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SHORT REPORT

Tuberculosis infection following anti-TNF therapy in inflammatory bowel disease, despite negative screening

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Abstract

We present two patients with inflammatory bowel disease who, despite negative tuberculosis screening, developed a de novo tuberculosis infection after the start of anti tumor necrosis factor alpha treatment. We discuss current screening methods and their limitations, the approach after positive screening and the timing to resume anti-TNFα treatment after TB infection. We shortly mention the immune reconstitution inflammatory syndrome (IRIS), described in a few cases after the stop of anti-TNFalpha while treating the tuberculosis infection. We conclude with some remaining questions concerning tuberculosis in IBD patients.
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1. Background

The introduction of TNF-alpha blocking agents has had a great impact on disease control of several immune-mediated conditions such as rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis and psoriasis. Because of the risk of reactivation of latent tuberculosis, screening for tuberculosis before starting anti-TNF became mandatory. At present screening for tuberculosis consists of a thorough history and clinical examination, a tuberculin skin testing and a chest X-ray.[1]

We recently observed two patients with de novo tuberculosis development under anti-TNF, and this despite negative screening. These cases raised a number of issues and questions with respect to the screening methods, to the incidence of de novo TB infections, and to the repetitive screening during anti-TNF therapy. Also, the literature that addresses when to resume anti-TNF therapy if tuberculosis is diagnosed is scarce. This article will discuss these questions and provide clinicians with guidance in this difficult matter.

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2. Cases

Our first patient is a 38-year old business development manager of Belgian origin. In April 2008, he was diagnosed with Crohn's disease, located in the terminal ileum and colon. The patient was initially treated with a short course of budesonide as a bridging therapy to azathioprine (150 mg/d). Due to persistent disease activity in 2010, anti-TNF was proposed. After a thorough questioning, a negative tuberculin skin test with a diameter of induration of 0 mm and a normal chest X-ray (Fig. 1), infliximab was started in February 2010 and treatment with azathioprine continued. Early April, the patient developed flu-like symptoms during skiing holiday in Switzerland. A local physician advised to stop azathioprine and prescribed norfloxacin 2 × 400 mg a day. Upon return to Belgium, he presented in our hospital with a non-productive cough, pancranial headache, anorexia, night sweats and myalgia. There was no other recent travel abroad. Except for high fever 39.6 °C, a thorough clinical examination was normal. Laboratory results showed CRP of 90 mg/L (upper limit of normal 5 mg/L), leukocytosis 13 400 with 16.5% monocytes and LDH of 509 U/L. X-ray of the lungs showed no consolidations. Chest CT imaging was compatible with miliary tuberculosis infection with mediastinal and hilar enlarged lymph nodes (Figs. 2−3). During bronchoscopy, there were no abnormalities seen. The first cultures were negative but based on the presentation of the patient and the CT scan, quadruple therapy with isoniazid, rifampicin, ethambutol and pyrazinamide was initiated. A quantiferon test was positive and Lowenstein−Jensen cultures of the bronchus aspirate became positive for *Mycobacterium tuberculosis* complex. New history taking revealed that the patient had changed jobs during his infliximab induction regime. He started to work for a Belgian computer company with an Indian offshoot company.

