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Optimal dose of maintenance steroid therapy for relapse of chronic eosinophilic pneumonia: a multicentre retrospective study

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ABSTRACT

Background Long-term maintenance steroid therapy (MST) is often necessary for repeated relapses of chronic eosinophilic pneumonia (CEP). Because relapse does not indicate a worse prognosis, determining the optimal steroid dose to avoid overtreatment presents a clinical challenge. Our primary objective was to evaluate the optimal MST dose to prevent repeated relapses, and the secondary objectives included identifying serum eosinophil count at relapse and background factors of relapse.

Methods A multicentre retrospective study was conducted on patients with steroid-treated CEP. Background characteristics were compared between the non-relapse and relapse groups. The optimal MST dose was determined based on dose at relapse and the final relapse prevention dose. Additionally, serum eosinophil count at relapse was assessed.

Results A total of 79 patients were included, with 44 in the non-relapse group and 35 in the relapse group. The prednisolone doses required to achieve relapse-free rates of 50% (ED_{50}) were 7.2 mg (95% CI, 4.6 to 23.6). The median serum eosinophil count at relapse was 1125/µL (IQR, 735–2108). No clinically significant background factors were identified between the non-relapse and relapse groups.

Conclusion Our study demonstrated that a prednisolone dose of 7.2 mg achieved a 50% relapse-free rate in the relapse group. Based on these findings, we encourage clinicians to evaluate individual minimum effective steroid doses.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Long-term maintenance steroid therapy is often necessary for repeated relapses of chronic eosinophilic pneumonia (CEP). Because relapse does not indicate a worse prognosis, determining the optimal steroid dose to avoid overtreatment presents a clinical challenge.

⇒ Reliable predictors of relapse have not yet been established.

WHAT THIS STUDY ADDS

⇒ This multicentre retrospective study demonstrated that a prednisolone dose of 7.2 mg achieved a relapse-free rate of 50% for relapses of CEP.

⇒ No clinically significant background factors were identified between the non-relapse and relapse groups.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results help address an unmet clinical need of evaluating individual minimum effective steroid doses for repeated relapses of CEP.

INTRODUCTION

Chronic eosinophilic pneumonia (CEP), first reported in 1969, is an idiopathic pulmonary disorder characterised by an abnormal and marked accumulation of eosinophils in the lungs.[1] Most patients with CEP respond well to systemic steroid therapy, but relapses are common after tapering or discontinuing steroids. Previous reports have shown relapse rates ranging from 37% to 58%, with 28% of relapsed patients experiencing two or more relapses.[2] Several predictors of relapse have been reported, including underlying asthma with a higher use of inhaled corticosteroids (ICS) and smoking history as negative predictors,[3 4] while centrilobular opacities on high-resolution CT scans and high serum surfactant protein D (SP-D) levels as positive predictors.[5] However, the predictors have shown inconsistent results among studies,[6 7] making it challenging to establish reliable predictors of relapse.

After successfully managing the initial episode, it is important to avoid overtreatment with steroid therapy and minimise potential side effects. Notably, relapse does not indicate a worse prognosis or increased morbidity, and airway obstructive abnormalities are typically of borderline clinical significance.[8] In the real

world, long-term maintenance steroid therapy (MST) is often necessary for managing repeated relapses. In such cases, the lowest effective dose (ED) of long-term MST is recommended to prevent relapse. Previous reports have indicated a range of prednisolone doses for MST, from 5.4 mg to 11.8 mg.[7–10] However, the optimal dose has not yet been identified. The primary objective of this study was to evaluate the optimal dose of MST required to prevent repeated relapses of CEP. Secondary objectives included identifying the serum eosinophil count at relapse and background factors of relapse. This study aims to minimise steroid doses for repeated relapses of CEP by evaluating the optimal MST dose.

