



Chapter 5

Therapeutic approach of hepatic sarcoidosis

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Abstract

Purpose of review

Surveillance of hepatic involvement in sarcoidosis has not been standardized. Therefore, management of hepatic involvement is a clinical challenge. This review analyses published data on the pharmacological treatment of hepatic sarcoidosis.

Recent findings

Only 5–30% of patients with hepatic sarcoidosis display symptoms. Occasionally, hepatic sarcoidosis has a rapid progressive course with serious complications, stressing an appropriate and carefully timed therapeutic approach. Because symptomatic hepatic involvement is uncommon, therapeutic studies are scarce. Answers to the questions when to initiate which treatment are lacking. Case reports describe beneficial effects of glucocorticosteroids and the augmentation of cytotoxic and anti-tumor necrosis factor- α (TNF- α) therapy. However, because of small sample sizes, no meaningful conclusions could be drawn. In symptomatic hepatic sarcoidosis patients, it is recommended to start to treat the sarcoidosis with glucocorticosteroids, preceded by ursodeoxycholic acid when signs of cholestasis are present. Furthermore, antioxidants can be considered. In refractory cases or when glucocorticosteroids weaning is impossible, cytotoxic drugs or TNF- α inhibitor therapy should be started.

Summary

This review illustrates the importance of an appropriate therapeutic approach of sarcoidosis patients with hepatic involvement. It emphasizes the need for future studies to evaluate treatment options to avoid disease progression and hepatic complications.

Introduction

Sarcoidosis is a systemic inflammatory granulomatous disease of unknown etiology that is characterized by a highly variable pattern of disease presentation, involving more than one organ of the body, and by a wide range of disease severity.¹ The lung is the most commonly affected organ. The degree of impairment ranges from minimal disease to life-threatening fibrosis with the risk of pulmonary hypertension.² In many cases, lung involvement stabilizes or improves over the first 2 years, but may worsen and become chronic.³ Devastating extrapulmonary complications may become apparent.⁴

Estimates of liver involvement in sarcoidosis vary from 11 to 80% of cases, with lower rates based on symptomatic disease, whereas higher rates reported in studies performing random liver biopsies.⁵⁻¹⁰ In one study of 736 newly diagnosed sarcoidosis patients, liver disease was more frequent in women and African-Americans.¹¹ However, in a retrospective review of over 1400 patients, liver disease was more common in men.¹² Most individuals with liver disease present asymptotically with evidence of hepatomegaly, increased liver tests, or computed tomography (CT) scan abnormalities.^{6,10,13-15} Nonspecific symptoms, including abdominal pain, fever, and weight loss are common in sarcoidosis liver disease, although patients may also present with pruritis, jaundice and chronic cholestasis. Cirrhosis, portal hypertension, Budd-Chiari syndrome, and variceal bleeding occur rarely. In cases of known sarcoidosis, a probable diagnosis of liver disease may be established on the basis of increased alkaline phosphatase, or transaminases, or CT findings with characteristic nodules consisting of low-attenuating lesions of varied but usually small size.¹⁴⁻¹⁶ Occasionally, a liver biopsy may be obtained, although this is usually not necessary to confirm liver sarcoidosis.¹⁴ Ultrasound may be obtained to assess portal hypertension and to exclude other causes of liver disease. In general, a diagnosis of hepatic sarcoidosis must be confirmed and other causes of liver disease must be excluded.¹⁴

Because symptomatic hepatic sarcoidosis is uncommon, studies investigating course, progression, and response to treatment of this sarcoidosis manifestation are limited. Hence, management of sarcoidosis patients with liver involvement is mainly empirical. A protocol with recommendations for when treatment should be initiated, drug choice, dosage, and appropriate duration of the therapy does not exist. Therefore, the purpose of this review is to analyse published data on the effectiveness of pharmacological treatment and to combine these data into recommendations for the therapeutic approach of hepatic sarcoidosis.

Methods

A computerized search of the literature from 1965 until 2012 was performed using the search terms 'sarcoidosis', 'liver' or 'hepatic', and 'therapy' or 'treatment'.

Unfortunately, few hits were identified. Reference lists of relevant studies were checked to identify additional research not found by database search.

