Liver Involvement in Systemic Lupus Erythematosus: Case Review of 40 Patients

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ABSTRACT. ***Objective.*** Subclinical liver involvement is frequent in systemic lupus erythematosus (SLE). We sought to determine the presence of endstage liver disease in patients with SLE.

Methods. We carried out a retrospective chart review of our cohort of patients with SLE. Endstage liver disease was defined as presence or development of cirrhosis, portal hypertension, or hepatic encephalopathy.

Results. Forty patients with liver enzyme abnormalities were identified. Major clinical diagnostic groups were drug-induced (n = 4), viral hepatitis (hepatitis B or C and cytomegalovirus; n = 8), non-alcoholic fatty liver disease (NAFLD; n = 8), autoimmune hepatitis (AIH; n = 6), primary biliary cirrhosis (PBC; n = 3), and miscellaneous [n = 11; liver involvement from infection (2), cryptogenic cirrhosis (2), lymphoma (1), and indeterminate (6)]. There were no differences in mean age, total and direct bilirubin, or aspartate aminotransferase and alkaline phosphatase levels. Alanine aminotransferase levels were higher in the miscellaneous group. Biopsies were performed in 20 patients and showed changes of NAFLD (n = 5), AIH (n = 4), PBC (n = 3), hepatitis C (n = 3), and cryptogenic cirrhosis (n = 2), and 1 each with phenytoin-induced liver injury, hepatic granulomas due to systemic candidiasis, and lymphomatous involvement of the liver. The median followup was 44 months (range 10–576). The estimated 5-year serious liver disease-free survival was 93% (95% confidence interval 84%–100%). Eight patients died. Mortality was not directly related to liver disease in any patient.

Conclusion. Complications of portal hypertension, cirrhosis, and hepatic encephalopathy are rare manifestations of SLE unless coexistent liver disease such as NAFLD, viral hepatitis, or AIH is present. (First Release Sept 15 2008; J Rheumatol 2008;35:2159–64; doi:10.3899/jrheum.080336)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS LIVER DISEASE PROGNOSIS

Clinical liver dysfunction is a rare manifestation of systemic lupus erythematosus (SLE). Initial studies by Kofman, *et al*[1] attributed the liver dysfunction in patients with SLE to "abnormal plasma protein patterns rather than actual hepatic parenchyma abnormality." Subsequently, several studies showed frequent liver enzyme abnormalities during the course of SLE[2-6]. Lupus patients have a 25%–50% chance of developing abnormal liver tests in their lifetime[4,5,7]. Liver abnormalities in lupus are commonly multifactorial and can be part of drug-induced or coincidental disease activity (e.g., alcoholic liver disease)[7,8]. Presence of antiphospholipid antibodies (aPL) can be associated with thrombotic manifestations like Budd-Chiari syndrome or nodular regenerative hyperplasia[9-11].

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After exclusion of secondary causes, hepatitis due to SLE may be seen in 3%–5% of cases[12,13]. Lupoid hepatitis was a term coined by MacKay in 1959[2]. Lupoid hepatitis was differentiated from classic lupus on the basis of liver lesion being initial and dominant and is now referred to as autoimmune hepatitis (AIH). New criteria for classification of AIH have been proposed and the 2 can be distinguished based on clinical, serologic, and pathologic categories[7,14,15].

Whether frequent and clinically significant liver involvement occurs in SLE has been controversial. Gibson and Myers found elevated liver enzymes in 45 (55%) of 81 patients[3]. The enzyme elevations were detected incidentally.

Runyon, *et al*[4] described a cohort of SLE patients with liver disease; among 206 tested, 43 met the study inclusion criteria. Death of 3 patients from liver failure led the authors to conclude that liver involvement in lupus is more common than recognized and fatal liver disease can occur[4].

A prospective study by Miller, *et al*[5] investigated the causes and prevalence of subclinical and clinical liver disease in patients with SLE. They also tried to determine correlation of the liver disease with lupus disease activity[5]. In that study liver enzyme elevations were observed in 61 patients out of 260 (23%), and clinical liver disease was seen in 6 patients (2%). In a subset of patients, liver enzyme elevation correlated with lupus activity[5].

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We undertook a retrospective study to examine the types and severity of liver involvement in patients with SLE. We also evaluated whether liver disease in lupus patients leads to endstage hepatic disease, namely development of cirrhosis, portal hypertension, and/or hepatic encephalopathy.

