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Research progress of ustekinumab in treatment of moderate-to-severe ulcerative colitis

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Abstract: As an emerging targeted biologic agent in recent years, ustekinumab (UST) can specifically bind to interleukin (IL)-12 and IL-23, block the activation of downstream proinflammatory factors, and achieve a broad inhibitory effect on systemic inflammatory responses. Its efficacy and safety have been confirmed in psoriasis and Crohn's disease (CD). As another type of inflammatory bowel disease (IBD), ulcerative colitis (UC) has high disability and mortality rates. Foreign experts recommend UST as a first-line treatment for moderate-to-severe UC, but clinical data on UST for treating moderate -to-severe UC remain limited in China. This article systematically reviews clinical studies of UST in UC, and summarizes its mechanism of action, clinical efficacy, safety, and response predictors. UST demonstrates rapid response, favorable efficacy, and high safety, which may provide a reference for individualized treatment of moderate-to-severe UC and theoretical guidance for the development of research related to UST treatment of moderate-to-severe UC.
Keywords: Ustekinumab; Ulcerative colitis; Inflammatory bowel disease; Clinical efficacy; Predictor
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Ulcerative colitis (UC) is a chronic inflammatory bowel disease that predominantly affects young and middle-aged adults. Along with changes in population lifestyle and dietary structure, its incidence and prevalence have been rising gradually in the past decade [1]. It is currently widely acknowledged that the pathogenesis of UC involves mucosal barrier defects and dysregulated immune responses in genetically susceptible individuals under the background of gut microbiota dysbiosis. This disease is characterized by a protracted course and high recurrence rate, which tends to impose a heavy economic burden on patients [2]. Biologics, which exert therapeutic effects by targeted inhibition of lymphocyte migration or pro-inflammatory factor release, have gradually become a critical treatment option for moderate-to-severe UC. The main categories of such agents include tumor necrosis factor (TNF)-α inhibitors, integrin antagonists, and cytokine-targeting antibodies. Ustekinumab (UST) is the world's first fully human "dual-target" inhibitor targeting interleukin (IL)-12 and IL-23. It was approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate-to-severe UC in 2019, and received its first marketing approval for clinical use in China in 2020 [3-4]. Given the relatively short history of UST application in China, relevant reports on its efficacy and safety remain insufficient. This article reviews the mechanism of action, clinical efficacy, safety profile, and predictive factors of treatment response of UST in the management of moderate-to-severe UC, with a view to providing theoretical support for the clinical application and individualized treatment of UST.

1 Overview of UC

UC is a type of nonspecific intestinal inflammatory disease, whose lesions originate from the anorectal junction, progress retrogradely in a continuous and diffuse pattern, and eventually involve the entire colon and even the terminal ileum [5]. Its main clinical symptoms include recurrent abdominal pain, diarrhea, and mucopurulent bloody stools. More than 90% of UC patients are complicated with rectal bleeding [6], and about 27% of them may develop extraintestinal manifestations (EIM) such as primary sclerosing cholangitis, peripheral arthritis, and pyoderma gangrenosum [7-8]. In recent years, the incidence of UC has been growing steadily in newly industrialized countries [9]. According to the epidemiological study on Crohn's disease and colitis in the Asia-Pacific region, the average incidence of inflammatory bowel disease (IBD) in Asia was 1.4 per 100,000 population in 2011, among which the number of UC patients was twice that of Crohn's disease patients [10]. The global number of UC patients was approximately 5 million in 2023 [7], while the incidence of UC in China is 1.2 per 100,000 population [11]. The pathogenesis of UC can be summarized as follows: multiple antigens in the external environment act on genetically susceptible individuals, causing gut microbiota dysbiosis and increased mucosal permeability, which further trigger intestinal immune imbalance and persistent inflammatory injury [12]. Specifically, reduced synthesis of intestinal epithelial mucin in UC patients leads to pathogen translocation, which activates dendritic cells to produce a variety of pro-inflammatory factors including TNF-α, IL-12, IL-23, IL-21, and IL-24. These cytokines enhance the proliferation and activation of lymphocytes through the Janus kinase pathway, driving the inflammatory cascade [13-14]. Among these factors, IL-12 promotes the differentiation of T helper (Th) 1 cells and stimulates natural killer cells to secrete interferon (IFN)-γ [15], while IL-23 induces Th17 polarization, which further aggravates inflammation by recruiting granulocyte chemokines [16].

