Efficacy of Ustekinumab on perianal fistulizing Crohn's disease: a retrospective single-center real-world analysis

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Research Article

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Abstract

Aim: Data of Ustekinumab (UST) in treating perianal fistulizing Crohn's disease (CD) are limited in China. We aimed to evaluate the efficacy of UST in the real-world setting.

Methods: We retrospectively analyzed patients with perianal fistulizing CD and receiving UST treatment from March 1, 2020 to October 30, 2021. Patients' characteristics, biomarker, and imaging were extracted from digital databases.

Results: Twenty patients were eligible (18 males; mean age of 29.4±2.6 years; mean disease duration of 6.3±0.9 years; 45.0% diagnosed as complex fistula; mean baseline Van Assche score of 7.7±1.1). Perianal Crohn's disease activity index (5.4±1.0 vs 8.7±1.0, P=0.027) and Crohn's anal fistula quality of life (29.4±4.8 vs 38.9±4.2, P=0.011) reduced significantly. Clinical remission appeared in 60.0% and clinical response in 85.0%; clinical fistula remission in 30.0%, clinical fistula response in 35.0%, and no response in 35.0% of patients. Eight patients received post-treatment MRI. Healing, partial response, no change, and deterioration appeared in 37.5%, 25.0%, 12.5% and 25.0% of the patients, respectively. The cut-off UST trough concentration predicting clinical fistula remission was 2.6 μg/ml (an area under the curve of 0.821, sensitivity 66.7%, specificity 85.7%).

Conclusions: UST is efficacious in promoting clinical and radiological fistula remission in patients with CD.

Introduction

Perianal fistula is the most common complication of Crohn's disease (CD), affecting approximately 40% of patients[1]. It represents an aggressive phenotype of CD, which may respond poorly to medications, have a high risk of relapse and disease-associated disability, and face earliy-onset surgery [2,3]. Patients with perianal fistulizing CD suffer from anal pain, purulent discharge, restricted sexual activity, accompany with abdominal symptoms, which undoubtedly lowers quality of life. Therefore, management and monitoring of perianal fistulizing CD remains a challenge.

Multidisciplinary approach is recommended in treating perianal fistulizing CD for its complexity. According to a global consensus established by Gecse in 2014[4], for patients with perianal abscesses and active draining fistula, seton or fistulotomy should be performed, followed by aggressive medical therapies. Infliximab and adalimumab, two monoclonal antibodies to tumor necrosis factor (TNF), are effective in treating perianal fistulizing CD, as shown by the results of ACCENT II[5] and CHARM[6] trials. However, it should not be ignored that a number of patients are primary non-responders to anti-TNF agents, and some have to switch to other biologics targeting different inflammatory pathways for the sake of loss of response or development of severe adverse effect.

Ustekinumab (UST), an antibody targeting interleukin (IL)12 and 23 shared p40 subunit, effectively induce disease remission supported by UNITI-1 and UNITI-2 clinical trials[7,8]. Recently, we have published

the first real-world study of UST in treating refractory CD in China, showing that clinical remission and endoscopic remission rates of 84.2% and 73.7% at week 16/20 after UST initiation[9]. However, there lacks strong evidence supporting the efficacy of UST in treating perianal fistulizing CD, despite a series of post hoc analyses or subgroup analyses.

We aimed to assess the short-term efficacy of UST in dealing with perianal fistulizing CD, and evaluate the UST trough concentration predicting clinical fistula remission. To our knowledge, this is the first real-word observational analysis in China to date.

Results

Patients' characteristics

Forty-one patients with CD and receiving scheduled UST treatment were enrolled. Fourteen patients were excluded for absence of active perianal fistula based on MRI scans, five patients for insufficient follow-up duration, and two for incomplete data (Figure 1). A total of twenty eligible patients were finally included, 90% of which were male, with a mean age of 29.4±2.6 years at diagnosis and a mean disease duration of 6.3±0.9 years. As for Montreal classification, 70% of the patients were assigned to B1 (non-stricturing, not-penetrating) and 85.0% to L3 (ileocolonic) phenotype. Most of the fistulas were inter-sphincteric (45.0%), followed by trans-sphincteric (25.0%), superficial (20.0%), and supra-sphincteric (10.0%). 45.0% of the fistulas were complex fistulas, with a mean baseline Van Assche scores of 7.7±1.1 determined by MRI scans. 20.0% of the patients suffered from perianal abscess, and 65.0% from proctitis. The baseline characteristics are listed in table 1.

