Retrospective Study
Predictive value of infliximab trough level in combination with inflammatory biomarkers on long-term endoscopic outcomes in Crohn’s disease with clinical remission during maintenance therapy

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Abstract
BACKGROUND
Infliximab trough level severely affect therapeutic outcome of Crohn’s Disease (CD) patients under Infliximab (IFX). Recently frontier researches have focused on identify IFX trough level based on different therapeutic targets. Although previous studies have elaborated clinical value of IFX trough level (ITL) monitoring on short-term outcome in CD patients during therapy, studies contraposing the predictive value of ITL on long-term endoscopic outcomes in CD patients are still scarce in the domestic and overseas.

AIM
To explore the predictive value of ITL in combination with inflammatory biomarkers on long-term endoscopic outcomes in CD with clinical remission during IFX maintenance therapy.

METHODS
CD patients with endoscopic remission under long-term IFX maintenance therapy in the First Affiliated Hospital of Zhejiang Chinese Medicine University from January 2012 to December 2020 were collected. ITL and inflammatory biomarkers were continuously
monitored during the therapy. The Step I study was conducted from weeks 14 to 54 of IFX treatment. The Step II study was conducted from weeks 54 to 108 of IFX treatment. Endoscopic outcome was defined as endoscopic activity (CDEIS Score > 2 points or Rutgeerts' Score > 1) and endoscopic remission (CDEIS Score ≤ 2 points or Rutgeerts' ≤ 1). Endoscopic relapse free survival was defined as endoscopic remission at the beginning of the study stage and maintaining endoscopic remission during the study stage.

RESULTS
(I) At week 14, low ITL [OR=0.666, 95% CI 0.514-0.862, P < 0.01] and high fecal calprotectin (FCP) level [OR=1.002, 95% CI 1.001-1.004, P < 0.01] increased the risk of endoscopic activity at week 54. At week 54, low ITL [OR=0.466, 95% CI 0.247-0.877, P < 0.01] and high C-reactive protein (CRP) level [OR=1.590, 95% CI 1.007-2.510, P < 0.01] increased the risk of endoscopic activity at week 108. (II) At week 14, ITL≤5.60ug/mL [AUC=0.83, SE=0.92, SP=0.69] and FCP > 238ug/g [AUC=0.82, SE=0.73, SP=0.91] moderately predicted endoscopic activity at week 54. ITL≤5.60ug/mL in combination with FCP > 238ug/g indicated 82.0% possibility of endoscopic activity. At week 54, ITL≤2.10ug/mL [AUC=0.85, SE=0.75, SP=0.93] and CRP > 3.00mg/L [AUC=0.73, SE=0.50, SP=0.95] moderately predicted moderate endoscopic activity at week 108. ITL≤2.10ug/mL in combination with CRP > 3.00mg/L indicated 100.0% possibility of endoscopic activity. (III) From weeks 14 to 54 of IFX treatment, patients with ITL>5.60ug/mL had higher rate of endoscopic relapse free survival than those with ITL≤5.60ug/mL [95.83% VS 46.67%, P < 0.0001]. From weeks 54 to 108 of IFX treatment, patients with ITL>2.10ug/mL had higher rate of endoscopic survival free relapsed rate than those with ITL≤2.10ug/mL [92.68% VS 30.77%, P < 0.0001].

CONCLUSION
Combination of ITL, CRP and FCP contribute to long-term endoscopic prognosis monitoring. During IFX maintenance treatment, low ITL, high CRP level and high FCP
level were independent risk factors of CD patients with clinical remission in adverse endoscopy outcomes within one-year follow-up.

**Key Words:** Infliximab Trough Level (ITL); C-reactive protein (CRP); Fecal Calprotectin (FCP); Crohn’s Disease (CD); Clinical Remission; Long-term Endoscopic Outcome.


