

## A 12-WEEK COMBINATION OF CLARITHROMYCIN AND PREDNISONE COMPARED TO A 24-WEEK PREDNISONE ALONE TREATMENT IN CRYPTOGENIC AND RADIATION-INDUCED ORGANIZING PNEUMONIA

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**ABSTRACT.** *Background:* Some data suggest that anti-inflammatory macrolides may be effective to treat organizing pneumonia (OP) and prevent relapses, but no formal comparison with prednisone alone is available. To explore this issue, we retrospectively compared the efficacy of a 12-week combined regimen of clarithromycin and prednisone with a 24-week prednisone alone regimen in OP. *Methods:* A standard 12-week regimen of combined clarithromycin and prednisone was designed for the treatment of cryptogenic or radiation-induced OP, aiming at reducing the cumulated prednisone dose and the relapse rate. Its use was left to the discretion of the treating physicians, members of the Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires. Data were compared to a historical control group treated with a standard 24-week prednisone alone regimen. *Results:* 16 patients were treated with combined therapy and 21 with prednisone alone. Complete radiological remission was achieved in 63% of the combined therapy group and 81% of the prednisone alone group ( $p=0.38$ ). Symptomatic relapses occurred in 81% of the combined therapy group, and 52% of the prednisone alone group ( $p=0.14$ ). No side effect of clarithromycin was reported. *Conclusions:* In patients with cryptogenic or radiation-induced OP, a 12-week regimen of clarithromycin and prednisone showed no benefit on remission rate and relapse rate as compared to a 24-week prednisone only regimen. (*Sarcoidosis Vasc Diffuse Lung Dis* 2018; 35: 230-238)

**KEY WORDS:** cryptogenic organizing pneumonia, lung diseases, interstitial, glucocorticoids, clarithromycin, treatment outcome, recurrence

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### INTRODUCTION

Organizing pneumonia (OP) is a distinct clinicopathological syndrome characterized by the subacute onset of cough, fever, dyspnea, patchy alveolar infiltrates at chest imaging, and buds of granulation tissue filling distal airspaces with overall preservation of the lung architecture (1-9). OP may be associ-

ated with various clinical conditions (secondary OP, SOP) or occur without detectable cause (cryptogenic OP, COP).

Corticosteroids are a very effective treatment of OP, but side effects occur in 25% of patients and relapses are common when steroids are tapered or stopped (3, 4, 10). We previously reported a standardized corticosteroid treatment regimen for COP (10), which proved highly effective and allowed a 50% reduction of the cumulative dose of prednisone as compared to other regimens. However, little attempts have been made to investigate the efficacy of other treatment modalities in OP.

In addition to antimicrobial effects, some macrolide antibiotics have anti-inflammatory properties, and several studies have demonstrated the beneficial effects of azithromycin in various conditions including cystic fibrosis (CF) (11), non-CF bronchiectasis (12), diffuse pan-bronchiolitis (13, 14), bronchiolitis obliterans syndrome after lung transplantation (15, 16) and chronic obstructive pulmonary disease (17-19). Besides inflammatory airway diseases, case reports and small retrospective series have suggested that erythromycin and clarithromycin could be of interest for the treatment of OP as an adjunct or an alternative to prednisone, and could reduce the relapse rate (20-24). Three studies also reported that macrolides decrease pro-inflammatory cytokine production alveolar macrophages and neutrophils in OP (24-26). However, macrolide treatment in OP has hitherto not been standardized and has not been formally compared to prednisone therapy.

The objective of the present study was to determine whether a standardized combination of clarithromycin and prednisone could allow to further reduce both the cumulative dose of prednisone and the relapse rate in OP, as compared to the previously published regimen of prednisone alone.