Efficacy of UST on CD

After administration of UST, the patients showed less inflammatory burden manifested by a significant decrease in CRP (10.4±4.4 vs 20.2±6.1, P=0.011), and improved nutrition manifested by an increase in hemoglobin (138.1±2.9 vs 127.6±4.5, P=0.014) and Alb (42.2±1.2 vs 39.3±1.0, P=0.009) (Table 2). Clinical remission was observed in 60.0%, and clinical response in 85.0% of the patients (Supplement figure 1, panel A).

Efficacy of UST on perianal fistulas

A marked reduction in PDAI (5.4±1.0 vs 8.7±1.0, P=0.027) and CAF-QoL (29.4±4.8 vs 38.9±4.2, P=0.011) indicated the mitigation of fistulas (Table 2). Clinical remission was observed in 30.0%, clinical response in35.0%, and no response in 35.0% of the patients (Supplement Figure 1, panel B). Only 76% (8/21) of the patients underwent MRI scans at week 16/20 after the initiation of UST. Percentages of patients with fistula healing (Supplementary figure 2), partial response, no change, and deterioration were 37.5%, 25.0%, 12.5%, and 25.0%, respectively (Figure 2 panel A). After UST treatment, Van Assche score

decreased (7.0[2.3, 16.5] vs 4.0[0, 16.3], P=0.344), but without statistical significance, indicating the amelioration in radiological fistula response (Figure 2 panel B).

Relationship of CD clinical remission and clinical fistula response

Clinical fistula remission/response showed up in 83.3% (10/12) of the patients who had achieved clinical remission, but just 37.5% (3/8) of those who had not (Supplement Figure 1 panel C).

Exposure-response effect of UST on perianal fistulizing CD

The mean UST trough concentration at week 16/20 was 1.9 (1.1, 2.8) μg/ml. In a quartile analysis of UST trough concentration, we found the rates of clinical fistula remission and response increased with the trough level (Figure 3). The cut-off UST trough concentration predicting clinical fistula remission was 2.6 μg/ml, with an area under the curve (AUC) of 0.821, a sensitivity of 66.7%, and a specificity of 85.7% (Figure 4).

Discussion

In this study, 30.0% and 35.0% of patients achieved clinical fistula remission and response at week 16/20 after UST initiation, respectively; 37.5% (3/8) achieved deep radiological fistula healing according to post-treatment MRI. Our clinical and radiological results verified an acceptable short-term efficacy of UST on perianal fistulizing CD.

Infliximab was the first proved effective biologics in promoting and maintaining CD-related fistula closure, supported by high-quality randomized controlled trials (RCTs) with the primary endpoint as fistula closure[5,10]. According to a multicenter, double-blind RCT conducted by Daniel and his colleagues[5], 40% of patients had complete fistula response at week 54 after scheduled infliximab administration. Adalimumab is effective in treating fistulizing CD with lower grade evidence though[11]. A majority of studies, prospective or retrospective, reported 30–50% of patients achieved clinical fistula remission after long-term anti-TNF therapies[5,10,12]. Our results showed that a relatively lower percentage (23%) of patients presented fistula closure. Given that this study focused solely on the short-term efficacy of UST, favorable long-term outcomes might be expected.

UST is the second-line biologics recommended for perianal fistulizing CD. A post hoc analysis of UNITI-1/UNITI-2 reported that 24.7% of patients achieved fistula closure at week 8 and that 80% of patients achieved clinical fistula response at week 44 after UST treatment[13]. A small sample-size retrospective study in Spain revealed that 61% (11/18) of patients demonstrated improvement in perianal fistula at 10 months after scheduled UST. A BioLAP study[14], including 207 perianal CD patients, was a retrospective trial with the largest sample size reported to date. It showed that therapeutic success reached in 38.5% of

patients treated by UST. A prospective observational study in Netherlands reported 35.7% (10/28) of patients achieved clinical fistula remission at week 24 after UST initiation[15]. However, unlike anti-TNF agents, there still lacks RCTs with fistula closure as the primary endpoint to evaluate the efficacy of UST on perianal fistula.