METHODS

Patients and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Study design and population

A multicentre retrospective study was conducted, reviewing the medical records of consecutive patients diagnosed with CEP between April 2016 and March 2023 at four Nippon Medical School hospitals. This human study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee Review Board at Nippon Medical School Hospital in Tokyo, Japan (approval no. M-0023–130). Informed consent was obtained using the opt-out method on the website as per the Ethics Committee's instructions.

Diagnostic criteria

CEP was diagnosed based on clinical symptoms consistent with CEP (eg, fever, cough, or dyspnoea) lasting more than 1 month, infiltrative shadows on chest radiographs and meeting at least one of the following inclusion criteria proposed by Mochizuki *et al*[11]: (1) histological diagnosis by surgical lung biopsy; (2) bronchoalveolar lavage fluid (BALF) or serum eosinophilia of 30% or higher; or (3) meeting two of the following three criteria: BALF eosinophilia of 10% or higher, serum eosinophilia of 6% or higher or eosinophil infiltration in transbronchial lung biopsy. Patients were excluded if they had secondary CEP caused by specific factors such as eosinophilic granulomatosis with polyangiitis, allergic bronchopulmonary mycosis, drugs or infection; comorbidities that may affect the clinical course of CEP; or spontaneous improvement without steroid therapy.

Data collection

To analyse background factors, patients with steroid-treated CEP were categorised into relapse and non-relapse groups. Relapse was diagnosed when two or more of the following criteria were met: (1) a recurrence of subjective symptoms, (2) new characteristic infiltrates on chest imaging or (3) a recurrence of serum or BALF eosinophilia. Histopathological confirmation of CEP was not required for a relapse diagnosis. The non-relapse group comprised patients who did not experience a relapse for at least 12 months after completing steroid therapy. Patients who continued steroid therapy without relapse were excluded owing to the difficulty in assessing potential relapse risk when reducing steroid dosage.

To compare baseline characteristics between the non-relapse and relapse groups, data on age, sex, height, weight, smoking status, asthma complications, concomitant ICS use, steroid pulse therapy use and initial steroid dose were collected. Serum biomarkers included white blood cell count, lactate dehydrogenase, C-reactive protein, serum immunoglobulin E, Krebs von den Lungen-6 (KL-6) and SP-D. Notably, KL-6 and SP-D are biomarkers of interstitial lung disease that are highly expressed on proliferated alveolar epithelial type II cells. The distribution of abnormal shadows on chest CT scans was assessed, and the number of affected lung lobes was recorded. The distribution of abnormal shadows was categorised as unilateral or bilateral. Additionally, the differential cell counts were recorded in the third aliquot of BALF. The time interval between the initiation of steroid therapy and the disappearance of shadows on the chest X-ray was recorded as the time to disappearance.

Review of treatment in the relapse group

For each event in the relapse group, the following parameters were analysed: prednisolone dose at relapse, serum eosinophil count at relapse and the final prednisolone dose of MST required to prevent relapse. Additionally, the relationship between serum eosinophil count and relapse rate was assessed. Patients treated with a combination of biologics and immunosuppressants were evaluated only for prednisolone dose and serum eosinophil count at relapse before initiating the combination therapy. Additionally, adverse events associated with steroid therapy were recorded.

Statistical analyses

Data were expressed as means with SD for continuous variables and numbers with percentages for categorical variables. Significant differences between the two groups were assessed using the Student's t-test for continuous variables and the Fisher's exact test for categorical variables. To examine the magnitude of effect size, r was used for continuous variables and Cramer's V for categorical variables, with values of 0.10, 0.30 and 0.50 indicating small, medium and large effects, respectively. The serum eosinophil count in the review of treatment in the relapse group was expressed as medians with the 25th and 75th percentiles of the IQR.

