

Sarcoidosis of the liver: to treat or not to treat?

G.J. Bakker[#], Y.C.L. Haan[#], L.J. Maillette de Buy Wenniger, U. Beuers^{*}

Department of Gastroenterology & Hepatology, Tytgat Institute for Liver and Intestinal Research, University of Amsterdam, Amsterdam, the Netherlands, ^{*}corresponding author: e-mail: u.h.beuers@amc.uva.nl, [#]both authors contributed equally to this paper

ABSTRACT

Introduction: Sarcoidosis is a non-caseating, granulomatous disease of incompletely understood aetiology that can affect nearly all organs including the liver. Hepatic involvement is thought to occur in 50-90% of patients but may remain undiagnosed in many cases. Evidence-based guidelines for the treatment of sarcoidosis of the liver are lacking. Patients usually receive no treatment or are treated pragmatically with corticosteroids. However, treatment with systemic corticosteroids has had mixed results. The use of ursodeoxycholic acid (UDCA) in the treatment of sarcoidosis-associated cholestasis has been reported by several groups, and is empirically prescribed to sarcoidosis patients with hepatic involvement.

Methods: The effect of UDCA on symptoms and serum liver tests was investigated in a retrospective cohort study in which hepatic sarcoidosis patients had received either no treatment, prednisolone treatment or UDCA treatment. For all patients, laboratory results on ASAT, ALAT, AP and GGT were collected. Patients described the severity of their symptoms before and after treatment on a numerical scale.

Results: A total of 17 patients participated in the study. Serum liver tests in the group treated with UDCA had improved as compared with the other groups. Also, symptomatic improvement of pruritus and fatigue was reported in the group treated with UDCA.

Conclusion: This retrospective cohort study supports the empirical first-line use of UDCA in the treatment of sarcoidosis of the liver, especially in symptomatic patients. Prospective randomised trials are needed to adequately support this concept.

KEYWORDS

Sarcoidosis, liver, cholestasis, ursodeoxycholic acid

INTRODUCTION

Sarcoidosis is a systemic non-caseating granulomatous disease of as yet enigmatic aetiology which can affect nearly every organ.¹ Sarcoidosis is diagnosed at all ages but incidence peaks between 20 and 40 years.² Women are more often affected than men.²⁻⁷ The prevalence in the United States was reported in a wide range between 1 and 40 per 100,000.⁸ Its exact prevalence in the Netherlands is unknown, but is expected to be in the same order of magnitude. Although sarcoidosis is described in all ethnicities,^{2,3} its prevalence in African descendants is at least two to threefold higher than in Caucasians.^{2,6,7,9,10} Remarkably, disease severity also differs between ethnicities with involvement of skin, liver, eye and bone marrow more frequently observed in patients of African origin than in Caucasians.²⁻⁶ The lungs are affected in up to 90% of patients.^{11,12}

Liver involvement in patients with sarcoidosis ranges from 50 to 90%,^{4,9,13} but may go unnoticed in case of mild serum liver test abnormalities in the absence of liver-related symptoms. Conversely, elevated serum liver tests and symptoms related to hepatic involvement may be among the earliest manifestations of this systemic disease.⁴ Clinical symptoms of liver involvement include fatigue, pruritus and right upper quadrant abdominal pain in 15%⁹ and jaundice, weight loss and fever in 5% of patients.^{4,9} Serum liver tests usually reveal a cholestatic pattern with elevation of serum alkaline phosphatase (AP) in up to 90% and often only mildly elevated serum transaminases in 50-70%.^{4,14-16} Decompensated liver disease with portal hypertension and development of varices, variceal bleeding, ascites, or hepatic encephalopathy are late complications of hepatic sarcoidosis. The risk factors for development of end-stage liver disease due to sarcoidosis of the liver are unclear, as is the exact percentage of patients who reach this stage after a chronic course of disease.

Evidence-based guidelines for treatment of sarcoidosis of the liver do not exist. Most patients remain untreated. Corticosteroids, which represent the standard treatment of advanced pulmonary, cerebral or ocular sarcoidosis, were administered in case series. However, treatment with systemic corticosteroids has had mixed results.^{13,17} Apparently, corticosteroids do not prevent development of portal hypertension.^{4,17,18} Thus, systemic corticosteroids have been recommended only when organ function is imminently threatened.¹³ The effects of targeted anti-TNF- α therapy, which in one randomised study has shown to be marginally effective in sarcoidosis of the lung when disease activity prohibited the tapering of corticosteroids,¹⁹ has not been evaluated for the hepatic manifestation.

Ursodeoxycholic acid (UDCA) has well-known anticholestatic and hepatoprotective properties²⁰ and is the evidence-based standard treatment of cholestatic disorders such as primary biliary cirrhosis²¹ and intrahepatic cholestasis of pregnancy,²² but is also applied in a number of other orphan chronic progressive cholestatic disorders for which no long-term therapeutic trials of adequate size and dose exist.²³ Although randomised controlled trials have not been performed in sarcoidosis of the liver, UDCA has been widely used.^{14,24,25} This practice is supported by the favourable safety profile of UDCA,¹⁴ and its efficacy in improving serum liver tests in hepatic sarcoidosis^{14,24,25} but not by improvement of validated surrogate markers of long-term prognosis.

