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Discordance between Deep Remissions Assessed by MRI and Long-term Clinical Remission after Combined Therapy with Infliximab and Seton Placement for Perianal Fistulizing Crohn's Disease

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Abstract

Objective: To investigate the correlation between deep remissions assessed by Magnetic Resonance Imaging (MRI) and long-term clinical remission after combined therapy for Perianal Fistulizing Crohn's Disease (PFCD).

Methods: This was a retrospective study. Patients with PFCD undergoing combined therapy who performed pelvic MRI before surgery and at the final follow-up were included in this study. The correlation between deep remission and long-term clinical remission was investigated. A logistic regression model was used to evaluate individual items in the Van Assche scoring system as well as other factors that may affect deep remission.

Results: Total of 57 eligible patients (men 68.4%) with PFCD was included in this study. The median follow-up period was 34.5 (IQR 22-58) months. The long-term clinical remission rate and response rate were 57.9% (33/57) and 42.1% (24/57), respectively. Among the 33 patients with long-term clinical remission, 16 (48.5%) achieved deep remission, as assessed by MRI. Univariate and multivariate analysis showed that IFX maintenance treatment ≤ 3 times (OR=4.30, 95% CI: 1.16-15.94) and fistula with a secondary track (OR=4.38, 95% CI: 1.12-17.04) were risk factors for deep remission; fistula located below the levator ani muscle (OR=0.18, 95% CI: 0.04-0.82) was a protective factor for deep remission.

Conclusion: There is discordance between deep remission assessed by MRI and long-term clinical remission after combined therapy for PFCD. Only half of patients with long-term remission can achieve deep remission. IFX maintenance treatment >3 times and fistula without secondary tract and located below the levator ani muscle are predictive factors for deep remission.

Keywords: Crohn's disease; Anal fistula; Long-term clinical remission; Deep remission; Predictive factors

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Introduction

Crohn's Disease (CD) is a chronic inflammatory disease of unknown causes that can affect any part of the digestive tract from the mouth to the anus. During the progression of CD, 35% to 45% of patients develop Perianal lesions, of which anal fistula is most common [1,2]. Perianal Fistulizing CD (PFCD) severely affects the quality of life of patients, and its treatment remains a challenge for clinicians [3]. With the clinical application of biological agents, the anti-TNF-α drug Infliximab (IFX) has gradually become the first line of treatment for PFCD. A 3-year follow-up showed that only 33% of patients treated with IFX alone can maintain clinical remission [4]. Yassin et al. [5] reported that combined therapy (anti-TNF-α/immunomodulatory and surgical treatment) is more effective than single therapy (anti-TNF-α, immunomodulatory, or surgical treatment) for achieving higher remission (52% *vs.* 43%). Combining IFX with Seton placement, without damage to anal sphincter function, can maintain adequate drainage of the fistula, prevent premature closure of the external orifice, and improve the clinical remission rate. This combination is currently the most widely used treatment strategy. Our previous study showed that IFX combined with Seton

placement significantly shortened the healing time of the fistula and improved the clinical remission rate and that 89.3% (25/28) of patients maintained clinical remission for 30 weeks after treatment [6]. Brochard et al. [7] retrospectively studied 70 patients with PFCD who were treated with IFX combined with Seton placement and found that approximately two-thirds of patients achieved clinical remission in the 4-year follow-up.

Clinical evaluation of PFCD is not accurate based on the discharge of the fistula [8]. Imaging studies may still show persistent fistula in patients with clinical remission after combined therapy. Ng [9] and Bell [10] confirmed that the disappearance of fistula discharge does not necessarily indicate the remission of anal fistula. Studies have shown that only 18% of fistulas are in an inactive stage on ultrasound examination in patients with clinically healed PFCD [11]. The presence of an active anal fistula on imaging examination may explain the high recurrence rate of PFCD after clinical remission. Magnetic Resonance Imaging (MRI) is recommended as the preferred imaging examination for the evaluation of PFCD by European Crohn's and Colitis Organization guidelines because of the high sensitivity and specificity of MRI in the Perianal tissue. Excluding patients who need immediate drainage at the beginning of diagnosis, MRI should be performed in patients with Perianal lesions [12]. The MRI-based Van Assche score further describes the anatomy (extension) and complexity (active inflammation or abscess) of fistula [4,13]. MRI monitoring confirmed a significant delay (12 months) between clinical remission (no discharge from the fistula) after anti-TNF-α treatment and deep remission of the anal fistula (T2-weighted image [T2WI] showing that the high-signal fistula was replaced by a low-signal fibrotic tissue) [4].

