



Original article

Systematic Review of Systemic Corticosteroids for Treatment of Organizing Pneumonia



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ABSTRACT

Introduction: Regardless corticosteroids are recommended for the treatment of organizing pneumonia there is limited evidence supporting this practice. Thus, we performed a systematic review of the literature on systemic corticosteroid treatment for organizing pneumonia.

Methods: A search was implemented in the PubMed database (Medline) for articles published in the last 20 years. Those studies with incomplete or insufficient data and case reports were excluded. We collected data including: demographics, clinical data, diagnostic procedures, aetiology, treatment regimen (drug, posology, duration, response) and evolution.

Results: A total of 135 publications were selected and finally 13 studies with 849 patients were included in the review: 12 retrospective observational studies and a single prospective observational study. Most of the patients were started on treatment with systemic corticosteroids – a total of 627 (30–100% depending on the series), but there was a great heterogeneity regarding drug, doses and duration. On those that started treatment, 226 (36%) presented a relapse of the disease during follow-up. Only one study provided information regarding treatment side-effects.

Conclusion: The findings of this systematic review show the low quality data supporting the use of corticosteroids for the treatment of organizing pneumonia. This highlights a need to undertake appropriately designed studies to investigate which is the most appropriate treatment regimen that trades off benefits and risks of prolonged corticosteroid administration.

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Revisión sistemática de los corticosteroides para el tratamiento de la neumonía organizativa

RESUMEN

Introducción: Aunque los corticosteroides están recomendados para tratar la neumonía organizada, hay pocos datos que respalden esta práctica, por lo cual efectuamos una revisión sistemática de la bibliografía sobre el tratamiento con corticosteroides sistémicos para la neumonía organizada.

Métodos: Se hizo una búsqueda en la base de datos PubMed (Medline) de artículos publicados en los últimos 20 años. Se descartaron los estudios con datos y casos clínicos incompletos o insuficientes. Los datos que recabamos abarcaron: datos demográficos, datos clínicos, técnicas diagnósticas, etiología, pauta terapéutica (fármaco, posología, duración, respuesta) y evolución.

Palabras clave:

Neumonía organizada

Corticosteroides

Esteroides

Tratamiento

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Resultados: Se eligieron 135 publicaciones en total y se incorporaron finalmente a la revisión 13 estudios con 849 pacientes: 12 estudios observacionales retrospectivos y un solo estudio observacional prospectivo. La mayor parte de los pacientes habían comenzado el tratamiento con corticosteroides sistémicos, un total de 627 (30%-100% en función de la serie), pero la duración, las dosis y el fármaco manifestaron una gran heterogeneidad. Entre los que habían empezado el tratamiento, 226 (36%) presentaron una recidiva de la enfermedad durante el seguimiento. Solo en un estudio se ofreció información sobre los efectos adversos del tratamiento.

Conclusión: Los resultados de esta revisión ponen de manifiesto la escasa calidad de los datos sobre el tratamiento de la neumonía organizada con corticosteroides. Este hecho destaca la necesidad de emprender estudios diseñados correctamente para investigar la pauta terapéutica más adecuada que compense los riesgos y beneficios de la administración prolongada de corticosteroides.

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Introduction

Organizing pneumonia (OP) is an interstitial lung disease (ILD) initially described as bronchiolitis obliterans with organizing pneumonia,¹ a label currently in disuse because the bronchiolitis is a minor finding.² OP is histologically characterized by intra-alveolar buds of granulation tissue composed of myofibroblasts and fibroblasts intermixed with connective tissue.³ It is thought of as a nonspecific response to a local or distant injury triggered in the lung.^{4,5} Clinical manifestations include an influenza-like syndrome – consisting of fever, cough, asthenia, and weight loss – that evolves to dyspnoea and different degrees of hypoxaemia. The typical clinical picture is non-specific, so a delay in diagnosis is frequent.^{2,6}

Cryptogenic organizing pneumonia (COP) is the idiopathic form of OP, while OP with a known trigger is referred to as secondary organizing pneumonia (SOP). Triggers for SOP include systemic autoimmune disease (SAD), infection, malignancy, drug, radiation, transplant, and aspiration. COP is diagnosed after ruling out known causes of OP in a compatible clinical, radiological, and histopathological setting.³ While there is no evidence of histological differences between COP and SOP,⁷ classification is important because appropriate management requires identification of the underlying cause or trigger of SOP.³ Pharmacological treatment for OP is based on the use of systemic corticosteroids, mainly – given the possibility of spontaneous remission – for symptomatic and progressive forms of OP.⁸ Corticosteroid treatment rapidly improves the clinical and radiological picture. However, dosage and treatment duration are not well established and relapse is common.⁵ Therapeutic recommendations vary widely between studies, which highlights the great heterogeneity in OP management.