MATERIALS AND METHODS

Case records of patients carrying a diagnosis of SLE seen at our institution from 1983 to 2002 were searched for liver involvement using the key words liver disease, hepatitis, steatohepatitis, cirrhosis, and portal hypertension. All these diagnoses were retrieved electronically using International Classification of Disease-9 codes. This search yielded 192 records; case records were then reviewed, and only patients who were seen concomitantly by a gastroenterologist/hepatologist were included. Patients were excluded if the records were incomplete, or if they had alcoholic liver disease (ICD-9 code, clinical impression, or biopsy) or did not fulfill at least 4 of the 1982 American College of Rheumatology criteria for lupus classification[16]. Forty patients were included for analysis.

The study protocol was approved by the Institutional Review Board.

SLE features. Data collected included age at onset of SLE, race, sex, disease duration prior to diagnosis, and interval between first liver manifestation and diagnosis of SLE. Clinical features at presentation were recorded. Serology was noted for antinuclear antibody (ANA) and double-stranded DNA (dsDNA) positivity, extractable nuclear antigens (ENA), complement levels, lupus anticoagulant (LAC), and aPL. Followup was recorded in months. The rheumatologists' impression of the SLE disease activity at last followup and causes of death were recorded.

Features of liver disease. Clinical features at presentation were recorded, specifically presence of hepatosplenomegaly, jaundice, or signs of liver cell failure. Patients were categorized according to the clinical diagnosis (supported by biopsy) of the treating gastroenterologist/hepatologist. Laboratory variables tested included total and direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyltransferase (GGT). Values that were available were recorded, as not all patients had ALT and GGT checked. Serum albumin, international normalized ratio (INR), ultrasound, or computed tomography scan of liver was noted. Viral serologies for hepatitis B and C were recorded. Results of anti-smooth muscle (ASMA), anti-liver-kidney-microsome (LKM), and antimitochondrial antibody (AMA) were noted. Results of liver biopsies were analyzed in patients who underwent that procedure. Cirrhosis and portal hypertension were diagnosed by combination of clinical, imaging (nodular contour, coarsened echo texture, splenomegaly, and development of portal-systemic venous channels), and/or biopsy characteristics. Patient data and biopsy were reviewed by a hepatologist (JJP).

Statistical analysis. Continuous variables were expressed as mean ± standard deviation. Nonparametric values were denoted by median. Levels of bilirubin and hepatic enzymes between various clinical groups were compared by ANOVA using SAS software (version 9, SAS Institute, Cary, NC, USA). The probability of patients free of serious liver disease was estimated using the Kaplan-Meier method[17]. A p value < 0.05 was considered statistically significant.

RESULTS

Demographic features (Table 1). The mean age of patients at presentation was 37 years (range 17–67); the female to male ratio was 4:1. The median duration of SLE prior to diagnosis was 24 months. Information on race was available in 27 patients, 21 were Caucasian, 4 African American, and 2 "other" (1 Middle Eastern and 1 Hispanic ethnicity). Among patients with organ involvement, renal disease was seen in 20 (50%), neuropsychiatric disease in 14 (35%), hematologic disease in 14 (35%), serositis in 15 (38%), and arthritis in 34 (85%). Skin involvement was seen in 33 (82%) patients: malar rash in 19, discoid rash in 3, and photosensitivity in 11. Renal biopsy was available in 18 patients and showed changes of membranoproliferative glomerulonephritis (1), focal segmental (3), diffuse proliferative (4), membranous (7), and predominantly sclerotic glomeruli (1 patient). One patient showed crescentic glomerulonephritis and 1 had changes of mesangioproliferative glomerulonephritis. Neurologic manifestations included 3 patients with seizures and 4 with lupus cerebritis. One patient each had migraine/headache, neuropathy, pseudotumor cerebri, psychosis, optic neuritis, and bipolar disorder. One patient had both temporal lobe epilepsy and peripheral neuropathy. Thrombotic manifestations were seen in 2 and consisted of deep vein thrombosis (DVT; 1), pulmonary embolism (1 with concomitant DVT), and jugular vein thrombosis (1). The patient with jugular vein thrombosis was heterozygous for factor V Leiden.

Table 1. Demographic features (n = 40).

