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Review article

Treatment of latent tuberculosis in patients with juvenile rheumatic diseases: a systematic review



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ABSTRACT

Introduction: Children and adolescents with rheumatic diseases receiving TNF blockers are at risk for the activation of latent *Mycobacterium tuberculosis* infection (LTBI). Although LTBI treatment is indicated in this group, there are different therapeutic regimens in the literature, without a definite consensus.

Objectives: To review in the literature therapeutic schemes used and indicated for the treatment of LTBI in these patients.

Methods: Systematic review of the literature, using health databases, selecting studies that addressed the treatment of LTBI in patients with juvenile rheumatic diseases using TNF blockers, from 1990 to 2015. All study designs were considered.

Results: A total of 162 studies were identified through the electronic databases and one was found through a manual search by the author, totaling 163 articles. We excluded studies that did not meet the mentioned inclusion criteria, and included a retrospective cohort study and two prospective cohort studies. The three studies addressed treatment with isoniazid (INH) for 9 months and one of them also addressed INH treatment associated with rifampicin for 3 months.

Conclusions: Only one case of LTBI activation was observed; there was good treatment adherence and absence of complications during follow-up. More studies are necessary to evaluate the response to the other available therapeutic regimens, with better tolerability assessment and a larger sample. However, the results showed that INH therapy for 9 months and INH therapy plus rifampicin for 3 months had a low rate of LTBI activation and complications.

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Tratamento da tuberculose latente em pacientes com doenças reumáticas juvenis: uma revisão sistemática

R E S U M O

Palavras-chave:

Doenças reumáticas
Criança
Adolescente
Fatores biológicos
Tuberculose latente

Introdução: Crianças e adolescentes com doenças reumáticas em terapia anti-TNF- α são grupo de risco para ativação da infecção latente por *Mycobacterium tuberculosis* (ILTb). Embora o tratamento da ILTB seja indicado nesse grupo, existem diferentes esquemas terapêuticos na literatura, sem um consenso definido.

Objetivos: Revisar na literatura esquemas terapêuticos usados e indicados para o tratamento da ILTB nesses pacientes.

Métodos: Revisão sistemática da literatura, nas bases de dados em saúde, selecionaram-se estudos que abordaram o tratamento da ILTB em pacientes reumáticos juvenis em uso de anti-TNF- α , de 1990 a 2015. Todos os desenhos de estudo foram considerados.

Resultados: Foram identificados através das bases de dados eletrônicas 162 estudos e um foi encontrado por meio de busca manual do autor, total de 163. Foram excluídos os estudos que não atenderam aos critérios de inclusão referidos, incluídos um estudo de coorte retrospectiva e dois de estudos de coorte prospectivas. Os três estudos abordaram o tratamento com isoniazida (INH) por nove meses e um deles abordou também o tratamento com INH associado a rifampicina por três meses.

Conclusões: Foi observado apenas um caso de ativação da ILTB; uma boa adesão ao tratamento e ausência de complicações durante o acompanhamento. Mais estudos são necessários para avaliar a resposta aos outros esquemas terapêuticos disponíveis, com melhor avaliação da tolerabilidade e maior amostra. Porém, os resultados mostraram que a terapia com INH por nove meses e a terapia com INH mais rifampicina por três meses têm baixo índice de ativação e complicações.

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Introduction

Even though the overall incidence of tuberculosis (TB) decreased by 18% in relation to the year 2000 when the Millennium Development Goals were established, TB is the fifth largest cause of death worldwide, when one includes deaths from TB in individuals infected with the human immunodeficiency virus (HIV). However, the possibility of cure is high when early diagnosis and treatment occur.¹

It is estimated that 9.6 million people had the disease in 2014, with one million children, although 37% of cases were not diagnosed or reported. Additionally, TB was responsible for the deaths of 1.5 million individuals in 2014, of which 140,000 were children.²

