Abatacept and tofacitinib in refractory sarcoidosis: drug survival, safety, and treatment response

H.C.B. Leffers, B. Baslund, J. Lindhardsen, S.B. Krintel, N. Graudal

Copenhagen Lupus and Vasculitis Clinic, Center for Rheumatology and Spine Diseases, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark.

Abstract

Objective

To describe drug survival, safety and treatment response in sarcoidosis patients treated with abatacept or tofacitinib in routine care.

Methods

We identified 41 sarcoidosis patients treated with abatacept and 12 patients treated with tofacitinib. Of the patients treated with tofacitinib 83% had previously been treated with abatacept. Drug survival and reasons for discontinuation of treatment was investigated. Treatment response was evaluated at least once within the first 6 months of treatment by at least one trained clinician and classified as responder or non-responder. No direct comparison of drugs was made.

Results

Median (range) disease duration was 3.5 (1–27) and 3 (1–16) years for abatacept and tofacitinib. The patients had previously received a median of 1 DMARD and 1 biological DMARD in both groups. Nearly all patients had been treated with at least one TNFi (95%/92 %). After 6 months, 90% (95%CI 85–90%) of the 41 patients in the abatacept group and 89% (79–99%) of the 12 patients in the tofacitinib group-maintained treatment. At 12 months, it was 80% (73–87%) and 74% (58–90%). No serious adverse events were recorded. For abatacept and tofacitinib 71% and 67% of patients were characterised as responders. In both treatment groups, there was a significant reduction in prednisolone dosage and levels of soluble IL2-receptor at all time points.

Conclusion

Sarcoidosis patients treated with abatacept and tofacitinib had long drug survival, achieved high response rates. Both drugs represent good and safe therapeutic options in sarcoidosis patient's refractory to previous TNFi therapy.

Key words

sarcoidosis, abatacept, tofacitinib, drug survival, safety

Henrik Christian Bidstrup Leffers, MD, PhD
Bo Baslund, MD, PhD
Jesper Lindhardsen, MD, PhD
Sophine B. Krintel, MD, PhD
Niels Graudal, MD, DMSc

Please address correspondence to:
Henrik Christian Bidstrup Leffers
Copenhagen Lupus and Vasculitis Clinic, Center for Rheumatology and Spine Diseases, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark.
E-mail: henrik.christian.bidstrup.leffers@regionh.dk

Received on January 8, 2024; accepted in revised form on April 22, 2024.

Competing interests: none declared.

Introduction

The available high-quality evidence derived from randomised controlled trials (RCTs) concerning the management of sarcoidosis is limited. Systemic steroid treatment has been substantiated to exhibit a significant impact (1-3), whereas inhaled steroids manifest no discernible effect (3-6). Only a handful of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) have undergone scrutiny in RCTs. A solitary RCT has demonstrated the steroid-sparing efficacy of methotrexate (7), and another has validated the notable impact of hydroxychloroquine on pulmonary sarcoidosis (8). However, other csDMARDs employed in sarcoidosis treatment, such as azathioprine, mycophenolate mofetil, and ciclosporin, lack RCT validation.

The pathogenesis of sarcoidosis is characterised by the development of granulomatous inflammation. Macrophages congregate around mononuclear inflammatory cells and undergo differentiation into epithelioid and giant cells, facilitated by cytokines such as tumor necrosis factor (TNF) (9), and the Janus kinase-signal transducer and activator of transcription pathway (JAK-STAT) (10). This cellular aggregation forms a central core encircled by T-cells in the granuloma periphery. Consequently, it is hypothesised that modern targeted DMARDs (tDMARDs), including TNF inhibitors (TNFi), T-cell inhibitors, and JAK inhibitors, may exert an effect on sarcoidosis. A prospective trial using PET/CT as outcome showed a significant reduction in standardised uptake value (SUV) of 18-fluorodeoxyglucose (FDG) in sarcoidosis patients treated with adalimumab (11). An RCT has demonstrated the impact of infliximab on pulmonary sarcoidosis (12) and another has shown the effect of adalimumab on dermal sarcoidosis (13). In contrast, etanercept, tested in an RCT for ocular sarcoidosis, failed to exhibit a significant effect (14). Consequently, the potential effectiveness of antibody-based TNFi (infliximab and adalimumab) has been substantiated through clinical trials including RCTs.

As a result of the existing RCT evidence, we have employed systemic steroids, methotrexate, and hydroxychloroquine as first-line treatments for sarcoidosis, while infliximab and adalimumab serve as second-line treatments. Pathophysiological studies in sarcoidosis patients reveal altered regulatory T-cell functions with diminished expression of CTLA-4 (CD152) (15). Thus, T-cell inhibition via the CTLA-4 Ig fusion protein, abatacept, is postulated to potentially exert a positive effect on sarcoidosis. A multicentre prospective open-labelled single-arm phase II study to test this has been planned but remains to be published (16). Since 2012, we have successfully utilised abatacept as a third-line treatment for sarcoidosis, treating a total of 41 patients with generally positive outcomes.

In December 2018, Damsky *et al*. elucidated the potential efficacy of the JAK inhibitor tofacitinib on refractory sarcoidosis (17). Subsequently, we incorporated JAK inhibitors as a fourth-line treatment for sarcoidosis in 12 patients.

