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Original article

Latent tuberculosis infection screening in juvenile idiopathic arthritis patients preceding anti-TNF therapy in a tuberculosis high-risk country

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ABSTRACT

Objectives: To evaluate, in an endemic country, the long-term efficacy of latent tuberculosis infection (LTBI) screening and primary prophylaxis in patients with JIA receiving TNF blockers.
Methods: This was a retrospective cohort that included JIA patients eligible to anti-TNF therapy. Patients were screened for LTBI prior to anti-TNF using tuberculin skin test (TST), chest X-ray and history of exposure to TB. Subjects were regularly followed at 2-month intervals.
Results: Sixty-nine JIA patients with current age of 17.4 ± 5.8 years, mean disease duration of 5.0 ± 4.9 years were included. Forty-seven patients received a single anti-TNF, while 22 patients switched to another anti-TNF once or twice: 57 were treated with etanercepte, 33 patients with adalimumab and 3 infliximab. LTBI screening was positive in three patients: one had TST-positive and history of TB exposure and two had solely TST-positive. No active TB was diagnosed during the study period (median of follow-up was 3.8 years).
Conclusion: Long-term evaluation revealed that LTBI screening and primary prophylaxis before anti-TNF treatment was effective in a high-risk country and TST was the most sensitive parameter to identify these patients.

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Rastreamento da infecção latente por tuberculose em pacientes com artrite idiopática juvenil previamente à terapia anti-TNF em um país de alto risco para tuberculose

Palavras-chave:
Artrite idiopática juvenil
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RESUMO

Objetivo: Avaliar, em um país endêmico, a eficácia em longo prazo do rastreamento à procura de infecção latente por tuberculose (ILTB) e profilaxia primária em pacientes com AIJ em uso de bloqueadores do TNF.

Métodos: Trata-se de uma coorte retrospectiva que incluiu pacientes com AIJ elegíveis para a terapia anti-TNF. Os pacientes foram rastreados à procura de ILTB previamente ao uso de anti-TNF por meio do teste tuberculínico (TT), radiografia de tórax e história de exposição à TB. Os indivíduos foram acompanhados regularmente em intervalos de dois meses.

Resultados: Incluíram-se 69 pacientes com AIJ com idade atual de 17,4 ± 5,8 anos, com média de duração da doença de 5 ± 4,9 anos; 47 pacientes receberam um único anti-TNF, enquanto 22 foram transferidos para outro anti-TNF uma ou duas vezes: 57 foram tratados com etanercepte, 33 com adalimumabe e três com infliximabe. O rastreamento à procura de ILTB foi positivo em três pacientes: um era TT positivo e tinha história de exposição à TB e dois apenas eram TT positivo. Não foi diagnosticado caso de TB ativa durante o período de estudo (mediana de seguimento de 3,8 anos).

Conclusão: A avaliação em longo prazo revelou que o rastreamento à procura de ILTB e a profilaxia primária antes do tratamento com anti-TNF foram eficazes em um país de alto risco para TB e o TT foi o parâmetro mais sensível para identificar esses pacientes.

Introduction

Juvenile idiopathic arthritis (JIA) is the most prevalent chronic rheumatic disease in children and adolescents.[1,2] The use of biologics, particularly TNF-α antagonists, led to a great improvement in the treatment and prognosis of JIA patients resistant to standard therapy.[2]

The main concern regarding anti-TNF therapy, as well as other biological agents, is the greater susceptibility to infections. Of note, the increase in the incidence of active tuberculosis (TB) among patients in use of TNF blockers brought up the attention to the physiological function of TNF-α in the immune response, especially in maintaining the latency of TB bacilli in granulomas.[2–4]

Moreover, rheumatic diseases themselves have been associated with a greater risk for TB independent of the use of TNF blockers.[3] A recent population-based study reported that TB risk is twice higher in JIA patients.[5] Notably, Brazil is an endemic country for TB, and the frequency of latent tuberculosis infection (LTBI) was described to double in JIA patients after one year of therapy with methotrexate.[6]

Ayaz et al. suggested that prevention of TB in JIA children receiving anti-TNF is efficient in a moderate risk country for tuberculosis.[1] However, the follow-up period was short and the study was limited to etanercept precluding a definitive conclusion about their finding. Another study from Turkey extended their finding to three classes anti-TNF agents and suggested that these drugs were not associated with an increased risk compared to adults.[2]

Therefore, the objective of the present study was to evaluate, in a high TB risk country, the long-term efficacy of LTBI screening and primary prophylaxis in patients with JIA receiving three classes of TNF blockers. We also evaluated disease and therapy parameters pre-anti-TNF therapy.