Selection criteria

Studies included for evaluation met the following criteria: the objective was to evaluate the effect of pharmacological treatment on disease course, progression, and complications; the population consisted of sarcoidosis patients with (among others) liver involvement; and the study was published in English.

Results

Most hepatic sarcoidosis patients do not require therapy as spontaneous remission is seen in the majority of cases.^{14,17} However, as mentioned previously, in some patients hepatic sarcoidosis can be a rapid progressive disease with the occurrence of complications in which timely implemented therapy might lead to preservation of liver function and restriction or avoidance of hepatic complications.^{5,6,10,12,13,18-22} In a retrospective study by Cremers et al.²³ liver test abnormalities were present in 204 of the 837 (24.4%) studied patients, among which 127 (15.2%) were suspected of having hepatic sarcoidosis. Moderate and severe liver test abnormalities seemed to be associated with more advanced histopathological disease.^{12,18,23,24} For patients with moderate or severe liver test abnormalities, a liver biopsy may be useful.

Pathogenesis

Sarcoidosis appears to be a multifactorial disease in which immunological, genetic, environmental, and oxidative stress factors play a role.^{1,2,5,25} Several immunological factors are involved in granuloma formation: after contact with antigenic material, predominant T helper 1 (Th1) cytokines and chemokines are released leading to the expression of, among others, tumor necrosis factor-alpha (TNF- α), facilitating granuloma formation.^{20,22} The formed granuloma can resolve spontaneously, but may persist and lead to a chronic inflammatory status.^{20,22} Genetic factors are likely to be involved in the pathogenesis.²⁶⁻²⁹ The nature of the antigens that stimulate the Th1 response are thought to be possibly infectious, although there is no definite evidence for specific micro-organisms.^{8,20,22,30} Oxidative stress, caused by reactive oxygen species (ROS) and low endogenous antioxidant levels, is suggested to be involved in initiating and mediating the inflammatory process in sarcoidosis.^{25,31,32} ROS are able to promote inflammation by activating transcription factors that induce pro-inflammatory cytokines and chemokines.^{25,32-34}

Pharmacological treatment

First, the sarcoidosis should be treated adequately. In general, that is enough to ensure the liver test abnormalities improve as well. Pharmacological treatment options when progressive granulomatous liver disease is present, include antioxidants, ursodeoxycholic acid (UDCA), and glucocorticosteroids.^{22,25,35} Glucocorticosteroids are considered first-line treatment option.²² In case of steroid-resistant sarcoidosis (disease progression during glucocorticosteroid treatment), second-line treatment options involve azathioprine (AZA), methotrexate (MTX), cyclosporine, cyclophosphamide, pentoxifylline (POF), thalidomide, or TNF- α inhibitors. Second-line agents can be used as steroid-sparing treatment as well.³⁶

Antioxidants

Recent studies suggest a beneficial effect of the antioxidant quercetin in patients with sarcoidosis of the lungs.³² It has been suggested that ROS play a crucial role in the chronic inflammation causing fibrosis in interstitial lung diseases, by the indirect evidence that two antioxidants are protective.³⁷ We noticed an improvement of liver test abnormalities with glutathione 600 mg 3 times a day, but these observations should be tested in a larger cohort of patients.

Ursodeoxycholic acid

Hepatic sarcoidosis can be associated with chronic cholestasis. The mechanism of UDCA in cholestasis includes inhibition of intestinal absorption and increasing biliary secretion of cholic and chenodeoxycholic acids, and immune response modulation with decreased cytokine and immunoglobulin production.³⁸⁻⁴⁰ UDCA also decreases human leukocyte antigen (HLA) class I antigen on hepatic surfaces and HLA class II antigen on cell membranes of biliary duct epithelial cells.^{38,41-43} Some case reports showed a beneficial effect of UDCA in sarcoidosis (Table 5.1).^{5,6,38,41,44-54} No improvement was seen histologically, but because of absence of progression of liver disease, UDCA may delay complications. UDCA should be administered at 10 mg/kg per day (300 mg orally twice daily).¹⁷ Reported side-effects are shown in Table 5.2.^{20,55}

Table 5.1 Overview of available studies on different pharmacological treatment options in hepatic sarcoidosis.

