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Outcomes in pulmonary sarcoidosis: results of a newly implemented prednisone protocol

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Abstract. *Background and aim:* Prednisone is used as first-line therapy for patients with pulmonary sarcoidosis. There is however no clear association between prednisone dose and FVC change in patients with pulmonary sarcoidosis. In order to improve our standard of care we introduced a more conservative prednisone protocol. *Methods:* This study is a single center observational study, applying value-based healthcare (VBHC) and quality improvement (QI) principles. Prednisone intake was reduced from a starting dose of 40 mg to a starting dose of 20 mg. Primary outcomes evaluated were FVC, FEV1 and DLCO % predicted. The secondary outcome measure was BMI. *Results:* 369 patients were included in the old-cohort and 215 in the new-cohort. In the old-cohort, 182 (49.0%) of the patients were treated with prednisone. In total, 114 patients (62.6%) were treated according to the old protocol with a mean initial prednisone dose of 32.1 ±14.2 mg. In the new-cohort, 93 patients (45.0%) were treated with prednisone of which 53 patients (57.0%) received prednisone according to the new protocol. The mean initial prednisone dose in the new-cohort was 21.4 ±9.8 mg. Changes in FVC and FEV1 % predicted did not vary. Change in % predicted DLCO was 2.4 ±9.3 for the old-cohort and -1.3 ±11.4 for the new-cohort (p = 0.01). No statistically significant changes in BMI were observed. *Conclusions:* Our results indicate that in more than half of the patients the new protocol was followed. Data support the observation that a more conservative prednisone regimen might be equally effective, looking at changes in pulmonary function and BMI.

Key words: Quality improvement, Healthcare quality improvement, Implementation science, Sarcoidosis

Introduction

Previously, a standard set for measuring and comparing outcomes over time was developed for patients with pulmonary sarcoidosis (1). Furthermore, the set has been evaluated on its feasibility and to assess whether changes in outcomes between centers were observed (2). In the literature, several standard sets have been developed applying value-based healthcare (VBHC) (3–6). One of the aims of VBHC is to measure clinical outcomes relevant for a specific patient group divided by the costs (7). However, efforts in applying these sets and the actual use of clinical outcomes to identify quality improvement (QI) initiatives are lacking (8).

Sarcoidosis is a multisystem disease which is histologically characterized by granulomatous inflammations (9). In 90% of the cases the lungs are affected. The first-line therapy option for patients

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with pulmonary sarcoidosis remains prednisone (9–11). The aim of therapy should be the treatment of inflammation and prevention of further deterioration of any organ damage and improving the quality of life, while avoiding negative side-effects such as weight gain (12–14, 27). Prednisone remains the first-line pharmacological treatment option for patients with pulmonary sarcoidosis. Prednisone effectively reduces systemic inflammation in most people, stopping and/or preventing further organ damage. Although prednisone treatment in patients with pulmonary sarcoidosis is reported to induce short-term benefits concerning the inflammation level, the balance between dosage level and adverse side effects remains unclear (11). Evidence for the most optimal prednisone treatment regimen is lacking. Protocols vary both nationally and internationally in prednisone dosage and tapering schemes. The suggested initial prednisone dose varies between 20-40 mg (9).

A study evaluating what dosing strategy has the best balance between effect on pulmonary function and side-effects showed there was no clear association between prednisone dose and FVC change in newly treated patients with pulmonary sarcoidosis (15). Weight gain on the other hand was correlated with cumulative prednisone dose. Long-term and high-dose prednisone therapy is associated with a large number of side-effects impacting patients' quality of life, such as weight gain, diabetes, mood swings and osteoporosis (14,16). Given the adverse effects of corticosteroids and the lack of studies evaluating the most optimal dosage regimen, it is advised to lower patients' initial prednisone dose and realize faster tapering (14,15). However, it is unknown how this new regimen impacts patients' pulmonary function test (PFT) results and BMI. Therefore, we aimed to evaluate the effectiveness of a newly developed prednisone protocol that was implemented in September 2017 at the St. Antonius hospital. We looked at how the new prednisone doses scheme affected patients' pulmonary function and weight over time.

