PostScript

LETTERS

Autoimmune hepatitis triggered by hepatitis A

We describe a case of autoimmune hepatitis triggered by an acute hepatitis A infection. A young woman presented with a 10 day history of nausea and dark urine having returned from Tunisia a month previously. She had marked transaminitis. Viral serology demonstrated positive hepatitis A immunoglobulin M. Other viral serology was negative. Autoantibody screening revealed positive antismooth muscle antibodies (titre 1 in 80) but negative anti-nuclear (ANA), antimitochondrial, and anti-liver, kidney and pancreas (LKM) antibodies. Immunoglobulin levels revealed normal IgA and IgG levels with a raised IgM at 5.53 g/l (range 0.60–2.50). Abdominal ultrasound scan was normal. She was diagnosed with acute hepatitis A.

Liver function tests normalised within two months. One month later her alanine aminotransferase levels began to increase. Autoantibody screen was positive for ANA (titre 1 in 40) and SMA was negative. However, immunoglobulin G was raised at 18.6 g/l (range 6–16) and serum electrophoresis showed a polyclonal increase in gamma globulins. Liver histology showed interface portal inflammation with plasma cell (fig 1) associated interface hepatitis with involvement of lobular and perivenular hepatocytes, consistent with autoimmune hepatitis (AIH). She was successfully treated with immunosuppression.

Studies suggesting triggering factors for the development of AIH have been reported in the past and include Epstein-Barr virus,¹ and

hepatitis B and hepatitis A infection.² Although SMA was initially positive in our patient, this was probably because of the viral infection.

Using the diagnostic scoring system of the American Association for the Study of Liver Diseases (AASLD) (see table 1) for the diagnosis of AIH, our patient scored 16 before steroid treatment (definite diagnosis is >15) and 18 after steroid treatment (definite diagnosis is >17). The sensitivity of this scoring system for the diagnosis of AIH is quoted by the AASLD as 97–100%.

Acute hepatitis secondary to hepatitis A infection is a common cause of viral hepatitis in humans and is usually self limiting and resolves within weeks. However, it may lead to fulminant liver failure in a small percentage of cases. Hepatitis A does not lead to chronic viral hepatitis. We have documented a patient with acute hepatitis A who subsequently went on to develop AIH. Hence diligent follow up of patients with acute hepatitis A needs to be carried out. Hepatitis A may not be, as has long been thought, an acute infection with no long term sequelae.

G Singh, S Palaniappan, O Rotimi, P J Hamlin
Centre for Digestive Diseases, The General Infirmary at Leeds, Leeds, UK

Correspondence to: G Singh, Leeds General Infirmary, Great George St, Leeds LS1 3EX, UK; drgurjitsingh@hotmail.com

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hepatitis in susceptible individuals. *Lancet* 1995;346:913.

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A randomised controlled trial of total immunosuppression withdrawal in stable liver transplant recipients

Total withdrawal of immunosuppression (TIW) without causing rejection has been reported in some stable liver recipients.^{1–3} Patient characteristics which predict this clinical tolerance have not been determined. Ursodeoxycholic acid (UDCA) has been reported to reduce the risk of early graft rejection following hepatic and cardiac transplantation.⁴ We conducted a double blind controlled trial of UDCA therapy followed by TIW in 26 liver recipients to (a) determine if UDCA would facilitate TIW, (b) assess the safety of attempting TIW and (c) determine predictors of success of TIW.

Patients and methods

Records were reviewed and all patients who had been free of rejection for a minimum of 2 years, and on single or double drug immunosuppression, with transaminase levels <1.5 times the upper limit of normal, were invited to participate. Twenty six (13 male) patients gave informed consent and entered the study. Baseline liver biopsies were obtained, and a priori data related to pre-transplant and post-transplant patient variables were recorded. UDCA (15 mg/kg) or identical placebo capsule was administered, followed by sequential withdrawal of azathioprine (AzA) or prednisone and then graded reduction in ciclosporin (CyA) dose. Endpoints were defined as graft dysfunction (alanine aminotransferase >2× normal) with biopsy confirmation of abnormalities, or 6 months of no immunosuppression and no rejection on repeated biopsy. Rescue therapy for rejection was reinstitution of previous treatment, bolus steroid treatment with tapering or conversion to Tacrolimus based therapy.

Results

The UDCA and placebo groups had similar baseline characteristics (table 1). Rejection episodes occurred in 6/14 (43%) patients in the UDCA group and in 9/12 (75%) of those on placebo ($p = 0.09$) (fig 1). Time to rejection, degree of rejection (blind biopsy review) and immunosuppression at the time rejection developed were similar in the two groups.