The present study aims to delineate the drug survival, treatment response, and safety outcomes in the cohort of 41 sarcoidosis patients treated with abatacept and the 12 patients treated with tofacitinib

Patients and methods

Danish citizens over the age of 18 years who were treated with abatacept or tofacitinib at the Department of Rheumatology at Rigshospitalet with a sarcoidosis code (D86.1–9) in the International Classification of Diseases, 10th revision (ICD-10) was eligible for this study and were followed as part of routine care. Off-label use of medicines is allowed in Denmark and does not require approval by an ethics committee. The diagnosis, diagnostic tests and follow-up was reviewed on clinical, radiological, and histological findings in the patients' medical records.

Data collected

From the patient charts we retrieved the following baseline data: sex, age, disease duration, number, and type of previous DMARDs, number and type of previous biological drugs, concomitant prednisolone, concomitant methotrexate, chest x-ray staging (18), lung

function tests and potential biomarkers levels: soluble IL-2 receptor (sIL-2R, unit: kU/L), angiotensin-converting enzyme (ACE, unit: U/L) and serum calcium. The organ in which sarcoidosis leads to the greatest negative impact on clinical function leading to initiation of abatacept and tofacitinib, respectively, was identified for each patient.

Drug survival

Drug survival was calculated as the number of months individual patients-maintained treatment, from start date until date of the first missed dose due withdrawal. All observations were censored at the last registered visit before October 2023. All patients were included in the survival analysis.

Treatment response

Treatment response with abatacept and tofacitinib was assessed interdisciplinary in cooperation with pulmonologists, neurologists, dermatologists, and cardiologists. The response was based on clinical outcomes, se ACE, s IL2r, pulmonary function test and PET/CT. Similar methods have previously been used to evaluate heterogenous outcomes in an observational study of sarcoidosis (19).

Treatment response was evaluated at least once within the first 6 months of treatment by at least one trained clinician and classified as responder or non-responder. Treatment duration ≤4 months were not evaluated. Number of- and type of individually affected organs as well as concomitant treatment with prednisolone or methotrexate were reported for each treatment response group.

Furthermore, data from patients, in both treatment groups, with a lung function test in which at least one parameter, forced vital capacity (FVC) or single-breath diffusing capacity of the lung for CO (DLCO-SB), is below 80% of the expected value at the start of treatment, at approximately 6 (3–9) and 12 (9–15) months, respectively, are presented. Lastly, in both treatment groups, as an additional measure of treatment response, prednisolone dosage and levels of sIL-2R are presented at start of treatment with abatacept and tofacitinib and at 3 and 6 months.

Table I. Characteristics of patients in the study population at start of treatment*.

	Abatacept (n=41)	Tofacitinib (n=12)
Male sex, n (%)	23 (56)	7 (58)
Age, years	50 (22-82)	53 (37-72)
Disease duration, years	3,5 (1-27)	3 (1-16)
Number of previous DMARDs	1 (0-4)	1 (0-4)
Previous DMARDs, %		
Azathioprine	26%	33%
Hydroxychlorochine	10%	8%
Methotrexate	76%	75%
Mycophenolate mofetil	7%	8%
Number of previous biological DMARDs	1 (0-2)	2 (1-2)
Previous biological DMARDs, %		
Adalimumab	41%	50%
Infliximab	73%	67%
Rituximab	2%	6%
Abatacept	-	83%
Tofacitinib	0%	-
≥1 TNF-α inhibitor, n (%)	39 (95%)	11 (92%)
≥1 biological drug of any kind, n (%)	40 (98%)	12 (100%)
Concomitant methotrexate, %	20%	24%
Concomitant prednisolone, %	60%	59%
Prednisolone dosage, mg/day[a]	5 (0-25)	10 (2.5-25)
Elevated biomarkers at time of diagnosis:		
ACE	27%	17%
sIL-2r	43%	42%
Serum calcium	7%	8%

*Except where indicated otherwise, values are the median (range). DMARDs: disease-modifying anti-rheumatic drugs; sIL-2R: soluble IL-2 receptor; ACE: angiotensin-converting enzyme; [a]Median (interquartile range) among patients receiving the drug.

Statistics

Statistical analyses were made using SPSS and R. For descriptive statistics, medians, numeric ranges, and interquartile ranges are presented. Kaplan-Meyer plots, 95% confidence intervals (95%CI) were used for drug survival analysis. Sex, concomitant methotrexate use (yes/no) and concomitant prednisolone use (yes/no) were included as categorical variables, whereas age, disease duration, number of previous biological treatments and prednisolone dose score were continuous variables. Wilcoxon matched pairs signed rank sum test was used for the comparison of continuous variables.

Results

Abatacept

A total of 41 patients treated with abatacept were included in the study. Abatacept was administered as intravenously (750 milligrams every fourth week) or subcutaneous (125 mg milligrams every week) in 40 and 11 patients, respectively. Of the patients, 58% were male with a disease duration of 3.5 years. The patients had previously received a median of 1 DMARD and 1 biological DMARD, Table I. Most patients (76%) had previously been treated with methotrexate. Nearly all patients (95%) had been treated with at least one TNFi. Concomitant MTX at baseline was given to 20%, whereas 60% were treated with prednisolone. Index organ was lungs and/or regional lymph nodes, joint/muscles, central nervous system (CNS), heart, fatigue, peripheral nervous system (PNS) and kidney for 44%, 20%, 17%, 7%, 5%, 3% and 3% of patients, respectively.