Although the literature has confirmed that 12 months are needed from clinical remission to deep remission, few studies are available concerning whether deep remission can be achieved in patients with PFCD after long-term clinical remission. The purpose of this study was to investigate the correlation between deep remission assessed by MRI and long-term clinical remission after combined therapy with IFX and Seton placement for PFCD and to identify predictive factors for deep remission.

Material and Methods

Patient inclusion

The study was reviewed and approved by the Ethics Committee of the Affiliated Hospital of Nanjing University of Chinese Medicine (2017NL-049-02). This was a retrospective analysis of data for patients with CD who were diagnosed and treated in the Department of Colorectal Surgery and registered in the hospital information system (HIS) of the Affiliated Hospital of Nanjing University of Chinese Medicine from August 2010 to October 2017. The inclusion criteria included the following: patients undergoing combined therapy with IFX and Seton placement, more than 1-year follow-up, and pelvic MRI before surgery and at the final follow-up were performed. Patients with non-Fistulizing CD, inadequate imaging or hospitalization data, and those who did not receive IFX treatment or surgery were excluded. Clinical data, including patient gender, age at the time of diagnosis, Body Mass Index (BMI), medical history, endoscopy, Montreal classification before treatment, and IFX treatment time, were collected. All patients underwent pelvic MRI at the last follow-up at the outpatient or inpatient service.

The clinical data were evaluated by a senior colorectal surgeon

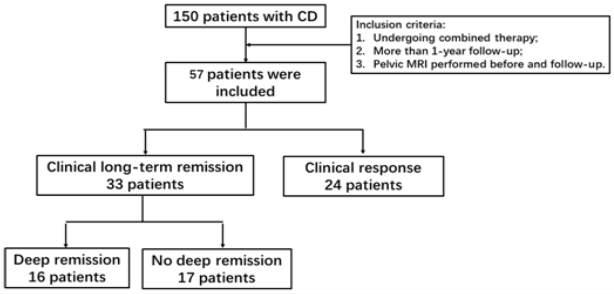

Figure 1: Research flowchart.

specializing in Inflammatory Bowel Disease (IBD), and all clinical examinations of the same patient were performed by the same doctor. Long-term clinical remission criteria were as follows: after more than 1-year follow-up, no discharge or pain in the fistula was present; external orifice was closed; internal orifice was not obvious; no abscess was present; and no further drainage with Seton placement was needed [7]. The clinical response refers to a >50% reduction in discharge or the number of external fistula orifices by clinical assessment [14]. Deep remission is defined as follows: at the last follow-up, high-intense signals of fistulas in T2WI have disappeared and are replaced with low-intense signals of fibrotic tissue. The research flowchart is shown in (Figure 1).

MRI data

An 8-channel phased-array coil examination (GE Ptima60 1.5 T superconducting coil) was performed. The patient did not require bowel preparation and was placed in a supine position. The center of the coil was placed in the pubic symphysis. Axial scanning was perpendicular to the anal canal. Coronal and sagittal scanning was parallel to the anorectal middle line. The patients were asked to breathe regularly and remain still for the MRI using the T1WI or T2WI sequence and fat-suppression sequence on axial, sagittal, and coronal planes (Table 1).

All patients underwent pelvic MRI prior to the combined therapy for preoperative assessment of anal fistula, and pelvic MRI was repeated at the end of the follow-up. The MRI images were read by two senior physicians in the Department of Gastrointestinal Radiology who were blinded to the patient's clinical information. The MRI data were collected according to Park's classification [15] and the Van Assche scoring system [13].

