Short-term efficacy of ustekinumab in patients with Crohn's disease and intestinal stricture

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Research Article

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Abstract

Objective: To estimate the short-term efficacy of ustekinumab (UST) in patients with Crohn's disease (CD) and intestinal stricture.

Design: This retrospective case-series included patients with CD and intestinal stricture. The characteristics and disease evaluation data of the included patients, including Crohn's Disease Activity Index (CDAI), Crohn's disease obstructive score (CDOS), fecal calprotectin (FCP), and hypersensitive C reactive protein (Hs-CRP), were collected at baseline. The primary endpoint was a success at week 24, defined as UST continuation without other treatments (steroids, other anti-tumor necrosis factors, surgery, or endoscopic dilation); secondary endpoints were improvement of clinical evaluation and laboratory data at week 24 in the whole cohort.

Results: A total 36 patients were screened, and 12 were included between July 2020 and July 2021. At week 24, 10/12 (83.3%) patients achieved success. Among these patients, 6/8 (75%) patients with symptomatic stricturing Crohn's disease (SSCD) achieved success. In SSCD patients with successful use of UST, CDOS and CDAI were significantly improved in all patients, and FCP improved in 5/6 (83.3%) patients at week 24. Only 2 (16.7%) patients accepted anal reconstruction or endoscopic balloon dilation (DBE) at follow-up. No severe adverse events occurred during the study.

Conclusions: A successful response to UST was observed in more than three-quarters of CD patients with an intestinal stricture. In addition, UST showed good efficacy and safety in SSCD.

Introduction

Crohn's disease (CD) is a chronic immune-mediated inflammatory bowel disease characterized by transmural inflammation of the intestine, which may cause severe complications such as strictures, fistulation, and abscess[1]. More than one-third of patients tend to develop one or more strictures during the natural course of CD[2]. Strictures can develop anywhere in the digestive tract; however, they are most commonly found in the ileum and are defined as luminal narrowing and bowel wall thickening resulting from inflammatory, fibrotic, or mixed causes[2–4].

Some studies support the value of systemic corticosteroids in obstructive symptoms; however, these are always limited by both intolerability and serious adverse events[5]. Mesalamine and azathioprine (AZA) seem not to directly affect intestinal fibrosis[6–7]. Among the biologics, there is a concern that anti-tumor necrosis factor (TNF) therapy could paradoxically aggravate in stricturing CD through rapid mucosal healing reduced by recently studies[8–16]. CREOLE study showed that two-thirds of CD patients with symptomatic stricturing Crohn's disease (SSCD) who received ADA standard therapy could achieve success at week 24, while more than half of patients were free of surgery after 4 years follow-up[8]. Although the results from the above studies are inspiring, the safety of anti-TNFs in stricturing CD cannot be ignored.

Anti-TNFs have been associated with potential adverse events (AE), including infusion reactions, increased risk of infections, and higher occurrence of free perforations. The number of AE per 100 person-years is 118.63[17–20]. Reactivation of latent tuberculosis (LTB) was also found to increase in CD patients with anti-TNFs, especially in Asian countries[17,20]. Up to 32% of patients in the CREOLE study suffered from serious adverse events at week 24[8]. Therefore, the need for safe and effective therapies in stricturing CD is of essential importance.

This retrospective case-series was conducted to evaluate the short-time efficacy and safety of ustekinumab (UST) in patients with stricturing CD.

Materials And Methods

Study population

Patients with stricturing CD who were treated with UST and were under follow-up at the inflammatory bowel disease (IBD) specialist clinic, Department of Gastroenterology, the Second Affiliated Hospital of Medical College of Zhejiang University between April 2020 and August 2021 were included in the study. This study was approved by the Ethics Committee of the Second Affiliated Hospital, School of Medicine of Zhejiang University, Hangzhou, Zhejiang Province, China.

Study design and data collection

Baseline and follow-up point dates of patients with stricturing CD, including demographic features, disease characteristics, treatment history, clinical evaluation, and laboratory tests, were collected from IBD database. Crohn's disease obstructive score (CDOS)[8] and Crohn's Disease Activity Index (CDAI) were used to evaluate patients' clinical condition. Hypersensitive C reactive protein (Hs-CRP) and fecal calprotectin (FCP) were the main analysis indexes in this study.

