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Tuberculosis Disease in Children and Adolescents on Therapy With Antitumor Necrosis Factor- α Agents: A Collaborative, Multicenter Paediatric Tuberculosis Network European Trials Group (ptbnet) Study

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(See the Editorial Commentary by Nolt on pages 2570–1.)

Background. In adults, anti-tumor necrosis factor- α (TNF- α) therapy is associated with progression of latent tuberculosis (TB) infection (LTBI) to TB disease, but pediatric data are limited.

Methods. Retrospective multicenter study within the Paediatric Tuberculosis Network European Trials Group, capturing patients <18 years who developed TB disease during anti-TNF- α therapy.

Results. Sixty-six tertiary healthcare institutions providing care for children with TB participated. Nineteen cases were identified: Crohn's disease ($n = 8$; 42%) and juvenile idiopathic arthritis ($n = 6$; 32%) were the commonest underlying conditions. Immune-based TB screening (tuberculin skin test and/or interferon- γ release assay) was performed in 15 patients before commencing anti-TNF- α therapy but only identified 1 LTBI case; 13 patients were already receiving immunosuppressants at the time of screening. The median interval between starting anti-TNF- α therapy and TB diagnosis was 13.1 (IQR, 7.1–20.3) months. All cases presented with severe disease, predominantly miliary TB ($n = 14$; 78%). One case was diagnosed postmortem. TB was microbiologically confirmed in 15 cases (79%). The median duration of anti-TB treatment was 50 (IQR, 46–66) weeks. Five of 15 (33%) cases who had completed TB treatment had long-term sequelae.

Conclusions. LTBI screening is frequently false-negative in this patient population, likely due to immunosuppressants impairing test performance. Therefore, patients with immune-mediated diseases should be screened for LTBI at the point of diagnosis, before commencing immunosuppressive medication. Children on anti-TNF- α therapy are prone to severe TB disease and significant long-term morbidity. Those observations underscore the need for robust LTBI screening programs in this high-risk patient population, even in low-TB-prevalence settings.

Keywords. tuberculosis; anti-TNF- α ; reactivation; miliary tuberculosis; children.

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Etanercept was the first tumor necrosis factor- α (TNF- α) inhibitor to be approved for the treatment of juvenile idiopathic arthritis (JIA) in 1998, and the same year infliximab was approved for the treatment of Crohn's disease. Several other anti-TNF- α agents have been approved since then, which are increasingly being used to treat children affected by JIA, inflammatory bowel disease (IBD), and other immune-mediated conditions.

In these patients, both the disease itself and the use of conventional immunosuppressant drugs and/or biologic agents are associated with an increased risk of serious infections, including tuberculosis (TB) [1–3].

In the human host immune response to mycobacterial infections TNF- α plays a critical role, particularly in the formation and maintenance of TB granulomas [4]. In adults, exposure to anti-TNF- α agents has been associated with reactivation TB and progression from latent TB infection (LTBI) to TB disease, commonly manifesting as extrapulmonary or disseminated forms of TB [5]. Most current guidelines therefore emphasize the need to rule out LTBI before commencing anti-TNF- α therapy [6–8]. There is general consensus that patients who are diagnosed with LTBI based on a positive tuberculin skin test (TST) or interferon- γ release assay (IGRA) result should receive anti-TB preventive therapy prior to commencing anti-TNF- α therapy. However, it currently remains uncertain if anti-TNF- α treatment has to be delayed until after the completion of preventive therapy, or whether it is safe to commence anti-TNF- α agents 1 or 2 months into preventive therapy.

Currently, the data on TB disease in children receiving anti-TNF- α therapy are very limited [9]. To our knowledge, fewer than 20 cases have been described in detail in the peer-reviewed literature so far [10–15]. Concerningly, several of those cases had a fatal outcome.

Using a well-established network of pediatric specialists providing healthcare for children with TB, the aim of this study was to identify children and adolescents who developed TB disease while receiving anti-TNF- α therapy and to describe their presentation, clinical course, and outcome.

METHODS

Participating Centers

We conducted a retrospective multicenter study within the Paediatric Tuberculosis Network European Trials Group (ptbnet) [16–19], a network of clinicians and researchers with an interest in pediatric TB, from September 2016 until March 2019. In March 2019 ptbnet comprised 252 members based in 32 European countries and 7 countries outside Europe, making it the largest pediatric TB network globally.