Clinical treatment

After successful epidural anesthesia, the patient was placed in the Jackson-knife prone position. According to the results of preoperative MRI and intraoperative exploration, Seton placement was performed with preservation of the sphincter. The internal orifice was fully treated during the operation, and a rubber band was used between the primary tract and the internal orifice for drainage. The granulation tissue in the secondary tract was removed by scraping to achieve complete drainage. The silicone tube was used for drainage after scraping if the fistula was located above the levator ani muscle. The wound was washed with metronidazole solution, and changed the dressing daily. The drainage tube above the levator ani muscle was removed after 2 weeks. The well-growing granulation tissue of the wound bed, no discharge observed during compression of the wound, the sensation of resistance upon flushing of the sinus tract or pulling the rubber band were indicators for gradually removing the

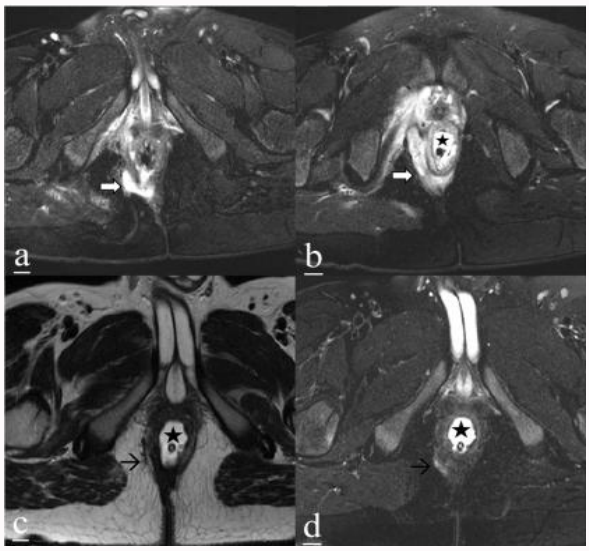

Figure 2: A 14-year-old male with perianal fistulizing CD. A, b: Preoperative MRI revealing a posterior transphincteric fistula (horse-shaped, white arrow); c, d, MRI at follow-up shows that the high-signal fistula replaced by fibrous scar tissue; T2WI shows hypo-intense signals and T2WI-FS shows slightly high-intense signals (black arrow). ★-A water sac placed in the rectal cavity.

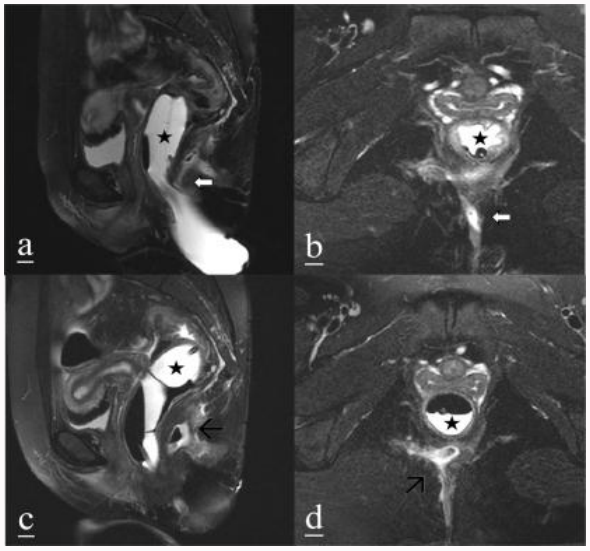

Figure 3: A 32-year-old woman with perennial fistulizing CD achieved clinical remission at the 48-month follow-up. A, b: Preoperative MRI showing a Suprasphincteric fistula in the deep postanal space (white arrows); c, d: Follow-up MRI showing the internal orifice of the anal fistula closed by fibrous tissue; the fistula in the deep space behind the anal canal is replaced by a fibrous scar; a closed sinus tract is seen in the intersphincteric space (black arrow). ★-A water sac placed in the rectal cavity.

rubber band.

According to promotion policy of drug purchase in the Xi'an Johnson-Johnson company in China (buy 4 doses of IFX and get 2 free doses), all patients were treated with IFX induction therapy (5 mg/kg, 0, 2, and 6 weeks) and at least 3 IFX maintenance therapies (5 mg/kg, once every 8 weeks), followed by an individualized maintenance regimen. Thirty-three patients underwent long-term IFX maintenance therapy with a median time of 12 (Interquartile Range (IQR), 8-16) months. Of these patients, 13 received IFX monotherapy, 14 received IFX combined with Azathioprine (AZA) (2 mg/kg/d), 6 received IFX combined with thalidomide (100 mg/d), 11 were treated with AZA alone (2 mg/kg/d), 1 was treated with thalidomide alone (100 mg/d), and 12 patients did not receive drug maintenance.