**Core Tip:** Previous investigations, contraposing CD patients under IFX maintenance therapy, have indicated that higher ITLs were associated with sustained drug response and clinical remission in inflammatory bowel disease (IBD) patients while lower ITLs were linked to secondary unresponsiveness of IFX. Currently, endoscopic remission or mucosal healing has been considered the main goal of biological therapy. Our study manifested that CD patients with higher levels of IFX blood concentration and lower levels of inflammatory biomarkers tended to have a better long-term endoscopic prognosis. Combining ITL, FCP, and CRP monitoring was helpful for the timely adjustment of IFX treatment strategy.
INTRODUCTION

Crohn’s Disease (CD) is a persistently progressive disease with nonspecific inflammation characterized by disease scope involving in the whole digestive tract and disease depth involving in the whole intestinal wall. The accumulation damage of intestinal walls contributes to the occurrence of stenosis, fistula and even abscess, reducing the life quality. Therefore, recent clinical studies have consistently concluded that therapeutic strategies and targets play a key role in controlling CD progression. Setting different therapeutic targets will have different disease outcomes. Clinical response, focusing only on the improvement of clinical symptoms, which can improve the quality of daily life but not affect long-term treatment outcomes. CD patients whose disease improvement is not up to the deep remission may aggravate persistently while achieving deep remission could reduce long-term hospitalization and surgery rates. Deep remission is mainly defined as endoscopic remission or mucosal healing in previous studies. Biologics, as an important step in the therapeutic strategy of CD, can effectively control the disease progression if conducted early and completely. In consideration of the wide use of Infliximab (IFX), precisely predicting the long-term endoscopic outcomes is stressed by more and more IBD physicians. Although the Infliximab Trough Level (ITL) has been proved to be closely related to the outcome of CD, ITL alone may be biased in predicting the outcome of CD. Monitoring inflammation biomarkers is one of the important links of IFX therapy, including C-reaction Protein (CRP), Fecal Calprotectin (FCP), etc. High inflammatory load affects the pharmacokinetics of IFX, inducing secondary nonresponse by decreasing blood drug concentration. Currently, it is believed that inflammatory biomarkers are good predictors of disease activity, but there is still a lack of reliable evidence for predicting disease remission. Therefore, this study intends to evaluate the long-term endoscopic outcomes of CD patients receiving IFX treatment by combining blood drug concentration and inflammatory biomarkers.

MATERIALS AND METHODS
Study Subjects Design

A single-center retrospective research has been implemented in the first affiliated hospital of Zhejiang Chinese Medical University. Crohn’s diseases patients under IFX therapy from January 2012 to December 2020 were collected. 181 CD patients underwent IFX treatment. 153 CD patients underwent enteroscopy as well as serum concentration monitoring at weeks 14 after the third dose of IFX induction therapy. Inclusion criteria, (I) endoscopic remission at week 14 (CDEIS Score ≤ 2 points or Rutgeerts’ ≤ i1), (II) clinical remission after IFX induction therapy without corticosteroids more than 6 mo, (III) therapeutic strategy during maintenance stage was designed as IFX 5mg/kg every 8 wk combined with AZA 50mg every day. Therapeutic strategic would be modulated if CD patients were confronted with clinical relapse or secondary lose of response (LOR) and data analysis would focus on the treatment course when patients received IFX 5mg/kg and AZA therapy regularly. Secondary lose of response (LOR) means a recurrence of the disease during IFX maintenance therapy. Two criteria should be met to determine LOR: the recurrence of symptoms of IBD in clinical remission after induction therapy, and symptoms caused by the inflammatory activity of IBD itself. Clinical relapse means CDAI > 150 points. Blood drug concentration monitoring, clinical, laboratory, endoscopic and imaging evaluation had been implemented every two months since the third dose of IFX induction therapy in all patients. The study was divided into two stages, step I study period defined as IFX maintenance therapy during weeks 14 to weeks 54, step II study period defined as IFX maintenance therapy during weeks 54 to weeks 108.