The treatment goal for UC is to achieve endoscopic mucosal healing and histological remission. With the in-depth research on the immune mechanism of IBD, its treatment paradigm has gradually shifted from conventional drugs to biologics targeting specific inflammatory pathways [17]. Although anti-TNF agents can reduce the disease activity of UC and improve the clinical remission rate [18-20], 1/3 of patients have primary non-response to these agents, and another 1/3 develop secondary non-response during maintenance treatment [21-23]. In addition, their potential immunosuppressive effect and cardiotoxicity limit the application in specific patient groups. Vedolizumab, the representative agent of α4β7 integrin inhibitors, can interfere with leukocyte trafficking and homing, while tofacitinib, a small-molecule drug, can block a large number of inflammatory signal transduction mediated by Janus kinase, but the clinical remission rate of both agents remains only 40%-45% [24-25]. As an upstream regulatory factor of TNF, Janus kinase and lymphocyte migration, IL-12/IL-23 has become an emerging therapeutic target. This paper aims to introduce the research progress of UST, a representative anti-IL-12/IL-23 agent, in the treatment of moderate to severe UC.

2 The mechanism of action of UST

UST is a fully humanized IgG1 monoclonal antibody that targets the shared p40 subunit of IL-12 and IL-23 [15]. It blocks the binding of these cytokines to the IL-12β1 receptor, thereby interrupting the differentiation of Th1 and Th17 cells, reducing the release of pro-inflammatory factors such as TNF and IFN, and suppressing inflammatory responses both inside and outside the intestinal tract. Experimental studies have shown that disruption of IL-12 signaling can prevent experimental autoimmune diseases, and animal models have confirmed that blocking IL-23 can alleviate T cell-mediated colitis [26-27].

3 Clinical efficacy of UST

The phase III UNIFI trial is a randomized, double-blind, placebo-controlled trial evaluating the clinical efficacy of UST in patients with moderate-to-severe UC. It is also the first trial to incorporate endoscopic mucosal healing as part of efficacy assessment, consisting of an 8-week induction phase and a 44-week maintenance phase [28-29]. A total of 961 eligible patients with moderate-to-severe UC were enrolled in the induction phase and randomly assigned to the UST group or the placebo group. At the end of the induction remission period, the clinical remission rate, clinical response rate, endoscopic improvement rate, and histological mucosal healing rate in the UST group were all higher than those in the placebo group ($P < 0.01$). A total of 523 patients who responded to induction therapy entered the maintenance phase and were randomly assigned to receive subcutaneous injection of UST (90 mg) every 8 weeks (q8w), every 12 weeks (q12w), or placebo. After 44 weeks of continuous administration, the primary endpoint, clinical remission rate, was 43.8% in the q8w subgroup and 38.4% in the q12w subgroup of the UST group, which were both higher than the 24.0% in the placebo group ($P < 0.01$, $P = 0.002$, respectively). For key secondary endpoints, the endoscopic improvement rate, mucosal healing rate, corticosteroid-free remission rate (CSFR), and sustained clinical remission rate in both the q8w and q12w subgroups were superior to those in the placebo group ($P < 0.01$). Data from the UNIFI trial indicate that UST is an effective treatment option for moderate-to-severe UC. It can achieve clinical remission while maintaining clinical response, and contributes to improved endoscopic improvement rate and histological mucosal healing.

Danese *et al.* [30] conducted a post-hoc analysis of the above study data, focusing on the initial efficacy of UST in patients with moderate-to-severe UC. According to the treat-to-target strategy for IBD released by the International Organization for the Study of Inflammatory Bowel Diseases (STRIDE) in 2022, the short-term treatment goal for UC patients is a 50% reduction in the two-item UC Patient-Reported Outcome (PRO2) to achieve rapid symptom improvement. PRO2 consists of two derived items from the Mayo score: rectal bleeding and stool frequency. The report showed that at week 2 of induction therapy, the proportion of patients achieving clinical remission in the UST group was significantly higher than that in the placebo group (20.0% *vs* 12.9%, $P = 0.012$). At week 8 of induction, the proportion of patients with a stool frequency subscore of 0 or 1 in the UST group was higher than that in the placebo group ($P < 0.05$). Meanwhile, the number of patients without concurrent rectal bleeding continued to increase during UST treatment. Since PRO2 is more convenient to use than the Simple Clinical Colitis Activity Index (SCCAI) for disease management and can provide comparable and accurate results, it has become the current standard for evaluating symptom remission in UC patients [31].

Another 3-year UNIFI Long-Term Extension (LTE) study [32] reported the efficacy and safety of long-term maintenance therapy with UST. After 3 years of follow-up, it was found that at week 152 of subcutaneous UST 90 mg administration, 56.3% and 54.1% of patients in the q8w and q12w groups achieved symptomatic remission, and 55.1% and 51.2% achieved CSFR, respectively. Meanwhile, the study used the Inflammatory Bowel Disease Questionnaire (IBDQ) to assess patients' quality of life. The results showed that 87.8%, 87.8%, and 74.4% of patients in the q8w group, and 92.0%, 88.5%, and 74.7% of patients in the q12w group achieved IBDQ remission at weeks 44, 92, and 152 of maintenance therapy, respectively, indicating that long-term UST administration can also significantly improve patients' social and psychological functions. In terms of safety, the LTE study found that 5.5% (n=22) of patients who received UST treatment up to week 156 tested positive for anti-drug antibodies (ADAs). No adverse events such as death, tuberculosis, or major cardiovascular events were observed during follow-up. This suggests that maintenance subcutaneous UST administration can achieve long-term effective symptomatic remission with good safety and low immunogenicity.