Three weeks after the start of quadruple antituberculous therapy, and 7 weeks after his last IFX infusion, he developed bloody diarrhea, and reactivation of his Crohn's colitis was confirmed on flexible sigmoidoscopy. CRP at that time was 32 mg/L. A new infliximab infusion was given and was followed
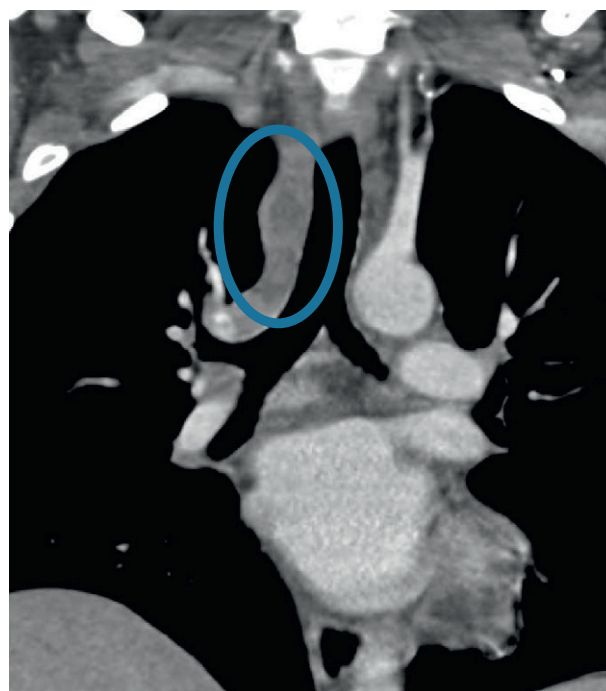

Figure 2 Chest CT imaging April 2010 (patient 1): adenopathy with ring-enhancement.

by maintenance IFX. Two months later, the patient felt well, no fever and no CRP elevation. At that time resistance to pyrazinamide was known and ethambutol and pyrazinamide were stopped; rifampicin and isoniazid were continued. In October 2010, he developed a sudden swelling in the neck, which on ultrasound was a cervical adenopathy with a diameter of 6 cm. Pus was aspirated and auramine−rhodamine staining was positive, as was the *M. tuberculosis* PCR. Cultures and Lowenstein−Jensen cultures remained negatively compatible with a cold abscess. Therapy with rifampicin and isoniazid only was continued until January 2011, during which time he
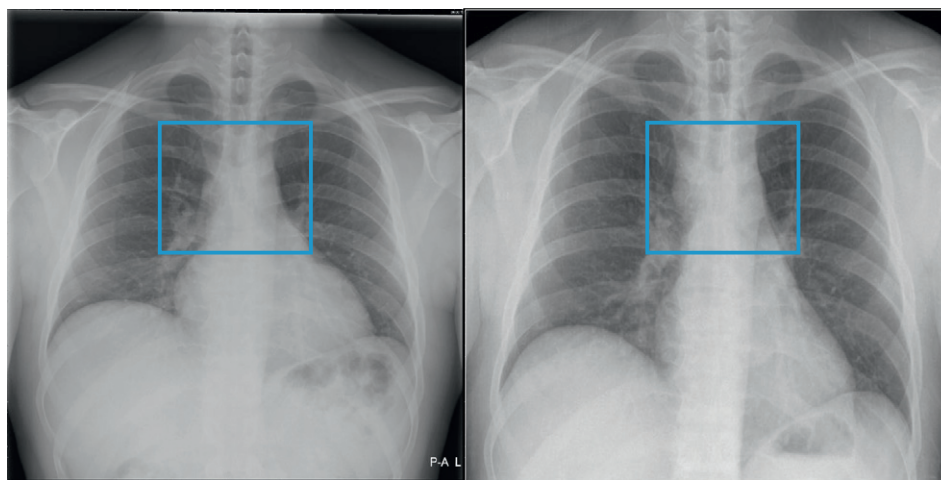

Figure 1 Evolution on chest X-ray (patient 1). Left: normal chest X-ray prior to administration of IFX (January 2010). Right: enlarged mediastinum after the start of IFX (April 2010).
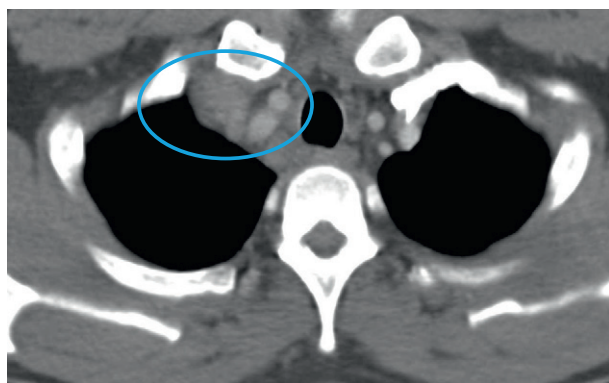
Figure 3 Chest CT imaging April 2010 (patient 1): cervical adenopathy.

received infliximab every 8 weeks (Fig. 4). At present, the patient is in remission on 8-weekly infliximab infusions.

