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Response to corticosteroids and alternative therapies in sarcoidosis-related hypercalcemia: A guideline-lacking retrospective analysis

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Abstract. *Background and aim:* Sarcoidosis is a systemic inflammatory disease of unknown etiology that can affect multiple organs including a known complication of hypercalcemia. Many therapies, both steroidal and non-steroidal, have been employed. However, the optimal therapy for hypercalcemia in sarcoidosis is unknown, with most data from case reports and small case series. More information is needed to determine which nonsteroidal agents control hypercalcemia in sarcoidosis patients, particularly for populations in whom steroids should be avoided. We sought to answer the question, which pharmacological agents control hypercalcemia in patients diagnosed with sarcoidosis? *Methods:* We performed a retrospective chart review on all adult patients at our hospital with a diagnosis of Sarcoidosis and Hypercalcemia and a recorded calcium level of greater than 10.4 mg/dL. We then determined which agents were able to control their calcium to a level of 10.4 mg/dL or less for at least 6 months and 12 months. *Results:* The most common efficacious treatments were prednisone, methotrexate, hydroxychloroquine, and prednisone + methotrexate. A positive linear relationship was found between ACE and highest calcium levels. No significant relationship between organ involvement or race and highest calcium levels were noted. *Conclusions*: There is currently little data or guidelines to best guide the treatment of hypercalcemia in sarcoidosis. This study represents the first with the primary aim to compare treatment options for hypercalcemia in sarcoidosis across a large cohort. Several non-steroidal options were identified that controlled hypercalcemia as a single agent. In addition, this study further investigated potential biomarkers for abnormal calcium metabolism as well as the relationship between calcium levels and organ involvement/race. Further work is needed to determine the most effective steroid sparing therapy to control hypercalcemia in sarcoidosis.

Key words: sarcoidosis, hypercalcemia, steroid-sparing-therapy, corticosteroids, retrospective studies

Introduction

Sarcoidosis is a systemic inflammatory disease of unknown etiology that can affect multiple organs. Hypercalcemia is a known complication of sarcoidosis, which has been suggested to affect 5-10% of patients with sarcoidosis (1-3), with hypercalciuria described in up to 62% of sarcoidosis patients (4). This is in contrast to hypercalcemia occurring in 0.2-4% of the overall population (5). Untreated hypercalcemia can lead to nephrolithiasis, renal insufficiency, and renal failure (5), with renal failure occurring in 42% of patients with untreated hypercalcemia (7). Treatment of hypercalcemia has been associated with improvement in both hypercalcemia and improved renal function (1). Corticosteroids are commonly used in the treatment of hypercalcemia in sarcoidosis (2,6), but are associated

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with a multitude of adverse effects, particularly with long-term use, including hyperglycemia, weight gain, fluid retention, osteoporosis, psychosis, and others (8,9). Calcium concentrations are tightly regulated to maintain homeostasis using calcium sensing receptors (CaSRs) located on parathyroid cells (10). Based on calcium levels in the blood, CaSRs either stimulates or inhibits parathyroid hormone secretion which in turn will either stimulate or inhibit calcium release in the bone, reabsorption in the kidneys, and absorption in the intestines (10). Additional regulation is accomplished through the active metabolite of vitamin D, 1,25-dihydroxyvitamind D (Calcitriol), which acts to stimulate intestinal absorption and renal reabsorption of calcium (10,11). However, 25 OH vitamin D must be hydroxylated in the kidneys to 1,25-dihydroxyvitamin D to exert this effect, and this is accomplished though stimulation of 1-α hydroxylase (CYP27B1) by parathyroid hormone (PTH) (10-12). Conversely, this hydroxylation is inhibited by fibroblast growth factor 23 (FGF 23) produced by mature osteoblasts and osteocytes in the bone in response to hyperphosphatemia (10). Further regulation is accomplished through the effect of calcitonin which reduces osteoclast activity and therefore calcium and phosphate release from the bone (10). Hypercalcemia in sarcoidosis is thought to occur though overproduction of Calcitriol by overproduction of 1-alpha hydroxylase within granulomas though may occur from other mechanisms as well (1,5). Several non-steroidal therapies have been used in the management of the systemic manifestations of sarcoidosis, including hypercalcemia, such as chloroquine, hydroxychloroquine, and ketoconazole (2). Methotrexate has also been described as a potential treatment option to manage hypercalcemia (13). In addition, Tumor Necrosis Factor Alpha (TNF-α) inhibitors, such as infliximab, have emerged as a steroid-sparing option for treatment of sarcoidosis as well as an option for hypercalcemia due to granulomatous disease (14-17). However, the optimal therapy for hypercalcemia in sarcoidosis is unclear and most data regarding non-steroidal treatments are from case reports and small case series. More information is needed to determine which nonsteroidal agents control hypercalcemia in sarcoidosis patients with hypercalcemia to reduce the progression to renal failure, particularly for populations in whom steroids should be avoided. This study aims to analyze which agents were able to control calcium levels in our population of patients with sarcoidosis as defined by maintaining normal calcium concentrations for at least 6 months.