In Brazil, the aim of reducing TB incidence, prevalence, and mortality by half in 2015 compared to 1990, as defined by the World Health Organization (WHO)¹ has been met. However, the country remains in the group of 22 countries with the highest rates of the disease. Brazil has an incidence of TB of 33.8³ and a mortality of 2.6 per 100,000 inhabitants.^{4,5}

In the state of Bahia, the incidence of TB was 30.5 new cases per 100,000 inhabitants and mortality of 2.1 per 100,000 inhabitants in 2014. São Paulo, Rio de Janeiro and Bahia are the three states with the highest number of TB cases in the country and together they were responsible for 44.5% of new cases in 2013.⁶

The WHO defines latent *Mycobacterium tuberculosis* infection (LTBI) as a state of persistent immune response to M.

tuberculosis antigen stimulation with no evidence of clinical manifestations of active TB. It is estimated that one-third of the world's population is infected by this bacterium. In Brazil, the incidence is 46 per 100,000 individuals. Despite the absence of symptoms, there is a risk that these patients will develop TB disease, especially in the first two years after the primary infection. Activation occurs in 5–10% of cases.⁷

Risk factors for the development of active TB include: HIV infection, contact with a case of pulmonary TB, therapy with TNF blockers, dialysis, organ transplantation or blood transfusion, and silicosis.⁸

The evaluation of contact with TB cases is important for the screening of LTBI. The Ministry of Health considers as contact every person living in the same environment as the index case at the time of TB diagnosis, and the assessment of the degree of contact exposure should be individualized, considering the form of the disease, the environment, and the time of exposure. Contacts under the age of five, people with HIV-AIDS and those at high risk should be considered as priorities in the process of contact evaluation and LTBI treatment.⁹

Thus, adequate screening and diagnosis are very important to prevent LTBI activation. The most widely used diagnostic methods include the tuberculin skin test (TST), Interferon-Gamma Release Assays (IGRAs),¹⁰ and chest X-rays.¹¹ TST is the most often used method, although the positive result can also occur due to active disease or previously resolved infection.^{12,13}

Considering that the risk of developing active TB is higher in individuals with impaired immune response due

Table 1 – Keywords used in article search.

Palavras-chave	Keywords
Adolescentes	Adolescents
Crianças	Children
Tuberculose Latente	Latent Tuberculosis
Doenças reumáticas	Rheumatic Diseases

to illness or immunosuppressive treatment, patients with inflammatory/autoimmune diseases using immunosuppressive medication need to undergo LTBI screening.¹³ Of these drugs, TNF blockers stands out. TNF- α is an essential cytokine for macrophage activation, leukocyte recruitment to the site of infection and granuloma formation and is more concentrated in organs affected by rheumatic diseases. TNF blockers inhibit this cytokine and, consequently, inhibit its inflammatory effects. This action of these drugs is very important in the treatment of rheumatic diseases; however, the inhibition of TNF- α -mediated inflammatory pathways may leave users susceptible to infections.^{12,13}

The Brazilian Registry of Biological Therapy Monitoring in Rheumatic Diseases – BiobadaBrazil – in its 2014 report, showed that the most important adverse events found in rheumatic patients submitted to biological therapies were infections and infestations. There were 19 cases of TB in the 2464 patients using biological agents and controls, and only one patient was in the control group (patients with rheumatoid arthritis, juvenile idiopathic arthritis, or ankylosing spondylitis, not taking biological agents). The analysis of the report also shows that the incidence of TB was 101/100,000 patient-years, higher than that found in the Brazilian population, which is 37.2 cases/100,000 person-years.¹⁴

Additionally, it is known that the frequency of TB is higher in rheumatic patients than in the general population, and this risk increases with the use of TNF blockers.^{13,15}

Therefore, the present article aims to review in the literature the therapeutic regimens used to treat latent tuberculosis in pediatric patients with rheumatic diseases and to identify the most appropriate therapeutic regimens for these patients.