The second case concerns a 46-year old male patient with a past history of spondyloarthropathy (HLA B27+), a traumatic fracture of the seventh dorsal vertebra, acute

necrotizing appendicitis with perforation and peritonitis. In 2004 he was diagnosed with pancolitis, suggestive of IBD. In 2005 the diagnosis of ulcerative colitis was made and therapy with systemic steroids and azathioprine was initiated. Despite this therapy, persistent pancolitis was seen and endoscopically classified as MAYO III. After a normal chest X-ray and PPD skin test with a diameter of induration of 0 mm, infliximab was started only once in compassionate use (no reimbursement at that time in Belgium for ulcerative colitis). The associated anemia and iron deficiency were corrected with 2 units packed cells. In September 2006 he relapsed on 5-ASA and azathioprine with active sigmoiditis on endoscopy. Maintenance infliximab was therefore indicated at a dose of 5 mg/kg every 8 weeks. Remission was achieved and azathioprine was stopped in 2007. In 2007 he was diagnosed with obstructive sleep apnea syndrome. At that time a chest X-ray was made and a limited pleural infusion was seen on the left side, without related symptoms (Fig. 5). In October 2008 he complained of fatigue, fever and cough. The chest X-ray showed at that time an infiltrate suprahilar of the left lung (Fig. 6). Infliximab was stopped and antibiotics were initiated. As no improvement was seen after 2 weeks, CT of the chest was performed and confirmed
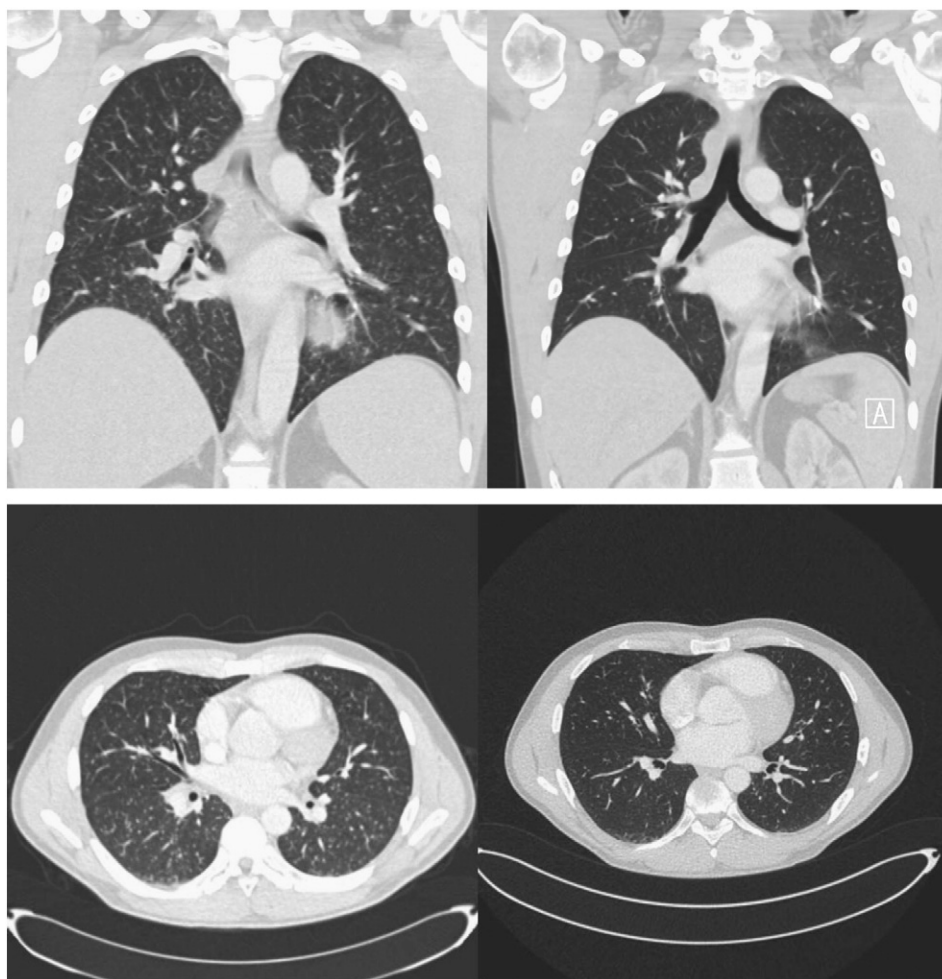