Study population and methods

This was a retrospective cohort that included 69 JIA patients (International League Against Rheumatism – ILAR classification criteria)[7] regularly followed in the Rheumatology outpatient clinic of a tertiary university hospital of Sao Paulo city, Brazil, from November 2007 to April 2015, and who were refractory to non-biologic disease-modifying antirheumatic (DMARDs) drugs and eligible to anti-TNF therapy. All subjects were regularly followed at 2-month intervals, with the possibility of unscheduled visits when necessary.

The ethics committee of our University Hospital approved the protocol.

LTBI screening

All patients were screened for LTBI prior to the introduction of anti-TNF treatment according to Brazilian national recommendations.[8,9] Screening tests included: tuberculin skin test (TST), chest X-ray and history of exposure to TB. A positive result for TST was considered when ≥5 mm. TST was performed according to Mantoux method using 0.1 mL of purified protein derivative (PPD) RT 23 antigen, equivalent to two tuberculin units,[8] injected intradermally into the volar surface of the forearm and results were assessed as the transverse diameter in millimeters of induration at 48–72 h.

Chest radiograph was evaluated for signs of previous TB (fibrotic lesions), and atypical findings were reassessed by computerized chest tomography. Exposure to TB was defined as present or past household, occupational and school contact with known TB cases at any time. When diagnosis of LTBI was established, treatment with isoniazid (INH) at 5 mg/kg (up to 300 mg/day) was started for 6 months, according to national guidelines.[8] Anti-TNF treatment was prescribed after 1 month of INH.

During follow-up, patients underwent a new TST in case of extended (>12 months) interruptions of the anti-TNF therapy or clinical suspicion of active TB.

Clinical and laboratorial assessments, disease scores and therapy of JIA patients

Demographic and clinical data were registered in an ongoing electronic protocol. Clinical assessments of JIA patients included: number of active joints (swelling within a joint, or limitation in the range of joint movement with joint pain or tenderness), number of limited joints, patient and physician global assessment of arthritis activity measured in cm on a 10 cm horizontal visual analogy scale (VAS) and validated Brazilian version of Childhood Health Assessment Questionnaire (CHAQ) that evaluated functional ability.[10] Disease activity in patients up to 18 years old was assessed by the Juvenile Arthritis Disease Activity Score (JADAS-27), defined as the linear sum of the scores of 4 components [physician global assessment of disease activity; parent/patient global assessment of well-being; number of active joints; and ESR] (range: 0–57 points).[11] Patients older than 18 years old were evaluated for disease activity using Disease Activity Score 28-Joint Counts (DAS28), which combines information from swollen joints, tender joints, acute phase response and patient self-report of general health into one continuous measure[12] and for functional disability using the validated Brazilian version of Health Assessment Questionnaire (HAQ).[13]

Laboratorial assessment included erythrocyte sedimentation rate (ESR) (Westergreen method), C-reactive protein (CRP) (nephelometry), antinuclear antibody (ANA) positivity by indirect immunofluorescence in HEp-2 cells (Euroimmun AG, Alemanha), rheumatoid factor (RF) by ELISA (INOVA Diagnostics Inc., San Diego, EUA).

Current treatment with non-steroidal anti-inflammatory drugs (NSAIDs), prednisone, DMARDs (methotrexate and leflunomide), immunosuppressive drugs (cyclosporine) and anti-TNF agents (adalimumab, etanercept and infliximab) were determined. All patients received anti-TNF therapy at standard doses.

Statistical analysis

Categorical variables were compared using Fisher's exact test. Continuous variables were presented as mean ± standard deviation or median (range) and compared using a two-sided Student's *t*-test or Mann–Whitney *U*-test. The statistical significance was set at p value <0.05.

Table 1 – Baseline demographic and clinical data of JIA patients before anti-TNF therapy.

