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A new side of sarcoidosis: medication and hospitalization use in a privately insured patient population

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Abstract. *Objective:* This study describes patterns of medication prescriptions for sarcoidosis patients in a large commercially insured U.S. population, with specific focus on prescribing practices across medical specialties and their associated hospitalization risk. *Methods:* Using the Marketscan Database we selected adult patients with a diagnosis of sarcoidosis by ICD-9 code during the 2012 calendar year. Differences in prescribing practices were evaluated between provider types. A multivariate model controlling for age, sex, and region assessed hospitalization risk associated with provider type, prednisone dose, and use of non-steroid sarcoidosis medications. *Results:* Using the described criteria, 11,042 total patients were identified. A majority were female, mean age 49.3 years. Of these, 1,792 (16.2%) had one or more hospital admissions (mean 1.6, SD 1.3) with a mean length of stay of 8.1 days (SD 14.5). 25.5% of patients were prescribed prednisone with a 1 year mean cumulative dose of 250mg. Pulmonary/Rheumatology providers prescribed the highest cumulative prednisone dose (961 mg) and were more likely to prescribe methotrexate and monoclonal antibody medications. Sarcoidosis patients receiving a cumulative prednisone dose >500 mg had an increased risk for hospitalization (OR 2.512, 2.210-2.855), while those prescribed methotrexate and azathioprine had decreased risk (OR 0.633, 0.481-0.833 and 0.460, 0.315-0.671). Monoclonal antibody use was associated with increased OR for hospitalization at 1.359. *Conclusion:* Sarcoidosis patients treated by subspecialists were more likely to receive higher doses of prednisone and non-steroid sarcoidosis medications. Higher doses of prednisone and monoclonal antibody use were associated with higher hospitalization risk while methotrexate and azathioprine were associated with lower hospitalization risk. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36 (2): 124-129)*

Key words: sarcoidosis, epidemiology, hospitalization, corticosteroids

Background

Sarcoidosis is a multisystem inflammatory disease characterized by the presence of noncaseating granulomas that affects 35.5 per 100,000 African Americans and 10.9 per 100,000 Caucasians in the United States (U.S.) (1, 2). Most sarcoidosis patients experience spontaneous resolution of their disease (3) and do not require treatment, but a third of patients will have chronic disease requiring prolonged treatment (3, 4). Corticosteroids are considered first line treatment for most forms of sarcoidosis, but can result in significant side effects and increased healthcare use (4). Patients with refractory disease may require treatment with second- or third-line medications, including methotrexate (MTX), azathioprine (AZA), and monoclonal antibody therapy (5).

Previous studies evaluating sarcoidosis treatment options have primarily addressed sarcoidosis patients from large referral centers which have reported treatment rates of 55-65% (4, 6). This contrasts starkly

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with a recent study which included a large, community population of patients with sarcoidosis in which only 22.8% of continuing cases received treatment (7). Scant data exists regarding prescribing patterns and outcomes in sarcoidosis patients from community-based practices. Large datasets from private insurers can provide insight into prescribing practices and associated outcomes across medical specialties from non-referral centers. The objectives of this study were to describe patterns of medication prescriptions for sarcoidosis patients in a large commercially insured U.S. population, with a specific focus on differences in prescribing practices across medical specialties and their associated hospitalization risk.

Methods

This retrospective analysis was conducted using the Truven Health MarketScan® Research Databases. These databases provide outcome measures including resource utilization and healthcare costs for inpatient and outpatient healthcare encounters of patients under employer-sponsored health insurance and Medicare-eligible individuals which covers approximately 143 million individuals. All database records were de-identified in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

Study Variables

Variables included in the analysis were demographic data (age, sex), date and duration of hospitalizations, geographic location, and International Classification of Diseases, Clinical Modification (ICD-9-CM) code details (specific code and date of code entry into record). The Marketscan database does not record race. Details of outpatient prescriptions included the specialty of the prescribing practitioner, medication name, daily dose and cumulative dose prescribed over the 12-month study period. Specific anti-sarcoidosis medications were selected for the analysis, including prednisone, MTX, AZA, hydroxychloroquine, and monoclonal antibody (MAB) which included infliximab and adalimumab. The prescriptions of other medications used in sarcoidosis, including Leflunomide and Mycophenolate, were too infrequent to include in the analysis.