Drug survival

After 6 months, 92% (95%CI 88–96%) of the 41 patients in the abatacept group-maintained treatment. At 12 months, it was 82% (75–89%) (Fig. 1).

Discontinuation of treatment

During the follow up period, 14 (36%) patients withdrew from treatment. A discontinuation summary is shown in Table II. The number of patients that withdrew from treatment with abata-

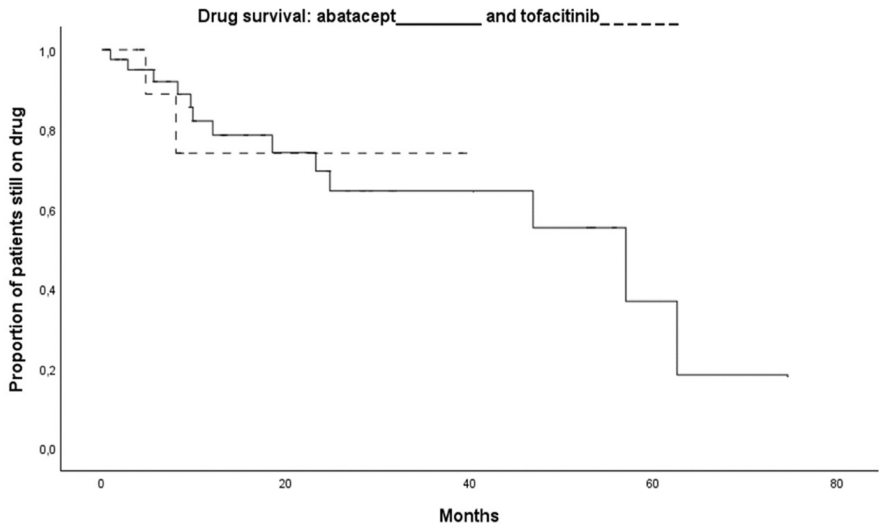

Fig. 1. Drug survival. The number of patients who withdrew from treatment during follow-up was 15 for abatacept and 2 for tofacitinib. The proportion of patients still on drug at different time points is shown.

Table II. Discontinuation summary for abatacept and tofacitinib*.

	Abatacept (n=41)	Tofacitinib (n=12)
Follow-up period, median (range)*	21 months (1-75)	7,5 months (1-40)
Total number of treatment withdrawals, n (%)	13 (32%)	2 (17%)
Reasons for withdrawal: [&]		
- No effect, n (%)	8 (20%)	2 (17%)
- Adverse events, n (%)[£]	4 (10%)	0 (0%)
- Others, n (%)	1 (2%)	0 (0%)

*Notice that the follow-up time for abatacept is longer than for tofacitinib.
[&] For abatacept and tofacitinib, 7 and 1 treatments were withdrawn due to both no effect and adverse events, respectively.
[£] Except for one infusion reaction (no adrenaline administered) no serious adverse events were recorded.

cept due to adverse events was 4 and except for one infusion reaction (no adrenaline administered), no serious adverse events were recorded.

Treatment response

For abatacept, 71% of patients were characterised as responders (29 out of 39 patients evaluated). Responders were characterised by a higher prevalence of eye-, joint/muscles and bone involvement with higher prevalence of concomitant prednisolone and MTX at start of treatment (relative difference between groups was >10 %), Table III. One patient discontinued MTX after start of treatment.

Lung function test

Of the 41 patients, nine had reduced lung function at start of treatment. The mean improvement in FVC at 6 months in both treatment groups was 6% (range -4 to 13). A more than 10% decrease in FVC was not observed in any patient. Change in DLCO-SB at 6 months in both treatment groups was 0.5% (range -9 to 13). A more than 10% decrease in DLCO was observed in only one patient (Fig. 2).

Prednisolone dosage

Of the 41 patients, 25 were treated with prednisolone at start of treatment and nine patients were tapered out at six months. There was a significant reduction in prednisolone dosage at both 3 and 6 months ($p<0.001$) compared to start of treatment. The prednisolone dosage in mg was 15 (5–25) median (IQR) at start of treatment, 8 (0–10) at month 3 and 5 (0–5) at month 6 (Fig. 3).

Levels of sIL2R

Of the 41 patients in total, 20 had measured elevated levels of sIL-2R at diagnosis and/or at start of treatment. There was a significant reduction in sIL-2R levels at both 3 and 6 months ($p<0.05$) compared to start of treatment. The level of sIL-2r was 593 (395–936)) median (IQR) at start of treatment, 482 (359–596) at month 3 and 449 (391-658) at month 6 (Fig. 3).

Tofacitinib

A total of 12 patients treated with tofacitinib were included in the study. Tofacitinib was administered perorally (5 milligram twice a day) for all patients. Of the patients, 58% were male with a disease duration of 3 years. The patients had previously received a median of 1 DMARD and 2 biological DMARDs (Table I). Of the 12 patients treated with tofacitinib 10 had previously been treated with abatacept. Most patients (75%) had previously been treated with methotrexate. Nearly all patients (92%) had been treated with at least one TNFi. Concomitant MTX at baseline was given to 24%, whereas 59% were treated with prednisolone. Index organ was lungs and/or regional lymph nodes, central nervous system (CNS), joint/muscles, eyes and skin for 33%, 33%, 17%, 8% and 8% of patients, respectively.