Methods

We performed a retrospective chart review of all adult patients at our university hospital system with an ICD-10 diagnosis of Sarcoidosis and Hypercalcemia or recorded calcium level of greater than 10.2 mg/dL. The study was approved by our Institutional Review Board (IRB-300010057). Medical Record Numbers (MRNs) were retrieved using our I2B2 system. Data was stored on a HIPAA compliant secure server using ShareFile (Microsoft, 2023). We excluded patients with the following criteria: ICD10 or 11 diagnosis of primary hyperparathyroidism, Secondary Hyperparathyroidism of Renal Origin, Familial Hypocalciuric Hypercalcemia, Other Specified Hyperparathyroidism, Unspecified Hyperparathyroidism, Secondary Hyperparathyroidism Not Elsewhere Classified, Malignant Melanoma, Hypervitaminosis D, International Classification of Disease-10 (ICD-10) diagnosis of End Stage Renal Disease, ICD-11 diagnosis of Chronic Kidney Disease Stage IV or V, or Parathyroid Hormone (PTH) level greater than 88.0 pg/mL. 838 patient MRNs were obtained using these criteria. After MRN retrieval, manual chart review was performed to confirm the diagnosis of sarcoidosis and hypercalcemia, determine organ involvement, biopsy proven status, and laboratory data (inflammatory markers (Angiotensin Converting Enzyme (ACE), Soluble Interleukin 2 Receptor), PTH level, PTH related Peptide, Calcium level, and vitamin D levels). The calcium cutoff was raised to greater than 10.4 mg/dL as it was determined that 10.4 mg/dL was the most commonly used cutoff in our laboratory. After confirmation of a diagnosis of sarcoidosis and hypercalcemia using the updated cutoff, 329 more patients were excluded, and 509 patients remained. Further manual chart review was performed to minimize confounders with 313 more patients excluded and 196 patients remained. Of those 313 patients, 220 were not on immunosuppression, 6 did not have documented calcium levels, 11 patients had an alternative explanation for their hypercalcemia, 62 did not have at least 6 months of follow-up labs, 4 had hypercalcemia that occurred after solid organ transplant, 5 did not have active sarcoidosis as determined by their

treating clinician, 3 had an unclear treatment history, and 2 never had their calcium controlled (as determined by their calcium reaching below 10.5 mg/dL) (Figure 1). We then determined which agents were able to control their calcium to a level of 10.4 mg/dL or less for at least 6 months and 12 months. Efficacious treatments were defined as those able to control calcium levels for at least 6 months.

Linear regression was used to assess the relationship between the calcium level and ACE, soluble IL2R, or 1,25 OH vitamin D. The calcium level, ACE and soluble IL2R levels between different racial groups were compared using Analysis of Variance (ANOVA). In addition, the calcium levels between different normal or sarcoid organs were compared using student t-test or Wilcoxon test where appropriate. The same method was used to compare the calcium level with/without biopsy. Finally, we conducted the exact Cochran-Mantel-Haenszel test to assess the association between recurrence of hypercalcemia and race. Statistical analysis was performed with SAS® 9.4 software (SAS Institute, Cary, NC, USA).

Results

Of those treated with prednisone only, the average daily prednisone dosing was 9.03 mg (2.5-40 mg; N=36). For two patients on prednisone, the exact prednisone dosing could not be determined. Of those treated with Methotrexate only, the average weekly dosing was 14.25 mg weekly (5-25 mg weekly; N=30). Average Cellcept daily dosing in