Study Definitions

Patients selected as having a diagnosis of sarcoidosis were those with an ICD-9-CM code of 135.xx on two separate outpatient encounters at least 7 days apart. Hospitalizations were defined as any inpatient admission at an acute care facility during the study period. The acute care facility designation is based on a UB04 claim indicating an acute care hospital admission or an emergency department claim record with a length of stay greater than 0 days. Provider categories, as defined by billing label in the Marketscan Database, were divided into primary care providers (PCP), Pulmonology/Rheumatology (P/R), Dermatology/Immunology (D/I), multiple subspecialty providers (Multi), and "Other" subspecialty (Other) which includes pediatric, surgical and other medical specialties. To ensure PCPs were representative of non-specialist prescribing practices, sarcoidosis patients receiving prescriptions in the PCP category were required to have no encounters with a specialty provider, while those seen by a specialist could also be seen by a PCP.

Statistical Analysis

For characteristics of the sarcoidosis patients in the Marketscan database we used descritptive statistics reporting mean and SD for continuous variables. Medication prescriptions are described by mean daily and cumulative dose. Differences between groups of providers where tested with univariate analysis using gamma distributed log link models to account for skewed distribution of data. Multivariate logistic regression controlling for age, sex, and region was used to assess hospital risk by provider, prednisone use/cumulative dose, and use of non-steroid sarcoidosis medications. Regions were defined in the MarketScan database as Northeast, North Central, South, West, and Unknown.

Results

Patient Characteristics

From January 1, 2012 to December 31, 2012, 11,042 patients met inclusion criteria (table 1). The cohort was predominately female (59.1%) with a mean age of 49.3 years.

Table 1. Patient characteristics

Total N	11,042
Sarcoidosis Prevalence by Age Group: (per 100,000)	
Age 18-34	7.0
Age 35-44	26.6
Age 45-54	42.4
Age 55-64	47.9
Mean Age (SD)	49.3 (9.8)
Female Sex (%)	6,520 (59.1)
Hospital Admission (%)	1,792 (16.2)
Number of Annual Hospital Admissions for Subjects with Admissions, Mean (SD) [IQR]	1.6 (1.3) [IRQ 1-2]
Prednisone Use (%)	2,817 (25.5)

IRQ=Interquartile range.

Medications

Review of the Marketscan database revealed that 2,817 sarcoidosis patients (25.5%) received a prescription for prednisone use during the study period. The mean annual prescribed cumulative dose across providers was 250 mg mg (SD 692). While there was significant variation in the cumulative dose between provider groups, the mean daily prednisone dose did not differ significantly between providers (Table 2).

Steroid sparing medications were not commonly prescribed (Table 3). Hydroxychloroquine was the most commonly prescribed non-steroidal anti-sarcoidosis medication after prednisone (4.0%), followed by MTX (2.7%) and AZA (1.2%). Hydroxychloroquine and MTX were also the most commonly prescribed medications in combination with prednisone (2.6% and 1.9%, respectively). Subspecialty providers provided at least 2/3 of all prescriptions for MTX, hydroxychloroquine, and monoclonal antibodies. No significant difference existed across provider groups in the number of prescriptions for AZA. Less than 1% of patients were on a combination of 2 non-steroidal medications, which was overwhelmingly prescribed (78.3%) by P/R specialties.

