

Cryptogenic Organizing Pneumonia Characteristics of Relapses in a Series of 48 Patients

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Cryptogenic organizing pneumonia (COP) is a clinicopathologic syndrome characterized by rapid resolution with corticosteroids, but frequent relapses when treatment is tapered or stopped. We retrospectively studied relapses in 48 cases of biopsy-proven COP. One or more relapses (mean 2.4 ± 2.2) occurred in 58%. At first relapse, 68% of patients were still under treatment for the initial episode. Compared with the no-relapse group, nine patients with multiple (≥ 3) relapses had longer delays between first symptoms and treatment onset (22 ± 17 versus 11 ± 8 wk, $p = 0.02$), and elevated γ -glutamyltransferase (124 ± 98 versus 29 ± 13 IU/L, $p = 0.001$) and alkaline phosphatase (190 ± 124 versus 110 ± 68 IU/L, $p = 0.04$) levels. Relapses did not adversely affect outcome. Corticosteroid treatment side effects occurred in 25% of patients. Standardized treatment in 14 patients allowed a reduction of prednisone cumulated doses ($p < 0.05$) without affecting outcome or relapse rate. We conclude that: (1) delayed treatment increases the risk of relapses; (2) mild cholestasis identifies a subgroup of patients with multiple relapses; (3) relapses do not affect outcome, and prolonged therapy to suppress relapses appears unnecessary; (4) a standardized treatment allows a reduction in steroid doses.

Bronchiolitis obliterans organizing pneumonia (BOOP) has been individualized in the past two decades as a distinct clinicopathologic entity (1–12). The main clinical features include subacute onset of cough, fever, dyspnea, sparse crackles at auscultation, and multiple patchy, often migratory, alveolar infiltrates on chest imaging. The characteristic histologic feature is the presence of buds of granulation tissue in the distal airspaces. BOOP has been causally related to various conditions such as drug injury, infections, collagen vascular diseases, malignancies (13–15), and more recently, radiation therapy (16). However, most frequently, no specific cause can be detected, leading to the diagnosis of idiopathic BOOP, better termed cryptogenic organizing pneumonia (COP) because organizing pneumonia is the major histologic criterion and bronchiolitis obliterans may be absent in some cases. COP usually responds spectacularly well to corticosteroid treatment and typically runs a benign course. However, relapses can occur when steroids are tapered or stopped. The issue of relapses

has been addressed in only one published study (17), and their management has not been clarified. The objectives of this study were to examine the pattern of relapses in COP, to determine whether relapses affect morbidity and mortality, to identify possible predictive factors of relapses, and to establish whether a standardized therapeutic protocol that we designed is beneficial.

METHODS

Recruitment of Cases

This study was undertaken by the Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O" P), a French collaborative group of pulmonary physicians dedicated to the study of rare (so-called "orphan") pulmonary diseases. Founded in 1993, the GERM"O" P includes over 200 physicians and 40 university hospitals distributed nationwide, with a coordination center based in Lyon, France. Members keep in regular contact through newsletters and an annual meeting, and thus constitute a homogenous and motivated group. A registry of "orphan" pulmonary diseases has been implemented as a tool for clinical research. Starting from April 1995, participating physicians were requested to report to the registry all prevalent and incident cases of selected "orphan" pulmonary diseases, including BOOP either idiopathic (COP) or secondary. Reports were nominative for patients who gave written consent, and anonymous otherwise. By August 1999, more than 1,100 cases of "orphan" pulmonary diseases had been reported to the registry.

Data Collection

In January 1998, a detailed questionnaire was sent to all physicians having reported cases of COP to the registry. Questionnaires were completed by reviewing the medical records. Retrieved items included past medical history, medication, clinical and biologic data, imaging, pulmonary function tests, bronchoalveolar lavage (BAL), histopathologic reports, treatment, and outcome. Special attention was paid to number, timing, and treatment of all relapses. Flow charts were used to record daily doses of prednisone during whole follow-up with the best possible accuracy. All previously published causes of BOOP such as infections, drugs, or collagen vascular diseases were explicitly searched for by the questionnaire. Data collection ended in October, 1998.

Selection of Cases

All questionnaires and histopathologic reports were carefully reviewed. All four of the following criteria were required for inclusion in the present study: (1) histopathologic diagnosis of COP, defined as the presence of buds of granulation tissue in the distal airspaces on surgical or transbronchial lung biopsy, as explicitly described on the histopathologic report, without mention of any other feature suggestive of another diagnosis; (2) clinical and imaging features compatible with COP; (3) absence of identifiable cause according to the published literature; and (4) patients treated by corticosteroids. Cases not meeting the aforementioned criteria were excluded from further analysis. Relapses of COP were defined as the appearance of characteristic new infiltrates on chest imaging, with compatible clinical features,

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BAL, and/or lung biopsy if available, and no identified cause. A histopathologic proof of COP was not required for the diagnosis of relapse, if typical.