## METHODS

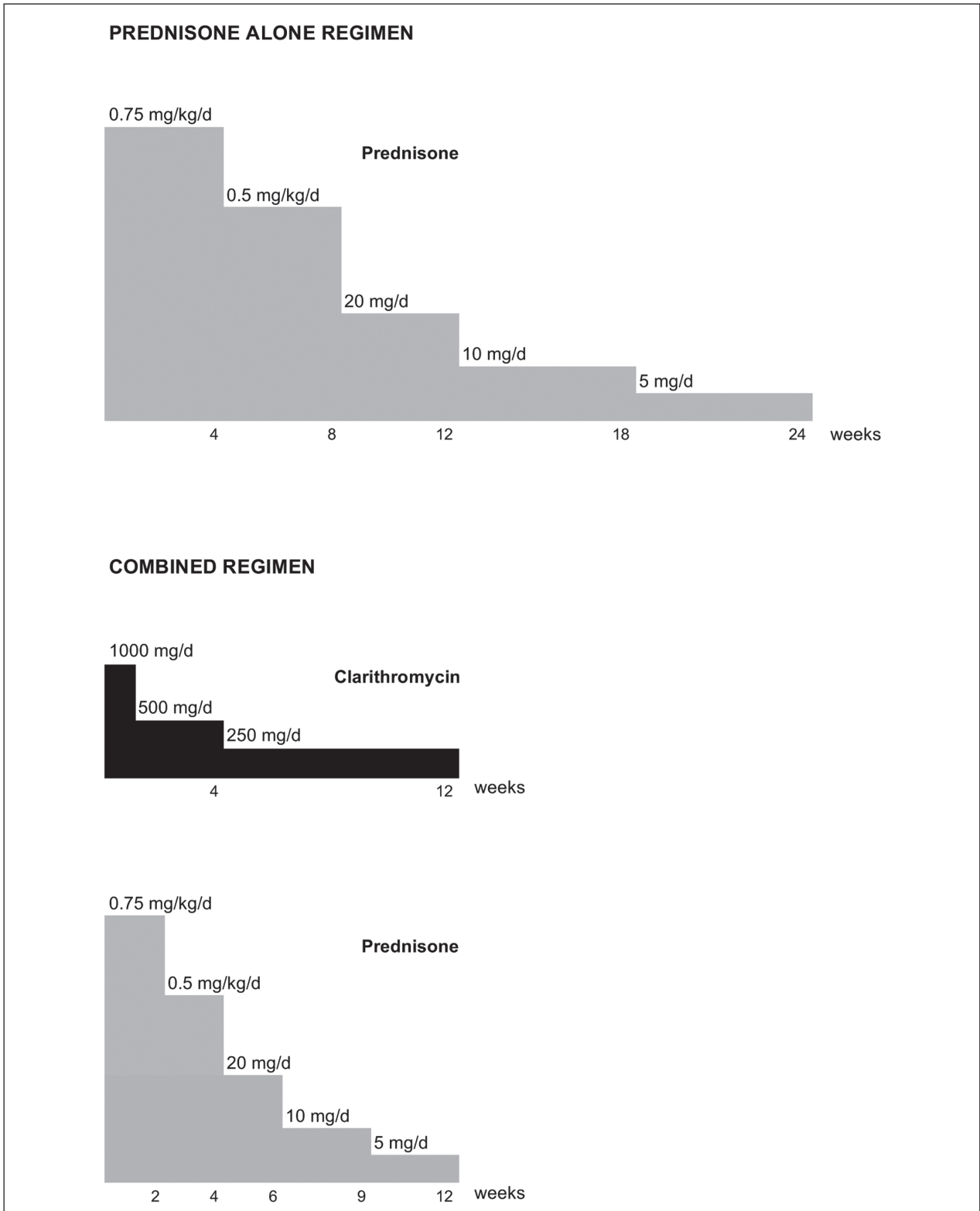
In 2008, a standard treatment protocol was defined by the Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P), a French group dedicated to the study of rare pulmonary diseases. This combined treatment protocol was based on the previously published prednisone alone protocol (10) with 2 changes: 1) addition of

clarithromycin to prednisone, and 2) reduction of the treatment duration from 24 to 12 weeks. This duration was based on previous reports showing that macrolides may provide response in this time frame (20, 22, 24, 27). Prednisone was added to provide a rapid relief of symptoms, because clarithromycin alone appeared to have a slow onset of action in previous reports, and it was considered unethical to treat patients without prednisone given its rapid effect and high efficacy in OP. The combined treatment regimen is shown in figure 1. Relapses occurring under or after combined therapy were treated with prednisone alone according to a previously published 24-weeks protocol for relapses (20 mg/d prednisone for 12 weeks, then 10 mg/d for 6 weeks, then 5 mg/d for 6 weeks) (10). The combined treatment protocol was proposed to GERM"O"P members as a treatment option which could be offered to patients with OP, at the discretion and under the responsibility of the treating physician, in the absence of contraindication to clarithromycin. Protocol modifications or switches to prednisone alone were allowed when deemed useful.

