Therapeutic Advances in Gastroenterology

Original Research

Levels of TB-IGRA may help to differentiate between intestinal tuberculosis and Crohn's disease in patients with positive results

Ther Adv Gastroenterol

2020, Vol. 13: 1–8

DOI: 10.1177/1756284820922003

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Abstract

Aim: The aim of this study was to investigate the significance of positive tuberculosis interferon gamma release assay (TB-IGRA) in the differential diagnosis of intestinal tuberculosis (ITB) and Crohn's disease (CD) patients, and to find a suitable threshold to help distinguishing CD from tuberculosis (TB), so as to provide better recommendations for clinical treatment.

Methods: A retrospective study was performed including 484 patients who underwent TB-IGRA testing for suspected CD or ITB treated in the Shanghai Tenth People's Hospital of Tongji University between January 2015 and May 2018. According to the diagnostic criteria, 307 patients, including 272 CD and 35 ITB patients, were recruited for the final analysis. We comprehensively and systematically collected their clinical manifestations, and analyzed the influence of TB-IGRA values referring to diagnosis criteria, and the possible causes of false positives. The receiver operator characteristic (ROC) curve and the cut-off value were applied to distinguish between ITB and CD patients.

Results: Of the 56 patients with suspected CD enrolled, 23 were finally diagnosed with CD and 33 with ITB. In patients with TB-IGRA $\geqslant$ 100 pg/ml, 4 cases were CD and 29 cases were ITB, while 19 cases were CD and 4 cases were ITB in patients with TB-IGRA $<$ 100 pg/ml ($p < 0.05$). TB-IGRA $\geqslant$ 100 pg/ml indicated a high possibility of TB infection, with a sensitivity of 88% and a specificity of 74%. Three out of the four CD patients with TB-IGRA $\geqslant$ 100 pg/ml had a history of tuberculosis, while only 1 of the 19 CD patients with TB-IGRA $<$ 100 pg/ml had a history of tuberculosis ($p < 0.05$). The average duration of ITB was 7 months, and that of CD was 46.8 months, thus a significant difference ($p < 0.05$) was observed. Perianal lesions such as anal fistula or abscess were found in all CD patients. Among ITB patients, 8 out of 15 patients with TB-IGRA $\geqslant$ 400 pg/ml experienced weight loss, while only 1 out of 18 patients with TB-IGRA $<$ 400 pg/ml underwent weight loss ($p < 0.05$).

Conclusion: Patients with CD have longer duration of disease, and perianal lesions are more common in CD. ITB patients with TB-IGRA $\geqslant$ 400 pg/ml experience weight loss more readily, which indicates that TB-IGRA value may be correlated positively with the severity of ITB. In patients with CD and ITB, TB-IGRA = 100 pg/ml may be a cut-off value of TB-IGRA. For patients with TB-IGRA $\geqslant$ 100 pg/ml, it is recommended to use diagnostic anti-TB treatment first. Comprehensive analysis and judgment are required for patients with TB-IGRA from 14 pg/ml to 99 pg/ml. TB-IGRA false positivity may occur in patients with a history of TB infection.

Keywords: Crohn's disease, intestinal tuberculosis, TB-IGRA

Received: 12 October 2019; revised manuscript accepted: 17 March 2020.

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Introduction

Crohn's disease (CD) is a chronic systemic inflammatory condition in the intestinal tract, characterized by its recurrent, progressive, and destructive nature. In recent years, the morbidity of CD has increased significantly worldwide, including in newly industrialized countries in Africa, Asia, and South America, including Brazil, whose annual percentage change (APC) for CD is + 11.1% [95% confidence interval (CI) 4.8–17.8] and Taiwan [APC for Crohn's disease + 4.0% (1.0–7.1)].[1] CD pathogenesis and clinical research faces great challenges.