Data Analysis

Patients were divided into two groups according to the presence (R group) or absence (NR group) of relapses, and compared to identify possible predictive factors and the influence of relapses on morbidity and mortality. The following variables were examined: sex, age, smoking status, symptoms and signs, sedimentation rate, C reactive protein, hemoglobin, blood count, alanine aminotransferase, aspartate aminotransferase, γ -glutamyltransferase, alkaline phosphatase, rheumatoid factor, antinuclear antibodies, antineutrophil cytoplasmic autoantibodies, imaging (solitary, multifocal, or diffuse opacities; ground glass, consolidation, air bronchogram, nodules), pulmonary function testing, arterial blood gases, BAL, delays between first symptoms and treatment onset, daily dose of prednisone at any time of the treatment period, initial use of intravenous corticosteroids and immunosuppressant drugs, delays for clinical recovery and chest X-ray clearing, treatment side effects, number and timing of relapses, occurrence of respiratory failure and death, clinical and imaging status at last visit, total and relapse-free follow-up duration.

The NR group was also compared with a subgroup (MR) with multiple (≥ 3) relapses for the same variables. This threshold of ≥ 3 relapses was set arbitrarily to compare the extremes of the study population (no relapse versus multiple ones) and uncover differences that could have been missed by the NR versus R comparison. To determine whether high-dose corticosteroids were beneficial for relapse treatment, we also compared patients receiving high (> 20 mg/d, H subgroup) and low (≤ 20 mg/d, L subgroup) initial steroid doses for first relapse. In another analysis, the whole study population was separated according to the steroid therapy regimen used for the initial episode of COP, i.e., a standardized protocol proposed by the GERM"O"P (A group), or other treatment modalities (B group). The standardized protocol was as follows: patients received 0.75 mg/kg/d prednisone during 4 wk, then 0.5 mg/kg/d during 4 wk, then 20 mg/d during 4 wk, then 10 mg/d during 6 wk, then 5 mg/d during 6 wk. Prednisone was given by oral route, except in critical situations where intravenous boluses of methylprednisolone (2 mg/kg/d) were given during the first 3 to 5 d. The total treatment duration for the initial episode of COP was 24 wk. Relapses occurring under prednisone < 20 mg/d were treated by increasing prednisone to 20 mg/d during 12 wk, then tapering doses as for the initial episode, i.e., 10 mg/d during 6 wk, and 5 mg/d during 6 wk. The total treatment duration for relapse was 24 wk. Doses of corticosteroids were expressed as prednisone equivalents. Numerical data were expressed as mean \pm SD, and compared by the two-way unpaired *t* test. Proportions were compared by the chi-square test.

RESULTS

Study Population

Forty-eight centers or physicians having reported cases to the registry participated in the study. Ninety-two filled questionnaires were available for analysis. Forty-four cases did not fit the inclusion criteria for the following reasons: typical clinicoradiologic cases but lung biopsy not performed (12 cases); missing or nondiagnostic histopathologic report, i.e., no explicit mention of buds of granulation tissue in distal airspaces (13 cases); identified or suspected causal agent of BOOP (15 cases); and spontaneous improvement without treatment (four cases). The remaining 48 patients were included in the present study.

Cases were evaluated between 1987 and 1998. There were 31 women (65%) and 17 men (35%). The mean age at diagnosis was 61 ± 11 yr (median 63, range 24 to 77). Thirty-four patients (71%) were nonsmokers. The proportion of nonsmokers was significantly higher among women (90 versus 45%, $p = 0.002$). The mean duration of symptoms before diagnosis was 13 ± 11 wk (median 9). Diagnostic histopathologic specimens

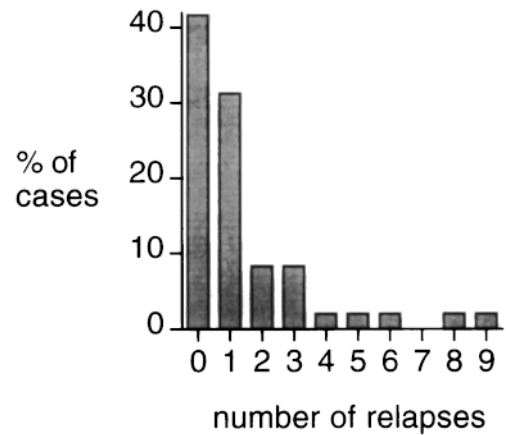


Figure 1. Distribution of 48 cases of COP according to the number of relapses. Values are expressed as percentage of the whole study population.

were obtained by surgical lung biopsy (either video-assisted thoracoscopy or open lung surgery) in 33 patients (69%), and transbronchial biopsy in 15 (31%). At imaging, 33 patients (69%) had multifocal opacities, 11 (23%) had a diffuse infiltrative pattern, and four (8%) had a solitary opacity. The mean daily dose of prednisone to treat the initial episode of COP was 50 ± 17 mg at onset, 19 ± 12 mg after 3 mo, 11 ± 8 mg after 6 mo, and 6 ± 3 mg after 12 mo. The mean follow-up duration after diagnosis was 35 ± 31 mo (median 23). The 15 cases evaluated by transbronchial biopsy only were followed for 19 ± 12 mo (median 15) with no incident that might put the initial diagnosis of COP into doubt.