Characteristic	Data
Mean age, yrs ± SD (range)	37.0 ± 15.5 (17–67)
Female, n (%)	32 (80)
Race (n = 27)	
Caucasian	21
African American	4
Other	2
Median duration of disease prior to diagnosis, mo ± SD (range)	24 ± 97 (1–480)
Organ involvement (%)	
Renal	20 (50)
Neuropsychiatric (%)	14 (35)
Seizures	3
Lupus cerebritis	4
Migraine/headache	1
Neuropathy	1
Pseudotumor cerebri	1
Optic neuritis	1
Temporal lobe epilepsy (and neuropathy)	1
Psychosis	1
Bipolar disorder	1
Hematologic (%)	14 (35)
Thrombotic manifestations	3
Deep vein thrombosis	1
Pulmonary embolism	1
Jugular vein thrombosis	1
Serositis (%)	15 (38)
Arthritis (%)	34 (85)
Dermatologic involvement (%)	33 (82)
Malar rash	19
Discoid rash	3
Photosensitivity	11

Serologic features. ANA was positive in 34 patients. Of 6 patients who were ANA-negative, 5 had biopsy-proven lupus nephritis and 1 was anti-Ro-positive. ENA antibody to

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U1RNP was seen in 4 (10%), Sm in 6 (15%), Ro in 10 (24%), and La in 5 (12%) patients. Antibody to dsDNA was tested in 37 patients and was positive in 20 (borderline positive in 4) and negative in 17. Antihistone and rheumatoid factor positivity was seen in 2 and 5 patients, respectively. IgM aPL alone were seen in 2 patients, LAC in 2, and both in 1 patient. False-positive syphilis serologies were seen in 4; only 1 had concomitant LAC. Perinuclear antineutrophil cytoplasm antibody (pANCA) was seen in 3 patients. Myeloperoxidase antibody was tested in 1 patient and was negative. The total median complement level was 44 mg/dl (range < 1 to 116). Median C3 level was 90 mg/dl (range 33–172) and median C4 level was 12 mg/dl (range 8–39.7). C3 was decreased in 10 patients (out of 30 tested) and C4 was decreased in 11 (24 tested).

Hepatic manifestations. In 8 patients, liver involvement preceded diagnosis of SLE by a median 48 months (range 13–324), and in 23 patients, liver involvement was seen a median 60 months after the diagnosis of lupus had been made (range 5–372). In 6 patients it was concurrent, while information was unavailable for 3 patients. Clinical examination showed icterus in 1, hepatomegaly in 10 (24%), and splenomegaly in 5 (12%) patients. Major clinical diagnostic groups were PBC (n = 3), drug toxicity (n = 4), AIH (n = 6), NAFLD (n = 8), chronic viral hepatitis (n = 8), and miscellaneous causes (n = 11; 2 cryptogenic cirrhosis, 1 each with lymphomatous infiltration, sepsis and hepatic granulomas due to systemic candidiasis, and 6 indeterminate).

The demographic features and laboratory values among various groups are given in Table 2. The mean age of patients with PBC was 51 years (range 44–57), drug-induced 31 years (range 17–63), lupus with autoimmune hepatitis overlap 45 years (range 27–60), steatohepatitis 40 years (range 18–67), viral hepatitis 34 years (range 18–61), and 31 years for patients with miscellaneous causes (range 20–52). The mean age, bilirubin, AST, and ALP data were similar among the various groups. ALT was higher in patients with miscellaneous causes (p = 0.03).

AMA were tested in 17 patients and were positive in 2 (12%); both patients had PBC. One patient with PBC was AMA-negative, but biopsy findings were compatible with PBC. ASMA were tested in 11 and were positive in 2; in 1 patient clinical impression and biopsy supported a diagnosis of steatohepatitis, and the other positive finding was seen in a patient with concomitant AIH. Anti-LKM was tested in 3 and was found negative.

Biopsy results. Biopsy was performed in 20 patients. Two patients were biopsied twice and one had 3 biopsies. Biopsy findings were as follows: steatohepatitis (n = 5), AIH (n = 4), PBC (n = 3), hepatitis C (n = 3), cryptogenic cirrhosis (n = 2), and one each with phenytoin-induced liver injury, hepatic granulomas due to systemic candidiasis and lymphomatous involvement of the liver. One patient who had 2 biopsies demonstrated steatohepatitis with mild fibrosis on the initial biopsy, followed by cirrhosis 11 years later. The second patient had PBC with moderate fibrosis that was unchanged after 1 year. In the third patient all biopsies showed stage 3 PBC. One patient died of multiorgan failure from staphylococcal septicemia; an autopsy showed inactive cryptogenic cirrhosis with extensive shock-induced necroses in regenerative nodules.