Data Collection

General data included age, sex, course, disease location, disease behavior, medication history and history of intestinal surgery. Laboratory indicators include white blood cell count (WBC), blood platelet count (PLT), C-reaction protein (CRP), erythrocyte sedimentation rate (ESR), serum albumin (ALB), fecal calprotectin (FCP), infliximab trough level (ITL), anti-infliximab antibody (ATI). Evaluation indicators of disease severity included CDAI score on clinical severity, CDEIS score on endoscopic
severity in CD patients without intestinal surgery and Rutgeerts score on endoscopic severity in CD patients with intestinal surgery.

**Outcome Definition**

Endoscopic outcomes at week 54 and week 108 after IFX initial therapy were evaluated by specialist physicians on IBD under electronic colonoscopy. Endoscopic remission was defined as CDEIS score ≤2 or Rutgeerts score ≤i1 and endoscopic activity was defined as CDEIS score >2 or Rutgeerts score >i1. Survival outcomes during IFX maintenance therapy were concentrated on endoscopic relapse-free survival defined as sustained endoscopic remission during step I study period or step II study period.

**Statistical analysis**

Descriptive statistical analysis was used to describe characteristics of CD patients. Number of cases (percentage) was used to describe categorical variable. Mean±(standard deviation) was used to describe continuous variable. Nonparametric test as Mann-Whitney test was used to compare two groups in enumeration data or measurement data without normal distribution. Two-sample t test was used to compare two groups in measurement data with normal distribution. One-way analysis of variance was used to compare multi-group if data satisfied homogeneity of variance. Nonparametric test as Kruskal-Wallis test was used to compare multi-group if data not satisfied homogeneity of variance. SPSS23.0 was used to analyze differences between groups. A p-value < 0.05 was considered significant.

Receiver-operating characteristic (ROC) analysis was used to identify the best cut off level of ITL on predicting endoscopic remission as well as sensitivity, specificity, positive predictive value, negative predictive value, area under the curve and Youden Index. Univariate logistic regression analysis was used to identify the association between endoscopic activity and predictors. Log-rank test was used to identify the association between endoscopic relapse and predictors. Graphad Prism9.0 was used to draw histograms and survival analysis curves and implement Log-rank test. MedCalc19.0 was used to draw ROC curve and analyze the predictive value of indicators on endoscopic outcomes. A p-value < 0.05 was considered significant.
RESULTS

Characteristics of study subjects

The study cohort totally collected 112 CD patients achieving clinical remission after IFX induction therapy. In step I study, 19 CD patients were excluded due to data absence ($n = 1, 5.26\%$) and endoscopic activity at week 14 ($n = 18, 94.74\%$) while 93 CD patients with endoscopic remission at week 14 were included. In step II study, 58 CD patients were excluded due to course of therapy shorter than two years ($n = 10, 17.24\%$), secondary non-response of IFX ($n = 12, 20.69\%$), suspension of IFX therapy within two years for disease remission ($n = 10, 17.24\%$) and endoscopic activity at week 54 ($n = 26, 44.83\%$) while 54 CD patients with endoscopic remission at week 54 were included. These 12 patients didn’t satisfy indications of operation and received hormonotherapy as the primary choice to alleviate disease for our center lacked other biological agents at that time. (FIGURE 1) All CD patients under IFX maintenance therapy combined with azathioprine. The dose of IFX was 5mg/kg every 8 wk and the dose of AZA was 50mg every day. Characteristics of CD patients included in study was shown in TABLE 1.

Correlation between Infliximab Trough Level, Inflammatory Biomarkers and Endoscopic Outcomes

In step I study, 67 CD patients (72.04\%) sustained endoscopic remission at week 54 among 93 CD patients included study. Multivariable regression analysis manifested that only ITL ($\text{OR}=0.666$, $95\%\text{CI} 0.514-0.862$, $P = 0.002$) and FCP ($\text{OR}=1.002$, $95\%\text{CI} 1.001-1.004$, $P = 0.002$) were independent risk of endoscopic activity at week 54 (TABLE 2). Based on incremental gain analysis, an Infliximab trough level range of 5.0–7.4µg/mL was correlated with sustained endoscopic remission rate more than 85% (FIGURE 3).

