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# Sarcoidosis Incidence after mTOR Inhibitor Treatment

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## Abstract

**Objective.—**Mechanistic target of rapamycin (mTOR) inhibitors are effective in animal models of granulomatous disease, but their benefit in sarcoidosis patients is unknown. We evaluated the incidence of sarcoidosis in patients treated with mTOR inhibitors versus calcineurin inhibitors.

**Methods.—**This was a cohort study using the Optum Clinformatics® Data Mart (CDM) Database (2003–2019), IBM® MarketScan® Research Database (2006–2016), and Danish health and administrative registries (1996–2018). Patients aged ≥18 years with ≥1 year continuous enrollment before and after kidney, liver, heart, or lung transplant treated with an mTOR inhibitor or calcineurin inhibitor were included. Patients diagnosed with sarcoidosis before, or up to 90 days after, transplant were excluded. The incidence of sarcoidosis by treatment group was calculated.

**Results.—**In the Optum CDM/IBM MarketScan cohort, 1,898 patients were treated with an mTOR inhibitor (mean age 49 years; 34% female) and 9,894 patients were treated with a calcineurin inhibitor (mean age 50 years; 37% female). The mean follow-up in the mTOR inhibitor group was 1.1 years, with no incident sarcoidosis diagnosed. In the calcineurin inhibitor group, the mean follow-up was 2.2 years, with 12 incident sarcoidosis cases diagnosed. In the Danish cohort, 230 patients were treated with an mTOR inhibitor (mean age 49; 45% female), with no incident sarcoidosis diagnosed. There were 3,411 patients treated with a calcineurin inhibitor (mean age 45; 40% female), with 10 incident cases of sarcoidosis diagnosed.

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Author Contributions:

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

**Conflicts of Interest:** None

**Conclusions.—**This study indicates a potential protective effect of mTOR inhibitor treatment compared with calcineurin inhibitor treatment against the development of sarcoidosis.

### Keywords

Sarcoidosis; granuloma; mTOR

## INTRODUCTION

Sarcoidosis is an immune-mediated inflammatory disease that is characterized by collections of immune cells called granulomas (1). Granulomas can form in various organs throughout the body and cause tissue damage and fibrosis. The lungs are most commonly affected, leading to significant morbidity and mortality (2, 3). Recent research using a murine model demonstrates that granuloma formation is driven by activation of the metabolic checkpoint kinase mechanistic target of rapamycin complex 1 (mTORC1) in macrophages (4). Constitutive mTORC1 activity in myeloid cells results in spontaneous multiorgan formation of granulomas. Moreover, treatment of these mice with the mechanistic target of rapamycin (mTOR) inhibitor everolimus results in dissolution of the granulomas. These findings have thus far not been extrapolated to patients with sarcoidosis with routine clinical care data.

Mechanistic target of rapamycin (mTOR) signaling is inhibited by several therapeutics that are primarily used in patients who have undergone solid organ transplantation. These include rapamycin, sirolimus, and everolimus. Alternatively, many post-transplant patients receive calcineurin inhibitors instead of mTOR inhibitors, including cyclosporin and tacrolimus. Case reports have indicated potential therapeutic benefit in sarcoidosis after treatment with both agents (5–10).

Given the potential therapeutic role mTOR inhibitors may play in reducing granulomas, we examined the risk of developing incident sarcoidosis in solid organ transplant patients treated with an mTOR inhibitor compared with solid organ transplant patients treated with a calcineurin inhibitor.

## MATERIALS AND METHODS

### Data Source and Study Cohorts.

In part one of this study, we used administrative health claims data from the de-identified Optum Clinformatics® Data Mart (CDM) Database (Optum) from December 1, 2003 to December 31, 2019 (https://doi.org/10.57761/phra-vp46) and from the IBM® MarketScan® Research Databases from December 31, 2006 to December 31, 2016 (https://doi.org/10.57761/ray7-1g16). The Optum CDM dataset is a de-identified database derived from a large, adjudicated claims data warehouse and includes over 15 million individuals annually from across the United States who are privately insured or Medicare Advantage Part D members. The IBM® MarketScan® data includes de-identified records of more than 250 million patients, contributed by large employers, managed care organizations, hospitals, electronic medical record providers, Medicare, and Medicaid. No linkage was performed

between these two datasets; our study was performed by combining data from both datasets into a common data model.