Variables	JIA patients ($n = 69$) n (%)
JIA subtypes	
Systemic JIA	19 (28)
Polyarticular JIA	31 (45)
Oligoarticular JIA	12 (17)
Enthesitis-related arthritis	6 (9)
Juvenile psoriatic arthritis	1 (1)
Demographic data	
Male gender	24 (35)
Age of JIA diagnosis, years	7.3 (1–19.8)
Age at anti-TNF start, years	13.3 ± 5.9
Duration of disease until anti-TNF start, years	2.9 (0.3–24.6)
Follow-up duration since anti-TNF start, years	3.8 (0.4–10.3)
Positive ANA	20 (29)
Positive RF	9 (13)
Disease activity	
CHAQ/HAQ	0.875 (0–2.375)
JADAS	12.5 (0–43)
DAS28	3.2 (1.9–6.1)
Physician global VAS	4.1 ± 2.1
Patient/parent global VAS	4.3 ± 3.0
ESR, mm/1st h	31 (2–75)
CRP, mg/L	11.5 (0.1–332.9)
Treatment	
NSAIDs	63 (91)
Prednisone	31 (45)
≥0.5 mg/kg/day	10 (14)
DMARDs	65 (94)
Methotrexate	60 (87)
Mean dose, mg/week	25 (5–50)
Leflunomide	23 (33)
Cyclosporine	13 (19)

JIA, juvenile idiopathic arthritis; TNF, tumor necrosis factor; ANA, antinuclear antibodies; RF, rheumatoid factor; CHAQ, Childhood Health Assessment Questionnaire; HAQ, Health Assessment Questionnaire; JADAS, Juvenile Arthritis Disease Activity Score; DAS28, Disease Activity Score 28-Joint Counts; VAS, visual analog scale; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NSAIDs, non-steroidal anti inflammatory drug; DMARDs, disease modifying anti-rheumatic drug.

Results

Sixty-nine JIA patients were included, with 19 (28%) systemic onset, 31 (45%) polyarticular, 12 (17%) oligoarticular, 7 (10%) enthesitis-related arthritis and 1 (1%) juvenile psoriatic arthritis. All patients were vaccinated with BCG during neonatal period. The median age of JIA diagnosis was 7.3 years (1–19.8), 24 (35%) were males and the mean disease duration until anti-TNF initiation was 2.9 years (0.3–24.6). At baseline, JADAS was 12.5 (0–43) and DAS28 3.8 (1.9–6.1). Sixty-three (91%) patients were under NSAIDs, 31 (45%) prednisone, 60 (87%) methotrexate, 23 (33%) leflunomide and 13 (19%) cyclosporine (Table 1).

Forty-seven (68%) patients were treated with a single anti-TNF agent, while 22 (32%) patients switched to another anti-TNF agent once or twice. At the end of follow-up,

Table 2 – Clinical data of JIA patients regarding anti-TNF therapy.

Variables	JIA patients ($n = 69$) n (%)
Anti-TNF agent	
Adalimumab	12 (17)
Etanercept	35 (51)
Etanercept → adalimumab	17 (25)
Adalimumab → etanercept	2 (3)
Etanercept → infliximab	1 (1)
Infliximab → etanercept → adalimumab	1 (1)
Etanercept → adalimumab → infliximab	1 (1)
Duration of anti-TNF exposure, months	29.6 (0.5–99.7)
Adalimumab, months, median (range)	21.4 (2.3–73.5)
Etanercept, months, median (range)	25.6 (0.5–95)
Infliximab, months, median (range)	1.9 (0.03–8.5)

JIA, juvenile idiopathic arthritis; TNF, tumor necrosis factor.

57 (83%) patients had received etanercept, 33 (48%) adalimumab and 3 (4%) infliximab. The median duration of treatment was 2.5 years (Table 2).

During follow-up, TST was repeated in two patients due to a long period (>1 year) of anti-TNF interruption, and TST conversion was observed in one of them (0–14 mm). At the end of study, LTBI screening was positive in three (4%) JIA patients. Patient 1 was a 9-year-old boy with polyarticular JIA onset with TST-positive (11 mm) and history of TB exposure at adalimumab introduction. Time interval between disease onset and anti-TNF therapy start was 1.6 year. Concomitant treatment included NSAID, methotrexate (20 mg/week) and leflunomide (10 mg/day). He was still under adalimumab therapy by the end of this study, with an exposure duration of 1.4 year. Patient 2, female, presented enthesitis-related arthritis and was 17 years old at etanercept onset, 2.9 years after JIA diagnosis. At screening, she had solely TST-positive (12 mm). She also received NSAID and methotrexate (25 mg/week), and was still under exposure by the end of the study, totalizing 0.4 year of follow up. Finally, patient 3 was an 11-year-old girl by the start of adalimumab, with a polyarticular JIA and refractory uveitis. She had been previously exposed to infliximab and etanercept (total time of exposure of 2.1 years) with a negative initial LTBI screening. TST was repeated prior to adalimumab introduction, resulting in 14 mm, although the patient was asymptomatic and did not present epidemiology for TB. She was in current use of prednisone (20 mg/day), methotrexate (20 mg/week) and cyclosporine (2.5 mg/kg/day) at adalimumab onset and was under anti-TNF therapy up to the end of follow up, exposure time after positive TST of 6 years.