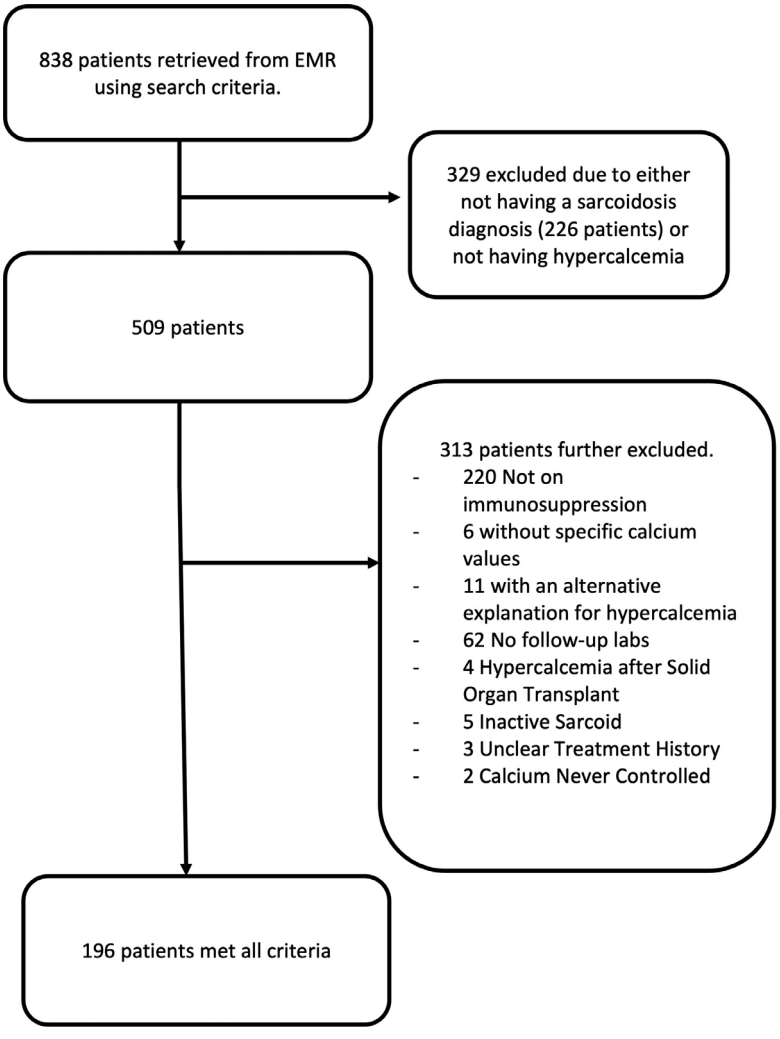

Figure 1. Flowchart. A total of 196 patients were included in the analysis.