In part two of this study, we analyzed data from Danish medical and administrative registries from January 1, 1996 to December 31, 2018 (11). The Danish National Health Service provides universal, tax-supported healthcare for all Danish residents (11). The Danish registries are linkable through a unique personal identifier, which is assigned at birth or upon immigration. The Danish National Patient Registry (DNPR) was used to identify all patients with transplantation, sarcoidosis, treatments received in hospital and to define comorbidities (12). The DNPR contains nonpsychiatric hospitalizations since 1977 and outpatient and emergency room visits since 1995. Diagnoses were coded using the eighth revision of the International Classification of Diseases (ICD-8) until 1993 and ICD-10 thereafter. The Danish National Prescription Registry was used to identify medications received out of the hospital (13). The Danish Civil Registration System was used to define the end of follow-up, date of birth, and sex for each member of the study population (14).

For both parts of this study, we included patients aged 18 years or older with at least one year of continuous enrollment in the dataset before the first Current Procedural Terminology (CPT) code or Nordic Medico-Statistical Committee (NOMESCO) code for kidney, liver, heart, or lung transplantation (Supplementary Table 1) and at least one year of continuous enrollment after the date of the CPT or NOMESCO code for transplantation (12). The exposed cohort included patients treated with an mTOR inhibitor (rapamycin, sirolimus, or everolimus), and the comparison cohort included patients treated with a calcineurin inhibitor (cyclosporine or tacrolimus). For the Optum CDM/IBM MarketScan cohort, patients who switched between an mTOR inhibitor and a calcineurin inhibitor were included as exposed and only the time treated with an mTOR inhibitor was included. For the Danish cohort, patients who switched from a calcineurin inhibitor to an mTOR inhibitor could contribute data to either group (i.e., if a patient started on a calcineurin inhibitor, they were included in the calcineurin inhibitor group until they switched to an mTOR inhibitor, at which time they began contributing to the mTOR inhibitor group; see Supplementary Figure 2). We excluded any patient with a diagnosis of sarcoidosis based on a single ICD-8, ICD-9, or ICD-10 code before the date of the transplantation or within 90 days after transplantation (Supplementary Table 1). Ninety days was chosen to exclude patients who were found to have sarcoidosis on the explanted tissue and therefore had preexisting sarcoidosis that was likely the cause of their transplant. For the Optum CDM/IBM MarketScan cohort, we excluded patients who received an mTOR inhibitor or calcineurin inhibitor any time before the date of the solid organ transplant (n = 1266). For the Danish cohort, we excluded patients who received an mTOR inhibitor or calcineurin inhibitor more than 30 days before the date of the solid organ transplant (n = 235).

For the Optum CDM/IBM MarketScan cohort, we extracted data on age, sex, race, geographic region, education, comorbidities, year of transplant, and days enrolled in the dataset after transplant. For the Charlson comorbidity score, all comorbidities in a 1-year period before the transplant date and 1-year period after the transplant date were used in the calculation. For the geographic region, a small number of patients were categorized as “Unknown.” Given the small number in several of the columns (i.e., less than 11),

we chose to aggregate the “Unknown” row with the “West” row in order to prevent any potential reidentification of patients. We also extracted concomitant immunosuppressive medication history, including glucocorticoid use, during the time patients were treated with either a calcineurin inhibitor or mTOR inhibitor. All glucocorticoids were converted into prednisone equivalent doses. For the Danish cohort, we extracted data on age at index, sex, comorbidities, year of transplant, and concomitant immunosuppressive medication history. The Charlson comorbidity score was calculated based on DNPR any time before the index date.

### Outcome Ascertainment.

The outcome was the diagnosis of incident sarcoidosis starting 90 days after the date of transplantation. Sarcoidosis was defined as two or more ICD-9 or ICD-10 codes for sarcoidosis separated by 14 days or more (Supplementary Table 1). As previously mentioned, this 90-day window was selected to exclude patients with preexisting sarcoidosis that was only discovered for the first time during, or shortly after, organ transplantation.

### Statistical Analysis.

In the Optum CDM/IBM MarketScan cohort, patients were followed from 90 days post-transplant until they were newly diagnosed with sarcoidosis, were no longer present in the dataset, or until the end of the follow-up period (December 31, 2019 for Optum CDM and December 31, 2016 for IBM MarketScan). In the Danish cohort, the index date was defined as 90 days after transplant, except for those mTOR inhibitor patients who switched from a calcineurin inhibitor: their index date was the date of the first mTOR inhibitor treatment. The end of time at risk in the cohort was date of death, immigration, sarcoidosis diagnosis, or end of study (December 31, 2018), whichever was sooner, except for those calcineurin inhibitor patients who switched to an mTOR inhibitor: their time at risk in the calcineurin inhibitor cohort ended at the start of their mTOR inhibitor treatment.

