# Brief Report

1423

## Clinical Course after Liver Transplantation in Patients with Sarcoidosis

F. Adrian Casavilla, MD; Robert Gordon, MD; Harlan I. Wright, MD; Judith S. Gavaler, PhD; Thomas E. Starzl, MD, PhD; and David H. Van Thiel, MD

*Annals of Internal Medicine.* 1993;118:865-866.

Sarcoidosis is a disease of unknown cause that primarily involves the lungs and lymph nodes but is known also to involve the skin, liver, lacrimal glands, and potentially any organ or tissue in the body (1). The disease is characterized by the presence of noncaseating granuloma consisting of epithelioid cells and activated $CD4^+$ T cells.

Sarcoidosis can cause liver disease as well as hepatosplenomegaly, presinusoidal portal hypertension, and, rarely, a diffuse intrahepatic biliary disease similar to that seen in patients with primary sclerosing cholangitis (2). In addition to being a cause of liver disease, sarcoidosis often coexists with other well-recognized liver diseases, such as primary biliary cirrhosis, alcoholic liver disease, and postnecrotic cirrhosis due to either chronic hepatitis B or hepatitis C virus infection.

In either setting, patients with sarcoidosis become candidates for liver transplantation as a consequence of end-stage liver disease. By necessity, liver transplantation is followed by a lifelong requirement for immunosuppressive therapy to prevent allograft rejection (3). Immunosuppression is used also as primary treatment for patients with advanced symptomatic sarcoidosis and for those with disease involving the pulmonary parenchyma, myocardial conduction system, eyes, and central nervous system. Studies suggest that such therapy is efficacious and prolongs life as well as organ function (4-9). The effects of liver transplantation and the subsequent use of cyclosporine in patients with sarcoidosis have not been reported previously. We report our experience with liver transplantation in 9 patients with sarcoidosis and in 36 recipients without sarcoidosis (18 with cholestatic liver disease and 18 with hepatocellular disease) who were matched for age, gender, and time of liver transplantation.

From the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania. For current author addresses, see end of text.

### Methods

#### Patients

From 1 January 1981 through 31 December 1991, nine adult patients with a diagnosis of sarcoidosis and with or without another cause of liver disease underwent orthotopic liver transplantation at the University of Pittsburgh. Their mean age was 45.1 ± 2.8 years. Four were male and five were female. Their mean UNOS (United Network for Organ Sharing) score at the time of liver transplantation was 2.8 ± 0.3. For each liver transplant recipient with sarcoidosis that was identified, four liver transplant recipients without sarcoidosis were identified who had undergone transplantation within 30 days of the patient with sarcoidosis: In each case, two of the patients underwent transplantation because of a parenchymal (hepatocellular) liver disease (mean age, 45.3 ± 1.9 years; UNOS score, 3.1 ± 0.2), and two underwent transplantation because of a cholestatic liver disease (mean age, 43.8 ± 2.0 years; UNOS score, 2.7 ± 0.2).

#### Chart Review

The medical and surgical records of the nine patients with sarcoidosis were reviewed to determine the tissue sites of sarcoid involvement, the course of sarcoidosis after liver transplantation, and the post-transplant course and prognosis as assessed by serial angiotensin-converting enzyme levels, pulmonary function tests, and chest radiographs.

#### Statistical Analysis

Life-table analysis for patient and graft survival was carried out using the methods of Kaplan and Meier (10). The differences in survival between the patients with sarcoidosis and the two comparison groups were analyzed (10).

### Results

The 9 patients with sarcoidosis, the 18 patients with cholestatic liver disease (8 with primary sclerosing cholangitis and 10 with primary biliary cirrhosis), and the 18 patients with parenchymal liver disease (8 with viral hepatitis, 8 with alcoholic liver disease, and 2 with cryptogenic liver disease) had similar demographic characteristics. None of the patients with parenchymal liver disease had hepatitis B, but eight did have hepatitis C.

Total bilirubin levels in the sarcoidosis, cholestatic disease, and parenchymal disease groups were 133.4 ± 25.7 μmol/L, 295.8 ± 37.6 μmol/L, and 35.9 ± 5.1