In this study, we performed a systematic review of the evidence on systemic corticosteroid treatment for OP in the last 20 years.

Materials and methods

Search strategy

A systematic literature search was implemented in May 2020 in the PubMed database (Medline) for articles published between January 1st 2000 and May 31st 2020. We decided to set our start date agreeing with the publication of international guidelines that specified the definition of OP in the context of other ILD.^{9,10} Articles were limited to those published in English and Spanish. The MeSH terms used for the search were “cryptogenic organizing pneumonia” (which includes the term “organizing pneumonia” and “bronchiolitis obliterans with organizing pneumonia”) and “corticosteroids”. Additional articles were sought in the reference lists of articles retrieved from PubMed. We followed the PRISMA guidelines for reporting systematics reviews.¹¹

Data extraction

Retrieved publications on OP treated with systemic corticosteroids were evaluated for inclusion in this systematic review by two authors (LC and AR). Due to the heterogeneity of the information retrieved, we excluded from the analysis those studies with incomplete or insufficient data and case reports.

Data analysis

Data extracted from the selected articles and compiled in a Microsoft Excel 2010 document included: demographics (age, sex), clinical data (comorbidities, symptoms, OP extension), procedures performed to obtain the diagnosis, suspected cause/s, treatment (drug, posology, duration, response), and relapse.

Results

The bibliography search flowchart is depicted in Fig. 1. The systematic search resulted in 135 publications. Of these, 13 were not included in the study because either the full text was unavailable or they were unrelated to the aim of the review. Then 122 articles were selected for reading.^{2,4–8,12–126} The most frequent exclusion criterion was sample size, as most publications were case reports. Finally 13 studies with 849 patients were included in the review: 12 retrospective observational studies and a single prospective observational study (Table 1).^{2,6,12–14,54,120–126} Sample size ranged between 19 and 176 patients. Clinical findings are summarized in Table 2. Radiological and laboratory data and diagnostic procedures are shown in the supplementary data (Tables A1 and A2).

Most of the 849 patients were started on treatment, 627 (74%) with systemic corticosteroids (30–100% depending on the series) (Fig. 2). A detail review of each study is shown in the supplementary data (Table A2). Overall, the studies reported a favourable initial response to the treatment in the majority of cases, including partial or complete resolution. Basarakodu et al.¹² found full resolution in 38 cases (67%), Yoo et al. in 40 cases (40%),¹²¹ while Okada et al. reported completed resolution in all patients treated with CS.¹⁴

The most widely prescribed corticosteroid was prednisone (5 studies), followed by methylprednisolone, although the corticosteroid type was not specified in 6 studies. Moreover, as the majority of the studies were retrospective the period of treatment and the timing of steroid tapering were not unified, which resulted in a huge variability regarding CS total dose and duration (Fig. 2). Altogether, patients were treated initially with high CS doses, with regimens superior to 0.5 mg/kg/day, at least 4 weeks, followed by gradual tapering in the following 6–12 months (Table A2).

About other therapies, spontaneous OP resolution was observed in 31 patients (3.6%), reported as asymptomatic or mild involvement cases, who received no specific treatment. Lung resection

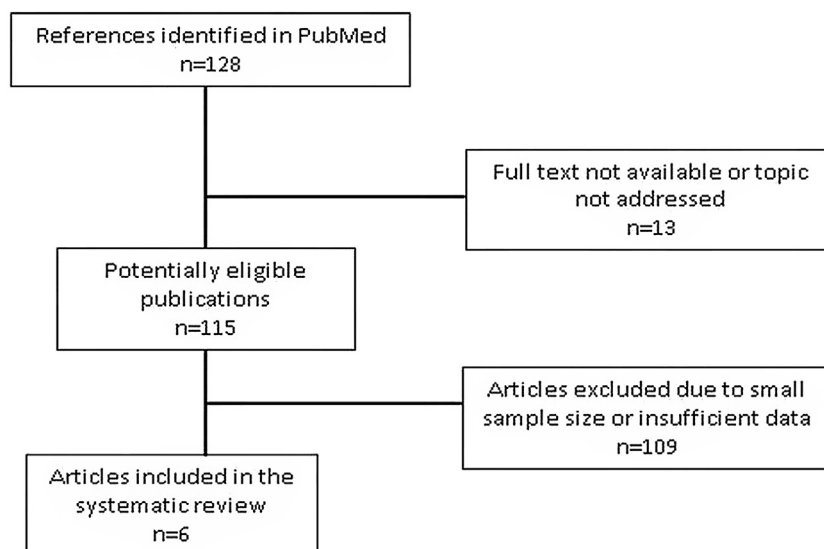


Fig. 1. Study selection flowchart.