Baseline characteristics of patients in both groups were compared. Standardized mean differences (SMD) were calculated. Missing data for the categorical variables are reported in Table 1 as “Unknown.” For the continuous variables, there were no missing data. The Wilcoxon rank-sum test was used to compare glucocorticoid usage between the two groups, and p-values were based on two-sided hypothesis tests, where $p<0.05$ was considered statistically significant.

Incidence rates (IRs) were calculated and reported as the number of sarcoidosis events per 1,000 person years, and 95% confidence intervals (CIs) were calculated using the Mid-p exact test (15). In the Optum CDM/IBM MarketScan cohort, incidence rates were calculated separately for each dataset and the pooled estimates across the two databases were calculated with the use of a fixed-effects meta-analysis of the weighted average of database-specific estimates, weighted by the inverse variance of the estimates, as previously described (16, 17).

Statistical analyses were conducted using R 4.0.2 with the ‘icd’ and ‘tableone’ package for the OptumCDM/IBM MarketScan cohort and in SAS for the Danish cohort.

This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies. Due to the deidentified nature of the Optum Clinformatics™ Data Mart Database and IBM® MarketScan® Research Database datasets, the US-based portion of the study was exempted from review by the Stanford University Institutional Review Board. The Denmark-based portion of the study was reported to the Danish Data Protection Agency (record number 2016–051-000001/1880).

## RESULTS

### Optum CDM/IBM MarketScan Cohort

**Patient characteristics.—**We identified 14,458 patients in Optum CDM and 21,215 patients in IBM MarketScan who underwent solid kidney, liver, heart, or lung transplant (Supplementary Figure 1). Of these patients, a total of 11,792 patients met the inclusion and exclusion criteria, with 1,898 being treated with an mTOR inhibitor and 9,894 being treated with a calcineurin inhibitor. The mean age in the mTOR inhibitor group was 49 years versus a mean age of 50 years in the calcineurin inhibitor group (Table 1). The percentage of females in the mTOR inhibitor group was 34% compared with 37% in the calcineurin inhibitor group. There was a higher proportion of patients with a Charlson comorbidity score of >6 (44%) in the mTOR inhibitor group than the calcineurin inhibitor group (37%). The two groups were generally well balanced with SMD values below 0.2, except for year of transplant.

**Follow-up and concomitant immunosuppression.—**The mTOR inhibitor group had a median follow-up of 1.1 years compared with 2.2 years in the calcineurin inhibitor group (Supplementary Table 2). Patients receiving calcineurin inhibitors were more likely to receive mycophenolate mofetil (85.5% versus 43.5%) and azathioprine (6.3% versus 3.0%) than patients receiving mTOR inhibitors (Supplementary Table 2). The median dose of prednisone in the calcineurin inhibitor group was 11.7 mg/day compared with 5.8 mg/day in the mTOR inhibitor group ($p<0.001$) (Supplementary Table 2).

**Outcome.—**There were zero incident cases of sarcoidosis diagnosed during follow-up in the mTOR inhibitor group compared with 12 incident cases diagnosed in the calcineurin inhibitor group (Table 2). This corresponded to IRs per 1,000 person-years (95% CI) of 0.00 (0.00, 0.51) and 0.41 (0.20, 0.68) for patients in the mTOR inhibitor group and calcineurin inhibitor group respectively (Table 2). Roughly half of the incident sarcoidosis cases were diagnosed more than one year after the date of organ transplantation (Figure 1).

### Danish Cohort

**Patient characteristics.—**We identified 6,175 patients in the DNPR who underwent solid kidney, liver, heart, or lung transplant (Supplementary Figure 2). Of these patients, a total of 3,459 patients met the inclusion and exclusion criteria, with 58 patients in the mTOR inhibitor group, 3,229 patients in the calcineurin inhibitor group, and 182 patients contributing data to both groups. The mean age in the mTOR inhibitor group was 49 years, versus a mean age of 45 years in the calcineurin inhibitor group (Table 3). The percentage of females in the mTOR inhibitor group was 45% compared with 40% in the calcineurin

inhibitor group. There was a higher proportion of patients with a Charlson comorbidity score of >6 (12%) in the mTOR inhibitor group than the calcineurin inhibitor group (2%). The two groups were generally well balanced with SMD values below 0.2, except for Charlson comorbidity scores, which were notably different between the two groups.