Figure 4 Evolution of patient 1. Left: April 2010: micronodular pattern with random distribution and presence of enlarged lymph nodes mediastinal and hilar. Right: February 2011: decrease of the micronodular pattern with still some enlarged hilar lymph nodes.
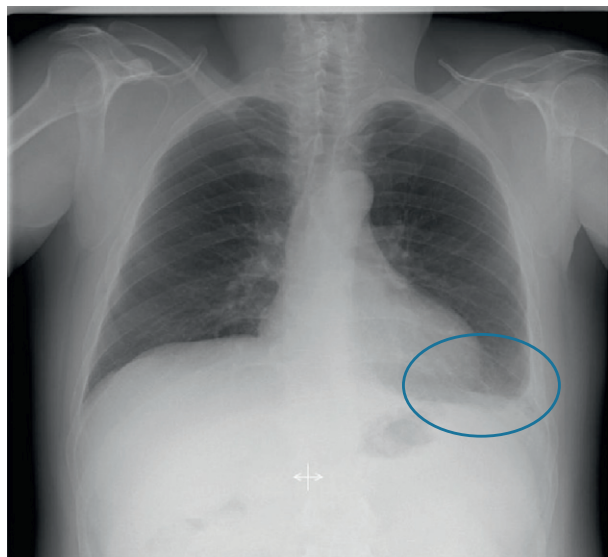
Figure 5   Patient 2: chest X-Ray with limited left sided pleural infusion (2007).

the pneumonic infiltrate and some enlarged mediastinal lymph nodes (Fig. 7–8). Bronchoscopy showed no abnormalities, and auramine staining of the bronchus aspirate was negative, as were the Ziehl cultures. Bronchial biopsies were taken and showed acute necrotizing, granulomatous inflammation. This led to the diagnosis of tuberculosis and quadruple anti-TB therapy was started for 9 months. During this period he received only 5-ASA (4 g/d) as maintenance therapy for his UC. After 9 months of treatment CT showed a regression of the inflammatory mass in the left lung and the mediastinal lymph nodes, leaving a bilateral pachypleura (Fig. 8). A relapse of left sided colitis with rectal blood loss and diarrhea occurred, classified as MAYO II on flexible
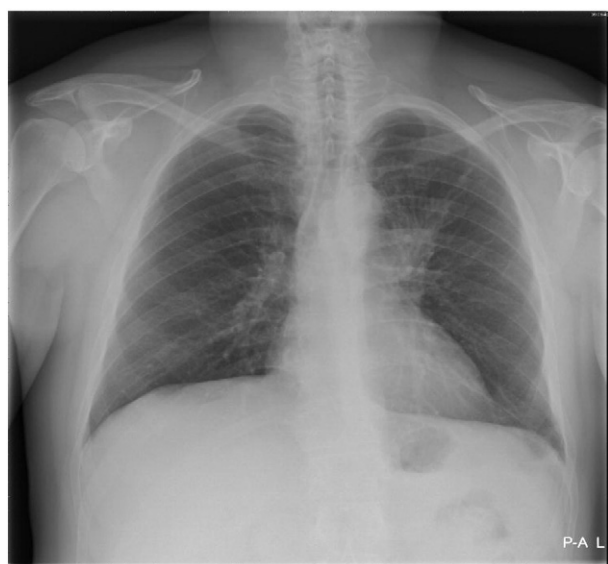

Figure 6   Chest X-Ray October 2008 with consolidation, suprahilar in the left lung (patient 2).

sigmoidoscopy. Because of the severity and the persistence of the complaints infliximab was restarted in December. The patient regained disease control with infliximab as maintenance therapy until present.

