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Randomised, placebo-controlled trial of dexamethasone for quality of life in pulmonary sarcoidosis

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ABSTRACT

Background: Many patients with pulmonary sarcoidosis experience reduced quality of life. Although oral corticosteroids are the most common agents used in sarcoidosis, very little is known on the effects on quality of life.
Methods: In this double-blind, placebo-controlled trial, newly diagnosed patients without an indication for high dose immunosuppressive therapy were randomised to once-daily dexamethasone 1 mg (6.5 mg prednisone equivalent) or placebo for 6 months. The primary study parameter was the subscale physical functioning of the 36-item Short Form health survey (SF-36). Secondary parameters included five other patient reported outcome measures, disease activity markers and plasma cytokine profiles.
Results: A total of 16 patients was randomised to dexamethasone (n = 7) and placebo (n = 9). During follow-up no significant difference for physical functioning was measured (p = 0.18). Dexamethasone treated patients showed a decrease in fatigue score (Checklist Individual Strength) from 106 (baseline) to 88 (3 months; p = 0.03); 86 (6 months; p = 0.05); 79 (9 months; p = 0.04); 90 (12 months; p = 0.03). Placebo treated patients showed no change: 96 (baseline) to 105 (3 months; p = 0.16); 91 (6 months; p = 0.48); 92 (9 months; p = 0.61); 95 (12 months; p = 0.90). During treatment with dexamethasone significant improvements in the SF-36 subscales vitality and pain, and a significant reduction in serum angiotensin-converting enzyme, soluble interleukin 2 receptor levels and serum cytokines and chemokines were measured.
Conclusions: Low-dose dexamethasone results in a reduction of the inflammatory profile and has the potential to improve quality of life parameters and fatigue.

1. Introduction

Sarcoidosis is a systemic, granulomatous disease of unknown aetiology that frequently presents with bilateral hilar lymphadenopathy and pulmonary infiltration [1]. It is characterised by T-lymphocyte infiltration and granuloma formation, mediated by the release of pro-inflammatory cytokines and chemokines such as interleukin (IL)-2, interferon γ (IFN-γ) and tumor necrosis factor (TNF)-α [1,2]. The clinical expression and prognosis of sarcoidosis are highly variable and spontaneous remissions occur in nearly two-thirds of patients [3]. Besides respiratory symptoms many patients suffer from persistent nonspecific symptoms such as weight loss, fatigue, arthralgia, muscle pain and general weakness [4]. Sarcoidosis patients experience a reduction in several domains of health-related quality of life (HRQL) and report fatigue, sleeping problems and depressive symptoms [5,6]. Even when sarcoidosis is in clinical remission, fatigue and reduced HRQL can be severe and long-lasting problems [7]. Inflammation and the release of cytokines such as IL-1 and TNF- α may play a central role in the pathogenesis of sarcoidosis associated fatigue [8,9].

In pulmonary sarcoidosis there is no general consensus regarding subgroups to be treated, treatment type, dose and duration [3]. Therapy with corticosteroids is often started in patients experiencing an intractable cough, dyspnea on exertion or progressive deterioration of pulmonary function [3,10]. The typical initial dose is 20–40 mg prednisone equivalent per day which is subsequently tapered, although there is evidence that a starting dose of 5–15 mg is already clinically beneficial

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[11–13]. It is estimated that one-third to one-half of patients with sarcoidosis gets treatment with corticosteroids [1]. Clinicians often initiate therapy based on the presence of granulomatous inflammation or physiologic change, even when there are no dangerous consequences and the patients quality of life is not affected appreciably [14]. On the other hand, treatment based on an unacceptably impaired quality of life in the absence of a large burden of systemic disease is highly subjective [10].

Current recommendations for treatment of sarcoidosis with corticosteroids are based on a very limited number of double-blind placebo-controlled trials [11]. Historically, such trials focused on changes in chest X-ray, lung function parameters and biomarkers, and not on HRQL and fatigue.

In this study, we hypothesised that gentle suppression of the inflammatory process with a low dose of dexamethasone in the first months upon diagnosis generates alleviation of acute fatigue and malaise, and improvement of HRQL in patients with troublesome inflammatory sarcoidosis.

2. Materials and methods

2.1. Study population

Eligible patients were diagnosed with pulmonary sarcoidosis in the past 6 months, were 18–60 years of age, and with no organ involvement requiring high dose immunosuppressive therapy. The diagnosis was made in accordance with the guidelines of the World Association of Sarcoidosis and Other Granulomatous diseases [1]. All diagnoses were confirmed by either histological proof in biopsy or a confirmative CD4/CD8 ratio (>3.5) in the BAL. Patients were required to experience a reduction of HRQL as measured by the Short Form 36 subscale physical functioning (SF-36 PF $\leq$ 70). Inclusion criteria for diagnosis and SF-36 PF were originally set at $\leq$ 3 months and $\leq$60 respectively and were adapted from participant no 4 onwards due to slow inclusion rate.

Exclusion criteria included an allergy to corticosteroids, current use of non-steroidal anti-inflammatory drugs without co-prescription of a proton-pump inhibitor, and current use of a potent inducer of cytochrome P450 liver enzymes. Patients with obesity (body mass index > 30), a diagnosis of glaucoma, a history of gastric ulcera in the past 12 months, a diagnosis of osteoporosis or a history of fractures were excluded as well as patients who were pregnant or lactating.

2.2. Study design and treatment

The study was a multi-center randomised, double-blind, placebo-controlled, phase III trial (acronym DEXSAR). Patients were included between June 2013 and September 2016 in the St Antonius Hospital, the Netherlands, and from 2014 also in 4 other sites in the Netherlands (Jeroen Bosch Hospital, Den Bosch; Martini Hospital, Groningen; Medisch Spectrum Twente, Enschede; Haaglanden Medical Center, the Hague). The majority of patients was included at the St Antonius Hospital, a national tertiary referral centre for sarcoidosis. The trial was terminated prematurely due to slow inclusion rate in September 2016. The minimal 12 months follow-up was completed by all included patients.

Patients were randomised 1:1 to receive dexamethasone 1 mg (6.5 mg prednisone equivalent) or placebo, orally, 1 tablet daily during 6 months and subsequently followed for an additional 6 months. Randomisation was performed by dedicated study personnel of the Dept of Clinical Pharmacy of the St Antonius Hospital, Nieuwegein, the Netherlands. A randomisation number was allocated to all primary packages of dexamethasone and placebo using a random-sequence generator. Patients were allocated to the sequentially numbered containers in order of the date of informed consent. All participants, physicians, trial nurses and investigators were blinded from the identity of the containers, which were kept and distributed by the study personnel of the Dept of Clinical Pharmacy. The randomisation list was concealed until study completion. Screening and enrolment of patients was performed by trial nurses and the investigators.