The above studies indicate that UST for moderate-to-severe UC can not only induce rapid clinical response and achieve short-term symptom improvement, but also enable patients to obtain sustained benefits during maintenance therapy, increase the rate of endoscopic mucosal healing, and improve quality of life. However, the study population of the UNIFI trial is not universally representative, so practical assessment of the efficacy and safety of UST in UC treatment is required.

At present, multiple real-world studies have confirmed that UST has favorable efficacy and safety in the treatment of moderate-to-severe UC, especially in patients with severe refractory UC who have failed previous therapies such as anti-tumor necrosis factor (TNF) agents and vedolizumab. It can be used as the preferred biologic agent and main treatment option after failure of conventional therapies. Ochsenkühn *et al.*[4] conducted a retrospective study of 19 UC patients, using real-world data to support UST as a first-line option for patients with moderate-to-severe UC who failed previous biologic therapy in the phase III UNIFI trial. The study used the Lichtiger score [modified Colitis Activity Index (CAI)] to assess disease activity. The results showed that after 40-50 weeks of UST treatment, 53% of the 19 patients achieved clinical remission within 1 year, and the Lichtiger score decreased from 8.5 at baseline to 2.0 at 1 year. In addition, indicators such as fecal calprotectin (FC) and Mayo endoscopic score continued to decline during treatment. Another multicenter real-world study from Italy also confirmed the external validity of the UNIFI trial. The results showed that among 68 patients treated with UST (97% of whom had received prior biologic therapy), the CSFR rates were 31% and 50% at week 24 and week 52, respectively [33]. A retrospective study conducted by Hong *et al.* [34] at two tertiary IBD centers in the United States further validated the above conclusions: the clinical remission rates at 3 months and 12 months of treatment were 43.0% and 45.0%, respectively, and the CSFR rates were 31.9% and 35.0%, respectively. Among patients who underwent colonoscopy at 12 months, the endoscopic remission rate reached 50% and the mucosal healing rate reached 33.3%.

A multicenter study proposed by Amiot *et al.* [35] verified the efficacy and safety of UST for induction and maintenance therapy in highly refractory UC. The study enrolled 103 patients from the GETAID centers, among whom 70% had received more than two anti-TNF agents and 85% had used vedolizumab previously. Short-term induction results showed that at weeks 12-16, the CSFR was 35.0%, the clinical remission rate was 39.8%, and 19.4% of patients had no rectal bleeding and normal defecation frequency. A total of 93 patients had endoscopic activity assessed at baseline, and re-evaluation of 49 patients at weeks 12-16 found that the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) decreased from 5.0±1.2 to 3.8±1.9 ($P < 0.01$), and the Mayo endoscopic score decreased from 2.7±0.5 to 2.2±1.0 ($P < 0.01$). Maintenance therapy results showed that at week 52 of UST treatment, the CSFR was 32%, the clinical remission rate was 34%, and 24.3% of patients had no rectal bleeding or increased stool frequency [36]. Among the 93 patients who underwent endoscopic assessment at baseline, 65 were re-evaluated during weeks 26-52: the UCEIS decreased from 5.0±1.1 at baseline to 3.6±1.1 ($P < 0.01$), and the Mayo endoscopic score decreased from 2.7±0.5 to 2.0±1.0 ($P < 0.01$). Chaparro *et al.* [37] analyzed data from the ENEIDA registry to further confirm the above findings. A total of 95 patients received UST for UC (80% of whom were refractory patients who failed previous treatment with two anti-TNF agents and vedolizumab). One-third of

the patients achieved clinical remission at week 16 of induction therapy, and one-third achieved CSFR at weeks 24 and 52 of follow-up. This was consistent with the results of Honap *et al.* [38], a retrospective study from the UK which also confirmed that UST can induce CSFR in 1/3 of patients with refractory UC.

In summary, UST provides an approximate 1/3 CSFR during both short-term induction and maintenance therapy in patients with highly refractory UC. When anti-TNF therapy is contraindicated, ineffective, or limited due to adverse effects, UST should be considered as an alternative. In addition, several studies have demonstrated that UST is also effective for extraintestinal manifestations such as psoriasis, erythema nodosum, pyoderma gangrenosum, and uveitis [39-40].

