Rheumatol Int (2012) 32:2675–2679
DOI 10.1007/s00296-011-2030-8

ORIGINAL ARTICLE

Is it safe to use anti-TNF-α agents for tuberculosis in children suffering with chronic rheumatic disease?

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Received: 7 February 2011 / Accepted: 10 July 2011 / Published online: 26 July 2011

Abstract To determine the incidence of latent tuberculosis infection and evaluate the follow-up protocol of the patients diagnosed with juvenile idiopathic arthritis (JIA) and other chronic rheumatologic diseases treated with anti-TNF-α treatment (etanercept, infliximab, adalimumab) in Turkey, 144 patients were evaluated retrospectively for the development of tuberculosis. Patients were evaluated every 6 months for tuberculosis using history, physical examination, tuberculin skin test (TST), chest radiographs, and, when required, examination of sputum/early morning gastric aspirates for acid-fast bacilli and chest tomography. A tuberculin skin test over 10 mm induration was interpreted as positive. Patients were diagnosed with JIA ($n = 132$), enthesitis-related arthritis (ERA; $n = 14$), juvenile psoriatic arthritis (JPsA; $n = 4$), chronic idiopathic uveitis ($n = 4$), and chronic arthritis related to FMF ($n = 8$). Mean age was 12.25 ± 3.96 years (4.08–19.41 years), mean duration of illness was 5.86 ± 3.77 years (0.66–15 years), and the mean duration of anti-TNF-α treatment was 2.41 ± 1.47 years (0.6–7 years). Anti-TNF-α agents prescribed were etanercept ($n = 133$), infliximab ($n = 30$), and adalimumab ($n = 6$). When unresponsive to one anti-TNF-α therapy, patients were switched to another. There was no history of contact with individuals having tuberculosis. During follow-up, seven patients (4.8%) with positive TST were given INH prophylaxis. One oligoarticular JIA patient (0.69%) diagnosed with secondary uveitis who had been followed for 5 years and had been using infliximab for 2 years, developed a positive Quantiferon-TB test while on INH prophylaxis. He was started on an anti-tuberculosis drug regimen. In conclusion, anti-TNF-α treatment in children with chronic inflammatory disease is safe. Follow-up every 6 months of children on anti-TNF-α treatment with respect to tuberculosis by the pediatric infectious disease department is important to prevent possible complications.

Keywords Juvenile idiopathic arthritis · Anti-tnf alpha treatment · Tuberculosis · Etanercept

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common childhood rheumatic disease and its chronic nature increases morbidity and mortality [1]. The use of biological agents in long-term treatment slows the progress of the disease. However, there are reports suggesting an increased incidence of tuberculosis infection in children with chronic rheumatic disease treated with anti-TNF agents [2]. Tuberculosis is one of the commonest infections causing mortality worldwide [3]. Reactivation of latent tuberculosis infection leads to significant morbidity and mortality, especially in immunsuppressed patients [4]. Physiologically, TNF-α leads to aggregation of neutrophils, eosinophils, and macrophages at the site of infection and plays a critical role in the defense against bacterial and viral infections. It increases cytokine and chemokine secretion and leads to activation of macrophages. It also increases the adhesion of T lymphocytes and augments the proliferation of T and B lymphocytes, with an increase in antigen presentation.

Tumor necrosis factor alpha (TNF-α) plays a critical role in the pathogenesis of chronic inflammatory diseases. It initiates inflammation by activating macrophages, leading to an increase in secretion of TNF-α, interleukin-1, and interleukin-6. It also leads to bone and joint damage by metalloproteinase secretion from chondrocytes, osteoclasts, and fibroblasts [5].

Biological agents developed as TNF-α inhibitors, including etanercept, infliximab, and adalimumab, have become the treatment of choice for those patients who are unresponsive to standard anti-inflammatory and immunosuppressive treatments. These agents have shown effectiveness in rheumatoid arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis. However, the incidence of opportunistic infections caused by microorganisms (Coccidioides, Histoplasma, Aspergillus, Nocardia) especially with tuberculosis and with other bacteria has increased in the patients prescribed these therapies [6]. Patients prescribed anti-TNF-α treatments need to be followed-up closely, especially for latent tuberculosis infection.

The aim of our study was to determine the incidence of latent tuberculosis infection and to evaluate the follow-up protocol of patients diagnosed with JIA and other chronic rheumatic diseases treated with anti-TNF-α in Turkey.