Materials and methods

Study structure and design

This study is a single center observational study, performed at the St. Antonius hospital in Nieuwegein, the Netherlands. The protocol for prednisone treatment was selected as an intervention after seven team meetings by the quality improvement team. In Table 1 more information is provided what was discussed during the meetings. This quality improvement team consisted of five team members including pulmonologists (n=2) and researchers (n=3). The final decision of the intervention was discussed with a specialized nurse from the interstitial lung disease (ILD) unit. After the intervention was selected, this was presented to the team of ILD nurses and one dietician. In Table 1, a full timeline is provided of the implementation process. We evaluated the implementation process of the QI project comparing it with the steps as described by the Implementation of Change Model (ICM) (17). The ICM has been used successfully in the process of implementing improvement initiatives (18).

Quality improvement process

During the quality improvement process, the outcome data of the earlier developed standard set for patients with pulmonary sarcoidosis were discussed. (1,2) During the seven meetings with the quality improvement team, the plan-do-study-act (PDSA) method was used as a tool to guide the process.(19) During the meetings, we discussed the outcome data and went through the following three questions: What do we want to accomplish? What outcomes do we wish to improve? What changes can we make that can potentially lead to an improvement (19)?

One of the quality improvement team members facilitated and prepared the presentations and meetings. After each session, additional data analyses were needed until we reached consensus concerning the final quality improvement initiative.

Prednisone protocol

The new prednisone protocol was lunched on the first of September 2017. The old scheme was re-evaluated after insights from the literature and previous outcomes (15). Differences between the old and new protocol were the initial prednisone dose of 40 mg and 20 mg, respectively. In addition, a consequent lower prednisone dose throughout the treatment was advised in the new protocol (Table 2). As for the old and new protocol, the protocol is used as guidance and allows for deviation. In the new protocol, it was advised that patients would not start on prednisone when: 1) patients had a BMI ≥25; 2)

Table 1. Implementation process and steps by the Implementation of Change Model (ICM).

Step of the Implementation of Change Model	Date	Description of the process
- Development of proposal for change	December 2016 - May 2017	Based on outcome data of the standard set developed for pulmonary sarcoidosis patients, 7 meetings of each 1 hour were organized with the quality improvement team in order to critically look at the data. The quality improvement team consisted of two pulmonologists, two senior researchers and one PhD student. Based on insights from 6 centers and 509 patients, baseline BMI values differed between centers. Specifically for our own center we have looked at the patients with long term prednisone use (≥2 years) and the change of BMI over time. We found that these patients had a higher BMI and that their BMI increased more compared to patients using prednisone for a shorter time, which is also known from the literature. As weight gain is a negative side-effect for patients with pulmonary sarcoidosis, we wanted to minimize weight gain.
- Analysis of actual performance, targets for change	December 2016 - May 2017	We analyzed the following data: - Mortality - Changes in pulmonary function (forced vital capacity (FVC), forced expiratory volume in 1 s, diffusing capacity of the lung for carbon monoxide) - Soluble interleukin-2 receptor (sIL-2R) change - Weight changes - Quality-of-life (QoL) measures - Osteoporosis - Clinical outcome status (COS) In addition, we have looked at prednisone use for only the St. Antonius hospital patients. Our targets for change were prednisone dosage and BMI change.
- Problem analysis of target group and setting	June 2017 - August 2017	We organized a meeting with a specialized nurse to present data and the rationale for the new protocol. A presentation was given to nurses, dieticians in order to get their input.
- Development and selection of strategies and measures to change practice	August 2017 -September 2019	A pulmonologist from the quality improvement team made sure that during the multi-disciplinary team meeting, the protocol would be guiding the treatment choices.
- Development, testing and execution of implementation plan	May 2017 - August 2017	We developed the implementation plan. The quality improvement team and a nurse from the ILD unit were involved. In the implementation plan we explained the rationale, objectives implementation actions and the analysis plan. The implementation plan was presented to the ILD nurses by the PhD student.
- Integration of changes in routine care	1st of September 2017	No pilot phase was integrated as this concerned the change of a protocol for prednisone treatment for routine care. An email was sent to all pulmonologists and residents with the information of the new prednisone protocol and the date was announced when the protocol would become the new golden standard.
- (Continuous) evaluation and (where necessary) adapting plan	September 2019 - March 2020	The protocol was evaluated 2 years after the protocol was implemented. No adjustments were made in the protocol after this was launched on September 1st, 2017.

Steps of the ICM adapted from Grol & Wensing (2013) (26).

Table 2. Doses regimen prednisone.