4 Safety of UST

UST has favorable safety and tolerability profiles. According to the phase III UNIFI study, the incidence of adverse events, serious adverse events, and infections were similar between the UST group and the placebo group in both the induction and maintenance phases, and no dose-dependent toxicity was observed during maintenance therapy [41]. One study showed that compared with anti-TNF agents, anti-IL-12/IL-23 agents are associated with a lower risk of infection, making them suitable for patients with complications or increased risk of adverse effects. In addition, UST treatment can reduce the risk of malignancy to a certain extent, and the use of UST in IBD patients with a history of malignancy does not increase the risk of cancer recurrence [42]. A series of meta-analyses and safety analyses have indicated that among thousands of patients followed up, only a small number of serious adverse events have been reported, and there is no definite association between cancer or death cases and UST treatment [43-44].

5 Predictors of treatment response to UST

Detection of specific biomarkers in the early stage of treatment to predict patients' response to drugs can help physicians identify individuals who are more likely to benefit, reduce the duration of ineffective interventions, and achieve optimal patient stratification and personalized treatment [45]. Currently, C-reactive protein (CRP) and FC have been identified as useful predictors for long-term treatment response to UST and intestinal inflammatory activity. Specifically, patients with a higher baseline CRP level (≥10 mg/L) have better treatment outcomes, which is particularly evident in patients who failed previous anti-TNF therapy [46]. An FC level <250 mg/kg at week 6 of treatment can accurately predict endoscopic remission at week 52 [47]. In addition, other available predictive markers include molecular factors, gut microbiota, pharmacological factors, etc., but there is still a lack of a single indicator for accurate assessment of UST treatment response. In the future, multi-parameter predictive models constructed based on bioinformatics and machine learning will play a more important role [48-50].

5.1 Molecular factors

A prospective study demonstrated that in patients with initial response to UST, serum IL-6 levels decreased significantly from baseline to week 10 of treatment, which was an independent predictor of clinical remission at 12 months of biologic therapy [51]. Another study found that IL-9 expression level at week 8 of biologic therapy was negatively correlated with mucosal healing after 54 weeks of follow-up [52]. Other trials have also indicated that patients with high intestinal mucosal IL-23 expression are more likely to achieve remission with UST [53-54]. Some experts also believe that measurement of the concentrations of IFN-γ, serum amyloid A, lipopolysaccharide-binding protein, and acid glycoprotein during UST treatment is helpful for adequate monitoring of treatment response in IBD patients [55]. A retrospective study in elderly patients found that regardless of the type of biologic agent used, a higher baseline serum triiodothyronine to thyroxine ratio (T3/T4) was positively correlated with the mucosal healing rate [56].

5.2 Gut microbiota

Dysbiosis caused by alterations in gut microbiota not only leads to barrier defects and bacterial translocation, but also interferes with drug metabolism and renders drugs inactive. Increasing evidence suggests that changes in gut microbiota composition can affect the efficacy of UST and predict individual treatment response [57]. Compared with non-responders, the microbial diversity in responders increases with the improvement of intestinal inflammation, mainly dominated by *Faecalibacterium*, *Escherichia coli*, and *Shigella*. The community diversity of patients in remission at 6 weeks after treatment is 1.7 times higher than that of patients with active disease [58-59].

5.3 Pharmacological factors

Reactive therapeutic drug monitoring can help identify patients who will benefit from optimized UST therapy. A multicenter study found that UST trough concentrations in the early stage of treatment were correlated with clinical remission and FC reduction, while trough concentrations during maintenance therapy were correlated with endoscopic healing and treatment optimization [60]. The UNITI trial reported the relationship between UST pharmacokinetics and clinical response, indicating that higher serum UST concentrations during induction were positively correlated with endoscopic remission, histological improvement, and reduction of biomarkers during maintenance therapy [61].

6 Summary and prospects

Currently, the cure of UC remains a global clinical challenge. An increasing number of patients face the risk of colectomy or even malignant transformation, and even long-term pharmacotherapy is associated with issues such as reduced treatment adherence, attenuated efficacy, and heavy economic burden. However, with the in-depth investigation of the immune mechanisms of IBD, treatment options have become more diversified, and biologic agents have emerged as a critical therapeutic modality for moderately to severely active UC. As a novel targeted agent, UST has multiple advantages including rapid response, flexible administration, long-term stable efficacy, favorable safety profile, and low immunogenicity. Relevant guidelines in Europe and the United States recommend UST as a first-line biologic agent for frail patients or those with contraindications to anti-TNF agents. Nevertheless, given the relatively short clinical application history of UST in China, the following issues still need to be addressed: (1) Lack of head-to-head trials comparing the efficacy and adverse effects between UST and other biologic agents; (2) The need for more accurate positioning of UST in the treatment algorithm for moderately to severely active UC; (3) Lack of efficacy evaluation of combination therapy with UST and other biologic agents; (4) Lack of long-term safety data of UST application in special populations including elderly patients, patients with malignancy, and pregnant patients. In the future, large-scale multicenter prospective studies are required to further explore the clinical efficacy of UST in Chinese patients with moderately to severely active UC.