In order to gain more insight into treatment response and pathogenesis of hepatic sarcoidosis, including the use of UDCA in these patients, we retrospectively investigated a group of 25 patients diagnosed with liver sarcoidosis in a tertiary care centre in the Netherlands (the Academic Medical Centre (AMC) in Amsterdam). Patients were interviewed and serum liver tests were analysed to determine subjective and biochemical effects of different treatment options. Patients had received either no treatment or treatment with prednisolone or UDCA.

METHODS

Design

In this retrospective cohort study, we investigated the effect of UDCA on symptoms and serum liver tests. A list of all patients known to be followed with sarcoidosis of the liver in the hepatology outpatient clinic of the AMC in Amsterdam, the Netherlands (a tertiary hospital) in the past five years was used to select patients for inclusion in this study. The following inclusion criteria were applied: patients diagnosed with sarcoidosis of the liver, regardless

of this being classical liver disease in which the disease is only manifest in the liver, or generalised disease, who were alive at the time of inclusion (1 January 2010). Patients whose aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase (AP) and gamma glutamyltransferase (GGT) values were not available for all time points outlined below were excluded from the biochemical response to treatment analysis.

Effect of treatment on clinical symptoms

To obtain information about the effects of treatment on liver-related symptoms, all patients were approached for active participation in this study. Those patients who provided informed consent were invited in person to the outpatient clinic to answer a series of questions on their demography and life history as well as on the course of their clinical symptoms. They were asked to retrospectively score their fatigue and itch as subjective measures of the efficacy of treatment, grading these symptoms on a scale ranging from 0 to 10 (0 being no fatigue or no itch, respectively; 10 being the worst imaginable fatigue or itch, respectively).

As the study only included face-to-face interviews and no medical interventions, the local medical ethics committee waived the necessity of a full medical ethical evaluation. Data were analysed using GraphPad Prism version 5.01. For statistic analyses paired t-tests were performed to evaluate the significance of changes over time within the treatment groups.

Biochemical response to treatment

In a second part of the study we retrospectively collected data on liver biochemistry before and after treatment. Demographic data, date of diagnosis, applied treatment and date of start of treatment were obtained from the medical files of the selected patients. Patients were grouped as having received either no treatment, prednisolone treatment or UDCA treatment. For all patients, serum liver tests (ASAT, ALAT, AP and GGT) before start of treatment, at start of treatment ($t = 0$) and at three months after start of treatment ($t = +3$ months) were collected. The time points used to determine biochemistry before start of treatment depended on the available laboratory data. The difference between start of treatment and available data from before start of treatment ranged from 3 to 188 days (median 49 days). For the group that received no treatment, the date of the first available laboratory investigation after onset of symptoms was used as the first time point.

Statistical evaluation

Data are given as mean $\pm$ SD or median. Clinical and biochemical results at start of treatment and after three months were analysed with a paired t-test. $P < 0.05$ was considered significant.

RESULTS

Study cohort

A total of 25 patients diagnosed with sarcoidosis of the liver were identified and approached by a patient information letter with background information to participate in the study. Contact was established with 20 patients, 17 of whom agreed to participate. These patients were invited to the hepatology outpatient clinic and asked to report their liver-related symptoms before treatment and after three months of treatment. One patient did not show up at the interview. Of the initial 25 patients, 17 met the criteria for inclusion in the biochemical analysis (figure 1).

Of the 16 interviewed patients, their country of birth was: Suriname (n=10), the Netherlands (n=2), Ghana (n=2), Curacao (n=1) and Morocco (n=1). The ethnic affiliation of 23 of 25 patients could be traced, Creole (n=13), Hindustani (n=4), Caucasian and Ghanaian (n=2 each) and Arabic (n=1). Concerning direct heredity of the disease we found that two patients had one second-degree relative diagnosed with sarcoidosis, and one patient had one first-degree and four second-degree relatives diagnosed with sarcoidosis. Questions regarding allergies/hypersensitivities and the exposure to potentially harmful substances did not yield any new insights. In nine patients the sarcoidosis was only manifest in the liver. A total of seven patients had extrahepatic manifestations of sarcoidosis. Reported comorbidities included: arterial hypertension (n=6), diabetes type 2 (n=5; 2 prednisolone-induced), sickle cell anaemia (n=1), and HIV positivity (n=1). In one patient a liver transplantation was performed during the course of the disease.