Drug survival

After 6 months, 89% (79%-99%) of the 12 patients, maintained treatment. At 12 months, it was 74% (58–90%) (Fig. 1).

Discontinuation of treatment

During the follow up period, 2 (17%) patients withdrew from treatment (Table II). No patients withdrew from treatment due to adverse events in the tofacitinib group.

Treatment response

For tofacitinib, 67% of patients were characterised as responders (6 out of 9 patients evaluated). Responders were characterised by a higher prevalence of reduced lung function, peripheral nerve system (PNS), eye, heart and joint/muscles involvement along higher prevalence of concomitant MTX at start of treatment (relative difference between groups was >10%). No patients discontinued MTX after start of treatment. For

Table III. Treatment responses for patients with specific organ involvements and concomitant treatment during the first 6 months of treatment with abatacept or tofacitinib.

	Abatacept (n=41)				Tofacitinib (n=12)			
	n (%)	Responder, (n=28)	Non-responder (n=10)	Not evaluable, (n=3)	n (%)	Responder (n=6)	Non-responder (n=3)	Not evaluable (n=3)
Organ involvement:								
Lungs and/or regional lymph nodes	38 (93)	68%	32%	3	8 (67)	63%	33%	3
Radiographic stage:								
0	19 (46)	100%	0%	2	5 (42)	60%	40%	1
1	8 (20)	65%	25%	0	0	-	-	1
2	7 (17)	86%	14%	0	3 (25)	67%	33%	0
3	4 (10)	50%	50%	0	1 (8)	100%	0%	1
4	3 (7)	67%	33%	0	0	-	-	0
Reduced lung function	9 (22)	78%	22%	0	1 (8)	100%	0%	1
CNS	9 (22)	44%	56%	1	4 (33)	0%	100%	2
PNS	5 (12)	60%	40%	0	1 (8)	100%	0%	0
Eyes	11 (27)	89%	11%	1	425)	100%	0%	2
Heart	4 (10)	75%	25%	0	1 (8)	100%	0%	0
Liver	4 (10)	25%	75%	0	1 (8)	-	-	1
Joints/muscles	19 (46)	94%	6%	4	4 (33)	75%	25%	0
Bone	5 (12)	75%	25%	0	1 (8)	0%	100%	0
Kidney	3 (7)	100%	0%	1	0	-	-	0
Skin	6 (15)	75%	25%	0	3 (25)	50%	50%	1
Fatigue	35 (85)	84%	16%	2	9 (75)	57%	43%	2
Constitutional symptoms	26 (63)	75%	25%	1	6 (50)	67%	33%	1
Concomitant prednisolone	21 (51)	81%	19%	2	5 (42)	60%	40%	1
Concomitant methtrexate	8 (20)	88%	12%	0	2 (17)	100%	0%	1
Duration of therapy months, median (range)		20 (8-29)	10 (1-57)	2	16	9 (7-20)	7 (5-40)	4

both treatment groups, non-responders were characterised by a higher prevalence of CNS involvement (relative difference between groups was >70%).

Lung function test

No patients in the tofacitinib group had reduced lung function at start of treatment.

Prednisolone dosage

Of the 12 patients in total, eight were treated with prednisolone at start of treatment and 4 were tapered out at six months. There was a significant reduction in prednisolone dosage at both 3 and 6 months (p<0.001) compared to start of treatment. The prednisolone dosage in mg was 17.5(5–25) median (IQR) at start of treatment, 3(0–7.5) at month 3 and 0(0–2.5) at month 6 (Fig. 3).

Levels of sIL2R

Of the 12 patients, 5 had measured elevated levels of sIL-2R at diagnosis and/or at start of treatment. There was a significant reduction in sIL-2R levels at both 3 and 6 months (p<0.05) compared to start of treatment. The level of sIL-2r was 689 (406-1660)) median (IQR) at start of treatment, 535 (380-805) at month 3 and 658 (560-692) at month 6 (Fig. 3).

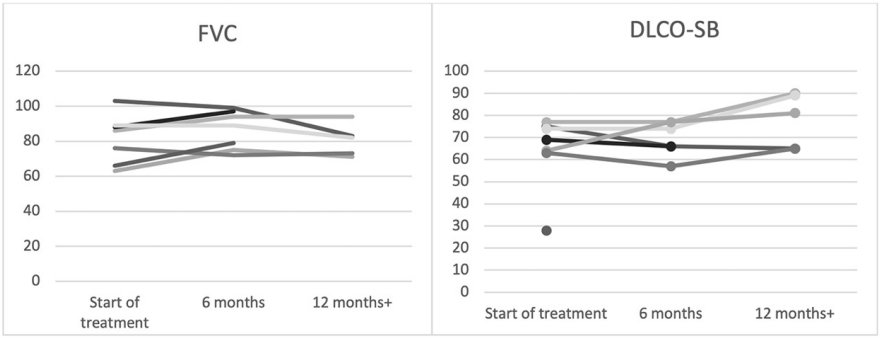

Fig. 2. Change from start of treatment in lung function parameters in patients (n=8, all treated with abatacept) with reduced (<80 Predicted% values) forced Vital Capacity (FVC) or single-breath diffusing capacity of the lung for CO (DLCO-SB) at any point after start of treatment.