The comparison between patients positive and negative for TST showed no difference in demographic characteristics, clinical and laboratory data, as well as in treatment ($p > 0.05$).

LTBI patients were treated with isoniazid (5 mg/kg/day, up to 300 mg/day) for 6 months, and none of them had TB. No active TB was diagnosed during the study period.

Discussion

This was the first study in the literature to demonstrate in an endemic country effective screening and primary prophylaxis for long-term risk of LTBI in JIA patients under anti-TNF therapy. In this population, TST was the most sensitive parameter to identify LTBI.

We demonstrated herein that only 4% of JIA patients required primary prophylaxis for positive screening test, a frequency much lower than the observed in the adult population in our Biological Unit (30%).[4] Our findings are in accordance to TB estimates registered in the literature that show a higher incidence of this infection in the adult population.[14,15]

TST was the single most sensitive screening test for LTBI, while in adults with rheumatoid arthritis TST and history of TB exposure were both relevant in the screening.[4] This latter parameter was uniformly absent in Turkish children with chronic rheumatic diseases.[2] We cannot exclude, however, that this low incidence may be also associated to the use of etanercept by the majority of the patients. The distinct mechanism of this drug on TNF receptor inhibition compared to monoclonal antibodies results in a less deleterious effect in mycobacteria immunity.[3] However, none of the patients that used adalimumab or infliximab presented TB activation.

Unexpectedly, the frequency of positive LTBI screening in children of the present study was lower than data from Turkey, a country with lower TB risk than Brazil.[1,2] In fact, in this country the official notification rate is 27/100,000,[1] whereas in Brazil this rate is 39.5/100,000 and in São Paulo city it is 53.2/100,000.[16] The reported use of multiple BCG doses by approximately 1/4 of their studied population and a single dose in our vaccination program may account for this finding, since it is known that BCG vaccination may increase TST positivity.[17] The lack of use of interferon-gamma release assay (IGRA) test does not explain this difference since TST was the standard screening method in the three reports.[1,2,4] Moreover, IGRA sensitivity in immunosuppressed subjects was demonstrated to be underestimated in high TB incidence regions.[6,18]

False negative TST results are unlikely since we used a lower TST cut-off than the reported in the two studies from Turkey.[1,2] Glucocorticoid use may also hamper TST response,[19] but Kilic et al. reported that the majority of the patients were under this therapy[2] contrasting to less than half of JIA patients in the present study. However, no data is provided regarding moderate/high dose glucocorticoid, a finding observed in more than 10% of our patients that may have reduced TST positivity. The complete absence of active TB during the long-term observation period of the present study makes this hypothesis highly improbable.

Disease activity was reported as an additional factor to affect the accuracy of TST response, particularly in adult rheumatoid arthritis.[20] This analysis was hampered in the present study because all patients presented active disease.

We confirmed previous observation of our group in the same tertiary hospital that LTBI screening was effective in adult rheumatoid arthritis (RA) patients[4] and two reports from Turkey in children prior to anti-TNF treatment.[1,2] We extended this observation demonstrating that this strategy is also effective in children of high TB risk country.

Finally, we demonstrate herein that a shorter course of prophylaxis is highly effective to prevent TB activation in our population. This treatment for LTBI comprises of 6 months of INH according to the national standard of practice,[8] contrasting with longer treatments performed in other countries.[1,2,21]

In conclusion, LTBI screening and short course INH primary prophylaxis before anti-TNF treatment in JIA patients of a high TB risk country appear to be effective in preventing TB activation, although more studies with larger cohorts and longer follow-up period are necessary to confirm these findings. TST was the most sensitive parameter to identify patients eligible for LTBI treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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