Definitions of stricture

Computed tomography enterography (CTE) or magnetic resonance enterography (MRE) shows the intestinal lesion with luminal narrowing > 50% and an increase in bowel wall thickness > 25% compared to a normal bowel. For strictures identified during an endoscopic procedure, they are defined as luminal narrowing with the inability to pass the endoscope across the narrowing[11].

Inclusion criteria

Inclusion criteria were the following: (a) definite diagnosis of Crohn's disease according to European Crohn's and Colitis Organization and the European Society of Gastrointestinal and Abdominal Radiology (ECCO-ESGAR) guidelines[21]; (b) definite intestinal stricture(s); (c) failure/contraindications to steroids or

immunosuppressive agents or anti-TNFs or vedolizumab (VDZ).

The primary endpoint was a success at week 24, defined as UST continuation with all the following criteria: (a) no use of a prohibited treatment (corticosteroids, parenteral nutrition, other biologics); (b) no endoscopic dilation; (c) no anal or bowel surgery for resection of stricture; (d) no severe adverse events leading to UST withdrawal. The secondary endpoints were the levels of clinical evaluation (CDAI and CDOS) and laboratory data (Hs-CRP and FCP) at week 24 compared to baseline.

Results

A total of 36 patients who received UST between April 2020 and August 2021 were screened, and 12 patients with stricturing CD were included in the analysis. Among these patients, 75% were male (Table 1). The average age of onset of the patients was 33.8 years. Four (33.3%) patients had previous surgery and 8 (66.7%) had an anal disease. The most common stricture site was the ileum [58.3%, n = 7]. In addition, 2 (16.7%) patients had stricturing duodenum, and anal and anastomotic stoma, respectively. Only 1 (8,3%) patient had colon stricture and ileocaecal, respectively. Eight (66.7%) patients received enteral nutrition; 5 (41.7%) patients received steroids, immunomodulators (IMM), and infliximab (IFX); 1 (7.7%) patient accepted adalimumab (ADA) or vedolizumab (VDZ); 10 (83.3%) patients achieved success at week 24.

Table 1
Characteristics of the 12 CD patients with bowel strictures

Patients Number	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12
Sex	M	F	F	M	M	M	F	M	M	M	M	M
Age of CD onset(Y)	39	38	53	28	22	25	50	38	24	30	28	31
Age of stenosis diagnosis (Y)	42	50	73	37	23	25	54	39	32	35	28	31
Surgery before diagnosis	No	Yes	Yes	No	No	No	No	No	Yes	No	Yes	No
Perianal disease at diagnosis	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Site of stenosis	Ileocaecal	Ileum, Anus	Ileum	Ileum, colon	Duodenum	Anus	Ileum	Ileum	Anastomotic stoma	Ileum	Anastomotic stoma	Duoc Ileum
Smoking	Yes	No	No	No	No	Yes	No	No	No	No	No	No
Latent tuberculosis	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes
Previous treatment	Steroids, EEN, ASA	IFX, IMM, ASA	VDZ, EEN, ASA	EEN, IMM, ASA	Steroids, EEN, ASA	EEN	Steroids, IFX, EEN, IMM,	IFX, EEN	Steroids, IFX, EEN, IMM, ASA	None	ADA, IMM	Sterc IFX
Success at week 24	Yes	Yes	Yes	Yes	Endoscopy dilation	Anal reconstruction	Yes	Yes	Yes	Yes	Yes	Yes
Adverse event	No	No	No	No	No	No	No	No	No	No	No	No

CD, Crohn's Disease; EEN, Exclusive Enteral Nutrition; ASA, Aminosalicylic Acid; IMM, Immunomodulators; IFX, Infliximab; VDZ, Vedolizumab; ADA, Adalimuma
CDOS, Crohn's Disease Obstructive Score; CDAI, Crohn's Disease Activity Index; FCP, Fecal Calprotectin; Hs-CRP, hyper-sensitive C reactive protein.

