，双靶治疗并不限于双生物制剂组合。一项真实世界研究纳入采用乌帕替尼联合VDZ治疗的9例DTT-CD患者，其中75%的患者达到临床应答或缓解，69%达到内镜缓解[16]。另一项来自中国的多中心研究纳入18例难治性IBD患者，其中CD为10例，双靶治疗方案中包括JAK抑制剂，治疗9个月临床应答率为100%，内镜应答率为88.89%，不良事件包括2例感染，但均经处理后继续治疗[17]。

关于双靶治疗在CD伴复杂肛周病变的应用，一项纳入33例伴有难治性肛周病变的CD患者的前瞻性单中心研究显示，强化剂量IFX联合UST治疗，48.5%的患者达到完全临床缓解，97.0%的患者主观症状改善，24.2%达到影像学缓解，同时大约46%的患者肠内病变和肠外表现改善，90.9%患者耐受性良好[18]。

需要指出的是，双靶治疗总体高质量证据仍偏少，研究类型以病例报告为主，因此，目前仍难以对最佳联合方案、给药时机、疗程及长期安全性给出确定结论。双靶治疗的药物选择主要遵循机制互补及个体化原则。临床实践中最常见的组合为抗TNF制剂联合VDZ，其次为UST联合VDZ或抗TNF制剂[19]。对于合并肠外表现的患者，联合治疗可依据疾病特异免疫通路进行靶点选择，例如脊柱关节炎患者优先考虑以抗TNF制剂为基础的联合方案，而银屑病患者则可结合IL-23/IL-17相关通路进行选择[20]。

4.2.2 多种药物的联合治疗 对于双靶治疗后疗效欠佳的患者，有研究探讨联合三种或以上不同机制的先进治疗，以期更充分抑制炎症反应及治疗复杂表型。来自EXPLORER开放标签Ⅳ期研究中选择VDZ、阿达木单抗及甲氨蝶呤三联方案，发现26周时内镜应答率为54.4%，内镜缓解率为34.5%，且研究中未见明确新的不良事件[21]。但该研究缺乏对照组，有待进一步证实在DTT-CD中的真实疗效。

目前多种药物联合治疗在CD中的高质量、前瞻性研究仍然较少，现有数据多来自小样本、短期随访的研究。另外需关注的是多种药物联合治疗的不良事件，在欧洲多中心COMBIO研究中，98例接受联合靶向治疗的IBD患者中约10%发生感染，且均为CD患者[22]。虽然目前现有的小样本研究尚未出现严重不良事件，但长期联合多个免疫机制抑制药物的治疗仍可能带来更高的免疫抑制负担及感染可能，仍需增加样本量以及随访时间来评估可能存在的风险。

4.3 基于基因异常的难治性CD患者的治疗选择 随着精准医学的发展，基于遗传及免疫特征的个体化治疗逐渐成为研究热点。对于病情严重或多线治疗失败的患者，应考虑单基因筛查[23]。一项纳入750例单基因IBD患者的研究发现生物制剂总体有效率仅约25.5%，提示常规IBD治疗在该人群中的疗效有限。通过单基因筛查发现异常的基因突变，选取相应的治疗，例如LRBA或CTLA4异常患者可考虑CTLA4-Ig治疗，而部分自身炎性疾病可考虑抗IL-1治疗[24]。此外有研究显示患者外周T细胞转录组特征对侵袭性疾病行为具有预测潜力，未来有望用于识别高风险患者并指导治疗选择[9]。

4.4 细胞治疗-造血干细胞治疗 自体造血干细胞移植（autologous hematopoietic stem cell transplantation，ASCT）被认为是对DTT-CD的潜在可行细胞治疗。一项纳入12项研究的临床荟萃分析显示，ASCT可显著降低疾病活动度，对复杂肛周病变也有一定疗效[25]。但ASCT也会导致不良事件，尤其是严重不良事件，主要包括1例肺静脉闭塞症、3例组织学证实的肾血栓性微血管病，另有1例死于呼吸衰竭、1例死于急性少尿性肾衰竭[26]。ASCT治疗风险不容忽视，因此，目前仍主要推荐其用于多线治疗失败、显著影响生活质量且无法通过进一步手术改善的难

治患者。未来随着动员和预处理方案更加安全，ASCT及其他细胞治疗可能推动治疗从单纯抑制逐步走向重建。

5 总 结

DTT-CD是当前临床管理中的重要挑战，约四分之一的中重度患者符合难治性疾病标准，其发生与穿透或狭窄行为、复杂肛周病变、治疗延迟等因素密切相关，早期识别高危人群并把握治疗窗口期至关重要。随着治疗格局由传统免疫抑制转向先进疗法的序贯应用、联合治疗通过同时靶向多条免疫通路，有望突破单药治疗的疗效限制。未来，随着新靶点药物、双特异性抗体以及精准医学指导的个体化应用，联合治疗时机与疗程的明确，DTT-CD的治疗有望实现更有效的机制导向干预，从而改善患者长期预后。

利益冲突 无

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