Methods

Literature search

This is a systematic review. The sources of information used for the literature search were health databases such as Medline (Pubmed) (www.ncbi.nlm.nih.gov/pubmed), Scopus (Elsevier) (www.scopus.com), The Cochrane Library (www.cochranelibrary.com), Web of Science (ISI) (webofknowledge.com), LILACS (Bireme) (www.bireme.br), Scielo (www.scielo.org) and CAPES Portal (www.periodicos.capes.gov.br).

The keywords in Portuguese are Descriptors in Health Sciences (DeCS), as well as the corresponding terms in English (Table 1). English-language analogs were selected from MeSH. The search was performed in December 2015.

In Medline (Pubmed), the keywords and the equivalent terms in the English language were cross-referenced in the advanced search using the Boolean operators “AND” and “OR”,

as follows: ((Latent tuberculosis) [All Fields] AND Rheumatic diseases [All Fields]) AND (Children [All Fields] OR Adolescents [All Fields]). Combined searches were performed using (#) prior to each set number in the query.

In the Cochrane Library database, keywords, equivalent terms, and terms widely used in the English language were cross-referenced in the advanced search using Boolean operators “AND” and “OR” as follows: Latent Tuberculosis (Search all text) AND [Rheumatic Diseases (Search All Text)] AND [children (Search all text) OR adolescents (Search all text)]. Combined searches were performed using (#) prior to each set number in the query.

In the LILACS database, keywords, equivalent terms, and terms widely used in the English language were cross-referenced in the advanced search using Boolean operators “AND” and “OR” as follows: [Latent tuberculosis (Words)] and [Rheumatic diseases (Words)] and [children (Words) OR adolescents (Words)]. In the search settings, the English language was selected as the “Interface language”.

As for the advanced search in the CAPES Portal, as there are only two fields to be filled out for the search, it was carried out as follows: {[Latent tuberculosis (any/contains)] AND [Rheumatic diseases (any/contains)]}. To refine the search, the date of publication determined included the last 20 years; for the topic “type of material”, we selected articles and the chosen language was English.

In the Scielo site, keywords, equivalent terms, and terms widely used in the English language were cross-referenced in the advanced search using Boolean operators “AND” and “OR” as follows: (Latent Tuberculosis) [all indices] AND (Rheumatic diseases) [all indices] AND (Children [all indices] OR Adolescents [all indices]).

In the Web of Science site, keywords, equivalent terms, and terms widely used in the English language were cross-referenced in the advanced search using Boolean operators “AND” and “OR” and the “TS” field label, which represents the topic, and comprises all records that contain the search terms in the fields of the title, abstract, or author’s keywords. The search was carried out as follows: [TS=(Latent Tuberculosis)] AND [TS=(Rheumatic diseases)] AND [TS=(children OR adolescents)]. Combined searches were performed using (#) prior to each set number in the query. Since there was a possibility in this site to refine the search, studies were searched between 1990 and 2015 and the selected language was English, since there were only two options, English and Korean languages.

In the Scopus (Elsevier) database, keywords, equivalent terms, and terms widely used in the English language were cross-referenced in the advanced search using Boolean operators “AND” and “OR” as follows: [Latent Tuberculosis (Article Title/Abstract/Keywords)] AND [Rheumatic Diseases (Article Title/Abstract/Keywords)] AND [children (Article Title/Abstract/Keywords) OR adolescents (Article Title/Abstract/Keywords)]. Combined searches were performed using (#) prior to each set number in the query. Studies published between 1990 and 2015 were assessed.