Eligibility Criteria and Definitions

All patients aged 0 to 18 years with confirmed TB disease (ie, microbiologically proven by culture or nucleic acid amplification tests) and unconfirmed TB disease, based on the consensus case definitions proposed by Graham et al [20], after initiation of anti-TNF- α therapy were eligible for inclusion. Severe TB disease was defined as per previously published criteria [21]. Significant hepatotoxicity was defined as serum aspartate aminotransferase or alanine aminotransferase

concentrations more than 5 times the upper limit of normal (ULN) in asymptomatic patients or more than 3 times the ULN in patients with symptoms (abdominal pain, nausea, vomiting, or jaundice) [22].

Data Collection and Analyses

A standardized data-collection tool (Supplementary Material 1) was designed and all ptbnet members were invited by e-mail to contribute cases to this study in September 2016. The data collection forms received were collated into an Excel database (Microsoft) hosted on a secure server. In addition, in March 2019, all ptbnet members were asked via the ptbnet online discussion forum and via e-mail reminders to confirm that no cases fulfilling the eligibility criteria had received care at their healthcare institution. Categorical variables were described as percentages and continuous variables as medians with interquartile ranges (IQRs). Confidence intervals (CIs) around proportions were calculated with the modified Wald method.

Ethics Approval

Ethical approval for this study was obtained from the Hospital Sant Joan de Déu (Barcelona, Spain) Ethics Committee (reference PIC 133-13). No personal or identifiable data were collected during the conduct of this study.

RESULTS

Collaborators from 66 tertiary and quaternary healthcare institutions providing care for children with TB participated in the study. Forty-nine (74%) centers reported that they had not encountered any patients fulfilling the case definitions during the preceding 5 years (Supplementary Material 2). A total of 19 patients (8 males, 11 females) receiving anti-TNF- α therapy diagnosed with TB disease between February 2011 and March 2019 were identified. The largest numbers of cases were reported from Spain, Germany, and the United Kingdom (each $n = 4$). One case each was reported from healthcare centers in Austria, Croatia, Latvia, Lithuania, Portugal, Switzerland, and Ukraine. Two of the cases (case 3 and case 4) (Table 1) had previously been described elsewhere in case reports [10, 11].

Characteristics of the Cases Identified

The majority of the cases were Caucasian ($n = 15$; 79%) and born in the country where they were diagnosed ($n = 17$; 89%). Eleven (58%) cases had been bacille Calmette-Guérin (BCG) vaccinated in the past; 8 (42%) were BCG unvaccinated. The median age at diagnosis of the underlying inflammatory condition was 9.7 (IQR, 6.6–12.8) years. The most common underlying conditions that prompted use of anti-TNF- α therapy comprised Crohn's disease ($n = 8$; 42%) and JIA ($n = 6$; 32%), as summarized in Table 1.

Table 1. Details of Patients With Tuberculosis Disease Following Initiation of Anti-Tumor Necrosis Factor- α Therapy

