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Daily home spirometry to detect early steroid treatment effects in newly treated pulmonary sarcoidosis

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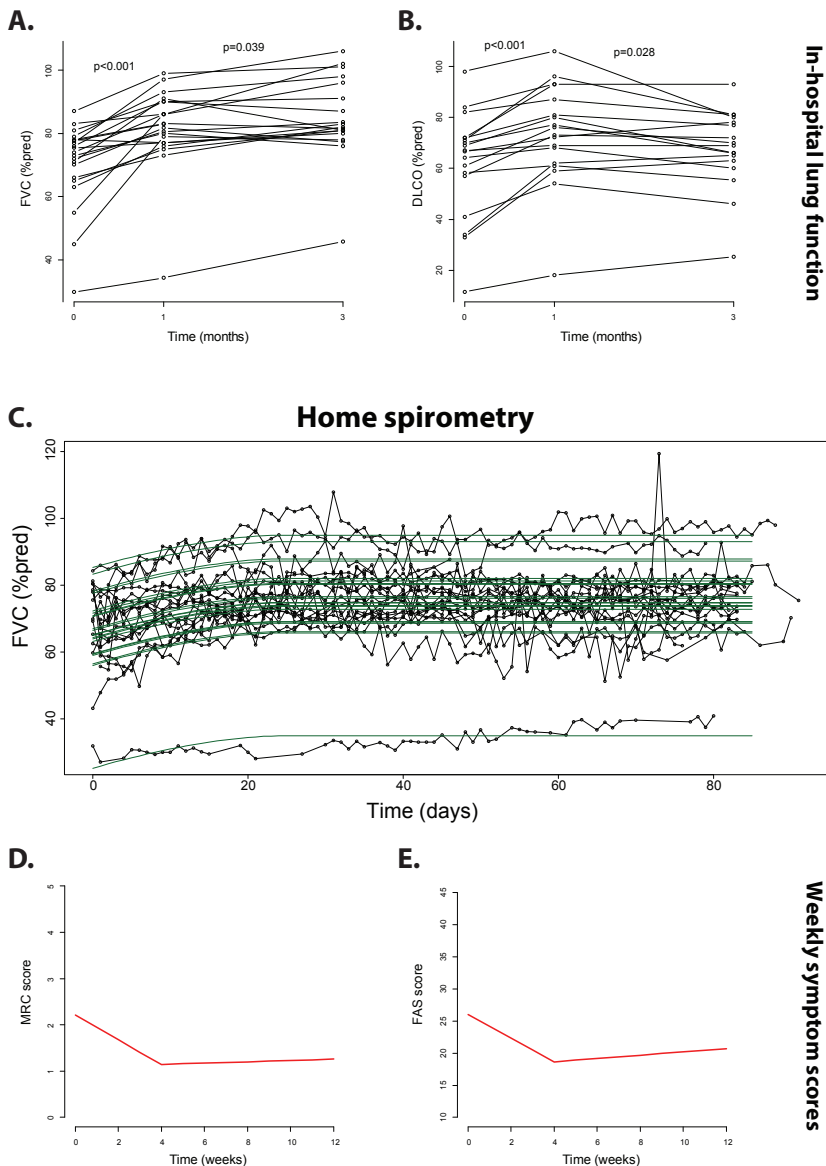[8]These authors contributed equally.

Prednisone is the mainstay of sarcoidosis treatment. However, prednisone treatment optimisation is warranted, since prolonged high-dose prednisone therapy is associated with burdensome and harmful side-effects.[1,2] Early prednisone dose tapering has the potential to reduce side-effects. Gaining insight in the early treatment response can help to determine when tapering could be initiated. To date, there are no prospective studies that look at early treatment response to prednisone in sarcoidosis by monitoring clinical symptoms and daily patient-administered lung function. Therefore, we initiated a multicentre, prospective and observational study with daily home spirometry to detect early steroid treatment effects in newly treated pulmonary sarcoidosis (Dutch National Trial Register NTR4328; www.trialregister.nl/trialreg).