Table 2. Prednisone prescribing practices

	PCP	P/R	D/I	Multi	Other	P-value
Mean daily prednisone dose, mg (SD) [IRQ]	14.9 (8.1) [10-20]	14.9 (8.0) [10-20]	15.4 (8.6) [10-20]	15.3 (8.3) 10-20]	14.9 (7.2) [10-20]	.7457
Mean cumulative prednisone dose, mg (SD) [IRQ]	866 (961) [150-1200]	961 (1138) [200-1500]	755 (939) [130-1040]	930 (954) [185-1290]	961 (1065) [180-1260]	<.0001

PCP=Primary Care Physician. P/R=Pulmonology/Rheumatology. D/I=Dermatology/Immunology. Multi=Multispecialty

Table 3. Number of patients receiving steroid sparing therapy

	Total Population	PCP	P/R	D/I	Multi	Other	P-value
Methotrexate, n (%)	298 (2.7)	24	219	26	17	12	<.0001
Azathioprine, n (%)	132 (1.2)	25	72	18	9	8	.0910
Hydroxychloroquine n (%)	441 (4.0)	56	298	52	16	19	<.0001
Any Mab, n (%)	64 (0.6)	6	44	6	5	3	.0017
Pred + MTX, n (%)	210 (1.9)	11	163	19	10	7	<.0001
Pred + AZA, n (%)	92 (0.8)	15	52	14	6	5	.2052
Pred + Any MAB, n (%)	36 (0.3)	2	26	3	3	2	.0102
Pred + Hydroxychl, n (%)	261 (2.6)	28	187	29	10	7	<.0001
No pred, ≥2 steroid sparing drugs, n (%)	92 (0.8)	6	72	7	5	2	<.0001

PCP=Primary Care Physician. P/R=Pulmonology/Rheumatology. D/I=Dermatology/Immunology. Multi=Multispecialty. Pred=prednisone

Hospitalization risk

Patients seen in P/R clinics had an increased risk of hospitalization compared to those seen only by a PCP, D/I, or Other provider (Table 4). Medication use was also correlated with hospitalization risk (Table 4). OR for prednisone use was grouped into three levels; no prednisone use, low-dose (1-500 mg cumulative yearly prednisone), and high-dose (>500 mg cumulative yearly prednisone). Low-dose prednisone correlated with a slightly higher risk for hospitalization compared to those who did not receive prednisone, while patients receiving high-dose prednisone had a substantial increase in hospitalization risk. MTX and AZA showed statistically significant decrease in hospitalization risk, while MAB showed an increased rate of hospitalization.

Table 4. Odds ratios for hospitalization

	OR (CI)
Provider (ref: Pulmology/Rheumatology)	
Primary Care Physician	.604 (.521-.699)
Dermatology/Immunology	.678 (.591-.777)
Multi-Specialty	.901 (.704-1.152)
Other	.776 (.638-.944)
Medication	
Pred: None vs 1-500	1.217 (1.035-1.431)
Pred: None vs >500	2.512 (2.210-2.855)
Any Monoclonal Antibody	1.359 (1.035-1.431)
Methotrexate	.633 (.481-.833)
Azathioprine	.460 (.315-.671)

*multivariable model controlling for effects of age, sex and region

Discussion

The goal of this study was to describe a group of privately insured sarcoidosis patients with respect to medication prescribing practices across provider groups and associated hospitalization risk. As previous studies have mainly described patient cohorts at large referral centers, this study evaluates a subset of patients who have not been well described historically. The recent study by Baughman, et al, evaluated a similar group using the Optum database, however their study centered around demographic differences and health care costs (7). Our study further evaluated hospitalization risk in reference to medication use and prescribing provider. Using the Marketscan dataset we demonstrated differences in prescribing practices across provider groups, with second- and third-line prescriptions being more common in subspecialty practices. Sarcoidosis referral center studies have often cited prednisone use in 55-65% of sarcoidosis patients, however this study found that only 25.5% of sarcoidosis patients in the Marketscan database were prescribed prednisone during the study period (4, 6). It should be noted, however, in the study by Judson, et al, 2012, their evaluation for prednisone use was described as 51% "at some point during the study period" which spanned 11 years of retrospective evaluation. This study does corroborate the findings of the Sarcoidosis in America study which found only 22.8% of patients in the Optum Database receiving therapy, of which 56% were prescribed prednisone (7). These disparities can partially be attributed to the increased severity of disease in patients seen in referral centers. In addition to prednisone, the rates of second line therapy use were more in line with those found in community studies as opposed to those observed at large referral centers.