Patient No.	Gender, Ethnicity, BCG Vaccination History	Underlying Disease, Age at Diagnosis (years)	Risk Factors and Medication at LTBI Screening Prior to Anti-TNF- α Therapy	Anti-TNF- α Drug Used, Age at Initiation (years)	Age at TB Diagnosis (years), New Risk Factors	Details Regarding TB Disease and Diagnostic Tests at Presentation	Anti-TB and Anti-inflammatory Drugs Used, Duration of Treatment (weeks)	TB Outcome
1	F; Caucasian, yes	JIA, 1.3	No risk factors; TST 3 mm, negative QFT-GIT, normal CXR; on MTX	ADA (5.2)	5.8, TB contact	Miliary TB diagnosed after 9 days of fever, cough, and anorexia. Positive QFT-GIT, sputum PCR-positive (cultures no growth).	HRZE (14), HRZ (18), steroids (12) for arthritis and uveitis flare; also MTX and ibuprofen; recommended on R (65) as "secondary" prophylaxis when immunosuppression was restarted	Cured without sequelae
2	F; Caucasian, yes	Systemic JIA, 3.0	Born and living in high-TB-prevalence country; negative TST, normal CXR; on meloxicam and MTX	ETN (9.0)	12.1, none	Cavitary lesion in left upper lobe after 2 weeks of fever, fatigue, cough, and anorexia; also developed left pleuritis, pericarditis and nodules in right lobe 4 weeks after initiation of anti-TB agents (probable immune reconstitution syndrome). TST 15 mm, sputum culture- and PCR-positive (fully susceptible MTB).	HRZE + OFLO + AMIK (4), HRZE (8), HRE (36), steroids (42); and MTX for JIA flare	Cured, pulmonary cavity and fibrosis
3	M; Caucasian, yes	Polyarticular JIA, 4.0	Born and living in high-TB-prevalence country; negative T-SPOT.TB, normal CXR; on MTX	ADA (8.1)	8.6, none	Miliary TB with pleural and pericardial effusion and ascites diagnosed after 4 weeks of fever, cough, headache, joint pain, abdominal distention, and weight loss. Positive T-SPOT.TB, gastric aspirates culture- and PCR-positive (fully susceptible MTB).	HRZE (10), HRE (37), steroids (10) for arthritis and polyserositis; also MTX and NSAIDs	Cured without sequelae
4	F; Caucasian, no	Oligoarticular JIA, 5.7	TB contact; positive TST (10 mm), normal CXR; on MTX and steroids; received H for 9 months	ETN (70); ADA (9.3)	9.6, TB contact	Miliary AND CNS TB diagnosed after 2 weeks of fever, left inguinal lymphadenitis and arthritis in left knee; TST 30 mm, synovial biopsy PCR-positive, gastric aspirates culture-positive (fully susceptible MTB).	HRZE (8), HR (18), treatment interruption due to significant hepatitis (4), HR (47); also had knee synovectomy and inguinal lymph node excision; steroids (8) for tuberculomas and arthritis	Cured, restricted range of movement in knee joint
5	F; Caucasian, no	JIA, 7.2	No risk factors; negative QFT-GIT, normal CXR, on MTX and steroids	ETN (8.3)	9.3, TB contact	Miliary TB, abdominal disease, cervical adenitis, and erythema nodosum after 4 weeks of cough, anorexia, and abdominal pain. Positive QFT-GIT, lymph node tissues culture- and PCR-positive (fully susceptible MTB).	HRZE (8), HR (41), steroids (6) for miliary TB	Cured without sequelae
6	F; Caucasian, yes	JIA, 9.8	Born in high-TB-prevalence country; indeterminate QFT-GIT, normal CXR, on steroids	ETN (14.3)	15.1, none	Miliary TB, inguinal lymphadenitis, abdominal disease, brain tuberculoma, and spinal TB after 8 weeks of fever, weight loss, and malaise. Indeterminate QFT-GIT, sputum culture- and PCR-positive (fully susceptible MTB).	HRZE + AMIK + MOXI (9), HR + MOXI (41), Z stopped due to significant hepatitis; AMIK stopped due to hearing impairment; adherence issues; steroids for miliary TB	Cured, spinal instability