The study was performed in accordance with the Declaration of Helsinki and its amendments. The protocol and subsequent amendment were approved by the regional Medical Ethics Committee (EudraCT number 2013-000242-18) and written informed consent for participation was obtained from all patients. The trial protocol can be accessed through the EU Clinical Trials Register (www.clinicaltrialsregister.eu/ctr-search/trial/2013-000242-18/NL). This study was designed and reported in agreement with the criteria as defined in the Consolidated Standards of Reporting Trials (CONSORT) [15]. A completed CONSORT checklist is provided as an appendix (Table A1).

2.3. Primary and secondary outcome parameters

Routine clinical visits were performed at baseline and at 3, 6, 9 and 12 months and included lung function tests and chest radiography as well as measurement of serum angiotensin converting enzyme (ACE) and soluble interleukin 2 receptor (sIL-2R). Patients requiring high dose immunosuppressive therapy because of progression of symptoms, progressive pulmonary deterioration or any other organ threat, could be withdrawn from the intervention. All adverse events reported spontaneously by the subject or observed by the trial nurses or investigators were recorded. Body weight was recorded at every study visit.

The SF-36 PF at 6 months was considered as the primary outcome parameter. Secondary parameters consisted of a panel of 5 questionnaires, which were completed one week prior to every visit. The SF-36 and EQ-5D-3L were used to assess health status [6,16,17]. The SF-36 scores eight dimensions of HRQL on a scale from 0 to 100 (maximum health state). The EQ-5D assesses five dimensions that can be summarised in an index value and a visual analogue scale (VAS) that ranges from 0 to 100 (maximum health state). The Checklist Individual Strength (CIS) is a generic instrument that measures fatigue, yielding a total score in the range 20–140 (maximum fatigue) [7]. The Four-Dimensional Symptom Questionnaire (4DSQ) assesses distress (scale 0 to 32), depression (scale 0 to 12), anxiety (scale 0 to 24) and somatisation (scale 0 to 32) with higher scores indicating more severe complaints [18].

The Pittsburgh Sleep Quality Index (PSQI) provides a generic measure of sleep quality on a scale from 0 to 21 (worst possible sleep quality) [19].

At every visit a cytokine/chemokine panel was measured, using a high sensitivity panel consisting of interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 p70, tumor necrosis factor (TNF)-α and interferon (IFN)-γ, and a regular panel containing IL-1α, interleukin 1 receptor antagonist (IL-1 RA), IL-18, TNF receptor 2 (TNF RII), interferon γ induced protein (IP)-10, monocyte chemoattractant protein (MCP)-1 (CCL2), macrophage inflammatory protein (MIP)-1α (CCL3), MIP-1β (CCL4), RANTES (CCL5), eotaxin-1 (CCL11), CTACK (CCL27), ENA-78 (CXCL5), MIG (CXCL9), CD40 and CD40 ligand (BioTechne, Abingdon, UK). Serum cortisol levels were determined at baseline and at 6 and 12 months.

2.4. Statistical procedures

Statistical analysis was performed with IBM SPSS 24.0 Statistics software (Statistical Package for the Social Sciences; IBM, Armonk, New York, USA). Based on own data from patients with sarcoidosis and a SF-36 PF score $\leq$70 (mean 54 and s.d. 12) we calculated beforehand that 70 (2×35) patients would be sufficient to detect a mean difference of 8 or more points between pre and post treatment measurements of the SF-36 PF (alpha 0.05 and power 80%).

Patient demographics were compared using an independent samples *t*-test, except for the comparison of gender for which the Pearson chi-square test was used. Within each treatment arm paired samples t-testing was used to test differences in parameters between follow-up

time points (delta change value). Subsequently, an independent samples *t*-test was applied to test these delta change values between treatment arms. Levene's test was performed to assess whether equality of variances could be assumed. As a conservative approach to address the limited sample-size, non-parametric testing (independent samples Mann-Whitney *U* test) was performed on the delta change values for all outcome parameters as well.

Treatment effects were analysed as per intention-to-treat analysis. For the primary outcome parameter an additional per-protocol analysis was performed restricted to patients who completed the intervention and did not suffer from physical trauma intervening with the primary outcome parameter. In all analyses all patients were included. In case one of the questionnaires of a patient at a certain time point beyond baseline was missing, the value of the previous time point was used in the analysis. In case of a missing questionnaire at baseline, the patient was not included in the analysis of the specific questionnaire.

3. Results

3.1. Study population

Overall, from 374 screened patients, a total of 16 patients consented to participate and was subsequently randomised to one of the two treatment arms (Fig. 1).

Demographic characteristics and scores on HRQL, fatigue and psychological symptoms at baseline were balanced between groups (Table 1). Overall, patients showed impairments on all SF-36 domains indicating a reduced HRQL with a predominance of limitations caused by physical impairment and bodily pain. Furthermore, fatigue was evidently reported as indicated by high scores on the CIS-20 fatigue instrument and low scores on the SF-36 vitality domain. Self-reported health as measured by the EQ-5D was low and sleep quality (based on the PSQI) reduced. Scores from the 4DSQ indicated serious distress but only mild symptoms of depression and anxiety.

Besides clinical characteristics, the baseline cytokine and chemokine levels were also balanced between groups and indicative of active sarcoidosis with detectable levels of sACE, sIL-2R, TNF RII, IP-10, MIP-1α, MIP-1β, RANTES, ENA-78 and CD40 (Table 2).

3.2. Primary outcome parameter

During follow-up no significant difference for the primary outcome parameter physical functioning (SF-36 PF at 6 months) was measured ($p = 0.18$). In the placebo treated group, SF-36 PF increased with 7 ± 13 points ($p = 0.13$) and in the dexamethasone treated group the SF-36 PF decreased with 6 ± 24 points ($p = 0.55$). In a per-protocol analysis a significant increase in SF-36 PF in the dexamethasone treated group was observed at 3 and 12 months with increases of 8 ± 3 points ($p = 0.01$) and 24 ± 9 ($p = 0.01$) respectively. In the placebo treated group the respective changes were 3 ± 9 ($p = 0.40$) and 13 ± 17 ($p = 0.06$). The difference between treatment arms did not reach statistical significance.

3.3. Secondary outcome parameters

In the placebo treated group, no improvements in secondary parameters were observed, except for SF-36 social functioning, which improved in both treatment arms (Table 3).