Number, Timing and Probability of Relapse

No relapse occurred in 20 of 48 (42%) patients (NR group). One or more relapses occurred in 28 of 48 (58%) patients (R group). Fifteen of 48 (31%) patients experienced only one relapse, whereas 13 of 48 (27%) had two or more relapses. Nine patients (19%) with multiple (≥ 3) relapses constituted the MR subgroup. Four or more relapses occurred in only five of 48 patients (10%). The distribution of cases according to the number of relapses is shown in Figure 1. In the R group, the mean number of relapses was 2.4 ± 2.2 (median 1, range 1 to 9). The mean delay between onset of treatment for initial episode and first relapse was 8 ± 9 mo (median 5, range 2 to 46). The first relapse occurred within 6 mo after the initial episode

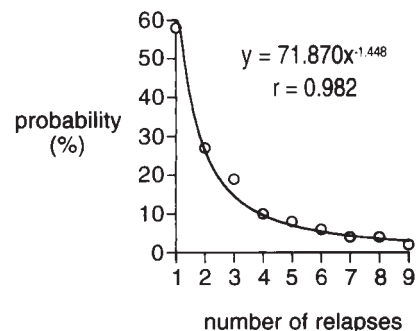


Figure 2. Probability of experiencing a given number of relapses at the time of the initial episode of COP. Probabilities were calculated as the number of patients experiencing a relapse of a given range (first, second, etc) divided by the total number of patients at risk ($n = 48$). The relationship is curvilinear and follows an inverse correlation pattern.

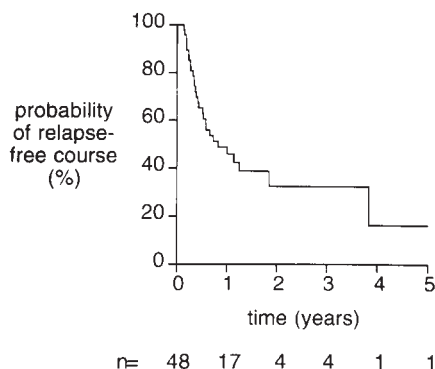


Figure 3. Probabilities of relapse-free course as a function of time after onset of treatment for the initial episode of COP (Kaplan-Meier method). n = number of patients at risk at each time point.

in 16 of 28 (57%) patients, and within 1 year in 23 of 28 (82%). First relapses occurring more than 15 mo after the initial episode were very uncommon (2 of 28 = 7%).

For the whole study population, the probability of having a given number of relapses at the time of initial episode is shown in Figure 2. The relationship was curvilinear and followed an inverse pattern ($y = 1/x$) with a high correlation coefficient ($r = 0.982$). The probability of relapse-free course as a function of time in the whole study population was analyzed by the Kaplan-Meier method. It was 65% at 6 mo, 49% at 1 yr, 32% at 2 yr, and 16% at 4 yr after the initial episode of COP (Figure 3). When considering patients with a determined outcome at given periods of time, the proportion of patients remaining relapse-free was 28 of 44 (64%) at 6 mo, 17 of 40 (43%) at 1 yr, and four of 31 (13%) at 2 yr. In summary, the risk of relapse was high, especially within the first year after the initial episode of COP. A subgroup was prone to multiple relapses. The probability of remaining relapse-free was as low as 13% at 2 yr after the initial episode.

Ongoing Treatment at the Time of First Relapse

Nineteen of 28 (68%) patients were still undergoing steroid therapy when the first relapse occurred, and nine of 28 (32%) had stopped treatment for a mean delay of 9 ± 20 mo (median 2). For the 19 patients still receiving steroids at first relapse, the mean daily dose was 12 ± 7 mg (median 10, range 2.5 to

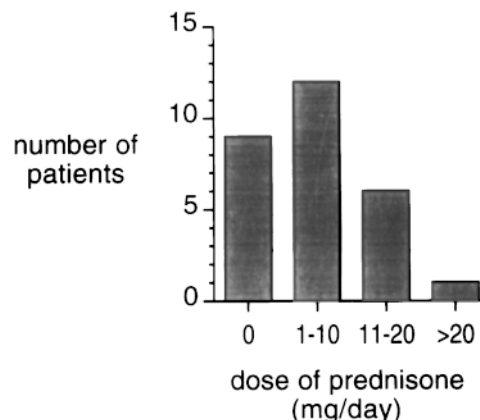


Figure 4. Distribution of the 28 cases of the R group according to the dose of prednisone taken for the initial episode of COP, when the first relapse occurred.