Table 1. Continued

Patient No.	Gender, Ethnicity, BCG Vaccination History	Underlying Disease, Age at Diagnosis (years)	Risk Factors and Medication at LTBI Screening Prior to Anti-TNF- α Therapy	Anti-TNF- α Drug Used, Age at Initiation (years)	Age at TB Diagnosis (years), New Risk Factors	Details Regarding TB Disease and Diagnostic Tests at Presentation	Anti-TB and Anti-inflammatory Drugs Used, Duration of Treatment (weeks)	TB Outcome
7	M, Caucasian, no	Crohn's disease, 8.8	No risk factors; negative QFT-GIT, on steroids	IFX (13.9)	14.7, none	Cavitating lesion, airway compression, and cervical lymphadenitis after 11 weeks of cough, anorexia, and night sweats. Negative QFT-GIT, sputum culture- and PCR-positive (fully susceptible MTB).	HRZE (12), HR (24), steroids to treat airway compression and Crohn's disease; IFX reinitiated 7 months after TB treatment completion	Cured, pulmonary fibrosis
8	F, Asian, yes	Crohn's disease, 9.7	Family from and travel to high-TB-prevalence country; negative QFT-GIT, on AZA and mesalazine	ADA (12.4)	13.7, trip to high-TB-prevalence country	Miliary TB diagnosed after 3 weeks of fever, cough, and weight loss. CXR and abdominal ultrasound showed miliary lesions. Indeterminate QFT-GIT initially (repeat after 8 weeks of anti-TB treatment positive), cultures no growth.	HRZE (12), HR (40), no steroids	Cured without sequelae
9	M, Caucasian, no	Crohn's disease, 11.6	No risk factors; no TST/IGRA done, normal CXR; on MTX and steroids	IFX (14.0); ADA (14.9)	15.8, trip to high-TB-prevalence country	Miliary TB diagnosed after 4 weeks of fever, cough, and weight loss. TST 10 mm, sputum PCR-positive.	HRZE (13); HR, then H + RIFAB, then H + LEVO due to leukopenia (142 in total), no steroids	Cured without sequelae; PCR-confirmed cutaneous TB at age 20.3 years (probable recurrence; no new risk factors)
10	F, Caucasian, no	Crohn's disease, 11.6	Lived in an urban area with a TB incidence of 70.0/100 000; negative TST, normal CXR; no immunosuppressive medication	ADA (12.2)	12.3, none	4 weeks of fever and per rectal bleeding; managed as flare of Crohn's disease with immunosuppression and surgery, without improvement. Pulmonary hemorrhage and multiorgan failure; died after 3 weeks. Miliary TB was diagnosed postmortem; liver, spleen, and gut tissue PCR-positive.	TB treatment never initiated	Died
11	F, Asian, yes	Crohn's disease, 13.0	Family from and travel to high-TB-prevalence country, known TB contact; no TST/IGRA done, abnormal CXR; on steroids and AZA	IFX (14.2)	14.3, none	Cavitary pulmonary TB diagnosed after 1 week of fever, headaches, cough, and night sweats. Positive T-SPOT.TB, sputum culture- and PCR-positive (fully susceptible MTB).	HRZE (2), then HE + MOXI + AMIKA due to significant hepatitis (2); HE + MOXI (61); H + MOXI due to blurred vision (17), no steroids	Cured, pulmonary cavity and persistent blurred vision
12	M, Asian, yes	Crohn's disease, 13.6	No risk factors; negative QFT-GIT, normal CXR; on steroids and AZA	IFX (17.1)	117.2, none	Abdominal TB diagnosed after 6 months of intermittent fever, abdominal pain, weight loss, vomiting, and diarrhea. Positive QFT-GIT, cultures no growth.	HRZE (9), HR (20), no steroids; continued on H when IFX was reinitiated after TB treatment completion	Cured without sequelae
13	M, Caucasian, yes	Crohn's disease, 13.7	No risk factors; indeterminate QFT-GIT; normal CXR; no immunosuppressive medication; received H for 9 months	IFX (15.8)	17.6, none	Miliary TB with upper left lobe consolidation and splenic nodules after 2 weeks of fever, cough, and pleuritic chest pain. Sputum culture- and PCR-positive (fully susceptible MTB).	HRZE + AMIK + LEVO (17), HR (35), steroids (38) for persistent fever and Crohn's flare	Good clinical progress (still on TB treatment)