Table 1
Articles included in the systematic review.

	Author, year	Country	Patients	Design
1	Cazzato, 2000 ⁵⁴	Italy	78	Retrospective observational
2	Lazor, 2000 ¹³	France	48	Retrospective observational
3	Basarakodu, 2007 ¹²	USA	57	Retrospective observational
4	Barroso, 2007 ¹²⁰	Spain	33	Retrospective observational
5	Drakopanagiotakis, 2011 ⁶	Greece/USA	61	Prospective observational
6	Yoo, 2011 ¹²¹	South Korea	100	Retrospective observational
7	Nishino, 2014 ¹²²	USA	26	Retrospective observational
8	Okada, 2016 ¹⁴	Japan	19	Retrospective observational
9	Onishi, 2016 ¹²³	Japan	75	Retrospective observational
10	Baha, 2018 ²	Turkey	56	Retrospective observational
11	Saito, 2019 ¹²⁴	Japan	33	Retrospective observational
12	Zhou, 2019 ¹²⁵	China	87	Retrospective observational
13	Zhang, 2020 ¹²⁶	China	176	Retrospective observational
Total patients			849	

surgery was the only treatment in 99 cases (11.6%), while antibiotics (anti-inflammatory treatment with macrolides) were used in 14 cases (1.6%). Information regarding other cytotoxic drugs is very limited, as only in one study half of the patients were under this regimen.¹²¹

Among the 849 patients included in the analysis, 66 deaths (7.7%) were reported. In 9 cases were documented as in-hospital, whereas for the remaining occurred during follow-up. The relation of this event with the diagnosis of OP was not described in all studies. Yoo et al. showed 23 deaths among 100 cases (23%), while disease-related was limited to 14 patients (14%).¹²¹

A non-negligible number of patients (240 of 849) experienced one or more relapses at some point during their follow-up: 28% of patients with OP, and 36% of patients treated with corticosteroids. Most relapses occurred when corticosteroids were tapered or suspended. The period of time until the event was wide. In Okada et al. relapses occurred at between 3 months and 14 years (mean 5.3 years) after OP diagnosis,¹⁴ and in Lazor et al. at between 2 and 46 months (mean 5 months) after starting treatment for the first OP episode.¹³ In this study, the subgroup with multiple relapses (≥ 3) was characterized by delayed treatment of the first OP episode and mild cholestasis in laboratory tests.¹³ Saito et al. found that radiographic findings, such as bilateral shadow pattern, traction bronchiectasis, and partial remission, may have possibility of predictive factors for COP relapse.¹²⁴ Zhou et al. showed that fever was more common (65% vs 32%, $p = 0.04$), serum CRP higher

(31.5 ± 39.4 mg/L vs 17.5 ± 32.2 mg/L, $p = 0.038$) and DLCO lower ($45.9 \pm 14.2\%$ vs $57.6 \pm 18.5\%$, $p = 0.05$) in the relapse group.¹²⁵ In other study, BAL neutrophilia (OR 1.07, CI 1.02–1.13, $p = 0.012$) and high levels of fibrin deposits (OR 17.4, CI 1.89–160.9, $p = 0.012$) were independent predictors of relapse.¹²³

With reference to CS side effects, it was not described in the majority of studies. Lazor et al. reported a rate of adverse effects as high as 25%,¹³ Barroso et al. up to 17 of 32 cases (53%),¹²⁰ while Onishi et al. described one or more adverse effects of corticosteroid therapy in 39 of the 75 patients (52%).¹²³ The most frequent side-effects were weight gain, myopathy, osteoporosis, hypertension, or systemic infection.