Conflict of interest None

Reference

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·学术前沿·

乌司奴单抗治疗中重度溃疡性结肠炎的研究进展

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摘要：乌司奴单抗（UST）作为近几年新兴的靶向生物制剂，可特异性结合白细胞介素（IL）-12和23，阻断下游促炎因子激活，达到广泛抑制全身多部位炎症反应的作用，其有效性和安全性已在银屑病和克罗恩病中得到证实。溃疡性结肠炎（UC）作为炎症性肠病（IBD）的另一类型，具有较高的致残率和病死率。国外专家推荐UST作为治疗中重度UC的一线选择，但我国目前仍缺乏有关UST治疗中重度UC的试验数据。本文系统整合了各项有关UST治疗UC的临床研究，并对UST治疗UC的作用机制、临床疗效、安全性和反应预测因素作一综述，发现UST具有应答迅速、疗效显著、安全性高等优点，可能为中重度UC患者个体化治疗方案的制定和实施提供一定参考，并为UST治疗中重度UC相关研究的开展提供理论指导。

关键词：乌司奴单抗；溃疡性结肠炎；炎症性肠病；临床疗效；预测因素
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Research progress of ustekinumab in treatment of moderate-to-severe ulcerative colitis

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Abstract：As an emerging targeted biologic agent in recent years，ustekinumab（UST）can specifically bind to interleukin（IL）-12 and IL-23，block the activation of downstream proinflammatory factors，and achieve a broad inhibitory effect on systemic inflammatory responses. Its efficacy and safety have been confirmed in psoriasis and Crohn's disease（CD）. As another type of inflammatory bowel disease（IBD），ulcerative colitis（UC）has high disability and mortality rates. Foreign experts recommend UST as a first-line treatment for moderate-to-severe UC，but clinical data on UST for treating moderate-to-severe UC remain limited in China. This article systematically reviews clinical studies of

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UST in UC, and summarizes its mechanism of action, clinical efficacy, safety, and response predictors. UST demonstrates rapid response, favorable efficacy, and high safety, which may provide a reference for individualized treatment of moderate-to-severe UC and theoretical guidance for the development of research related to UST treatment of moderate-to-severe UC.

Keywords: Ustekinumab; Ulcerative colitis; Inflammatory bowel disease; Clinical efficacy; Predictor

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溃疡性结肠炎(ulcerative colitis, UC)是一类多累及青壮年的慢性肠道炎性疾病,随着人们生活习惯和饮食结构的改变,其发病率和患病率在近10年逐渐上升[1]。目前普遍认为,UC发病机制涉及遗传易感个体在肠道菌群失调背景下出现的黏膜屏障缺陷及免疫调节异常,该病具有病程迁延、复发率高等特点,易造成沉重的经济负担[2]。生物制剂通过靶向抑制淋巴细胞迁移或促炎因子释放,已逐渐成为中重度UC的重要治疗选择,主要包括肿瘤坏死因子(tumor necrosis factor, TNF)-α抑制剂、整合素拮抗剂及细胞因子抗体。乌司奴单抗(ustekinumab,UST)是全球首个全人源"双靶向"白细胞介素(interleukin, IL)-12/23抑制剂,于2019年被美国食品药品监督管理局(FDA)批准用于治疗中重度UC,2020年首次在中国批准使用[3-4]。限于UST在国内使用时间较短,疗效和安全性方面缺乏相关报道,本文就UST治疗中重度UC的机制、临床疗效、安全性和治疗反应预测因素作一综述,为UST的临床应用和个体化治疗提供理论支持。

1 UC概述

UC是一种非特异性肠道炎症,病变始于肛门直肠交界处,以连续弥漫的方式逆行进展,最终累及全结肠甚至回肠末端[5],主要症状是反复发作的腹痛、腹泻、黏液脓血便,超过90%的患者合并直肠出血[6],约27%可并发肠外表现(extraintestinal manifestation, EIM),如原发性硬化性胆管炎、外周关节炎、坏疽性脓皮病等[7-8]。近年来,UC发病率在新型工业化国家稳步增长[9]。根据亚太地区克罗恩病及结肠炎流行病学研究表明,2011年亚洲炎症性肠病(inflammatory bowel disease, IBD)的平均发病率为1.4/10万,其中UC患者为克罗恩病的2倍[10]。2023年UC的全球发病人数约500万例[7],中国UC的发病率为1.2/10万[11]。UC的发病机制概括为外界环境中的多种抗原作用于遗传易感者,引起肠道微生物失调、黏膜通透性增加,继而引起肠道免疫失衡及持续炎症损伤[12]。具体而言,UC患者的肠上皮黏蛋白合成减少导致病原体易位并激活树突状细胞产生多种促炎因子,如TNF-α、IL-12、IL-23、IL-21、IL-24,这些细胞因子通过Janus激酶通路增强淋巴细胞的增殖与活化,驱动炎症级联反应[13-14]。其中,IL-12促进辅助性T细胞(Th)1分化并刺激自然杀伤细胞分泌干扰素(IFN)-γ[15],而IL-23诱导Th17极化,后者通过募集粒细胞趋化因子进一步加剧炎症[16]。