Outcome of liver disease. A total of 40 patients were followed up for a median of 44 months (range 10–576). Severe liver disease was defined as the presence or development of cirrhosis or clinical features of portal hypertension. Complete resolution of enzyme abnormalities was seen in 19 patients, and persistent enzyme elevations without sequelae were seen in 8. Serious liver disease was present in 2 patients (5%) at the time of diagnosis of SLE. An estimated 7% of subjects developed serious liver disease by 5 years after SLE diagnosis (95% CI 0%–16%) and 13% developed serious liver disease by 10 years after SLE diagnosis (95% CI 0%–27%).

Figure 1 shows a Kaplan-Meier plot of percentage of patients with severe liver disease. The estimated 5-year serious liver disease-free survival was 93% (95% CI

Table 2. Clinical diagnosis in SLE patients with liver involvement. Values are mean ± SD. Normal laboratory values are given in the Appendix.

	PBC, n = 3	Drugs, n = 4	AIH, n = 6	NAFLD, n = 8	Viral Hepatitis* n = 8	Miscellaneous, n = 11†	p
Mean age, yrs (range)	51 ± 5 (44–57)	31 ± 22 (17–63)	45 ± 14 (27–60)	40 ± 19 (18–67)	34 ± 15 (18–61)	31 ± 12 (20–52)	0.20
Total bilirubin, mean mg/dl (range)	3.7 ± 5.4 (0.3–9.9)	0.9 ± 0.7 (0.2–1.9)	0.5 ± 0.3 (0.2–2.9)	0.9 ± 0.9 (0.2–2.5)	0.8 ± 0.8 (0.3–2.7)	1.9 ± 1.6 (0.6–5.6)	0.16
Direct bilirubin, mean, mg/dl (range)	3.0 ± 4.7 (0–8.4)	0.4 ± 0.7 (0–1.2)	0.4 ± 0.3 (0.2–0.7)	0.5 ± 0.6 (0.1–1.8)	0.4 ± 0.6 (0.1–1.7)	0.5 ± 0.5 (0.1–1.3)	0.16
Mean AST, U/l (range)	74 ± 43 (26–110)	40 ± 13 (25–57)	92 ± 100 (16–272)	163 ± 158 (40–506)	75 ± 60 (16–197)	335 ± 563 (13–1780)	0.44
Mean ALT, U/l (range)	81 ± 11 (73–88)	28 ± 9 (22–41)	57 ± 48 (8–134)	69 ± 41 (15–112)	97 ± 103 (19–277)	220 ± 134 (57–380)	0.03
Mean alkaline phosphatase, U/l (range)	754 ± 547 (244–1332)	400 ± 315 (152–822)	438 ± 481 (135–1400)	525 ± 240 (172–869)	291 ± 182 (71–642)	260 ± 181 (116–541)	0.18

* Viral hepatitis includes HCV (n = 6), HBV (n = 1), and cytomegalovirus (n = 1). † Lymphoma (1), sepsis (1), granulomatous inflammation from candida (1), cryptogenic cirrhosis (2), and indeterminate causes (6). PBC: primary biliary cirrhosis; AIH: autoimmune hepatitis; NAFLD: nonalcoholic fatty liver disease.

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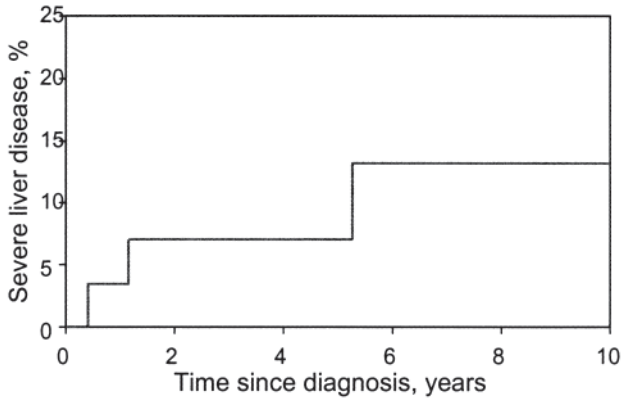

Figure 1. Percentage of SLE patients with endstage hepatic disease (cirrhosis, portal hypertension, and hepatic encephalopathy) over time.

84%–100%) and the 10-year estimate was 87% (95% CI 73%–100%).