Table 1. Continued

Patient No.	Gender, Ethnicity, BCG Vaccination History	Underlying Disease, Age at Diagnosis (years)	Risk Factors and Medication at LTBI Screening Prior to Anti-TNF- α Therapy	Anti-TNF- α Drug Used, Age at Initiation (years)	Age at TB Diagnosis (years), New Risk Factors	Details Regarding TB Disease and Diagnostic Tests at Presentation	Anti-TB and Anti-inflammatory Drugs Used, Duration of Treatment (weeks)	TB Outcome
14	M, Caucasian and Caribbean, yes	Crohn's disease and primary sclerosing cholangitis, 13.3	No risk factors; negative T-SPOT.TB, normal CXR; on AZA	IFX (14.9); ADA (15.3)	16.1, none	Lower left lobe and lingula consolidation with multiple parenchymal abscesses, pericarditis, and splenic nodules after 16 weeks of gradually progressive dyspnea, chest pain, cough, fever, weight loss, and night sweats. Positive T-SPOT.TB, lung biopsy tissue PCR-positive.	HRZE + CLARITHRO + AMIK (3), HRE (18), HR (38), no steroids; continued on H when IFX was reinitiated after TB treatment completion	Cured without sequelae
15	F, Caucasian, yes	Ulcerative colitis, 8.0	Born and living in high-TB-prevalence country; no LTBI screening done (years earlier normal CXR and TST 10 mm); did not receive anti-TB treatment	Alternating IFX and ADA (9.3)	10.6, none	Miliary TB, pleural and pericardial effusions after 3 weeks of fever, weight loss, worsening intestinal symptoms, and cough. Streptomycin-resistant MTB in gastric aspirates.	HRZE + quinolones (23), RZ (9), HR (14); steroids and mesalazine for colitis flare; ADA was not interrupted	Cured without sequelae
16	F, Latin American, yes	UCTD, 14.2	Born in high-TB-prevalence country; negative QFT-GIT, normal CXR; on MTX	ETN (15.6)	15.9, none	Pleural TB diagnosed after 1 week of fever and respiratory distress (bilateral basal infiltrates). TST and QFT-GIT negative; sputum culture- and PCR-negative.	HRZE (8), HR (20); steroids (6) for pleuritis; also tacrolimus and MMF	Cured without sequelae
17	M, Caucasian, no	Psoriasis vulgaris guttata, 12.6	No risk factors; no TST/IGRA done, normal CXR; no immunosuppressive medication	ADA (13.7)	14.7, none	Miliary TB with abdominal and CNS involvement diagnosed after 8 weeks of fever, cough, headaches, dizziness, and weight loss. TST 12 mm, positive QFT-GIT, sputum PCR- and culture-positive (fully susceptible MTB).	HRZE (3 days), HRZ + MOXI (16), HR (41), steroids (8) for tuberculomas; ADA reinitiated 12 months after TB treatment completion	Cured without sequelae
18	M, Caucasian, no	Dermatomyositis, 6.0	No risk factors; negative TST, normal CXR; on tacrolimus and steroids	ETN (11.0); ADA (12.5)	17.1, TB contact	Miliary TB diagnosed after 10 weeks of fever, cough, and headaches. Negative TST, sputum culture-positive (fully susceptible MTB), CSF culture- and PCR-negative.	HRZE (9), HR (poor adherence, intermittently 126), steroids (8) for meningeal and chorioid disease	Lost to follow-up 31 months after diagnosis
19	F, Caucasian, no	Chronic anterior uveitis, 7.7	No risk factors; negative QFT-GIT; on MTX	ADA (11.5)	11.9, none	Miliary TB after 5 weeks of fever, weight loss, cough, and diarrhea. Positive QFT-GIT; gastric aspirates culture- and PCR-negative.	HRZE (4), HR (43), steroids (33)	Good clinical progress (still on TB treatment)

Abbreviations: ADA, adalimumab; AMIK, amikacin; AZA, azathioprine; BCG, bacille Calmette-Guérin; CLARITHRO, clarithromycin; CNS, central nervous system; CSF, cerebrospinal fluid; CXR, chest X-ray; ETN, etanercept; E, ethambutol; F, female; H, isoniazid; IGRA, interferon- γ release assay; IFX, infliximab; JIA, juvenile idiopathic arthritis; LTBI, latent tuberculosis infection; LEVO, levofloxacin; M, male; MOXI, moxifloxacin; MMF, mycophenolate mofetil; MTB, *Mycobacterium tuberculosis*; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; OFLO, ofloxacin; PCR, polymerase chain reaction; QFT-GIT, QuantiFERON Gold-in-Tube (Cellestis/Diagen); RIFAB, rifabutin; R, rifampicin; TB, tuberculosis; TNF- α , tumor necrosis factor- α ; T-SPOT.TB (Oxford Immunotec Ltd); TST, tuberculin skin test; UCTD, undifferentiated connective tissue disease; Z, pyrazinamide.

Risk Factors for Tuberculosis and Screening for Latent Tuberculosis Infection

Almost half of the patients ($n = 9$; 47%) had risk factors for TB, including birth in, residence in, or travel to a high-TB-prevalence country; residence in an urban area with high TB incidence; and/or contact with an individual with TB disease before anti-TNF- α therapy was commenced. Screening for LTBI before starting anti-TNF- α therapy, either by TST or IGRA, was performed in 15 patients. Only 1 case had a positive TST result (case 4), and 2 had an indeterminate QuantiFERON Gold-in-Tube (QFT-GIT; Cellestis/Qiagen) result (cases 6 and 13). Two of these cases received a 9-month course of isoniazid prior to starting anti-TNF- α therapy (cases 4 and 13). Importantly, 13 (87%) of those 15 patients were receiving immunosuppressive therapy at the time when the TST and/or IGRA was performed. A chest X-ray was performed in 15 patients prior to commencing anti-TNF- α therapy; only 1 patient had abnormal radiological findings (case 11), comprising a calcified left supraclavicular lymph node without pulmonary changes.

