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Review article

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

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ARTICLE INFO

Article history:

Received 2 July 2016

Accepted 24 November 2016

Available online xxx

Keywords:

Rheumatic diseases

Child

Adolescent

Biological factors

Latent tuberculosis

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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<http://dx.doi.org/10.1016/j.rbre.2017.01.009>

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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

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