SLE was active in 18% (3 NAFLD, 2 viral hepatitis, and 2 AIH) and inactive in 45% of patients (2 NAFLD, 4 viral hepatitis, 2 drug-induced, 2 AIH, 3 PBC, and 5 miscellaneous) at last followup. Information was unavailable for 7 patients. Eight patients died; causes of death included sepsis (2), thrombocytopenia (1), respiratory failure (1), suicide (1), malignancy (2; metastases unrelated to hepatocellular carcinoma in 1 and lymphoma in 1), and unknown cause in one. Sepsis was secondary to vancomycin-resistant enterococcus in a patient with kidney and liver transplant and to staphylococcus bacteremia in the other patient. The patient with thrombocytopenia had erythromycin-induced cholestasis with no evidence of portal hypertension. The estimated 5-year survival was 85% (95% CI 72%–100%).

DISCUSSION

Subclinical liver disease in SLE especially at times of disease activity has been reported frequently. We analyzed patients with SLE and report that endstage hepatic disease, namely development of portal hypertension, cirrhosis, and hepatic encephalopathy, occurs rarely in patients with SLE. We should keep in mind, however, that this was a small retrospective series and the followup period was limited.

There are several case reports and reviews on liver disease in SLE[7,18-21]. A large pathologic series of 73 patients with SLE showed hepatic arteritis in 15.1%, PBC in 2.7%, nodular regenerative hyperplasia in 6.8%, and AIH in 2.7%[22]. Other causes of liver disease included fatty liver in 73%, viral chronic hepatitis or cirrhosis in 4.1%, and drug-induced hepatitis or cholangitis in 2.7%. A recent study found a higher prevalence of 9.8% of autoimmune liver disease in patients with juvenile SLE, compared to 1.3% in adult patients[23]. There was no difference with respect to disease activity in other organs or damage between patients with and those without autoimmune liver disease. In the juvenile group, liver disease preceded diagnosis of SLE by a mean of 22 months. This highlights the need for continued vigilance for development of SLE in juvenile patients with autoimmune hepatitis. Compared to previous series[3-5], our patients had roughly similar ages (Table 3). Our series had some clinical features of lupus that were similar to those described in the series from Runyon, *et al*[4]. We found comparable data for cerebritis (36% in Runyon vs 27% in our series) and malar rash (45% in Runyon vs 55% in our series). Renal involvement and arthritis were more frequent in our series (33% in Runyon vs 49% in our series and 30% in Runyon vs 85.4% in our series, respectively). Of 34 patients with arthritis only 9 were taking nonsteroidal anti-inflammatory drugs (NSAID) at the time of diagnosis of liver involvement; however, in no patient were NSAID felt to be contributory. Serositis was seen in 79% of patients in the series of Runyon, *et al* versus 37% in our study. Hepatomegaly and jaundice findings in our series were more comparable to those of Gibson, *et al*[3]. However, we saw more patients with splenomegaly compared to previous series.

We found AMA in 2 patients; both had PBC. An additional patient had clinical and/or histologic features of PBC (with positive biopsy) but was AMA-negative. The association of PBC with SLE is very rare and only a handful of cases are reported[24]. In that study AMA, the serologic hallmark of PBC, was reported in 15/66 hospitalized patients with SLE. Four patients had turned negative at the end of hospitalization and 5 had decreasing titers. However, the clinical significance of these findings is not clear and longer followup studies are needed to determine if these patients would develop PBC. One of our patients with biopsy-proven steatohepatitis had positive ASMA; it has been reported in 3% of patients with steatohepatitis[25]. Presence of autoantibodies was associated with a more advanced stage of fibrosis, higher necroinflammatory grade, and higher serum concentrations of gamma-globulins and a higher frequency of hypergammaglobulinemia. Although 88% of patients fulfilled criteria for AIH set out by the International Autoimmune Hepatitis Group[15], only 8% had biopsy-proven AIH. This emphasizes the importance of biopsy investigation in formulating treatment instead of relying on serology alone.

We have classified patients according to clinical diagnosis as supported by biopsy and other investigations. NAFLD and chronic hepatitis C were the most common causes of liver dysfunction in our cohort. Hepatitis C virus (HCV) infection can present with many rheumatologic manifestations, including SLE[26]. Autoantibodies like ANA (10%–30%), rheumatoid factor (71%), and ASMA (66%) may be seen[27]. Some studies report prevalences of HCV in SLE patients were similar to those found in the general population (0.5%–1%) using anti-HCV antibodies[28,29]. Other studies using polymerase chain reaction investigations, however, found 10%–13% higher prevalence of HCV in SLE

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Table 3. Demographic and clinical data, and causes of liver dysfunction in published series (numbers may not sum to 100% due to rounding).