**Follow-up and concomitant immunosuppression.—**The length of follow-up was shorter in the mTOR inhibitor group (median of 3.3 years) compared with the calcineurin inhibitor group (median of 7.8 years) (Supplementary Table 3). Patients receiving calcineurin inhibitors were more likely to receive prednisone (47% versus 31%) than patients receiving mTOR inhibitors (Supplementary Table 3). The median dose of prednisone was also higher in the calcineurin inhibitor group (2.0 mg/day) compared with the mTOR inhibitor group (1.2 mg/day) ($p<0.685$) (Supplementary Table 3).

**Primary outcome.—**There were zero incident cases of sarcoidosis diagnosed during follow-up in the mTOR inhibitor group compared with 10 incident cases diagnosed in the calcineurin inhibitor group (Table 2 and Figure 2). This corresponded to IRs per 1,000 person-years (95% CI) of 0.00 (0.00, 2.81) and 0.34 (0.17, 0.60) for patients in the mTOR inhibitor group and calcineurin inhibitor group respectively.

## DISCUSSION

In this large cohort study, we found that in two independent databases spanning two different countries, among solid organ transplant patients, there were zero patients treated with an mTOR inhibitor who developed incident sarcoidosis, whereas 12 patients in the US-based datasets and 10 patients in the Denmark-based dataset who were treated with a calcineurin inhibitor developed incident sarcoidosis. This was observed despite a higher percentage of patients in the calcineurin inhibitor group being on antimetabolite medications and receiving higher doses of glucocorticoids. We would expect this additional immunosuppression to have a protective effect, if any, against the development of sarcoidosis.

Although the outcome was a rare event, the findings in this study remain striking. However, the small number of events do not permit the statistical comparison of rates between the two subgroups (18).The overlapping confidence intervals of the sarcoidosis incidence rates in the two treatment groups suggest no statistically significant difference. A practical interpretation of this finding is that even though no sarcoidosis incidence can be observed in the mTOR inhibitor subgroup, this is not necessarily unexpected statistically due to the low person-years and the rareness of the disease.

A small literature base suggests that mTOR inhibitors may be effective for the treatment of sarcoidosis. Several case reports demonstrated successful treatment of sarcoidosis with an mTOR inhibitor (5–7). Recent preclinical data implicate mTORC1 as a key driver of granuloma formation (4). Mice with constitutively active mTORC1 in myeloid cells formed granulomas in the lungs, liver, and lymph nodes. After three weeks of treatment with the mTORC1 inhibitor everolimus, the granulomas resolved. Furthermore, activated mTORC1 signaling was found in 33% of granulomatous lesions from sarcoidosis patient samples. In addition to findings from this study, it is known that glucocorticoids downregulate

mTOR signaling, which may contribute to their therapeutic effect in sarcoidosis (19–21). However, glucocorticoids have a number of significant side effects, which limit their long-term use (22). Taken together, these studies indicate a potential therapeutic role for mTOR inhibitors in sarcoidosis. Our study provides evidence that mTOR inhibitors may protect against the development of sarcoidosis in patients who have undergone solid organ transplantation. Alternatively, these data may suggest that calcineurin inhibitors can potentially induce sarcoidosis in a small subset of patients, as has been described with other immunosuppressive medications (23–26). Given that roughly half of the incident sarcoidosis cases in the calcineurin group occurred in the first year, it is conceivable that the medication triggered a paradoxical granulomatous reaction, however to our knowledge this has not been previously described with calcineurin inhibitors.

Our study has several limitations. As this was an unadjusted study using claims data and registry data, there may be uncontrolled confounding. We examined baseline characteristics including age, sex, and Charlson comorbidity score, which appeared to be relatively well balanced. We did not have data on certain variables in all datasets such as race, occupation, BMI, or smoking, which can be associated with sarcoidosis. We do not believe these factors should have impacted whether patients received an mTOR inhibitor versus a calcineurin inhibitor and thus believe they are likely nondifferential between the two groups, however we cannot be certain of this. There may be reasons why certain patients were chosen to receive an mTOR inhibitor instead of a calcineurin inhibitor that are not evident in the data, which theoretically may have biased against developing sarcoidosis. We used ICD-8, ICD-9, ICD-10, CPT, and NOMESCO codes for identification of diseases and outcomes which could have led to misclassification of variables and outcomes. In particular, we used the standard definition for the outcome of sarcoidosis, which includes two ICD codes separated by 14 days or more, which could be prone to error in a transplant population susceptible to granulomatous infections that may not reveal themselves as such for more than 14 days. However, we would expect this to be nondifferential between the two groups. We could not account for the competing risk of death in the Optum/MarketScan dataset due to limitations of the data. We could not determine the degree of medication compliance in either of the groups or confirm that patients truly received the treatment during the time it was prescribed. Lastly, our analysis does not differentiate according to the length of exposure. The estimation of a single incidence rate for the total length of exposed time period implicitly assumes that the rate is constant over time regardless of how long the patient was actually exposed.