3. The worldwide burden of tuberculosis

The WHO reported a world-wide 8.8 million estimated cases of TB in 2010, or an equivalent to 128 cases per 100,000 persons. Most of the patients originate from Asia (59%) and Africa (26%). The incidence of TB is decreasing since 2006. Also TB mortality is falling globally. In 2010, there were approximately 1.4 million deaths due to TB infection.[2]

4. Susceptibility to tuberculosis with anti-TNFalpha treatment

It is well known that patients receiving anti-TNFα therapy are more susceptible for tuberculosis. After the introduction of anti-TNF over a decade ago, an increase in TB infections was seen. Keane et al. reported a close temporal association with the start of anti-TNFα and the onset of tuberculosis. He also pointed-out the atypical disease presentation of tuberculosis infections in patients receiving anti-TNF therapy. The majority of patients suffer from extrapulmonary TB and 20% have a disseminated disease. The presentation is comparable to the presentation of TBC in immunocompromised patients. The diagnosis is therefore not always clear cut.[1]

Following this landmark study, screening for latent TB infection became mandatory when treatment with anti-TNFα therapy is suggested.[1] The association between tuberculosis and tumor necrosis factor alpha neutralizing agent is easy to comprehend on the basis of the pathogenesis of a tuberculosis infection. When a person is infected with tuberculosis, the bacterium is not killed directly by the immune system but gets sequestered within granulomas. In this way *M. tuberculosis* is able to survive in a host for years to decades. TNFα has a specific role in the formation and maintenance of the granulomas. It recruits different cells necessary to form the granulomas and maintain this structure. If TNFα is no longer present, granulomas will no longer control the tuberculosis infection and reactivation is possible.[3,4] TNF is not only important to control the disease, but also suspected to be responsible for some of the symptoms of tuberculosis disease like weight loss, night sweats and tissue destruction.[5] Not all TNFα blockers are associated with the same tuberculosis risk. Treatment with etanercept does not seem to significantly increase the risk for tuberculosis infection. This is probably due to different mechanism of action of etanercept.[1]

5. Screening methods: TST or IGRA?

The standard screening procedure includes a thorough medical history, a chest X-ray and a tuberculin skin test (TST).[1] Until 2001 the only test available was TST. A positive TST result is associated with an elevated risk for future or current active tuberculosis (Table 1). But there are well-known disadvantages to the TST. First the TST has to be well administered,
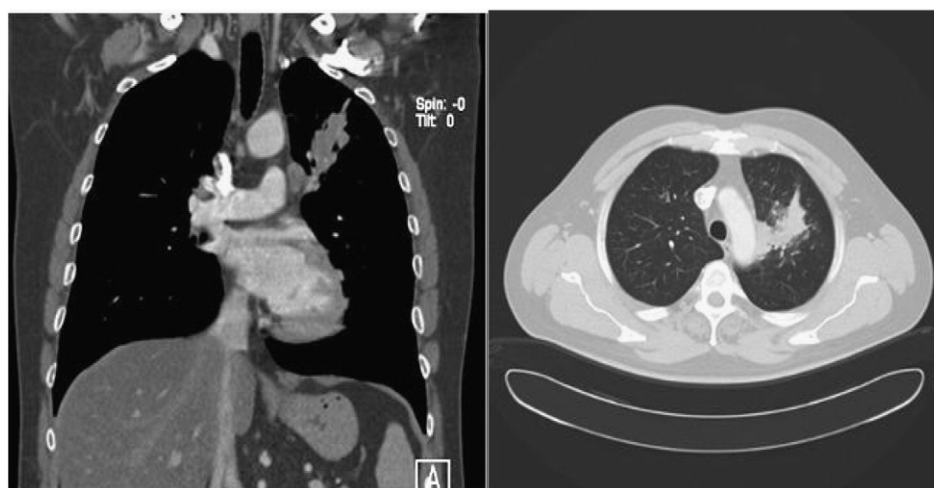
Figure 7   Patient 2: CT chest with pneumonic consolidation and enlarged mediastinal lymph nodes.