Intestinal tuberculosis (ITB) is caused by mycobacterium tuberculosis and results in chronic intestinal inflammation. CD and ITB have different pathogeny and treatments, while they share some similarities in clinical or endoscopic manifestation, which makes clinical diagnosis difficult.[2] Therefore, without etiology or other strong evidence, it is difficult to clinically distinguish CD from ITB. Therapeutic anti-tuberculosis trial (ATT trial) is an experimental anti-consumption treatment. According to the comprehensive evaluation of the therapeutic effect, it can provide a decisive basis for diagnosis. However, there are potential risks of delay or aggravation of the disease in ATT experiments. Meanwhile, sufficient attention should be paid to the adverse effects caused by anti-tuberculosis drugs.

The tuberculosis (TB) interferon-gamma (IFN-γ) release assay (TB-IGRA) has adopted the enzyme-linked immunosorbent assay (ELISA) principle to test human IFN in whole blood specimens stimulated by specific recombinant antigen of mycobacterium tuberculosis *in vitro*.[3] IGRA adds TB-specific antigen to blood samples or isolated peripheral monocytes from subjects that are then incubated in culture. If the subject had been infected by mycobacterium tuberculosis, the memory T cells activated by the TB bacterium could respond to these specific antigens, proliferating, differentiating and releasing r-interferon and other cytokines. The level of IFN-γ can be quantified by ELISA, determining the presence of TB. IGRA has some difficulties in distinguishing active TB infection from latent TB infection, but it is useful in differentiating TB from other diseases. IGRAs have a high sensitivity and specificity for the diagnosis of ITB, and specificity is consistent from study to study. IGRA may have a supplementary role in the differential diagnosis between ITB and CD when conventional results are not diagnostic.[4–6] The level of IGRA may be important, but it has not been widely studied.

In this study, a retrospective study was conducted to include 272 CD and 35 ITB patients, in which 23 CD and 33 ITB patients were TB-IGRA positive The clinical significance of TB-IGRA positive CDs and the possible causes of false positivity were verified by confirmed CD. Therefore, these results may provide a diagnosis direction of TB-IGRA positive patients.

Patients and methods

Materials

A total of 484 cases of suspected CD who underwent TB-IGRA tests treated in the Shanghai Tenth People's Hospital of Tongji University were included in this retrospective study. All were ⩾16 years old. The research was approved by the hospital's ethics committee (No.:SHSY-IEC-4.1/19-203/01) and obtained "exemption from informed consent" approved by the Shanghai Tenth People's Hospital. Exclusion criteria included (1) ulcerative colitis (UC); (2) Behcet's disease; (3) irritable bowel syndrome (IBS); (4) lack of information; and (5) loss to follow up. A total of 307 patients were enrolled in our analysis, including CD and ITB, no matter what their TB-IGRA values were. Among the 81 patients with positive results, 12 were diagnosed UC, 3 had Behcet's disease, and 10 had incomplete information or loss to follow up. Finally, 23 CD and 33 ITB were recruited according to the inclusion criteria (Figure 1). There were 39 males and 17 females. The mean age of patients at baseline was 43.5 years (range 16–74 years).

Diagnostic criteria

CD diagnostic criteria. CD diagnostic criteria were based on the Inflammatory Bowel Disease (IBD) Diagnosis and Treatment Consensus of 2018.[7] Lacking a diagnostic gold standard, diagnosis is supposed by combining clinical features (symptoms, signs, and related complications), laboratory tests [routine blood test, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum

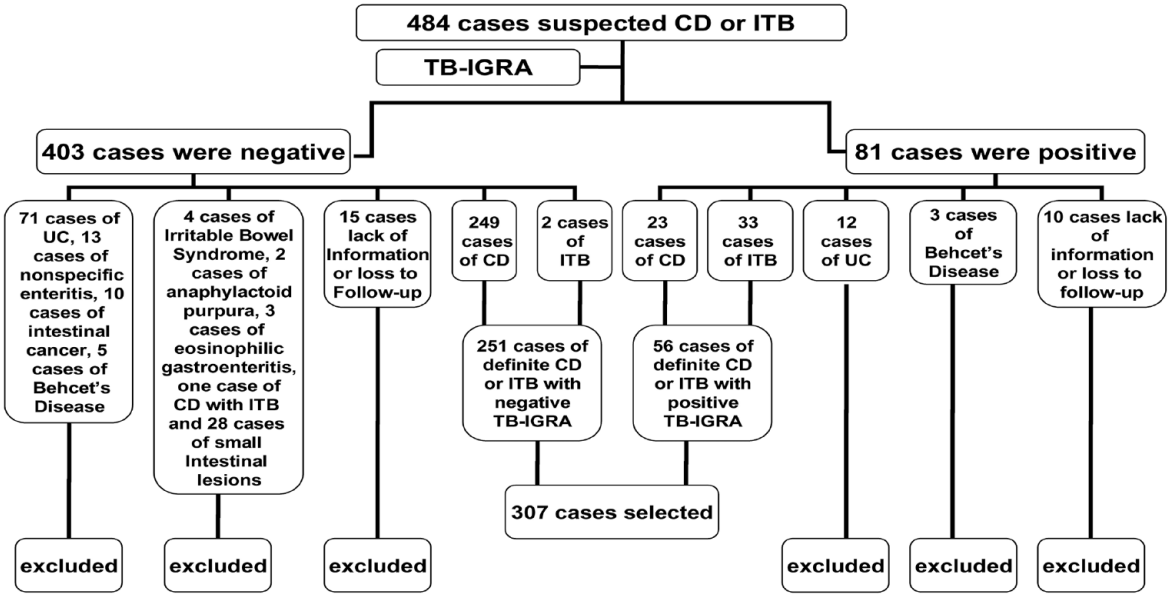

Figure 1. The 484 patients and their outcomes.
CD, Crohn's disease; IGRA, interferon gamma release assay; ITB, intestinal tuberculosis; UC, ulcerative colitis.

albumin], imagology examination [small bowel computed tomography (CT) and small bowel magnetic resonance (MR)], endoscopy (colonoscopy, capsule endoscopy and enteroscopy if necessary) and histopathology results, excluding intestinal tuberculosis, Behcet's disease, infectious enteritis, ischemic colitis, radioactive enteritis, drug-induced enteritis, eosinophilic enteritis, various rheumatic diseases manifested by intestinal lesions, malignant intestinal lymphoma, diverticulitis, bypass enteritis and so on.

ITB diagnostic criteria. ITB was diagnosed according to the 15th version of *Practical Internal Medicine* of People's Health Publishing House, Bejing, China. With a history of parenteral TB infection (open pulmonary TB) or not, clinical features (digestive tract symptoms and systemic symptoms abdominal signs), laboratory tests [purified protein derivative (PPD), TB-IGRA, etc.], imagology examination (pulmonary CT and small intestine CT), histopathological examination (acid fast stain, etc.), diagnostic anti-TB therapy on suspected patients, follow-up visits, excluding CD, Behcet's disease, colonic neoplasms, amiba, or schistosomiasis granuloma, are combined for diagnosis.

TB-IGRA

The T-cell detection kit for TB infection (*in vitro* release ELISA) was purchased from Beijing Wantai Biopharmaceutical Co. Ltd, Bejing, China. The operation was carried out strictly according to the kit instructions. The detection range is from 2 to 400 pg/ml; results which are $\geqslant$14 pg/ml and $\geqslant$ N/4 (N is background controlled culture tube detection value) are determined as positive.

Statistical analysis

SPSS 21.0 was used for statistical analyses. Measurement data is indicated by $x \pm s$; counting data is expressed in numbers and percentages; continuous variable is shown in mean $\pm$ standard deviation (SD) and, when SD is too high, it is presented in median and range; intergroup comparison adopts χ^2 tests or Fisher's exact probability method; evaluation of diagnostic efficacy is based on analysis of the receiver operator characteristic (ROC) curve, calculating the correlation sensitivity, specificity, and area under the curve. Results were considered statistically significant when $p < 0.05$.