In the dexamethasone treated group, significant improvements in

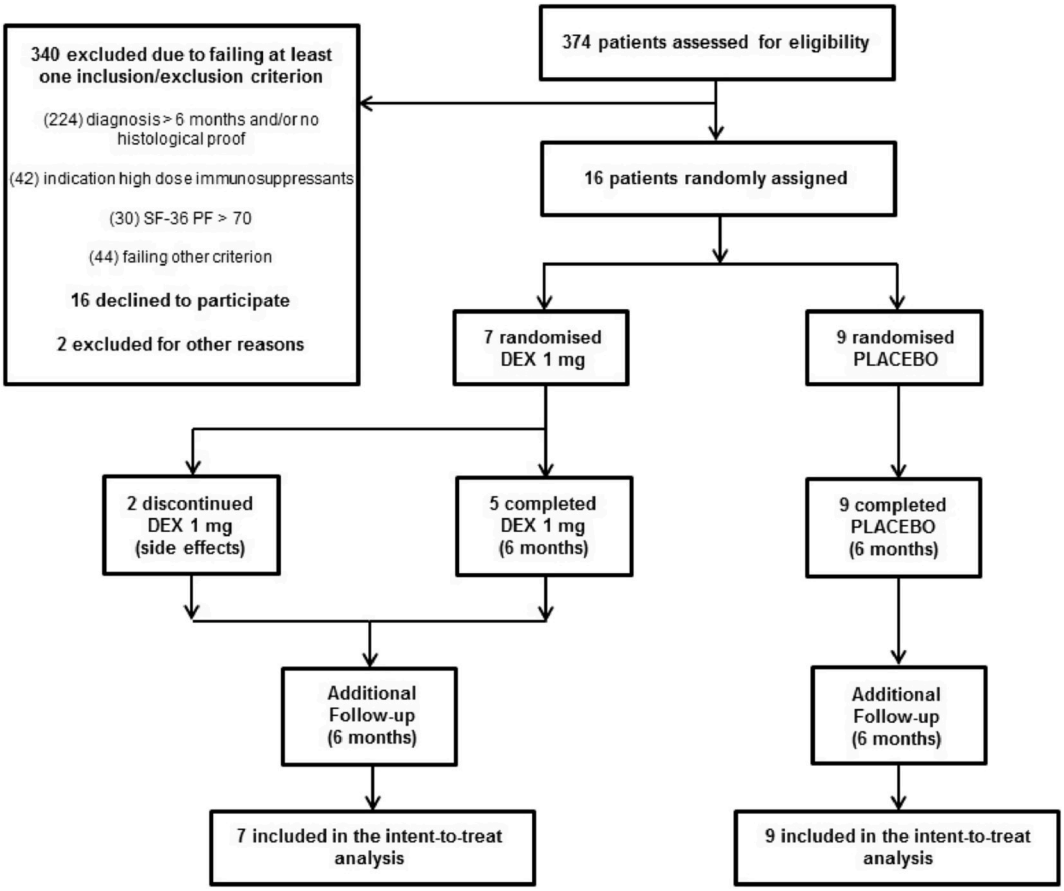

Fig. 1. CONSORT flowchart. DEX: dexamethasone. In the dexamethasone treated group 5 from 7 patients completed the intervention, 2 discontinued due to side effects. In the placebo treated group, all 9 patients completed the intervention. All patients completed the additional follow-up of 6 months (total follow-up 12 months).

Table 1
Baseline patient characteristics.

	Placebo[#]	Dexamethasone[¶]	p
Age years	42.0 ± 9.7	40.6 ± 7.6	0.76
Male	6 [66.7]	3 [42.9]	0.34
BMI kg.m^{-2}	25.5 ± 4.5	26.2 ± 2.2	0.68
sIL-2R pg/ml*	1162 ± 574	1258 ± 724	0.77
sACE U/l	55 ± 38	51 ± 24	0.78
SF-36 PF	47 ± 18	60 ± 13	0.12
SF-36 RP	9 ± 13[+]	14 ± 38	0.73
SF-36 BP	50 ± 22[+]	48 ± 23	0.84
SF-36 GH	33 ± 15[+]	34 ± 20	0.90
SF-36 VT	31 ± 21[+]	22 ± 16	0.37
SF-36 SF	31 ± 31[+]	39 ± 37	0.65
SF-36 RE	50 ± 53[+]	71 ± 49	0.44
SF-36 MH	63 ± 13[+]	63 ± 28	0.99
CIS-20	96 ± 18	106 ± 32	0.42
EQ-5D VAS	61 ± 16[++]	49 ± 19	0.20
EQ-5D Index	0.67 ± 0.27	0.63 ± 0.35	0.78
4DSQ Distress	14 ± 9	14 ± 12[¶¶]	0.99
4DSQ Depression	0.56 ± 0.88	3.2 ± 5.2[¶¶]	0.27
4DSQ Anxiety	2.2 ± 2.2	1.8 ± 2.6[¶¶]	0.76
4DSQ Somatisation	14 ± 8	11 ± 6	0.43
PSQI	10 ± 5	7 ± 3	0.17

Data are presented as mean ± sd or n [%]. All analyses performed using an independent samples *t*-test, except for the comparison of gender which was tested using the Pearson chi-square test. BMI: body mass index; sIL-2R: soluble interleukin-2 receptor; ACE: angiotensin converting enzyme; SF-36: Medical Outcomes Short Form 36; PF: physical functioning; RP: role limitation caused by physical impairment; BP: bodily pain; GH: general health; VT: vitality; SF: social function; RE: role limitation caused by emotional impairment; MH: mental health; CIS: Checklist Individual Strength; VAS: visual afferent scale; 4DSQ: four-dimensional symptom questionnaire; PSQI: Pittsburgh sleep quality index; #: n = 9; ¶: n = 7; *: research essay yielding results approximately 5 times lower than routine clinical assay; +: n = 8 due to missing baseline questionnaire patient 4; ++: n = 8 due to missing baseline questionnaire patient 15; ¶¶: n = 6 due to missing baseline questionnaire patient 10.

several parameters were observed (Table 3). There was a significant reduction in the SF-36 bodily pain score at 3 months with a change of 16 ± 8 ($p < 0.001$) which was significant compared to placebo ($p = 0.03$). The SF-36 vitality domain also showed significant improvements at 3, 6 and 12 months, with changes in score of 18 ± 17 ($p = 0.03$); 23 ± 21 ($p = 0.03$) and 21 ± 15 ($p = 0.01$) respectively. Furthermore, significant improvements on the CIS-20 fatigue score were observed at 3, 6, 9 and 12 months: -18 ± 18 ($p = 0.03$); −21 ± 22 ($p = 0.05$); −27 ± 27 ($p = 0.04$) and −17 ± 15 ($p = 0.03$) respectively. The delta change compared to placebo reached significance at 3 months ($p = 0.01$). EQ-5D self-reported health was improved at all time points, reaching significance at 9 months only (increase of 8 ± 8; $p = 0.03$). Although reductions were observed in 4DSQ distress scores as well, none of these differences reached statistical significance.