Reported liver-related symptoms and change during treatment

A total of ten patients reported liver-related symptoms. The most common liver-related symptoms were fatigue (n=9) and itch (n=8). Patients were asked to rate their fatigue and itch before and three months after treatment was initiated on a visual analogue scale from 0 to 10 (0 = lowest, 10 = highest). Figure 2 shows the effect of no treatment, prednisolone and UDCA treatment on fatigue, and figure 3

Figure 2. Evaluation of fatigue symptoms scored on an intensity scale and change after three months of therapy (intensity of 0 representing no symptoms and 10 representing the maximum imaginable intensity of the symptom). Only patients treated with UDCA reported a significant reduction of fatigue three months after start of treatment. * $p < 0.05$ (paired t-test)

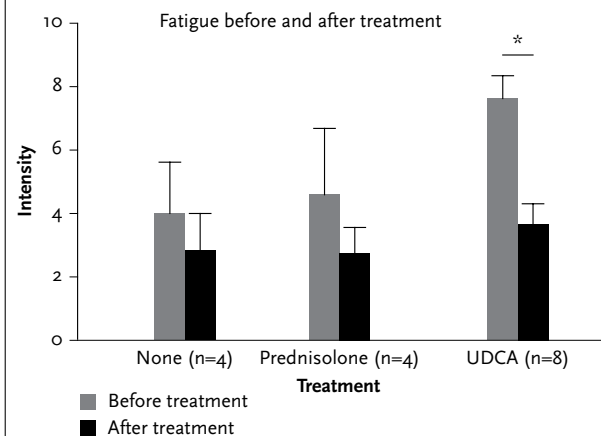


Figure 1. Flowchart of the study

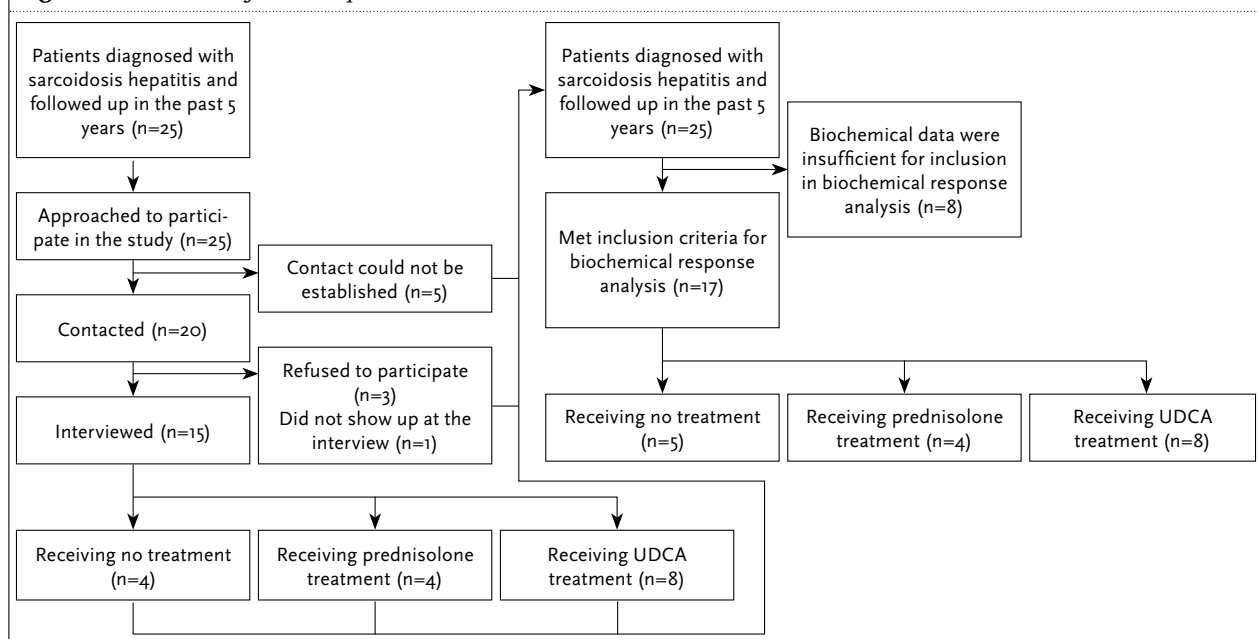
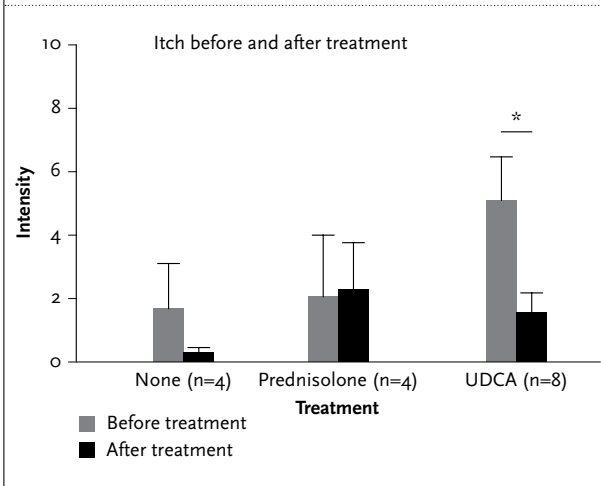