This study has several strengths. We used two large claims databases in the United States covering patients in a wide geographic area, which enabled us to create a large enough cohort of solid organ transplant patients to identify incident sarcoidosis, which is a rare outcome. We also used Danish medical and administrative data to confirm our results. We compared patients receiving mTOR inhibitors to those receiving calcineurin inhibitors, which provided a similar comparison group of patients also receiving immunosuppression to help isolate the potential effect of mTOR inhibition specifically. We were able to follow patients for up to 15 years to ascertain the outcome. We were able to ask a question that has not yet been asked in any prospective, interventional studies.

## CONCLUSION

In conclusion, we observed a lower incidence of sarcoidosis in solid organ transplant patients receiving mTOR inhibitors compared with patients receiving calcineurin inhibitors. Our work suggests that mTOR inhibitors may protect against the development of sarcoidosis. Prior preclinical data and case reports have demonstrated that mTOR inhibitors may provide therapeutic benefit in patients with sarcoidosis. Given the current body of evidence, future interventional studies with mTOR inhibitors for the treatment of sarcoidosis could be considered.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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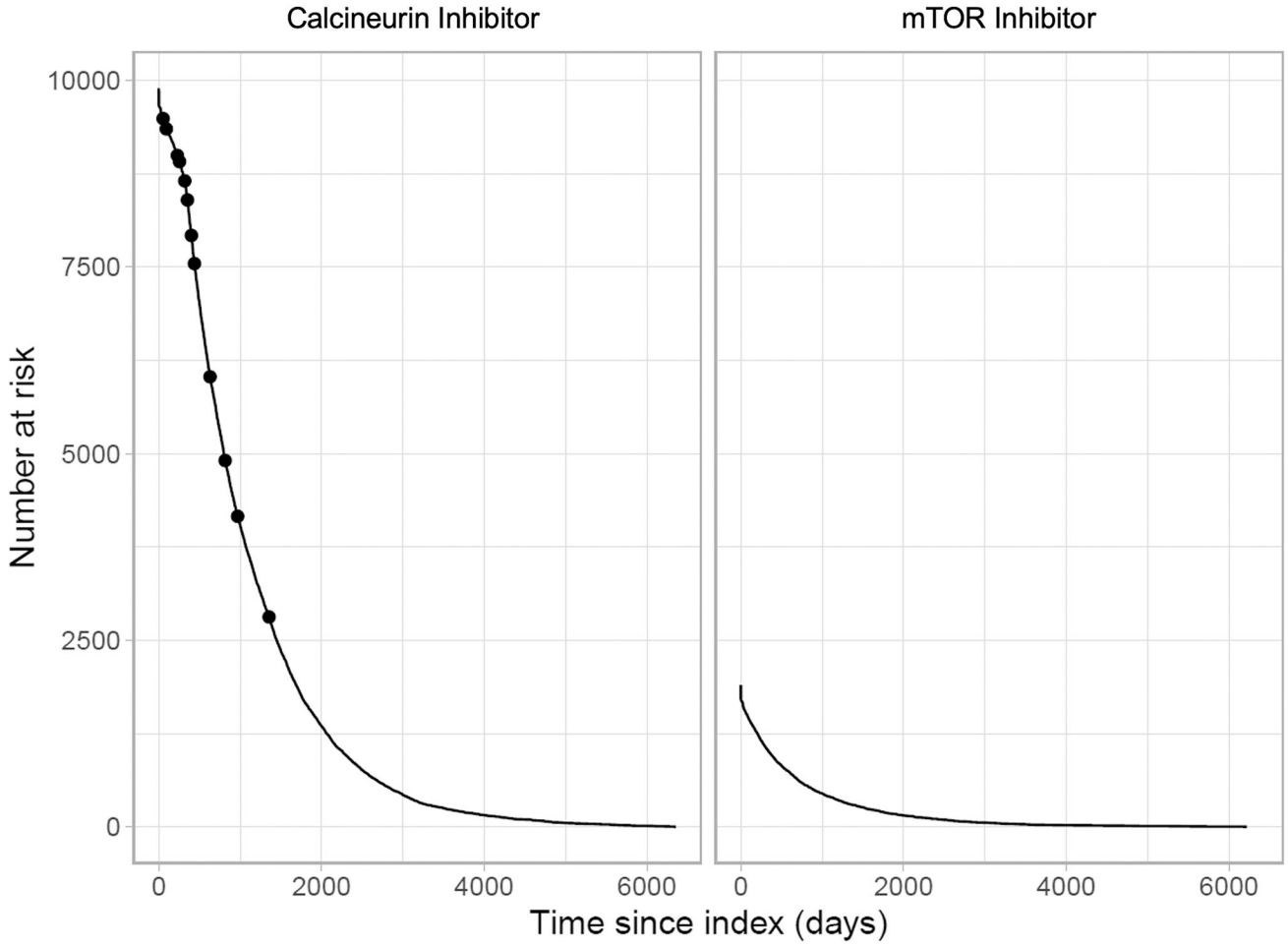