In step II study, 42 CD patients (77.78\%) sustained endoscopic remission at week 108 among 54 CD patients included study. Multivariable regression analysis manifested that only ITL ($\text{OR}=0.466$, $95\%\text{CI} 0.247-0.877$, $P = 0.018$) and CRP ($\text{OR}=1.590$, $95\%\text{CI} 1.007-2.510$, $P = 0.047$) were independent risks of endoscopic activity at week 108.
(TABLE 2). Based on incremental gain analysis, an Infliximab trough level range of 2.0—3.9μg/mL was correlated with sustained endoscopic remission rate more than 85% (FIGURE 3).

**Predictive Value of Infliximab Trough Level and Inflammatory Biomarkers on Endoscopic Outcomes**

In step I study, the ROC analysis demonstrated that the best cut off level of ITL and FCP at week 14 on predicting endoscopic relapse at week 54 was 5.60μg/mL (AUC=0.83, 95%CI: 0.73-0.90; Sensitivity=0.92; Specificity=0.69; *P*≤0.001) and 238μg/g (AUC=0.82, 95%CI: 0.72-0.89; Sensitivity=0.73; Specificity=0.91; *P*≤0.001) (TABLE 3 AND FIGURE 2). CD patients with ITL≤5.60μg/mL and FCP≥238μg/g at week 14 had 82% probability of endoscopic relapse at week 54. However, CD patients with ITL>5.60μg/mL and FCP≥238μg/g at week 14 had 98% probability of sustained endoscopic remission at week 54.

In step II study, the ROC analysis demonstrated that the best cut off level of ITL and CRP at week 54 on predicting endoscopic relapse at week 108 was 2.10μg/mL (AUC=0.85, 95%CI: 0.72-0.93; Sensitivity=0.75; Specificity=0.93; *P*≤0.001) and 3.00mg/L (AUC=0.73, 95%CI: 0.60-0.84; Sensitivity=0.50; Specificity=0.95; *P*=0.012) (TABLE 3 AND FIGURE 2). CD patients with ITL≤2.10μg/mL and CRP≥3.00mg/L at week 54 had 100% probability of endoscopic relapse at week 108. However, CD patients with ITL>2.10μg/mL and CRP≤3.00mg/L at week 54 had 97% probability of sustained endoscopic remission at week 108.

**Correlation between Infliximab Trough Level, Inflammatory Biomarkers and Endoscopic Relapse-free Survival**

In step I study, 26/93(27.96%) CD patients had experienced endoscopic relapse from weeks 14 to weeks 54 of IFX maintenance therapy. The estimated endoscopic relapse-free rate was 46/48(95.83%) in CD patients with ITL > 5.6μg/mL and 21/45(46.67%) in CD patients with ITL≤5.6μg/mL. The median time to endoscopic relapse of CD patients with ITL≤5.6μg/mL was 32.00w shorter than those with ITL>5.6μg/mL (HR=16.19, 95%CI: 7.44-35.22, *P* < 0.0001) (FIGURE 4A). The estimated
endoscopic relapse-free rate was 6/25 (24.00%) in CD patients with FCP > 238ug/g and 61/68 (89.71%) in CD patients with FCP ≤ 238ug/g. The median time to endoscopic relapse of CD patients with FCP > 238ug/g was 21.00w shorter than those with FCP ≤ 238ug/g (HR = 11.25, 95% CI: 4.26-29.73, P < 0.0001) (FIGURE 4B).