Clinical Presentation of Tuberculosis Disease

The median (IQR) age at diagnosis of TB disease was 14.3 (11.3–15.8) years. Eleven patients were receiving adalimumab, 4 infliximab, and 4 etanercept at the time they were diagnosed with TB disease. The median (IQR) time interval between starting anti-TNF- α therapy and TB being diagnosed was 13.1 (7.1–20.3) months. Six (32%) patients (including 4 who had previously been screened for LTBI) had new risk factors for TB that occurred after commencing anti-TNF- α therapy, comprising recent contact with a TB disease case ($n = 4$) and travel to a high-TB-prevalence country ($n = 2$); in the remaining 13 (68%) patients no new risk factors were identified. In 6 (32%) of the patients, no risk factors for TB were identified either at initiation of anti-TNF- α therapy or subsequently.

All patients presented with predefined severe disease, including miliary TB ($n = 14$; 74%), abdominal TB ($n = 8$; 42%), central nervous system TB ($n = 4$; 21%), pulmonary cavitation ($n = 4$; 21%), pericarditis ($n = 4$; 21%), osteoarticular TB ($n = 2$; 11%), and eye disease ($n = 1$; 5%). Additional, nonsevere disease manifestations comprised peripheral lymphadenitis ($n = 4$; 21%) and pleuritis ($n = 3$; 16%).

The median (IQR) time interval between onset of symptoms and TB diagnosis was 3.3 (2.0–7.3) weeks. One patient was only diagnosed at a postmortem examination (case 10). In 15 (79%) of the cases TB disease was microbiologically confirmed by culture or nucleic acid amplification tests; the remaining 4 (21%) cases were diagnosed with TB disease based on symptoms and radiological findings consistent with TB.

Of the non-confirmed cases, case 8 presented with fever and weight loss, and imaging revealed widespread miliary lesions in the lungs, liver, and spleen; the initial IGRA result was indeterminate, but on re-testing the IGRA result converted to

positive. Case 12 had intermittent fevers and weight loss and abnormal abdominal magnetic resonance imaging (MRI) findings and showed IGRA result conversion. Case 16 presented with fever and respiratory distress, and imaging revealed bilateral basal consolidation and right-sided pleural effusion; both TST and IGRA results were negative. Case 19 presented with fever, cough, weight loss, and diarrhea, chest X-rays showed miliary changes and the IGRA result converted. All 4 patients responded to anti-TB treatment, with complete resolution of their constitutional symptoms.

Performance of Immune-based Tuberculosis Tests at Presentation

In 16 patients 1 or more immune-based TB tests were performed when they presented with TB disease. A TST was performed in 6 patients: 4 had a positive result, while 2 had a negative test result (case 4 already had a positive TST at baseline LTBI screening, but the induration diameter increased from 10 to 30 mm). A QFT assay was performed in 9 patients: 5 had a positive, 2 a negative, and 2 an indeterminate test result. Only 2 patients had a T-SPOT.TB assay (Oxford Immunotec Ltd) performed; both were positive. Therefore, the test sensitivities of TST, QFT assays, and T-SPOT.TB assays at presentation with TB disease were 66.7% (95% confidence interval [CI], 29.6–90.1%), 55.6% (95% CI, 26.6–81.1%), and 100% (95% CI, 29.0–100%), respectively.

Treatment of Tuberculosis Disease

One case was diagnosed postmortem and never received anti-TB treatment (case 10). All remaining 18 patients were initially commenced on quadruple anti-TB treatment with rifampicin, isoniazid, pyrazinamide, and ethambutol; 1 case was switched to another regimen after 3 days (case 17). The median (IQR) duration of anti-TB treatment was 50 (46–66) weeks. Although all isolated *Mycobacterium tuberculosis* strains were susceptible to first-line oral anti-TB agents, second-line drugs were used in 7 cases, either before the sensitivity pattern was known (due to concerns regarding possible drug resistance) or because of toxicity with first-line agents. Four patients experienced drug-induced adverse events related to anti-TB treatment, including significant hepatotoxicity (cases 4, 6, and 11), leukopenia (case 9), persistent blurred vision attributed to ethambutol (case 11), and hearing impairment that resolved after discontinuation of amikacin (case 6). Only 1 patient (case 4) underwent surgical intervention.

Additional Treatment

Anti-TNF- α therapy was discontinued at TB diagnosis in all patients, except for one (case 15). Thirteen patients were commenced on corticosteroids, either as adjunctive treatment for TB disease and/or to treat flare-ups of their underlying immune-mediated disease. Five patients were commenced on other anti-inflammatory drugs to manage their underlying disease.