Statistical analysis

Quantitative variables are expressed as the median and percentile (IQR: 25% and 75%), and categorical variables are expressed as the number of queue objects and percentage. Continuous values were tested by the Kruskal-Wallis test. A logistic regression model was used to assess predictive factors for deep remission. A p value <0.05 was considered statistically significant.

Ethical considerations

The study was reviewed and approved by the Ethics Committee of the Affiliated Hospital of Nanjing University of Chinese Medicine (2017NL-049-02). Patients were informed that their blinded data were being collected for scientific or teaching purposes (University Hospital) and provided consent for this use.

Results

Baseline data

A total of 57 eligible patients (39 males) with PFCD were enrolled in this study. The patients were between 14 years and 58 years of age (mean age: 24 years) with a median CD duration of 9 (IQR, 1-41) months. The median follow-up period was 34.5 (IQR, 22-58) months. Three (5.3%) patients had a history of abdominal surgery, and 30

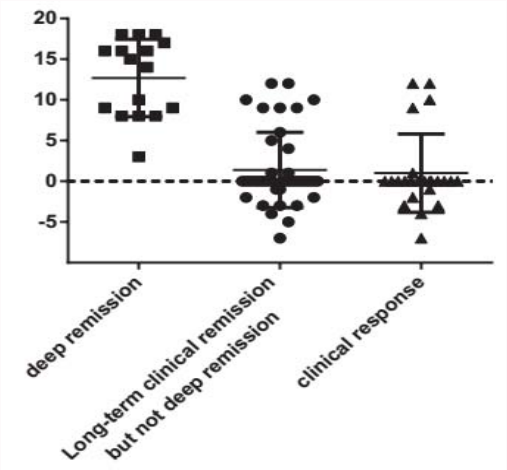

Figure 4: Van Assche scoring before treatment and during follow-up. The Van Assche score was significantly before and after surgery in patients with deep remission (15.5 ± 4.0 *vs.* 0 ± 2.2) than patients with long-term clinical remission without deep remission (16 ± 4.5 *vs.* 11 ± 5.2) and patients with clinical response (19 ± 3.9 *vs.* 19 ± 5.2), p=0.046.

(52.6%) patients had a history of perianal surgery. Colonoscopy showed that 40 (70.2%) patients had intestinal lesions located in the ileum and colon, 7 (12.3%) in the colon, and 10 (17.5%) in the ileum. Twenty-four (42.1%) patients had active proctitis. Eighteen (31.6%) patients had stricturing disease; 1 (1.7%) patient accompanied with intestinal fistula. Preoperative MRI showed intersphincteric fistula in 7 (12.1%), transphincteric fistula in 27 (46.6%), suprasphincteric fistula in 16 (27.6%), and extrasphincteric fistula in 8 (13.8%) patients. Multiple fistulae were identified in 11 (19.3%), fistula with secondary tracts in 28 (49.1%), and perianal abscesses in 38 (66.7%) patients. Fistula located below the levator ani muscle in 34 (59.6%) patients and 19 (33.3%) patients had active proctitis. There was no difference in active proctitis in baseline between endoscopic findings and MRI