Inclusion and exclusion criteria

We included studies that addressed the treatment of latent infection by *Mycobacterium tuberculosis* in children and

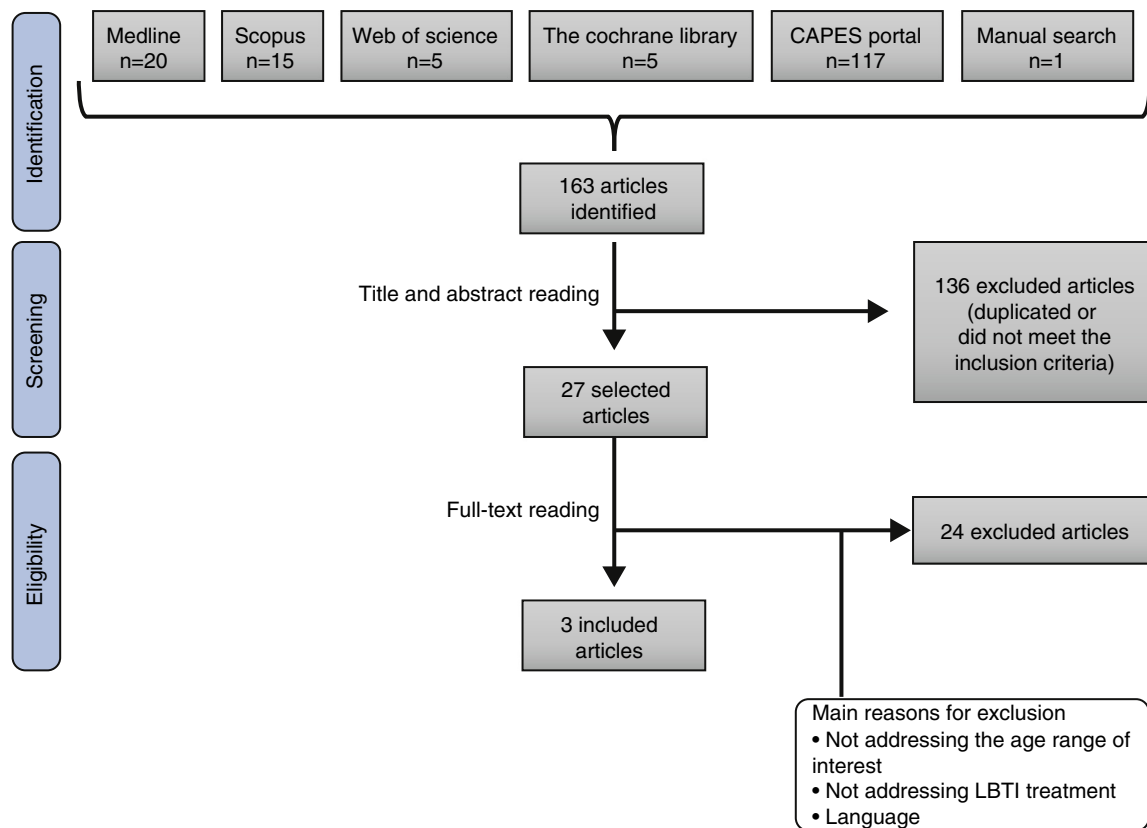


Fig. 1 – Flow chart of article identification and eligibility in the systematic review.

adolescents between 1 and 18 years of age with rheumatic diseases, within a publication period of 25 years (1990 to 2015) and studies published in English and Portuguese. All study designs were considered relevant. We excluded studies that did not meet the previously established inclusion criteria.

Methods of analysis

Initially, all the results, except duplicates were analyzed by reading the title and abstract, to select the possible articles that would be included in the study.

After this previous study selection, based on the analysis of the title and the abstract, the texts were read in full and only after that, the studies were definitively included in the systematic review, if they met the previously established inclusion criteria. At this moment, when studies were read in full to define eligibility, the author also performed a manual search of the references included in these studies, aiming at the identification of articles that were not found during the database search, but that could be found in the references.

As the articles in the references were not identified in the results of this study, they were selected for overall reading to determine if they would be included in the study.

Table 2 shows the authors, titles, year of publication, database, inclusion, or exclusion justification of all studies selected for full reading. Furthermore, it contains the article selected by manual search performed by the author.