UST was first approved for the treatment of CD in 2016 in America, but in 2020 in China. The efficacy of UST on CD has been rarely reported in China, and never on perianal fistulizing CD. To our knowledge, this is the first real-world study in China reporting the effectiveness of UST on perianal fistulizing CD. The clinical fistula remission rate was 30.0%, approximating those reported previously[16]. Further, MRI scans showed a deep radiological fistula healing rate of 15.6%, lower than the clinical fistula remission rate. It indicates that radiological fistula healing lags behind the clinical fistula closure, calling for a greater effort to realize the former.

Pelvis MRI is a pivotal tool for perianal fistula diagnosis, classification, severity evaluation, and disease monitoring. Radiological fistula healing continues after clinical fistula closure, for internal tracks may persist despite the closure of external opening, thus leading to a higher rate of relapse[17]. Patients who achieve radiological fistula remission may maintain fistula resolution, regardless of continuation or stop of anti-TNF therapy[18]. In this study, all the eligible patients enrolled had a precise diagnosis and classification of perianal fistula based on MRI scans. Besides, 38.1% (8/21) of patients underwent MRI scans in post-therapy follow-up. Radiological fistula healing rate was 37.5%, indicating an ideal efficacy of UST on complete fistula closure. Follow-up imaging can assist disease monitoring and therapeutic management.

Perianal fistulizing CD exerts profound effects on patient's psychosocial state and daily life[19]. Limited data have been obtained regarding the quality of life affected by perianal fistula to date. PDAI is widely used to measure CD-associated perianal disease activity. It is neither specific to perianal fistula and nor patient-centered [20]. CAF-QoL is the first disease-specific and patients-reported outcomes index in clinical practice, involving factors such as burden of symptoms and treatment, and negative impact on quality of life[21]. In this study, we combined PDAI and CAF-QoL to evaluate the impact of perianal fistula on CD patients. Favorable changes in both PDAI and CAF-QoL were found after UST therapy.

It has been reported that IFX concentration of 12μg/ml was associated with fistula remission. Optimizing biologics correlates to a higher response rate in perianal fistulizing CD patients[22]. Nevertheless, no studies have proposed the cut-off UST trough level associated with fistula healing yet. Sands et al. drew a conclusion that perianal fistula resolution was not associated with a higher UST serum concentration[23]. In contrast, one observational study noted that 50% of patients with UST escalation into q4w or q6w administration intervals achieved clinical response in perianal disease[24]. In this study, we did manifest exposure-effect relationship between clinical fistula remission and UST trough level. The cut-off value of UST we reported was 2.6μg/ml, much higher than 1.12 μg/ml, a cut-off value of UST associated with

clinical remission (defined as CDAI < 150) we reported previously[9]. Undoubtedly, more high-quality studies are needed to further testify the relationship of UST escalation and fistula outcomes.

There are limitations in this study. First, the evidence from this retrospective study should be further validated. Moreover, it was a single-center study with a relatively small sample size and a short-term follow-up; the long-term efficacy of UST on perianal fistula was missing. The strengths of this study include strict definitions, radiological evaluation combined with clinical assessment, and emphasis on quality of life. Not covered by the insurance system, the cost of UST is high in China, and a small number of Chinese patients can afford UST. Most of Chinese patients come to our center to seek UST treatment, enabling us to release these data in a real-world setting for the first time.

Conclusion

In conclusion, UST is efficacious in promoting clinical and radiological fistula remission in patients with CD. A trough concentration of UST higher than 2.6μg/ml is associated with clinical fistula remission at week 16/20. More RCTs with fistula closure as the primary outcome should be conducted to evaluate the efficacy of UST in treating perianal fistula.