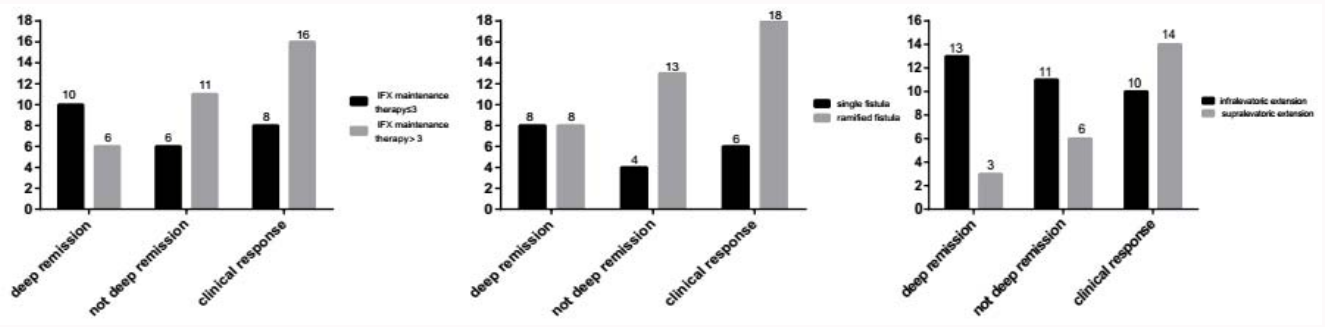

Figure 5: IFX maintenance treatment ≤ 3 times (P=0.029) and fistula with a secondary tract (P=0.033) are risk factors for deep remission of fistula. Fistula located under the levator anti muscle (P=0.026) is a protective factor for deep remission.

(X2 test, P=NS).

Deep remission assessed by MRI and long-term clinical remission

Of the 57 patients with CD, 33 (57.9%) achieved long-term clinical remission, and 24 (42.1%) had a clinical response. Among patients with long-term clinical remission, postoperative T2WI in the follow-up MRI showed the disappearance of the high-signal fistula image and replacement by a fibrotic tissue image, i.e., an indication of deep remission, in 48.5% (16/33) of patients (Figure 2). The other 17 patients had no clinical symptoms but high-intense signals of fistula in the T2WI. Deep remission assessed by MRI is clearly inconsistent with long-term clinical remission (Figure 3).

The Van Assche score was significantly lower in 16 patients with deep remission (15.5 ± 4.0 *vs.* 0 ± 2.2). Seventeen patients with long-term clinical remission but not achieving deep remission had a reduced score before and after surgery (16 ± 4.5 *vs.* 11 ± 5.2). The patients with a clinical response had no significant change in scores (19 ± 3.9 *vs.* 19 ± 5.2). According to the Kruskal-Wallis test, the P value was 0.046, and the differences among the three groups were statistically significant (Figure 4).

Predictive factors for deep remission

Univariate analysis showed that deep remission was significantly associated with fistula located below the levator ani muscle (18.8% *vs.* 35.1%, P=0.047). Multivariate analysis showed that fistula located below the levator ani muscle (81.3% *vs.* 51.2%, odds ratio (OR)=0.18, 95% Confidence Interval (CI): 0.04-0.82) was as a protective factor for deep remission; IFX maintenance treatment ≤ 3 times (62.5% *vs.* 34.1%, OR=4.30, 95% CI: 1.16-15.94) and fistula with a secondary tract (50% *vs.* 75.6%, OR=4.38, 95% CI: 1.12-17.04) were adverse outcome for deep remission of the fistula. Although the studies reported that active proctitis is a major factor responsible for the failure of PFCD surgery, this study showed that the difference in rectal involvement was not statistically significant in both Univariate analysis (18.8% *vs.* 39.0%, P=0.934) and multivariate analysis (P=0.285, OR=0.41, 95% CI: 0.08-2.11). This result suggests that active proctitis is not necessarily a risk factor for recurrence of PFCD in patients undergoing biotherapy (Figure 5).

Discussion

At present, the main methods for clinical evaluation of PFCD treatment include perianal disease activity index (PDAI) and anal fistula discharge assessment. The main drawback of these two clinical evaluation methods is that the drug treatment (especially biological agents) can reduce discharge and facilitate closure of the external orifice of the anal fistula, but active fistulas may still persist in the proximal or deep tissue [4,16]. Pelvic MRI can accurately assess the morphological characteristics of anal fistulas and reveal perianal abscesses, and thus, it is considered the gold standard for evaluating anal fistulas. The use of MRI can more accurately assess deep remission of anal fistulas.