Results

A total of 162 studies were initially identified through search in the electronic databases (Medline 20, Scopus 15, The Cochrane Library 5, Web of Science 5, LILACS 0, Scielo 0 and CAPES Portal 117) and 1 was identified by manual search performed by the author, totaling 163 studies. Of these, 136 were excluded because they were identical articles, i.e., the same publication was found in different databases, and because they did not meet the objectives and/or inclusion criteria of the systematic review, based on the reading of the title and the abstract.

The 27 articles that were not excluded at the screening based on the reading of titles and abstracts, were fully evaluated to determine if they met the eligibility criteria. Of these, 3 were included in this study. Fig. 1 shows the flowchart that represents the selection and eligibility of the studies. Table 3 indicates the articles included in the study highlighting the author, year of publication, study design, sample size, age group and LBTI treatment used.

Study characteristics

Kilic et al.,¹⁶ in a retrospective cohort study, followed a group of 144 patients with rheumatic diseases taking a TNF blocker (etanercept, infliximab and adalimumab). Every 6 months, patients were evaluated for the development of TB through clinical history, physical examination, TST, chest X-ray and, when necessary, sputum/morning gastric aspirate analysis

Table 2 – Studies selected for full-text reading.

Authors	Title	Year	Inclusion or justification for exclusion	Database
Tandon, VR; Mahajan, A; Khajuria, V	TNF blockers and tuberculosis: an Indian concern	2006	Does not address the age range of interest of the study	CAPES Portal
Vanhoof, J; Landewe, S; Van Wijngaerden, E; Geusens, P	High incidence of hepatotoxicity of isoniazid treatment for tuberculosis chemoprophylaxis in patients with rheumatoid arthritis treated with methotrexate or sulfasalazine and anti-tumour necrosis factor inhibitors	2003	Does not address the age range of interest of the study	CAPES Portal
Diana Maria de Almeida Lopes; Valéria Goes Ferreira Pinheiro; Helena Serra Azul Monteiro; José Ajax Nogueira Queiroz; Lucivaldo Dos Santos Madeira; Mônica Maria de Almeida Lopes	Diagnosis and treatment of latent tuberculosis in patients with chronic inflammatory diseases: use of TNF-alpha-targeting biological products	2011	Age range: ≥ 11 years	CAPES Portal
Trajman, A.; Steffen, R. E.; Menzies, D.	Interferon-gamma release assays versus tuberculin skin testing for the diagnosis of latent tuberculosis infection: an overview of the evidence	2013	Does not address the age range of interest of the study	CAPES Portal
Winthrop, KL	Update on tuberculosis and other opportunistic infections associated with drugs blocking tumour necrosis factor α	2005	Does not address the age range of interest of the study	CAPES Portal
Keane, Joseph; Bresnihan, Barry	Tuberculosis reactivation during immunosuppressive therapy in rheumatic diseases: diagnostic and therapeutic strategies	2008	Does not address the age range of interest of the study	CAPES Portal
Kurt, Ozlem Kar; Kurt, Bahar; Talay, Fahrettin; Tug, Tuncer; Soy, Mehmet; Bes, Cemal; Hayran, Mutlu	Intermediate to long-term follow-up results of INH chemoprophylaxis prior to anti-TNF-alpha therapy in a high-risk area for tuberculosis	2013	Does not address the age range of interest of the study	CAPES Portal
Haroon, Muhammad; Martin, Una; Devlin, Joe	High incidence of intolerance to tuberculosis chemoprophylaxis	2013	Does not address the age range of interest of the study	CAPES Portal
Carmona, Loreto; Gómez-Reino, Juan J; Rodríguez-Valverde, Vicente; Montero, Dolores; Pascual-Gómez, Eliseo; Mola, Emilio Martin; Carreño, Luis; Figueroa, Manuel	Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists	2005	Does not address the age range of interest of the study	CAPES Portal
Moosig, F.; Dalhoff, K.	Infectious pulmonary complications of rheumatic diseases	2009	Article written in German	CAPES Portal
Nobre, Christiane; Callado, Maria; Lima, José; Gomes, Kirla; Martiniano, Germana; Vieira, Walber	Tuberculosis infection in rheumatic patients with infliximab therapy: experience with 157 patients	2012	Does not address the age range of interest of the study	CAPES Portal
Kilic, Omer; Kasapcopur, Ozgur; Camcioglu, Yildiz; Cokugras, Haluk; Arisoy, Nil; Akcakaya, Necla	Is it safe to use anti-TNF- α agents for tuberculosis in children suffering with chronic rheumatic disease?	2012	Included	CAPES Portal, Medline (Pubmed), Scopus, Web of Science
Diel, R.; Hauer, B.; Loddenkemper, R.; Manger, B.; Krüger, K.	Recommendations for tuberculosis screening before initiation of TNF- α -inhibitor treatment in rheumatic diseases	2009	Does not address the age range of interest of the study	CAPES Portal
Valls, Victoria; Ena, Javier	Short-course treatment of latent tuberculosis infection in patients with rheumatic conditions proposed for anti-TNF therapy	2015	Does not address the age range of interest of the study	CAPES Portal