Outcome

Of the 18 patients who were alive at presentation, 10 (56%) were cured without long-term sequelae, 2 (11%) are still receiving anti-TB treatment with good clinical progress and 5 (28%) were cured but have significant long-term sequelae resulting from TB disease, including pulmonary fibrosis/cavitation (cases 2 and 7), persistent visual problems (case 11), restricted movement in the knee joint (case 4), and spinal instability (case 16). One case was lost to follow-up while still receiving treatment (case 18). Only in 4 patients was anti-TNF- α treatment subsequently reintroduced after completion of TB treatment (cases 7, 12, 14, and 17), without any adverse events.

DISCUSSION

To our knowledge, this is the largest study of TB disease associated with anti-TNF- α therapy in pediatric patients to date. The fact that only 19 cases were reported throughout our network indicates that TB disease may be a less common complication in children receiving anti-TNF- α therapy than in adults, considering the large number of specialist centers involved in this study.

The relatively low number of TB cases may be the result of one or several of the following factors: (1) lower incidence of LTBI in children compared with adults, (2) low background TB prevalence in countries where anti-TNF- α agents are commonly used (which applies to all Northern, Western, and Southern European countries), and (3) successful implementation of LTBI screening prior to commencing anti-TNF- α therapy in the pediatric setting. Of the 32 European countries where ptbnet members are based currently, only 5 are high-TB-prevalence countries: Lithuania (TB notifications in 2018: 49.9/100 000), Moldova (101.8/100 000), Romania (68.5/100 000), Russia (84.1/100 000), and Ukraine (76.7/100 000). The majority of the remaining 27 countries have TB incidences below 10.0 per 100 000 [23]. Given that anti-TNF- α agent use in children was uncommon for the first years after etanercept and infliximab had been approved, relatively few children would have received those drugs before the first report showing a strong association between anti-TNF- α agents and TB disease was published [24]. Following that report, routine LTBI screening prior to anti-TNF- α therapy, both in adults and in children, was incorporated into most national and international guidelines [6, 25].

Recent data from other studies further support the notion that TB disease is a relatively uncommon complication of anti-TNF- α therapy in children and adolescents in Europe. A multicenter study in Finland that included 348 patients with JIA, the majority of whom were children and adolescents at the time anti-TNF- α therapy was commenced, did not identify any cases of TB disease [26]. A German registry-based study that included 3350 pediatric patients with rheumatological conditions who received anti-TNF- α agents also did not identify any patients with TB disease [27]. Recently, a pharmacovigilance

study that combined the data of 15 284 patients with JIA from different registries reported 14 cases of TB disease among children and adolescents receiving anti-TNF- α agents, although no details on disease manifestations were included [28]. Additional data kindly provided by the senior author (N. Ruperto; personal communication) revealed that only 12 of those cases had occurred in Europe, and that cases reported from the Russian Federation, where ptbnet currently only has 1 participating center, accounted for the majority of those cases ($n = 7$), providing further reassurance regarding the robustness of our data.

Our study highlights the great severity of TB disease in children receiving anti-TNF- α therapy, consistent with previous case reports [10, 11, 13–15]. All patients captured by our study presented with severe disease. Three-quarters had miliary TB, which is associated with significant morbidity and mortality. This finding stands in stark contrast to TB disease in immunocompetent individuals, where miliary TB accounts for only about 2% of cases overall [29].

Our study demonstrates the importance of routine LTBI screening in pediatric patients prior to commencing anti-TNF- α therapy, and simultaneously highlights the limitations of immune-based LTBI screening in patients who are already receiving immunosuppressive therapy. Of the 15 cases screened for LTBI among our cohort, only 1 case had a positive test result. Of the remaining 14 patients, only 4 reported additional risk factors for acquiring TB after screening, comprising contact with an individual with TB disease and travel to a high-TB-prevalence country ($n = 3$ and $n = 1$, respectively). In those 4 patients de novo infection acquired after the screening procedure appears likely. Considering the absence of new risk factors after LTBI screening in the remaining 10 cases, reactivation of latent infection is the most likely underlying mechanism. As most of those patients were receiving immunosuppressive treatment (other than anti-TNF- α agents) prior to LTBI screening, it is likely that their screening test results were false negative, as both TSTs and IGRAs rely on the detection of intact antimycobacterial immune responses.