Figure 3. Evaluation of fatigue symptoms scored on an intensity scale and change after three months of therapy (intensity of 0 representing no symptoms and 10 representing the maximum imaginable intensity of the symptom). Only patients treated with UDCA reported a significant reduction of itch three months after start of treatment. * $p < 0.05$, paired t-test



shows the effect of treatment on itch. The average ratings of fatigue of patients treated with prednisolone changed from 4.1/10 to 2.8/10 ($p = 0.51$), and the ratings of itch changed from 2.0/10 to 2.3/10 (significance of change within treatment group $p = 0.82$). The average ratings of itch of patients treated with UDCA changed from 5.0/10 to 1.5/10 after treatment ($p < 0.05$). The patients receiving no treatment were asked to rate their fatigue and itch at the time of diagnosis and at the time of the interview ($p = 0.39$). Of the eight patients who received UDCA, the only reported side effect was short-term diarrhoea (reported by two patients, not leading to treatment discontinuation).

Patients included in the biochemical response analysis

Seventeen patients met the criteria for inclusion in the biochemical response analysis (figure 1). Based on the medication history documented in the medical files and the electronic medication information system, patients were grouped as those who did not receive treatment ($n = 5$), those who received prednisolone treatment ($n = 3$, initial dose up to 30 mg/day before tapering down), and those who received UDCA treatment ($n = 9$, doses of 10-15 mg/kg/day). Patient characteristics are summarised in table 1. Table 2 shows the baseline serum values of ALAT, ASAT, AP and GGT of the patients.

Biochemical response to treatment

The biochemical response to prednisolone and UDCA treatment in patients with sarcoidosis of the liver was compared with the course of biochemical tests of patients that did not receive any treatment (figures 4 and 5).

Table 1. Characteristics of 17 patients with sarcoidosis of the liver included in the biochemical response analysis

	Total (n=17)	No treatment (n=5)	Prednisolone (n=3)	UDCA (n=9)
Median age, years (range)	50 (37-77)	46 (42-77)	61 (51-75)	48 (37-59)
Sex (%)				
- Male	10 (59%)	2 (40%)	3 (100%)	5 (56%)
- Female	7 (41%)	3 (60%)	0 (0%)	4 (44%)

Table 2. Serum liver tests at start of treatment ($t = 0$) of patients included in the biochemical response analysis

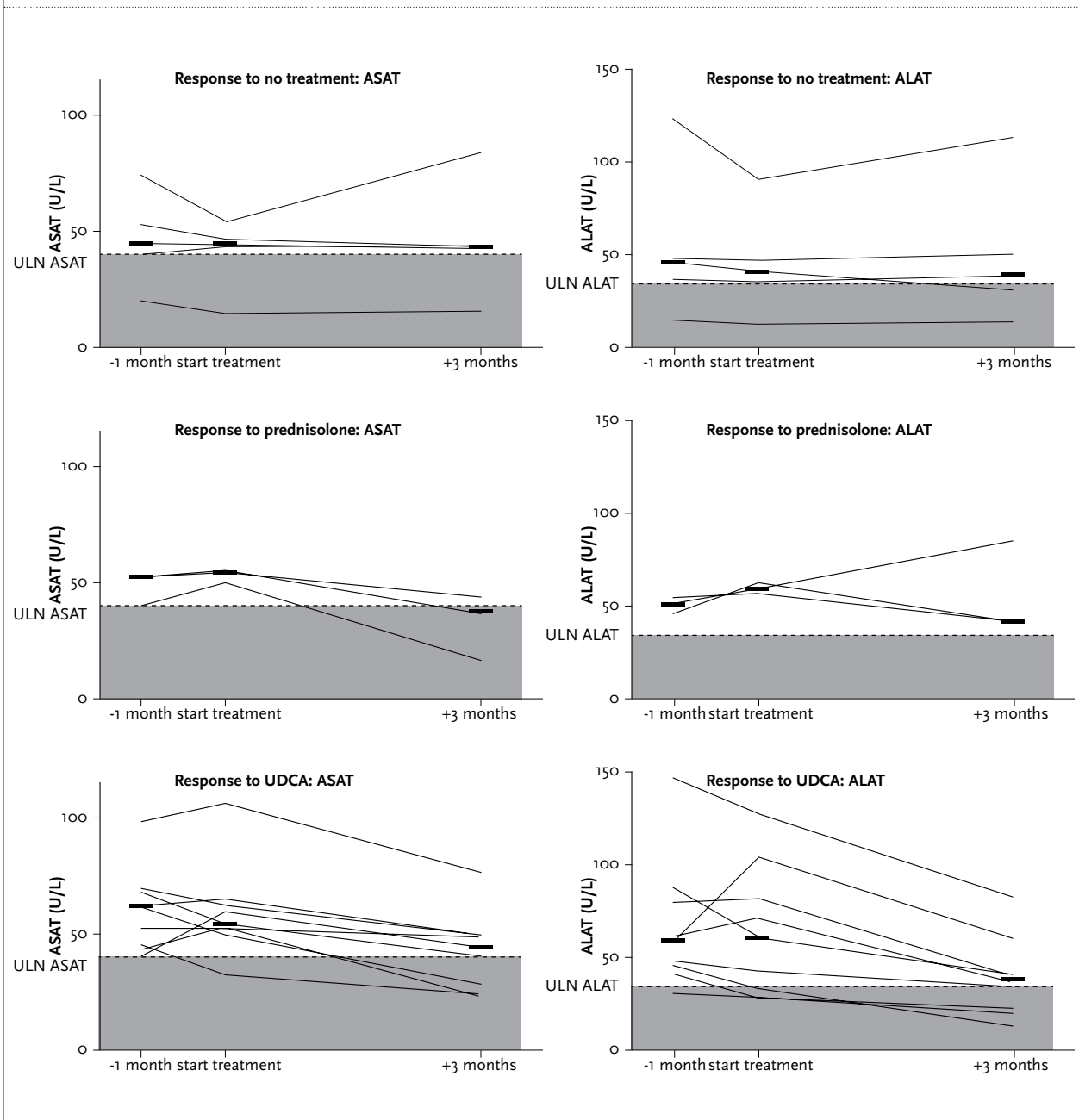
	Total (n=17)	No treatment (n=5)	Prednisolone (n=3)	UDCA (n=9)
ASAT [IU/l], median (range)	54 (15-107)	44 (15-54)	55 (50-56)	55 (33-107)
ALAT [IU/l], median (range)	57 (12-128)	41 (12-90)	60 (57-63)	62 (29-128)
AP [IU/l], median (range)	325 (58-1161)	176 (58-438)	549 (198-1161)	363 (109-625)
GGT [IU/l], median (range)	340 (23-1544)	342 (23-644)	337 (317-1544)	337 (112-1119)