Treatment-naïve sarcoidosis patients in whom prednisone therapy was about to be initiated for a pulmonary indication were eligible. Patients were intended to be treated with the following prednisone regimen: 4 weeks 40 mg·day^{-1}, 2 weeks 30 mg·day^{-1}, 2 weeks 20 mg·day^{-1}, 2 weeks 15 mg·day^{-1}, 2 weeks 10 mg·day^{-1} (unless the treating physician decided that the clinical situation demanded deviation). During these 3 months, daily home monitoring of forced vital capacity (FVC) was performed by the patient on a calibrated hand-held spirometer (Micro Diary; Carefusion, Hoechberg, Germany). Additionally, patients were asked to fill out a Medical Research Council (MRC) dyspnoea and Fatigue Assessment Scale (FAS) score at the end of each week in a diary. Data are presented as mean±SD unless stated otherwise. More details on the study design can be found in the trial register online.

The study group consisted of 21 patients (13 male and eight female; age 43±11 years). The majority of the patients (76%) were diagnosed with Scadding stage II sarcoidosis. Routine in-hospital lung function monitoring showed a significant FVC increase following treatment from 69.7±13.9 to 81.5±13.7 % predicted at month 1 (mean change 11.8±9.2, p<0.001) (figure 1a). A smaller FVC improvement was observed between month 1 (81.5±13.7) and month 3 (84.8±13.2) (mean change 3.3±6.4, p=0.039) (figure 1a). The estimated mean FVC change obtained using daily home spirometry over time was calculated using a fixed effect model, meaning that the regression lines of all 21 individual patients were incorporated (figure 1c). A maximal mean increase of 9.7 (95% CI 8.4–10.9) % pred FVC was estimated after treatment initiation. Interestingly, a plateau of FVC increase was observed at 24 days (95% CI 14–33) and 90% of the total FVC increase was already reached by day 18 (95% CI 10–28).

Together, these data show that most of the improvement in FVC occurs within 2–3 weeks after prednisone therapy initiation in a cohort of newly treated sarcoidosis patients.

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A.

In-hospital lung function

B.

C.

Home spirometry

D.

E.

Weekly symptom scores

FIGURE 1. a) In-hospital clinical monitoring of forced vital capacity (FVC; n=19) and b) diffusing capacity of the lung for carbon monoxide (D_{LCO}) (corrected for haemoglobin levels; n=17) values at baseline, month 1 and month 3 during prednisone treatment of patients with data available at all three time-points. Lines represent paired results from one patient. Significance was determined using a two-tailed paired t-test. c) Daily best FVC measurements recorded on the home spirometer (Micro Diary; Carefusion) per individual patient over time (in days) as % predicted, including regression lines of all 21 individual patients. Daily FVC measured during home monitoring was used as the outcome in a fixed effect model (fixed effect nonlinear least squares model). Regression line of all d) weekly Medical Research Council (MRC) dyspnoea scores and e) Fatigue Assessment Scale (FAS) scores filled out in a home diary per individual patient over time (in weeks). A multilevel model was used that modelled linear splines with a knot at 4 weeks

Our results are in line with other studies that have suggested that the major increase in FVC during prednisone treatment in sarcoidosis occurs within 1 month.[3,4] However, these studies were either performed retrospectively in patients experiencing an exacerbation who previously were shown to be responsive to prednisone and/or evaluated changes on in-hospital lung function equipment at pre-determined time-points, possibly missing early and daily changes in FVC.[3,4]

No single clinical test has been found to accurately assess disease burden in pulmonary sarcoidosis.[5] Therefore, it is important to evaluate whether other outcomes improve as well. Multilevel analyses of the weekly filled out MRC scores showed that dyspnoea symptoms decreased significantly with 0.3 (95% CI 0.2–0.4) MRC points per week (p<0.001), stabilising after 1 month (figure 1d). Similarly, FAS scores decreased significantly with 1.8 (95% CI 1.5–2.2) FAS points per week (p<0.001), stabilising after 1 month (figure 1e). Importantly, this is the first study to evaluate early therapy effects on dyspnoea (MRC) and fatigue (FAS)[6], and the early improvements observed strengthen our home spirometry data.