The final maintenance dose of prednisolone in the relapse group was above the minimum required to prevent repeated relapses of CEP but may not have been optimal. Therefore, a sigmoid dose-response curve

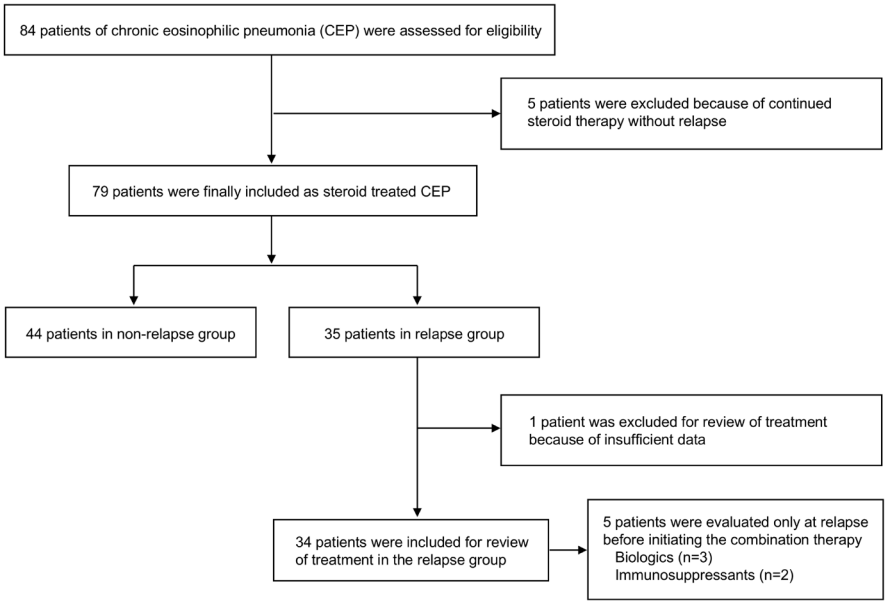

Figure 1 Screening flow chart of patient selection. Of the 84 patients with steroid-treated chronic eosinophilic pneumonia, 79 were included in the study: 44 were classified into the non-relapse group and 35 into the relapse group. One patient was excluded because of insufficient data; thus, the remaining 34 patients were included for treatment review in the relapse group. Of the 34 patients in the relapse group, five were evaluated only at relapse before initiating the additional combination therapy (biologics in three cases and immunosuppressants in two cases).

was calculated from the non-relapse rate for each dose of MST to estimate the prednisolone dose required to achieve a 50% (ED_{50}) relapse-free rate in the relapse group. Evaluation based on a counting process model was used, treating each repeated relapse event as a separate observation. This model assumed a Markov process where the relapse group had a permanent possibility of relapse regardless of the previous steroid treatment, and the number of relapses did not alter the steroid treatment effect. This model was based on a study evaluating MST for the relapse of cryptogenic organising pneumonia.[12] All statistical analyses were conducted using JMP14 software (SAS Institute, Cary, NC, USA), with a two-sided p value of less than 0.05 considered statistically significant.

RESULTS

Patient inclusion

Figure 1 illustrates the patient screening process. A total of 84 patients with CEP who received steroid therapy at the time of diagnosis were assessed for eligibility. Five patients were excluded from the analysis due to continued steroid therapy without relapse during the follow-up period. The remaining 79 patients were included in the steroid-treated CEP.

Clinical features

Table 1 summarises the baseline characteristics of the non-relapse (n=44; 55.7%) and relapse (n=35; 44.3%) groups. There were no significant differences in age, sex, height, weight, smoking status, asthma complications or concomitant use of ICS between the two groups. The proportion of patients treated with steroid pulse therapy and the initial prednisolone dose did not differ between the two groups. Serum biomarkers, including white blood cell count, lactate dehydrogenase, C-reactive protein, KL-6 and serum immunoglobulin E levels, did not differ between the two groups. Although the effect size was moderate (−0.30), SP-D levels were significantly lower in the relapse group than in the non-relapse group (141±84 *vs* 203±132 ng/mL; p=0.029). In contrast, the number of affected lung lobes and the proportion of bilateral shadows on chest CT scans did not differ between the two groups. Similarly, the BALF percentages did not differ between the two groups. Furthermore, the time from the initiation of steroid therapy to the disappearance of shadows on chest X-rays was not significantly different between the two groups.