Authors	Patients treated (n)	Patients responding (n)	Organ involvement	Combi/mono therapy	Dosage	Symptoms/signs prior to therapy	Effect therapy
Ursodeoxycholic acid							
Becheur et al. ³⁸	1	1	Liver, skin, mediastinum	Mono therapy	10 mg/kg per day, intermittent during resp. 6, 15, and 22 months	Fatigue, pruritus, abdominal pain, LT abnormalities	Improvement of symptoms and LTs during treatment, relapse after discontinuation, stability in histological features
Baratta et al. ⁴⁴	1	1	Liver	Mono therapy	10 mg/kg per day, 6 months	Nausea, pruritus, vomiting, hepatosplenomegaly, LT abnormalities	Resolution of symptoms, decrease in hepatosplenomegaly, improvement of LTs after 6 months, stability in histology
Mueller et al. ⁵	1	0	Liver, skin, colon, kidney	Mono therapy	3 g per day, 1 month	Fatigue, weight loss, hepatomegaly, LT abnormalities	No effect on LTs
Alenezi et al. ⁴¹	1	1	Liver, stomach, skin	Mono therapy	10 mg/kg per day, 69 months	No symptoms, hepatomegaly, LT abnormalities	Improvement of hepatomegaly and LTs (10–15% of initial) after 6 months of therapy, stability histology
Azathioprine							
Kennedy et al. ⁶	2	2	Liver, unknown	Combination with prednisone	Unknown	LT abnormalities, symptoms unknown	Normalization of LTs
Malhotra et al. ⁴⁵	1	1	Liver	Combination with prednisone 40 mg per day	Unknown, 12 months	Abdominal pain and distention, fever, ascites, LT abnormalities, liver cirrhosis, hepatosplenomegaly	Resolution of clinical symptoms, improvement of LTs to near normal
Methotrexate							
Lower and Baughman ⁴⁶	2	2	Liver, other organs unknown	Combination with prednisone	Unknown	LT abnormalities, symptoms unknown	Improvement of LTs
Kennedy et al. ⁶	2	2	Liver	Combination with prednisone	Unknown	LT abnormalities; symptoms unknown	Normalization of LTs
Leflunomide							
Sahoo et al. ⁴⁷	1	1	Liver, lung, cutaneous, ocular, sinonasal	Monotherapy	20 mg per day	LT abnormalities	

Authors	Patients treated (n)	Patients responding (n)	Organ involvement	Comb/mono therapy	Dosage	Symptoms/signs prior to therapy	Effect therapy
Cyclosporine							
Casavilla et al. ⁴⁸	9	9	Liver, followed by liver transplantation, involvement other organs unknown	Monotherapy, prevention of allograft rejection and sarcoidosis recurrence after liver transplantation	Unknown, 4 years		Prevention of hepatic sarcoidosis recurrence
Cyclophosphamide							
Das et al. ⁴⁹	1	1	Liver	Combination with prednisone	100 mg per day, 3 years	Fever, night sweats, weight loss, LT abnormalities, not responding to other second-line agents	Improvement of LTs, development of renal cell carcinoma possibly because of cyclophosphamide use
Pentoxifylline							
No studies on the treatment of hepatic sarcoidosis are available							
Thalidomide							
Nguyen et al. ⁵⁰	3	1	Liver, cutaneous and other organ involvement	1 monotherapy, 2 combination therapy with corticosteroids	100–200 mg per day, 7–12 months	Unknown	Improvement of skin and LTs
Infliximab							
Ulbricht et al. ⁵¹	1	1	Liver, lung, joints	Combination with prednisone (20 mg per day)	3 mg/kg at week 0, 2, 6, every 8 weeks thereafter	Fever, dyspnea, arthritis, lung and liver granulomas, no LT abnormalities	Reduction of fever, dyspnea, arthralgia, remission hepatic granulomas
Doty et al. ⁵²	1	1	Liver	Combination with prednisone (30 mg per day) and methylprednisolone (16 mg per day)	5 mg/kg at week 0, 2, 6; thereafter prednisolone 16 mg per day	Fatigue, fever, night sweats, pruritus, right upper quadrant abdominal pain, hepatomegaly, jaundice, LT abnormalities	Improved fatigue, pruritus, pain, resolution hepatomegaly and jaundice, improvement of LTs