In step II study, 12/54 (22.22%) CD patients had experienced endoscopic relapse from weeks 54 to weeks 108 of IFX maintenance therapy. The estimated endoscopic relapse-free rate was 38/41 (92.68%) in CD patients with ITL > 2.1ug/mL and 4/13 (30.77%) in CD patients with ITL ≤ 2.1ug/mL. The median time to endoscopic relapse of CD patients with ITL ≤ 2.1ug/mL was 40.00w shorter than those with ITL > 2.1ug/mL (HR = 13.14, 95% CI: 3.07-56.27, P < 0.0001) (FIGURE 4D). The estimated endoscopic relapse-free rate was 4/8 (50.00%) in CD patients with CRP > 3.00mg/L and 40/46 (86.96%) in CD patients with CRP ≤ 3.00mg/L. The median time to endoscopic relapse of CD patients with CRP > 3.00mg/L was 50.00w shorter than those with CRP ≤ 3.00mg/L (HR = 7.85, 95% CI: 1.31-46.85, P < 0.0001) (FIGURE 4C).

**DISCUSSION**

Several studies have confirmed that different ITLs brought about different outcomes of CD under IFX therapy (TABLE 4). Tang et al. [1] discovered that CD patients achieving mucosal healing at week 14 of IFX therapy with ITL > 2.5ug/mL at week 14 had 71% chance of mucosal healing at week 54 while patients with ITL < 2.5ug/mL had only 33% chance. ITL ≥ 3ug/mL at the beginning of IFX maintenance therapy has been confirmed as a predictor of sustained response to IFX in CD patients [2]. Recently a prospective study in Japan verified that CD patients with ITL ≥ 3ug/mL at week 14 after IFX initial therapy had much better long-term clinical outcome than patients with ITL < 3ug/mL, of which survival analysis indicated 100% probability of clinical remission at week 108 in the former and 33.3% probability in the latter [3]. A meta-analysis manifested that ITL > 2.0ug/ml of IBD patients under IFX maintenance therapy contributes to better prognosis such as clinical remission or mucosal healing [4].
Similarly, this study results manifested that CD patients with ITL > 5.6ug/mL at week 14 had large chance of achieving sustained endoscopic remission during IFX maintenance therapy as well as CD patients with ITL > 2.1ug/mL at week 54. Borren et al. [5] implemented a multi-center retrospective study and concluded that low ITL in IBD patients during IFX maintenance therapy could not be a good predictor of clinical relapse in the next two years, suggesting that proactive therapeutic drug monitoring was not suitable in this group. However, this study discovered that CD patients with ITL ≤ 5.6ug/mL at week 14 were more likely to occur endoscopic relapse during the one-year follow-up period as well as ITL ≤ 2.1ug/mL at week 54.

According to previous studies, the challenge for IBD physicians is to frame the more suitable blood trough level of IFX to achieve better disease prognosis in the clinical therapy. The elements associated with the blood trough level of IFX can be classified into three areas. Above all, the better the therapeutic goal desired by IBD physicians or patients, the higher the blood trough level of IFX is required. An observational study contrapositing to CD patients with history of intestinal surgery by Imaeda et al. verified that mucosal healing required higher ITLs as more than 4.0ug/mL comparing to those to achieve normalization of routine clinical markers [6]. Papamichael et al. [7] considered that ITL surpassing 9.7ug/mL indicated 80% probability of endoscopic remission in CD patients under IFX maintenance therapy while ITL surpassing 2.2ug/mL was associated only with biochemical remission. Recently a prospective study verified that ITL > 8.0ug/mL was highly correlated with histological emission and sustained histological remission in IBD patients [8]. Perianal fistula, the most universal complications of CD patients, is another therapeutic goal. A retrospective cross-sectional study by Plevris et al. manifested that perianal fistula healing or closure is associated with higher ITLs as more than 7.1ug/mL [9].