Review of treatment in the relapse group

Out of 79 patients, 35 (44.3%) experienced a relapse after reducing or discontinuing steroid therapy. All relapses were managed by either resuming or increasing steroid therapy. One patient was excluded from the analysis due to insufficient post-relapse data; thus, the relapse group included 34 patients for treatment review (figure 1). Among the 34 patients, five were evaluated only at relapse before initiating the additional combination therapy, which included biologics (mepolizumab in one case and benralizumab in two cases) and immunosuppressants (intravenous cyclophosphamide in one case

Table 1 Baseline characteristics in the non-relapse and relapse groups

Variables	Non-relapse group (n=44)	Relapse group (n=35)	Difference (95% CI)	Effect size*	*P* value†
Age (year)	58.0±15.3	59.7±16.4	1.7 (–5.5, 8.9)	0.06	0.64
Male, n (%)	14 (32)	15 (43)		0.11	0.35
Height (cm)	160.1±8.1	161.9±9.4	–1.8 (–2.2, 5.8)	–0.11	0.38
Weight (kg)	53.3±12.0	55.6±8.7	2.3 (–2.3, 6.9)	–0.11	0.32
Smoking (pack-year)	14.5±28.6	10.2±19.2	–4.2 (–15.0, 6.5)	–0.09	0.43
Asthma complications, n (%)	20 (45)	16 (46)		0.00	1.00
Concomitant ICS use, n (%)	17 (39)	16 (46)		0.07	0.65
Steroid therapy					
Steroid pulse, positive, n (%)	12 (27)	17 (49)		0.22	0.06
Initial prednisone dose (mg)	31.0±8.5	32.7±10.7	1.7 (–2.7, 6.1)	0.10	0.45
Serum biomarkers					
WBCs (/μL)	13,132±4792	13,966±7676	834 (–2,143, 3,811)	0.08	0.58
Neutrophils (/μL)	6,249±2659	6,106±2402	–142 (–1,279, 994)	–0.03	0.80
Lymphocytes (/μL)	1,550±620	1,586±592	36 (–237, 309)	0.03	0.79
Eosinophils (/μL)	4,762±4519	5,693±6915	931 (–1,779, 3,642)	0.08	0.49
Eosinophils (%)	32.1±20.1	31.8±22.1	–0.3 (–9.9, 9.3)	–0.01	0.94
LDH (IU/L)	266±75	252±79	–15 (–49, 20)	–0.10	0.41
CRP (mg/dL)	5.3±5.1	5.2±4.7	–0.1 (–2.3, 2.1)	–0.01	0.93
KL-6 (U/mL)	425±619	374±315	–51 (–271, 168)	–0.06	0.32
SP-D (ng/mL)	203±132	141±84	–62 (–118, 6.7)	–0.30	0.029
IgE (IU/L)	1,917±4581	910±1023	–1007 (–2,596, 581)	–0.20	0.21
Chest CT scan findings					
Number of affected lobes	3.8±1.3	3.7±1.2	–0.1 (–0.7, 0.5)	0.03	0.80
Bilateral, no. (%)	41 (93)	34 (97)		0.09	0.63
Bronchoalveolar lavage fluid					
Macrophages (%)	31.7±22.6	30.1±24.7	–1.6 (–13.4, 10.2)	–0.03	0.79
Neutrophils (%)	4.7±6.6	4.3±5.9	–0.4 (–3.5, 2.7)	0.03	0.79
Lymphocytes (%)	8.6±5.6	10.7±9.6	2.1 (–1.9, 6.1)	0.15	0.30
Eosinophils (%)	55.6±24.3	54.5±25.7	–1.0 (–13.3, 11.2)	0.02	0.87
Time to disappearance (day)‡	21.6±13.0	24.0±15.6	2.3 (–4.6, 9.3)	0.09	0.50