In 2012, a detailed questionnaire was sent to physicians having reported cases of OP treated with the clarithromycin + prednisone combination, to analyze its efficacy retrospectively. Questionnaires were filled by reviewing medical records. Retrieved items included demographic data, co-morbidities, cigarette smoking, medication, symptoms, laboratory values, pulmonary function testing, results of biopsies, bronchoalveolar lavage, chest X-rays and CT-scan results, and follow-up information. All previously published causes of OP such as infections, drugs, or collagen-vascular diseases where explicitly looked for.

Cases were included if they met all the following criteria:

- 1) Clinical and imaging features characteristic of OP, with no follow-up event which could challenge the initial diagnosis.
- 2) Diagnosis of COP, or OP due to radiation therapy for breast cancer. This particular cause of OP was accepted as its clinical presentation is highly similar to COP, and because its cause can be confidently identified.
- 3) Histopathological proof of OP pattern at surgical or transbronchial lung biopsy in COP. This criterion was not required for OP due to radiation therapy for breast cancer, as the



**Fig. 1.** Prednisone alone and combined clarithromycin and prednisone protocols

clinical and imaging features in this particular context allow a confident diagnosis in the absence of lung biopsy.

- 4) Treatment with a combination of clarithromycin and prednisone according to the 2008 protocol prescribed for the first episode of OP, on an intention-to-treat basis.

Cases were excluded if they met any of the following criteria:

- 1) OP other than cryptogenic or secondary to radiation therapy for breast cancer
- 2) Lack of histological proof of OP pattern in COP.
- 3) Treatment of clarithromycin and prednisone prescribed for a relapse.

A historical control group consisted of consecutive patients treated with the previously published prednisone alone protocol for COP or OP due to radiotherapy for breast cancer in GERM"O"P participating centers before 2008 and/or after 2012.

The main endpoints were the radiological response rates and the relapse rate. Treatment efficacy was categorized by the treating physician as follows based on radiological assessment: 1) complete remission, 2) more than 50% improvement, 3) less than 50% improvement, 4) no improvement.

Numerical data were expressed as medians and interquartile range. Comparisons between continuous variables were made by the Mann-Whitney test. Proportions were compared by the chi-square test.

## RESULTS

### *Case selection and study population*

Twenty-nine questionnaires were available for analysis. Thirteen cases were excluded for the following reasons: OP associated with systemic sclerosis (n=1), combined treatment given for a relapse (n=7), and COP without histological proof (n=5). The remaining 16 cases (9 COP and 7 OP due to radiation therapy for breast cancer) were included. All patients had a compatible clinicoradiological picture and no event during follow-up which could challenge the diagnosis of OP. Histopathological specimens were available in all cases of COP, either by surgical lung biopsy (6 cases), or transbronchial biopsy (3 cases).

The control group consisted of 21 patients

treated for a first episode of OP with the standard prednisone alone protocol. There were 4 cases of OP secondary to radiation therapy and 17 COP. Seven cases of COP were proven by surgical lung biopsy, and 10 by transbronchial biopsy.

Patients' baseline characteristics are shown in Table 1. There were no statistically significant differences between groups for demographic variables, clinical features, laboratory data, lung function tests, chest imaging and BAL. The median follow-up duration was similar in both groups (1.7 vs 1.3 years,  $p=0.510$ ).

### *Response to treatment and relapse rate*

Treatment response data were available for all patients. The response rates and the relapse rates are shown in Table 2. Fifteen patients (94%) received exactly the planned doses of clarithromycin and prednisone, and in one case the combination therapy was altered at the discretion of the treating physician. Complete remission was observed in 63% of the combined treatment group and in 81% of the prednisone alone group ( $p=0.38$ ). All the remaining patients had a >50% improvement, except one in the prednisone alone group who was considered to have <50% improvement.