We found the mean daily dose of prednisone per patient to be similar across provider groups, but the cumulative yearly dose of prednisone was significantly higher for P/R than PCP or D/I. This is consistent with the expectation that sarcoidosis patients seen by pulmonologists and rheumatologists are more likely to have refractory disease requiring a longer duration of steroids. The hospitalization rate in the overall cohort was similar to that reported in other studies (8), and there was an increased risk of hospitalization in patients followed by P/R. While this could be related to greater disease severity, sarcoidosis patients followed by P/R also had higher cumulative doses of prednisone which has been previously been associated with increased healthcare use in sarcoidosis patients (9). We similarly found significant correlation between high cumulative doses of prednisone and increased risk of hospitalization. While this supports the concept that higher doses of prednisone are indicative of patients with more severe disease who have a higher hospitalization risk, an potential alternative explanation is that increased hospitalizations are a result of the adverse effects related to higher steroid exposure. This would agree with previous data published by Broos et. al. and others that found strong associations between increased cumulative prednisone dose and a higher prevalence of comorbidities and

healthcare use (9, 10). We believe this correlation deserves further evaluation in prospective studies.

Interestingly, this is the first study to show reduced hospitalization rates associated with MTX and AZA use. This was unexpected since patients on MTX and AZA are typically considered to have refractory disease and one would expect higher hospitalization rates. In addition, it is difficult to reconcile this with the finding that the majority of MTX and AZA prescriptions (67.7%) were in P/R patients, who had increased hospitalization risk compared to PCP-only patients in which only 11.4% were prescribed MTX or AZA. Potential explanations for the lower hospitalization risk include improved disease control with these agents and/or their use as "steroid-sparing agents" resulted in lower cumulative prednisone use which in turn could have led to decreased hospitalizations. Unfortunately, due to the retrospective nature of this study we are unable to make a causative distinction with our current analysis. While these findings could suggest that earlier initiation of steroid sparing therapies could lower hospitalization risk, prospective studies are needed to evaluate this further.

Finally, MAB use was correlated with increased OR for hospitalization. MAB are considered third-line agents in sarcoidosis (11, 12), which supports the suggestion that patients who were started on MAB are more likely to have advanced disease which could explain the increased OR for hospitalization. Additionally, certain MAB therapy has been correlated both increased morbidity in the setting of increased infection risk (13, 14) and congestive heart failue (15) which could lead to higher hospitalization risk in this cohort.

Limitations

This study evaluated a large group of commercially insured patients with a documented diagnosis of sarcoidosis. Uninsured status is associated with younger age, poverty, and in racial minorities (16, 17). Limiting our cohort to insured patients likely excludes some patients with greater disease severity, and limits the generalization of our results. It should be noted also that the age groups in the Marketscan database stop at 64, which also limits generalization of our findings to all sarcoidosis patients. Additional limitations of our study are those commonly found in retrospective database studies. The documentation of diagnosis in this study was evaluated by 2 separate billing code for sarcoidosis at least 7 days apart. While this is a commonly used method of patient identification in database studies, there exists an inherent risk that some patients in our cohort may have been incorrectly identified as having sarcoidosis. Additionally, we used billing codes for medication prescriptions however this does not represent actual medication compliance. As it specifically relates to prednisone use, the analysis was limited by the one-year duration of the study. Many patients on prednisone were likely started on their regimens prior to the evaluated calendar year while others continued their courses into the following calendar year. This would likely affect the cumulative dose analysis. We did not attempt to exclude patients with other diseases that may be treated with immunosuppressing medications, which raises the possibility that some patients may have received prednisone and other medications included in our analysis for reasons other than sarcoidosis treatment.

Conclusions

In this study we utilized a large database of privately insured patients to identify medication use and hospitalization risk for patients with sarcoidosis. We found that patients treated by subspecialists were more likely to receive higher cumulative doses of prednisone and additionally more likely to non-steroid sarcoidosis medications. Higher doses of prednisone and MAB use were associated with higher hospitalization risk while MTX and AZA were associated with lower hospitalization risk.

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