Old doses regimen	New doses regimen
- 4 weeks 40 mg/day	- 3 weeks 20 mg/day
- 4 weeks 30 mg/day	- 3 weeks 17,5 mg/day
- 4 weeks 20 mg/day	- 3 weeks 15 mg/day
- -2,5 mg per4 weeks until maintenance dose of 10 mg/day	- 3 weeks 12,5 mg/day
	- Maintenance dose of 10 mg/day

patients were diagnosed with diabetes mellitus; 3) patients were known with pseudo-resistant hypertension or 4) when patients were diagnosed with osteoporosis. Reasons to stop prednisone therapy would be: 1) limited response to prednisone (persistent activity); 2) weight gain of > 5% of initial weight

before the patient started with prednisone; 3) the patient developed steroid-induced DM/hypertension or osteoporosis or 4) due to other side-effects (e.g., insomnia, mood swings, etc.).

If it concerned a patient who was being referred to us and prednisone was started elsewhere (often higher dosage), the details of changes made in the respective prednisone scheme at our clinic were used for evaluation. If e.g., a referral patient was switched to 2nd and/or 3rd line therapy or a tapering scheme was initiated by the pulmonologist, the patient was considered as being treated according to the (new) protocol. In case of serious organ threat, methylprednisone was chosen, followed by the lower prednisone schedule.

Measures and outcomes

For this study, the main outcome measures were pulmonary function test (PFT) results and weight change over time. Specifically, we aimed to observe whether changes in forced vital capacity (FVC) % predicted, forced expiratory volume in 1 second (FEV1) % predicted, diffusing capacity of the lung for carbon monoxide (DLCO) % predicted and weight occurred after the new protocol was initiated. Secondly, we wanted to compare the mean initial dosage of prednisone before and after the initiation of the protocol. In addition, we aimed to study in how many patients the protocol was being followed when receiving treatment with prednisone. Medical records were reviewed for diagnostic data, demographics, weight, pulmonary function parameters, and initial prednisone dose. The minimum clinically important difference (MCID) margin for % predicted FVC, FEV1 and DLCO was defined as when there was more than a 10% worsening in PFT compared to the before-cohort. All patients provided informed consent as part of the overall biobank policy. This is a broader informed consent form where patients agree their medical data and biobank material can be used for scientific purposes.

Patient and public involvement

Patients were not involved in the design of the study. During a research meeting, data and the idea to adjust the prednisone protocol was presented to a patient representative. The patient did not comment on the manuscript.

Statistical analysis

The comparison of means of continuous variables was tested with the student t-test. Next, a Mann-Whitney U test or Chi-square test was performed. FVC, FEV1 and $DLCO_c$ is shown as mean percent (%) predicted (± standard deviation (SD)) or as mean absolute change of % predicted (± SD) compared to baseline. All pulmonary function results are based on the European Community for Steel and Coal reference equations (20).

Weight is shown as mean kg (± SD) or as mean absolute change (± SD) in kg compared to baseline. Prednisone dose is shown as mean daily dose in mg. All analyses were performed in SPSS (IBM SPSS Statistics version 24). A p-value of <0.05 was considered statistically significant.

Results

Description of the cohorts

A total of 369 patients were included in the old-cohort and 215 patients in the new-cohort. First mean % predicted FVC was 96.9 ±19.5 in the old-cohort and 98.3 ±18.8 in the new-cohort. First mean % predicted FEV1 was 88.5 ±21.1 in the old-cohort and 89.0 ±20.4 in the new-cohort. Mean % predicted DLCO was 74.8 ±16.2 for the old-cohort and 77.9 ±18.7 ($p = 0.01$) for the new-cohort (Table 3). Average body mass index (BMI) was 28.2 ±5.5 kg/m2 in the old-cohort and 28.0 ±5.7 kg/m2 in the new-cohort. In the old-cohort 58.3% were men, in the new-cohort 53.5% were men. The mean change between the first and last % predicted FVC and FEV1 improved in both cohorts. The mean change of % predicted FVC and DLCO was significantly different between the two cohorts. Additional characteristics are shown in Table 3.

Patients treated with prednisone

In the old-cohort, 182 (49.3%) patients needed treatment with prednisone. In the new-cohort, 93 (43.7%) patients needed treatment with prednisone. The mean initial prednisone dose in the old-cohort was 32.1 ±14.2 mg. Mean initial prednisone dose in the new-cohort was significantly lower, 21.4 ±9.8 mg ($p < 0.001$). In the old-cohort, 62.6% of the patients started on ≤40 mg prednisone. In the new-cohort

Table 3. Characteristics of old-cohort versus new-cohort.