One or more relapses occurred in 13 (81%) patients of the combined treatment group and in 11 (52%) of the prednisone alone group ( $p=0.14$ ). The diagnosis of relapse was clinical and radiological in all but one patient who had a surgical lung biopsy. The time to the first relapse was similar in both groups (median 17 vs 18.3 weeks,  $p=0.931$ ). Among the patients who relapsed, the median number of relapses was 1 in the combination group and 2 in the prednisone group (range 1 to 5,  $p=0.688$ ). In the combined treatment group, 3/13 (23%) patients were still on prednisone (5 to 10mg/d) and clarithromycin (250 to 500mg/d) at the time of first relapse. In 10/13 (77%), the first relapse occurred after the end of therapy. Of the 11/21 patients who relapsed in the prednisone alone group, 9/11 (82%) were still on prednisone at the time of relapse (doses ranging from 2.5 to 20mg/d, median 10mg/d). All relapses were treated with the same protocol of prednisone only, starting with 20mg/d of prednisone, except patients who relapsed on higher doses of prednisone.

**Table 1.** Patients characteristics

	CLA+PRED (n=16)		PRED (n=21)		P
	median or %	IQR	median or %	IQR	
<i>Demographics</i>					
Female sex, %	75		52		0.288
Age at diagnosis, yr	62	[52 - 74]	67	[50 - 71]	0.951
Etiology cryptogenic, %	56		81		0.204
<i>Clinical presentation</i>					
Cough, %	81		91		0.743
Fever, %	81		62		0.362
Weight loss, %	44		58		0.621
Fatigue, %	75		80		0.964
Sweating, %	31		26		0.957
Arthralgia, %	13		16		0.835
Dyspnea, %	75		81		0.974
Dyspnea NYHA stage	2	[2 - 3]	2	[2 - 3]	0.778
Chest pain, %	25		29		0.896
Lung crackles, %	88		84		0.835
<i>Laboratory</i>					
CRP, mg/l	62	[43 - 109]	36	[16 - 72]	0.080
Hemoglobin, g/l	120	[111 - 128]	125	[116 - 135]	0.167
Leucocytes, G/l	7.6	[6.0-11.5]	9.2	[7.5-10]	0.496
Neutrophils, G/l	5.1	[3.5 - 7.2]	7.0	[4.8 - 8.2]	0.204
Eosinophils, G/l	0.2	[0.2 - 0.4]	0.1	[0.0 - 0.3]	0.078
Diagnosis by TBB (%)	25		33		0.852
Diagnosis by SLB (%)	38		52		0.093
<i>Lung function</i>					
FEV1, %pred	90	[76 - 99]	84	[57 - 100]	0.662
FVC, %pred	98	[85 - 111]	84	[67 - 104]	0.171
<i>Imaging</i>					
Multifocal form, %	87		67		0.329
Unifocal, %	0		10		0.623
Diffuse, %	13		24		0.723
Bilateral, %	80		76		0.892
Migratory, %	47		29		0.522
Ground glass, %	47		40		0.961
Consolidation, %	100		95		0.884
Nodules, %	27		24		0.845
Cavities, %	0		10		0.599
Subpleural distribution, %	40		33		0.953
Central distribution, %	27		14		0.618
Central+subpleural distribution, %	33		52		0.427
Pleural effusion, %	27		10		0.364
Lymphadenopathy, %	27		19		0.892
<i>Bronchoalveolar lavage</i>					
Neutrophils, %	7	[5 - 11]	7	[3 - 13]	0.920
Lymphocytes, %	21	[5 - 35]	31	[16 - 51]	0.393
Eosinophils, %	6	[0 - 12]	2	[1 - 9]	0.668

TBB: Transbronchial biopsy, SLB: surgical lung biopsy, IQR: interquartile range, CLA: clarithromycin, PRED: prednisone, CRP: c-reactive protein, FEV1: forced expiratory volume in one second, FVC: forced vital capacity

### Outcome

No death or respiratory failure occurred. Thirty-three percent of the patients in the prednisone group, and 20% of patients in the combination group were

still on prednisone when last seen. 73% in the combination group and 67% in the prednisone group had normal chest X-ray at last visit (p=0.951). No relevant side effects were reported.