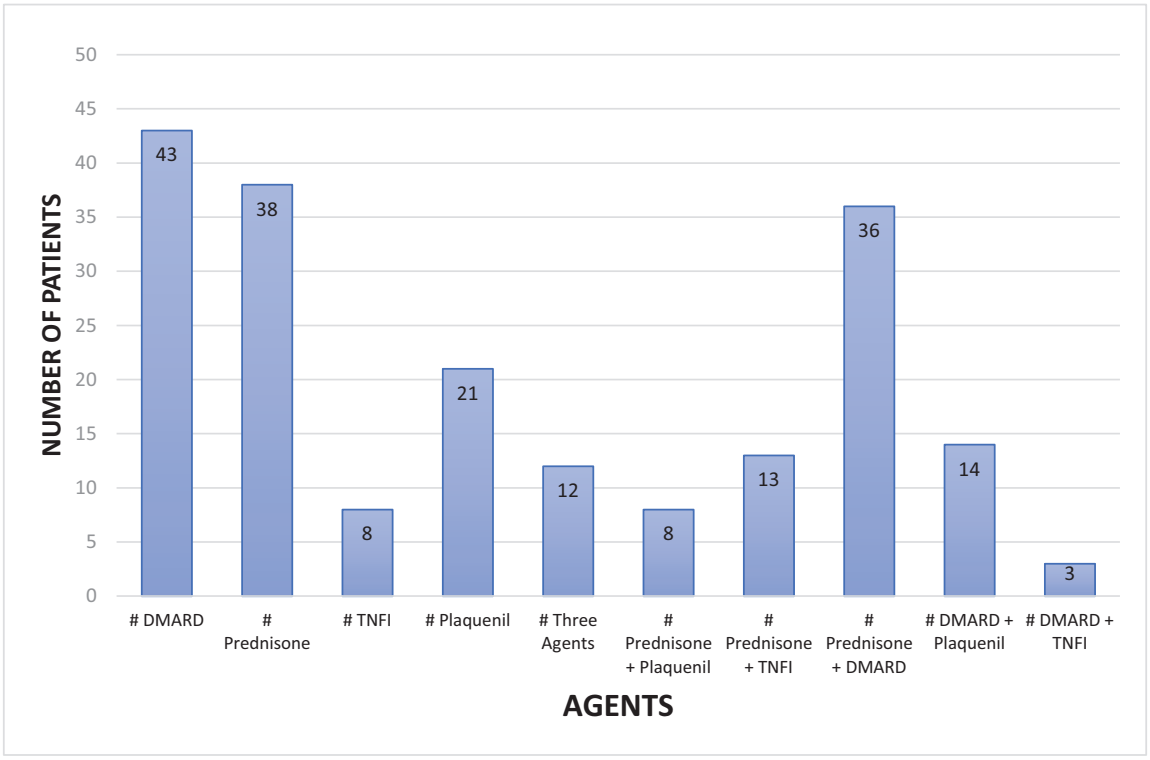

Figure 2. List of agent groupings which were able to control calcium levels to a level of 10.4 mg/dL or less for at least 6 months and the number of patients for each agent. DMARD classification included Methotrexate (30 patients), Cellcept (7 patients), Azathioprine (6 patients). TNFI included Infliximab (7patients) and adalimumab (1 patient). *Abbreviations:* TNFI= Tumor Necrosis Factor Inhibitor. DMARD = Disease Modifying Antirheumatic Drug.

mg was 1714.28 mg (1000-2000mg; N=7). Average Azathioprine dosing was 125 mg daily (100-200 mg; N=6). Average daily hydroxychloroquine dosing was 342.9 mg daily (200-400 mg; N=21). Of the single agents used that controlled hypercalcemia for at least 6 months, the most common were: Prednisone (38 patients), Methotrexate (30 patients), Hydroxychloroquine (21 patients), Cellcept (7 patients), Azathioprine (6 patients), Infliximab (7 patients), Adalimumab (1 patient) (Figure 2).

Of the 145 patients that were biopsy proven, 35 were diagnosed via transbronchial biopsy (TBBx), 27 diagnosed via endobronchial ultrasound (EBUS), 18 via non-endobronchial lymph node biopsy (LNO), 12 via mediastinoscopy (MED), 11 via skin biopsy, 11 via multiple different biopsies, 10 via liver biopsy, 7 via other biopsy location (kidney, pituitary), 6 via video-assisted thoracoscopic (VATS) biopsy, 2 via bone marrow biopsy (BMBx), 2 via brain biopsy, 2 via unknown location (UNK), 1 via endoscopic ultrasound, and 1 via spleen biopsy (Figure 3).

Our mean age was 55.6 (N=174; SD 13.8). 59.69% were female. 73.98% had biopsy proven disease (9.69% were unknown with 16.33% not biopsy proven. 23.35% had recurrence of hypercalcemia as defined by having a follow-up calcium level about 10.4 mg/dL at any point after initially having control for at least 6 months (Table 1). 110/196 (56.1%) were controlled on a single agent (Figure 4). Our patients were 58.33% Black or African American, 36.46% White, and 5.21% Asian.

Organ manifestations in our population included the following: 72.31% pulmonary, 39.49% lymph node, 20.51% cutaneous, 7.69% ocular, 16.92% neuro, 11.28% hepatic, 9.23% cardiac, 3.59% splenic, 12.31% other extrapulmonary disease. In our population, we demonstrated a positive linear relationship between highest calcium level and ACE

