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Toxicity risk from glucocorticoids in sarcoidosis patients☆

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ABSTRACT

Background: Glucocorticoids (GC) are considered first-line therapy for treating sarcoidosis, but there are few data about the adverse consequences of GC. Although there are several steroid-sparing medications available for treatment, a large proportion of patients are treated with prolonged courses of GC. The toxicities of GC in sarcoidosis populations have not been carefully evaluated.
Methods: We performed a retrospective cohort study of all newly diagnosed sarcoidosis patients who had the entirety of their medical care in a single health system. We analyzed the time to development of a composite toxicity end-point, including diabetes, hypertension, weight gain, hyperlipidemia, low bone density and ocular complications of GC using Cox proportional hazards analysis.
Results: One hundred and five patients were ever treated with GC, whereas 49 were not treated during a median follow-up of 101 months. GC-treated patients developed 1.3 ± 1.1 toxicities during therapy, versus 0.6 ± 1.0 in the non-treated group. After adjustment for age, gender, race and preexisting conditions, the hazard ratio for ever-treated patients was 2.37 (1.34–4.17) for the composite end-point. Age and the presence of preexisting conditions also were associated with reaching the end-point. Similar effects were seen when analyzed for cumulative GC dose and for duration of GC use. For individual end-points, weight gain (HR 2.04) and new hypertension (HR 3.36) were associated with any use of GC.
Conclusions: Our data suggest that GC are associated with clinically important toxicities in sarcoidosis patients, associated with both the cumulative dose and duration of treatment.

1. Introduction

Glucocorticoids (GC) are widely accepted as first-line therapy for pulmonary and extra-pulmonary sarcoidosis [1–3]. The primacy of GC is based on decades of clinical experience using them as well as their effectiveness, low cost, relatively quick onset of action, ease of titration, and clinician familiarity. Despite their widespread use, there are few prospective controlled trials, and no rigorous studies comparing them with other extant anti-sarcoidosis medications. In the few prospective trials of GC, there is little mention of their toxicity profile. Thus, an accurate assessment of the costs and benefits of GC is currently impossible.

Perhaps due to the perception that sarcoidosis usually resolves spontaneously, many patients are not treated with GC-sparing medications until their disease is persistent, and often not at all. In recent trials of chronic pulmonary sarcoidosis [4,5] only 43-49% of patients were using GC-sparing therapy while the mean baseline prednisone dose at enrollment ranged from 12 to 13 mg/day (personal communication with Elliot Barnathan, M.D.). While some patients with chronic, treatment resistant sarcoidosis may have failed GC-sparing medications, it is not uncommon to encounter patients who have been treated for prolonged time-periods with GC monotherapy. A regularly-promulgated notion is that prednisone doses less than 10 mg/day are relatively safe for long-term use. However, data from rheumatology cohorts suggest that there is a continuous relationship between some toxicities and GC dose, whereas for other toxicities the threshold dose is less than 10 mg

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Abbreviations

BMI	body mass index
CI	confidence interval
CNS	central nervous system
DM	diabetes mellitus
EMR	electronic medical record
FVC	forced vital capacity
GC	glucocorticoids
GI	gastrointestinal
HbA1C	hemoglobin A1c
HR	hazard ratio
HTN	hypertension
IQR	interquartile range
LDL	low density lipoprotein
SD	standard deviation
SFN	small fiber neuropathy
WHO	World Health Organization

[6].

While it is widely accepted that GC cause untoward toxicity, the magnitude of harm has not been systematically assessed to date. We aimed to quantify the toxicities of GC in usual clinical practice among patients with sarcoidosis who had the entirety of their medical care, and therefore all relevant health information, in a single health system. We performed a retrospective cohort study of patients from the time of their sarcoidosis diagnosis to estimate the rate of complications associated with GC.

2. Materials and methods

All patients with a first-ever diagnosis of sarcoidosis made at our institution from 2004 until 2010 were eligible for this study; we excluded referrals with pre-existing diagnoses. All patients had a diagnosis of sarcoidosis according to WASOG/ATS/ERS standards [3], all primary and specialist medical care provided within the Cleveland Clinic Health System (implying that all medical data are available within the electronic medical record [EMR]). A minimum of two visits in the sarcoidosis clinic were mandatory as well as absence of concurrent medical conditions that required pre-existing or baseline GC therapy (e.g. connective tissue disease). This study was approved by the Cleveland Clinic Institutional Review Board (13-031).

