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# No evidence found for an association between prednisone dose and FVC change in newly-treated pulmonary sarcoidosis

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ABSTRACT

*Background:* Prednisone is used as first-line therapy for pulmonary sarcoidosis. What dosing strategy has the best balance between effect and side-effects is largely unknown. We analyzed change in forced vital capacity (FVC) and weight during different prednisone doses used in daily practice for treatment naïve pulmonary sarcoidosis patients.

*Methods:* Multilevel models were used to describe FVC and weight change over time. Correlations were calculated using linear regression models.

*Results:* Fifty-four patients were included. FVC changed over time ($p < 0.001$), with an average increase of 9.6% predicted (95% CI: 7.2 to 12.1) at 12 months. Weight changed significantly over time ($p < 0.001$), with an average increase of 4.3 kg (95% CI: 3.0 to 5.6) at 12 months. Although FVC and weight changed significantly over time, there was little correlation between prednisone dose and FVC change, while weight increase correlated significantly with cumulative prednisone dose at 24 months. In patients treated with a high cumulative prednisone dose, baseline FVC was on average lower ($p = 0.001$) compared to low dose treated patients, while no significant differences were observed in need for second/third-line therapy or number of exacerbations. A strategy leading to a low cumulative dose at 12 months was defined by rapid dose tapering to 10 mg/day within 3.5 months.

*Conclusions:* These results suggest that prednisone therapy aimed at improving or preserving FVC in newly-treated pulmonary sarcoidosis can often be reduced in dose, using a treatment regimen that is characterized by early dose tapering.

## 1. Introduction

Sarcoidosis is a multisystem, granulomatous disease affecting the lungs in 90% of the cases [1]. Approximately 30–50% of the patients develop progressive and debilitating disease with need for therapy [1,2]. The recommended first-line therapy for pulmonary sarcoidosis is prednisone [1,3–5]. Although prednisone treatment in pulmonary sarcoidosis is reported to induce short-term benefits on clinical symptoms and inflammation, it remains unclear whether the therapy modifies long-term progression of the disease [4]. Therapy should therefore primarily be aimed at symptom relief, inflammation control to prevent (further) organ damage and improving patient's quality of life while avoiding unnecessary side-effects [6–9].

A meta-analysis of corticosteroids for pulmonary sarcoidosis concluded that evidence for the best corticosteroid treatment strategy is lacking [4]. The suggested initial prednisone dose varies between 20 and 40 milligrams (mg) [1] or 0,5 mg per kilogram (kg) [5] per day for 1–3 months. Subsequently, prednisone dose should be tapered to a maintenance dose of 5–10 mg/day, which is commonly continued for 6–12 months before discontinuation [1,5]. As these guidelines include a broad range in recommended prednisone doses, variation in treatment regimen in clinical practice is suspected, varying from low- to high-dose

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**Abbreviations**

| | |
|---|---|
| FVC | Forced vital capacity |
| CI | Confidence interval |
| Kg | Kilograms |
| Erasmus MC | Erasmus Medical Center |
| SD | Standard deviation |
| DLCO | Diffusing capacity of the lung for carbon monoxide |
| BMI | Body mass index |
| Mg | Milligrams |
| MEC | Medical Ethical Committee |
| SPSS | Statistical Package for the Social Sciences |

treated patients. Prolonged high dose corticosteroid therapy is associated with numerous side-effects, including weight gain, diabetes and osteoporosis [7,10].

What dosing strategy has the best balance between effect and side-effects is largely unknown. Therefore, in this study we aimed to evaluate treatment effect on forced vital capacity (FVC) (effect) and weight (side-effect) of different prednisone doses used in daily practice.

## 2. Materials & methods

### 2.1. Study design

This study is a multicenter retrospective study, performed in one academic sarcoidosis referral center (Erasmus MC) and three regional training hospitals (Franciscus Gasthuis & Vlietland, Ikazia hospital and Amphia hospital) in the Netherlands. Medical records were reviewed for demographic and diagnostic data, organ involvement, radiographic Scadding stage, prednisone dose, weight, pulmonary function parameters and exacerbations. An exacerbation was determined as an increase in daily prednisone dose from 5 to 10 mg/day maintenance dose to ≥ 20 mg/day or if patients restarted prednisone after prior discontinuation. Data that was available up to 5 years following therapy initiation were collected per patient. Individual prednisone regimens were analyzed. Weight was collected from pulmonary function records.