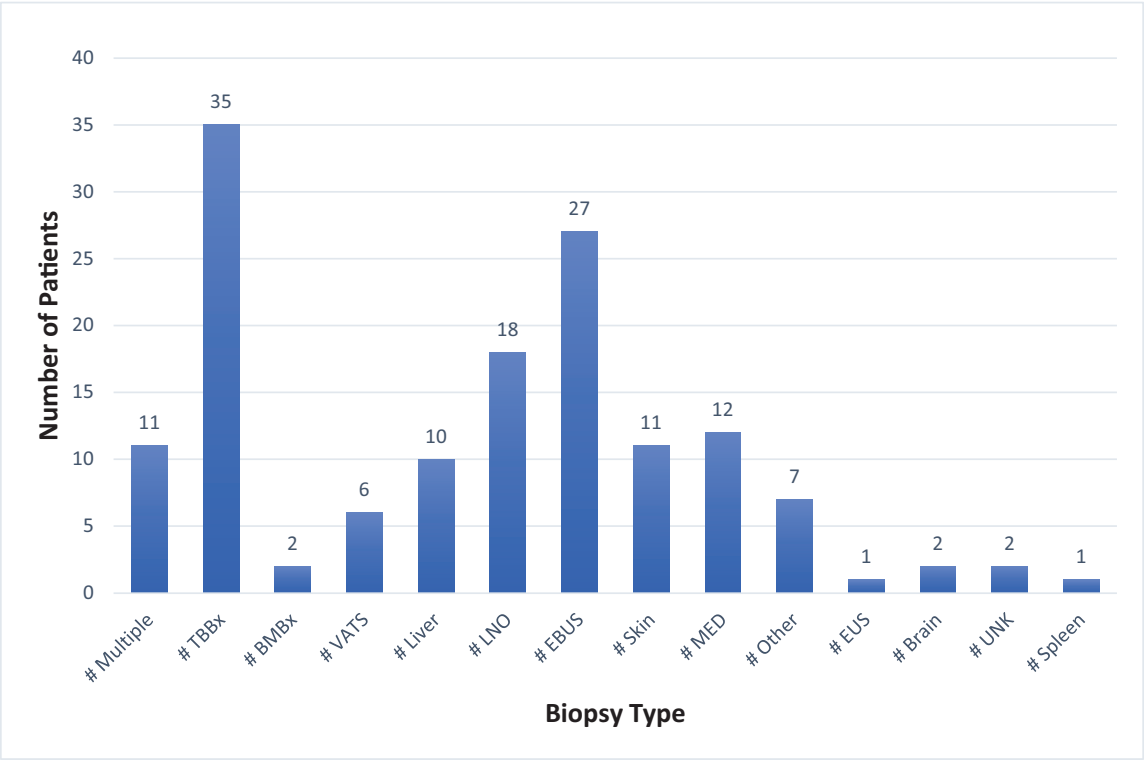

Figure 3. List of biopsy locations for those patients who were biopsy proven (n=145). *Abbreviations:* TBBx= Transbronchial Biopsy; EBUS= Endobronchial Ultrasound; LNO= Non-Endobronchial Lymph Node Biopsy; MED= Mediastinoscopy; VATS= Video-assisted thoracoscopic; BMBx= Bone Marrow Biopsy; UNK= Unknown Location; EUS= Endoscopic Ultrasound.

Table 1. Baseline clinical characteristics of our population, including percentage of organ involvement in our total population. n total is 196 patients.

Age, years	**55.6 ±13.8**
Male sex, n (%)	79 (40.3%)
Female sex, n (%)	117 (59.7%)
Recurrence of Hypercalcemia, n (%)	46 (23.5%)
Biopsy proven status, n (%)	145 (73.9%)
Organ Involvement, n (%)	
- Pulmonary	141 (72.3%)
- Lymph Node	77 (39.9%)
- Cutaneous	40 (20.5%)
- Ocular	15 (7.7%)
- Neuro	33 (16.92%)
- Hepatic	22 (11.3%)
- Cardiac	18 (9.2%)
- Splenic	7 (3.6%)

(Table 2). There were no significant relationships between highest calcium level and soluble IL2R, highest calcium level and race, race and ACE, race and Soluble IL2R, highest calcium level and type of organ involvement, race and recurrence of hypercalcemia at any point, 1,25 OH Vitamin D (calcitriol) and highest calcium, or biopsy proven patients and highest calcium. There were no significant differences between calcium levels across racial groups, soluble IL2R across racial groups, or ACE levels across racial groups. In those with disease recurrence, 25 were Black or African American Race (54.3%), 19 were White (41.3%), 1 was Asian, and 1 identified multiple races. 28/46 (60.9%) were biopsy proven (9 via EBUS, 4 via TBBx, 1 via TBBx + salivary gland, 1 via VATs, 1 via VATs + cardiac biopsy, 1 via pituitary, 2 via mediastinoscopy, 1 via liver biopsy, 4 via skin, 1 via parotid gland, 3 via LNO). In terms of treatment in those with disease recurrence, 8 were on