UC的治疗目标是达到内镜下黏膜愈合和组织学缓解。随着对IBD免疫机制的深入,其治疗模式已从传统药物逐渐转为靶向特定炎症通路的生物制剂[17]。尽管抗TNF药物可降低UC的疾病活动度,提高临床缓解率[18-20],但有1/3的患者存在原发性失应答,另有1/3在维持治疗期间出现继发性失应答[21-23],此外,其潜在的免疫抑制和心脏毒性限制了在特殊患者中的使用。α4β7整合素抑制剂的代表药维得利珠单抗可干扰白细胞的运输和归巢,小分子药物托法替尼可阻断Janus激酶介导的大量炎症信号转导,但二者的临床缓解率仅保持在40%~45%[24-27]。作为TNF、Janus激酶或淋巴细胞迁移的上游,IL-12/IL-23是一个新兴的治疗靶点,本文旨在介绍抗IL-12/IL-23因子的代表药物UST治疗中重度UC的研究进展。

2 UST的作用机制

UST是一种全人源化IgG1单克隆抗体,能靶向作用于IL-12和IL-23共享的p40亚基[15],阻断其与IL-12β1受体结合,从而中断Th1和Th17的分化,降低TNF、IFN等促炎因子释放,抑制肠道内外的炎症反应。实验表明,破坏IL-12可预防实验性自身免疫性疾病且动物模型证实阻断IL-23可减轻T细胞介导的结肠炎[28-29]。

3 UST的临床疗效

Ⅲ期UNIFI是一项评估UST治疗中重度UC患者临床疗效的随机、双盲、安慰剂对照试验,也是第一项将内镜黏膜愈合情况纳入疗效评估的试验,包括8周诱导和44周维持治疗[30-31]。共961名符合标准的中重度UC患者被纳入诱导治疗并随机分配至UST组和安慰剂组,诱导缓解期结束时,UST的临床缓解率、临床应答率、内镜改善率、组织黏膜愈合率均高

于安慰剂组（P<0.01）。诱导期应答的523名患者进入维持期，并随机分配至每8周（q8w）或12周（q12w）皮下注射UST（90 mg）或安慰剂组。经44周持续注射后，主要终点即临床缓解率，UST组中q8w亚组为43.8%、q12w亚组为38.4%，分别高于安慰剂组的24.0%（P<0.01，P=0.002）；关键次要终点为q8w亚组和q12w亚组的内镜改善率、黏膜愈合率、无类固醇激素缓解率（corticosteroid-free remission rate，CSFR）、持续临床缓解率均优于安慰剂组（P<0.01）。UNIFI试验数据表明，UST是治疗中重度UC的有效治疗选择，可在实现临床缓解的同时，维持临床应答，有助于提高内镜改善率和组织黏膜愈合。

Danese等[32]对上述研究数据进行事后分析，重点描述中重度UC患者使用UST后的初始疗效。根据2022年国际IBD研究组织（STRIDE）发布的IBD治疗达标策略，UC患者的短期治疗目标为两项UC患者结局报告（PRO2）下降50%，目的是达到快速的症状改善，PRO2由Mayo评分的两个衍生项目组成，即直肠出血和大便频率。报告显示，诱导治疗第2周时，与安慰剂组相比，UST组达临床缓解的患者比例显著增加（20.0% *vs* 12.9%，P=0.012）；诱导第8周时，UST组中大便频率子评分为0或1的患者比例高于安慰剂组（P<0.05）；同时，在使用UST治疗的过程中未并发直肠出血的患者人数持续增加。由于利用PRO2比临床疾病活动指数（SCCAI）管理更便捷，同时PRO2也可提供类似且准确的结果，目前已成为评估UC患者症状缓解的现行标准[33]。