Comorbidity and drug selection

Of the 43 individual patients treated with abatacept and/or tofacitinib, 28 (65%) had no registered comorbidity items (20). Of the 12 patients with comorbidities in the abatacept group, 4 patients had cardiac comorbidity attributable to cardiac sarcoidosis. Three other patients suffered from heart failure, ischaemic heart disease and cor pulmonale, respectively. Two patients had chronic obstructive pulmonary disease, one had steatosis not directly attributable to sarcoidosis and one had inflammatory bowel disease. Of the two patients with comorbidity in the tofacitinib group, one had heart failure and one had inflammatory bowel disease. Two patients started tofacitinib with no prior abatacept treatment. One had previously been treated for rheumatoid arthritis with abatacept and developed sarcoidosis accordingly. One had a sarcoidosis syndrome similar to his monozygotic twin who had a good response to tofacitinib.

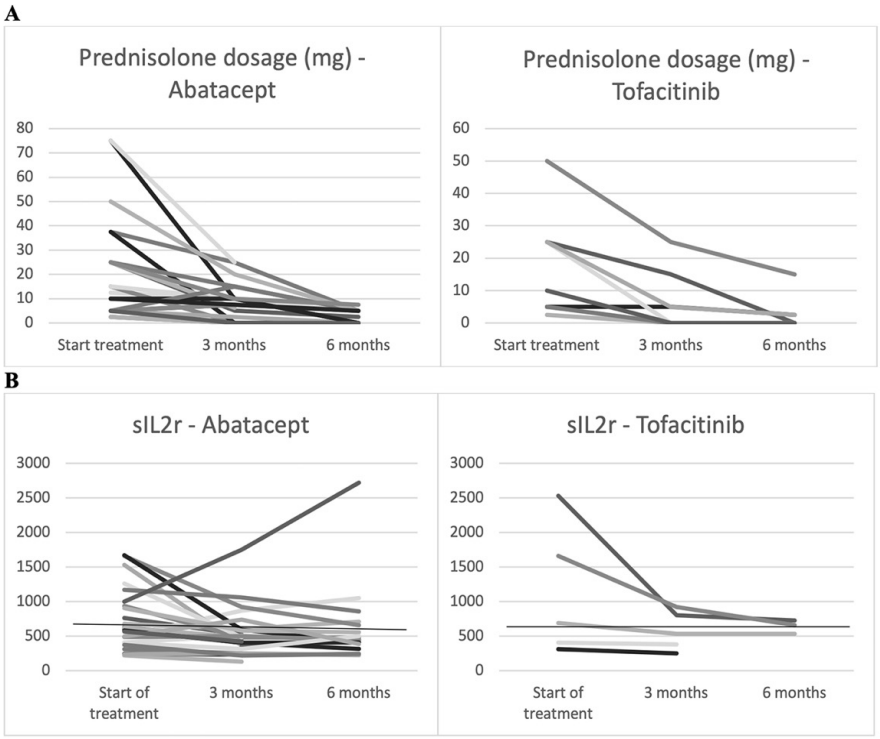

Fig. 3. A: Change from start of treatment in prednisolone dosage in patients (n=33) receiving prednisolone at start of treatment.
B: Change from start of treatment in sIL2r-levels in patients (n=34) with at least two measurements during first 6 months of treatment.

Discussion

To our knowledge, this is the largest observational study documenting the drug survival, safety, and treatment responses of abatacept and tofacitinib in sarcoidosis patients. Abatacept and tofacitinib were found to be good treatment options in such patients of whom nearly all had previously failed csDMARDs and TNF inhibitors (>90 had failed at least one TNFi). For abatacept and tofacitinib, 92% and 89% were still on the drug after 6 months. And 82% and 74% after 12 months.

According to the present study both drugs seem well tolerated with no serious adverse events. For abatacept and tofacitinib, 78% and 67% of patients were evaluated as responders with no deterioration in lung function and significant reduction in both prednisolone dosage and levels of sIL2r for all patients. For both treatment groups, non-responders were characterised by a higher prevalence of CNS involvement. A recent large survey of sarcoidosis treatment in USA including more than 3000 patients showed that no centre used abatacept al all, and only one centre had used tofacitinib in a few patients (21). We have only been able to identify one report of the efficacy of abatacept in sarcoidosis (22). Of note, the first prospective clinical study regarding safety and efficacy is currently conducted in a phase II trial (16).

For tofacitinib, safety and efficacy has also only been reported in very small observational studies and case series (17, 23-27). Studies have mainly studied the effect on cutaneous- and to a lesser extent on pulmonary sarcoidosis. From these studies, tofacitinib seems safe and may have the ability to induce remission. We have used a maximal dose of tofacitinib of 10 mg in a period where warnings have been given concerning risk of thrombosis, especially at doses higher than 10 mg per day (28). These warnings are probably wrong (29), and as some studies have indicated positive dose-response relationships up 20 mg per day (30), such doses may be relevant in the future in patients with insufficient response to 10 mg. As mentioned, our sequence of using biological drugs (1) TNF inhibitors, 2) abatacept, 3) JAK inhibitors) is a consequence of the timeline of the development of the drugs but it is likely that the effect of these drugs is equal and that other factors in the future should decide the order of treatment, such as economy, types of organs involved, and patient preferences (subcutaneous, intravenous or oral administration).