Table 2 – (Continued)

Authors	Title	Year	Inclusion or justification for exclusion	Database
Bray, Marie-Gaëlle; Poulain, Cécile; Dougados, Maxime; Gossec, Laure	Frequency and tolerance of antituberculosis treatment according to national guidelines for prevention of risk of tuberculosis due to tumor necrosis factor blocker treatment	2010	Does not address the age range of interest of the study	CAPES Portal
Chu, Alvina D; Polesky, Andrea H; Bhatia, Gulshan; Bush, Thomas M	Active and latent tuberculosis in patients with systemic lupus erythematosus living in the United States	2009	Does not address the age range of interest of the study	CAPES Portal
Dinser, R; Fousse, M; Sester, U; Albrecht, K; Singh, M; Köhler, H; Müller-Ladner, U; Sester, M	Evaluation of latent tuberculosis infection in patients with inflammatory arthropathies before treatment with TNF-alpha blocking drugs using a novel flow-cytometric interferon-gamma release assay	2008	Does not address the age range of interest of the study	CAPES Portal
Xie, Xi; Li, Fen; Chen, Jin-Wei; Wang, Jia	Risk of tuberculosis infection in anti-TNF- α biological therapy: From bench to bedside	2014	Does not address the age range of interest of the study; limited approach for LTBI treatment	CAPES Portal
He, Dongyi; Bai, Fengmin; Zhang, Shu; Jiang, Ting; Shen, Jie; Zhu, Qi; Yue, Tao; Shao, Lingyun; Gao, Yan; Feng, Yun; Weng, Xinhua; Zou, Hejian; Zhang, Ying; Zhang, Wenhong	High incidence of tuberculosis infection in rheumatic diseases and impact for chemoprophylactic prevention of tuberculosis activation during biologics therapy	2013	Does not address the age range of interest of the study	CAPES Portal, Medline (Pubmed), Scopus, Web of Science
Bieber, Jeffrey; Kavanaugh, Arthur	Consideration of the risk and treatment of tuberculosis in patients who have rheumatoid arthritis and receive biologic treatments	2004	Does not address the age range of interest of the study	CAPES Portal
Mariette, X; Salmon, D	French guidelines for diagnosis and treating latent and active tuberculosis in patients with RA treated with TNF blockers	2003	Does not address the age range of interest of the study	CAPES Portal
Abud-Mendoza, Carlos; Martínez-Martínez, Marco Ulises; De Jesús Macías-Mendoza, José; Magaña-Aquino, Martín	Should tuberculin skin test be positive to give latent tuberculosis treatment before tumor necrosis factor-alpha inhibitors in selected patients in developing countries?	2010	Does not address the age range of interest of the study	CAPES Portal
Scivo, Rossana; Armignacco, Orlando	Tuberculosis risk and anti-tumour necrosis factor agents in rheumatoid arthritis: a critical appraisal of national registry data	2014	Does not address the age range of interest of the study	CAPES Portal
Calzada-Hernández J(1), Anton-López J(2), Bou-Torrent R(3), Iglesias-Jiménez E(4), Ricart-Campos S(5), Martín de Carpi J(6); Carmen García de Vicuña Muñoz de la Nava, Torrente-Segarra V(7), Sánchez-Manubens J(8), Giménez-Roca C(9), Rozas-Quesada L(10), Juncosa-Morros MT(11), Fortuny C(12), Noguera-Julian A(13)	Tuberculosis in pediatric patients treated with anti-TNF α drugs: a cohort study	2015	Included	Medline (Pubmed)
Santos MJ(1), Fonseca JE, Canhão H, Conde M, José Vieira M, Costa L, Costa M, Salgado M, Melo Gomes JÁ	Guidelines for prescribing and monitoring biologic therapies in juvenile idiopathic arthritis	2007	Very limited approach of LTBI treatment	Medline (Pubmed), Scopus, Web of Science