second, there is an inaccuracy and bias in the reading of the test and third, the test has low specificity. Individuals who received a BCG (Bacille Calmette–Guerin) vaccine, may have a positive TST test. Also patients infected with non-tuberculosis mycobacteria may have a positive test. Additionally, the sensitivity of the test is negatively influenced by immunodeficiency. The two-step tuberculin skin test, with a second administration for 1 or 4 weeks after the first, could be considered for patients who were vaccinated with BCG or originate from an area with a high TB incidence. The Belgian guidelines do not recommend booster TST and therefore a second skin test was not performed in our two patients.[6]

The knowledge that interferon gamma has a critical role in the immune-response to *M. tuberculosis*, laid the groundwork for new tuberculosis detection tests. Nowadays there are several IGRAs (interferon gamma release assays) developed and approved. One of the main advantages of the current IGRAs is the improvement of the specificity. The IGRAs are enzyme-linked immunosorbent assay (ELISA) tests that measure the amount of interferon gamma release in response to certain proteins compared with a control. These proteins are present in all *M. tuberculosis* but are absent in BCG vaccine and in most nontuberculous mycobacteria. Therefore the specificity of IGRAs is markedly better as compared to the TST. The Quantiferon-TB Gold in-Tube (QFT-G-IT) uses an ELISA to measure antigen-specific production of interferon-gamma by circulating T-cells in whole blood being challenged with *M. tuberculosis*-specific antigens. T-spot-TB uses the Elispot technique to measure peripheral blood mononuclear cells that produce interferon-gamma.[7]

Immunosuppressive therapy can lead to false negative TST results, making IGRA more suitable for detection of *M. tuberculosis* infection in immunocompromised patients (Table 2). Patients with inflammatory bowel disease are often on steroids and/or immunomodulating agents prior to starting anti-TNF therapy. However, immunosuppression of T-cells can also influence IGRAs. This was seen in patients with HIV.[8,9] In contrast, IBD patients treated with immunomodulators normally stay well above the normal level of CD4 cell count.
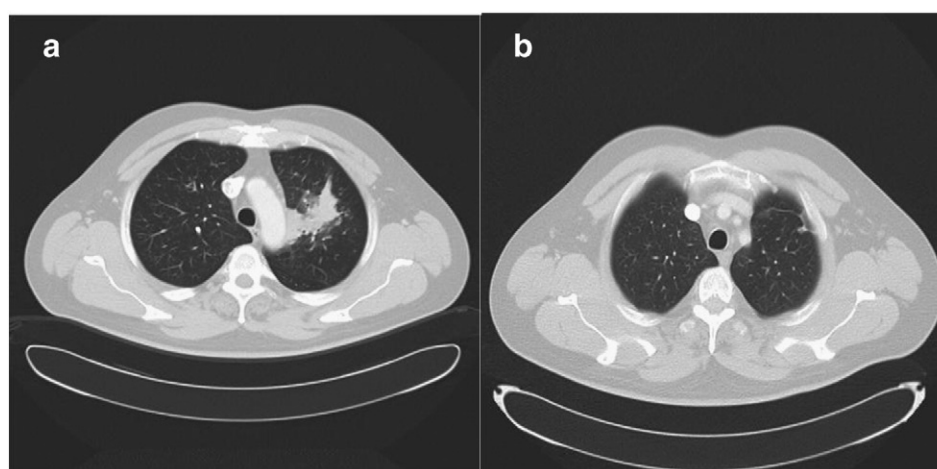

Figure 8   Evolution of patient 2. a: CT-scan November 2008: pneumonic consolidation in the left lung and enlarged mediastinal lymph nodes. b: CT-scan May 2009: resolution of the pneumonic consolidation in the left lung.