The clinical presentation of sarcoidosis is highly heterogenic, spontaneous remission occurring in up to 50% of patients and thus, responses to treatment are heterogeneous too (31-38). Evidence concerning the choice of treatment for specific organ manifestations is scarce, as for sarcoidosis in general, and treatment is guided by severity of progressive organ impairment and signs of ongoing inflammation. Inflammation includes aberrant production of cytokines such as TNF along reduced expression of CTLA4 (39) and JAK/STAT pathway activation signatures in patients with sarcoidosis. TNFi have shown to be effective in randomised and observational studies (11, 12, 19, 40) and a *post-hoc* analysis has suggested that infliximab may be more efficient in treating extrapulmonary sarcoidosis. Reduced expression of CTLA4-IgG from lung studies in sarcoidosis, followed by hyperreactive T-cells may suggest that abatacept can downregulate this hyperreactivity in lung sarcoidosis. Inhibition of JAK may also exert its effect by inhibiting STAT3 signalling pathway, which is thought to be a key mediator of T_H17 cell differentiation and hereby reduce inflammation and fibrosis (39, 41).

In this study, we used drug survival as our main outcome. Drug survival, in our opinion, may indirectly account for both efficacy and safety of a drug used to treat highly heterogenic organ manifestations. Next, as appropriate, treatment responses were determined in clinical conferences with specialists from different subspecialties who were experienced in the clinical presentation and management of sarcoidosis patients, and thus, the decision on treatment response was reached interdisciplinary. We found response rates for third line treatment of 44–100% for all organ manifestations. For fourth line treatment there was no observed clinical response on CNS or bone manifes-

tations, however also a very limited number of observations (n=3).

The percentages of patients using concomitant MTX were relatively low (around 25%) in both groups. This is unusual, and one may hypothesise that this may be a result of channelling bias, *i.e.* that the cohort include patients with intolerance to previous biological drugs, and possibly also to MTX. It was a goal to discontinue or at least reduce GC, but it was not a goal to discontinue MTX, which we used as first line drug. MTX would be discontinued in the case of lack of effect or side effects, but patients who reached the third (abatacept) and fourth (JAK inhibition) treatment lines would continue methotrexate, if it had not been discontinued previously.

In Denmark, biological treatment is considered in sarcoidosis patients with an insufficient treatment response to DMARDs (mainly MTX) in adequate doses.

Usually, the first biological treatment is a TNFi, and if the response is insufficient after 3–4 months, the patient is switched to a different biological drug. Treatment with biological drugs can only be prescribed and administered by hospital departments of rheumatology. The expenses are reimbursed by the public health system. In the present study, these structural aspects are likely to reduce confounding by indication.

Limitations to this study include missing data arising from varying time points for follow-up visits and varying diagnostic tests performed due to the non-protocolised setting of the study. Consequently, common clinical diagnostics /lung function tests, prednisolone dosage and sIL2r were individualised accordingly. We acknowledge that this assessment of treatment response was not standardised and/or validated.

Due to the non-randomised setting, the very small datasets and sequential use of the drugs (>80% of patients treated with tofacitinib had been treated with abatacept prior), it was not possible meaningfully to compare the drug survivals and response rates of abatacept and tofacitinib. Different treatment responses between individual treatment responses for abatacept and tofacitinib may be related to the specific pathways involved in the inflammatory process in each individual patient and must be addressed in larger future studies.

In conclusion, we find that patients treated with both abatacept and tofacitinib had long drug survival, achieved high response rates and that both drugs represent good and safe therapeutic options in sarcoidosis patient's refractory to previous TNFi therapy.

