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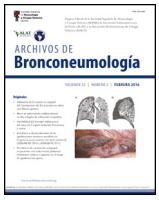

Original Article

Adjunctive Corticosteroids for *Pneumocystis jirovecii* Pneumonia in Non-HIV-Infected Patients: A Systematic Review and Meta-Analysis of Observational Studies☆

Yuji Fujikura,[a,*] Toshie Manabe,[b,c] Akihiko Kawana,[a] Shigeru Kohno[d]

[a] *Division of Infectious Diseases and Respiratory Medicine, Department of Internal Medicine, National Defense Medical College, Saitama, Japan*
[b] *Department of Pulmonary Medicine, University of Tsukuba, Graduate School of Comprehensive Human Science, Ibaraki, Japan*
[c] *Department of Hygiene and Public Health, Teikyo University, School of Medicine, Tokio, Japan*
[d] *Nagasaki University, Nagasaki, Japan*

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ABSTRACT

Introduction: The clinical benefits of adjunctive corticosteroids for *Pneumocystis jirovecii* pneumonia in patients not infected with the human immunodeficiency virus (HIV) has not been evaluated by meta-analysis.
Methods: We conducted a systematic review of published studies describing the effects of adjunctive corticosteroids on outcome in non-HIV *P. jirovecii* pneumonia patients. Two investigators independently searched the PubMed and Cochrane databases for eligible articles written in English. A meta-analysis was performed using a random-effects model for measuring mortality as the primary outcome, and the need for intubation or mechanical ventilation as the secondary outcome.
Results: Seven observational studies were eligible. In these studies, adjunctive corticosteroids did not affect mortality in non-HIV patients (odds ratio [OR] 1.26; 95% CI 0.60–2.67) and there was no beneficial effect in patients with severe hypoxemia (PaO_2 <70 mmHg) (OR 0.90; 95% CI 0.44–1.83). No significant effect on the secondary outcome was observed (OR 1.34; 95% CI 0.44–4.11).
Conclusions: Although the studies were observational, meta-analysis showed that adjunctive corticosteroids did not improve the outcome of *P. jirovecii* pneumonia in non-HIV patients. The results warrant a randomized controlled trial.

Tratamiento complementario con corticoides en la neumonía por *Pneumocystis jirovecii* en pacientes no infectados por VIH: revisión sistemática y metanálisis de los estudios observacionales

Palabras clave:
Corticoides
Huésped inmunocomprometido
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Pneumocystis jirovecii
Revisión

RESUMEN

Introducción: Los beneficios clínicos del tratamiento complementario con corticoides de la neumonía por *Pneumocystis jirovecii (P. jirovecii)* en pacientes no infectados por el virus de la inmunodeficiencia humana (VIH) no se han evaluado mediante metanálisis.
Métodos: Realizamos una revisión sistemática de los estudios publicados que describen los efectos del tratamiento complementario con corticoides sobre la evolución de pacientes con neumonía por *P. jirovecii* no infectados por VIH. Dos investigadores hicieron búsquedas independientes de artículos elegibles

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* Corresponding author.
E-mail address: fujikura@ndmc.ac.jp (Y. Fujikura).

escritos en inglés en las bases de datos PubMed y Cochrane. Se efectuó un metanálisis con un modelo de efectos aleatorios para determinar la mortalidad como variable principal, y la necesidad de intubación o ventilación mecánica como variable secundaria.
Resultados: Siete estudios observacionales resultaron elegibles. En ellos, el tratamiento complementario con corticoides no afectó a la mortalidad en los pacientes no infectados por VIH (*odss ratio* [OR] 1,26; IC 95% 0,60–2,67) y no tuvo ningún efecto beneficioso para los pacientes con hipoxemia intensa (PaO_2 < 70 mmHg) (OR 0,90; IC 95% 0,44–1,83). No se observó ningún efecto significativo sobre la variable secundaria (OR 1,34; IC 95% 0,44–4,11).
Conclusiones: Aunque los estudios eran observacionales, el metanálisis mostró que el tratamiento complementario con corticoides no mejoraba la evolución de los pacientes con neumonía por *P. jirovecii* no infectados por VIH. Estos resultados justifican la realización de un ensayo controlado aleatorizado.