Methods

Study design

This was a single-center retrospective cohort study based on the data of CD patients from March, 1, 2020 to October, 30, 2021 in the Sixth Affiliated Hospital of Sun Yat-Sen University (Guangzhou, China). This study has been approved by the Ethics Committee of Sun Yat-Sen University (2021ZSLYEC-066) and the Clinical Trial Registry (NCT04923100). Dataset used in the study are publicly available. Consent from the patients was waived for all the data we used was anonymous. All methods were performed in accordance with the Declaration of Helsinki.

Patients

Consecutive patients meeting the following inclusion criteria were included: First, patients were comprehensively diagnosed as CD according to internationally accepted criteria[25,26] with supportive clinical, endoscopic, radiological, and histopathological findings. Second, perianal fistula was confirmed by baseline magnetic resonance imaging (MRI). Third, patients were treated with UST and followed up till the third infusion at week 16 or 20, with a drug interval of q8w or q12w, respectively. Patients with incomplete data, a follow-up period less than 16 weeks, inactive perianal fistula at baseline were excluded.

All the patients were first infused with intravenous UST (260mg for those weighing <55kg, 520mg for those weighing >85kg, and 390mg for those weighing between 55kg and 85kg), and subcutaneous UST

(90mg every 8 or 12 weeks) afterward[27]. Perianal surgeries were performed if needed before the initiation of UST infusion. Concomitant antibiotics were allowed. UST trough concentration and antidrug antibodies were detected before the third infusion of UST. Data about patient characteristics, serologic biomarkers (including C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], platelet, hemoglobin, and albumin [Alb], and imaging were extracted from hospital digital records.

Definition

CD was classified using the widely-accepted Montreal classification system[28]. Crohn's disease activity index (CDAI)[29], perianal Crohn's disease activity index (PDAI)[30], and Crohn's anal fistula quality of life (CAF-QoL)[21] were evaluated at baseline and at week 16/20. A CDAI below 150 was defined as clinical remission while a reduction >70 in CDAI or/and a CDAI below 150 was defined as clinical response[29]. Clinical fistula remission was defined as absence of any draining fistula, while clinical fistula response as more than 50% decrease in the number of draining fistulas according to fistula drainage assessment index (FDA)[31].

MRI was performed to evaluate the status of fistula. The number of fistulas, anatomical classification, hyperintensity on fat saturated T2 sequence, and track thickness and volume were recorded. Simple fistula was defined as superficial/inter-sphincteric/trans-sphincteric fistula with only one track, but neither extension nor abscess. Complex fistula was defined as inter-sphincteric/trans-sphincteric fistula with more than one track, or supra-sphincteric/extra-sphincteric/rectovaginal fistula[11,32]. Four MRI-based radiological outcomes were described, including healing, improvement, no change, and deterioration. Radiological fistula healing was defined as absence of high-signal track on fat saturated T2 sequences. Improvement was defined as reduction in the number and volume of fistula, and more than 10% decrease in MRI signal. No change was defined as the same in the number of fistula and volume of inflammation. Deterioration was defined as increase in the size and number of fistula tracks[33]. Van Assche scores[34] ranging from 0 to 22 reflected fistula activity, involving fistula number, location, extension, hyperintensity on T2, collections and rectal wall involvement. Two specialists from Colorectal Department (HZ and BH) made diagnoses of active perianal fistulizing CD and assessed improvement of perianal fistula based on gentle compression, examination under anesthesia, and MRI scans. Two experienced radiologists (WTC and WRL) read the MRI scans, evaluated the radiological outcomes, and recorded Van Assche scores. MRI scans were recommended at week 16/20.

Statistical analysis

Continuous data were presented as mean ± S.D.E or median with interquartile range (IQR), while categorical data as percentages. Student's t-test or Wilcoxon test were performed to compare indicators prior and after UST treatment. Receiver operating characteristic (ROC) curve was established to figure out the cut-off value of UST trough concentration predicting clinical fistula remission with area under the

curve (AUC), sensitivity, and specificity calculated. All the analyses were conducted using SPSS 22.0 software. Two-sided P value <0.05 was considered as statistical significance.