References

1. GERKE AK: Treatment of sarcoidosis: a multidisciplinary approach. *Front Immunol* 2020; 11: 545413. https://doi.org/10.3389/fimmu.2020.545413
2. BAUGHMAN RP, VALEYRE D, KORSTEN P *et al*.: ERS clinical practice guidelines on treatment of sarcoidosis. *Eur Respir J* 2021; 58(6). https://www.ncbi.nlm.nih.gov/pubmed/34140301
3. PARAMOTHAYAN NS, LASSERSON TJ, JONES PW: Corticosteroids for pulmonary sarcoidosis. *Cochrane Database Syst Rev* 2005; 2005(2):Cd001114. https://doi.org/10.1002/14651858.cd001114.pub2
4. SCHUTT AC, BULLINGTON WM, JUDSON MA: Pharmacotherapy for pulmonary sarcoidosis: a Delphi consensus study. *Respir Med* 2010; 104(5): 717-23. https://doi.org/10.1016/j.rmed.2009.12.009
5. MELANI AS, SIMONA A, ARMATI M, D'ALESSANDRO M, BARGAGLI E: A comprehensive review of sarcoidosis diagnosis and monitoring for the pulmonologist. *Pulm Ther* 2021; 7(2): 309-24
6. MILMAN N, GRAUDAL N, GRODE G, MUNCH E: No effect of high-dose inhaled steroids in pulmonary sarcoidosis: a double-blind, placebo-controlled study. *J Intern Med* 1994; 236(3): 285-90. https://doi.org/10.1111/j.1365-2796.1994.tb00798.x
7. BAUGHMAN RP, WINGET DB, LOWER EE: Methotrexate is steroid sparing in acute sarcoidosis: results of a double blind, randomized trial. *Sarcoidosis Vasc Diffuse Lung Dis* 2000; 17(1): 60-6.
8. BALTZAN M, MEHTA S, KIRKHAM TH, COSIO MG: Randomized trial of prolonged chloroquine therapy in advanced pulmonary sarcoidosis. *Am J Respir Crit Care Med* 1999; 160(1): 192-7. https://doi.org/10.1164/ajrccm.160.1.9809024
9. ZHANG H, COSTABEL U, DAI H: The role of diverse immune cells in sarcoidosis. *Front Immunol* 2021; 12: 788502. https://doi.org/10.3389/fimmu.2021.788502
10. TORIOLA SL, SATNARINE T, ZOHARA Z *et al*.: Recent clinical studies on the effects of tumor necrosis factor-alpha (TNF-alpha) and janus kinase/signal transducers and activators of transcription (JAK/STAT) antibody therapies in refractory cutaneous sarcoidosis: a systematic review. *Cureus* 2023; 15(9): e44901. https://doi.org/10.7759/cureus.44901
11. MILMAN N, GRAUDAL N, LOFT A, MORTENSEN J, LARSEN J, BASLUND B: Effect of the TNF-alpha inhibitor adalimumab in patients with recalcitrant sarcoidosis: a prospective observational study using FDG-PET. *Clin Respir J* 2012; 6(4): 238-47. https://doi.org/10.1111/j.1752-699x.2011.00276.x
12. ROSSMAN MD, NEWMAN LS, BAUGHMAN RP *et al*.: A double-blinded, randomized, placebo-controlled trial of infliximab in subjects with active pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2006; 23(3): 201-8.
13. PARISER RJ, PAUL J, HIRANO S, TOROSKY C, SMITH M: A double-blind, randomized, placebo-controlled trial of adalimumab in the treatment of cutaneous sarcoidosis. *J Am Acad Dermatol* 2013; 68(5): 765-73. https://doi.org/10.1016/j.jaad.2012.10.056
14. BAUGHMAN RP, LOWER EE, BRADLEY DA, RAYMOND LA, KAUFMAN A: Etanercept for refractory ocular sarcoidosis: results of a double-blind randomized trial. *Chest* 2005; 128(2): 1062-47. https://doi.org/10.1378/chest.128.2.1062
15. BROOS CE, VAN NIMWEGEN M, IN 'T VEEN JC *et al*.: Decreased cytotoxic T-lymphocyte antigen 4 expression on regulatory T cells and Th17 cells in sarcoidosis: double trouble? *Am J Respir Crit Care Med* 2015; 192(6): 763-5. https://doi.org/10.1164/rccm.201503-0635le
16. FRYE BC, RUMP IC, UHLMANN A *et al*.: Safety and efficacy of abatacept in patients with treatment-resistant SARCoidosis (ABASARC) - protocol for a multi-center, single-arm phase IIa trial. *Contemp Clin Trials Commun* 2020; 19: 100575. https://doi.org/10.1016/j.conctc.2020.100575
17. DAMSKY W, THAKRAL D, EMEAGWALI N, GALAN A, KING B: Tofacitinib treatment and molecular analysis of cutaneous sarcoidosis. *N Engl J Med* 2018; 379(26): 2540-46. https://doi.org/10.1056/nejmoa1805958
18. SCADDING JG: Prognosis of intrathoracic sarcoidosis in England. A review of 136 cases after five years' observation. *Br Med J* 1961; 2(5261): 1165-72. https://doi.org/10.1136/bmj.2.5261.1165
19. HOSTETTLER KE, STUDLER U, TAMM M, BRUTSCHE MH: Long-term treatment with infliximab in patients with sarcoidosis. *Respiration* 2012; 83(3): 218-24. https://doi.org/10.1159/000328738
20. CHARLSON ME, POMPEI P, ALES KL, MACKENZIE CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40(5): 373-83. https://doi.org/10.1016/0021-9681(87)90171-8
21. HAMMAM N, EVANS M, MORGAN E *et al*.: Treatment of sarcoidosis in US rheumatology practices: data from the American College of Rheumatology's Rheumatology Informatics System for Effectiveness (RISE) Registry. *Arthritis Care Res* (Hoboken) 2022; 74(3): 371-76. https://doi.org/10.1002/acr.24496
22. VENKATARAJ M, PIEROTTI T, SONDHI M, BALMURI S, HAYAT S: Novel approach in cardiac sarcoidosis: a case report highlighting abatacept as a promising treatment option. *Cureus* 2023; 15(9): e45805. https://doi.org/10.7759/cureus.45805
23. DAMSKY W, THAKRAL D, MCGEARY MK, LEVENTHAL J, GALAN A, KING B: Janus kinase inhibition induces disease remission