另一项为期3年的UNIFI长期扩展研究（LTE）[34]报告了UST长期维持治疗的有效性和安全性，经过3年的随访发现，皮下注射UST 90 mg至第152周时，实现症状缓解的患者在q8w和q12w中分别占56.3%和54.1%，实现CSFR的分别占55.1%和51.2%。同时，该研究使用炎症性肠病问卷（IBDQ）评估患者的生活质量。结果发现，q8w组分别有87.8%、87.8%、74.4%的患者，q12w组分别有92.0%、88.5%、74.7%的患者，于维持治疗的第44、92、152周达到IBDQ缓解，这表明长期应用UST还可明显改善患者的社会及心理功能。在安全性方面，LTE发现接受UST治疗至第156周的患者中有5.5%（n=22）出现抗药物抗体（ADAs）阳性，在随访进程中未发现死亡、结核或重大心血管等不良事件。由此可见，维持皮下注射UST可达到长期有效的症状缓解，且安全性良好，不易产生ADAs。

上述研究表明，UST治疗中重度UC不仅可以诱导快速临床应答，实现短期症状改善，还可使患者在维持治疗中持续获益，提高内镜黏膜愈合比例，改善生活质量。然而UNIFI试验的研究人群并不具备普适性，因此需要对UST治疗UC的有效性和安全性进行实际评估。

目前，已有多项来自真实世界的研究证明UST在治疗中重度UC，尤其是经历抗TNF药物、维得利珠单抗等治疗失败的重度难治性UC方面具有良好的疗效和安全性，可作为传统疗法失败后的首选生物制剂和主要治疗方式。Ochsenkühn等[4]对19例UC患者进行回顾性研究，以真实数据支持UST在Ⅲ期UNIFI试验中作为既往生物制剂治疗失败中重度UC患者的一线选择。该研究采用Lichtiger评分[修正的结肠炎活动指数（CAI）]评估疾病活动度，结果发现19例患者在使用UST治疗40~50周后有53%在1年内实现临床缓解，Lichtiger评分从基线时的8.5降至一年后的2.0。另外，粪便钙卫蛋白（fecal calprotectin，FC）和Mayo内镜评分等指标均在治疗期间持续下降。另一项来自意大利的多中心真实世界研究也证实了UNIFI试验的外部有效性，其结果显示，68名经UST治疗的患者（97%既往接受过生物制剂治疗）在第24周和第52周的CSFR分别为31%和50%[35]。Hong等[36]在美国2个3级IBD中心开展的回顾性研究进一步验证上述结论，治疗第3个月和第12个月的临床缓解率分别为43.0%和45.0%，CSFR分别为31.9%和35.0%，在第12个月进行结肠镜检查的患者中内镜缓解率达50%，黏膜愈合率达33.3%。

Amiot等[37]开展的一项多中心研究验证了UST诱导和维持治疗高度难治性UC的有效性和安全性，该研究纳入了来自GETAID中心的103例患者，其中70%曾接受超过2种抗TNF药物治疗，85%使用过维得利珠单抗。短期诱导的结果表明第12~16周时，CSFR为35.0%，临床缓解率为39.8%，19.4%的患者无直肠出血，排便频率正常。有93名患者在基线评估内镜活动，其中49名在第12~16周重新评估时发现UC内镜严重程度指数（UCEIS）从5.0±1.2下降至3.8±1.9（P<0.01），Mayo内镜评分从2.7±0.5下降至2.2±1.0（P<0.01）。维持治疗结果显示，UST治疗第52周的CSFR为32%，临床缓解率为34%，24.3%的患者未出现直肠出血和便频[38]。在基线进行内镜评估的93名患者中，有65名在第26~52周期间重新评估，UCEIS从基线时的5.0±1.1降至3.6±1.1（P<0.01），Mayo内镜评分从2.7±0.5降至2.0±1.0。Chaparro等[39]分析ENEIDA注册数据进一步证实了上述观点，共95名患者使用UST治疗UC（其中80%为既往使用两种抗

TNF 和维得利珠单抗治疗失败的难治性患者），1/3 的患者在诱导治疗第 16 周达到临床缓解，1/3 的患者在随访的第 24 周和第 52 周达到 CSFR。这与 Honap 等[40]的研究结果一致，这项来自英国的回顾性研究同样证实了 UST 可诱导 1/3 的难治性 UC 患者实现 CSFR。

综上所述，UST 对高度难治性 UC 患者，在短期诱导和维持治疗期间仍提供了约 1/3 的 CSFR。当存在抗 TNF 治疗禁忌、失败或因副作用而受到限制时，应考虑使用 UST 作为替代方案。另外，一些研究已经证明，UST 对一些肠外表现如银屑病、结节性红斑、坏疽性脓皮病、葡萄膜炎也同样有效[41-42]。