As compared with the values on day 1 of treatment ($t = 0$), we found a mean change of ASAT, ALAT, AP and GGT after three months of $-40.0\% \pm 23.6\%$, $-6.5\% \pm 42.0\%$, $-54.0\% \pm 41.3\%$ and $-15.2\% \pm 60.9\%$, respectively, in the group treated with prednisolone, of $-28.1\% \pm 13.1\%$, $-37.2\% \pm 14.2\%$, $-30.8\% \pm 27.4\%$ and $-41.1\% \pm 40.9\%$, respectively, in the group treated with UDCA; and a mean change of $+10.7\% \pm 25.6\%$, $+6.9\% \pm 18.9\%$, $-2.4\% \pm 9.0\%$ and $+4.4\% \pm 17.1\%$, respectively, in the group that did not receive any treatment aimed at the liver sarcoidosis. Within the treatment groups ASAT, ALAT, AP and GGT at $t = 3$ months as compared with $t = 0$ did not differ significantly for the no treatment and prednisolone groups, while serum liver tests were significantly lower in the UDCA group after three months of treatment ($p < 0.05$ for ASAT, ALAT, AP, GGT, paired t-tests).

DISCUSSION

Sarcoidosis of the liver is a barely studied and probably under-diagnosed manifestation of sarcoidosis. It may progress to cirrhosis and subsequent complications of portal hypertension. Patients often receive no treatment, or are pragmatically treated with corticosteroids. The present retrospective study compared the effects of prednisolone to those of the anticholestatic bile acid ursodeoxycholic acid (UDCA). The results suggest that UDCA improves