25). The distribution of cases according to the dose of prednisone at the time of first relapse is shown in Figure 4. Twenty-one of 28 patients (75%) were receiving zero to 10 mg/d, and six of 28 (21%) were receiving 11 to 20 mg/d. Only one patient (4%) was receiving more than 20 mg/d. In summary, the great majority of first relapses occurred under ≤ 20 mg/d of prednisone.

Predictors of Relapse Occurrence

R and NR groups were compared in search of factors predictive of relapses. No differences were found for sex, age, smoking history, season of onset, frequency of symptoms and signs, sedimentation rate, hemoglobin, blood count, liver enzymes, presence of autoantibodies, and imaging features. BAL characteristics and pulmonary function tests during the initial episode are shown in Table 1. No significant difference was found between groups for any variable. The frequency of functional abnormalities was also similar in both groups (data not shown). The average delay between first symptoms and treatment onset tended to be longer in the R group, without reaching statistical significance (16 ± 12 versus 11 ± 8 wk, $p = 0.1$). However, at a cutoff delay of 16 wk, the proportion of patients undergoing treatment was significantly lower in the R group (54 versus 90%, $p = 0.02$). Data on outcome are shown in Ta-

TABLE 1
INITIAL BAL AND PULMONARY FUNCTION TESTS IN
NONRELAPSING (NR) AND RELAPSING (R) GROUPS

	n	NR Group	% pred	n	R Group	% pred	p Value
BAL							
n		14		20			
Total cell count, cell/ μ l		417 ± 310		341 ± 235			NS
Macrophages, %		54 ± 25		53 ± 28			NS
Lymphocytes, %		32 ± 21		25 ± 18			NS
Neutrophils, %		9 ± 9		13 ± 16			NS
Eosinophils, %		5 ± 10		8 ± 13			NS
Pulmonary function tests							
FEV ₁ , L	15	1.8 ± 0.6	71 ± 22	17	1.8 ± 0.6	79 ± 18	NS
FVC, L	15	2.4 ± 0.7	75 ± 20	17	2.4 ± 0.7	81 ± 16	NS
FEV ₁ /FVC, %	15	74 ± 11	94 ± 14	17	75 ± 12	97 ± 14	NS
TLC, L	12	4.6 ± 1.3	85 ± 13	14	4.5 ± 1.4	84 ± 15	NS
RV, L	12	2.0 ± 0.8	101 ± 30	14	1.7 ± 0.7	96 ± 36	NS
Tl _{CO} , % pred	9		74 ± 21	13		90 ± 25	NS
Resting Pa _{O₂} , mm Hg	16	68 ± 11		15	72 ± 8		NS

Definition of abbreviations: RV = residual volume; Tl_{CO} = carbon monoxide transfer factor.

TABLE 2
FOLLOW-UP IN NR AND R GROUPS

	NR Group	R Group	p Value
Outcome after initial episode of COP			
Delay to 50% improvement on CXR, wk	3 ± 3	4 ± 4	NS
Delay to CXR normalization, wk	15 ± 12	10 ± 7	NS
Respiratory failure, %	5	0	NS
Death, %	5	4	NS
Last follow-up visit			
Follow-up duration, mo	19 ± 19	47 ± 33	0.001
Still taking steroids, %	30	36	NS
Dose of prednisone, mg/d	4 ± 8	5 ± 10	NS
Normal CXR, %	80	78	NS

Definition of abbreviation: CXR = chest X-ray.

ble 2. The delays for chest radiograph clearing under treatment were not significantly different between groups. At the last follow-up visit, the proportion of patients receiving steroids, and the mean prednisone dose were also similar. Follow-up duration was significantly shorter in the NR group (19 ± 19 versus 47 ± 33, $p = 0.001$). In summary, the R group was characterized by a lower proportion of patients with treatment started within 16 wk of symptoms duration, and a longer follow-up.

The NR group was further compared with the MR subgroup (multiple relapses). The mean delay between first symptoms and treatment onset was significantly longer in the MR subgroup (22 ± 17 versus 11 ± 8 wk, $p = 0.02$). The proportion of patients with treatment started within 16 wk of symptoms duration was also lower in the MR subgroup (44 versus 90%, $p = 0.03$). Another difference between NR and MR groups lies in liver enzymes. The MR subgroup had higher mean values of γ -glutamyltransferase (124 ± 98 versus 29 ±

13 international units per liter [IU/L], $p = 0.001$), alkaline phosphatase (190 ± 124 versus 110 ± 68 IU/L, $p = 0.04$) and alanine aminotransferase (34 ± 26 versus 19 ± 9 IU/L, $p = 0.05$) concentrations. Similarly, the MR subgroup was characterized by a significantly greater proportion of patients having γ -glutamyltransferase level > 50 IU/L (60 versus 6%, $p = 0.04$), alkaline phosphatase level > 150 IU/L (63 versus 11%, $p = 0.02$) and alanine aminotransferase level > 40 IU/L (38 versus 0%, $p = 0.04$). Aspartate aminotransferase concentration and all other biologic variables were not significantly different. No difference was found for severity of impairment at pulmonary function testing. BAL cell counts were also similar. In summary, the MR subgroup was characterized by delayed treatment for the initial episode of COP and mild cholestasis.