Analysis of the serum inflammatory, cytokine and chemokine panel yielded significant effects from dexamethasone versus placebo (Table 2). Dexamethasone, but not placebo, resulted in significant reductions of sACE levels with dexamethasone normalising the sACE values from 51 ± 24 U/l to 22 ± 6.0 (3 months versus baseline; $p = 0.01$) and 23 ± 6.6 (6 months versus baseline; $p = 0.03$) with delta change versus placebo being significant at both time points ($p = 0.00$ and $p = 0.02$ respectively). Similarly, dexamethasone reduced sIL-2R values from 1258 ± 724 to 848 ± 655 (3 months versus baseline; $p < 0.001$) and 700 ± 309 (6 months versus baseline; $p = 0.02$). The delta change sIL-2R for dexamethasone versus placebo reached significance at 3 months ($p = 0.02$).

Furthermore, at 3 months reductions in concentrations were observed for IL-18 ($p = 0.02$); TNFα ($p = 0.01$); TNF RII ($p = 0.03$); MIP-1β ($p = 0.04$); CTACK ($p < 0.001$); ENA-78 ($p = 0.03$) and CD40 ($p = 0.02$) and an increase in eotaxin-1 ($p = 0.01$). At 6 months, differences remained for TNFα ($p = 0.05$); eotaxin-1 ($p = 0.03$) and ENA-78 ($p = 0.03$).

3.4. Disease progression and safety

In the dexamethasone treated group no patients required additional immunosuppressive therapy due to disease progression in the first 6-month period. In the placebo treated group, three patients required immunosuppressive therapy. In two cases sarcoidosis was the indication for initiation of therapy: one patient received oral prednisone due to night sweats, and one patient received inhaled steroids due to cough. In the third case the indication for treatment was gout and oral prednisolone was initiated by the primary care physician.

Weight gain was observed in both treatment arms, although significantly higher in the dexamethasone group: 9.9 ± 6.7 versus 3.3 ± 4.6 kg (dexamethasone and placebo respectively; 6 months; $p = 0.04$) and 7.8 ± 5.9 versus 5.8 ± 9.5 kg (12 months; $p = 0.65$). This corresponds to an increase in BMI of 3.3 ± 2.2 versus 0.93 ± 1.2 (6 months; $p = 0.02$) and 2.6 ± 2.0 versus 1.7 ± 2.6 (12 months; $p = 0.46$). Weight gain was the reason for discontinuing dexamethasone in both instances of treatment cessation, after having used the study drug for approximately 5–5.5 months. Weight gain was already significant after 3 months (increase of 4.7 ± 3.6; $p = 0.01$) but increased with longer exposure and seemed partially reversible after discontinuing dexamethasone.

4. Discussion

To the best of our knowledge, this is the first randomised, placebo-controlled trial investigating the effects of oral corticosteroids on HRQL, fatigue, psychological symptoms and inflammation markers in serum.

The positive effects on the CIS fatigue scores in dexamethasone treated patients were observed at 3 months and were maintained up until 12 months, and confirmed by the SF-36 vitality scores, another well-known fatigue outcome parameter. Although, for the CIS no minimal important difference (MID) is established in literature, the scores of dexamethasone treated patients improved with 25% towards the cut-off value of 76 that puts the individual at risk for subsequent sick leave or work disability [20]. Furthermore, the improvement in SF-36 vitality exceeded the MID which ranges from 7.3 to 11.3 [21]. This indicates that the improvements observed in dexamethasone treated patients were clinically meaningful. Our findings are relevant considering that fatigue is reported in up to 50–70% of sarcoidosis patients and there is evidence that it is one of the most important, negative predictors of quality of life in sarcoidosis [9,22]. In a recent, international survey, sarcoidosis patients ranked quality of life as the most important treatment outcome for sarcoidosis therapies [23].

Although the aetiology of sarcoidosis associated fatigue is poorly understood, it may have a link with the inflammatory state and cytokine release [8,9]. Our results are supportive to such an immunological basis considering the finding of a colinear improvement of fatigue and relevant inflammatory markers. In this study we selected biomarkers that reflect the activation status of the cell types involved in the sarcoid process, such as the CD4 T helper cells, monocyte/macrophages and alveolar macrophages. Dexamethasone treatment did have direct effects on the well-known inflammation markers ACE, sIL-2R, TNFα and related factors TNF-RII, MIP-1β and ENA-78, demonstrating its direct effects on the sarcoid inflammatory process [1,2]. Immunosuppressive and immunomodulatory therapies are known to reduce ACE and sIL-2R levels and dexamethasone induced suppression of the spontaneous release of TNF-α, TNF-RII, and MIP-1β from cultured alveolar macrophages has been reported [24–26]. Lowering of IL-18 and CD40 concentrations also indicate macrophage activity is reduced by dexamethasone treatment. The increase in eotaxin-1 is interesting. This chemokine can be produced by various cell types in the lung, thereby attracting eosinophils and/or CD4 T helper 2 cells expressing the cognate receptor [27]. An increased concentration may result in a shift

Table 2
Serum cortisol, cytokine and chemokine panel: baseline and treatment effects.