	Old-cohort n=369	New-cohort n=215	p-value §
Gender			
Male (n, %)	215 (58.3)	115 (53.5)	0.35
Female (n, %)	150 (40.7)	99 (46.0)	
Age (mean, sd)	49 ±12.2	51 ±13.0	0.09
BMI at first PFT (kg/m2)	28.2 ±5.5	28.0 ±5.7	0.47
Weight at first PFT	86.5 ±17.7	84.9 ±18.7	0.19
Treated with prednisone (n, %)	182 (49.3)	93 (43.7)	0.18
Mean first PFT (mean, sd)			
% predicted FVC	96.9 ±19.5	98.3 ±18.8	0.19
% predicted FEV1	88.5 ±21.1	89.0 ±20.4	0.64
% predicted DLCO	74.8 ±16.2	77.9 ±18.7	0.03
Mean change (mean, sd) R			
% predicted FVC	1.9 ± 9.4	0.9 ±9.9	0.04
% predicted FEV1	0.9 ±9.3	0.3 ±10.1	0.60
% predicted DLCO	2.3 ±8.5	-0.5 ±9.7	0.00

§ p-values were calculated with a Mann-Whitney U test or Chi-square test. [R] Number of months between 1st and last PFT was 23.1 ±13.4 (cohort 2015-2017) and 16.0 ±13.6 (cohort 2017-2019). *Abbreviations:* DLCOc: diffusing capacity of lung for carbon monoxide (corrected for hemoglobin levels), PFT: pulmonary function, FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second, kg: kilograms, mg: milligrams, m: meter.

57.0% of the patients started with prednisone according to the new protocol (i.e., on ≤20 mg prednisone). For some patients the explanation why their initial prednisone dose was higher than the protocol was provided by a pulmonologist (Table 4). Often the dose was higher when it concerned patients coming from a referral center. Before entering our cohort, the patients already started on a higher prednisone dose in another hospital. When arriving at our hospital, the 13 patients described in Table 4 were all put on prednisone tapering schemes and/or second-line therapy was introduced.

Pulmonary function

First mean % predicted FVC was 94.6 ±19.8 in the old-cohort and 94.1 ±22.0 in the new-cohort. First mean % predicted FEV1 was 84.8 ±22.0 in the old-cohort and 84.5 ±22.6 in the new-cohort. Mean % predicted DLCO was 73.2 ±16.5 for the old-cohort and 74.8 ±21.4 for the new-cohort (Table 5).

Average body mass index (BMI) was 27.6 ±5.6 kg/m2 in the old-cohort and 27.9 ±6.0 kg/m2 in the new-cohort. The mean change between the first and last % predicted FVC and FEV1 improved in both cohorts. The mean change of % predicted DLCO was significantly different between the two cohorts with 2.4 ±9.3 increase and 1.3 ±11.4 decrease in the old-cohort and new-cohort, respectively. This difference was not clinically relevant. Additional baseline characteristics are presented in Table 5.

BMI

First BMI measured for patients treated with prednisone in the old (n=182) and new (n=97) cohort did not differ between the cohorts, which was 27.6 ±5.6 for the old and 27.9 ±6.0 for the new-cohort. The second measured BMI was 27.5 ±5.5 for the old and 28.1 ±6.0 for the new-cohort. In Table 6, BMI measured at different time points is given for patients being treated with prednisone. BMI did not significantly differ at any point in time between the patients from the old and new-cohort.

Discussion

Statement of principal findings

In this study, we observed unchanged clinical outcome data after implementing a more conservative

Table 4. Overview of patients with higher initial prednisone dose.