in cutaneous sarcoidosis and granuloma annulare. *J Am Acad Dermatol* 2020; 82(3): 612-21. https://doi.org/10.1016/j.jaad.2019.05.098
24. FRIEDMAN MA, LE B, STEVENS J *et al*.: Tofacitinib as a steroid-sparing therapy in pulmonary sarcoidosis, an open-label prospective proof-of-concept study. *Lung* 2021; 199(2): 147-53. https://doi.org/10.1007/s00408-021-00436-8
25. TALTY R, DAMSKY W, KING B: Treatment of cutaneous sarcoidosis with tofacitinib: a case report and review of evidence for Janus kinase inhibition in sarcoidosis. *JAAD Case Rep* 2021; 16: 62-64. https://doi.org/10.1016/j.jdcr.2021.08.012
26. KERKEMEYER KL, MEAH N, SINCLAIR RD: Tofacitinib for cutaneous and pulmonary sarcoidosis: a case series. *J Am Acad Dermatol* 2021; 84(2): 581-83. https://doi.org/10.1016/j.jaad.2020.10.016
27. COLLABORATIVE GROUP MISG: Glucocorticoid sparing in sarcoidosis using the Janus kinase (JAK) inhibitor tofacitinib. *Eur J Intern Med* 2022; 98: 119-21. https://doi.org/10.1016/j.ejim.2021.12.016
28. VERDEN A, DIMBIL M, KYLE R, OVERSTREET B, HOFFMAN KB: Analysis of spontaneous postmarket case reports submitted to the FDA regarding thromboembolic adverse events and JAK inhibitors. *Drug Saf* 2018; 41(4): 357-61. https://doi.org/10.1007/s40264-017-0622-2
29. ALVES C, PENEDONES A, MENDES D, MARQUES FB: Risk of cardiovascular and venous thromboembolic events associated with janus kinase inhibitors in rheumatoid arthritis: a systematic review and network meta-analysis. *J Clin Rheumatol* 2022; 28(2): 69-76. https://doi.org/10.1097/rhu.0000000000001804
30. DAMSKY W, WANG A, KIM DJ *et al*.: Inhibition of type 1 immunity with tofacitinib is associated with marked improvement in longstanding sarcoidosis. *Nat Commun* 2022; 13(1): 3140. https://doi.org/10.1038/s41467-022-30615-x
31. BELPERIO JA, SHAIKH F, ABTIN FG *et al*.: Diagnosis and treatment of pulmonary sarcoidosis: a review. *JAMA* 2022; 327(9): 856-67. https://doi.org/10.1001/jama.2022.1570
32. SPAGNOLO P, ROSSI G, TRISOLINI R, SVERZELLATI N, BAUGHMAN RP, WELLS AU: Pulmonary sarcoidosis. *Lancet Respir Med* 2018; 6(5): 389-402. https://doi.org/10.1016/s2213-2600(18)30064-x
33. MARKATIS E, AFTHINOS A, ANTONAKIS E, PAPANIKOLAOU IC: Cardiac sarcoidosis: diagnosis and management. *Rev Cardiovasc Med* 2020; 21(3): 321-38. https://doi.org/10.31083/j.rcm.2020.03.102
34. SOHN DW, PARK JB: Cardiac sarcoidosis. *Heart* 2023; 109(15): 1132-38. https://doi.org/10.1136/heartjnl-2022-321379
35. BRADSHAW MJ, PAWATE S, KOTH LL, CHO TA, GELFAND JM: Neurosarcoidosis: pathophysiology, diagnosis, and treatment. *Neurol Neuroimmunol Neuroinflamm* 2021; 8(6):e1084. https://doi.org/10.1212/nxi.0000000000001084
36. BRADSHAW MJ, PAWATE S, KOTH LL, CHO TA, GELFAND JM: Neurosarcoidosis: pathophysiology, diagnosis, and treatment. *Neurol Neuroimmunol Neuroinflamm* 2021; 8(6): e1084. https://doi.org/10.1212/nxi.0000000000001084
37. GOSSELIN J, ROY-HEWITSON C, BULLIS SSM *et al*: Neurosarcoidosis: phenotypes, approach to diagnosis and treatment. *Curr Rheumatol Rep* 2022; 24(12): 371-82. https://doi.org/10.1007/s11926-022-01089-z
38. VALEYRE D, PRASSE A, NUNES H, UZUNHAN Y, BRILLET PY, MÜLLER-QUERNHEIM J: Sarcoidosis. *Lancet* 2014; 383(9923): 1155-67. https://doi.org/10.1016/s0140-6736(13)60680-7
39. GRUNEWALD J, GRUTTERS JC, ARKEMA EV, SAKETKOO LA, MOLLER DR, MULLER-QUERNHEIM J: Sarcoidosis. *Nat Rev Dis Primers* 2019; 5(1): 45. https://doi.org/10.1038/s41572-019-0096-x
40. JUDSON MA, BAUGHMAN RP, COSTABEL U *et al*: Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. *Eur Respir J* 2008; 31(6): 1189-96. https://doi.org/10.1183/09031936.00051907
41. CELADA LJ, KROPSKI JA, HERAZO-MAYA JD *et al*.: PD-1 up-regulation on $CD4^+$ T cells promotes pulmonary fibrosis through STAT3-mediated IL-17A and TGF-β1 production. *Sci Transl Med* 2018; 10(460). https://doi.org/10.1126/scitranslmed.aar8356