Authors	Patients treated (n)	Patients responding (n)	Organ involvement	Combi/mono therapy	Dosage	Symptoms/signs prior to therapy	Effect therapy
Saleh et al. ⁵³	3	2	Liver, skin, nervous system	Combination with prednisone	3 mg/kg at week 0,2,4,6, 10, and 14, every 8 weeks thereafter if necessary	Fever, weight loss, dizziness, memory loss, ataxia, skin involvement, elevated ALP	Skin lesions improved, ALP decreased, CT brain improved, died of abdominal bleeding
Judson et al. ⁵⁴	15 (placebo n=3)	7	Liver Multisystemic	Unknown Combination with prednisone	3 mg/kg or 5 mg/kg at 0,2,6,12,18, and 24 weeks	Abdominal pain, intra-abdominal lymphadenopathy, splenomegaly, skin lesions LT abnormalities Not described in detail (combination of clinical presentation, laboratory and radiological findings)	Improvement of abdominal pain and lymphadenopathy, symptoms recurred 2 months after sixth injection Improvement of fatigue and LTs Improvement in ePOST ^a (not described in detail)
Adalimumab							
No studies on the treatment of hepatic sarcoidosis are available							

^a ePOST, extrapulmonary physician organ severity tool assessing the severity of sarcoidosis extrapulmonary organ involvement in 17 organs. ALP, alkaline phosphatase; CT, computed tomography; LT, liver test; n, number.

Glucocorticosteroids

The mechanism by which glucocorticosteroids lead to suppression of the granulomatous inflammation is not completely understood. Steroids might have an anti-inflammatory effect on T cells, macrophages, and granulocytes, and might enhance transforming growth factor-beta (TGF- β) expression by T cells.²² Glucocorticosteroids are the first-choice in the treatment of pulmonary sarcoidosis.^{5,36,56} Only a few case reports described the use of steroids in hepatic sarcoidosis.⁵ Improvements in clinical symptoms, normalization of liver tests, and reduction of hepatomegaly have been demonstrated.^{7,10} However, serial biopsies demonstrate that corticosteroids rarely lead to total resolution of hepatic sarcoidosis and do not prevent hepatic progression.^{5,7,36} In line with this, Kennedy et al.⁶ showed that treatment with glucocorticosteroids may improve liver tests without benefit to liver histology. In this study, 67% of patients showed clinical response after steroid therapy, with one-third showing complete response. Maddrey et al.²⁴ reported that patients with cirrhosis from sarcoidosis had little response to glucocorticosteroids. On the other hand, patients with biliary obstruction due to porta hepatis adenopathy may have total resolution of their hyperbilirubinemia with steroid therapy.^{57,58} Dosage of prednisone is usually 20–40 mg/day for the first 4–6 weeks. Dose reduction can be achieved by 5–10 mg decrements every 4–8 weeks. The maintenance dose is the lowest effective dose.^{17,36,59} Relapse can occur after discontinuation of steroids.^{17,36}

Because of the significant toxic side-effects (Table 5.2), the use of glucocorticosteroids cannot be justified in asymptomatic patients or patients with mild disease that may spontaneously remit.^{20,36} Although steroids usually are the first-choice therapy, up to a third of patients may not respond. When no response to glucocorticosteroids is noted, cytotoxic agents are a good alternative.⁶⁰

Azathioprine

AZA is a purine analogue and is hydrolysed in the blood to 6-mercaptopurine by the enzyme thiopurine S-methyltransferase (TPMT).^{22,61} AZA inhibits nucleotide synthesis by feedback inhibition in the early stages of purine metabolism and it prevents T cell and B cell proliferation.²² The experience with AZA as treatment option in hepatic sarcoidosis is limited. Kennedy et al.⁶ reported normalization of liver tests in two patients and Malhotra et al.⁴⁵ reported one patient with improvement in symptoms and liver tests after treatment (Table 5.1). AZA dosage is 50–150 mg/day, starting at a relatively low dose.⁶² Blood counts must be checked before increasing the dose.⁶² Possible toxicity is shown in Table 5.2. Long-term monitoring of complete blood count and hepatic function should be done every 2 months.⁶² Because of genetic mutations, in up to 6 in 1000 people TPMT deficiency is present, with potentially life-threatening bone marrow toxicity when treated with conventional doses of AZA. Measuring TPMT enzyme activity should be considered in all patients starting on AZA.^{61,63}