In a sub-cohort of patients, participating at a select number of study sites, diffusing capacity of the lung for carbon monoxide (*D*LCO) (corrected for haemoglobin level) was measured. A significant increase in *D*LCO % pred was observed within 1 month from 60.4±20.6 to 72.5±19.7 (mean change: 12.0±8.5, p<0.001). However, *D*LCO decreased somewhat again between month 1 and 3 to 67.5±15.6 (mean change −5.0±8.5, p=0.028) (figure 1b). These data may indicate subclinical worsening of the disease during prednisone tapering, as *D*LCO measurements may reflect earlier interstitial changes in sarcoidosis.[7] However, we cannot be certain that this is a relevant change, as reproducibility of *D*LCO measurements is well known to be lower than FVC measurements, and only a major change (>15%) in *D*LCO has been suggested to reliably exclude confounding by measurement variation.[5] Furthermore, daily home spirometry and weekly dyspnoea and fatigue scores showed that the initial improvement was retained in the majority of patients up to 3 months while prednisone dose was tapered. In addition, inflammatory markers that are thought to reflect disease activity in sarcoidosis, such as angiotensin-converting enzyme and soluble interleukin-2 receptor[5,8], decreased significantly within 1 month, also remaining stable up to 3 months (data not shown). However, it remains to be investigated whether these outcomes remain stable in the long term.

Quality of life was also captured in this study during hospital visits at baseline, month 1 and month 3. The St George's Respiratory Questionnaire improved significantly at 1 month, exceeding the reported minimal clinically important difference (table 1).[9,10] Interestingly, questionnaires that were more focused on general health status, such as

the Short-Form Health Survey and King's Sarcoidosis Questionnaire general health status, showed either no or less pronounced changes during prednisone treatment in our study group than scores purely including physical symptoms such as the MRC, FAS and King's Sarcoidosis Questionnaire lung scores (table 1). This may have been caused by concurrent side-effects that occur during prednisone treatment, counterbalancing the positive outcomes of prednisone treatment. Indeed, in our study a number of adverse events were reported that are associated with prednisone treatment, including weight gain. Weight significantly increased within the first 3 months of treatment (mean increase 5.2±4.1 kg, p<0.001). These data confirm that it remains relevant to continuously evaluate benefit–risk ratio of prednisone treatment in consultation with the individual patient.[2,11,12]

This study is the first to perform daily home spirometry in pulmonary sarcoidosis. Daily home spirometry could facilitate a personalised approach to treatment for each patient, aiming at achieving the maximum effect of lung function and symptom improvement

Table 1. Symptoms and quality of life (QoL) assessed during prednisone treatment

Symptom and/or QoL-related questionnaire	Patients	Baseline	Month 1	Month 3[#]
MRC score	18	2.44±1.04	1.33±0.91*	1.39±0.92*
FAS score	18	27.4±10.8	21.0±6.6*	20.7±7.6*
SGRQ				
Symptoms	17	45.0±21.1	29.7±22.4*	27.5±25.1*
Activity	17	55.9±24.9	38.8±27.0*	36.8±28.4*
Impact	17	28.4±23.5	18.5±15.7	18.2±15.1*
Total	17	40.2±21.8	26.5±18.1*	25.4±19.1*
SF-36				
PCS	15	39.0±6.9	40.2±6.9	37.4±6.9
MCS	15	33.5±6.3	36.2±7.0	39.2±8.0*
KSQ				
GHS	11	61.9±14.5	72.0±18.2*	67.0±15.0[¶]
Lung	10	59.0±13.5	70.4±23.1	70.1±20.2*

Data are presented as n or mean±sd. MRC: Medical Research Council; FAS: Fatigue Assessment Scale; SGRQ: St George's Respiratory Questionnaire; SF-36: Short-Form health survey; PCS: physical component score; MCS: mental component score; KSQ: King's Sarcoidosis Questionnaire; GHS: general health status. [#]: none of the values are statistically significant at month 3 compared with values at month 1; [¶]: p=0.055; *: p<0.05 compared with baseline, using a paired sample t-test.

with the lowest possible dose of prednisone, in order to minimise side-effects. This study shows that reliability of daily measured home spirometry in sarcoidosis patients is high;

Pearson correlation between FVC measurements on the home spirometer and the in-hospital lung function equipment was 0.98 (p<0.001).

Together, our data argue that monitoring FVC changes at approximately 2–3 weeks after initiation of therapy, either at home or in clinic, can help physicians to better evaluate response to therapy in newly treated sarcoidosis patients. Consequently, physicians might decide on earlier dose tapering and/or the need for initiation of second-line steroid-sparing therapies than is now advised.[13,14] Future studies are needed to evaluate whether home monitoring of prednisone treatment (including FVC and symptom scores) and personalised dose titration[15] will allow for a non-inferior treatment effect compared to current clinical practice, while reducing side-effects and increasing the quality of life for patients with pulmonary sarcoidosis.

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