Secondly, each clinical study had different stages of Infliximab drug monitoring, especially during maintenance therapy. ITL continues to decrease as time passed during Infliximab maintenance therapy [10]. A cross-sectional study of IBD patients under IFX therapy with fixed dose more than 6 mo manifested that IBD patients with
ITL≥3.4ug/mL had a 73% chance of endoscopic mucosal healing [11], Kang et al. [12] manifested that ITL≥5ug/mL during IFX maintenance therapy could identify mucosal healing in pediatric CD patients with 80% specificity. Feng et al. [13] innovatively integrated ITL levels in different time stages to identify endoscopic mucosal healing in CD patients, indicating that patients with ITL > 4.85ug/mL at week 14 and ITL > 2.85ug/mL at week 30 had an 80% chance of achieving endoscopic mucosal healing. Based on incremental gain analysis in our study, sustained endoscopic remission rate at week 54 reached only 54.63% at an ITL range of 2.5 to 4.9ug/mL at week 14 while corresponding numbers at week 108 was 89.47% at an ITL range of 2.0 to 3.9ug/mL at week 54. Therefore, the study held the view that CD patients with endoscopic remission need more higher Infliximab trough level at the beginning of IFX maintenance therapy (≥25.6µg/mL at week 14) than after IFX maintenance therapy over a half year (≥2.1µg/mL at week 54). What’s more, CD patients achieving endoscopic remission after IFX induction therapy and sustained endoscopic remission more than a half year may not need high ITL to maintain endoscopic remission.

The third element is therapeutic optimization of IFX in IBD. Adverse Infliximab response as high ATI level or low ITL may occur in a few CD patients during IFX maintenance therapy. Several clinical studies held the view that severe inflammatory activity of CD patients could change pharmacokinetics of anti-TNFα biology [14-16]. Therapeutic optimization as increasing fixed dose from 5mg/kg to 10mg/kg or shortening injection interval form every 8 wk to 4-6 wk contributes to increase ITL and decrease ATI level. Greece study manifested that the initial measurement after therapeutic adjustment discovered that ITL increased from 1.47ug/mL to 8.50ug/mL in patients with therapeutic optimization while ITL decreased from 5.65ug/mL to 3.8ug/mL in patients without therapeutic optimization [10]. A multi-center randomized clinical trial conducted by Dreesen et al. manifested CD patients under IFX maintenance therapy as 5mg/kg had high probability of no mucosal ulcer under endoscopy at week 54 with ITL more than 7.3mg/L and CD patients under intensified dose IFX therapy as 10mg/kg had 94% probability of no mucosal ulcer under endoscopy with ITL rising to
more than 10.6mg/L\textsuperscript{17}. Therefore, intensified therapy may contribute to mucosal healing in CD patients with ulceration if IFX injection dose is less than 10mg/kg and ITL is less than 10.6ug/mL. However, a few CD patients will accept combination therapy of Infliximab and immunosuppressant to boost the efficacy, especially AZA and 6-MP. AZA is a precursor of 6-MP and two components ultimately produce 6-TGN to exert clinical effect during metabolism. Study verified that 6-TGN concentration more than 125pmol/8×10\textsuperscript{8} RBC could enhance ITL to 8.3ug/mL or more and decrease positive rate of AT1\textsuperscript{18,19}. Hence, this study mainly included CD patients with sustained clinical remission more than 6 mo under fixed therapeutic strategy of IFX 5mg/kg every 8 wk combined with AZA 50mg every day. Retrospective records of CD patients included would suspend if therapy strategy changed, such as intensive therapy of IFX, conversion therapy of other biologics and combination therapy of surgery or other medications. The study design eliminated the influence of therapeutic adjustment on ITL.