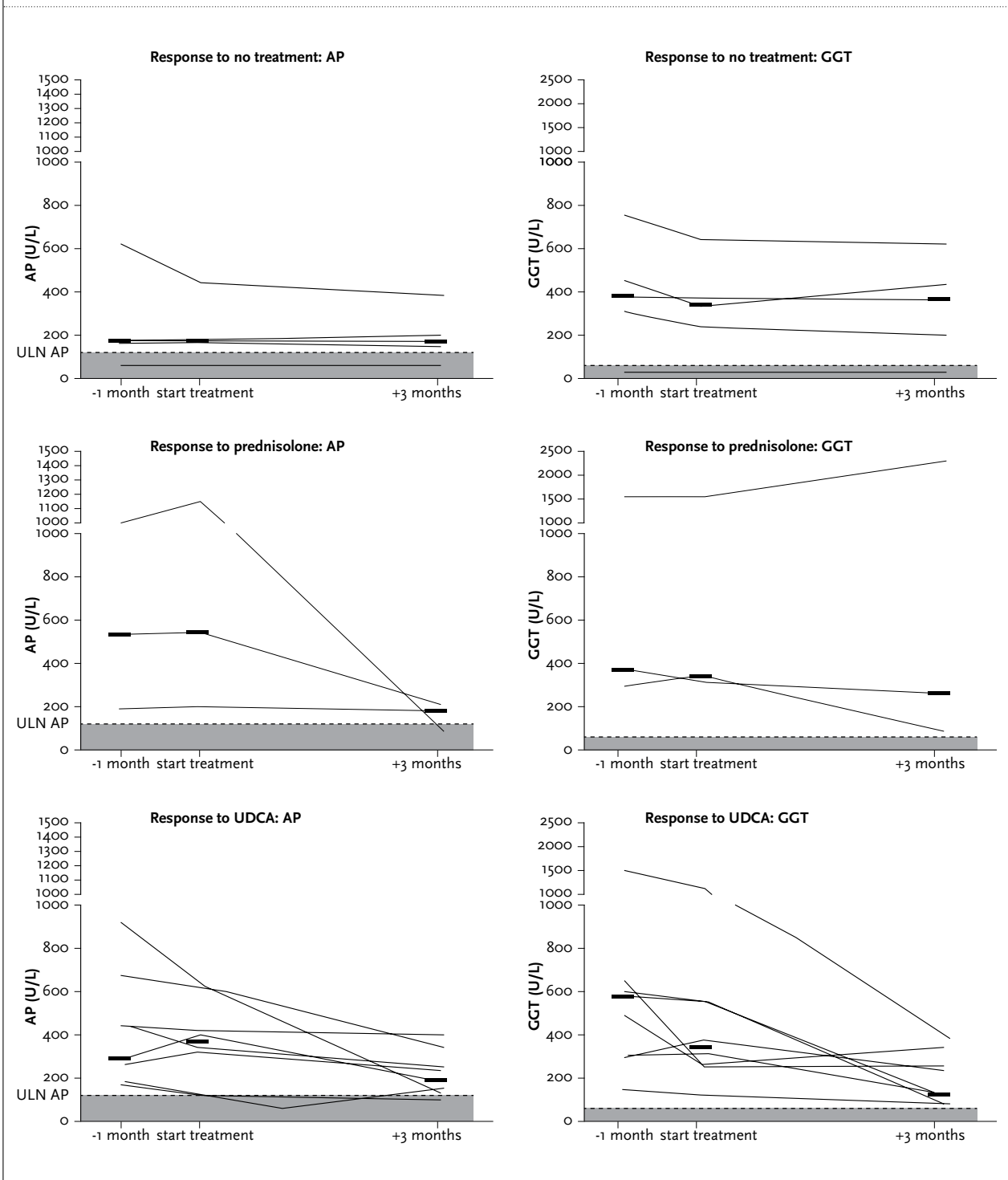
Figure 4. Biochemical response to treatment: ASAT and ALAT. Values for ASAT and ALAT are shown for all individual patients (thin lines), and median values are shown (thick horizontal bars) for $t = -1$ month, $t = 0$ and $t = +3$ months. ULN = upper limit of normal



not only serum liver tests, but also clinical symptoms of fatigue and pruritus in patients with sarcoidosis of the liver. The short-term effect of UDCA was superior to that of prednisolone in the cohort under study. The effect of corticosteroids on sarcoidosis of the liver has never been assessed in properly controlled trials.²⁶ Corticosteroids may be ineffective in improving serum liver tests as surrogate markers of cholestasis and tissue inflammation, and do not seem to prevent portal hypertension.^{4,17,18}

The rationale to use UDCA as a first-line drug and potential alternative to corticosteroid treatment in liver sarcoidosis is based on its beneficial effect in other chronic cholestatic liver diseases. UDCA is today regarded as standard treatment of primary biliary cirrhosis (PBC), a florid, destructive, non-purulent, granulomatous cholangitis.²³ In PBC, UDCA markedly improves serum liver tests and histological inflammatory activity, delays development of fibrosis, cirrhosis and complications of portal hypertension and normalises life expectancy in two

Figure 5. Biochemical response to treatment or no treatment: AP and GGT. Values are shown for all individual patients (thin lines). Median values (thick horizontal bars) are shown for $t = -1$ month, $t = 0$ and $t = +3$ months. ULN = upper limit of normal



of three treated patients.²³ UDCA is also regarded as the first-line treatment of intrahepatic cholestasis of pregnancy (ICP) where it improves serum liver tests in the mother, effectively reduces pruritus and may prolong time to often premature delivery in ICP towards normal.^{22,23} UDCA is a well-characterised drug with an exceptionally mild

side effect profile²⁷ when applied at therapeutic doses of 13-15(-20) mg/kg daily.