This study included 57 patients undergoing combined therapy with IFX and Seton placement, more than 1-year follow-up, and pelvic MRI before surgery and at the final follow-up. The median follow-up period was 34.5 months. Of the patients, 57.9% (33/57) achieved long-term clinical remission, and 48.5% (16/33) achieved deep remission. Ng et al. [9] reported 26 patients with PFCD who were treated with IFX (n=19) or adalimumab (n=7). Of these patients, 46% achieved clinical remission after treatment, but only 30% patient reached deep remission after an 18-month follow-up. A prospective study showed that in 49 patients with PFCD who were treated with anti-TNF-α maintenance therapy, 53.1% (26/49) achieved long-term clinical remission after a 40-month follow-up, but only 32.7% (16/49) achieved deep remission [14]. The current study showed that more than half of patients treated with IFX and seton placement could maintain long-term clinical remission and confirmed the disconnect between deep remission assessed by MRI and long-term clinical remission; only half of patients with long-term remission could achieve deep remission.

The Van Assche score is the most commonly used index for MRI assessment of PFCD. It is a quantitative standardization tool for assessing the clinical outcome of PFCD and, thereby, can avoid the subjective intention of clinicians and patients in determining improvement or deterioration of perianal lesions [16]. A study reported that the Van Assche score was significantly lower in follow-ups of short-term (median, IQR, 11.0 [10.0, 12.5] weeks) and mid-term (median, IQR, 44.0 [28.7, 46.3] weeks), while there was no significant change in long-term follow-ups (median, IQR, 94.5 [75.3, 139.3] weeks). The authors suggest that MRI is a reliable technique to assess PFCD in the first year of IFX treatment, but it is not superior to clinical evaluation in long-term monitoring beyond this period [17]. Multiple studies have shown that changes in the Van Assche score are consistent with clinical outcomes [17,18]. This study showed significant differences in Van Assche scores among patients with deep remission assessed by MRI, patients with long-term clinical remission but not deep remission, and patients with a clinical response. This result suggests good correlations between the Van Assche score and long-term clinical remission and deep MRI remission.

There are few studies on the correlation between individual items in the Van Assche scoring system and clinical outcomes. Determining the correlation of a single item in the Van Assche scoring system with deep remission of anal fistula is particularly important for initial intervention strategies in clinical practice. This study showed that fistula with a secondary tract (OR=4.38, 95% CI: 1.12-17.04) is a risk factor for deep remission; the fistula located below the levator ani muscle (OR=0.18, 95% CI: 0.04-0.82) is a protective factor for deep remission. These findings confirm that fistulas without secondary tract and located below the levator ani muscles are more likely to achieve deep remission. A study by Thomassin et al. [14] suggested that no proctitis is the only predictive factor for deep remission of fistulizing CD. The presence of proctitis is highly correlated with anal fistula treatment and prognosis [19]. The study by Panés et al. [16] has shown that rectal involvement is associated with a high rectal resection rate compared with no rectal involvement (4.0% to 13.6% *vs.* 29.0% to 77.6%); active proctitis is an independent predictive factor for a reduced fistula remission rate and increased recurrence rate. In contrast to the above findings, the current study showed that deep remission was not significantly associated with rectal involvement determined by endoscopy or Van Assche scores. This result suggests that in the era of biotherapy, active proctitis is not necessarily a risk factor for the recurrence of PFCD after surgery. However, this conclusion must be verified in further multi-center, large-sample-sized studies.

The complex pathological structure of anal fistula is an important factor in the recurrence of PFCD after surgery. Complex anal fistula has a higher recurrence rate than simple anal fistula (41.9% *vs.* 26.7%) and is more likely to require permanent fecal diversion (63.8% *vs.* 26.7%) and rectal resection (25.5% *vs.* 6.7%) [1]. According to Park's classification for anal fistulas, the most common glandular anal fistulas are intersphincteric fistula (45%), followed by transphincteric fistula (30%), suprasphincteric fistula (20%), and extrasphincteric fistula (5%). Oliveira et al. [20] described 96 patients with perianal fistulizing CD, including 37 (38.5%) with transphincteric anal fistula and 35.4% with intersphincteric fistula. In this study, preoperative MRI showed transphincteric fistula in 27 (46.6%), suprasphincteric fistula in 16 (27.6%), extrasphincteric fistula in 8 (13.8%), and intersphincteric fistula in 7 (12.1%) patients. On the one hand, MRI assessment is not required in patients with some types of simple fistula before surgery; on the other hand, perianal fistulizing CD is more complicated than glandular anal fistula. However, the statistical results showed no difference between long-term clinical remission and deep remission while using combined therapy for different types of anal fistula.