Data are presented as mean±SD or n (%)
* Results of *r* or Cramer's *V*
†Results of the Student's t-test or the Fisher's exact test
‡The time interval between the initiation of steroid therapy and the disappearance of shadows on the chest X-ray
CRP, C-reactive protein; ICS, inhaled corticosteriods; IgE, immunoglobulin E; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; SP-D, surfactant protein D; WBC, white blood cell.

and oral cyclosporine in one case) (online supplemental table S1). Adverse events related to steroid therapy were reported in eight of 34 patients (24%): five cases of diabetes and three of osteoporosis/bone fracture. No fatal adverse events occurred. Table 2 summarises the number of relapse events and patients under relapse control per steroid maintenance dose. A total of 61 relapse events were recorded, with 34 occurring for the first time, 19 for the second time, three for the third time, two for the fourth time, two for the fifth time and one for the sixth time. Excluding the five patients who received the additional combination therapy, 29 relapsed patients were analysed. Of these, eight were under relapse control without steroid therapy, and 21 were under relapse control on long-term steroid monotherapy. Figure 2 illustrates the dose-dependent curve calculated from the data in table 2. The effective prednisolone doses required to achieve relapse-free rates of 50% (ED_{50}) were 7.2 mg

Table 2 The number of relapse events and patients under relapse control per maintenance steroid dose

Maintenance prednisolone dose (mg)	Number of relapse events (total 61)*	Number of patients under relapse control (total 29)†
0.0	27	8
0.5	1	0
1.0	6	0
2.0	3	0
2.5	2	2
3.0	1	2
4.0	3	1
5.0	10	10
6.0	3	1
7.0	1	1
7.5	2	1
8.0	1	2
9.0	0	1
10.0	1	0

Note: Review of steroid therapy in 34 patients in the relapse group.
*Distribution of relapse events per maintenance prednisolone dose, including multiple events per patient: 34, 19, three, two, two and one for the first, second, third, fourth, fifth and sixth relapse, respectively.
†Distribution of final maintenance prednisolone doses under relapse control for 29 patients, excluding five who received additional biological or immunosuppressant combination therapy.

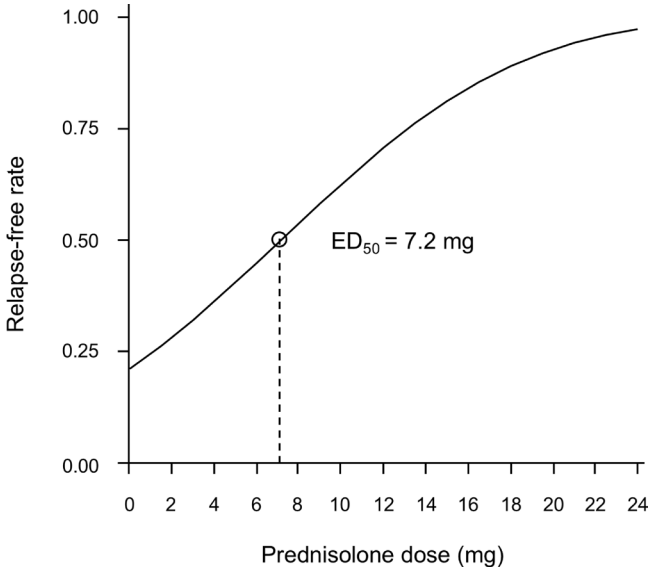

Figure 2 The dose-response curve calculated from relapse-free rate for each maintenance prednisolone dose. The effective dose (ED) of prednisolone required to achieve relapse-free rates of 50% (ED_{50}) was 7.2 mg (95% CI, 4.6 to 23.6).