Mechanisms and sites of action of UDCA in cholestatic liver diseases have increasingly been unravelled.²⁷ UDCA acts as a posttranscriptional secretagogue both in hepatocytes and cholangiocytes and, thereby, stimulates

impaired hepatobiliary secretion.²⁷ In addition, UDCA has antiapoptotic properties and decreases bile cytotoxicity by reducing the levels of endogenous, potentially toxic hydrophobic bile acids.²⁸⁻³⁰

Our retrospective cohort study in a tertiary care centre provides support to the practice of treating symptomatic sarcoidosis of the liver with UDCA. Although the available literature shows no reduction of lesions in liver biopsies after treatment with either corticosteroids or UDCA,^{14,24,31} both treatment options seem to have a positive effect on liver biochemistry. Patients in our study group who received no treatment showed no significant changes in liver enzyme levels. These findings are in line with earlier case reports of patients with sarcoidosis of the liver who were successfully treated with UDCA.^{14,24,25}

The subjective effects of treatment are an important measure of drug efficacy. In this study we addressed this issue by asking patients to retrospectively score their fatigue and pruritus on a scale from 0 to 10 before treatment and at the moment of the interview. We found a consistent decrease of pruritus in the group treated with UDCA. Furthermore, subjective measures of fatigue had improved in both the group treated with corticosteroids and the group treated with UDCA. With the only reported side effect being transient diarrhoea in two out of eight patients treated with UDCA, this therapy appeared generally well tolerated.

The prevalence of sarcoidosis of the liver is at least two to threefold higher in African Americans than in Caucasians.^{2,6,7,9} This is supported by our findings, as the majority of our cohort has a Creole ethnicity (16/25). We did not find any conclusive explanation in the literature for this overrepresentation of individuals whose genealogy can at least in part be tracked back to forbears originating from the many peoples of Africa.

Our study has several important limitations. First of all, as sarcoidosis of the liver is a rare disease and as this was a single-centre study, we had to resort to a retrospective study design, and still our number of patients was limited. As the data were collected in a retrospective, cross-sectional manner several possibilities for bias exist. The interviews with patients were conducted at different time points during the follow-up of their disease, and patient answers may therefore be less reliable. Furthermore, as no standardised and validated questionnaires exist for the evaluation of liver sarcoidosis symptoms we relied on a self-composed questionnaire which has not been tested in other studies.

The collection of biochemical data is another possible source of bias. We collected data from the laboratory

database using the start date of therapy which was noted in the patient file or in the electronic patient record, and took the blood tests which most closely followed on a calculated date three months after this start date for our analysis of the biochemical response to therapy. In a possible follow-up study data acquisition should be performed in a prospective manner.

Another weakness of the study design is that it was not a prospective study and patients were not randomised to different treatment arms. To our knowledge no randomised controlled clinical trials evaluating the efficacy of different treatment modalities on biochemical and clinical parameters have ever been performed in patients with liver sarcoidosis and although it is understood that there will be substantial difficulties to obtain sufficient patient numbers, funding and organisational support it would be laudable if such a study could be initiated.

Despite the methodological shortcomings of this study, we feel that this rare patient group deserves a higher level of attention, both focusing on the aetiology of the disease and on the optimal therapeutic strategy for these individuals. In our data we see a definite indication that UDCA rather than prednisolone should be evaluated as a first-line drug for the treatment of non-cirrhotic patients with sarcoidosis of the liver.

CONCLUSION

Our retrospective cohort study in a tertiary care centre supports the empirical use of UDCA in the treatment of sarcoidosis of the liver, especially in patients suffering from pruritus. Probably due to its ability to improve impaired biliary secretion and bile flow, its effects in modulating the bile acid composition towards a more hydrophilic and less toxic bile acid pool and its anti-inflammatory effects, UDCA may aid to reduce cholestasis and hepatic and biliary inflammation. Given the very favourable side effect profile at therapeutic daily doses of 13-15(-20) mg/kg and relative low costs of treatment, there seem to be few objections to the pragmatic treatment of hepatic sarcoidosis with UDCA. Based on the published experience with UDCA, both in sarcoidosis and in other cholestatic disorders, we think that patients with hepatic sarcoidosis should be offered UDCA as a first line of treatment, especially in cases with predominant pruritic complaints, as long as no prospective randomised controlled trials are available.

CONFLICTS OF INTEREST

Dr. Beuers has received lecture fees from Falk Foundation, Gilead, Roche and Zambon. He received research support

for 2011 from Zambon. He signed a consultant agreement with Intercept (obeticholic acid). The other authors have no conflicts of interest to declare.

FUNDING

This work was partially supported by a PhD scholarship from the University of Amsterdam Academic Medical Center to LMdBW and a research grant 'Primary sclerosing cholangitis' from the Deutsche Crohn-Colitis-Vereinigung to UB.