Declarations

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflict of interest disclosure

The authors declare no competing interests.

Ethics approval statement and clinical trial registration

This study was approved by the Ethics Committee of Sun Yat-Sen University (2021ZSLYEC-066) and was approved by the Clinical Trial Registry (NCT04923100).

Patient consent statement

Due to the retrospective study design, which used anonymous data, written informed consent from the patients was waived.

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Tables

Table 1

Characteristics of overall patients.

Variables	Total patients
Male, n (%)	18(90)
Age at diagnosis, [years, mean±S.D.E]	29.4±2.6
Disease duration, [years, mean±S.D.E]	6.3±0.9
Montreal classification	
Age, n (%)	
A1(≤16 years)	1(5.0)
A2(17-40 years)	16(80.0)
A3(>40 years)	3(15.0)
Disease behavior, n (%)	
B1(non-stricturing, non-penetrating)	14(70.0)
B2(stricturing)	4(20.0)
B3(penetrating)	2(10.0)
Disease location, n (%)	
L1(ileal)	2(10.0)
L2(colonic)	1(5.0)
L3(ileocolonic)	17(85.0)
L4(upper GI)	0(0.0)
Fistula type, n (%)	
Simple	11(55.0)
Complex	9(45.0)
Fistula location, n (%)	
Superficial	4(20.0)
Inter-sphincteric	9(45.0)
Trans-sphincteric	5(25.0)
Supra-sphincteric	2(10.0)
Extra-sphincteric	0(0)
Van Assche at baseline, median (IQR)	7.7±1.1
Proctitis, n (%)	13(65.0)

Perianal abscess, n (%)	4(20.0)
Previous medication, n (%)	
Steroids	11(55.0)
Immunosuppressants[1]	17(85.0)
Anti-TNF agents[2]	17(85.0)
Previous intestinal surgery, n (%)	7(35.0)
Extraintestinal manifestation, n (%)	4(20.0)

1 Immunosuppressants includes thiopurines, methotrexate, cyclophosphane, and thalidomide.

2 Anti-TNF agents refers to infliximab or/and adalimumab.

Table 2

Clinical evaluation of UST on perianal fistulizing CD patients. （n=20, mean±S.D.E）

Variables	Baseline	Wee 16/20	P value
Inflammatory burden			
CRP (mg/L)	20.2±6.1	10.4±4.4	0.011
ESR (mm/h)	22.0±4.8	19.8±4.8	0.651
Platelet (×10^9/L)	297.3±22.6	293.4±21.0	0.872
Nutritional state			
Hemoglobin (g/L)	127.6±4.5	138.1±2.9	0.014
Alb (g/L)	39.3±1.0	42.2±1.2	0.009
BMI	19.5±0.6	18.8±1.2	0.447
CD Clinical response			
CDAI	236.3±18.2	120.0±9.4	0.011
Fistula clinical response			
PDAI	8.7±1.0	5.4±1.0	0.027
CAF-QoL	38.9±4.2	29.4±4.8	0.011

CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; Alb: albumin; BMI: body mass index; CDAI: Crohn's disease activity index; PDAI: perianal Crohn's disease activity index; CAF-QoL: Crohn's anal fistula

quality of life;