To determine whether differences in therapy for the initial episode of COP could explain the occurrence of relapses, we compared the average daily dose of prednisone during the first year in R and NR groups. Results are shown in Figure 5. To avoid bias, patients were excluded from the initial cohort whenever one of the three following events occurred: treatment cessation, first relapse requiring increase of the steroid dose, or end of follow-up. This explains why the number of patients contributing to calculation of average dose decreased over time in both groups, and more rapidly in the R group (Figure 5). However, this method allowed a valid comparison of mean prednisone daily doses at any time between onset of treatment and occurrence of first relapse. The mean prednisone daily doses in NR and R groups were respectively 19 ± 10 and 18 ± 14 mg after 3 mo, 8 ± 5 and 16 ± 10 mg after 6 mo, and 8 ± 4 and 4 ± 1 mg after 12 mo following treatment onset for the initial episode of COP ($p =$ not significant [NS]). No significant difference was found in mean daily doses, doses/kg body weight, and cumulative doses at any time during the treatment period. In summary, relapse occurrence in the R group was not the result of lower doses of corticosteroids.

Effect of Relapses on Morbidity and Mortality

At last follow-up visit, the proportion of patients with normal chest radiograph was similar in NR and R groups (80 versus 78%, respectively). Last available pulmonary function tests performed remote from any acute disease were not significantly different, except for a reduction of residual volume in the R group (79 ± 18 versus 105 ± 26% of predicted value, $p = 0.009$). Carbon monoxide transfer factor and arterial blood gases were not different. In summary, relapses did not result in poorer outcome at imaging and pulmonary function testing.

Respiratory failure requiring mechanical ventilation with a favorable outcome occurred in one of 20 (5%) patients of the NR group, and in zero of 28 (0%) patients of the R group ($p =$ NS). Two patients died during the follow-up period. One 78-yr-old man of the R group died 7 yr after the initial episode of COP. He had experienced six relapses, all responding well to steroid therapy. Death was attributed to massive pulmonary embolism. The second death occurred in a 75-yr-old woman of the NR group 8 wk after the initial episode of COP, while she was in complete remission and taking 30 mg/d prednisone. Death was due to accidental rupture of a renal artery during balloon angioplasty. In summary, no death could be attributed to COP or relapses.

One or more complications of corticosteroid therapy were reported in 12 of 48 (25%) patients. Complications included weight gain (7 patients), myopathy (2), osteoporosis (1), hypertension (1), diabetes (1), edema (1), pulmonary abscess (1), increased intraocular pressure (1), electrolyte disorders (1), and epigastralgia (1). One or more complications were reported in four of 20 (20%) patients of the NR group, and eight

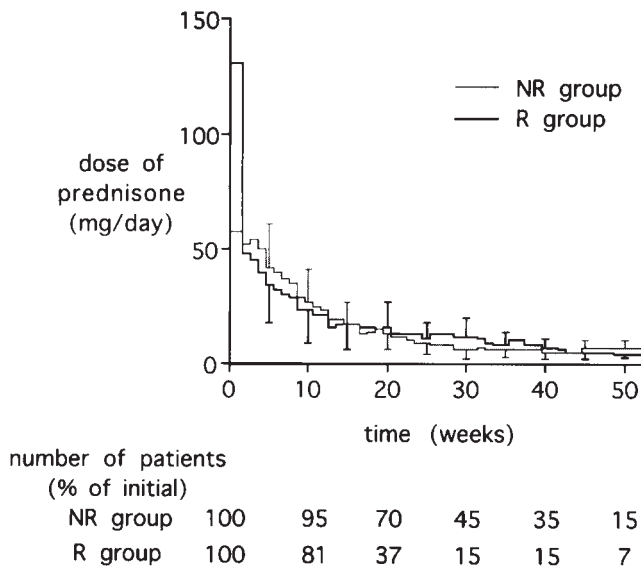


Figure 5. Mean daily dose of prednisone as a function of time in NR and R groups. Time zero is the onset of treatment for the initial episode of COP. The number of patients at each time point is indicated as percentage of the initial number (R group: $n = 28$, NR group: $n = 20$). The number of patients decreased over time owing to: (1) end of treatment, (2) end of follow-up, or (3) occurrence of a relapse requiring an increase of steroid treatment. The elevated average dose in the R group during the first week is caused by large methylprednisolone boluses (1,000 mg/d) in two patients, but the difference with the NR group was not significant.

of 28 (28%) patients of the R group ($p = \text{NS}$). In summary, treatment complications were common, and tended to be more frequent in the R group.