Table 5.2 Toxicity of pharmacological agents in the treatment of hepatic sarcoidosis.^{20,22,36,55,62}

Drug	Dosage	Gastrointestinal	Mucositis	Haematological	Teratogenic	Cardiogenic	Reactivation of TB	Other
Adalimumab	40 mg s.c./2 weeks					x	x	Infections
Azathioprine	50–150 mg/day	x	x	x	x	x		Liver
Cyclophosphamide	50–150 mg/day	x	x	x	x	x		Bladder, liver, menstrual irregularity
Cyclosporine	25–200 mg/day					x		Renal, hirsutism, hypertension, infections
Glucocorticosteroids	1–2 mg/kg per day	x						Bone, skin, diabetes mellitus, depression, psychosis, weight gain
Infliximab	5 mg/kg 0, 2, 6 weeks; thereafter 5 mg/kg every 4–8 weeks	x		x		x	x	SLE, liver, infections
Leflunomide	20 mg/day	x						Liver, neuropathy, lungs, hair loss, visual disturbance, arthralgia
Methotrexate	10–15 mg/week	x	x	x	x			Liver, lungs, skin, renal
Pentoxifylline	400–1200 mg/day	x						Liver, hypotension
Thalidomide	50–200 mg/day	x		x	x			Skin, liver, neuropathy, cardiovascular
Ursodeoxycholic acid	600 mg/day	x			Unclear			Dry skin, hair thinning, headache

Sc, subcutaneous; SLE, systemic lupus erythematosus; TB, tuberculosis.

AZA can cause an acute hepatitis, which usually responds to withdrawal of the drug, but may also require glucocorticosteroid therapy. Therefore, acute worsening of liver tests in a hepatic sarcoidosis patient on AZA should lead to withdrawal of the drug.

Methotrexate

MTX is a folic acid analogue inhibiting dihydrofolate reductase, which leads to the depletion of tetrahydrofolate and inhibition of thymidylate synthesis, a step that is required for DNA replication in actively dividing cells.⁶⁴ MTX suppresses TNF, interleukin (IL)-6, and IL-8 release from macrophages, ROS and TNF release from neutrophils, and it suppresses lymphocyte proliferation.⁶⁴

Four cases of successful treatment of hepatic sarcoidosis with MTX have been described (Table 5.1).^{6,46} Relapses are frequent after discontinuation, which suggests that MTX suppresses but does not cure the disease.³⁶ MTX has to be administered once a week at an initial dosage of 10 mg with a maximum dose of 15 mg.²² Toxic side-effects are listed in Table 5.2. Because of bone marrow and renal toxicity risks, a complete blood count with renal function tests should be performed every 1–3 months.^{22,62} Furthermore, MTX has the potential for hepatic toxicity with the development of severe cirrhosis in about 14% of sarcoidosis patients.^{22,55} Toxicity of MTX can be reduced by the use of folic acid.²²

In using MTX for rheumatoid arthritis or psoriasis, liver test monitoring is recommended every 1–3 months to control for MTX toxicity. Patients with persistent transaminase elevation should be considered for drug withdrawal or liver biopsy.⁵⁵ In sarcoidosis, liver test abnormalities may be due to the underlying sarcoidosis or MTX. In a study of 100 liver biopsies performed on sarcoidosis patients undergoing MTX treatment, 47 had granulomatous disease due to sarcoidosis and 14 had changes consistent with MTX toxicity.⁵⁵ Transaminase levels were higher for those with hepatic sarcoidosis than those with MTX toxicity.⁵⁵ For sarcoidosis patients being treated with MTX, serial liver test monitoring is recommended. A rise in transaminase levels should lead to either MTX withdrawal or a liver biopsy to evaluate for MTX toxicity.⁶⁵