Figures

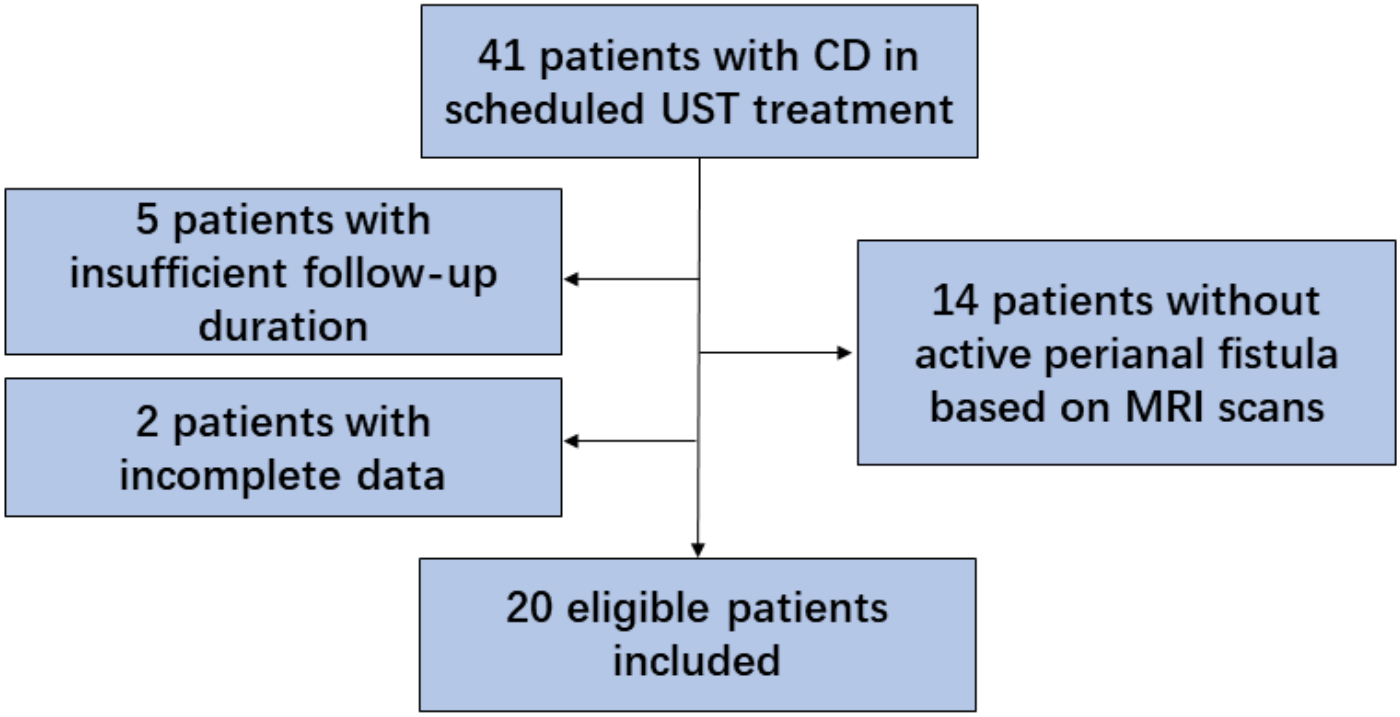

Figure 1

Flow chart of this study.