Materials and method

Patients

In total, 144 patients diagnosed with JIA, chronic idiopathic uveitis, or familial Mediterranean fever (FMF) were followed at the Pediatric Rheumatology Outpatient Clinics, Istanbul University, Cerrahpasa Medical Faculty, Turkey. These patients were being treated with anti-TNF-α (etanersept, infliximab, adalimumab) therapies due to unresponsiveness to standard disease-modifying anti-rheumatic drug (DMARD) treatments. To be included, patients had to be prescribed anti-TNF-α therapies for over 6 months. These patients were evaluated retrospectively for the development of tuberculosis.

Patients were evaluated every 6 months for tuberculosis by reviewing the patient history, physical examination, tuberculin skin test (TST), chest radiographs, and, when required, examination of sputum/early morning gastric aspirates for acid-fast bacilli and chest tomography. TST was applied with the Mantoux method in which five tuberculin test units of purified protein derivative was injected intradermally into the volar surface of forearm, and results were assessed as the transverse diameter in millimeters of induration at 48–72 h. A positive result was accepted as a reaction $\geq$10 mm. The diagnosis of tuberculosis was confirmed by the presence of nodular parenchymal infiltration on chest radiographs. Tuberculosis prophylaxis was achieved by 10 mg/kg/day (maximum, 300 mg/day) isoniazid (INH) for 9 months.

Statistical analysis

Data were analyzed using the SPSS software (ver. 11.0 for Windows). Variables are denoted as means $\pm$ standard deviation. Categorized variables are presented as numbers and percentages.

Results

Demographic and clinical data of the patients are presented in Table 1. There were 62 (43%) men and 82 (57%) women. The underlying conditions of the patients were systemic JIA ($n = 19$), polyarticular JIA ($n = 73$), oligoarticular JIA ($n = 22$), enthesitis-related arthritis (ERA; $n = 14$), juvenile psoriatic arthritis (JPsA; $n = 4$), chronic idiopathic uveitis ($n = 4$), and chronic arthritis related to FMF ($n = 8$). The mean patient age was 12.25 ± 3.96 years (4.08–19.41 years), the mean duration of illness was 5.86 ± 3.77 years (0.66–15 years), and the mean duration of anti-TNF-α treatment was 2.41 ± 1.47 years (0.6–7 years). Therapies used prior to anti-TNF-α treatment included prednisolone ($n = 116$), methotrexate ($n = 114$), cyclosporine ($n = 11$), colchicine ($n = 17$), azathioprine ($n = 3$), sulphasalazine ($n = 22$), and thalidomide ($n = 1$). Anti-TNF-α agents included etanercept ($n = 133$), infliximab ($n = 30$), and adalimumab ($n = 6$). If the patient was unresponsiveness to an anti-TNF-α therapy, they were prescribed one of the alternatives. This was often the case for patients with uveitis.

Evaluation of tuberculosis

Patients were reviewed for BCG vaccination via the presence of a scar; there were 20 patients with no scar, 96 patients with one, 39 patients with two, and one patient with three scars. None of the patients had any known contact with a person with tuberculosis. Evaluation prior to anti-TNF-α treatment highlighted 21 (14.5%) patients with latent tuberculosis infection. These individuals were given INH prophylaxis and after 1 month were prescribed anti-TNF-α therapies (11 infliximab, 10 etanercept). Tuberculosis was not observed in any patient after 9 months. Clinical signs related to the primary rheumatic disease also improved with anti-TNF-α treatment. Anti-tuberculosis treatment (INH, rifampicin, pyrazinamide) was started in two polyarticular JIA (1.3%) patients diagnosed with pulmonary tuberculosis. Treatment consisted of three anti-tuberculosis drugs for a period of 6 months. After this,

Table 1 Demographic and clinical features of the patients

Mean age (year), mean (range)	12.25 ± 3.96 (4.08–19.41)	
Sex (*n*, %)	Female (82, 57)	
	Male (62, 43)	
Primary disease (*n*, %)		
	Juvenile idiopathic arthritis (132, 91.7)	Systemic JIA (19, 13.2)
		Polyarticular JIA (73, 50.7)
		Oligoarticular JIA (22, 15.3)
		Enthesitis-related arthritis (14, 9.7)
		Juvenile psoriatic arthritis (4, 2.8)
	Chronic idiopathic uveitis (4, 2.8)	
	Familial mediterranean fever (8, 5.5)	
Mean duration of primary disease (year), mean (range)	5.86 ± 3.77 (0.66–15)	
Anti-TNF-α agent used (*n*, %)		
Etanercept	115, 79.9	
Infliximab	17, 11.8	
Etanercept + Infliximab	6, 4.1	
Infliximab + Adalimumab	4, 2.8	
Etanercept + Adalimumab	2, 1.4	
Mean duration of anti-TNF-α treatment (year), mean (range)	2.41 ± 1.47 (0.5–7)	
Number of BCG scars (*n*, %)		
0	18, 12.5	
1	92, 63.9	
2	33, 22.9	
3	1, 0.7	