	Placebo#	Dexamethasone*		Delta change dexamethasone versus placebo		
Time	Baseline			3	6	12
Cortisol	252 ± 122	270 ± 198	p = 0.82	–	−330 [-482, −179] **p < 0.001**$^{\#\#}$	−160 [-293, −27] **p = 0.02**$^{\#\#}$
sIL-2R** (pg/ml)	1162 ± 574	1258 ± 724	p = 0.77	−376 [-668, −84] **p = 0.02**$^{\#\#}$	−261 [-711, 188] p = 0.23	200 [-265, 665] p = 0.37
sACE (U/l)	55 ± 38	51 ± 24	p = 0.78	−27 [-43, −11] **p < 0.001**$^{\#\#}$	−25 [-45, −4] **p = 0.02**$^{\#\#}$	14 [-17, 46] p = 0.35
IL-1α (pg/ml)	6 ± 1	6 ± 1	p = 0.79	−1 [-3, 1] p = 0.25	2 [-1, 4] p = 0.17	−1 [-3, 1] p = 0.41
IL-1 RA (pg/ml)	772 ± 249	1070 ± 513	p = 0.15	−257 [-1015, 500] p = 0.48	−165 [-808, 477] p = 0.59	−248 [-854, 357] p = 0.39
IL-6 (pg/ml)	1 ± 1	1 ± 0	p = 0.30	0 [-1, 2] p = 0.60	0 [0, 1] p = 0.34	0 [-2, 1] p = 0.78
IL-8 (pg/ml)	8 ± 9	11 ± 6	p = 0.43	−3 [-11, 5] p = 0.42	−2 [-8, 3] p = 0.37	−2 [-7, 3] p = 0.47
IL-18 (pg/ml)	360 ± 164	427 ± 272	p = 0.55	−58 [-104, −11] **p = 0.02**$^{\#\#}$	−34 [-166, 98] p = 0.59	−27 [-167, 113] p = 0.69
TNFα (pg/ml)	8 ± 3	11 ± 3	p = 0.11	−5 [-8, −2] **p = 0.01**$^{\#\#}$	−3 [-5, 0] **p = 0.05**	−2 [-6, 2] p = 0.27
TNF RII (pg/ml)	3068 ± 1144	4290 ± 1789	p = 0.12	−1563 [-2972, −154] **p = 0.03**$^{\#\#}$	−843 [-2070, 383] p = 0.16	−16 [-1155, 1123] p = 0.98
IP-10 (pg/ml)	76 ± 52	49 ± 24	p = 0.20	−8 [-58, 43] p = 0.74	17 [-23, 56] p = 0.39	32 [-12, 75] p = 0.14
MCP-1 (pg/ml)	281 ± 126	304 ± 98	p = 0.70	26 [-131, 184] p = 0.72	86 [-123, 294] p = 0.39	3 [-166, 171] p = 0.98
MIP-1α (pg/ml)	181 ± 32	186 ± 14	p = 0.64	−30 [-65, 5] p = 0.09	−7 [-42, 28] p = 0.68	−5 [-50, 40] p = 0.82
MIP-1β (pg/ml)	337 ± 97	307 ± 56	p = 0.48	−50 [-96, −4] **p = 0.04**	−22 [-69, 25] p = 0.33	0 [-79, 79] p = 1.0
RANTES (pg/ml)	25104 ± 16922	39833 ± 31359	p = 0.25	893 [-21608, 23394] p = 0.93	−6598 [-34038, 20842] p = 0.61	−12874 [-39173, 13425] p = 0.31
Eotaxin-1 (pg/ml)	101 ± 64	86 ± 36	p = 0.60	48 [16, 78] **p = 0.01**$^{\#\#}$	50 [6, 93] **p = 0.03**$^{\#\#}$	2 [-57, 61] p = 0.93
CTACK (pg/ml)	470 ± 195	479 ± 118	p = 0.91	−186 [-284, −89] **p < 0.001**$^{\#\#}$	−43 [-168, 81] p = 0.47	0 [-141, 141] p = 1.0
ENA-78 (pg/ml)	862 ± 930	1471 ± 1299	p = 0.29	−540 [-1021, −58] **p = 0.03**	−596 [-1129, −64] **p = 0.03**	−593 [-1142, −45] **p = 0.04**
CD40 (pg/ml)	415 ± 204	470 ± 95	p = 0.52	−103 [-185, −22] **p = 0.02**$^{\#\#}$	−44 [-120, 31] p = 0.23	49 [-101, 199] p = 0.50
CD40 ligand (pg/ml)	4467 ± 3352	4470 ± 3228	p = 0.90	548 [-3999, 5094] p = 0.80	2460 [-2320, 7239] p = 0.29	−1708 [-6074, 2659] p = 0.42

Data are presented as mean ± sd (baseline values) or expressed as mean difference [95% confidence interval of the difference]. Baseline values were compared using an independent samples *t*-test. The delta change between all three time points versus baseline were compared using an independent samples *t*-test. Statistically significant results ($p < 0.05$) are set in bold. IL: interleukin; IL-1 RA: interleukin 1 receptor antagonist; sIL-2R: soluble interleukin 2 receptor; TNF: tumor necrosis factor; IFN: interferon; IP-10: interferon γ induced protein; MCP-1: monocyte chemoattractant protein (also CCL2); MIP-1: macrophage inflammatory protein (also CCL3); MIP-1β (also CCL4); RANTES (also CCL5); eotaxin-1 (also CCL11); CTACK (also CCL27); ENA-78 (also CXCL5); MIG (also CXCL9); #: n = 9; *: n = 7; **: research essay yielding results approximately 5 times lower than routine clinical assay; ##: statistically significance ($p < 0.05$) on non-parametric test. Results for IL-1β, IL-2, IL-4, IL-5, IL-10, IL-12 p70, IFN-γ and MIG < lower limit of quantitation. Data for time point 9 months not shown.

Table 3
Primary and secondary outcome parameters: patient reported outcome measures.

