

Review

Tuberculosis in patients with systemic rheumatic or pulmonary diseases treated with glucocorticosteroids and the preventive role of isoniazid: a review of the available evidence

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Abstract

Development of tuberculosis (TB) is a concern in patients who receive glucocorticosteroids for the treatment of chronic rheumatic or pulmonary diseases. However, the incidence of development of TB in such patients and the prophylactic role of isoniazid (INH) are unclear. We evaluated the available evidence from 20 relevant prospective and retrospective cohort and case–control studies identified in the PubMed and Cochrane databases. The frequency of development of TB in the populations studied varied from 0% to 13.8%. This figure was low in studies performed in countries with a low incidence of TB (0% in the USA and Greece, 0.6% in France and 1.35% in Spain). In contrast, the frequency of development of TB in the studied cohorts was high in studies performed in countries with a moderate to high incidence of TB (from 2.5% in South Korea to 13.8% in The Philippines). Isoniazid prophylaxis (INHP) was found to decrease the incidence of development of TB in two of four studies that examined this intervention. The available evidence suggests that patients who receive steroids for the treatment of chronic rheumatic or pulmonary diseases and who live in countries with a high incidence of TB have a high risk of development of TB in contrast to patients who live in countries with a low incidence of the infection. However, the role of INHP even for patients living in countries where TB is endemic is unclear because the effectiveness of INH in preventing TB development in such patients is not well established and there are cost-effectiveness and safety issues.

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1. Introduction

The use of glucocorticosteroids is a very common therapeutic modality in patients with various systemic rheumatic and chronic pulmonary diseases. A considerable number of patients with such diseases require moderate to high doses of glucocorticosteroids for prolonged periods of time [1–20]. It is generally accepted that these patients are susceptible to several types of infections owing to suppression of their immune system caused by steroid treatment or by their disease itself [21–23]. One of these infections is tuberculosis (TB), however there has been no review in the medical literature evaluating the risk of development of TB in patients receiving glucocorticosteroids for the treatment of various

systemic rheumatic and chronic pulmonary diseases compared with the risk of TB in the general population [5,19].

Furthermore, there is much controversy among clinicians regarding the role of isoniazid prophylaxis (INHP) in preventing reactivation of old or development of new TB infection in these immunosuppressed patients [24–28]. There are data suggesting that INHP is effective in purified protein derivative (PPD) tuberculin skin test-positive patients with haematological malignancies and chronic renal haemodialysis as well as renal transplant recipients [29,30], although the clinical utility of such a strategy has not been fully clarified in clinical practice. The American Thoracic Society recommends the use of INHP in patients receiving glucocorticosteroids at doses equivalent to prednisolone (≥ 15 mg per day) if they have a positive PPD test [31,32]. However, the British Thoracic Society does not specifically address this issue [33].

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The aim of the current article was to critically review and to evaluate the available medical literature regarding the risk of glucocorticosteroid-treated patients developing TB and the role of INHP in this population.

2. Literature search

Two of the authors (P.T.V. and A.G.A.) independently performed the literature search, study selection and data extraction. Any disagreement between the reviewers was discussed in meetings with the third author (M.E.F.). The literature search was based on the PubMed and Cochrane databases. Keywords included various combinations of the following: steroid, glucocorticosteroid, prednisolone, prednisone, isoniazid, prophylaxis, prevention, tuberculosis, systemic rheumatic disease, systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, scleroderma, progressive systemic sclerosis, respiratory disease, pulmonary disease and asthma. Additional relevant publications were also identified from the reference lists of the initially identified articles.

3. Study selection

Relevant prospective and retrospective cohort and case–control studies identified in the PubMed and Cochrane databases without time limitation were selected for inclusion in the review. Case reports and studies that concerned human immunodeficiency virus (HIV) patients and patients with renal transplantation, chronic renal haemodialysis or haematological malignancies who received long-term steroid treatment and developed TB were not included as it was considered that these patients comprise a different population than those focused on in this review. In addition, articles focused on children who received steroids for a long period of time, especially due to chronic respiratory problems, were excluded.

4. Data extraction

Data were extracted from the studies included in the review with regard to details of the detection of TB (description of chest radiograph findings, microbiological data, histological findings and clinical manifestations of TB). Data regarding the dose and duration of immunosuppressant drugs as well as data for the evaluation of the PPD test and the adverse effects of INHP were also extracted.

5. Definitions

When it was not given, the incidence of TB in the studied cohorts was calculated (if it was possible from the data reported) as: number of patients with active TB/(total stud-

ied population $\times$ duration of follow-up). The frequency of TB was defined as: number of steroid-treated patients who developed TB/number in the studied population.

6. Studies reviewed

Data were extracted from 20 studies (16 retrospective, 3 prospective and 1 case–control study) that fulfilled the inclusion criteria of the current review. Seventeen of the studies included reported the frequency of TB in the studied population, whilst 10 reported data that permitted a comparison of the frequency and/or incidence of TB in the studied cohort of patients and the general population. Four of the studies also included data regarding the effectiveness of INHP by comparing the incidence of TB between the steroid-treated patients who received prophylaxis and those who did not.

7. Characteristics of the studied cohorts

Table 1 presents data regarding the demographic and clinical characteristics of the patient populations in the 20 studies included in the review [1–20]. Most of the studies were performed in countries and areas with a moderate or high incidence of TB such as Hong Kong, India, Japan, South Korea, Mexico, The Philippines, South Africa and Singapore [3,5–12,14–16,18,19], whilst some were performed in countries with a lower incidence of TB such as Spain, France, Turkey, Greece, Israel and the USA [1,2,4,13,17,20]. The majority of patients included in the studies reviewed had systemic rheumatic diseases, the most frequent being systemic lupus erythematosus (SLE) and rheumatoid arthritis. Six studies included patients taking steroids for respiratory diseases, with the most frequent being asthma [6,9,12,17,18,20].

In all studies of patients with rheumatic diseases, the majority of the population were women, except for the study by Cowie and King [18] that included exclusively Black men. The mean age of the studied populations differed, but in most studies it was 25–50 years. In nine studies, data regarding history of TB in the population studied (through medical history or chest radiographs) were reported [2,4,6,8–10,13,15,20].

8. Comparative incidence of TB in the studied cohorts and the general population

Table 2 presents data regarding exposure of the patients studied to steroids and other immunosuppressive drugs (if any) as well as the comparative incidence of TB in the studied cohorts and the general population. In only three of the studies was PPD testing included as a screening tool for the detection of patients with old TB in the studied population [10,13,20]. The majority of patients studied received a moderate or high dose of steroid treatment (>15 mg/day of prednisolone). There was considerable variability in the

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