Treatment of Relapses

All relapses were treated by resuming or increasing steroid treatment. The mean prednisone dose at onset of treatment for first relapse was 31 ± 14 mg/d, which was significantly lower than for the initial episode of COP (50 ± 17 mg/d, $p < 0.001$). Twenty-six of 28 patients improved while taking steroids. The mean delay to obtain $\geq 50\%$ improvement on chest radiograph was 5 ± 5 wk (median 5), and for complete chest radiograph clearing, it was 15 ± 12 wk (median 12). These delays were not different from those of the initial episode of COP (data not shown).

We tried to determine whether high doses of prednisone (> 20 mg/d) were beneficial for relapse treatment. Treatment of first relapse was initiated with ≤ 20 mg/d in 12 of 28 patients (low dose, L subgroup), whereas 16 of 28 received > 20 mg/d (high dose, H subgroup). The mean initial dose was 18 ± 6 mg/d in the L subgroup and 40 ± 10 mg/d in the H subgroup ($p < 0.0001$). Six months after the onset of this treatment, the cumulative dose was 29 ± 12 mg/kg in the L subgroup and 59 ± 30 mg/kg in the H subgroup ($p = 0.004$). The difference remained significant after 1 yr (38 ± 23 mg/kg versus 75 ± 50 mg/kg, respectively, $p = 0.03$). The delay for chest radiograph clearing tended to be shorter in the H subgroup (11 ± 11 versus 20 ± 10 wk, $p = 0.07$), but the proportion of normal chest X-ray at last visit was not different (82 versus 75%). The number of relapses was similar (H: 2.8 ± 2.6 , L: 1.8 ± 1.4 , $p = 0.2$). The rate of treatment side effects was significantly higher in the H subgroup (50 versus 8%, $p = 0.05$). In summary, treatment of first relapse with high-dose corticosteroids was associated with higher cumulative doses and a higher rate of treatment side effects, without objective benefit.

Effect of a Standardized Treatment

To determine whether a standardized therapeutic strategy could favorably influence the relapse rate, the study population was divided into two groups according to the corticosteroid treatment used for the initial episode of COP. Starting from October 1995, a standardized protocol was proposed to all physicians of the GERM"O" P as a therapeutic option for their patients with COP (*see METHODS*). Fourteen patients received this protocol on an intention-to-treat basis (A group). The remaining 34 patients (B group) received other therapeutic regimens, most of them because they were treated before October 1995 (28 of 34 = 82%). Data were analyzed retrospectively. A and B groups did not differ for clinical, imaging, and biologic characteristics (data not shown). The cumulative dose of prednisone was significantly lower in the A group at any time starting from 20 wk after the initial episode of COP ($p < 0.05$) (Figure 6). Delays for clinical recovery and chest radiograph clearing under treatment were similar in both groups (data not shown). The rate of relapse was eight of 14 (57%) in the A group and 20 of 34 (59%) in the B group ($p = \text{NS}$). The median number of relapses was 1.0 in both groups. Clearing of chest radiograph after the initial episode of COP was achieved in 11 of 14 (79%) patients of the A group and 27 of 34 (79%) of the B group. Side effects of corticosteroids were reported in three of 14 (21%) patients of the A group and nine of 34 (26%) patients of the B group ($p = \text{NS}$). No death occurred in the A group. In summary, patients treated with the standardized protocol received significantly less corticosteroids, without experiencing higher relapse rate, morbidity, and mortality.

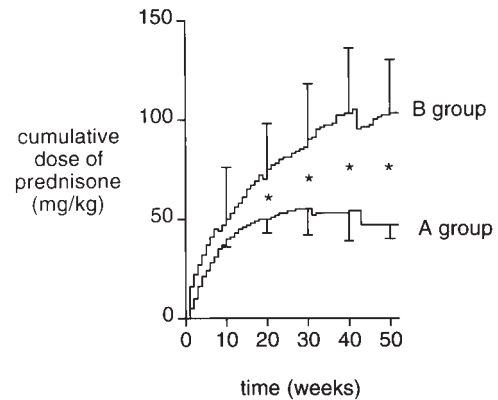


Figure 6. Cumulative dose of prednisone over time during the first year of treatment in patients receiving the GERM"O" P's protocol (A group, $n = 14$), and other therapeutic regimens (B group, $n = 34$). Doses are expressed in mg/kg body weight. Time zero is the onset of treatment for the initial episode of COP. * $p < 0.05$.