Figure 5.1 demonstrates an fluorine-18-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG PET) scan before and after MTX therapy. The marked reduction of uptake associated with treatment supports the effectiveness of MTX in treating this patient's liver and extrahepatic disease. Besides the assessment of inflammation, serial PET scanning has recently been demonstrated to be useful in follow-up.⁶⁶⁻⁶⁹

Chlorambucil

Chlorambucil has been reported by one group as useful in treating hepatic sarcoidosis.⁴³ Given the increased malignancy risk of chlorambucil compared with other cytotoxic agents, it has been replaced by other agents.

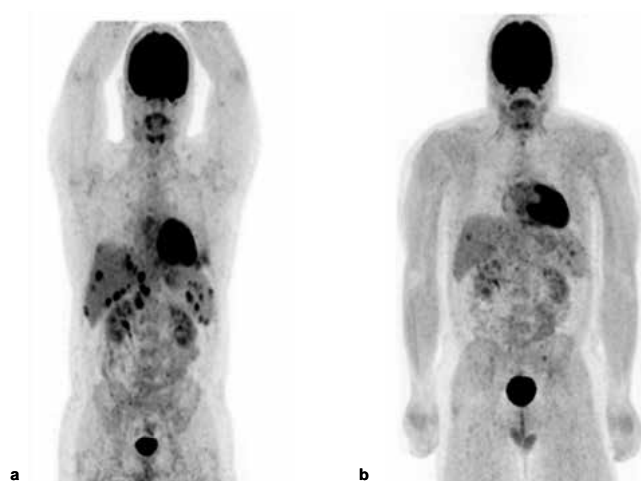


Figure 5.1 ^{18}F -FDG PET scans of a patient with mainly liver and splenic sarcoidosis involvement. The scans are before (a) and after (b) 6 months of treatment with methotrexate 12.5 mg once a week, 5 mg folic acid once a week and 10 mg prednisone once a day orally. Enhanced activity (nodules) was seen in liver, spleen, and porta hepatis lymph nodes prior to therapy. The liver, spleen, and lymph node lesions have significantly less activity after therapy.

Cyclosporine

Cyclosporine is a fungal peptide that suppresses T cell activation.²² Casavilla et al.⁴⁸ showed cyclosporine to be effective for the prevention of allograft rejection and sarcoidosis recurrence in patients who underwent liver transplantation (Table 5.1). Because of the unknown effectiveness, the major adverse effects and an increased malignancy risk, cyclosporine should be restricted to the most serious cases (Table 5.2).²² Recommended dosage is 25–200 mg/day.

Cyclophosphamide

Cyclophosphamide is metabolized in the liver into active alkylating metabolites, which inhibit lymphocyte proliferation with consequent anti-inflammatory effects.²² Das et al.⁴⁹ showed one case report with improvement in liver test abnormalities after therapy with glucocorticosteroids in combination with cyclophosphamide (Table 5.1). Dosage is 50–150 mg/day.⁶² Use of intermittent, intravenous bolus cyclophosphamide at 500–1500 mg every 2–4 weeks has also been reported as useful for refractory sarcoidosis with less toxicity than daily oral dosing.^{70,71} Cyclophosphamide is associated with, among others, bone marrow suppression, bladder carcinoma, and hepatotoxicity (Table 5.2).⁶²

Thalidomide

Thalidomide is a synthetic derivative of glutamic acid and has several molecular targets.⁷² The most important function in sarcoidosis is the inhibition of TNF- α production.²² Nguyen et al.⁵⁰ showed effectiveness of thalidomide in a patient with cutaneous and hepatic sarcoidosis (Table 5.1). Because of major side-effects, its use is limited to a second- or third-line therapy (Table 5.2). Recommended dosage is 50–200 mg/day.²²

Pentoxifylline

POF is a methylxanthine derivative that inhibits a number of pro-inflammatory cytokines including TNF- α . There is evidence supportive of a potential role for POF in sarcoidosis.^{60,73} In addition, POF may have hepatoprotective effects. Zein et al.⁷⁴ demonstrated that POF improves nonalcoholic steatohepatitis (NASH) and reduces progression of liver fibrosis in NASH.