We abstracted data from the EMR, including biochemical studies, medication doses, and the results of imaging tests. Each clinical note from all health care encounters was manually reviewed to confirm the accuracy of GC regimens compared to the EMR medication list. Any indication from chart review suggesting that a patient received GC from outside our EMR system or the presence of a discrepancy of dosage between encounter notes and the EMR medication list lead to exclusion of the patient. For patients who had prednisone tapering between office visits, we calculated the daily equivalent dose of prednisone assuming that patients adhered to provider instructions. A GC course was defined as a regular uninterrupted regimen regardless of duration and dosage and any prescribed discontinuation was considered completion of the course. All GC other than prednisone were converted into prednisone-equivalent doses [7]. Patients were followed from the date of diagnosis, and the duration to end-points was compared between those treated with or without GC. Organs involved were noted per clinical assessment of the treating physician.

The primary end-point was a composite reached by the development of any single potential toxicity, including diabetes mellitus (DM), hypertension, hyperlipidemia, increase in body mass index (BMI) by 3 points or greater, ophthalmologic complications including cataract or glaucoma, or new osteoporosis/osteopenia. For patients with pre-existing disorders, we measured the time until worsening of the condition.

The end-point components were defined as follows. New diabetes required a HbA1c of 6.5% or greater per ADA guidelines [8]. Worsening of DM was defined as either a rise in HbA1C by one point or any escalation of therapy, i.e. increase in dose of any anti-hyperglycemic medication or addition of another agent. New hypertension was diagnosed when the blood pressure was >140/90 mm Hg [9]. For patients with a prior history of hypertension, a sustained increase in systolic or diastolic blood pressure by 10 mm Hg or an increase in dose or addition of another anti-hypertensive agent was defined as worsening hypertension [9]. Hyperlipidemia was defined as a total cholesterol level of >200 mg/dL or LDL >130 mg/dL based on the National Cholesterol Education Panel's Adult Treatment Program-3 guidelines [10] or addition of an HMG-CoA reductase inhibitor associated with a new chart diagnosis of hyperlipidemia. Worsening was defined as a rise in LDL or total cholesterol levels of any magnitude employing the upper limit of normal as per Cleveland Clinic Laboratory thresholds of $\geq$130 mg/dL for LDL or $\geq$200 mg/dL or for total cholesterol, or an escalation of statin dosing. Osteoporosis was defined as bone mineral density scan revealing a T-score of < -2.5 and osteopenia as a T-score between -1 and -2.5 per WHO guidelines [11]. Worsening osteoporosis was not included as an end-point due to the absence of a standard definition. Change in BMI was defined as a rise of 3 or more points. This was selected over change in WHO obesity class as average BMI was noted to be rather close to meeting criteria for obesity and change in BMI was thought to better reflect changes relevant to patients compared with absolute thresholds of WHO obesity classes [12]. New or progression of glaucoma/cataract on ophthalmologic examination by an ophthalmologist while on GC was defined as new ophthalmologic side effect of GC.

We summarized continuous variables using mean ± standard deviation (SD) or median (interquartile range (IQR)). Categorical variables are presented as n (%). We compared numerical variables using *t*-test or Mann-Whitney-Wilcoxon test, when appropriate. Categorical variables were compared with Chi-square or Fischer exact test. Time to development of GC associated complications was tested using Cox proportional-hazards modeling adjusted for pre-specified variables. The starting point for the analysis was the date of the sarcoidosis diagnosis. Patients were censored at the end of follow up or the development of a single GC toxicity in the combined analysis or the end-point of interest in secondary analysis, e.g. new or worsening DM when testing the impact of GC on only this condition. Results of Cox analyses are expressed as hazard ratios (HR) with the corresponding 95% confidence intervals (CI). A p value of <0.05 was considered as indicative of statistical significance. Statistical analyses were performed using the statistical package SPSS version 17 (Armonk, N.Y., USA).

3. Results

One-hundred fifty-four patients met the enrollment criteria, including 82 (53.2%) females, with a mean age of 47.2 ± 12.1 years. The population consisted of 92 Caucasian (59.7%), 61 African-American (39.6%) and 1 Asian patient (Table 1). The most common sites of involvement were: lungs (144, 93.5%), followed by eyes (27, 17.5%) and skin (11, 7.1%). Multi-organ involvement was documented in 48 (31.2%) of the cohort (Table 2).