**Figure 1:**

Incident sarcoidosis in the Optum CDM/IBM MarketScan cohort ninety days or more after solid organ transplant.

Each dot represents an incident case of sarcoidosis.

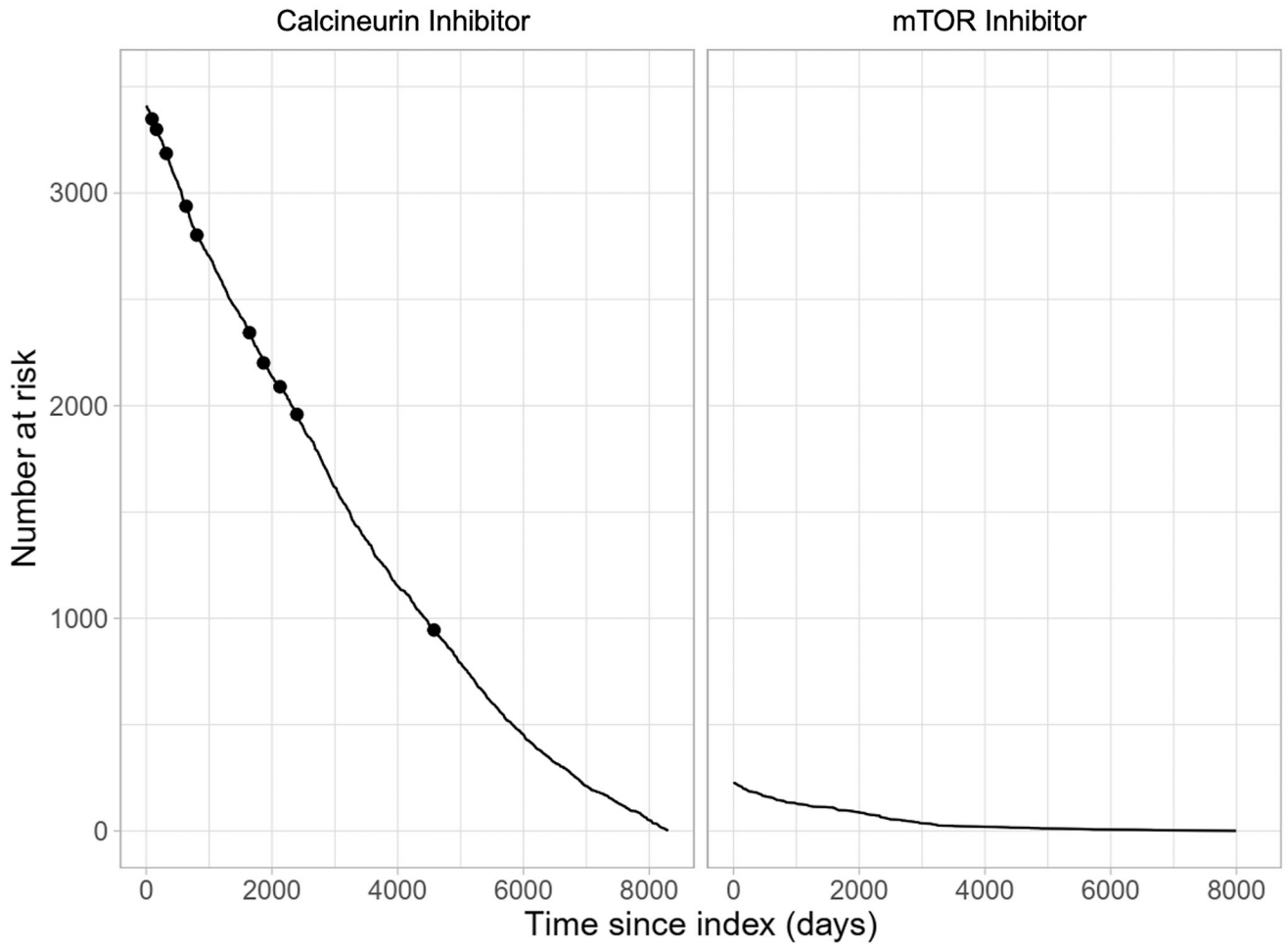


**Figure 2:**

Incident sarcoidosis in the Danish cohort ninety days or more after solid organ transplant. Each dot represents an incident case of sarcoidosis.

**Table 1.**

Baseline characteristics of patients in the Optum CDM and IBM MarketScan cohort.

| | Optum CDM | | | IBM MarketScan | | | Combined Cohort | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Calcineurin Inhibitor (*n* = 4810)** | **mTOR Inhibitor (*n* = 1040)** | **SMD** | **Calcineurin Inhibitor (*n* = 5084)** | **mTOR Inhibitor (*n* = 858)** | **SMD** | **Total Cohort (*n* = 11792)** | **Calcineurin Inhibitor (*n* = 9894)** | **mTOR Inhibitor (*n* = 1898)** | **SMD** |
| Age in years, mean (SD) | 52.8 (14.6) | 50.2 (15.3) | 0.174 | 47.6 (13.8) | 47.2 (14.6) | 0.024 | 49.9 (14.6) | 50.1 (14.4) | 48.9 (15.0) | 0.085 |
| Gender, n (%) | | | 0.077 | | | 0.080 | | | | 0.078 |
| Female | 1801 (37.4) | 351 (33.8) | | 1883 (37.0) | 285 (33.2) | | 4320 (36.6) | 3684 (37.2) | 636 (33.5) | |
| Male | 3009 (62.6) | 689 (66.2) | | 3201 (63.0) | 573 (66.8) | | 7472 (63.4) | 6210 (62.8) | 1262 (66.5) | |
| Race, n (%) | | | 0.188 | - | - | | - | - | - | |
| White | 2954 (61.4) | 697 (67.0) | | - | - | | - | - | - | |
| Black | 623 (13.0) | 98 (9.4) | | - | - | | - | - | - | |