	Change placebo[#]			Change dexamethasone[¶]			Delta change		
Time (months)	3	6	12	3	6	12	3	6	12
SF-36 PF	3 ± 9 p = 0.40	7 ± 13 p = 0.13	13 ± 17 p = 0.06	8 ± 13 p = 0.17	−6±24 p = 0.55	4 ± 26 p = 0.73	5 [-7, 17] p = 0.38	−13 [-33, 7] p = 0.18	−9 [-35, 16] p = 0.44
SF-36 PF[§]	3 ± 9 p = 0.40	7 ± 13 p = 0.13	13 ± 17 p = 0.06	8 ± 3 **p = 0.01**	−1±26 p = 0.93	24 ± 9 **p = 0.01**	5 [-6, 16] p = 0.36	−8 [-31, 15] p = 0.44	11 [-9, 31] p = 0.26
SF-36 RP	0 ± 19[+] p = 1.0	19 ± 40[+] p = 0.22	16 ± 38[+] p = 0.28	4 ± 9 p = 0.36	36 ± 45 p = 0.08	7 ± 19 p = 0.36	4 [-14, 21] p = 0.66	17 [-30, 64] p = 0.45	−8 [-43, 26] p = 0.59
SF-36 BP	−6±21[+] p = 0.44	9 ± 20[+] p = 0.26	2 ± 20[+] p = 0.82	16 ± 8 **p < 0.001**	12 ± 21 p = 0.18	−1±26 p = 0.95	22 [3, 40] **p = 0.03**[##]	4 [-19, 26] p = 0.75	−2 [-28, 23] p = 0.85
SF-36 GH	−6±8[+] p = 0.10	5 ± 10[+] p = 0.20	4 ± 16[+] p = 0.46	6 ± 12 p = 0.22	2 ± 16 p = 0.70	5 ± 17 p = 0.50	12 [0, 24] **p = 0.05**	−2 [-17, 12] p = 0.72	0 [-18, 19] p = 0.98
SF-36 VT	−2±19[+] p = 0.79	9 ± 19[+] p = 0.23	2 ± 25[+] p = 0.84	18 ± 17 **p = 0.03**	23 ± 21 **p = 0.03**	21 ± 15 **p = 0.01**	20 [0, 40] p = 0.05	14 [-8, 37] p = 0.20	19 [-4, 42] p = 0.10
SF-36 SF	9 ± 28[+] p = 0.38	25 ± 28[+] **p = 0.04**	16 ± 36[+] p = 0.27	16 ± 14 **p = 0.02**	21 ± 31 p = 0.12	14 ± 26 p = 0.20	7 [-19, 32] p = 0.58	−4 [-36, 29] p = 0.82	−1 [-37, 35] p = 0.94
SF-36 RE	21 ± 56[+] p = 0.33	33 ± 47[+] p = 0.09	29 ± 45[+] p = 0.11	29 ± 49 p = 0.17	24 ± 42 p = 0.18	14 ± 54 p = 0.51	8 [-51, 66] p = 0.78	−10 [-60, 40] p = 0.69	−15 [-70, 40] p = 0.57
SF-36 MH	−4±16[+] p = 0.54	3 ± 16[+] p = 0.62	4 ± 19[+] p = 0.63	9 ± 11 p = 0.08	9 ± 17 p = 0.20	14 ± 21 p = 0.12	13 [-3, 28] p = 0.10	6 [-12, 24] p = 0.48	11 [-11, 33] p = 0.32
CIS-20	9 ± 17 p = 0.16	−5±19 p = 0.48	−1±19 p = 0.90	−18 ± 18 **p = 0.03**	−21 ± 22 **p = 0.05**	−17 ± 15 p = **0.03**	−27 [-46, −8] **p = 0.01**[##]	−16 [-38, 6] p = 0.13	−16 [-35, 3] p = 0.09
EQ-5D VAS	−4±17[++] p = 0.55	4 ± 20[++] p = 0.60	−2±27[++] p = 0.87	10 ± 14 p = 0.11	10 ± 20 p = 0.22	9 ± 12 p = 0.12	13 [-4, 31] p = 0.12	7 [-16, 29] p = 0.53	10 [-14, 34] p = 0.37
EQ-5D Index	0 ± 0.2 p = 0.78	0 ± 0.3 p = 0.71	0 ± 0.3 p = 0.98	0.1 ± 0.2 p = 0.37	0 ± 0.3 p = 0.68	0.1 ± 0.3 p = 0.35	0.1 [-0.1, 0.3] p = 0.44	0 [-0.3, 0.3] p = 0.95	0.1 [-0.2, 0.4] p = 0.44
4DSQ Distress	1 ± 4 p = 0.45	−2±4 p = 0.14	−2±3 p = 0.12	−5±10[¶¶] p = 0.29	−6±10[¶¶] p = 0.21	−7±13[¶¶] p = 0.28	−6 [-13, 2] p = 0.13	−4 [-14, 7] p = 0.42	−5 [-18, 9] p = 0.44
4DSQ Depression	0.1 ± 1 p = 0.76	0.1 ± 1 p = 0.80	0.1 ± 2 p = 0.84	−2±5[¶¶] p = 0.29	−2±5[¶¶] p = 0.36	−2±5[¶¶] p = 0.34	−2 [-7, 3] p = 0.27	−2 [-7, 3] p = 0.35	−2 [-8, 3] p = 0.33
4DSQ Anxiety	−1±1 p = 0.15	0 ± 2 p = 1.0	0 ± 1 p = 0.56	−1±1[¶¶] p = 0.10	−1±2[¶¶] p = 0.06	−1±1[¶¶] p = 0.14	0 [-1, 2] p = 0.87	−1 [-3, 1] p = 0.23	−1 [-2, 1] p = 0.32
4DSQ Somatisation	3 ± 5 p = 0.12	−1±5 p = 0.37	0.1 ± 5 p = 0.95	0 ± 2 p = 1.0	1 ± 3 p = 0.45	−2±5 p = 0.44	−3 [-7, 1] p = 0.16	2 [-2, 7] p = 0.26	−2 [-7, 4] p = 0.53
PSQI	0 ± 2 p = 0.88	−2±3 p = 0.13	−2±4 p = 0.11	0 ± 3 p = 0.71	0 ± 2 p = 0.74	0 ± 4 p = 0.79	0 [-2, 3] p = 0.67	1 [-1, 4] p = 0.32	2 [-2, 6] p = 0.38

The changes in primary and secondary parameters for placebo and dexamethasone are reported as mean change, standard deviation and 2-tailed significance for all time points versus baseline. The delta change for all three time points versus baseline are reported as mean difference (dexamethasone versus placebo), 95% confidence interval of the difference and 2-tailed significance. Within each treatment arm paired samples t-testing was performed, comparing the results at time points 3, 6 and 12 months with baseline. The delta change between all three time points versus baseline were compared using an independent samples *t*-test. Statistically significant results ($p < 0.05$) are set in bold. SF-36: Medical Outcomes Short Form 36; PF: physical functioning; RP: role limitation caused by physical impairment; BP: bodily pain; GH: general health; VT: vitality; SF: social function; RE: role limitation caused by emotional impairment; MH: mental health; CIS: Checklist Individual Strength; VAS: visual afferent scale; 4DSQ: four-dimensional symptom questionnaire; PSQI: Pittsburgh sleep quality index; #: n = 9; ¶: n = 7; §: per protocol analysis in which three patients from the dexamethasone group were excluded: patient 10 discontinued the intervention after 5.5 months and suffered from a dislocated kneecap, patient 11 suffered from an inguinal hernia and patient 16 discontinued the intervention after 5 months; +: n = 8 due to missing baseline questionnaire patient 4; ++: n = 8 due to missing baseline questionnaire patient 15; ¶¶: n = 6 due to missing baseline questionnaire patient 10; ##: statistically significance ($p < 0.05$) on non-parametric test. Data for time point 9 months not shown.

from CD4 T helper 1/17 towards a more T helper 2 profile in sarcoidosis [28,29]. We were not able to detect differences in biomarkers of lymphocyte activity, such as IL-2, IL-4 or IFN-γ, as serum concentrations in this cohort were below detection limit.

Until now, RCTs investigating oral corticosteroids in sarcoidosis and reporting HRQL parameters have been lacking. Other studies on the effects of oral corticosteroids on HRQL and fatigue, often case-control studies, have yielded contradictory results [6,30–34]. Our results confirm those from two recent prospective interventional studies. A study in which patients were treated with 6-month oral prednisolone in an initial dose of 0.75 mg/kg/day, as well as a study in which repository corticotropin was investigated, observed statistically significant and clinically meaningful improvements in HRQL and fatigue [35,36]. In a recent systematic review we have evaluated the effects of pharmacological agents including immunosuppressive and/or immunomodulatory agents on HRQL and fatigue in sarcoidosis patients with an indication for systemic therapy. The results indicated that immunosuppressive and/or immunomodulatory agents might improve HRQL and fatigue as long as there is ongoing activity of disease (based on clinical symptoms and/or disease activity markers) and provided patients are untreated or not yet fully stabilised or therapy refractory. The results from the DEXSAR trial seem to be in accordance with the conclusions in the systematic review [37].

For this trial we selected dexamethasone because of the absence of significant mineralocorticoid effects and the longer plasma half-life over prednisone. The dose of 1 mg equals 6.5 mg prednisone. Despite this low dose, we observed significant weight gain that increased with longer exposure and patients should be monitored accordingly. Not all treatment effects observed at 3 months were maintained up until 6 months, which can potentially be explained by the treatment discontinuation by 2 out of 7 dexamethasone treated patients due to weight gain. The results at 12 months suggest waning effects after treatment cessation, although the significant improvements on vitality and fatigue in the dexamethasone treated group were maintained at 12 months. Considering our findings, treatment for a shorter duration, e.g. 3 months, might result in a more balanced benefit to safety ratio.