Discussion

The thirteen studies analyzed in this systematic review reveal a widespread use of systemic corticosteroids to treat OP, with most of the 849 patients responding favourably in terms of their symptoms and radiological abnormalities. However, our analysis also shows that there is currently no consensus regarding the most appropriate corticosteroid, its dose, and the duration of treatment. A significant number of relapses were reported during follow-up, even in those that had been treated with CS. However, key clinical questions as causes of non-response to steroids, recurrence and the usefulness of other drugs in OP remain answered with the information derived from these articles.

Table 2

Characteristics and symptoms of patients with organizing pneumonia (n = 849).

	Cazzato, 2000, ⁵⁴ n = 78	Lazor, 2000, ¹³ n = 48	Basarakodu, 2007, ¹² n = 57	Barroso, 2007, ¹²⁰ n = 33	Yoo, 2011, ¹²¹ n = 100	Drakopan- agiotakis, 2011, ⁶ n = 61	Nishino, 2014, ¹²² n = 26	Onishi, 2016, ¹²³ n = 75	Okada, 2016, ¹⁴ n = 19	Baha, 2018, ² n = 56	Saito, 2019, ¹²⁴ n = 33	Zhou, 2019, ¹²⁵ n = 87	Zhang, 2020, ¹²⁶ n = 176
Mean (SD) age (years)	61 ± 12	61 ± 11	63 ± 15 (COP) 59 ± 15 (SOP)	62 ± 10	54.8 ± 12.3 (CTD-OP)/56.0 ± 11.5 (COP)	60.5 ± 13.6	62.5 (39–78)	69.9 ± 10.3	61.9 ± 8	57.1 ± 12.7	Relapse: 71 ± 10; No relapse: 74 ± 14	56.1 ± 10.4 (31–75)	Unilateral 55.9 ± 9.4 Bilateral 55.8 ± 10.0
Sex (F)	36 (46%)	31 (65%)	26 (46%)	18 (55%)	65 (65%)	34 (56%)	8 (31%)	32 (43%)	12 (63%)	27 (48%)	15 (45%)	42 (48%)	73 (41%)
Smokers	53 (68%)	14 (29%)	–	10 (30%)	15 (15%)	33 (54%)	1 (4%)	–	7 (37%)	33 (59%)	14 (42%)	24 (28%)	55 (31%)
Lung disease	–	–	12 (21%)	–	–	–	–	–	4 (21%)	–	–	–	–
Fever	49 (63%)	–	16 (28%)	26 (76%)	–	39 (64%)	–	42 (56%)	15 (79%)	24 (43%)	22 (67%)	40 (46%)	–
Cough	41 (53%)	–	26 (46%)	29 (88%)	–	40 (66%)	–	44 (59%)	8 (42%)	40 (71%)	27 (82%)	73 (84%)	–
Dyspnoea	45 (58%)	–	45 (79%)	19 (58%)	85 (85%)	38 (62%)	–	17 (23%)	6 (32%)	37 (66%)	20 (61%)	54 (32%)	–
Asthenia	30 (38%)	–	16 (28%)	–	–	44 (72%)	–	–	–	36 (64%)	–	–	–
Weight loss	10 (13%)	–	8 (14%)	14 (42%)	–	17 (28%)	–	–	–	14 (25%)	–	9 (10%)	–
Flu-like symptoms	21 (27%)	–	2 (3.5%)	7 (21%)	–	15 (26%) arthralgia	–	–	–	–	–	–	–
Chest pain	2 (3%)	–	16 (28%)	18 (52%)	–	18 (30%)	–	–	–	7 (12.5%)	1 (3%)	4 (5%)	–
Haemoptysis	1 (1%)	–	–	12%	–	–	–	–	–	4 (7%)	–	5 (6%)	–
Asymptomatic	10 (13%)	–	–	–	–	–	–	7 (9%)	–	–	–	–	–
Aetiology	53 (68%) COP 25 (32%) SOP: 7 (9%) drugs 5 (6%) radio-therapy 5 (6%) CTD	48 (100%) COP	30 (53%) COP 27 (47%) SOP: 8 (14%) infections 7 (12%) CTD 7 (12%) drugs	33 (100%) COP	76 (76%) COP 24 (24%) CTD–OP: 7 (7%) RA 6 (6%) SS 3 (3%) PM	40 (66%) COP 21 (34%) SOP: 6 (10%) drugs 5 (8%) solid tumours 4 (7%) CTD	26 (100%) COP	40 (53%) COP; 35 (47%) SOP: 18 (24%) SAD, 6 (8%) infec- tions, 11 (15%) others	19 (100%) SOP: 18 (95%) RA 1 (5%) bacterial infection	37 (66%) COP 19 (34%) SOP: 4 (7%) RA, 3 (5%) SS, 1 (4%) SLE, 2 (4%) lym- phoma	33 (100%) COP	87 (100%) COP	176 (100%) COP