4　UST 的安全性

UST 具有良好的安全性和耐受性。根据Ⅲ期 UNIFI 研究报道，无论在诱导还是维持阶段，UST 组和安慰剂组之间的不良事件、严重不良事件、感染的发生率均相似，且维持治疗期间未观察到剂量依赖性毒性[43]。一项研究显示，与抗 TNF 相比，抗 IL-12/IL-23 药物可降低感染风险，适用于有并发症或副作用风险增加的患者，此外，使用 UST 治疗可在一定程度上降低恶性肿瘤的发生风险，在既往罹患恶性肿瘤的 IBD 患者中使用 UST 不会增加癌症复发的风险[44]。一系列 Meta 和安全性分析均指出，在随访的上千名患者中，仅少数报道严重不良事件，癌症和死亡病例与使用 UST 治疗之间无明确联系[45-46]。

5　UST 治疗反应的预测因素

在治疗早期通过检测特定标志物来预测患者对药物的反应可以帮助医生识别更有可能获益的个体，减少无效干预的时间，以实现最佳定位和个性化治疗[47]。目前，C 反应蛋白和 FC 已被确定可用于预测 UST 的长期治疗反应和肠道炎症活动度。其中，基线时拥有较高 C 反应蛋白水平（≥10 mg/L）的患者治疗效果更佳，在既往抗 TNF 治疗失败的患者中尤为明显[48]；而治疗第 6 周时 FC<250 mg/kg 能准确预测第 52 周的内镜缓解[49]。除此之外，可用于预测的标志物还包括分子因素、肠道菌群、药理因素等，但仍缺乏精准评估 UST 治疗反应的单一指标。未来，一些基于生物信息学和机器学习构建的多参数预测模型会发挥更大作用[50-52]。

5.1　*分子因素*　一项前瞻性研究证明对 UST 产生初始应答的患者，血清 IL-6 水平从基线到治疗第 10 周显著降低，是生物治疗 12 个月时临床缓解的独立预测因子[53]；另一项研究发现生物制剂治疗第 8 周时的 IL-9 表达量与随访 54 周后的黏膜愈合呈负相关[54]；亦有试验指出肠黏膜高表达 IL-23 的患者更可能通过 UST 获得缓解[55-56]。还有部分专家认为在 UST 治疗期间测量 IFN-γ、血清淀粉样蛋白 A、脂多糖结合蛋白、酸性糖蛋白的浓度有助于充分监测 IBD 患者的治疗反应[57]。一项针对老年患者的回顾性研究发现，无论使用哪一种生物制剂，基线时较高的血清三碘甲状腺原氨酸与甲状腺素比值（T3/T4）与黏膜愈合率呈正相关[58]。

5.2　*肠道菌群*　肠道菌群改变引起的生态失调不仅导致屏障缺陷、细菌异位，还可以干扰药物代谢使其失去活性。越来越多的证据表明，肠道菌群成分变化能影响 UST 的疗效并预测个体是否对其产生应答[59]。与无应答患者相比，应答患者的菌群多样性将随着肠道炎症改善而增加，其中以粪杆菌、大肠杆菌和志贺菌为主，治疗后 6 周处于缓解期患者的群落多样性比活动期患者高 1.7 倍[60-61]。

5.3　*药理因素*　反应性治疗药物监测可以帮助识别那些将从 UST 优化治疗中受益的患者。一项多中心研究发现 UST 治疗早期药物谷浓度与临床缓解、FC 降低相关，而维持期间的药物谷浓度与内镜愈合和治疗优化相关[62]。UNITI 试验报道了 UST 药物动力学和临床反应之间的关系，指出诱导期间较高的血清 UST 浓度与维持治疗时的内镜缓解、组织学改善、生物标志物降低呈正相关[63]。

6　总结与展望

如今，如何治愈 UC 已成为困扰世界的难题，越来越多的患者面临结肠切除甚至癌变的风险，即使接受长期药物治疗也存在依从性降低、疗效衰减、经济压力大等问题，但随着对 IBD 免疫机制的探究，治疗选择变得更加多元，生物制剂已成为治疗中重度 UC 的重要手段。UST 作为新型靶向药物具有应答迅速、给药灵活、长期稳定、良好的疗效和安全性以及低免疫原性等优点，欧美国家相关指南推荐 UST 作为体弱患者或存在抗 TNF 药物禁忌证患者的一线生物制剂。尽管如此，鉴于 UST 在我国的临床应用时间较短，仍存在以下几方面问题需要解决：（1）缺乏 UST 和其他生物制剂间疗效和副作用比较的头对头试验；（2）在中重度 UC 的治疗算法中如何更准确地定位 UST；（3）缺乏 UST 和其他生物制剂联合治疗的效果评价；（4）缺乏 UST 在老年、癌症、妊娠患者中长期应用的安全数据。未来，需要进一步开展大规模

多中心的前瞻性研究以深入探索UST对我国中重度UC患者的临床疗效。

利益冲突 无

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