The main limitation of this study is the small sample size and consequently the statistical power to detect differences in the outcome parameters was limited. From the a priori sample size estimation totalling 70 patients, only 16 could be included. The main reason for that was that approximately 60% of patients in our screened population was diagnosed >6 months prior to screening or was lacking histological confirmation. Of the remaining population 30% had an indication for immunosuppressive therapy and 20% had a baseline SF-36 PF score >70 (indicating that their HRQL was not reduced). The consequence of this large non-exclusion is that the external validity of the present study is limited to the strict population that could be included. For the design of future studies, we would advise against limiting the inclusion based on the time since diagnosis. Considering the results of the current trial, and the results of our systematic review, the presence of ongoing activity of disease seems to be crucial for benefiting from immunosuppressive therapy, not the duration of disease [37].

In conclusion, our results indicate that a low dose of oral dexamethasone can improve HRQL and fatigue in patients with newly diagnosed troublesome inflammatory sarcoidosis. Further research is warranted to evaluate the role of immunosuppressive therapy in treatment of sarcoidosis associated fatigue and reduced HRQL.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Roeland Vis: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing - original draft. **Ewoudt M.W. van de Garde:** Conceptualization, Funding acquisition, Methodology, Writing - review & editing. **Bob Meek:** Formal analysis, Writing - review & editing. **Ingrid H.E. Korenromp:** Conceptualization, Funding acquisition, Methodology, Resources, Project administration, Writing - review & editing. **Jan C. Grutters:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2020.105936.

References

[1] 1999 joint statement of the American thoracic society (ATS), the European respiratory society (ERS) and the World association of sarcoidosis and other granulomatous disorders (WASOG) adopted by the ATS board of directors and by the ERS executive committee, statement on sarcoidosis, Am. J. Respir. Crit. Care Med. 160 (1999) 736–755, https://doi.org/10.1164/ajrccm.160.2.ats4-99.

[2] M.J. Loza, C. Brodmerkel, R.M. Du Bois, M.A. Judson, U. Costabel, M. Drent, M. Kavuru, S. Flavin, K.H. Lo, E.S. Barnathan, R.P. Baughman, Inflammatory profile and response to anti-tumor necrosis factor therapy in patients with chronic pulmonary sarcoidosis, Clin. Vaccine Immunol. 18 (2011) 931–939, https://doi.org/10.1128/CVI.00337-10.

[3] J.C. Grutters, J.M.M. van den Bosch, Corticosteroid treatment in sarcoidosis, Eur. Respir. J. 28 (2006) 627–636, https://doi.org/10.1183/09031936.06.00105805.

[4] R.M. Wirnsberger, J. de Vries, E.F. Wouters, M. Drent, Clinical presentation of sarcoidosis in The Netherlands an epidemiological study, Neth. J. Med. 53 (1998) 53–60, https://doi.org/10.1016/S0300-2977(98)00058-8.

[5] R.M. Wirnsberger, J. de Vries, M.H.M. Breteler, G.L. van Heck, E.F.M. Wouters, M. Drent, Evaluation of quality of life in sarcoidosis patients, Respir. Med. 92 (1998) 750–756, https://doi.org/10.1016/S0954-6111(98)90007-5.

[6] C.E. Cox, J.F. Donohue, C.D. Brown, Y.P. Kataria, M. a Judson, Health-related quality of life of persons with sarcoidosis, Chest 125 (2004) 997–1004, https://doi.org/10.1378/chest.125.3.997.

[7] I.H.E. Korenromp, C.J. Heijnen, O.J.M. Vogels, J.M.M. van den Bosch, J. C. Grutters, Characterization of chronic fatigue in patients with sarcoidosis in clinical remission, Chest 140 (2011) 441–447, https://doi.org/10.1378/chest.10-2629.

[8] A. Baydur, B. Alavy, A. Nawathe, S. Liu, S. Louie, O.P. Sharma, Fatigue and plasma cytokine concentrations at rest and during exercise in patients with sarcoidosis, Clin. Res. J. 5 (2011) 156–164, https://doi.org/10.1111/j.1752-699X.2010.00214.x.

[9] M. Drent, E.E. Lower, J. De Vries, Sarcoidosis-associated fatigue, Eur. Respir. J. 40 (2012) 255–263, https://doi.org/10.1183/09031936.00002512.

[10] P. Spagnolo, G. Rossi, R. Trisolini, N. Sverzellati, R.P. Baughman, A.U. Wells, Pulmonary sarcoidosis, Lancet. Respir. Med. 6 (2018) 389–402, https://doi.org/10.1016/S2213-2600(18)30064-X.