Table 2 – (Continued)

Authors	Title	Year	Inclusion or justification for exclusion	Database
Demir, S.a, Sadi Aykan, F.a, Öztuna, D.b	Latent tuberculosis treatment results in patients that taken TNF-alpha blockers at Ankara Numune training and research hospital chest diseases clinic for last 8 years (2006–2013)	2014	Does not address the age range of interest of the study	Scopus
Nuray Aktay Ayaz, Erkan Demirkaya, Yelda Bilginer, Uğur Özçelik, Nazan Çobanoğlu, Nural Kiper, Nesrin Besbas, Aysin Bakkalo, ğlu Seza Özen	Preventing tuberculosis in children receiving anti-TNF treatment	2010	Included	Author's manual search

and chest tomography. An TST ≥ 10 mm was considered positive. At the pre-anti-TNF- α therapy assessment, 21 patients were detected with LTBI and treated with INH (isoniazid) at 10 mg/kg/day (maximum, 300 mg/day) for 9 months starting 1 month before anti-TNF- α therapy. No TB disease was detected in these patients after 9 months. During follow-up, 7 children had positive TST and received treatment for LTBI with INH at 10 mg/kg/day (maximum, 300 mg/day) for 9 months during anti-TNF- α therapy. A 13-year-old female patient with juvenile idiopathic arthritis and secondary uveitis developed positive IGRA during treatment with INH. Anti-TB treatment was started and, after 18 months, TB-related signs disappeared.

Calzada-Hernández et al.,¹⁷ in a prospective cohort study, assessed 221 children and adolescents with rheumatic diseases using TNF blockers. Before treatment, patients were submitted to TST or QuantiFERON Gold-In Tube (QTF-G) test and chest X-ray, and an TST ≥ 5 mm was considered positive. During treatment, patients were assessed every 6 months through clinical history and physical examination. TST/QTF-G

and chest X-rays were performed only when necessary. LTBI was diagnosed in 3 patients with juvenile idiopathic arthritis. They were treated for LTBI and then the anti-TNF- α treatment was reintroduced. One patient received treatment with INH for 9 months and, in two, the treatment consisted of INH and Rifampicin for 3 months. Treatment adherence was observed in all three cases, and there were no problems related to tolerance and evidence of TB activation. There were no changes in liver enzyme levels aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

Ayaz et al.,¹⁸ in a prospective cohort study, followed 36 patients diagnosed with juvenile idiopathic arthritis taking etanercept. All children and family members were screened for LTBI and active TB prior to etanercept therapy. Screening consisted of clinical history, physical examination, TST, and chest X-ray. The children were re-evaluated every 3 months. Seven patients had TST >10 mm and were treated with full dose of INH for 4–8 weeks, plus 9 months after the start of the anti-TNF- α therapy. There was no TB activation in these patients or other complications during follow-up.

Table 3 – Characteristics of included studies.