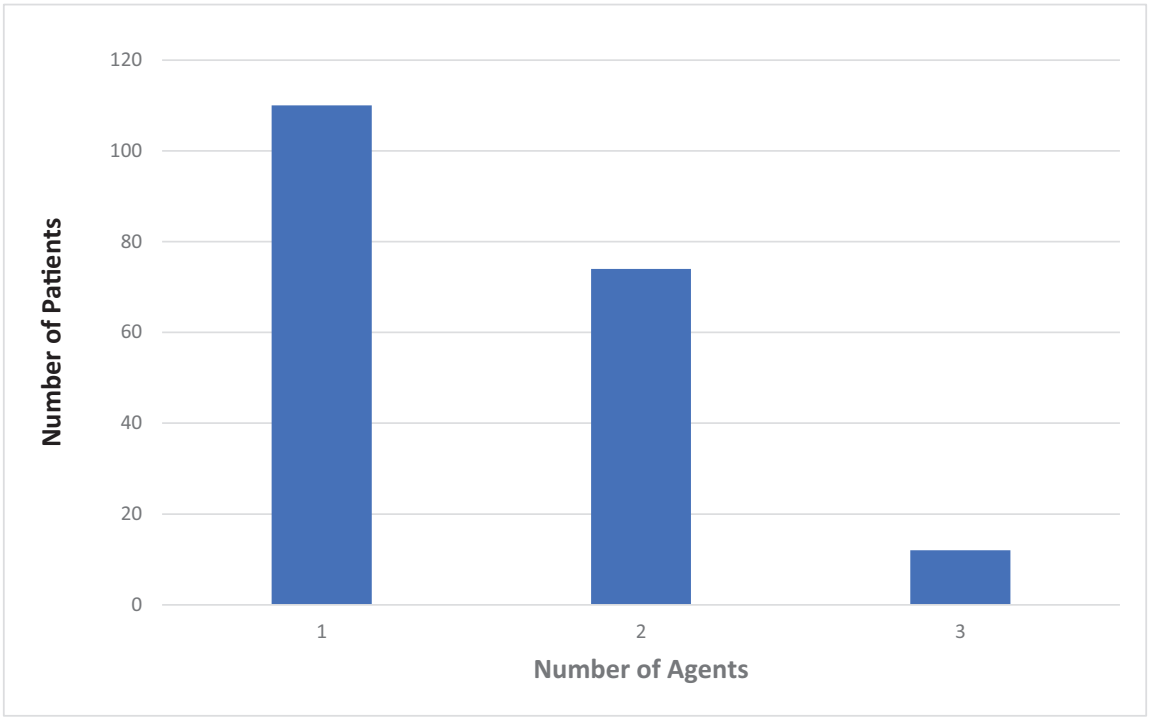

Figure 4. Number of patients controlled on either a single agent, two agents, or three agents.

Table 2. Descriptive statistics of our total population. Demonstrates significant relationship between ACE and highest calcium level (p=0.0178), but not Soluble IL2 or 1,25 OH vitamin D level and highest calcium level. There was a significant relationship between neuro involvement and highest calcium level (p=0.003). However, no significant relationship between any other organ involvement and highest calcium level.

Relationship between*	**P value**
ACE and Highest Calcium level	0.0178
Soluble IL2 Receptor and Highest Calcium Level	0.8761
1,25 OH Vitamin D and Highest Calcium Level	0.069
Organ Involvement and Highest Calcium Level	
- Pulmonary	0.66
- Lymph Node	0.056
- Cutaneous	0.86
- Ocular	0.33
- Neuro	0.003
- Hepatic	0.18
- Cardiac	0.11
- Splenic	0.64

*Comparison using student t-test or Wilcoxon test where appropriate

prednisone alone with average dose of 12.1 mg daily, 6 were on hydroxychloroquine alone, 2 on infliximab alone, 7 on Methotrexate alone, 2 on Azathioprine alone, and 21 were on combination therapy (17 on two agents and 4 on three agents). 32 (69.6%) had pulmonary involvement, 14 (30.4%) had lymph node involvement, 11 (23.9%) had cutaneous involvement, 3 (6.5%) had ocular involvement, 9 (19.6%) had neurological involvement, 3 (6.5%) had hepatic involvement, 4 (8.7%) had cardiac disease, 3 (6.5%) had splenic involvement, 4 (8.7%) with joint involvement, 2 (4.3%) with parotid gland involvement, and 1 (2.2%) with renal involvement. We also demonstrated a positive linear relationship between neurological involvement and highest calcium level (p=0.003). There were 33 patients with neurological involvement. Of these patients, 21 had biopsy proven disease. Of those with biopsy proven disease, there were 6 diagnosed via EBUS, 4 via TBBx, 5 via LNO, 1 via mediastinoscopy, 1 via gastric biopsy, 1 via pituitary biopsy, 2 via brain biopsy, and 1 via LNO as well as liver biopsy. 9 had recurrence of hypercalcemia at