**Table 2.** Response to treatment

	CLA+PRED (n=16)		PRED (n=21)		P
	median or %	IQR	median or %	IQR	
<i>Radiological response to treatment</i>					
Complete, %	63		81		0.378
>50% radiological improvement, %	38		14		0.214
<50% radiological improvement, %	0		5		0.890
<i>Relapses</i>					
Any relapse, %	81		52		0.140
Time to 1st relapse, weeks	17.0	[14 - 22.7]	18.3	[12.3 - 27.9]	0.931
Prednisone dose at relapse, mg/d	10	[7.5 - 10]	15	[8.8 - 20]	0.238
Number of relapses	1	[1 - 2]	2	[1 - 2]	0.688

IQR: interquartile range, CLA: clarithromycin, PRED: prednisone

## DISCUSSION

This retrospective study is the first to compare the standard treatment regimen to an alternative regimen for OP. Contrary to our hypothesis, we found that a 12-week combined treatment regimen of clarithromycin and prednisone resulted in a lower response rate and a higher relapse rate as compared to a previously published 24-week prednisone alone regimen. These findings suggest that clarithromycin cannot replace prednisone in the initial treatment of OP, and challenge previous reports suggesting a beneficial effect of anti-inflammatory macrolides in this condition.

Ishikawa et al. first reported the use of erythromycin in organizing pneumonia (27) soon after a publication showing its efficacy in chronic pan-bronchiolitis. In the following years, case reports and small series suggested that macrolide antibiotics such as erythromycin and clarithromycin could be of interest for the treatment of OP as an adjunct or an alternative to prednisone, and could reduce the relapse rate (20-24). Two *in vitro* studies also showed that macrolides decrease pro-inflammatory cytokine production by alveolar macrophages and neutrophils in OP (25, 26). The findings of the clinical studies are summarized in table 3.

Most previous reports suggested that the initial response to macrolide therapy in OP is less predictable than the response to prednisone. In a series of 12 patients treated with clarithromycin for 3 months, only 7 (58%) had complete response and 3 (25%) had to be switched to prednisone because they showed no improvement at all (22). Stover et al reported com-

plete response in only 2/6 patients (33%) and improvement in 3/6 (50%), while the response was not well specified in one case (20). Pathak et al. reported complete response in only one of 4 cases (25%) (23). In contrast, Ishikawa and Kastelik reported a complete response in respectively 6/6 and 3/3 cases (21, 27), and in one recent study, a complete response was reported in 22/26 cases treated with clarithromycin 1000 mg/day for 3 months (24). The complete response rate observed in the present study with a combined clarithromycin and prednisone regimen (58%) is similar or higher than in most previous reports with clarithromycin alone, but appears lower than with the prednisone alone regimen (81%). One could hypothesize that the lower cumulative dose of prednisone and the shorter treatment duration in the combined regimen, which were both reduced 50% as compared to the prednisone alone regimen, were the cause of a lesser disease control and the lower rate of complete treatment response.

The relapse rate observed in our study with combined therapy (81%) was the highest among all series of macrolide therapy in OP, and also one of the highest reported in OP overall. However, the relapse rate could have been underestimated in some previous studies because of short follow-up. For instance, in the study by Ichikawa et al., the mean follow-up was only 3.6±1.8 months (27). In contrast to our findings, Radzikowska et al. reported no relapse in 11 patients treated with clarithromycin alone for 3 to 4 months and followed for a mean duration of 42 months (22). More recently, the same authors reported only 2 relapses in 26 patients with COP treated with clarithromycin alone 1000 mg/day for