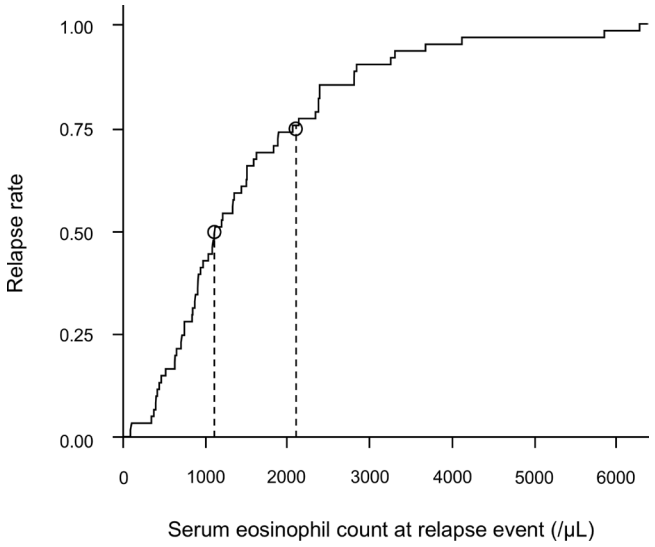

Figure 3 Relationship between serum eosinophil count at relapse events and relapse rate in the relapse group. The median serum eosinophil count was 1125/μL (IQR, 735–2108).

(95% CI, 4.6–23.6). Figure 3 illustrates the relationship between serum eosinophil count at relapse and relapse rate in 54 relapse events in the relapse group. The median serum eosinophil count was 1125/μL (IQR, 735–2108).

DISCUSSION

In this study, the prednisolone doses required to achieve relapse-free rates of 50% (ED_{50}) were 7.2 mg (95% CI, 4.6 to 23.6) in the relapse group. To the best of our knowledge, no other study has assessed the optimal MST dose associated with CEP relapse. In cases of repeated relapse, tapering of steroids to near ED_{50} should be prioritised once the disease is controlled. Additionally, clinicians should evaluate individual minimal EDs and consider indications for additional biological therapy.

Relapses are typically managed by resuming or increasing steroid therapy. A previous prospective study has shown no significant difference in the relapse rate between the 3- and 6 month prednisolone treatment groups for CEP.[6] This result supports our hypothetical model assuming a Markov process where the relapse group had a permanent possibility of relapse regardless of previous steroid treatment. The ED_{50} of prednisolone doses in this study was 7.2 mg, falling within the average range of 5.4–11.8 mg reported in previous studies.[7–10] One issue contributing to variability in maintenance doses reported across studies is overtreatment because of non-optimised dosing for relapse prevention. The 7.2 mg prednisolone dose calculated as ED_{50} in this study may not represent the optimal MST dose, as individual requirements vary. Another issue involves determining steroid doses relative to body weight. Prednisolone was calculated as a pure dose owing to the narrow distribution of mean (±SD) height (161.9±9.4 cm) and weight (55.6±8.7 kg) in the relapse group. For individuals with

obesity, the dose should be based on ideal, rather than total, body weight. Obesity affects the uptake, storage and metabolism of glucocorticoids; however, findings on this relationship are mixed. One study reported that each 1% increase in baseline body mass index was linked to a 2.9% decrease in cortisol wake-up levels and total area under the curve, suggesting that a higher body mass index suppresses cortisol.[13]

Long-term steroid therapy is a significant independent predictor of numerous adverse effects, which are dose- and duration-dependent. Major risks include infections, cardiovascular disease, diabetes and osteoporosis.[14] Furthermore, even doses of prednisolone less than 5 mg/day have been associated with an increased risk of fractures and serious infections.[15 16] However, short-term use may also lead to serious adverse effects, particularly at higher doses. One study reported that 30 mg/day of prednisolone for 1 month carried a similar risk of serious infection as 5 mg/day for 3 years.[17] Some studies have suggested that very low doses of steroids (eg, prednisolone at a dose less than 5 mg/day) are associated with fewer adverse effects.[18 19] A placebo-controlled trial of 5 mg/day add-on prednisolone over 2 years in patients with rheumatoid arthritis revealed an increase in mild to moderate infections, with other glucocorticoid-specific adverse effects being rare.[20] However, the threshold duration for steroid therapy where adverse events become more frequent remains unclear. In steroid therapy for repeated relapses of CEP, the decision to continue maintenance therapy at the optimal dose or to discontinue therapy and resume therapy at relapse remains an issue for future investigation. Alternate-day low-dose prednisone therapy may also help reduce side effects, but the optimal dose for preventing relapse has not been clearly defined.