Introduction

Pneumocystis jirovecii pneumonia (PJP) is life-threatening opportunistic infection affecting immunocompromised individuals.[1] CD4+ T-cells play crucial roles in host defense against *P. jirovecii* in response to antigens and the production of interferon-gamma.[2] CD4+ T-cells are especially suppressed in cases of advanced human immunodeficiency virus (HIV) infection; however, other causes of immunosuppression are frequently observed in clinical settings, such as continuous corticosteroid use, hematological malignancies, solid organ tumors, and organ transplants.[3,4] PJP is most common in patients with HIV; however, PJP in non-HIV patients should not be overlooked, particularly in immunocompromised patients.

The epidemiology and clinical presentations differ between HIV and non-HIV patients. PJP in non-HIV patients occurs at older age, with higher neutrophil levels and a lower density of *P. jirovecii* in bronchoalveolar lavage compared with HIV patients.[5] Furthermore, the onset of respiratory failure is abrupt in non-HIV patients, whereas it is slower in HIV patients.[1] Overall, the outcome of PJP is less favorable in non-HIV than HIV-infected patients due to a variety of underlying medical conditions.[2]

The therapeutic strategy for PJP has been widely studied, especially in HIV-infected individuals. Sulfamethoxazole-trimethoprim is generally adminstered,[6] and HIV-PJP patients with substantial hypoxemia are prescribed concurrent adjunctive corticosteroids, based on randomized controlled trials from 1990.[7] Recently, a meta-analysis and systematic review showed that adjunctive corticosteroid treatment had a beneficial effect on mortality in patients with hypoxemia (arterial oxygen partial pressure >70 mmHg or an alveolar-arterial gradient <35 mmHg on room air).[8]

The value of adjunctive corticosteroid in non-HIV-PJP patients, however, remains unclear. Although several observational studies have been published, they do not show a definitive effect on outcome. There have been no randomized controlled studies conducted to date; this might due to variations in underlying diseases and pathophysiology, and the relative rarity of non-HIV-PJP cases. However, since the pathophysiology of non-HIV-PJP patients differs from HIV-infected PJP patients, there may be factors associated with the use of adjunctive corticosteroids that affect the clinical course.

We conducted a systematic review and meta-analysis of published observational studies focusing on adjunctive corticosteroids in non-HIV-PJP patients.

Methods

Study Search

A literature search was performed by 2 investigators (YF and TM) who independently searched PubMed and the Cochrane Database of Systematic Reviews for eligible articles published from 1949 to June 2015. We used free search terms, MeSH terms, and combinations of search terms "*Pneumocystis*", "pneumonia, *Pneumocystis* [MeSH]", "*Pneumocystis* infections [MeSH]", "*Pneumocystis carinii* [MeSH]", "*Pneumocystis jirovecii* [MeSH]", "PCP", "PJP", AND "non-HIV", "non-AIDS", "non-HIV-infected", "HIV-uninfected", "AIDS uninfected", "HIV-negative", AND "steroids", "corticosteroids", "hydroxycorticosteroids", "glucocorticoids", "prednisolone", "hydroxycortisone", and "hydrocortisone", with language restricted to English.

Eligibility Criteria and Outcome Measures

Studies that met the eligibility criteria were included in the meta-analysis. (1) Study design: randomized controlled trials (RCT) and observational studies; (2) population: non-HIV patients with PJP; (3) intervention: administration of adjunctive corticosteroids; (4) comparison intervention: no adjunctive corticosteroids or no increase in corticosteroid use, according to each study definition; (5) outcome variables: mortality as primary endpoint, and intubation rate (or need for mechanical ventilation) as the secondary endpoint. In addition, for the studies in patients with hypoxemia, we also focused on mortality due to severe hypoxemia (PaO_2 <70 mmHg) in non-HIV cases of PJP. We excluded articles that did not define HIV status in the study population or did not extract exact data for evaluation.

Statistical Analysis

Meta-analysis was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis)[9] and MOOSE (Meta-analysis Of Observational Studies in Epidemiology) recommendations.[10] Data were analyzed using Review Manager (RevMan) 5.3.5 (Cochrane Collaboration, Copenhagen) and R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) software with an open source statistical package for meta-analysis. A random effect model was used to aggregate data, and the odds ratio (OR) was used in summary. The heterogeneity of original studies was evaluated with I^2 statistics. Significance levels were two-tailed in all analyses, and $P < .05$ was considered significant. A funnel plot examined publication bias.

Results

Search Results and Study Characteristics

Following discussions between the 2 reviewers, 7 observational studies[11–17] were collected by systematic searches according to the PRISMA statement (Fig. 1). The reviewers were in complete agreement about the search performed and data extracted. Of the 82 studies screened, 7 were included in a qualitative synthesis.