COP: cryptogenic organizing pneumonia; COPD: chronic obstructive pulmonary disease; CTD: connective tissue disease; F, female; HBV: hepatitis B virus; IBD: inflammatory bowel disease; ILD: interstitial lung disease; M, male; OSAS: obstructive sleep apnoea syndrome; PMR: polymyalgia rheumatica; POEMS: peripheral neuropathy, organomegaly, endocrinopathy, monoclonal plasma-cells proliferative disorder and skin change syndrome; RA: rheumatoid arthritis; SAD: systemic autoimmune disease; SS: Sjögren syndrome; PM: polymyositis; SLE: systemic lupus erythematosus; SOP: secondary organizing pneumonia.

Cazzato, 2000⁵⁴ n=78 <ul style="list-style-type: none"> • T: MPN (77%) • D: 40 mg/d (range 20-120) • E: 3 (4%) • R: 15 (26%) 	Lazor, 2000¹³ n= 48 <ul style="list-style-type: none"> • T:PDN (100%) • D: 50+- 17mg • E: 1 (4%) • R: 28 (58%) 	Basarakodu,2007¹² n= 57 <ul style="list-style-type: none"> • T: CS (100%) • D: not specified • E: 9 (16%) • R: 30 (53%) 	Barroso,2007¹²⁰ n= 33 <ul style="list-style-type: none"> • T: CS (91%) + antibiotics • D: 56+/-12mg • E: 7 (21%) • R: 18 (56%) 	Yoo, 2011¹²¹ n= 100 <ul style="list-style-type: none"> • T: PDN (97%) + cytotoxic (50%) • D: COP 54.6 +/- 12.6 mg, CTD-OP 56.8 +/-24.4 • E: 23 (23%) • R: 22 (22%)
Drakopanagiotakis, 2011⁶ n=61 <ul style="list-style-type: none"> • T: CS (67%) • D: not specified • E: 8 (15%) • R: 17 (38%) 	Nishino, 2014¹²² n= 26 <ul style="list-style-type: none"> • T: CS= 14 (54%) • D: No data • E: 0 • R: 7 (27%) 	Onishi,2016¹²³ n= 75 <ul style="list-style-type: none"> • T: CS (100%) • D: 0.5-0.8 mg/kg/day • E: 7(9.3%) • R: 31 (41%) 	Okada,2016¹⁴ n= 19 <ul style="list-style-type: none"> • T: CS = 12 (63%) • D: 0.8-1 mg/kg/day • E: 2 (10.5%) • R: 4 (21%) 	
Baha, 2018² n=56 <ul style="list-style-type: none"> • T: CS(61%) • D: not specified • E: 2 (3.5%) • R: lost follow-up 	Saito, 2019¹²⁴ n= 33 <ul style="list-style-type: none"> • T: CS (100%) • D: not specified • E: - • R: 10 (30%) 	Zhou,2019¹²⁵ n= 87 <ul style="list-style-type: none"> • T: PDN or equivalent(84%) • D: 0.75 mg/kg/d • E: 0 • R: 23 (32%) 	Zhang,2020¹²⁶ n= 176 <ul style="list-style-type: none"> • T: MPN i.v (30%) • D: 56+/-12mg • E: 3 (5.3%) • R: 35 (66%) 	

Fig. 2. Summary of corticosteroids prescription and response for the treatment of organizing pneumonia. T: therapy; D: initial dose; E: death; R: relapse; CS: corticosteroids; PDN: prednisone; MTP: methylprednisolone; COP: cryptogenic organizing pneumonia; CTD-OP: connective tissue disease-organizing pneumonia.

Based on the reviewed studies, OP is characterized by a non-specific clinical picture with respiratory and constitutional symptoms, radiological images of bilateral multifocal lung consolidation, and in the absence of any infectious processes. For diagnostic purposes as a first option, before considering more invasive techniques such as surgical biopsy, most authors used a combination of BAL (which typically shows lymphocyte predominance) and transbronchial biopsy. In most cases, a triggering factor was not detected and the condition was classified as COP.