Table 1. Comparison of clinical features between CD and ITB.

Characteristics	Numbers (%)	CD [*n* (%)]	ITB [*n* (%)]	Statistics	*p* value
Sex				0.04	0.841
Male	215 (70.03)	191 (70.22)	24 (68.57)		
Female	92 (29.97)	81 (29.78)	11 (31.43)		
Average age (years old)	40.39	34.46 ± 13.63	46.31 ± 14.03		
Mean duration (years)	2.44	3.97	0.91	6.628	<0.001
Median (range)		3 (1 week ~ 30 years)	0.25 (3 days ~ 7 years)		
Clinical manifestations					
Fever	97 (29.64)	84 (30.88)	13 (37.14)	0.562	0.453
Weight loss	71 (23.13)	62 (22.79)	9 (25.71)	0.149	0.7
Diarrhea	166 (54.07)	156 (57.35)	10 (28.57)	10.344	0.001
Bloody	73 (23.78)	69 (25.37)	4 (11.43)	3.324	0.068
Abdominal pain	217 (70.68)	193 (70.96)	24 (68.57)	0.085	0.771
Ascites	42 (13.68)	32 (11.76)	10 (28.57)	0.062	0.014
Complications					
Abdominal abscess	15 (4.89)	15 (5.51)	0 (0)	1.016	0.154
Perianal lesion	105 (34.20)	104 (38.24)	1 (2.86)	17.246	<0.001
Bowel perforation	16 (5.21)	16 (5.88)	0 (0)	1.144	0.285
Bowel obstruction	28 (9.12)	27 (9.93)	1 (2.86)	1.114	0.291

CD, Crohn's disease; ITB, intestinal tuberculosis.

Results

Clinical manifestation of selected patients (diagnosis of CD or ITB)

Clinical characteristics of the patients in this study are shown in Table 1. Weight loss refers to the European Society of Clinical Nutrition and Metabolism (ESPEN) consensus for the diagnosis of malnutrition in 2015: weight loss of more than 5% of normal weight in the last 3 months in acute disease, or more than 10% of normal weight in chronic process over an uncertain period of time.[8]

The results showed that there was a statistical difference in the length of disease duration between the two groups. CD patients had a longer duration of disease and chronic recurrent symptoms. If ITB is diagnosed promptly, the prognosis is relatively good.

For clinical manifestations, no significant differences were observed in the overall summary of fever, hematozoa, and abdominal pain in patients with CD and ITB. Diarrhea was more common in patients with CD, while ascites were more common in patients with ITB. In addition to the history of anal fistula in one ITB patient, other perianal lesions were found in all CD patients, with statistical difference ($p < 0.05$).

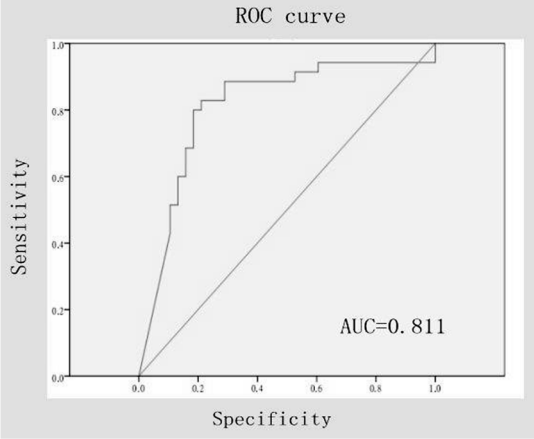

Figure 2. ROC curve analysis of TB-IGRA in diagnosis of TB infection
AUC, area under the curve; ROC, receiver operator characteristic; TB-IGRA, tuberculosis-interferon gamma release assay.