Table 1 Cut off for positive TST according to underlying disease.[7]

	Characteristics of the patients
Reaction of ≥5 mm of induration	HIV+ persons, recent contact with TB case patients, changes on chest X-ray with prior TB, patients with organ transplants and other immunosuppressed patients (receiving equivalent of ≥15 mg of prednisone/day ≥1 month).
Reaction of ≥10 mm of induration	Recent immigrants from high-prevalence countries, Residents and employees of following high-risk congregate settings [a], mycobacteriology laboratory personnel, persons with specific conditions that place them at high risk [b], children <4 years or infants, children and adolescents exposed to adults at high risk.
Reaction of ≥15 mm of induration	Normal individual

[a] High risk congregate setting: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with AIDS, and homeless shelters.

[b] Conditions with high risk for TBC: silicosis, diabetes mellitus, chronic renal failure, some hematological disorders, weight loss of ≥10% of ideal body weight, gastrectomy and jejunoileal bypass.

There have been suggestions to use IGRAs in every IBD patient and certainly in those undergoing immunosuppressive therapy who will receive anti-TNFα treatment.[10] It is important to realize that sensitivity and accuracy of both tests cannot be compared, due to the lack of a golden standard for the diagnosis of TB. The most recent ECCO guidelines still only recommend the use of IGRAs in BCG vaccinated individuals.[11] We cannot rule out that the TB infections of our patients were latent infections, after a false negative TST. Both patients were treated with immunosuppressive treatments prior to the start of anti-TNF. Further studies are needed to compare performance of IGRA and TST in IBD patients.

6. When to start anti-TNF after a positive screening?

Screening for tuberculosis before the start of anti-TNF treatment will detect inactive or active tuberculosis infections.[5,11] There is no clear consensus about the duration and type of antituberculous therapy before anti-TNF therapy can be initiated safely. In general, 6 to 9-month therapy with isoniazid has been recommended most often. However, an emerging problem is that of multidrug-resistant tuberculosis. Depending on the geographic area and the patient's background, the risk of drug resistance should be evaluated. If latent tuberculosis is diagnosed the ECCO guidelines recommend to delay the start of anti-TNF for at least 3 weeks, if

possible.[11,12] However in some cases earlier initiation of infliximab is indispensable for disease control of IBD. Therefore, a serious consideration of the benefit-risk ratio should be undertaken before starting anti-TNF therapy. In the London position statement on biological therapy, active infections and untreated latent tuberculosis are contraindications for anti-TNF therapy.[14]

7. When to resume anti-TNF after active TB infection? The problem of paradoxical reaction

Following a negative screening and start of anti-TNF, it is important to stay vigilant for symptoms of active tuberculosis. As mentioned above, the presentation is not always typical.[1]

When a diagnosis of active tuberculosis is made, infliximab should be stopped.[11] The Belgian guidelines state to start quadruple combination therapy with rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months and to continue with isoniazid and rifampicin for another 4 months. In particular cases, like meningitis, or miliary TB, it may be necessary to continue the treatment even after 6 months. Triple therapy, without ethambutol is only recommended in certain cases where resistance to the antibiotics is excluded. After the start of the combination therapy it can be necessary to adjust the treatment if the *Mycobacterium* shows resistance to an antibiotic.[13]

Table 2 Comparison of TST and IGRA.

	PPD TST	Interferon gamma release assay
Reproducibility	Poorly reproducible	
Sensitivity	May be false negative after use of immunosuppressive therapy	May be false negative after suppression of T-cells
After BCG vaccination	May be false positive in vaccinated patients	Not influenced by vaccination
Nontuberculous infection	False positive in non-tuberculous mycobacteria	Not influenced by non-tuberculous mycobacteria
Cost		Higher cost
Immunosuppressive therapy		Controversy on validity in patients on immunosuppressive treatment

If there is a medical necessity to restart IFX, current guidelines recommend to do so at the earliest two months after antituberculous agents are stopped.[11,12]