| Asian | 249 (5.2) | 36 (3.5) | | - | - | | - | - | - | |
| Hispanic | 614 (12.8) | 105 (10.1) | | - | - | | - | - | - | |
| Unknown | 370 (7.7) | 104 (10.0) | | - | - | | - | - | - | |
| Geographic region, n (%) | | | 0.152 | | | 0.178 | | | | 0.169 |
| Northeast | 384 (8.0) | 68 (6.5) | | 896 (17.6) | 128 (14.9) | | 1476 (12.5) | 1280 (12.9) | 196 (10.3) | |
| North Central | 1135 (23.6) | 309 (29.7) | | 1222 (24.0) | 266 (31.0) | | 2932 (24.9) | 2357 (23.8) | 575 (30.3) | |
| South | 2275 (47.3) | 441 (42.4) | | 2053 (40.4) | 328 (38.2) | | 5097 (43.2) | 4328 (43.7) | 769 (40.5) | |
| West or Unknown | 1016 (21.1) | 222 (21.3) | | 913 (18.0) | 136 (15.9) | | 2287 (19.4) | 1929 (19.5) | 358 (18.9) | |
| Education, n (%) | | | 0.023 | - | - | | - | - | - | |
| High school or < | 1188 (24.7) | 236 (22.7) | | - | - | | - | - | - | |
| < Bachelor's | 2539 (52.8) | 534 (51.3) | | - | - | | - | - | - | |
| Bachelor's or > | 817 (17.0) | 190 (18.3) | | - | - | | - | - | - | |
| Unknown | 266 (5.5) | 80 (7.7) | | - | - | | - | - | - | |
| CCS, n (%) | | | 0.145 | | | 0.182 | | | | 0.174 |
| 0 | 0 (0.0) | 0 (0.0) | | 0 (0.0) | 0 (0.0) | | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| 1–2 | 504 (10.5) | 99 (9.5) | | 939 (18.5) | 120 (14.0) | | 1662 (14.1) | 1443 (14.6) | 219 (11.5) | |
| 3–4 | 993 (20.6) | 199 (19.1) | | 1391 (27.4) | 224 (26.1) | | 2807 (23.8) | 2384 (24.1) | 423 (22.3) | |
| 5–6 | 1237 (25.7) | 221 (21.2) | | 1294 (25.5) | 202 (23.5) | | 2954 (25.1) | 2531 (25.6) | 423 (22.3) | |