any point (27.3%). 23 were Black or African American (69.7%), 1 declined to identify race, 8 were white (24.2%), and 1 was Asian. In terms of efficacious treatment in those with neurological involvement, 8 were controlled on prednisone alone with average dose of 15 mg daily. There were 3 on infliximab alone, 2 with methotrexate alone, 2 on azathioprine alone, 2 on Cellcept alone, 2 on Methotrexate in addition to hydroxychloroquine, 1 on Azathioprine in addition to prednisone, 1 on Cellcept in addition to prednisone, 1 on hydroxychloroquine in addition to prednisone, 1 on prednisone in addition to Myfortic, 7 on prednisone in addition to infliximab, and 3 on prednisone in addition to methotrexate. In those with neurological involvement, 1 presented with seizures with compatible MRI findings, 4 with transverse myelitis, 3 with other spinal disease not specified as Transverse Myelitis, 1 with Diabetes Insipidus and Bell's Palsy, 3 with cranial nerve disease, 1 with neuromyopathy, 3 with hydrocephalus, 2 with vascular disease presenting as stroke, 1 with cranial nerve as well as vascular disease, and 14 with multiple neurological system involvement.

Discussion

Sarcoidosis is overall a rare disease with highest incidence in Scandinavian countries with estimated incidence of 11.5 per 100,000 followed by The United States with an incidence estimated between 8-11 per 100,000, highest in Black Americans (18). Multiple comorbidities of sarcoidosis have been described, including pulmonary hypertension, pulmonary fibrosis, obstructive sleep apnea, and cardiovascular disease which complicates the diagnosis and management of sarcoidosis (19). Hypercalcemia is a known complication of sarcoidosis, affecting around 5-10% of patients with sarcoidosis (1-3), with hypercalciuria described in up to 62% of patients with sarcoidosis (4). It is more common in men and patients of Caucasian descent (3). Hypercalcemia in sarcoidosis is thought to be associated with the abnormal production of calcitriol by macrophages, resulting in increased bone reabsorption and intestinal calcium absorption. Other conditions have also been implicated in calcitriol-mediated hypercalcemia with similar pathophysiology, including hematological malignancies (Non-Hodgkin's lymphoma, Hodgkin's lymphoma, and CLL), solid organ malignancies (Ovarian clear cell cystadenocarcinoma, seminoma, squamous cell carcinoma, adenocarcinoma, and non-small-cell lung carcinoma), infections (*Mycobacterium tuberculosis*, *Mycobacterium avium* complex, *Mycobacterium bovis*, and invasive histoplasmosis), and other granulomatous conditions including foreign body granulomatosis (20). Subsequent parathyroid hormone induced suppression by increased vitamin D and calcium levels can lead to hypercalciuria, which can progress to nephrolithiasis, renal insufficiency, and renal failure if untreated (21). Little information is available regarding optimal treatment options for hypercalcemia in sarcoidosis, with most studies limited to case reports (13,22). Steroids are commonly used in the treatment of sarcoidosis and hypercalcemia in the setting of sarcoidosis (2). Steroids are thought to decrease serum calcium levels through inhibition of calcium absorption, increase in urinary calcium excretion, and inhibition of 1-α-hydroxylase activity (23). Other therapies include hydroxychloroquine, ketoconazole, methotrexate, and TNF-α inhibitors, such as infliximab (2,13-17). Hydroxychloroquine and ketoconazole have both been shown to decrease extrarenal production of calcitriol and lower serum calcium levels, though the precise mechanism of this is unknown (2). It has been suggested that this is achieved from the suppression of 1-α-hydroxylase (5). Methotrexate has also been shown to be effective in the treatment of SAHC with unclear mechanisms, though reduction in overall disease burden and inhibition of osteoclast activity has been suggested (13). Infliximab has been shown to be effective in the treatment of resistant SAHC, though again the exact mechanism is unclear (14-17). Increasingly, steroid sparing therapies are being sought to manage various organ manifestations of patients with sarcoidosis. In this study, we describe the prescribing patterns of a large cohort of SAHC patients at a large quaternary referral center recognized as a Sarcoidosis Center of Excellence by the Foundation for Sarcoidosis Research (FSR). We also describe organ manifestations of patients with SAHC (Figure 2). Notably, there was no significant relationship between organ manifestation and highest calcium in this cohort outside of the relationship between highest calcium level and neuro involvement (Table 2). Hypercalcemia has previously been associated with