JIA juvenile idiopathic arthritis, *FMF* familial mediterranean fever, *TNF* Tumor necrosis factor

patients with clinically active rheumatic disease were prescribed etanercept. Tuberculosis symptoms were not evident in patients whose conditions were relieved with anti-TNF-α treatment. These patients were evaluated every 3 months with gastric aspirate cultures for tuberculosis; no organism was isolated.

During follow-up, seven patients (4.8%) with a positive TST were given INH prophylaxis (Table 2). None of these patients had any pathological finding on their chest radiograph. No organisms were evident in the culture of gastric aspirates of these patients. INH prophylaxis was prescribed for 9 months during anti-TNF-α treatment.

The Quantiferon-TB test was positive in a 13-year-old man diagnosed with oligoarticular JIA and secondary uveitis. This patient had been followed for 5 years and prescribed infliximab for 2 years. He was also prescribed antituberculosis therapies (INH, rifampicin, pyrazinamide) due to a positive TST. After 18 months of treatment, all signs related to tuberculosis infection disappeared. Also, hepatotoxicity was not observed during tuberculosis prophylaxis or treatment.

Discussion

Clinical improvement with the use of biologic agents treating rheumatic disease is accompanied by an increased risk of infection. The primary cytokines in the defense against tuberculosis are TNF-α, secreted by activated macrophages and T lymphocytes, and IFN-γ secreted by CD4, CD8, and NK cells. These two cytokines lead to granule formation and provide tuberculostatic activity. Because of this, the incidence of reactivation and development of tuberculosis are increased in patients prescribed anti-TNF-α treatment [7–9]. Several reports have suggested the risk of tuberculosis was increased with infliximab compared with etanercept (1.9/1–5.9/1) therapy [10, 11]. The median time from treatment initiation to diagnosis of tuberculosis was also shorter (17/48 weeks) with infliximab [8, 10]. The reason behind the differences was associated with the different receptor affinities of these two agents, infliximab showing affinity to TNF receptor 1 (TNFR1) and etanercept to TNFR2. TNFR2 plays a less significant role in the defense against tuberculosis [6]. It has been reported that infliximab and

Table 2 Clinical features of the patients administered INH prophylaxis during anti-TNF alpha treatment

Patient no	Age (year)	Sex	Diagnosis	Time of diagnosis (year)	TNF α therapy	TNF α treatment duration (year)	BCG scar number	TST at onset (mm)	Chest X ray at onset	Previous INH prophylaxis	Control TST (mm)	Control CXR	Gastric aspirate AFB	Thorax CT
1	14.66	F	P JIA	5.41	Eta	3.25	2	6	N	–	11	N	–	N
2	10.5	F	Üveitis	3	İnf, Ada, Eta	1.8	0	0	N	–	15	N	–	N
3	14	M	P JIA	2.5	İnf	1.1	1	9	N	–	15	N	–	N
4	15.41	M	ERA	3	Eta	1.8	2	20	N	+	19	N	–	N
5	11.83	F	P JIA	1.92	Eta	1.83	2	0	N	–	13	N	–	N
6	16.83	M	S JIA	13	Eta	3.5	2	12	N	+	20	N	–	N
7	11.91	F	P JIA	0.83	Eta	0.75	2	0	N	–	15	N	–	N

TNF tumor necrosis factor, *BCG* Bacillus Calmette–Guerin, *INH* isoniazid, *TST* tüberkülin cilt testi, *AFB* acid-fast bacilli, *CT* computed tomography, *JIA* juvenile idiopathic arthritis, *P* polyarticular, *S* systemic, *ERA* enthesitis-related arthritis, *Eta* etanercept, *İnf* infliximab, *Ada* adalimumab

adalimumab decreased IFN-γ production by 65–70%, in contrast to etanercept, which produced no significant effect [12]. Suppressed IFN-γ production in patients on infliximab and adalimumab therapy increases the risk of tuberculosis reactivation.