ROC curve analysis of TB infection diagnosed by TB-IRGA

The positive criteria of the TB-IGRA kit is ⩾14 pg/ml. However, among the 71 TB-IGRA positive cases of suspected CD, the distribution of CD and ITB detection values displayed obvious regional aggregation, which indicated that the positive threshold can be further optimized so that it can guide the timing of diagnostic anti-TB treatment as the first choice.

Taking the clinical diagnosis of TB infection as the gold standard, a ROC curve was drawn to evaluate the diagnostic efficiency of TB-IGRA. Our results demonstrated that the cut-off value of TB-IGRA for the diagnosis of TB infection is 100 pg/ml, with a sensitivity of 88%, and a specificity of 74% (Figure 2). Thus, 100 mg/ml was considered as the cut-off value for follow-up analysis.

Distribution of CD and ITB in TB-IGRA positive results

Among 56 cases with TB-IGRA positive results, 23 were <100 pg/ml and 33 were ⩾100 pg/ml. The median of TB-IGRA is 47 (range from 17 to >400) pg/ml in the CD group and 324 (range from 32 to >400) pg/ml in the ITB group. Among the cases whose TB-IGRA < 100 mg/ml, there are 19 CDs (5 cases of surgical and pathological diagnosis, 3 cases of endoscopic biopsy pathology diagnosis, 11 cases of comprehensive analysis diagnosis, 4 cases improved after mesalazine treatment; 7 cases were switched to CD treatment after ineffective anti-TB treatment: 3 cases with mesalazine; 3 cases with infliximab treatment; 1 case improved after combined mesalazine and glucocorticoid) and 4 ITBs (1 case diagnosed by surgical and pathological, 1 case diagnosed as acid-fast bacilli indicated ascites examination, 2 are diagnostic anti-TB therapy). In the cases which TB-IGRA ⩾ 100 pg/ml, there were 4 CDs (2 cases diagnosed by surgical and pathological results; 1 case diagnosed by endoscopic biopsy pathology; 1 case switched to combination of mesalazine and glucocorticoid after ineffective anti-TB therapy) and 29 ITBs (3 cases diagnosed by surgical and pathological results, 1 case diagnosed by endoscopic biopsy for definite pathological results, 25 cases through diagnostic therapy for definite diagnosis, of which 23 cases were anti-TB treatment, and 2 cases switched to anti-TB treatment after mesalazine treatment failure. Of cases with TB-IGRA ⩾ 100 pg/ml, 25 who received diagnostic anti-TB therapy had clinical remission after 2–3 months of treatment. Of these 25, 16 got better, identified by colonoscopy review, and 2 lowered their TB-IGRA value. The above results show that TB-IGRA ⩾ 100 pg/ml is associated with higher possibility of TB infection over CD ($\chi^2 = 27.8$, $p < 0.05$) (Table 2), with susceptibility of 87.9% (29/33) and specificity of 82.6% (19/23).

Table 2. Distribution of CD and ITB in TB-IGRA positive region [n (%)].

TB-IGRA	Number	CD	ITB
14 ~ 99 pg/ml	23	19 (82.6)	4 (17.4)
⩾100 pg/ml	33	4 (12.1)	29 (87.9)

CD, Crohn's disease; ITB, intestinal tuberculosis; TB-IGRA, tuberculosis interferon gamma release assay.

The history of TB infection and TB-IGRA

Among the four cases of TB-IGRA ⩾ 100 pg/ml but diagnosed as CD in the end, two had a history of TB, 1 had a history of ITB, and one had an unknown history of TB. However, among the 19 CD cases with TB-IGRA < 100 pg/ml, just 1 case had a history of TB pleurisy. The result showed that positive TB-IGRA results can result from a history of TB infection ($p = 0.0087$) (Table 3).

Table 3. History of TB infection in CD patients with a positive IGRA result [n (%)].

TB-IGRA	Numbers	No history of TB infection	History of TB infection
14~99 pg/ml	19	18 (94.7)	1 (5.3)
⩾ 100 pg/ml	4	1 (25)	3 (75)

CD, Crohn's disease; ITB, intestinal tuberculosis; TB-IGRA, tuberculosis interferon gamma release assay.