In our study, the prednisolone dose at the time of relapse was 10 mg or lower in all relapse groups. Relapses with high doses of prednisolone should trigger a thorough investigation for other potential causes of eosinophilic pneumonia, such as vasculitis, drugs, fungal or parasitic infections. Biological therapies approved for severe asthma may offer a safer alternative to control relapses of idiopathic CEP, allowing for a reduction in steroid dose and sometimes replacing steroid therapy. However, the available evidence is limited and primarily composed of case reports and series.[21] Given that 46% of the relapse group had asthma complications, the low rate of concomitant biologic use is notable. Therefore, more aggressive combination therapy with biologics should be considered, especially for patients on high-dose or long-term MST.

Our study revealed that the median serum eosinophil count was 1125 /µL (IQR, 735–2108). Currently, symptoms and chest imaging remain the most reliable and efficient guides for therapy. The absence of absolute serum eosinophil count criteria for steroid therapy complicates determining optimal doses for repeated relapses. Although relapse generally does not worsen prognosis and airway obstructive abnormalities are of borderline clinical significance,[8] CEP can cause long-term issues, including persistent pulmonary impairment[7] and irreversible fibrosis.[22 23]

Our study also revealed a significant increase in serum SP-D levels at diagnosis in the non-relapse group. In contrast, a previous report demonstrated a higher SP-D level as a significant factor of relapse.[5] Elevated SP-D levels have been reported in severe asthma with mixed eosinophil and neutrophil inflammation.[24] Serum SP-D has been identified as a more sensitive marker than KL-6 in reflecting the inflammatory response in acute eosinophilic pneumonia.[25] However, our study found no significant differences in asthma complications, smoking status, serum and BALF eosinophil count or serum and BALF neutrophil count between the non-relapse and relapse groups. Generally, SP-D is an unreliable marker for diagnosing CEP. These findings suggest that serum SP-D may not be a reliable background factor of non-relapse, given a medium effect size value of 0.30. Other background factors listed in the Introduction (eg, asthma complications, concomitant ICS use and smoking history) also showed no replication in this study.

Our study has several limitations. First, the steroid taper protocol was not standardised due to the retrospective study design, resulting in varying exposure to a constant MST dose in each case. A large-scale prospective clinical trial with a standardised treatment protocol is required to validate our findings. Second, the optimal MST dose was assessed using a counting process model that considered repeated relapse events as separate observations, assuming that the relapse group had a permanent possibility of relapse regardless of previous steroid treatment. Evaluating only the first relapse was problematic because of data loss after the second relapse and the inability to assess the effect of steroid treatment over time. The separate model, which evaluates separately by the number of relapses, had a small sample size and biased estimates. Finally, quantitative assessment of steroid side effects was challenging in this retrospective study. Future controlled studies should quantitatively assess the side effects of continuous optimal-dose steroid therapy vs intermittent steroid therapy for repeated relapse, including bone densitometry using dual-energy X-ray absorptiometry scans.

In conclusion, our study demonstrated that a prednisolone dose of 7.2 mg achieved a 50% relapse-free rate in the relapse group. Based on these findings, we encourage clinicians to evaluate individual minimum effective steroid doses.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This human study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee Review Board at Nippon Medical School Hospital in Tokyo, Japan (approval no. M-0023-130). Informed consent was obtained using the opt-out method on the website as per the Ethics Committee's instructions.

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