The studies showed that most patients with organizing pneumonia respond favourably to corticosteroids in the short-term, which support the value of this therapy for this entity. This correlates with current clinical practise and guidelines.¹⁰ Some authors have proposed a regimen based on oral prednisone at a dose of 1 mg/kg/day, tapered off over 12 months, given the risk of relapse after dose reduction or treatment discontinuation.^{127–130} However, the interpretation of the efficacy is limited because the heterogeneity of the data collected, as each study assesses different outcomes. Prednisone is the most widely used corticosteroid for treatment of OP. There is less experience with other drugs, like methylprednisolone, and none of the reviewed studies used dexamethasone. This is probably due to the safety profile of prednisone and its common use in other chronic respiratory diseases. Regarding the dose, the majority of the studies used a regimen higher than 0.5 mg/kg/day, but with a high variability within the same studies. The doses might have been adjusted based on patient's comorbidities and weight, but this was not clearly stated in the study methods. This highlights the significant heterogeneity in the corticosteroids regimens to treat OP in clinical practise.

An issue of interest is that the prolonged corticosteroid use has traditionally been justified by the risk of relapse. Treatment

regimens tended to last at least 6 months and corticosteroid dose was progressively tapered off to minimize the risk of relapse. This is confirmed by the reviewed studies, which reported relapse rates as high as 21–66% depending on the study. Lazor et al. concluded that a delay in initiating treatment increased the risk of relapse, although prolonged treatment did not seem to have any effect on the incidence of relapses.¹³

There is a scarcity of data to identify patients at greater risk of experiencing a relapse. In Lazor et al.,¹³ the relapse rate was 68% during treatment (primarily (96%) with prednisone at doses of ≤ 20 mg/day) and 32% after treatment discontinuation. In Drakopanagiotakis et al.,⁶ the relapse rate was 37.8%, with no differences between COP and SOP, and with no correlation with hypoxaemia, hypoalbuminemia, BAL lymphocytosis, or a reticulonodular pattern on high-resolution CT. In another study, radiographic findings were not independently associated with the risk of relapse in multivariate analysis.¹²⁴ Conversely, 90% of patients in Baha et al. achieved complete remission, mostly patients with ground glass opacity on high-resolution CT.² Some authors, including Cazzato et al.,⁵⁴ have suggested that elevated BAL lymphocytosis might predict a good response to corticosteroid treatment, although subsequent studies have reported different results.^{6,13} In short, although relapse is clinically crucial in the natural history of OP, to date no clinical data enables identification of treatment responders. This would avoid potential adverse effects of unnecessary corticosteroid treatment.

Surprisingly, the issue of the adverse effects of corticosteroid treatment was only reflected in a minority of studies, that reported a rate of adverse effects as high as 53%, mainly weight gain, myopathy, and osteoporosis. Undoubtedly, in addition to avoidance of relapse, reduced mortality may be a justification for the acceptance

of such high adverse effect rates. In the reviewed studies, while mortality ranged between 0% and 23%, it is not known which patient profiles was associated with a poorer response to corticosteroids and worse outcomes.

The conclusions of this review of OP studies are clearly limited by the poor quality of currently available studies. Indeed, most existing studies are case reports, while larger studies have limitations in terms of the reported data, with insufficient details on the drugs used, effectiveness, treatment duration, and rates of adverse effects. There is both a lack of studies specifically designed to evaluate this issue and a large heterogeneity in treatment, irrespective of OP aetiology (cryptogenic or secondary). All these unanswered questions highlight the need to undertake appropriately designed studies and to develop a consensus on the most appropriate treatment regimen for patients with OP that trades off benefits (reduced risk of pulmonary sequelae, relapses, and mortality) and risks (side effects) of prolonged corticosteroid administration.

Corticosteroids are widely used to treat OP, despite the lack of clinical trials specifically designed to support this practice. This systematic review of the literature points to an urgent need to implement appropriate studies aimed at developing treatment protocols with regard to compounds, dosage and duration, identifying factors associated with relapse and prognosis, and adequately monitoring adverse effects.

Authors' contributions

All authors contributed to the manuscript. Laia Cendon, Albert Rafecas and Diego Castillo were responsible for study design, analysis of data and manuscript draft. Laia Cendon and Albert Rafecas did the literature search and data collection. All the authors contributed to the interpretation of the results and the proof reading of the manuscript.

Ethical approval

Due the characteristic of the study, that is a systematic review of previous literature, ethical approval was waived.

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Conflicts of interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.opresp.2022.100211](https://doi.org/10.1016/j.opresp.2022.100211).

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