DISCUSSION

This study provides the first detailed analysis of relapses in COP, and the first description of a standardized steroid treatment for this condition. The main findings can be summarized as follows. At least one relapse occurred in most patients with COP, usually within 1 yr after the initial episode. Most relapses occurred under low-dose prednisone (≤ 10 mg/d). Delayed treatment onset for the initial episode of COP could favor the occurrence of relapses. A subgroup with multiple relapses had elevated markers of cholestasis. Relapses did not adversely affect morbidity and mortality. Treatment of first relapse with high-dose corticosteroids had no advantage and was associated with more frequent side effects. A standardized therapeutic protocol allowed a reduction in prednisone doses without adversely affecting outcome and relapse rates.

Study Population

Our patients did not markedly differ from those of previous series regarding demographic data (2, 7, 8, 10–12, 18, 19), except for two characteristics. First, the female predominance (65% of cases) found in this series has not been previously observed. Second, a majority of nonsmokers was found in our study, in agreement with some previous series (8, 11, 18, 20). Although COP has usually been considered as unrelated to smoking (7, 10, 13), our data further suggest that an inverse relationship could exist. Interestingly, this putative protective effect of smoking on the development of COP could provide an explanation for the female predominance in our series, because women were characterized by a significantly lower proportion of smokers compared with men (10 versus 55%, $p = 0.002$). This is in agreement with the lower prevalence of smokers among women in France (women 21%, men 35%), and especially in the 60 to 69 age group corresponding to the mean age of our study population (women 6%, men 21%) (Institut National de la Statistique et des Etudes Economiques, France, 1996). Thus, if smoking has a protective effect against COP, and because the prevalence of smoking is lower among women, they could be at greater risk to develop COP compared with men. Further studies are needed to confirm this hypothesis.

Number, Timing, and Probability of Relapse

Our study population was characterized by a rather high relapse rate (58%), as compared with previously published large

(≥ 15 cases) series (2, 6–8, 10, 12, 17–19), where it varied from 9% (10, 12) to 39% (17). It might be related to different as yet unidentified causal factors, closer follow-up resulting in better detection of relapses, or different therapeutic strategies to treat the initial episode of COP. In addition, the duration of illness prior to diagnosis was longer in this study compared with some (2, 17–19) although not all (1, 3–5, 7, 8, 10, 11) previous series. This provides another possible explanation for our high relapse rate because, as shown in the present study, delayed treatment could increase the risk of relapse. Finally, one cannot rule out a recruitment bias resulting in overrepresentation of cases with relapses. However, because inclusion in the study was based on diagnosis of COP and not on any follow-up event, such a bias appears unlikely.

The risk of having a determined number of relapses declined in a curvilinear fashion (Figure 2), and followed an inverse relationship with a high correlation coefficient ($r = 0.982$). This points to an excess of relapses in some patients and shows that a subgroup is prone to multiple relapses. Additionally, this curvilinear decline can also be viewed as reflecting the overall attenuation of disease activity in the whole study population. This suggests that the initial episode and the relapses constitute a unique, continuous, and self-governing process, rather than unconnected events triggered separately.

Most first relapses in our series occurred within 1 yr after the initial episode of COP, the majority of them within the first 6 mo (Figure 3). In only two cases, first relapses occurred more than 15 mo after the initial episode. The Kaplan-Meier method disclosed a relapse probability of 68% at 2 yr (Figure 3), and the analysis of cases with determined outcomes showed that 27 of 31 (87%) relapsed within 2 yr. These data allow prediction of the probability of relapse for an individual patient, and give accurate information regarding risk and timing of such an event. More studies are needed to determine whether our results apply to other populations.

Ongoing Treatment at the Time of First Relapse

When the first relapse occurred, 68% of patients of the R group were still treated by corticosteroids for the initial episode of COP, and 32% had stopped treatment for a median delay of 2 mo. In all but one case, the current prednisone dose at the time of first relapse was ≤ 20 mg/d (Figure 4). These data have important practical value, because they precisely define conditions in which relapses are expected to occur. In our opinion, the occurrence of relapse at high doses of corticosteroid (> 20 mg/d) should prompt the search for other diagnoses, particularly vasculitis or lymphoma, especially if a histologic proof of COP has not been obtained initially.

Predictors of Relapse Occurrence

Delays between first symptoms and treatment onset tended to be longer in the R group. This appeared even more clearly for the subgroup with multiple relapses (MR). This suggests that delayed treatment could favor the occurrence of multiple relapses. The MR subgroup was also characterized by significantly higher serum levels of γ -glutamyltransferase, alkaline phosphatase, and alanine aminotransferase. Elevated markers of cholestasis have been previously described in 12 cases of seasonal COP (20). However, in our patients, the abnormalities were milder and no seasonal pattern was observed. We tried to determine whether steroid doses taken before occurrence of a relapse differed between the NR and R groups (Figure 5). In fact, no difference was found at any time during the first year of treatment. This demonstrates that relapses were not the result of lower steroid treatment in the R group. Follow-up duration was shorter in the NR group, probably re-

flecting the uncomplicated disease course. Alternatively, some patients could have been attributed to the NR group only because enough time was not allowed for a relapse to occur. Predictive factors of relapses in COP have been examined in only one previous study (17). Initial PaO₂ levels were significantly lower in patients who relapsed (17). We did not confirm this finding in the present study (Table 1).