A study reported from Spain, with a similar rate of tuberculosis (25/100,000) to Turkey, followed 4,102 patients using anti-TNF-α agents due to chronic inflammatory disease. It reported that the rate of development of tuberculosis after a 4-year follow-up was 0.83% [13]. Cagatay et al., from Turkey, reported the rate of tuberculosis development to be 0.85% in patients using anti-TNF-α agents [14]. In the present study, the rate of tuberculosis development was 0.69%, indicating no increase in incidence. This could be attributable to the close follow-up of our patients by rheumatology and infectious disease departments with respect to latent tuberculosis infection and its effective treatment.

It was found effective to closely follow patients using biological agents with respect to latent tuberculosis and to give appropriate treatment [13, 15]. Several guidelines recommend asking for a history of contact with anyone with tuberculosis, and to perform a tuberculin skin test and chest X-rays [16–18]. In countries with low rates of INH resistance, INH for 9 months is recommended for the prophylaxis of latent tuberculosis infection. Alternatively, rifampisin is used for 4 months [7, 19, 20]. It is recommended to start anti-TNF-α therapy 1 month after the initiation of prophylaxis [13, 17, 20].

TST is the most commonly used diagnostic for tuberculosis infection. It has a delayed onset sensitivity reaction by T lymphocytes against the tuberculin antigen via intradermal injection. However, the sensitivity and reliability of the test are affected by the immunosuppressive therapy and the underlying inflammatory disease [21, 22]. Sensitivity can be improved by accepting the positivity limit of the TST test as 5 mm of induration and repeating a negative test after 7–10 days.

Induration of 5 and 10 mm is accepted as a positive result in several guidelines [18, 19]. Accepting 5 mm of induration as a positive result would lead to more patients receiving INH prophylaxis and decrease the rate of development of tuberculosis. There is no defined limit of TST positivity in children. In Turkey, the rate of tuberculosis is 27/100,000. The risk of tuberculosis is considered moderate and BCG vaccination is included in the country's immunization schedule. Thus, in our analysis, we accepted 10 mm of induration as a positive test due to the possibility of the booster effect of a previous BCG vaccination. This leads to no increase in the rate of tuberculosis. In a further study involving 36 children, 10 mm of induration was again accepted as positive and the results showed no development of tuberculosis [23]. Interpreting an induration of 10 mm as a positive result is appropriate for surveillance of tuberculosis in children when compared with adults.

It has been suggested that increased TNF-α levels during rheumatic diseases decrease the TST response, and during anti-TNF-α treatment the TST response recovers. This may be due to the suppression of disease activity by the treatment and decreased need of concomitant immunosuppressive therapy. Cagatay et al. reported that the TST result, after the first year of anti-TNF-α treatment, was significantly higher than that at the onset of treatment [24]. Further studies are needed to aid the interpretation of the TST results during anti-TNF-α treatment with respect to latent tuberculosis infection.

Tests measuring IFN-γ secreted by the T lymphocytes in vitro after a challenge with specific antigens of tuberculosis are being used for the diagnosis of latent tuberculosis infection. These antigens, called "early secreted antigenic target 6 (ESAT6)" and "culture filtrate protein 10 (CFP10)," are not produced by the mycobacteria involved in BCG vaccine or by the nontuberculous mycobacteria. Tests with a higher sensitivity and specificity than TST would help in preventing unnecessary prophylaxis due to false positive results and thus avoid possible side effects associated with prophylactic treatment. Studies are needed to investigate the use of these tests in patients on anti-TNF-α therapy.

In conclusion, anti-TNF-α agents used in the treatment of chronic inflammatory disease resulted in an improvement in the control of disease progression. It is crucial to evaluate patients on anti-TNF-α treatment with respect to tuberculosis by a thorough history, TST, and chest X-rays, and to effectively treat patients with latent tuberculosis infection. According to our study, anti-TNF-α treatment in children with chronic inflammatory disease seems to be safe and is not associated with an increased risk compared with adults.

Follow-up of children on anti-TNF-α treatment with respect to tuberculosis every 6 months by the pediatric infectious disease department is important in preventing possible complications. Multicenter studies with larger sample sizes are needed to further investigate the relationship between anti-TNF-α treatment and tuberculosis in children.

Conflict of interest None.

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