Patient	Treated according to protocol	Short therapy overview by pulmonologist
1	Yes	Rightly treated according to protocol here. At first visit to our hospital prednisone was already reduced by the referral hospital to 10 mg (started elsewhere before being referred to us at 60 mg). Steroid-saving MTX included.
2	Yes	On first visit 20 mg prednisone. Started with 60 mg elsewhere. Then reduced by 2.5 mg per month to a maintenance dose of 10 mg.
3	Yes	On first visit 20 mg prednisone. Started with 60 mg elsewhere. Started steroid-sparing after MTX evaluation. Reduction here also slightly slower (2.5 mg per 4 weeks instead of every 3 weeks).
4	Yes	Started with 60 mg prednisone due to renal sarcoidosis elsewhere. Hereafter the patient started with MTX and prednisone was reduced.
5	No	Started with prednisone on 60 mg elsewhere due to cardiac sarcoidosis. When the patient was first seen at our clinic, the patient continued with 60 mg prednisone. MTX (steroid-sparing) was started immediately on the first visit, however this had to be discontinued due to hepatic MTX-toxicity. Therefore, prednisone was continued in quite a high dose with Azathioprine as a steroid-sparing therapy. So here due to circumstances and severity of cardiac sarcoidosis, a higher dose of prednisone was deliberately chosen for a longer period.
6	Yes	Started with 40 mg prednisone elsewhere. After being referred to our hospital, MTX was started as steroid-sparing therapy and prednisone was tapered off (in 8 weeks to 10 mg).
7	Yes	Started with 40 mg prednisone elsewhere. After being referred to our hospital, steroid-sparing therapy with MTX and tapering of prednisone was started (adjusted tapering schedule, but in 3 months to 10 mg maintenance).
8	Yes	Patient (with BMI of 28) came in with 10 mg of prednisone after being referred to us. Patient started with MTX steroid-sparing therapy. Prednisone was tapered off.
9	Yes	Started prednisone elsewhere, starting dose unknown. When entering our clinic, patient used 15 mg prednisone. Elsewhere MTX was started (to introduce steroid-sparing therapy). At our center, prednisone was directly further reduced to 10 mg as the maintenance dose.
10	Yes	Came in with 20 mg of prednisone, which was started elsewhere. Starting dose elsewhere was 40 mg. At our center patient received a tapering scheme (due to BMI of 39). MTX was started (to introduce steroid-sparing therapy).
11	Yes	Entering from elsewhere with 10 mg prednisone and 15mg MTX (from a steroid-sparing point of view). Prednisone immediately decreased to 0 mg (2.5 mg per 4 weeks) under plaquenil which was started with the purpose of also decreasing the MTX and providing plaquenil as monotherapy.
12	Yes	Came in with 10 mg prednisone. Started with 40 mg elsewhere. Started with steroid sparing MTX at our center and prednisone was tapered (tapering schedule 2.5 mg every 4 weeks).
13	Yes	Came in with 5 mg prednisone and received methylprednisolone at our center in due to severe cardiac sarcoidosis. Afterwards, MTX was started as steroid-sparing therapy due previous weight gain with prednisone.

Abbreviations: BMI: body mass index, MTX: methotrexate.

prednisone protocol in our sarcoidosis center. Specifically, the mean initial prednisone dose in the old-cohort was 32.1 ±14.2 mg and in the new-cohort 21.4 ±9.8 mg.

Comparing the old- and new-cohort, BMI did not significantly differ at any point in time, and change in % predicted FVC and FEV1 did not vary between the groups. These data suggest that a more conservative prednisone treatment has the potential to be equally effective in treating patients with pulmonary sarcoidosis. Change in % predicted DLCO was significantly different between the two groups. However, this difference was not clinically relevant.

The data of this study indicated that many referral patients from other clinics came in with a high dose of prednisone. Despite their high dose, these patients were treated following the new prednisone protocol in our center. Some did not meet the new start criteria (BMI> 25, DM, hypertension or osteoporosis) beforehand or met the new stop criteria. Often, prednisone was being phased out and/or a treatment indication for second-line treatment was started. This was the case in all 13 patients from whom therapy decisions were described in more detail. In addition, in one case due to circumstances and severity of (cardiac) sarcoidosis, pulmonologists

Table 5. Characteristics of patients on prednisone old-cohort versus the new-cohort.

	Old-cohort n=182	New-cohort n=93	p-value §
Gender			
Male (n, %)	109 (60.2)	50 (53.8)	0.46
Female (n, %)	72 (39.8)	43 (46.2)	
Age (mean, sd)	48 ±12.2	50 ± 12.8	0.18
Mean prednisone dose at start in mg (mean, sd)	32.1 ±14.2	21.4 ±9.8	0.00
BMI at first PFT (mean, sd)	27.6 ±5.6	27.9 ±6.0	0.86
Weight at first PFT (mean, sd)	84.8 ±17.5	84.5 ±18.7	0.74
Treated according to protocol (n, %)			
Yes, %	114 (62.6)	53 (57.0)	0.01
Mean initial prednisone dose (n, %)			
> 10 ≤ 20 mg	45 (24.7)	49 (52.7)	0.00
> 21 ≤ 30 mg	42 (23.1)	16 (17.2)	
> 31 ≤ 40 mg	27 (14.8)	6 (6.5)	
> 41 ≤ 50 mg	1 (0.5)	2 (2.2)	
> 51 ≤ 60 mg	15 (8.2)	1 (1.1)	
> 61 mg	2 (1.1)	0	
Initial dose missing, %	50 (27.5)	19 (20.4)	
Mean first PFT (mean, sd)			
% predicted FVC	94.6 ±19.8	94.1 ±22.0	0.95
% predicted FEV1	84.8 ± 22.0	84.5 ±22.6	0.87
% predicted DLCO	73.2 ±16.5	74.8 ±21.4	0.82
Mean change (mean, sd) R			
% predicted FVC	2.6 ±10.2	2.0 ±9.4	0.25
% predicted FEV1	1.1 ±10.3	1.5 ±9.3	0.89
% predicted DLCO	2.4 ±9.3	-1.3 ±11.4	0.01