Our data also highlight the suboptimal performance of TSTs and IGRAs as adjunctive tests in the diagnostic workup for suspected TB disease in patients receiving anti-TNF- α therapy. Although the number of test results available was relatively small, resulting in estimates with wide CIs, the data indicate that only approximately half of those patients have a positive QFT assay result, a far lower proportion than previously reported in immunocompetent children [30]. This observation is in concordance with a recent study that showed that anti-TNF- α agents impair the performance of QFT assays substantially [31].

It is well documented that the performance of TSTs is impaired in immunocompromised individuals, including patients with primary or secondary immunodeficiency and patients receiving immunosuppressive therapy [32]. Although some authors have stipulated that the performance of IGRAs

is maintained in immunosuppressed individuals, recent data from in vitro studies show that a range of immunosuppressive agents—including corticosteroids, infliximab, and calcineurin inhibitors—have a detrimental impact on IGRA performance, resulting in false-negative test results in a substantial proportion of patients [31, 33, 34]. Therefore, as highlighted previously [35], we strongly believe that patients with immune-mediated inflammatory conditions should be screened for LTBI at the point when their diagnosis is established before commencing any immunosuppressive medication, as also suggested by a recent guideline [36].

Following initiation of immunosuppressive therapy, patients should be tested simultaneously with a TST and an IGRA to achieve greater sensitivity [35]. In this setting, positive TST or IGRA test results remain useful for management decisions, but negative test results become uninterpretable, as it is currently impossible to determine whether a negative result in this setting reflects the absence of TB infection or, alternatively, a false-negative result caused by the inhibitory action of the immunosuppressive medication.

Current guidelines do not recommend repeat LTBI screening at regular intervals unless the patient develops symptoms consistent with TB or has new risk factors [7, 36]. Notably, nearly one-third of the cases in our cohort had new risk factors after starting anti-TNF- α therapy, comprising known TB contact or overseas travel. Therefore, we believe that it is important to enquire about new TB risk factors at each patient contact during anti-TNF- α therapy. In patients who report a new risk factor, LTBI screening should be performed with a TST and an IGRA. If either test result is positive, LTBI treatment should be commenced once TB disease has been ruled out. In patients with concordantly negative results, clinicians should decide whether or not to start LTBI treatment based on a risk assessment (ie, age of the patient, infectiousness of the index case, intensity of contact).

Only 4 of the patients were recommenced on anti-TNF- α treatment after completion of active TB treatment: 2 continued on isoniazid as prophylaxis, while the remaining patients did not continue on any anti-TB drugs. None of these patients developed recurrence of TB. Given the limited published experience on re-introduction of anti-TNF- α agents after TB disease, it currently remains uncertain whether or not “secondary” prophylaxis is warranted routinely.

The main limitation of this study is its retrospective design, which can result in recall bias. However, it appears unlikely that any of the participating TB experts would not have recalled a patient who developed TB disease while receiving anti-TNF- α agents, as this is a well-known risk factor. Furthermore, our methodology does not allow us to estimate the incidence of TB disease in children receiving anti-TNF- α therapy as the denominator (ie, number of children receiving anti-TNF- α therapy across all centers) is unknown. Additionally, we cannot

exclude that further cases presented to other healthcare institutions that did not participate in this study. However, for many countries one or several leading national pediatric TB centers participated in this study, and it appears unlikely that those centers would not have been contacted for advice if a case had occurred elsewhere in the country. Finally, we cannot exclude that there were additional cases with subclinical TB disease that was not diagnosed or cases who died before a diagnosis was established.

In summary, our data indicate that TB disease may be less common in children and adolescents receiving anti-TNF- α therapy than in adults. However, the data show that children receiving anti-TNF- α therapy who develop active TB are prone to severe TB disease, especially miliary TB. The disease severity and the short- and long-term morbidity observed in those patients underscore the need for robust LTBI screening programs in this high-risk patient population, even in low-TB-prevalence settings. Both patients receiving anti-TNF- α drugs and prescribing physicians need to be aware of the risks related to TB and have a low threshold to initiate targeted investigations should a patient have new risk factors or develop symptoms compatible with TB disease. Additional, prospective research is needed to determine whether regular LTBI screening during anti-TNF- α therapy can help to further reduce the incidence of TB disease in children receiving long-term treatment.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. M. T. has received QuantiFERON assays at reduced pricing or free of charge for TB diagnostics projects from the manufacturer (Cellestis/Qiagen), and has received support for conference attendance from Cepheid. The manufacturers had no influence on the study design, data interpretation, writing of the manuscript or decision to submit the data for publication. The rest of authors do not have conflicts of interest to disclose.

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