The retrospective analysis by Jones et al. [21] in 73,004 inpatients in the United States from 1993 to 2004 showed that IFX did not reduce the surgical rate for PFCD but increased the amount of perianal abscess drainage by three times. Approximately 11% of patients develop perianal abscess during anti-TNF-α therapy [22]. Poritz [23] and Osterman et al. [24] have suggested that IFX can cause premature closure of the anal fistula, leading to incomplete drainage of the deep fistula and increasing the risk of infection. However, several studies have confirmed that long-term maintenance therapy with IFX and adalimumab can increase the long-term remission rate of fistula [25,26]. The Toronto Consensus on Clinical Guidelines for the Treatment of perianal fistulizing CD recommends that anal fistula patients who have achieved clinical remission using anti-TNF therapy should continue maintenance therapy [27]. The multivariate analysis of this study has shown that IFX maintenance treatment >3 times is a protective factor for maintaining deep remission of anal fistula, indicating that combined therapy and long-term IFX maintenance therapy can effectively prevent local infection and optimize efficacy.

This study has certain limitations. First, the study was based on a retrospective analysis of a single-center prospective database with a small sample size. Second, preoperative MRI assessments were only performed in patients with complicated anal fistula and perianal sepsis. Next, some patients with long-term clinical remission refused to undergo MRI at the end of follow-up. Therefore, some bias may exist in the final data.

In summary, this study has demonstrated the disconnect between deep remission assessed by MRI and long-term clinical remission in combined therapy with IFX and Seton placement for perianal fistulizing CD; only 1/2 of patients with long-term clinical remission can achieve deep remission. IFX maintenance treatment >3 times and fistula with a secondary tract and located below the levator ani muscle are predictive factors for deep remission.

Ethics Approval and Consent to Participate

This study were approved (Permission No: 2017NL-049-02) by the Ethics Committee of Jiangsu Province Hospital of TCM, Nanjing, China.

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References

1. Molendijk I, Nuij A, van der Meulen-de Jong AE, van der Woude CJ. Disappointing durable remission rates in complex Crohn's disease fistula. Inflamm bowel dis. 2014;20(11):2022-8.
2. Molendijk I, Peeters KC, Baeten CI, Veenendaal RA, van der Meulen-de Jong AE. Improving the outcome of fistulising Crohn's disease. Best pract res Clin gastroenterol. 2014;28(3):505-18.
3. Mahadev S, Young JM, Selby W, Solomon MJ. Quality of life in perianal Crohn's disease: what do patients consider important?. Dis Colon Rectum. 2011;54(5):579-85.
4. Tozer P, Ng SC, Siddiqui MR, Plamondon S, Burling D, Gupta A, et al. Long-term MRI-guided combined anti-TNF-α and thiopurine therapy for Crohn's perianal fistulas. Inflamm bowel dis. 2012;18(10):1825-34.
5. Yassin NA, Askari A, Warusavitarne J, Faiz OD, Athanasiou T, Phillips RK et al. Systematic review: the combined surgical and medical treatment of fistulising perianal Crohn's disease. Aliment pharmacol ther. 2014;40(7):741-9.
6. Yang BL, Chen YG, Gu YF, Chen HJ, Sun GD, Zhu P, et al. Long-term outcome of infliximab combined with surgery for perianal fistulizing Crohn's disease. World J Gastroenterol. 2015;21(8):2475-82.
7. Brochard C, Landemaine A, L'Heritier AM, Dewitte MP, Tchoundjeu B, Rohou T, et al. Anal Fistulas in Severe Perianal Crohn's Disease: Mri Assessment in the Determination of Long-Term Healing Rates. Inflamm bowel dis. 2018;24(7):1612-18.
8. Schwartz DA, Wang A, Ozbay B, Skup M, Eichner SF, Lin J, et al. Comparison of Health Care Utilization and Costs Between Patients with Perianal Fistulizing Crohn's Disease Treated with Biologics with or Without Previous Seton Placement. Inflamm bowel dis. 2017;23(10):1860-

66.