§ p-values were calculated with a Mann-Whitney U test or Chi-square test. R Number of months between 1st and last PFT was 24.1 ±15.3 (cohort 2015-2017) and 12.3 ±11.4 (cohort 2017-2019). *Abbreviations:* DLCOc: diffusing capacity of lung for carbon monoxide (corrected for hemoglobin levels), PFT: pulmonary function, FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second, kg: kilograms, mg: milligrams, m: meter.

needed to deviate from the protocol. Thus, for referral patients we have managed to lower the burden due to prednisone therapy.

Interpretation within the context of the wider literature

A retrospective study from The Netherlands consisting of 54 patients with pulmonary sarcoidosis concluded there was no clear association between prednisone dose and FVC change in newly treated patients with pulmonary sarcoidosis (15). Weight gain on the other hand was correlated with cumulative prednisone dose. Therefore, the authors concluded that prednisone treatment with a lower cumulative dose in the long term has the potential to be equally effective in treating patients with pulmonary sarcoidosis versus treatment with a higher dose strategy.

In our study we were unable to incorporate other potential side effects that may be reduced due to the lower dose of corticosteroids. It is known that the status of bone health in patients with sarcoidosis is deteriorated due to the use of corticosteroids. The use of corticosteroids may cause decreased bone formation, increased bone resorption and can induce a net bone loss (28). Other studies have however also investigated the effect of lowering prednisone dosage in relation to other side-effects, besides the effect on

Table 6. BMI of patients treated with prednisone in the 2015-2017 versus the 2017-2019 cohort.

	Old-cohort	New-cohort	P-value
	n=182	n=97	
BMI at 1st[d] PFT (mean, sd)	27.6 ±5.6	27.9 ±5.9	0.63
	n=182	n=97	
BMI at 2rd PFT (mean, sd)	27.5 ±5.5	28.1 ±6.0	0.40
	n=157	n=50	
BMI at 3rd PFT (mean, sd)	27.2 ±5.3	27.9 ±6.0	0.46
	n=132	n=36	
BMI at 4th PFT (mean, sd)	28.0 ±5.4	27.5 ±7.1	0.62
	n=105	n=14	
BMI at 5th PFT (mean, sd)	27.0 ±4.7	26.9 ±3.7	0.95

Continuous data are presented as mean ± standard deviation. *Abbreviations:* BMI: body mass index (kg/m^2), PFT: pulmonary function test, kg: kilograms, m: meter. Time in months between the 1st, 2nd, 3rd, and 4th BMI measures were: 24.1 ±15.3, 26.5 ±14.8, 28.8 ±14.6, 31 ±15.2, respectively. For the new-cohort time in months was 12.3 ±11.4, 16.7 ±11.2, 19.3 ±12.0 and 29.3 ±14.2.

weight. Moreover, lower dose prednisone treatment can reduce side-effects such as weigh gain, mood swings and the development of diabetes (and/or infections) (14). Due to the adverse effects of prednisone and the lack of knowledge concerning the most optimal balance between dose and side-effects, lower (initial) dose and faster tapering seem to be equally effective (14,15).

Although a more detailed analysis would be needed to conclude this, it seems that from what is known from the literature in combination with our analysis, the new protocol is equally effective. In order to have solid evidence, the correlation between cumulative prednisone dose and the absolute change in weight from the onset of treatment and various time points after receiving treatment should be evaluated. The analysis as carried out by others incorporated a linear regression model (15). It would be useful for the literature to conduct a similar analysis in patients from other clinics/countries to further support the effect of lowering the dose of corticosteroids on pulmonary function in relation to weight changes.