Infliximab

Infliximab is a biological chimeric ‘humanized’ monoclonal antibody that binds to free TNF- α , blocking its interaction with the TNF-receptor, and sometimes to cell surface TNF- α .²²

Two double-blinded randomized controlled trials are available, which evaluate the use of infliximab in chronic sarcoidosis. The study of Baughman et al.⁷⁵ showed a small benefit of infliximab on forced vital capacity and chest radiograph scores after 24 weeks. Judson et al.⁵⁴ used an extrapulmonary physician organ severity tool for evaluation of specific organ involvement in sarcoidosis. Although the sample size was low, their results suggest that infliximab may be beneficial in extrapulmonary sarcoidosis including liver involvement.

In Table 5.1, an overview of reports on the treatment of hepatic sarcoidosis with infliximab is shown. Ulbricht et al.⁵¹ showed remission of hepatic granulomas and other clinical features of sarcoidosis during treatment with prednisone and infliximab. Doty et al.⁵² reported improvement of 10 patients resistant to conventional therapy, including one with hepatic sarcoidosis. Saleh et al.⁵³ showed improvement of three patients with hepatic sarcoidosis. However, in one patient, symptoms recurred 2 months after the sixth injection.

The induction treatment is 5 mg/kg at weeks 0, 2, and 6, and then maintenance of 5 mg/kg every 4 weeks.³⁶ The main risk of infliximab is reactivation of tuberculosis, which could be mistaken as worsening of sarcoidosis (Table 5.2).³⁶ Infliximab can generate antimurine antibody immune reactions that limit its use and require MTX comedication.^{76,77}

Adalimumab

Adalimumab is a recombinant fully human monoclonal antibody against TNF- α .⁷⁸ No information is available about its effectiveness in hepatic sarcoidosis. Adalimumab has also been associated with reactivation of tuberculosis (Table 5.2).³⁶

Transplantation

Organ transplantation can be the final treatment option in complicated hepatic sarcoidosis.^{6,79} Liver transplantation because of sarcoidosis accounts for 0.01% of total liver transplantations.¹⁷ Rates of graft and patient survival were equivalent between hepatic sarcoidosis and other causes of liver failure.^{79,80} However, recurrence of disease in the allograft has been documented in a few case reports.^{79,81,82}

Discussion

Data are scarce and there are no controlled trials evaluating liver involvement in sarcoidosis specifically. There are similarities with NASH or non-alcoholic fatty liver disease (NAFLD).⁸³ Like in sarcoidosis, cytokines including TNF- α are believed to play an important role in hepatocellular damage, inflammation, and fibrogenesis in NASH.^{84,85} As there are no controlled trials, recommendations in sarcoidosis are based on clinical experience, retrospective case series, and both NASH and NAFLD treatment recommendations, including lifestyle interventions.^{60,83,84}

The first advice is to assess sarcoidosis in general to determine whether there is a need for therapeutic intervention. The majority of patients with hepatic sarcoidosis do not require therapy. These include patients with asymptomatic disease and mildly elevated liver tests, no evidence of cholestasis (normal bilirubin), and normal liver synthetic function (e.g., prothrombin time (PT)), or without hepatomegaly noted on physical examination and/or without radiographic abnormalities. These individuals should be followed using liver function tests to determine whether they develop evidence of cholestasis or abnormal PT, which would be considered reasons for starting systemic therapy. Liver test abnormalities may resolve spontaneously over time or with treatment aimed at other organ involvement (e.g., lung disease).