[11] R.P. Baughman, H. Nunes, N.J. Sweiss, E.E. Lower, Established and experimental medical therapy of pulmonary sarcoidosis, Eur. Respir. J. 41 (2013) 1424–1438, https://doi.org/10.1183/09031936.00060612.
[12] D.G. James, L.S. Carstairs, J. Trowell, O.P. Sharma, Treatment of sarcoidosis. Report of a controlled therapeutic trial, Lancet 2 (1967) 526–528.
[13] H.L. Israel, D.W. Fouts, R.A. Beggs, A controlled trial of prednisone treatment of sarcoidosis, Am. Rev. Respir. Dis. 107 (1973) 609–614, https://doi.org/10.1164/arrd.1973.107.4.609.
[14] M.A. Judson, Quality of life assessment in sarcoidosis, Clin. Chest Med. 36 (2015) 739–750, https://doi.org/10.1016/j.ccm.2015.08.014.
[15] D. Moher, S. Hopewell, K.F. Schulz, V. Montori, P.C. Gøtzsche, P.J. Devereaux, D. Elbourne, M. Egger, D.G. Altman, CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials, BMJ 340 (2010) c869, https://doi.org/10.1136/bmj.c869.
[16] J.A. Chang, J.R. Curtis, D.L. Patrick, G. Raghu, Assessment of health-related quality of life in patients with interstitial lung disease, Chest 116 (1999) 1175–1182, https://doi.org/10.1378/chest.116.5.1175.
[17] M.A. Spruit, M.J. Thomeer, R. Gosselink, T. Troosters, A. Kasran, A.J.T. Debrock, M.G. Demedts, M. Decramer, Skeletal muscle weakness in patients with sarcoidosis and its relationship with exercise intolerance and reduced health status, Thorax 60 (2005) 32–38, https://doi.org/10.1136/thx.2004.022244.
[18] B. Terluin, H.W.J. van Marwijk, H.J. Adèr, H.C.W. de Vet, B.W.J.H. Penninx, M.L. M. Hermens, C.A. van Boeijen, A.J.L.M. van Balkom, J.J.L. van der Klink, W.A. B. Stalman, The Four-Dimensional Symptom Questionnaire (4DSQ): a validation study of a multidimensional self-report questionnaire to assess distress, depression, anxiety and somatization, BMC Psychiatr. 6 (2006) 34, https://doi.org/10.1186/1471-244X-6-34.
[19] D.J. Buysse, C.F. Reynolds, T.H. Monk, S.R. Berman, D.J. Kupfer, The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research, Psychiatr. Res. 28 (1989) 193–213.
[20] U. Bultmann, M. Vries, A. Beurskens, G. Bleijenberg, J. Vercoulen, I. Kant, Measurement of prolonged fatigue at work in the maastricht cohort study: determination of a cutoff point for the checklist individual strength, J. Occup. Health Psychol. 5 (2000) 411–416, https://doi.org/10.1037//1076-B998.5.4.411.
[21] Å. Nordin, C. Taft, Å. Lundgren-Nilsson, A. Dencker, Minimal important differences for fatigue patient reported outcome measures - a systematic review, BMC Med. Res. Methodol. 16 (2016), https://doi.org/10.1186/s12874-016-0167-6.
[22] M. Drent, R. Marcellis, A. Lenssen, J. De Vries, Association between physical functions and quality of life in sarcoidosis, Sarcoidosis, Vasc. Diffus. Lung Dis. Off. J. WASOG. 31 (2014) 117–128.
[23] J. Boyd, R.P. Baughman, D. Valeyere, A.R. Álvarez Rodríguez, L. Charvoz, H.-P. Faber, C. Knoet, F. Martone, D.I. Novel, B. Quadder, J. Richardson, G. Spitzer, G. Ziosi, J. Hochreiter, Sarcoidosis treatment and outcomes: what is most important to patients?, in: Sarcoidosis and Other Granulomatous ILD/DPLD European Respiratory Society, 2018, p. PA5219, https://doi.org/10.1183/13993003.congress-2018.PA5219.
[24] J. Müller-Quernheim, K. Kienast, M. Held, S. Pfeifer, U. Costabel, Treatment of chronic sarcoidosis with an azathioprine/prednisolone regimen, Eur. Respir. J. 14 (1999) 1117–1122, https://doi.org/10.1183/09031936.99.14511179.
[25] A.D.M. Vorselaars, C.H.M. van Moorsel, P. Zanen, H.J.T. Ruven, A.M.E. Claessen, H. van Velzen-Blad, J.C. Grutters, ACE and sIL-2R correlate with lung function improvement in sarcoidosis during methotrexate therapy, Respir. Med. 109 (2015) 279–285, https://doi.org/10.1016/j.rmed.2014.11.009.
[26] Z. Tong, H. Dai, B. Chen, Z. Abdoh, J. Guzman, U. Costabel, Inhibition of cytokine release from alveolar macrophages in pulmonary sarcoidosis by pentoxifylline: comparison with dexamethasone, Chest 124 (2003) 1526–1532, https://doi.org/10.1378/chest.124.4.1526.
[27] B. Lamkhioued, P.M. Renzi, S. Abi-Younes, E.A. Garcia-Zepada, Z. Allakhverdi, O. Ghaffar, M.D. Rothenberg, A.D. Luster, Q. Hamid, Increased expression of eotaxin in bronchoalveolar lavage and airways of asthmatics contributes to the chemotaxis of eosinophils to the site of inflammation, J. Immunol. 159 (1997) 4593–4601.
[28] J. Ramstein, C.E. Broos, L.J. Simpson, K. Mark Ansel, S.A. Sun, M.E. Ho, P. G. Woodruff, N.R. Bhakta, L. Christian, C.P. Nguyen, B.J. Antalek, B.S. Benn, R. W. Hendriks, B. Van Den Blink, M. Kool, L.L. Koth, IFN-γproducing t-helper 17.1 cells are increased in sarcoidosis and are more prevalent than t-helper type 1 cells, Am. J. Respir. Crit. Care Med. 193 (2016) 1281–1291, https://doi.org/10.1164/rccm.201507-1499OC.
[29] Y. Kaiser, R. Lepzien, S. Kullberg, A. Eklund, A. Smed-Sörensen, J. Grunewald, Expanded lung T-bet+RORγT+ CD4+ T-cells in sarcoidosis patients with a favourable disease phenotype, Eur. Respir. J. 48 (2016) 484–494, https://doi.org/10.1183/13993003.00092-2016.
[30] J. De Vries, M. Drent, Relationship between perceived stress and sarcoidosis in a Dutch patient population, Sarcoidosis, Vasc. Diffus. Lung Dis. Off. J. WASOG. 21 (2004) 57–63.
[31] R.G.J. Marcellis, A.F. Lenssen, M.D.P. Elfferich, J. De Vries, S. Kassim, K. Foerster, M. Drent, Exercise capacity, muscle strength and fatigue in sarcoidosis, Eur. Respir. J. 38 (2011) 628–634, https://doi.org/10.1183/09031936.00117710.
[32] S. De Boer, M.L. Wilsher, Validation of the sarcoidosis health questionnaire in a non-US population, Respirology 17 (2012) 519–524, https://doi.org/10.1111/j.1440-1843.2012.02134.x.
[33] M.A. Judson, H. Chaudhry, A. Louis, K. Lee, R. Yucel, The effect of corticosteroids on quality of life in a sarcoidosis clinic: the results of a propensity analysis, Respir. Med. 109 (2015) 526–531, https://doi.org/10.1016/j.rmed.2015.01.019.
[34] D. Jastrzębski, D. Ziora, M. Lubecki, K. Zieleźnik, M. Maksymiak, J. Hanzel, A. Początek, A. Kolczyńska, L. Nguyen Thi, A. Zebrowska, J. Kozielski, Fatigue in sarcoidosis and exercise tolerance, dyspnea, and quality of life, Adv. Exp. Med. Biol. 833 (2015) 31–36, https://doi.org/10.1007/5584_2014_18.
[35] A.N. Aggarwal, K.K. Sahu, D. Gupta, Fatigue and health-related quality of life in patients with pulmonary sarcoidosis treated by oral Corticosteroids, Sarcoidosis, Vasc. Diffus. Lung Dis. Off. J. WASOG. 33 (2016) 124–129.
[36] R.P. Baughman, N. Sweiss, R. Keijsers, S.S. Birring, R. Shipley, L.A. Saketkoo, E. E. Lower, Repository corticotropin for chronic pulmonary sarcoidosis, Lung 195 (2017) 313–322, https://doi.org/10.1007/s00408-017-9994-4.
[37] R. Vis, E.M. van de Garde, J.C. Grutters, The effects of pharmacological interventions on quality of life and fatigue in sarcoidosis: a systematic review, Eur. Respir. Rev. 29 (2020), https://doi.org/10.1183/16000617.0057-2019.