As this improvement initiative was part of a value-based healthcare (VBHC) program, the new protocol was evaluated using data from daily clinical practice in combination with data from the literature. As reported elsewhere, despite the increasing interest in research on how to apply and translate knowledge into daily clinical practice and improve healthcare, the scientific knowledge in this field is slow (21). Therefore, rigorous evaluation of outcomes should remain part of research programs (21), also for future quality improvement initiatives for patients with pulmonary sarcoidosis.

Strengths and limitations

The structure of realizing the QI project was shaped making use of the PDSA cycle. This made it possible to have structure and support during the meetings and in the process of defining the QI initiative, which was also acknowledged by others (22).

A limitation of this study is that we performed a before-after analysis. This study design does not control for bias that might have occurred at the same time (23). Therefore, it remains difficult to determine whether the protocol change itself was responsible for the observed effect. Bias could have been that pulmonologists were already more conservative with prescribing prednisone before the new protocol was introduced based on insights from the literature. Also, it would have been useful to study and evaluate the mean cumulative prednisone dosage over time and compare this to weight and BMI, which was done by other authors (15). By doing this, it would be possible to draw conclusions that are more rigorous on the effect of the new dosage scheme. We were unable to collect detailed information concerning the cumulative dosage retrospectively. It was hard to get detailed trustworthy data in retrospect.

Another limitation is that not all patients were treated according to the protocol. In total, 53 patients (57.0%) were treated according to the protocol. Should this percentage have been higher, there

could have been a stronger association between the mean BMI and respective difference between the old- and new-cohort. Also, before launching the new protocol, clinicians were already more careful with prednisone dosage, which can also partially explain there are no significant differences in BMI.

As presented in the results, in the old-cohort 62.6% and in the new-cohort 57.0% of the patients were treated according to the protocol. This clearly affected the results, as the other patients were treated with a different prednisone regimen. Due to circumstances and severity of extra-pulmonary sarcoidosis (such as cardiac sarcoidosis), a higher dose of prednisone was deliberately chosen for a longer period. Also, sometimes referral patients were on a high dosage of prednisone, but often our clinicians tried to tapper down when possible. If more patients would have been treated according to the protocol, the results could have been stronger. However, the differences in mean initial dosage between the cohorts are quite significant (32 mg vs. 21 mg). Therefore, the results of this observational study are still meaningful.

Another limitation is that we did not provide regular (e.g., monthly) updates on how many patients started on prednisone and what their initial dosage was. This concerns step seven of the ICM model, providing continuous evaluation and feedback on the number of patients being treated with prednisone and their respective dosage scheme. It would have been useful to discuss the data of the number of patients starting on prednisone and their respective dosage after the implementation of the new protocol with the pulmonologists and the nurses from the ILD department.

Implications for policy, practice and research

As stated elsewhere, claims made from improvements are sometimes far stronger than is warranted (23,24). We therefore suggest that our results can be used as a proof of concept, but we do suggest that the most optimal balance between prednisone dose, pulmonary function and side-effects should be studied in further detail. This can also be done as part of a prospective QI project, where the cumulative dosage of prednisone is also being monitored prospectively.

The continued work of measuring and comparing outcomes will allow discussing best practices and challenges in a multicenter setting. When there is constant monitoring of health outcomes, this may have positive effects on outcomes. In a VBHC pilot study among IBD patients, positive trends such as fewer ED visits, fewer hospitalization and less long-term corticosteroid use were observed (25). When consistently monitoring outcomes in care delivered for patients with sarcoidosis, this can empower participating centers to implement and monitor QI efforts throughout the full cycle of care.

Conclusions

In summary, our study shows that VBHC principles can be applied in a sarcoidosis center. Furthermore, the collected outcome data support the observation that a more conservative prednisone regimen might be equally effective. Future research should however perform a more rigorous assessment of the clinical effectiveness of the different regimens on radiological improvement, extrathoracic disease improvement and quality of life.

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References

1. Kampstra NA, Grutters JC, van Beek FT, et al. First patient-centred set of outcomes for pulmonary sarcoidosis: a multicentre initiative. BMJ open Respir Res 2019; 6(1):e000394.
2. Kampstra NA, van der Nat PB, Dijksman LM et al. Results of the standard set for pulmonary sarcoidosis: feasibility and multicentre outcomes. ERJ Open Res 2019; 5(4):00094-2019.
3. Daeter EJ, Timmermans MJC, Hirsch A et al. Defining and Measuring a Standard Set of Patient-Relevant Outcomes in Coronary Artery Disease. Am J Cardiol 2018; 121(12):1477-1488.