**Table 3.** Previous reports of macrolide use in OP

Author	year	n	diagnosis	biopsy	macrolide	macrolide dose (mg/d)	associated prednisone	treatment duration (mo)	onset of action (wk)	response	mean follow-up duration (mo)	relapse rate (%)
Epler (2)	1985	3	OP	3/3	ERY, tetracycline	N/A	no	N/A	N/A	response in 3/3	N/A	N/A
Ichikawa (27)	1993	6	OP	6/6	ERY	600	no	3	>2-4	complete response at 3 mo in 6/6	3.6	0
Arbetter (28)	1999	1	RAD	1/1	N/A	N/A	no	1	N/A	response in 1/1	N/A	0
Stover (20)	2005	6	3 COP, 3 RAD	6/6 (1 not showing OP)	CLA	not uniform. 500-1000 initially, 250 at treatment end	no	1-6	1-4	complete 2/6, partial 3/6, N/A 1/6	unknown in 3/6, 40 mo in 3/6	33
Kastelik (21)	2006	3	COP	not specified	CLA	1000	in 1/3	3-12	N/A	complete 3/3	N/A	N/A
Radzikowska (22)	2008	12	COP	12/12	CLA	1000	no	3-4	N/A	complete 7/12, partial 2/12, none 3/12	42	0
Pathak (20)	2014	4	3 COP, 1 dronedarone	4/4	CLA	500 to 1000 initially	in 2/4	N/A	N/A	complete 1/4, partial 2/4, N/A 1/4	N/A	N/A
Ding (28)	2015	1	COP	1/1	AZM	500	in 1/1	6	N/A	complete 1/1	12	0
Radzikowska (24)	2016	26	COP	26/26	CLA	1000	in 4/26	3	N/A	complete 22/26, partial 2/26, none 2/26	53	8

ERY: erythromycin, CLA: clarithromycin, AZM: azithromycin, RAD: OP induced by radiation therapy for breast cancer, N/A: data not available.

3 months and followed for a mean duration of 53 months (24). The cause of this striking difference in relapse rate is unclear. One could hypothesize that the patients reported in these 2 series (22, 24) had a less severe disease and were less prone to relapses. Another hypothesis is that prednisone used in our protocol in addition to clarithromycin could have favored the occurrence of relapses after treatment tapering as compared to clarithromycin alone. However, the relapse rate in the combined regimen (81%) was higher than in the prednisone alone regimen (52%), whereas the opposite would have been expected if prednisone therapy was favoring the occurrence of relapses. Alternatively, the different relapse rate could be explained by different doses of clarithromycin, which was tapered in our protocol

but maintained at 1000 mg/day for 3 months in the study by Radzikowska (24).

Our study represents real-life experience with a standardized clarithromycin-prednisone protocol in several centers. We only included well-documented cases of OP, all with compatible clinico-radiological features, and all cases of COP with histological proof of diagnosis. 94% of patients received the combination treatment as planned. All cases treated with the combination treatment by GERM"O"P members were reported, thus reducing the bias resulting from overreporting of successful cases.

Our study also had weaknesses. The treatment allocation was not randomized. As the choice of treatment was left to the physician, a selection bias could have occurred. The treatment efficacy was

evaluated by the treating physician. A review of all radiological files by an independent radiologist would have been preferable but could not be done for practical reasons. Follow-up pulmonary function tests were not available for analysis. Due to small sample size, no formal comparison between COP and radiation-induced OP was made. Despite these limitations, we believe that the very high relapse rate observed with the combined regimen could not be explained by chance or bias alone, and that we can confidently conclude that this combined regimen does not prevent relapses effectively.

In summary, the present study does not suggest a role for a combination of clarithromycin and prednisone in the treatment of OP, neither to reduce the cumulative dose of prednisone, nor to reduce the relapse rate. However, as suggested by other authors (24), it is possible that clarithromycin alone at higher doses is of interest in the situation. A randomized controlled trial comparing clarithromycin alone with prednisone alone would be needed to address this issue.

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## Ethics approval and consent to participate:

This retrospective study was approved by the Review Board of the French Learned Society for Respiratory Medicine (Société de Pneumologie de Langue Française) under the reference CEPRO 2012 019.

## Authors' contributions

Study conception and design: all authors; data acquisition: all authors; data analysis and interpretation: NP, VC, JFC, RL; manuscript drafting: NP, VC, JFC, RL; critical manuscript revision: all authors; final manuscript approval: all authors.

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