| | Optum CDM | | | IBM MarketScan | | | Combined Cohort | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Calcineurin Inhibitor (*n* = 4810)** | **mTOR Inhibitor (*n* = 1040)** | **SMD** | **Calcineurin Inhibitor (*n* = 5084)** | **mTOR Inhibitor (*n* = 858)** | **SMD** | **Total Cohort (*n* = 11792)** | **Calcineurin Inhibitor (*n* = 9894)** | **mTOR Inhibitor (*n* = 1898)** | **SMD** |
| > 6 | 2076 (43.2) | 521 (50.1) | | 1459 (28.7) | 312 (36.4) | | 4368 (37.0) | 3535 (35.7) | 833 (43.9) | |
| Year of transplant, n (%) | | | 0.399 | | | 0.103 | | | | 0.314 |
| 2003–2007 | 1016 (21.1) | 399 (38.4) | | 0 (0.0) | 0 (0.0) | | 1415 (12.0) | 1016 (10.3) | 399 (21.0) | |
| 2008–2014 | 1841 (38.3) | 352 (33.8) | | 4563 (89.8) | 795 (92.7) | | 7551 (64.0) | 6404 (64.7) | 1147 (60.4) | |
| 2015–2019 | 1953 (40.6) | 289 (27.8) | | 521 (10.2) | 63 (7.3) | | 2826 (24.0) | 2474 (25.0) | 352 (18.5) | |

CDM = Clinformatics® Data Mart; SMD = standardized mean difference; SD = standard deviation; CCS = Charlson comorbidity score.

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**Table 2.**

Incidence rate of sarcoidosis after transplant by treatment group.

| | Optum CDM/IBM MarketScan Cohort | | Danish Cohort | |
|---|---|---|---|---|
| | **Calcineurin Inhibitor (*n* = 9894)** | **mTOR Inhibitor (*n* = 1898)** | **Calcineurin Inhibitor (*n* = 3411)** | **mTOR Inhibitor (*n* = 230)** |
| Number of events, n (%) | 12 (0.12) | 0 (0.00) | 10 (0.29) | 0 (0.00) |
| Person-years | 29274 | 3608 | 29495 | 1069 |
| IR (95% CI) | 0.41 (0.20, 0.68) * | 0.00 (0.00, 0.51) * | 0.34 (0.17, 0.60) | 0.00 (0.00, 2.81) |

CDM = Clinformatics® Data Mart; IR = incidence rate per 1,000 person-years; 95% CI = 95% confidence interval.

* Pooled estimate of Optum and IBM Marketscan datasets using meta-analysis.

**Table 3.**

Baseline characteristics of patients in the Danish Cohort.

| | Total Cohort (*n* = 3641) | Calcineurin Inhibitor (*n* = 3411) | mTOR Inhibitor (*n* = 230) | SMD |
|---|---|---|---|---|
| Age in years, mean (SD) | 45.2 (15.8) | 45.0 (15.8) | 48.8 (16.6) | 0.235 |
| Gender, n (%) | | | | 0.113 |
| Female | 1455 (40.0) | 1351 (39.6) | 104 (45.2) | |
| Male | 2186 (60.0) | 2060 (60.4) | 126 (54.8) | |
| CCS, n (%) | | | | |
| 0–2 | 1688 (46.4) | 1626 (47.7) | 62 (27.0) | 0.438 |
| 3–4 | 1350 (37.1) | 1265 (37.0) | 85 (37.0) | 0.003 |
| 5–6 | 494 (13.6) | 439 (12.9) | 55 (23.9) | 0.288 |
| > 6 | 109 (3.0) | 81 (2.4) | 28 (12.1) | 0.384 |
| Year of transplant, n (%) | | | | 0.314 |
| 1996–2003 | 1066 (29.3) | 1004 (29.4) | 62 (27.0) | 0.055 |
| 2004–2011 | 1371 (37.7) | 1267 (37.1) | 104 (45.2) | 0.164 |
| 2012–2018 | 1204 (33.1) | 1140 (33.4) | 64 (27.8) | 0.122 |

SMD = standardized mean difference; SD = standard deviation; CCS = Charlson comorbidity score.