4. Kim AH, Roberts C, Feagan BG et al. Developing a standard set of patient-centred outcomes for inflammatory bowel disease—an international, cross-disciplinary consensus. J Crohn's Colitis 2017; 12(4):408-418.
5. Michelotti M, de Korne DF, Weizer JS et al. Mapping standard ophthalmic outcome sets to metrics currently reported in eight eye hospitals. BMC Ophthalmol 2017; 17(1)1-8.
6. Morgans AK, van Bommel ACM, Stowell C et al. Development of a standardized set of patient-centered outcomes for advanced prostate cancer: an international effort for a unified approach. Eur Urol 2015; 68(5)891-898.
7. Porter ME. What is value in health care? N Engl J Med 2010; 363(26):2477-2481.
8. Van Veghel D, Daeter EJ, Bax M et al. Organization of outcome-based quality improvement in Dutch heart centres. Eur Hear Journal-Quality Care Clin Outcomes 2019; 6(1):49-54.
9. Costabel U, Hunninghake GW. ATS/ERS/WASOG statement on sarcoidosis. Eur Respir J 1999; 14:735-737.
10. Schutt AC, Bullington WM, Judson MA. Pharmacotherapy for pulmonary sarcoidosis: a Delphi consensus study. Respir Med 2010; 104(5):717-723.
11. Paramothayan NS, Lasserson TJ, Jones P. Corticosteroids for pulmonary sarcoidosis. Cochrane Database Syst Rev 2005; 2:CD001114.
12. Wijsenbeek MS, Culver DA. Treatment of sarcoidosis. Clin Chest Med 2015; 36(4):751-767.
13. Baughman RP, Costabel U, du Bois RM. Treatment of sarcoidosis. Clin Chest Med 2008; 29(3):533-548.
14. Grunewald J, Grutters JC, Arkema EV et al. Publisher Correction: Sarcoidosis. Nat Rev Dis Primers 2019; 5(45).
15. Broos CE, Poell LHC, Looman CWN et al. No evidence found for an association between prednisone dose and FVC change in newly-treated pulmonary sarcoidosis. Respir Med 2017; 138:S31-S37.
16. Baughman RP, Drent M, Culver DA. Endpoints for clinical trials of sarcoidosis. Sarcoidosis Vasc Diffus lung Dis 2012; 29:90-98.
17. Grol R, Wensing M, Eccles M et al. Improving patient care; the implementation of change in health care. John Wiley & Sons, 2013.
18. Zipfel N, Van Der Nat PB, Rensing BJWM et al. The implementation of change model adds value to value-based healthcare: A qualitative study. BMC Health Serv Res 2019; 19(1):1-12.
19. Deming WE. Out of the Crisis. MIT press, 2018.
20. Quanjer PH, Tammeling GJ, Cotes JE et al. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J 1993; 6(5):40.
21. Wensing M, Grol R. Knowledge translation in health: How implementation science could contribute more. BMC Med 2019; 17(1)1-6.
22. Peterson A, Gudbjornsdottir S, Lofgren UB et al. Collaboratively Improving Diabetes Care in Sweden Using a National Quality Register: Successes and Challenges-A Case Study. Qual Manag Health Care 2015; 24(4):212-221.
23. Portela MC, Pronovost PJ, Woodcock T et al. How to study improvement interventions: A brief overview of possible study types. Postgrad Med J 2015; 91(1076):343-354.
24. Benn J, Burnett S, Parand A et al. Studying large-scale programmes to improve patient safety in whole care systems: Challenges for research. Soc Sci Med 2009; 69(12):1767-1776.
25. van Deen WK, Spiro A, Burak Ozbay A et al. The impact of value-based healthcare for inflammatory bowel diseases on healthcare utilization: a pilot study. Eur J Gastroenterol Hepatol 2017; 29(3):331-337.
26. Grol R, Wensing M. Effective implementation of change in healthcare: A systematic approach. Chapter 3 (40-63) from the book: Improving patient care; the implementation of change in health care. John Wiley & Sons, 2013.
27. Kahlmann V, Moor CC, Veltkamp M et al. Patient reported side-effects of prednisone and methotrexate in a real-world sarcoidosis population. Chron Respir Dis 2021; 18:1-4.
28. Sweiss, NJ, Lower EE, Korsten P et al. Bone health issues in sarcoidosis. Curr Rheumatol Rep 2011; 13:265-272.