9. Ng SC, Plamondon S, Gupta A, Burling D, Swatton A, Vaizey CJ, et al. Prospective evaluation of anti-tumor necrosis factor therapy guided by magnetic resonance imaging for Crohn's perineal fistulas. Am j gastroenterol. 2009;104(12):2973-86.

10. Bell SJ, Halligan S, Windsor J, Williams AB, Wiesel P, Kamm MA. Response of fistulating Crohn's disease to infliximab treatment assessed by magnetic resonance imaging. Aliment pharmacol ther. 2003;17(3):387-93.

11. Aguilera-Castro L, Ferre-Aracil C, Garcia-Garcia-de-Paredes A, Rodriguez-de-Santiago E, Lopez-Sanroman A. Management of complex perianal Crohn's disease. Ann Gastroenterol. 2017;30(1):33-44.

12. Gomollón F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. J Crohns Colitis. 2017;11(1):3-25.

13. Van Assche G, Vanbeckevoort D, Bielen D, Coremans G, Aerden I, Noman M, et al. Magnetic resonance imaging of the effects of infliximab on perianal fistulizing Crohn's disease. Am j gastroenterol. 2003;98(2):332-9.

14. Thomassin L, Armengol-Debeir L, Charpentier C, Valerie Bridoux, Edith Koning, Guillaume Savoye, et al. Magnetic resonance imaging may predict deep remission in patients with perianal fistulizing Crohn's disease. World j gastroenterol. 2017;23(23):4285-92.

15. Parks AG, Gordon PH, Hardcastle JD. A classification of fistula-in-ano. Br J Surg. 1976;63(1):1-12.

16. Panés J, Rimola J. Perianal fistulizing Crohn's disease: pathogenesis, diagnosis and therapy. Nat Rev Gastroenterol Hepatol. 2017;14(11):652-64.

17. Karmiris K, Bielen D, Vanbeckevoort D, Vermeire S, Coremans G, Rutgeerts P, et al. Long-term monitoring of infliximab therapy for perianal fistulizing Crohn's disease by using magnetic resonance imaging. Clin Gastroenterol Hepatol. 2011;9(2):130-6.

18. Horsthuis K, Ziech W, Bipat S, Spijkerboer AM, de Bruine-Dobben AC, Hommes DW, et al. Evaluation of an MRI-based score of disease activity in perianal fistulizing Crohn's disease. Clin imaging. 2011;35(5):360-5.

19. Gecse KB, Bemelman W, Kamm MA, Stoker J, Khanna R, Ng SC, et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. Gut. 2014;63(9):1381-92.

20. Oliveira IS, Kilcoyne A, Price MC, Harisinghani M. MRI features of perianal fistulas: is there a difference between Crohn's and non-Crohn's patients?. Abdom Radiol. 2017;42(4):1162-68.

21. Jones DW, Finlayson G. Trends in surgery for Crohn's disease in the era of infliximab. Ann surg. 2010;252(2):307-12.

22. Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med. 1999;340(18):1398-405.

23. Poritz LS, Rowe WA, Koltun WA. Remicade does not abolish the need for surgery in fistulizing Crohn's disease. Dis colon rectum. 2002;45(6):771-75.

24. Osterman MT, Lichtenstein GR. Infliximab in fistulizing Crohn's disease. Gastroenterol Clin North Am. 2006;35(4):795-820.

25. Sands BE, Anderson FH, Bernstein CN, William Y Chey, Brian G Feagan, Richard N Fedorak, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Eng J Med. 2004.350:876-85.

26. Colombel JF, Schwartz DA, Sandborn WJ, Kamm MA, D'Haens G, Rutgeerts P, et al. Adalimumab for the treatment of fistulas in patients with Crohn's disease. Gut. 2009;58(7):940-8.

27. Steinhart AH, Panaccione R, Targownik L, Bressler B, Khanna R, Marshall JK, et al. Clinical Practice Guideline for the Medical Management of Perianal Fistulizing Crohn's Disease: The Toronto Consensus. Inflamm bowel dis. 2019;25(1):1-13.