In summary, no clear-cut difference was found between the NR and R groups. This suggests that both belong in essence to the same population, and further leads one to consider the initial episode of COP and the relapses as a unique and continuous phenomenon, rather than separate events. In other words, in such a continuum, the occurrence of a relapse was not a discriminative event. However, comparing the two extremes of this continuum (i.e., no relapse versus multiple ones) revealed that delayed treatment could favor relapse occurrence, and that mild cholestasis could be a predictor of multiple relapses.

Effect of Relapses on Morbidity and Mortality

The effects of relapses on morbidity were assessed by comparing the NR and R groups for persisting abnormalities at imaging and pulmonary function testing. At the last follow-up visit, the proportion of patients with normal chest radiograph was very similar in the two groups. The last available pulmonary function tests measured remote from any acute disease did not disclose any significant difference between groups, except for reduced residual volume in the R group. This suggests that the occurrence of relapses, and even multiple relapses, did not result in increased long-term functional morbidity. A nonfatal respiratory failure occurred in only one case of our series. Two other patients died, but deaths were unrelated to COP or relapses. The 5-yr survival was 98% in our series, compared with 73% in the series by Lohr and coworkers (19) despite a much higher relapse rate in our patients (58% versus 13%). Thus, our data suggest that relapses in COP are not associated with an increased mortality.

Treatment of COP and Relapses

Although there is general agreement on the use of steroids in COP, treatment modalities have not been precisely defined. Some guidelines have been proposed in the recent literature (14, 15). Epler starts with 1 mg/kg/d prednisone (60 mg/d) for 1 to 3 mo, then decreases to 40 mg/d for 3 mo, then 10 to 20 mg/d for a total of 1 yr (14). King suggests initiating therapy with 1 to 1.5 mg/kg/d prednisone for 4 to 8 wk, then tapering to 0.5 to 1 mg/kg/d for the ensuing 4 to 6 wk (15). Although precise comparison with our data is not possible, the steroid doses used in our patients seem to be in a lower range. This could explain the higher relapse rate in our series. However, because relapses do not increase morbidity and mortality, we consider that their suppression might not be a crucial therapeutic objective. On the other hand, treatment-related morbidity occurred in one-fourth of our cases. Therefore, after achieving control of the initial episode and providing a return to baseline function, we feel that the strategy should aim at minimizing the adverse effects of corticosteroids, and avoiding overtreatment. Patients' preferences should also be taken into account. Some may be anxious to experience a relapse, whereas prolonged corticosteroid therapy may be a matter of concern for others. Well-informed patients may decide whether they would prefer to have risk for more relapses and less side effects of corticosteroids, or the opposite. Regarding treatment of relapses, it has been suggested that "therapy should be reinstated aggressively with any sign of recurrence" (15). In our series, the subgroup treated more aggressively for first relapse had a higher complication rate without any long-term benefit. Therefore, aggressive treatment of relapses does not appear necessary. In

an attempt to better define treatment modalities in COP, we proposed a standardized protocol to physicians of the GERM“O”P as a therapeutic option for their patients. This regimen allowed a significant reduction in cumulative steroid doses, without adversely affecting outcome and relapse rate. In view of the previously defined therapeutic objectives, this protocol appears useful in providing standardization and avoiding overtreatment.

This study provides a clearer view of the well-known but poorly understood phenomenon of relapses in COP. First, it suggests that the initial episode of COP and subsequent relapses may be viewed as the continuum of a single process, which progressively attenuates over time. Second, two possible predictors of multiple relapses have been identified: delayed treatment for the initial episode and increased markers of cholestasis. Third, our data defined the frame in which relapses are expected to occur, with respect to probability, timing, and current steroid treatment at relapse. This may help to identify unusual situations, in which the initial diagnosis should be reconsidered. Fourth, this study provides evidence that relapses do not adversely affect morbidity and mortality. Thus, the occurrence of relapses in COP could be regarded as a relatively benign and acceptable phenomenon, rather than a dangerous event requiring aggressive management. We suggest that reducing the relapse rate may not be a major therapeutic objective. Instead, the strategy should aim at obtaining a well-equilibrated balance between using an efficient treatment protocol, and minimizing adverse effects of corticosteroids by use of lower doses and shorter treatment duration. This has been approached in our group by the use of a standardized therapeutic protocol. Finally, this detailed analysis of relapses in COP may provide a basis for comparison with other treatment policies.

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