Table 4. Efficacy of diagnostic anti-TB therapy in IGRA positive patients [*n* (%)].

TB-IGRA	Numbers	Ineffective in anti-TB treatment	Effective in anti-TB treatment
14~99 pg/ml	9	7 (77.8)	2 (22.2)
⩾100 pg/ml	26	1 (3.8)	25 (96.2)

TB-IGRA, tuberculosis interferon gamma release assay.

Table 5. Weight and TB-IGRA in ITB patients [n (%)].

TB-IGRA	Numbers	No weight loss	Loss of weight
14~99 pg/ml	18	17 (94.4)	1 (5.6)
⩾100 pg/ml	15	7 (46.7)	8 (53.3)

ITB, intestinal tuberculosis; TB-IGRA, tuberculosis interferon gamma release assay.

The curative effect of diagnostic anti-TB therapy in TB-IGRA-positive patients

The pathological detection rate of endoscopic biopsy in patients with ITB is low, so the TB-IGRA value provides evidence for whether diagnostic treatment is needed or not. Among the 23 cases of TB-IGRA < 100 pg/ml patients, diagnostic anti-TB therapy was effective in 2 out of 9 patients. However, among the 33 cases of TB-IGRA ⩾ 100 pg/ml, diagnostic anti-TB therapy was effective in 25 out of 26 cases ($p < 0.05$) (Table 4). This demonstrated that, for patients with TB-IGRA ⩾ 100 pg/ml but no definite pathological diagnosis, diagnostic anti-TB therapy is preferred; for those with TB-IGRA ranging from 14 to 99 pg/ml and no definite pathological diagnosis, comprehensive analysis including clinical symptoms is warranted, and a diagnostic anti-TB therapy has to be applied with caution.

Significance of differential diagnosis of clinical symptoms in TB-IGRA-positive patients

Regarding clinical symptoms, CD patients usually experience a long duration of disease; 73.9% (17 cases) had had CD for more than 1 year and the average duration was 3.9 ± 6.6 years. ITB patients had relatively short duration of disease; 84.8% (28 cases) lasted less than 1 year ($\chi^2 = 19.61$, $p < 0.05$) and the average was 0.6 ± 1.4 years. Perianal lesions were found in five CD patients, but in no ITB patients. Furthermore, most of those ITB patients with TB-IGRA ⩾ 400 pg/mL had undergone weight loss ($p = 0.004$) (Table 5). Our results showed that, in TB-IGRA-positive patients, clinical symptoms such as duration of disease, perianal lesions, and weight loss all have great value in the diagnosis of CD and ITB.

Discussion

China has the second highest incidence of TB in the world. In 2013, the World Health Organization calculated that the number of new cases of TB in China was about 820,000, and the proportion of the extrapulmonary TB was 3.8%.[9] In 2017, there were about 770,000 cases of TB, and the number of extrapulmonary TB accounted for 5%.[10] The incidence rate of IBD in our country has also shown an increasing tendency in recent years. From 1950 to 2000, the prevalence of CD in Asia was about 0.848/100,000.[1,11] In China, the incidence of CD in Guangzhou reached 1.22 million.[12] As a common type of extrapulmonary TB, the ITB is similar to CD in clinical manifestations, imaging, and endoscopic features, as well as histopathological changes. It is difficult to obtain a clinical diagnosis based on bacteriology. However, the treatments of CD and ITB are completely different. Misdiagnosis may delay

treatment of the original disease and even exacerbate the disease. If ITB is misdiagnosed as CD, treatment with a glucocorticoid biological agent may even result in the spread of TB; meanwhile, if CD is mistreated as ITB, anti-TB treatment may lead to aggravation of the disease.[5,6,13] Therefore, differential diagnosis of CD and ITB is necessary and important.