Author (year)	Study type	Sample treated	Screening method	Treatment used	Observed outcomes
Kilic (2012) ¹⁶	Retrospective cohort study	28 patients	History and physical examination, TST (≥ 10 mm), chest X-ray and, when necessary, gastric aspirate culture every 6 months	10 mg/kg/day (maximum, 300 mg/day) of INH for 9 months.	1 case of TB activation during treatment with INH. Resolved with TB treatment. There were no other complications regarding TB activation
Calzada-Hernández (2015) ¹⁷	Prospective cohort study	3 patients	TST and QuantiFERON Gold-In Tube [®] test (QTF-G), history and physical examination	INH for 9 months and INH + rifampicin for 3 months	There were no cases of TB disease or other complications
Ayaz (2010) ¹⁸	Retrospective cohort study	7 patients	History, physical examination, TST (>10 mm) and chest X-ray every 3 months	Initial treatment for 4–8 weeks with full-dose INH and treatment continuation for a further 9 months after the start of treatment with TNF blocker	There were no complications related to TB reactivation or pulmonary symptoms

Discussion

In the literature, it is possible to identify different therapeutic regimens for the treatment of LTBI. The Ministry of Health recommends INH at the dose of 5 mg/kg to 10 mg/kg of weight up to a maximum dose of 300 mg/day for a minimum period of 6 months. However, there are 4 options recommended by the WHO: INH for 6 or 9 months; Rifampentine weekly for 3 months plus INH; INH for 3–4 months plus Rifampicin; 3–4 months of rifampicin.⁸

Due to the greater susceptibility of the at-risk population to develop the active disease, the correct treatment is very important. In the case of newborns cohabiting with the infected index case, newborns should not be vaccinated at birth. INH is administered for a period of three months, after which the TST is performed. Chemoprophylaxis is maintained for another 3 months if the TST is ≥ 5 mm. Otherwise, INH is discontinued and the individual is vaccinated with BCG.⁹

For children who are contact with infected individuals, treatment is indicated when the TST is ≥ 5 mm in children not vaccinated with BCG, in children vaccinated for more than two years or in the presence of any immunosuppressive condition. It is also indicated when the TST ≥ 10 mm in children vaccinated with BCG for less than two years. Children that acquired LTBI up to the age of 5 are considered priorities for LTBI treatment.⁹

However, the number of studies included in the review shows the scarcity of studies evaluating the treatment of LTBI in children with rheumatic diseases. The presence of these children in the risk group, as well as the disease mortality, make it important to carry out studies comparing the different available therapies. It is observed that, due to this fact, the best therapy for these patients is yet to be defined. Only the study by Kilic et al.¹⁶ showed a case of TB activation. The low incidence of TB disease in these patients is probably due to the continuous follow-up and screening of these children during the chronic disease treatment.

On the other hand, only one study showed data related to liver enzyme alterations during treatment. Although not frequent and reversible, INH-induced hepatotoxicity in children with LTBI has been described in the literature.¹⁹ However, the behavior of the hepatic profile in children with rheumatic diseases receiving this medication has not been described. Because this is a group of children with chronic systemic diseases receiving other medications, information about tolerability may be valuable in clinical practice.

Good adherence to treatment in all three studies may also have occurred due to the medical monitoring these chronic patients need to undergo. Silva et al.²⁰ showed that, in children without comorbidities, 8.9% did not return for the TST reading and 12.65% did not adhere to treatment.

Of the therapeutic regimens recommended by the WHO, the following were not observed: INH for 6 months; Rifampicin for 3 months weekly plus INH; 3–4 months of rifampicin. The use to these schemes would be important for the comparison.

Thus, the best therapeutic regimen for the treatment of LTBI in pediatric patients with rheumatic diseases cannot yet be determined. More studies are required to evaluate the

response to the other available therapeutic regimens, with better tolerability assessment and larger sample size.

Finally, the results of the studies showed that INH therapy for 6–9 months and INH therapy plus rifampicin for three months may have a low activation rate; however, the duration is controversial, which emphasizes the need to perform further studies.¹²

Conflicts of interest

The authors declare no conflicts of interest.

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