On the basis of information gathered from the literature, a therapeutic approach of patients with hepatic sarcoidosis is proposed (see Figure 5.2). Hepatic sarcoidosis can be subdivided into symptomatic and asymptomatic disease. In asymptomatic disease (absence of clinical signs and symptoms and absence of cholestasis with a low risk of developing hepatic complications), no treatment is needed, but a regular follow-up of liver tests (every 3–6 months) is recommended. As previous studies showed that severity of liver test abnormalities is associated with severity of histopathological disease, worsening of liver test abnormalities or abnormal synthetic liver function is an important reason to start pharmacological therapy.²³

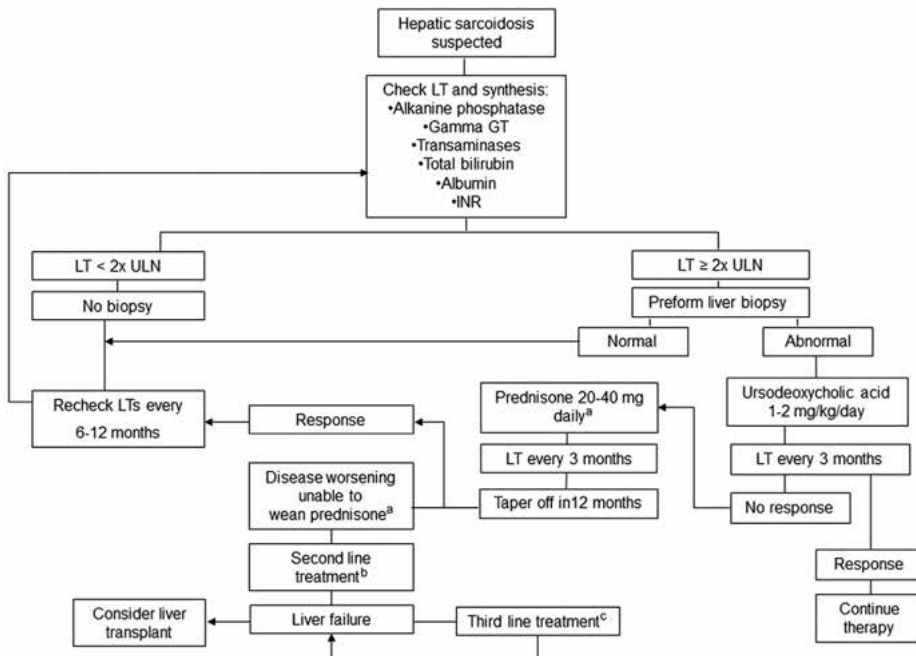


Figure 5.2 Decision flowchart. ^a Where prednisone is indicated, an equivalent dose of glucocortico-steroids (i.e., methylprednisolone) could also be used. ^b Cytostatic drug, including azathioprine, methotrexate, and leflunomide. ^c Anti-TNF- α treatment. GT, glutamyl transferase; INR, international normalized ratio; LT, liver test; TNF- α , tumor necrosis factor-alpha; ULN, upper limit of normal.

In symptomatic liver involvement (presence of clinical signs and symptoms or presence of cholestasis characteristics with a high risk of developing hepatic complications), pharmacological treatment is recommended.^{40,74,86,87} In cases of jaundice, cholestasis, or pruritis, UDCA must be considered as first treatment option. In absence of response or when non-cholestasis symptoms are present, prednisone should be considered (20–40 mg/day). Dosage must be tapered off when stable disease or recovery is seen, after which regular follow-up of liver tests is recommended. Cytotoxic drugs or TNF- α inhibitors can be considered in cases of disease worsening or impossibility of tapering off glucocorticosteroids. Finally, liver transplantation can be the only therapeutic option in cases of liver failure.

Conclusion

The cornerstone of sarcoidosis disease management involves careful baseline assessment of disease distribution and severity by organ, with emphasis on vital target organs. Because the clinical course can be unpredictable, regular monitoring for signs of disease progression in known organs of involvement and disease development in other organs is necessary. Because hepatic sarcoidosis can be rapidly progressive with the occurrence of serious complications, an appropriate therapeutic approach is important. However, therapeutic studies are rare. It is recommended to treat symptomatic hepatic sarcoidosis with glucocorticosteroids, preceded by UDCA when cholestasis is present. Furthermore, antioxidants can be considered. Cytotoxic drugs or TNF- α inhibitor therapy should be started when disease worsening or impossibility of weaning from glucocorticosteroids is present. Future randomized controlled studies are really necessary to assess the effect of treatment on disease progression and complications. Moreover, there is need for a more individualized process that addresses each individual's requirements with no redundancy of investigation and, probably more importantly, no unnecessary treatment with its risk of adverse events.

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