REFERENCES

- Wirnsberger RM, de Vries J, Wouters EF, Drent M. Clinical presentation of sarcoidosis in The Netherlands an epidemiological study. *Neth J Med*. 1998;53:53-60.
- Rybicki BA, Major M, Popovich J, Jr., Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. *Am J Epidemiol*. 1997;145:234-41.
- Pietinalho A, Hiraga Y, Hosoda Y, Lofroos AB, Yamaguchi M, Selroos O. The frequency of sarcoidosis in Finland and Hokkaido, Japan. A comparative epidemiological study. *Sarcoidosis*. 1995;12:61-7.
- Maddrey WC, Johns CJ, Boitnott JK, Iber FL. Sarcoidosis and chronic hepatic disease: a clinical and pathologic study of 20 patients. *Medicine (Baltimore)*. 1970;49:375-95.
- Nagai S, Izumi T. Pulmonary sarcoidosis: population differences and pathophysiology. *South Med J*. 1995;88:1001-10.
- Gideon NM, Mannino DM. Sarcoidosis mortality in the United States 1979-1991: an analysis of multiple-cause mortality data. *Am J Med*. 1996;100:423-7.
- Rybicki BA, Iannuzzi MC. Epidemiology of sarcoidosis: recent advances and future prospects. *Semin Respir Crit Care Med*. 2007;28:22-35.
- Henke CE, Henke G, Elveback LR, Beard CM, Ballard DJ, Kurland LT. The epidemiology of sarcoidosis in Rochester, Minnesota: a population-based study of incidence and survival. *Am J Epidemiol*. 1986;123:840-5.
- Devaney K, Goodman ZD, Epstein MS, Zimmerman HJ, Ishak KG. Hepatic sarcoidosis. Clinicopathologic features in 100 patients. *Am J Surg Pathol*. 1993;17:1272-80.
- Caldwell SH, Harris DM, Patrie JT, Hespenheide EE. Is NASH underdiagnosed among African Americans? *Am J Gastroenterol*. 2002;97:1496-500.
- Lynch JP, 3rd, Sharma OP, Baughman RP. Extrapulmonary sarcoidosis. *Semin Respir Infect*. 1998;13:229-54.
- Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med*. 2001;164(10 Pt 1):1885-9.
- Ebert EC, Kierson M, Hagspiel KD. Gastrointestinal and hepatic manifestations of sarcoidosis. *Am J Gastroenterol*. 2008;103:3184-92; quiz 93.
- Alenezi B, Lamoureux E, Alpert L, Szilagyi A. Effect of ursodeoxycholic acid on granulomatous liver disease due to sarcoidosis. *Dig Dis Sci*. 2005;50:196-200.
- Israel HL, Margolis ML, Rose LJ. Hepatic granulomatosis and sarcoidosis. Further observations. *Dig Dis Sci*. 1984;29:353-6.
- Baughman RP. Sarcoidosis. Usual and unusual manifestations. *Chest*. 1988;94:165-70.
- Blich M, Edoute Y. Clinical manifestations of sarcoid liver disease. *J Gastroenterol Hepatol*. 2004;19:732-7.
- Valla D, Pessegueiro-Miranda H, Degott C, Lebrec D, Rueff B, Benhamou JP. Hepatic sarcoidosis with portal hypertension. A report of seven cases with a review of the literature. *Q J Med*. 1987;63:531-44.
- Baughman RP, Drent M, Kavuru M, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. *Am J Respir Crit Care Med*. 2006;174:795-802.
- de Caestecker JS, Jazrawi RP, Petroni ML, Northfield TC. Ursodeoxycholic acid in chronic liver disease. *Gut*. 1991;32:1061-5.
- Kaplan MM, Gershwin ME. Primary biliary cirrhosis. *N Engl J Med*. 2005;353:1261-73.
- Kondrackiene J, Beuers U, Kupcinskas L. Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. *Gastroenterology*. 2005;129:894-901.
- EASL Clinical Practice Guidelines: management of cholestatic liver diseases. *J Hepatol*. 2009;51:237-67.
- Becheur H, Dall'osto H, Chatellier G, et al. Effect of ursodeoxycholic acid on chronic intrahepatic cholestasis due to sarcoidosis. *Dig Dis Sci*. 1997;42:789-91.
- Baratta L, Cascino A, Delfino M, et al. Ursodeoxycholic acid treatment in abdominal sarcoidosis. *Dig Dis Sci*. 2000;45:1559-62.
- Vatti R, Sharma OP. Course of asymptomatic liver involvement in sarcoidosis: role of therapy in selected cases. *Sarcoidosis Vasc Diffuse Lung Dis*. 1997;14:73-6.
- Beuers U. Drug insight: Mechanisms and sites of action of ursodeoxycholic acid in cholestasis. *Nat Clin Pract Gastroenterol Hepatol*. 2006;3:318-28.
- Poupon RE, Chretien Y, Poupon R, Paumgartner G. Serum bile acids in primary biliary cirrhosis: effect of ursodeoxycholic acid therapy. *Hepatology*. 1993;17:599-604.
- Paumgartner G, Beuers U. Ursodeoxycholic acid in cholestatic liver disease: mechanisms of action and therapeutic use revisited. *Hepatology*. 2002;36:525-31.
- Dilger K, Hohenester S, Winkler-Budenhofer U, et al. Effect of ursodeoxycholic acid on bile acid profiles and intestinal detoxification machinery in primary biliary cirrhosis and health. *J Hepatol*. 2012;57:133-40.
- Nores JM, Chesneau MC, Charlier JP, de Saint-Louvent P, Nenna AD. [A case of hepatic sarcoidosis. Review of the literature]. *Ann Gastroenterol Hepatol (Paris)*. 1987;23:257-60.