$CD4^+$ T cells can be recognized by mycobacterium tuberculosis antigen, and the memory T cell can produce IFN-γ after being stimulated again by the related antigen.[14] TB-IGRA can detect the concentration of IFN-γ released by specific T cells. Thus, we can identify whether an individual is infected by mycobacterium tuberculosis or not.

The most common clinical features of CD and ITB patients are bellyache and diarrhea, but the difference between them has no statistical significance.[2,15] Most patients with CD have perianal lesions and fistula formation. Clinical manifestations of TB-IGRA-positive CD and ITB patients included in this study were consistent with those reported in previous literature,[13] but there was a significant difference in the duration of the two diseases. The duration of CD was relatively long, while the duration of ITB was usually within 1 year. ITB patients with TB-IGRA $\geqslant$ 400 pg/ml were more likely to suffer from weight loss, suggesting that TB-IGRA may be related to the severity of TB infection.

Previous studies have shown that levels of IFN-γ produced from specific T cells in peripheral blood was significantly higher in patients with active TB than those with inactive TB, in both intrapulmonary or extrapulmonary TB.[16] Positive TB-IGRA indicates mycobacterium tuberculosis infection, but it should not be used for clinical differentiation between active TB and latent TB infection.[17] The use of immunosuppressive agents or biological agents in the treatment of CD patients has a potential risk in active TB infection. In this study, we obtained diagnostic efficacy by evaluating TB-IGRA for TB infection in 71 patients who were suspected for CD but positive in TB-IGRA, and finally confirmed to be CD by follow up. The feasibility of differentiating CD from ITB by using the cut-off value of TB-IGRA (100 pg/ml) obtained from the ROC curve as a threshold will be analyzed further, but we arrived at this conclusion based on all diagnosed CD and ITB patients, which has validated meaning. Diagnostic anti-TB treatment was given to patients with TB-IGRA $\geqslant$ 100 pg/ml, and the symptoms of most patients improved. Therefore, if there are intestinal manifestations that cannot be diagnosed by colonoscopy and biopsy pathology, if TB-IGRA $\geqslant$ 100 pg/ml, the possibility of ITB should be considered first, and diagnostic anti-TB treatment should be recommended.

Although TB-IGRA has high specificity in diagnosis of TB infection, it cannot exclude the possibility of infection caused by non-TB Mycobacterium strains containing RD1 (region of difference 1) genome region, such as mycobacterium marinum, mycobacterium Kansas, mycobacterium Gordon, mycobacterium sugaris, etc.[18,19] The results showed that TB-IGRA $\geqslant$ 100 pg/ml had high sensitivity and specificity (87.9% and 82.6%) in differential diagnosis between ITB and CD. However, previous TB infection history in patients with non-ITB (CD) could lead to TB-IGRA $\geqslant$ 100 pg/ml. Therefore, the possibility of false positivity in TB-IGRA caused by previous TB infection should be considered clinically.

In conclusion, TB-IGRA has high specificity and sensitivity in the diagnosis of TB infection. Compared with the traditional PPD test, quantitative detection is more accurate and measurable. By reducing the use of experimental anti-TB drugs, it can greatly help reach a precise treatment. In patients with CD and ITB, 100 pg/ml may be a positive threshold for TB-IGRA, which plays an important guiding role in differential diagnosis and following treatment. TB-IGRA $\geqslant$ 100 pg/ml is of great significance in the diagnosis of ITB, and diagnostic anti-TB treatment is recommended as the first choice. TB-IGRA $<$ 100 pg/ml should be comprehensively analyzed and judged, and anti-TB treatment is still recommended for those who have no definite diagnostic evidence or cannot exclude TB infection. In addition, the detection value of TB-IGRA may be correlated with the activity of TB infection. Previous TB infection history may lead to false positives in TB-IGRA results. Due to the small sample size of this study, the above conclusions need to be verified in further studies with larger sample size.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Supported by Natural Science Foundation of Shanghai (No. 16ZR1426600)

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