	Gibson[3]	Runyon[4]	Miller[5]	Present
Number	45/81	43/206	67/260†	40/192
Age, yrs	33	38	40	37
Demographics	73 F, 8 M	194 F, 12 M	212 F, 48 M	32 F, 8 M*
Race	—	91% Caucasian 6% Black 3% American Indian	91.5% Caucasian 4.2% AA 4.2% Asian	84% White 16% AA
Hepatomegaly	22 (27%)	39%	—	24%
Splenomegaly	4%	6%	—	12%
Jaundice	2%	24%	—	2.4%
Clinical diagnosis	Liver related 33 (drug 14), other 12 (HA, myositis, MI, PE, CHF)	19 Unknown 14 Unknown	Salicylate 28, alcohol 8, HepB-related 2, other 5 (CHF, DM, drug reaction, carcinoma pancreas); unknown 24	NAFLD 8, viral 8, drugs 4, AIH 6, miscellaneous 11, PBC 3
Biopsy	Normal 2, CHF 3, CHF 1 (received INH), round cell infiltration 6, CAH 1, fatty 1, mild portal inflammatory infiltrate 1	Steatosis 12, cirrhosis 4, CAH 4, granulomatous 3, cholestasis 1, centrilobular necrosis 3, with CPH 2, microabscess 2, PBC 1, hemochromatosis 1, nonspecific reactive 1	—	NAFLD 5, chronic hepatitis C 3, AIH 4, lymphomatous infiltration 1, candidiasis 1, cirrhosis 2, PBC 3, drug 1
Total mortality	—	6		8
Due to liver failure		3		0

† (clinical + subclinical). * gender in those with liver involvement. HA: hemolytic anemia; MI: myocardial infarct; PE: pulmonary embolism; CHF: congestive heart failure; INH: isoniazid; CAH: chronic active hepatitis; CPH: chronic persistent hepatitis; PBC: primary biliary cirrhosis; DM: diabetes mellitus; NAFLD: non-alcoholic fatty liver disease; AIH: autoimmune hepatitis.

compared to blood donors[29,30]. Treatment of hepatitis C with interferon may cause development of SLE[31,32].

The majority of patients in our study had resolution of liver enzyme abnormalities with no serious sequelae. In support of this, large multicenter studies of mortality in SLE have shown that liver disease was not a major cause of morbidity or mortality[33-37].

One limitation of our study is that we may have missed some patients who were not seen by a gastroenterologist. However, as our major outcome was development of end-organ liver disease, we believe most patients with serious liver disease would have been referred to our hepatobiliary clinic for evaluation.

We conclude that while liver test abnormalities are common in patients with SLE, endstage liver disease complicated by portal hypertension, hepatic encephalopathy, and cirrhosis is relatively rare unless liver diseases such as nonalcoholic fatty liver disease, viral hepatitis, or autoimmune hepatitis are also present.

APPENDIX: Normal laboratory values

Total bilirubin: 0.1–1.1 mg/dl; direct bilirubin: 0.0–0.3 mg/dl

AST: 12–31 U/l

ALT: Men 10–32 U/l (1983-1990), 10–45 U/l (1991-2002) Women 9–24 U/l (1983-1990), 9–29 U/l (1991-2002)

ALP: Men age ≥ 18 years 90–239 U/l (1983-1989), 98–251 U/l (1990); age = 18 years 113–482 U/l (1991-2002); age ≥ 19 years 98–251 U/l (1991-2002); age = 18 years 52–222 U/l (2003); men age ≥ 19 years 45–115 U/l (2003)

Women age < 45 years 76–196 U/l, > 45 years 87–250 U/l (1983-1989); age 17–23 years 114–312 U/l, 24–45 years 81–213 U/l, 46–50 years 84–218 U/l, 51–55 years 90–234 U/l, 56–60 years 99–257 U/l, 61–65 years 108–282 U/l, ≥ 65 years 119–309 U/l (1990); age 17–23 years 114–312 U/l, 24–45 years 81–213 U/l, 46–50 years 84–218 U/l, 51–55 years 90–234 U/l, 56–60 years 99–257 U/l, 61–65 years 108–282 U/l, ≥ 66 years 119–309 U/l

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