### 2.2. Patients

Treatment naïve sarcoidosis patients, in whom prednisone therapy was started for a pulmonary indication between January 2000 and December 2013, were included in this study. Patients were identified by screening medical records of patients that were in hospital-specific databases that track sarcoidosis diagnosed patients over time. Patients were included when they met standard criteria for diagnosis of the disease [1], were treatment naive and had a treatment indication for pulmonary sarcoidosis as determined by the treating physician. Patients were excluded when they were: 1. primarily treated for a non-pulmonary indication; 2. treated solely with methotrexate for a pulmonary indication; and 3. when there were less than two hospital visits documented.

### 2.3. Ethical requirements

Formal consultation with the Medical Ethical Committee of the Erasmus MC learnt that, under the Dutch act for medical research involving human subjects (Wet Medisch Onderzoek), approval of this study by the Medical Ethical Committee was not required. The local institution review board of all participating centers approved with registration number MEC-2014-089.

### 2.4. Statistical analysis

The comparison of means of continuous variables were tested with the student *t*-test, the categorical variables were tested with the $X^2$ or the Fisher exact test. Absolute changes in FVC and weight were used as outcome in multilevel models. Log time appeared to be an adequate transformation to enter as fixed factor in the model, while patient functioned as a random intercept. For different points in time we analyzed the correlation between cumulative prednisone dose and the absolute change in outcome between start of treatment and the specific time point. Correlations were calculated using linear regression models.

FVC is shown as mean percent (%) predicted ( ± standard deviation (SD)) or as mean absolute change of % predicted (including a 95% confidence interval (CI)) compared to baseline. Weight is shown as mean kg ( ± SD) or as mean absolute change (including 95% CI) in kg compared to baseline. Prednisone dose is shown as mean daily dose in mg or as cumulative dose in mg.

For pulmonary function tests the European Community for Steel and Coal 1993 prediction equations were used in all hospitals.

Statistical analyses were performed using SPSS (version 21.0.0.1) and R software (version 3.2.2). Figures were created with R software. A p-value $< 0.05$ was considered as statistically significant.

## 3. Results

### 3.1. Patients

A total of 54 treatment naïve sarcoidosis patients that were initiated on prednisone therapy for a pulmonary indication were identified for this study; two third from regional hospitals and one third from an academic referral center for sarcoidosis. Mean % predicted FVC at start of prednisone treatment was 83.4 ± 20.4, and mean % predicted diffusing capacity of the lung for carbon monoxide (DLCO) (corrected for hemoglobin levels) was 69.9 ± 25.0 (Table 1). Average weight was 79.2 ± 19.2 and average body mass index (BMI) was 26.6 ± 5.9 kg/$m^2$; 48.1% of the patients were men and 71.1% of the patients had Scadding stage II sarcoidosis. Additional baseline characteristics are shown in Table 1.

### 3.2. FVC change upon prednisone treatment

Mean initial prednisone dose was 32.6 ± 8.7 mg (Table 1). On average, prednisone was tapered to 10 mg/day at approximately 6 months (e-Fig. 1). Mean FVC (% predicted) change over time was calculated using a multilevel model that incorporated regression lines of all 54 individual patients (e-Fig. 2). FVC changed significantly over time ($p < 0.001$), with an average increase of 7.4% predicted (95% CI: 5.5 to 9.3) at 3 months and 9.6% predicted (95% CI: 7.2 to 12.1) at 12 months (Fig. 1). At 24 months, an average increase of 10.8 (95% CI: 8.0 to 13.5) was observed (Fig. 1), which was largely preserved in patients with data available at 3 and 5 years following therapy initiation (e-Fig. 2A). FVC increase over time significantly depended on baseline FVC ($p = 0.002$), whereby a higher increase was observed in patients with a lower FVC at start than patient with a higher FVC at start. Interestingly, the major increase in FVC occurred within 1–3 months of treatment (Fig. 1).

### 3.3. FVC change and prednisone dose

The association between change in FVC and prednisone dose used, was determined. Although all correlations were weakly positive, no significant correlation was found between FVC change and cumulative prednisone dose used in the short-term (3 (Fig. 2A), 6 (not shown) and 9 months (not shown)) and long-term (12 (Figure 2B) and 24 months (Fig. 2C)). At 12 months, the correlation became almost zero after