male sex and Caucasian race in the ACCESS study (3) and with the HLA DRB1*1101 allele as well as insecticide exposure (3). Interestingly, the HLA DRB1*1101 allele and insecticide exposure were also associated with cardiac sarcoidosis (24). To our knowledge, there have been no specific investigations into associations between organ manifestations and hypercalcemia. In a study by Baughman et al (1), there was a positive linear relationship between Calcitriol and vitamin D. However, our study did not find a statistically significant relationship between these two, possibly suggesting other sources of dysregulated calcium production outside of the sarcoid granuloma (1,5). In fact, despite the general consensus that sarcoidosis associated hypercalcemia (SAHC) is non-PTH mediated, there have been cases of coexisting hyperparathyroidism and SAHC (25,26). There is also suggestion of seasonal variation associated with ultraviolet light exposure (27). In addition, concomitant vitamin D therapy, excessive sun exposure, and malignancy may be associated with increased risk of renal complications in patients with sarcoidosis (21). These all suggest that SAHC may be multifactorial in nature. There was also a positive linear relationship between highest calcium levels and neurological involvement noted in this study. To our knowledge, this correlation has not been described previously. There have been case reports of neurosarcoidosis presenting with hypercalcemia and pituitary involvement (28,29). Increased concentrations of Vitamin D binding protein have also been found in exosomes extracted from CSF in patients with neurosarcoidosis (5,30). One possible explanation could include an increased likelihood of dehydration, subsequent worsening of hypercalcemia, particularly in patients with pituitary involvement and associated hypothalamic-pituitary dysfunction. More investigation is needed to further assess these correlations and associated mechanisms. ATS suggests that determining better biomarkers for abnormal calcium metabolism than calcium or vitamin D testing (11). In contrast to a study by Lawrence et. al. (31), our study demonstrated no linear relationship between soluble interleukin 2 receptor (Soluble IL2R) and highest calcium levels. Our study did demonstrate a positive linear relationship between highest calcium levels and ACE levels, suggesting that this may be a potential marker of abnormal calcium metabolism. In a study Donavan et. al. (20), which investigated causes of calcitriol-mediated hypercalcemia, serum ACE levels were significantly higher in patients with sarcoidosis compared to other etiologies, though elevated serum ACE levels were also noted in other etiologies, particularly malignancy. Examining this relationship prospectively is needed to determine if elevated ACE levels in non-hypercalcemic patients is related to future development of hypercalcemia. The largest known study to this date is a study by Baughman et al (1), which sought to determine the prevalence of SAHC in one cohort as well as the relationship between vitamin D and SAHC in another cohort. In that study, treatment and response was analyzed in 97 patients with SAHC in cohort one with 15 patients being controlled on prednisone alone, 15 patients with hydroxychloroquine alone, 4 with methotrexate alone, 2 with azathioprine alone, and 2 with leflunomide alone (1). To our knowledge, this study is the first with the primary aim to compare treatment options for hypercalcemia in sarcoidosis across a large cohort, with a total of 196 patients ultimately included in this review. Our study also demonstrated several non-steroidal options that were able control calcium to a level of 10.4 mg/dL for at least 6 months with 50 patients being controlled with a single non-steroidal therapy alone (88 patients controlled on a single agent with 38 patients controlled on prednisone alone) (Figure 4), with the 3 most common including methotrexate, hydroxychloroquine, and azathioprine with 30 patients, 21 patients, and 7 patients respectively. More research is needed in this patient population to determine the most effective steroid sparing therapy to control SAHC. Currently, there are no guidelines for controlling SAHC regarding choice of treatment or length of therapy. While this study does demonstrate several nonsteroidal options to control SAHC, it is limited by its retrospective nature. In addition, this cohort only represents a single center patient population, with these findings subject to local prescribing patterns and regional differences in this specific cohort. Prospective and multicenter trials are likely needed to most effectively answer which agents are most efficacious in controlling hypercalcemia in this population.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors' Contribution: DR: design of the study, IRB submission, Data acquisition/chart review, background data retrieval/review of the literature, data analysis, manuscript writing, final approval/accountable for all aspects of the study; DC: data acquisition/chart review, background data retrieval/review of the literature, manuscript writing, final approval/accountable for all aspects of the study; HZ: data/statistical analysis, writing of manuscript, final approval/accountable for all aspects of the study. JB: substantial contribution to design of the study/IRB approval, background data retrieval/review of the literature, manuscript writing, final approval/accountable for all aspects of the study.

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