These recommendations seem clear-cut and easy to understand. Nevertheless there are some remarkable side-effects described after stopping anti-TNF such as an immune reconstitution inflammatory syndrome (IRIS) or paradoxical reaction (PR). IRIS was first described in HIV positive patients with tuberculosis who received HAART therapy.[15] IRIS is defined as a worsening of clinical or radiological signs of TB following the initiation of antituberculous treatment in the absence for evidence of disease relapse or the presence of another diagnosis.[16] Not only worsening or development of lymphadenopathy or pulmonary infiltrates, but also development of pleurisy, cerebral tuberculomas and meningitis can be seen. All these symptoms typically occur while antituberculous treatment is ongoing. Usually IRIS is a mild transient and self-limited phenomenon.[15,17,18] This syndrome has also been described in patients after discontinuation of infliximab. There are some common factors: in HIV patients there is a depletion of CD4+ cells, needed to control tuberculosis infection. Mouse models have shown that IRIS develops if there has been a microbial infection without an appropriate pro-inflammatory response, due to HIV or anti-TNFα. When the immune system is restored, there is a pathological overshoot, resulting in IRIS.[19] It is important to differentiate this phenomenon from failure of the antituberculous drugs, drug-induced reactions or other causes of inflammation during tuberculosis. Fig. 9 summarizes how to evaluate a possible presentation of IRIS. It is important to realize that, if symptoms are related to IRIS, continuation of anti-TB drugs can be the solution.[15] The treatment for IRIS is mostly based on the approach in HIV patients. Corticosteroids are currently the main treatment.[19] Often the exacerbation can be controlled with medical treatment, as mentioned above, but sometimes surgery is

needed. It has been suggested that maintenance of low dose of anti-TNF therapy can be administered to diminish the immune response.[17] Further research for more specific therapies based on the knowledge of the underlying pathogenesis is needed.

8. Remaining questions and areas for further research

There are still remaining questions. Our two patients make a case to revisit the guidelines for screening: if the TST is negative, should we routinely perform an IGRA test, if the patient was treated with immunosuppressive therapy? And after negative screening for TB, and while on maintenance anti-TNF, should patients routinely be checked for TB? Can routine screening prevent de novo symptomatic TB? The Belgian guidelines do not recommend the use of booster TST. Should we consider adding this test to our guidelines? Another important question relates to traveling and close contacts with people from TB endemic countries, like India. These contacts should be considered risk factors for acquisition of TB. When can a patient with TB and anti-TNF therapy resume travels to TB-endemic countries and should he or she receive again prophylactic therapy? Finally immunosuppressive therapy is not necessarily contra-indicated in patients being treated for TB with active drugs. The phenomenon of IRIS is not yet fully understood. Therefore, ongoing registries of opportunistic infections remain necessary to hopefully give answers to some of these questions.

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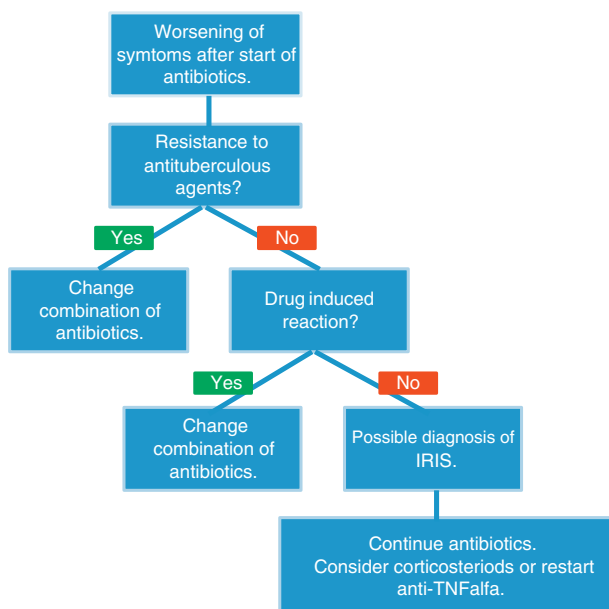
Figure 9 How to respond to worsening of tuberculosis in IBD-patients after the stop of infliximab?

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