The CDAI improved in 11 (91.7%) patients, while the remaining patient (P7) maintained clinical remission (CDAI < 150) at week 24 (Fig. 1). Of 8 patients with SSCD, 6 ameliorated at week 24; 4 (33.3%) patients remained asymptomatic at week 24. Ten patients got a hs-CRP test at both baseline and week 24, where 3 (30.0%) of them who were with abnormal hs-CRP at baseline improved at week 24, while 5 (50.0%) continued normally. The remaining two had worse results at follow-up, i.e., 5.4 and 6.7 mg/L, respectively. Ten patients got a fecal-protein test at both baseline and week 24, where 8 (80.0%) of them improved at week 24, while others worsened. A total of 2 (16.7%) patients underwent surgery or DBE, including one patient who underwent anal reconstruction surgery and one patient who accepted DBE of the duodenum.

None of the patients had severe adverse events secondary to UST during periods, including 3 patients with LTB. During an endoscopic evaluation at week 24, some patients showed improvement compared to baseline (Fig. 2).

Discussion

Stricturing CD is a challenging clinical condition, where patients are usually required to repeat endoscopic dilation or surgery as medical therapy can hardly reverse it. Unlike reverse fibrotic stricture, anti-TNFs can improve strictures with the dominant inflammatory component by reducing bowel wall edema, where initiating early treatment can improve the prognosis of disease[8–16]. A recent real-world study that included 59 patients with anti-TNFs therapy reported the cumulative probability of treatment success at 1, 2, and 5 years of 69%, 51%, and 28%, respectively. Also, adverse events were found in 10 (16.9%) patients [11]. In addition, some previous case reports showed that UST could induce and maintain remission in CD patients as monotherapy or with VDZ or after EBD[22–24]. Our results revealed that 83.3% of patients achieved success at week 24. Among these, 8 patients were with SSCD, and the UST treatment in clinical practice in the short-time period was found to be effective in 6 of them, which is similar to ADA efficacy in the CREOLE study[8]. The other 4 patients, who were with asymptomatic strictures, were in the early stage of disease or with anastomotic stenosis and could only be diagnosed by imaging examination or endoscopy. UST shows no recurrence in 4 patients with surgery history. For refractory patients, other studies indicated that UST could be effective as a second-line therapeutic option for inducing and maintaining response[25]. In addition, our results revealed that also UST showed great efficacy for patients with structuring CD and those who previously received steroids or biologics like IFX, ADA, and VDZ, as all 7 of these patients achieved success at week 24. The FCP of 2 patients (P2 and P7) increased at week 24. As both of these patients were IFX resistant, further intensive UST therapy is required (infusion interval narrow to 4-6w). Two patients with UST failure had recurrent obstructive symptoms, and their stricture sites included the duodenum or anus; thus, they were not likely to be improved by the sole use of medicine. After several times of UST therapy and imaging or endoscopy evaluation, we found no improvement of stricture in these patients. Therefore, these patients decided to accept surgery or EBD, which rapidly alleviated their symptoms, thus proving surgery was more effective than medicine for fibrous stricture. The remaining 8 patients were without further additional therapy, which indicated that UST monotherapy could be considered as a treatment of choice in the stricturing CD.

The focus of treatment in CD is shifting from achieving the remission of clinical symptoms and inflammation to modifying the natural history of the disease by reducing irreversible intestinal damage. Therefore, an important evaluation point of the medical treatment is avoiding or delaying surgery in stricturing CD, which was also the primary endpoint of the CREOLE study[8]. In the present study, 2 patients (16.7%) accepted surgery or endoscopy dilatation during 24 weeks of follow-up. Besides, we found no severe adverse events in patients including patients with LTB, which UST seems prior than anti-TNFs. Nevertheless, it is difficult to ascertain the exact role of UST in stenosis due to the short period of our study and the absence of the control group. Nonetheless, our results suggest that UST could be a great choice in treating stricturing CD.

Our study has several limitations. First, this is an observational study with only 12 patients. A controlled clinical trial of UST versus any other treatment or control group is needed to further verify the reported results. Second, the period of this study was only 24 weeks, which is too short of analyzing the long-term effect of UST in stricturing CD.