All responded to rescue therapy; none developed chronic rejection. All rejection episodes developed during CyA tapering, with a mean daily dose of 105 mg with whole blood levels <50 ng/ml in all patients. Only 1/6 patients (17%) with alcoholic liver developed rejection. Nine of the remaining 11 patients developed graft dysfunction without evidence of rejection. Three of four patients (75%) with autoimmune hepatitis (AIH) had recurrence of the disease with immunosuppression withdrawal.

Figure 1 Liver histology revealing multiple plasma cells (arrowed).

Table 1 Diagnostic scoring system of the American Association for the Study of Liver Diseases

Category	Factor	Score
Sex	Female	+2
ALP:AST (or ALT) ratio	>3	-2
	<1.5	+2
γ-globulin or IgG (× above upper limit of normal)	>2.0	+3
	1.5–2.0	+2
	1.0–1.5	+1
	<1.0	0
ANA, SMA or anti-LKM1 titres	>1:80	+3
	1:80	+2
	1:40	+1
	<1:40	0
AMA	Positive	-4
Viral markers of active infection	Positive	-3
	Negative	+3
Hepatotoxic drugs	Yes	-4
	No	+1
Alcohol	<25 g/day	+2
	>60 g/day	-2
Concurrent immune disease	Any non-hepatic disease of an immune nature	+2
Other autoantibodies	Anti-SLA/LP, actin, LC1, pANCA	+2
Histological features	Interface hepatitis	+3
	Plasma cells	+1
	Rosettes	+1
	None of the above	-5
	Biliary changes	-3
	Atypical features	-3
HLA	DR3 or DR4	+1
Treatment response	Remission alone	+2
	Remission with relapse	+3
Pretreatment score		
Definite diagnosis		>15
Probable diagnosis		10–15
Post-treatment score		
Definite diagnosis		>17
Probable diagnosis		12–17

ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibodies; ANA, antinuclear antibodies; anti-SLA/LP, antibodies to soluble liver antigen/liver pancreas; anti-LC1, antibodies to liver cytosol type 1; AST, aspartate aminotransferase; LKM, antiliver, kidney and pancreas antibodies; pANCA, perinuclear antineutrophil cytoplasmic antibodies.

One year after withdrawal only two patients were completely free of immunosuppression use but 4/5 previous users of prednisone were using no steroids, and the mean dose of CyA was <50% of that at entry. Age greater than 60 years, underlying primary alcoholic liver disease (ALD) and no (CyA+AzA) immunosuppression regimen were the only three

favourable variables that could predict successful total immunosuppression withdrawal in 82% of cases.

Discussion

UDCA did not appear to decrease the frequency of acute rejection although the number of

patients is insufficient to exclude an effect. UDCA may prevent rejection by decreasing HLA class I antigen and interleukin 6 expression, both important mediators in the process of transplant rejection.^{5–7} Although the rate and intensity of rejection were similar to that of previous reports,^{1–3} all but one patient responded to rescue therapy and no cases of chronic rejection or mortality were seen. The mechanism of recurrence of AIH early after withdrawal of immunosuppression is unknown. However, HLA-DR3 or HLA-DR4 positive recipients are at risk of recurrence regardless of donor HLA status.⁸

The reasons why liver grafts develop tolerance in ALD patients after immunosuppression withdrawal is unclear. One explanation is that these patients may have continued to drink alcohol after liver transplantation which maintains some degree of immunosuppression⁹; however, liver biopsy at 6 months did not show any evidence of alcoholic injury. Whether these patients had more liver endothelial cell chimerism or more diminished dendritic cell numbers than those experiencing rejection is under investigation.

Conclusion

We have shown that late total immunosuppression withdrawal in stable liver transplant recipients is safe but seldom successful and most useful for patients transplanted for ALD and not for patients transplanted for autoimmune liver disease. We suggest that the search for an accurate means of identifying allograft tolerance among immunosuppressed recipients should become a priority in liver transplantation.

N Assy, P C Adams, P Myers, V Simon, C N Ghent

Liver Unit, Sieff Hospital, Safed, Technion Institute, Israel, and Multi Organ Transplant Unit and Department of Medicine, London Health Science Centre, London, Ontario, Canada

Correspondence to: Dr N Assy, Head Liver Unit, Sieff Hospital, Safed, 13100, Upper Galilee, Israel; assy.n@ziv.health.gov.il

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Figure 1 Number of patients with acute rejection in the ursodeoxycholic acid (UDCA) and placebo groups after complete immunosuppression withdrawal.