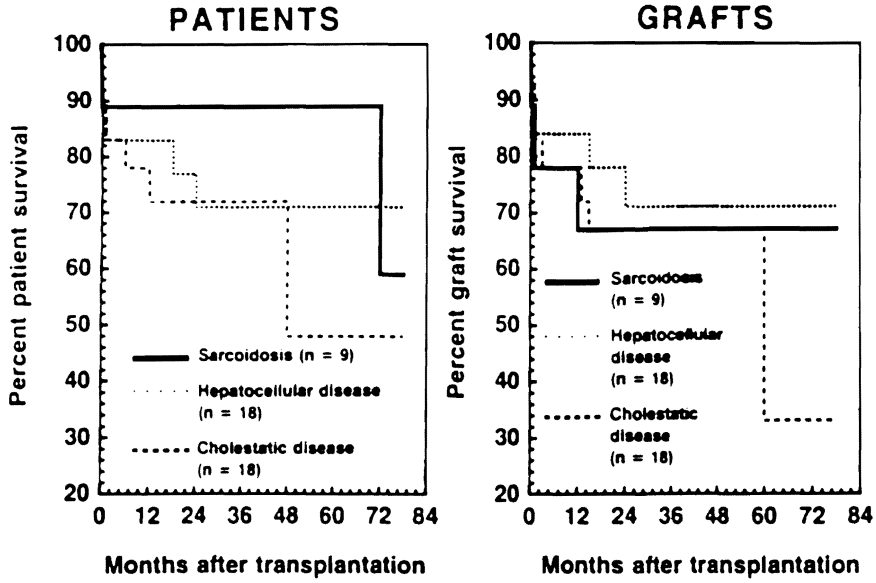


**Figure 1. Patient and graft survival in the three study groups.**

μmol/L, respectively; albumin levels were 27 ± 4 g/L, 33 ± 2 g/L, and 23 ± 4 g/L, respectively; and prothrombin times were 15.1 ± 0.2 s, 13.1 ± 0.2 s, and 17.3 ± 0.2 s, respectively. In each instance, liver function measurements for the sarcoidosis group fell midway between the measurements for the two comparison groups.

In patients with sarcoidosis, tissue involvement was demonstrated histopathologically. All nine patients had hepatic involvement; seven had pulmonary and mediastinal node involvement; three had lacrimal gland and skin involvement; and three had upper airway disease. The serum angiotensin-converting enzyme level and the peripheral blood helper (CD4+)/suppressor (CD8+) cell ratio were determined before liver transplantation in all nine patients with sarcoidosis: The patients had an elevated angiotensin-converting enzyme level (mean, 136 ± 11 U) and a $CD4^+/CD8^+$ ratio of 1.9 ± 0.2. All nine patients received cyclosporine. Graft and patient survival in the three groups is shown in Figure 1. No statistical difference between the three groups for either graft or patient survival was evident through 76 months (6.3 years). Although not significant, patient survival in the sarcoidosis group was arithmetically better through the first 5 years than that in the two comparison groups. The three deaths that occurred in the sarcoidosis group at 6 years were caused by metastatic hepatocellular cancer; recurrent non-A, non-B hepatitis; and cryptogenic cirrhosis.

The most recent laboratory test results for the survivors in each group were normal. No evidence of disease progression or continued disease activity was seen. The hepatic disease in each case was eliminated by the total hepatectomy required as part of the liver transplant procedure. The lack of disease progression or continued disease activity involving the lungs, skin, and lacrimal glands reflects the intensity of the immunosuppressive therapy.

## Discussion

Our retrospective study showed that patients with sarcoidosis who receive a liver allograft and are required to take immunosuppressive agents at doses that prevent allograft rejection experience a remission of their sarcoidosis. These data confirm the beneficial efforts of cyclosporine in patients with clinically active sarcoidosis and those with disease involving critical organs (6-10).

Our results, when combined with those from earlier series of patients with sarcoidosis who did not receive an organ allograft, define the dose range within which patients with active sarcoidosis can be treated and their disease controlled completely without producing unacceptable drug-associated toxicities. Such information is particularly important in patients with sarcoidosis, who may require prolonged immunosuppressive therapy.

*Requests for Reprints:* F. Adrian Casavilla, MD, Transplantation Institute, Falk 5C, Pittsburgh, PA 15213.

*Current Author Addresses:* Drs. Casavilla, Gordon, Wright, Gavaler, Starzl, and Van Thiel: 3601 Fifth Avenue, Falk 5C, Pittsburgh, PA 15213.

### References

1. **Duffell GM.** Sarcoidosis. In: Hurst JW; ed. Medicine for Practicing Physicians. Third edition. Boston: Butterworth-Steineman; 1992: 962-3.
2. **Pereira-Lima J, Schaffner F.** Chronic cholestasis in hepatic sarcoidosis with clinical features resembling primary biliary cirrhosis. Am J Med. 1987;83:144-8.
3. **Starzl TE, Demetris AJ, Van Thiel DH.** Medical progress: Liver transplantation. N Engl J Med 1989;221:600-3, 1014-22.
4. **York EL, Kovithavongs T, Man SF, Rebuck AS, Sproule BJ.** Cyclosporine and chronic sarcoidosis. Chest. 1990;98:1026-9.
5. **Gupta AK, Ellis CN, Nickoloff BJ, Goldfarb MT, Ho VC, Rocher LL, et al.** Oral cyclosporine in the treatment of inflammatory and noninflammatory dermatoses. A clinical and immunopathologic analysis. Arch Dermatol. 1990;126:339-50.
6. **Hammond JM, Bateman ED.** Successful treatment of life-threatening steroid-resistant pulmonary sarcoidosis with cyclosporine in a patient with systemic lupus erythematosus. Respir Med. 1990;84:77-9.
7. **Martinet Y, Pinkston P, Saltini C, Spurzem J, Muller-Quernheim J, Crystal RG.** Evaluation of the in vitro and in vivo effects of cyclosporine on the lung T-lymphocyte alveolitis of active pulmonary sarcoidosis. Am Rev Respir Dis. 1988;138:1242-8.
8. **Cunnah D, Chew S, Wass J.** Cyclosporine for central nervous system sarcoidosis. Am J Med. 1988;85:580-1.
9. **Bielory L, Holland C, Gascon P, Frohman L.** Uveitis, cutaneous and neurosarcoid: treatment with low-dose cyclosporine. Transplant Proc. 1988;20:144-8.
10. **Lee ET.** Statistical Methods for Survival Data Analysis. Belmont, California: Wadsworth, Inc; 1980:122.