Conclusion

UST is associated with good short-term efficacy and safety in CD patients with intestinal stricture, including patients with SSCD.

Declarations

Ethics approval and consent to participate

The study protocol conforms to the ethical principles of the 1975 Declaration of Helsinki (6th revision, 2008), and was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Zhejiang University (Approval Number: [2022]0047). Informed written consent was obtained from all patient for application of relevant information.

Consent for publication

Written informed consent for publication has been obtained from all patients.

Availability of data and material

All data generated during this study are included in this published article.

Competing interests

We declare that none of the authors has any conflicts of interest to this research.

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Not Applicable.

Authors' contributions

QQW collected data of patients and wrote the manuscript. YC revised the manuscript. Both authors read and approved the final manuscript.

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Figures

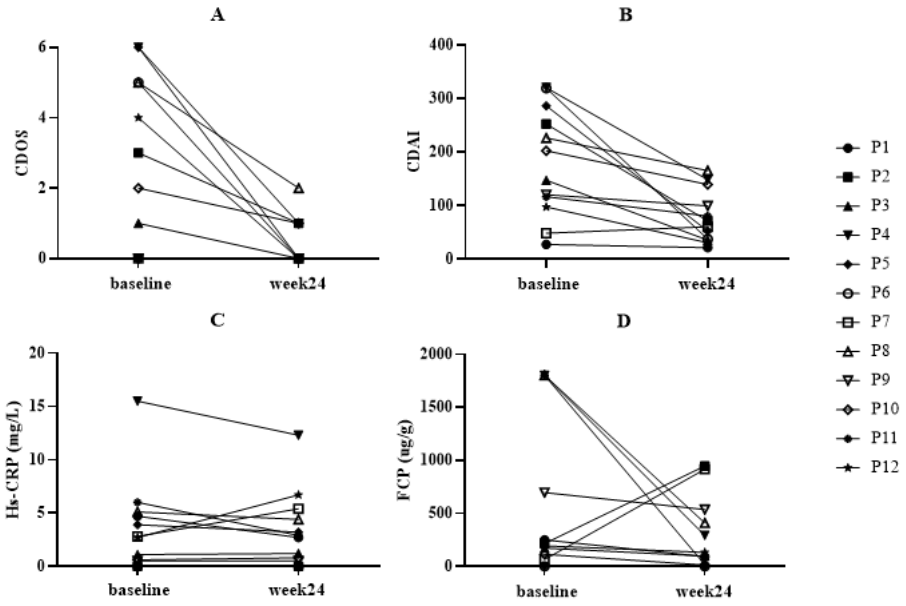

Figure 1. The secondary endpoints of clinical evaluation and laboratory data at weeks 24 compared to baseline.

Figure 1

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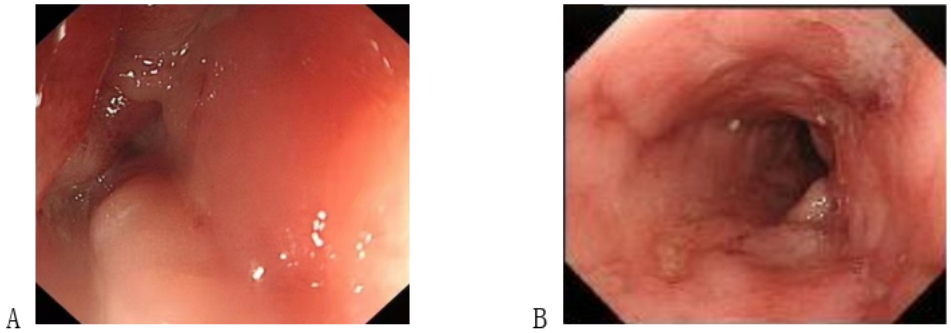

Figure 2

(A) The colon endoscopy found sigmoid colon stricture, mucosal edema with an ulcer, and its passage was disrupted at baseline. (B) The stricture of the sigmoid colon improved at week 24, during UST therapy, compared to baseline.