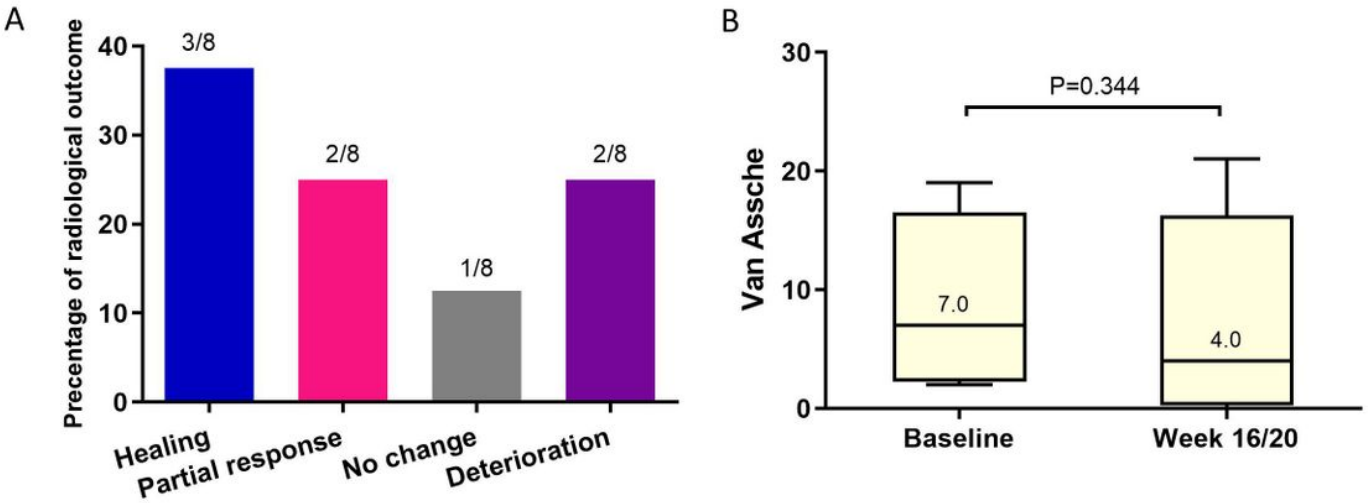

Figure 2

Radiological evaluation of perianal fistulas. (Panel A: Radiological outcomes of perianal fistulas at week 16/20; Panel B: Van Assche scores based on MRI at baseline and week 16/20. N=8)

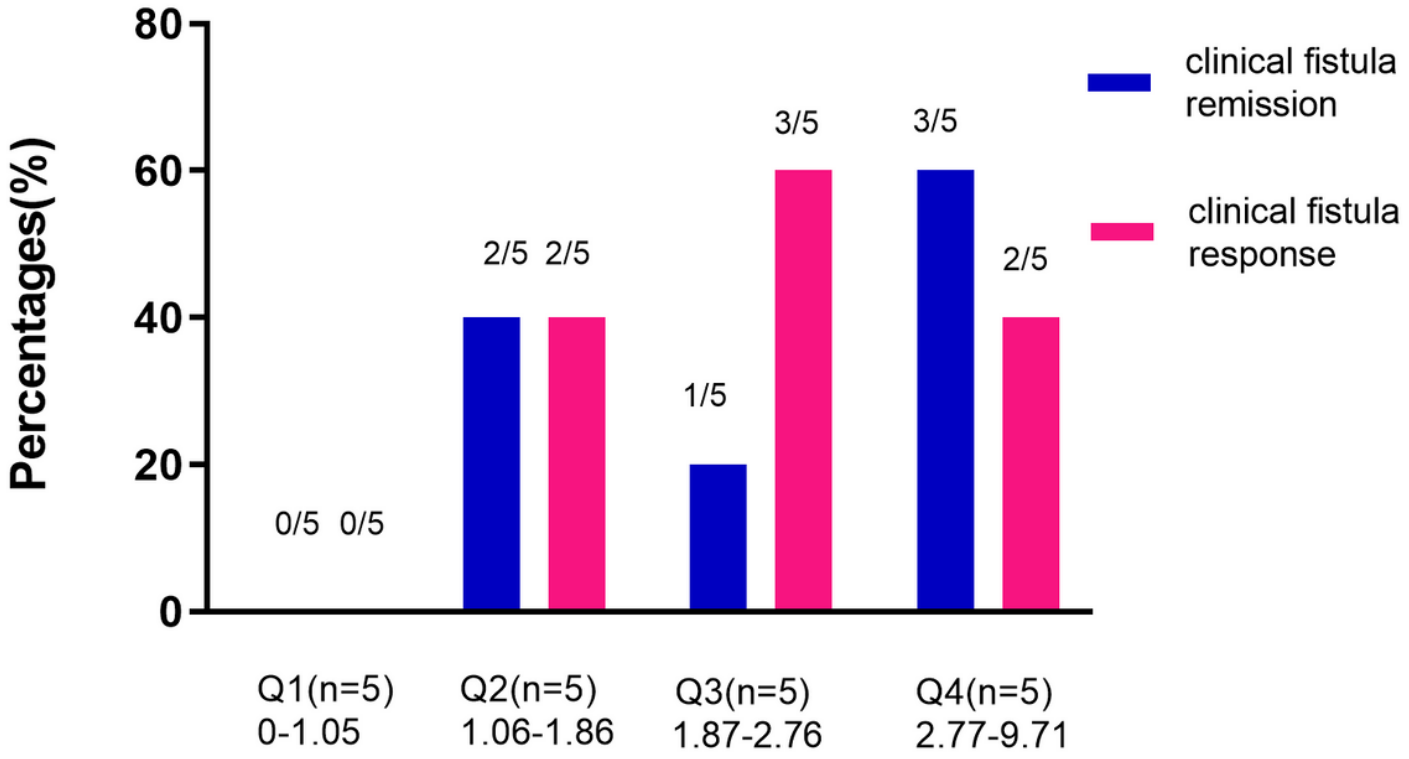

Figure 3

Exposure-response effect of UST on clinical fistula remission based on the quartile analysis of UST trough concentration.