The greatest strength of inflammatory biomarkers compared with blood trough level is unaffected by time during different monitoring stages of biological therapy in IBD patients. This study showed that ITL \(>5.6\text{ug/mL}\) combined with FCP\(\leq238\text{ug/g}\) at week 14 moderately predicted sustained endoscopic remission during the one-year follow-up period on CD patients with positive predictive value more than 95% as well as ITL \(>2.1\text{ug/mL}\) combined with CRP\(\leq3.00\text{mg/L}\) at week 54, superior to use ITL as the only predictor. FCP and CRP are considered as the most universal and typical biomarkers of inflammatory evaluation in IBD, also verified to be the independent risk factors of adverse endoscopic outcomes. The study confirmed that combining blood trough level with inflammatory biomarkers contributed to improving the accuracy of the prediction on endoscopic outcomes. A post hoc analysis from the CALM study manifested that CD patients with FCP\(<250\text{ug/g}\) mostly achieved CDEIS\(<4\) without deep ulceration, regardless of whether CRP <5mg/L. However, among patients with CRP<5mg/L but FCP\(\geq250\text{ug/g}\), only 16.7% achieved CDEIS\(<4\) without deep ulceration\textsuperscript{20}. The result indicated that the correlation between FCP normalization and endoscopic
mucosal healing in CD patients was stronger than that of CRP normalization. Previous study verified that FCP is suitable for distinguishing mild endoscopic activity from endoscopic remission, while it is difficult to distinguish partial endoscopic remission from complete endoscopic remission [21]. Similar to blood trough level, the optimal cut off value of FCP for distinguishing endoscopic activity from endoscopic remission ranges from 71μg/g to 250μg/g with moderate diagnose performance [22-27]. The study identified that FCP >276μg/g predicted endoscopic activity at week 54 of CD patients with clinical remission at week 14 moderately with 84.6% SE and 92.1% SP. Unlike FCP, the sensitivity of CRP to mild intestinal inflammation is low and the level of CRP increases much more dramatically in CD patients with moderate to severe inflammation. Therefore, previous study prefers to utilize CRP to distinguish moderate to severe endoscopic activity from mild to moderate endoscopic activity rather than distinguish mild endoscopic activity from endoscopic remission. A Spanish study manifested that FCP >155μg/g in combination with CRP >6.7mg/L could identify endoscopic activity with 82% SP [27].

However, the study has shortcomings in some areas. Firstly, the retrospective single-center study with small sample, inferior to prospective multi-center with greater sample, comprised some confounding factors. More real-world studies and randomized controlled trials on guidance significance of ITL to therapeutic outcomes in IBD need to be conducted. Secondly, the study primarily concentrated on mucosal inflammation located in large intestinal ignoring small intestinal due to the high cost and the incomplete scoring system of small intestinal evaluation accompanied by the poor compliance of patients and the laborious operation of endoscopists. Correlation between ITL and various small intestinal examination including endoscopy or imageology may be the focus of the future study. Last but not the least, definition of deep remission on CD have been tightened. Considering transmural inflammation of CD, endoscopy is confined to mucosal inflammation and macroscopical evaluation while imageology can accurately evaluate complete volume of intestinal wall and histopathological examination contributes to microscopical examination.
Notwithstanding endoscopic remission considered as the main targets and histological remission considered as a novel target, the new concept of ‘disease clearance’ which includes clinical, endoscopic and microscopic remission has drawn more and more attention from IBD physicians and may bring about a new upsurge of studies on IFX monitoring and new therapeutic targets [28].

CONCLUSION

In conclusion, during IFX maintenance treatment, low ITL, high CRP level and high FCP level were independent risk factors of long-term adverse endoscopy outcomes in CD patients with clinical remission. Combination of ITL, CRP and FCP contribute to long-term endoscopic prognosis monitoring. The best cut off values of ITL for predicting endoscopic activity within one-year follow up was 5.60ug/mL at week 14 and 2.10ug/mL at week 54. What’s more, ITL≤5.60ug/mL in combination with FCP>238ug/g at week 14 as well as ITL≤2.10ug/mL in combination with CRP>3.00mg/L at week 54 increased the precision of prediction on endoscopic outcomes at week 54 and week 108 respectively. Therapeutic optimization is still recommended in CD patients achieving endoscopic remission, provided that low ITLs or high levels of inflammatory biomarkers such as CRP or FCP arises, to prevent endoscopic recurrence as soon as possible.
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