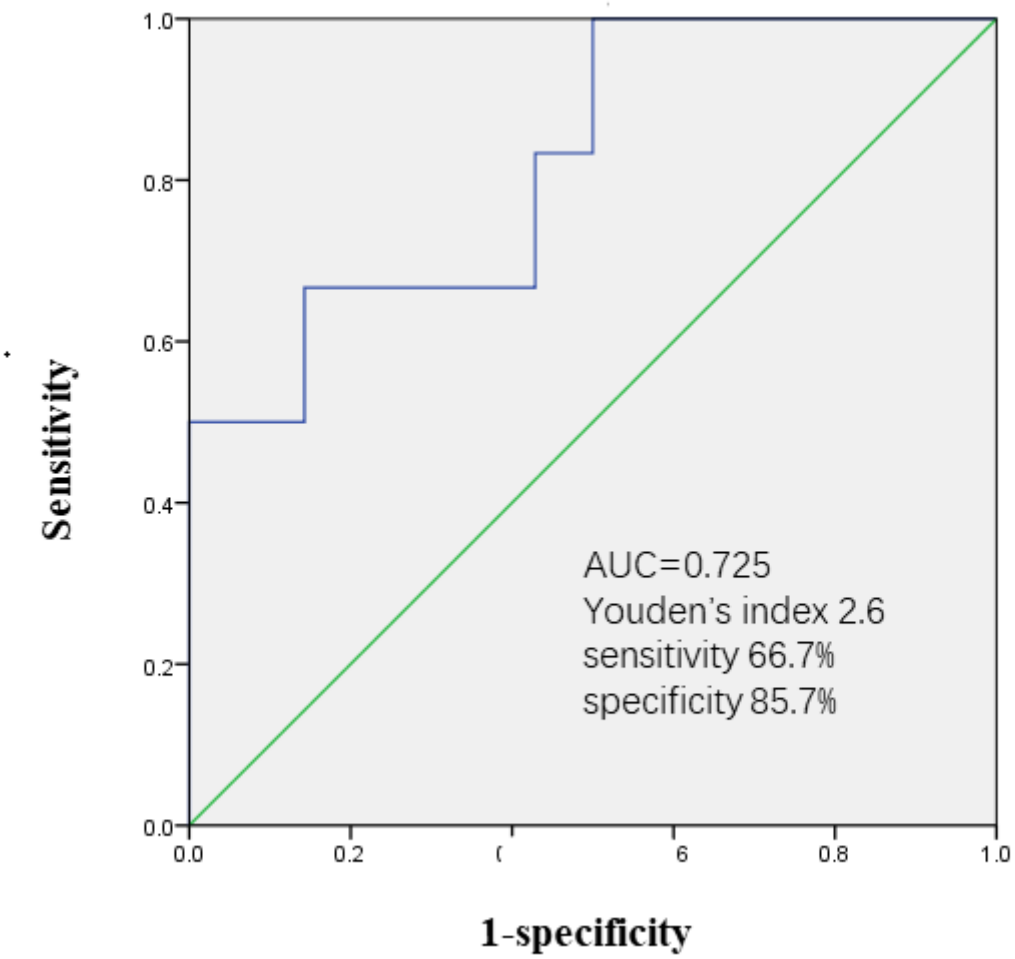

Figure 4

ROC curve of UST trough concentration at week 16/20 predicting clinical fistula remission. (The cut-off UST trough concentration was 2.6 μg/ml, with an AUC of 0.725 [95%CI: 0.618-1.0], a sensitivity of 66.7%, and a specificity of 85.7%)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfigures.docx