Liver transplantation and autoimmunity

E. Jaeckel, H. L. Tillmann, M. P. Manns

Department Gastroenterology / Hepatology, Hannover, Germany.

Abstract

Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) represent good indications for orthotopic liver transplantation (OLT). While there is effective treatment for AIH (steroids with or without azathioprine) and PBC (ursodeoxycholic acid) no such treatment is currently established for PSC. The need of transplantation can be delayed for AIH and PBC with appropriate therapies, while treatment options for PSC are still controversially discussed. Although the time point for liver transplantation can be roughly estimated for AIH by failure of immunosuppressive therapy and for PBC by prognostic models, the prediction of survival in patients with PSC is more difficult, and further complicated by the risk of developing cholangiocellular carcinoma. Long term (5-year) outcome after liver transplantation approaches 80 to 90% for autoimmune liver diseases unless cholangiocellular carcinoma complicates PSC at the time of OLT. The risk of disease recurrence has been recognised for each of these entities although its clinical relevance is controversial and not exactly determined today. As survival after liver transplantation is steadily increasing, recurrent autoimmune liver disease may become a clinical problem in the future. Recently de novo autoimmune hepatitis after liver transplantation has been reported from several transplant centres, although its importance still needs to be established. (Acta gastroenterol. belg., **1999**, 62, **323-329**).

Key words : primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, prognostic model, liver transplantation, disease recurrence, de-novo autoimmune hepatitis.

1) Timing of liver transplantation for autoimmune liver disease

There are three major entities of liver diseases with presumed autoimmune background, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH) eventually leading to liver cirrhosis and subsequent liver failure (1).

A major goal of caring for patients with AILD is to preserve or improve liver function by slowing disease progression, and to identify patients at risk of deterioration and eventually need of liver transplantation. For the latter patients it is important to identify the most optimal time point for liver transplantation. This point is reached when the quality of the patient's life is sufficiently diminished, life threatening complications of end-stage organ dysfunction or portal hypertension are likely to occur and when liver transplantation has the best chance of achieving maximal survival success with minimal complications compared to the natural course of the disease.

Autoimmune hepatitis (AIH)

Although there are different types of autoimmune hepatitis the clinical presentation might be similar with only slight differences. The different forms are characterised by specific autoantibody patterns (1). While prognosis of untreated autoimmune hepatitis is unfavourable, the ten year survival of adequately treated adult patients was similar to that of an age and gender matched cohort in a recent report (2). However, in children the disease often runs a more severe course despite adequate treatment (3).

The standard treatment achieving remission in most patients compromises prednisolone either alone or in combination with azathioprine (4,5). In adults deterioration of liver function despite adequate immunosuppression is associated with prolonged prothrombin time, low level of serum albumin and histological evidence of confluent necrosis (2). In children prolonged prothrombin time as well as high bilirubin levels have been shown to predict a poor outcome (3). In adult patients the presence of HLA DRB1 is associated with poor treatment response, further augmented by the presence of DRB3, which both encode a leucine at position 71 of the DRβ polypeptide (6).

As the vast majority of patients with autoimmune hepatitis are likely to respond to immunosuppressive treatment even at advanced stages of the disease, the decision regarding transplantation should be made carefully. Liver transplantation should be especially considered if no remission can be achieved with standard immunosuppression. Alternative treatment options like cyclosporine (2), budenoside (3), tacrolimus or mycophenolate are under investigation. As autoimmune hepatitis can resolve after bone marrow transplantation (7), adoptive transfer of cellular immunity might be a future option for patients with autoimmune hepatitis.

The American Association for the Study of the Liver (AASLD) and the American Society of Transplant Physicians recommend liver transplantation for patients with a Child-Pugh score equal or higher than 7 or

Corresponding author : Michael P. Manns, MD, Medizinische Hochschule Hannover, Department Gastroenterology / Hepatology, Carl Neuberg Str. 1, D-30625 Hannover, Germany.

Table 1. — **Prognostic models for PBC without OLT**

	Yale (13)	European (15)	European II (17)	Mayo (16)
Patients	280	248	237	312
Year	1983	1985	1993	1989
Follow-up	6.9	*	2.9 y	6.3 y
Cross verified	no	yes	yes	yes
Prognostic index	no	yes	yes	yes
Independent risk factors	Age Bilirubin Hepatomegaly	Age Bilirubin Albumin	Age Bilirubin Albumin Ascites Variceal bleeding	Age Bilirubin Albumin Prothrombin time Edema
Histology	Fibrosis/Cirrhosis	Cirrhosis Cholestasis	(Cirrhosis) (Cholestasis) (Low IgM)	

Table 2. — **Prognostic index formulas for PBC**

Mayo (16)	PI = 0.00696* ((Age yrs-20)/10) + 2.52*$\log_{10}$(Bilirubin µmol) - 0.5*(Albumin g/l) + 0.88*(Cirrhosis P/A) + 0.68*(Cholestasis P/A) + 0.52*(Not treated with azathioprine)
European (15)	PI = 0.039*(Age yrs) + 0.87*$\log_e$(Bilirubin mg/dl) - 2.53*(Albumin g/dl) + 2.38*loge(Prothrombin time sec) + 0.859*(Oedema P/A)
European II (17)	PI = 0.040*(Age yrs - 55) + 2.53*$\log_{10}$(Bilirubin µmol/ - 1.53) + 0.085*(Albumin g/l - 34.3) + 1.39*(Ascites P/A) + 0.65*(Variceal bleeding P/A)
Europ.II histo (17)	PI = 0.027*(Age yrs - 55) + 2.26*$\log_{10}$(Bilirubin µmol/ - 1.53) - 0.070*(Albumin g/l - 34.3) + 1.18*(Ascites P/A) + 0.95*(Variceal bleeding P/A) + 0.87*(Cirrhosis bleeding P/A) + 1.22*(Cenral Cholestasis P/A) - 0.9*log10(IgM g/l - 0.47)

P = 1 if present ; A = 0 if absent.

showing portal hypertensive gastrointestinal bleeding (9). Additionally the occurrence of ascites despite adequate treatment of the underlying disease is an indication for OLT (6).

Autoimmune hepatitis usually presents as a chronic disease, however, it can also cause fulminant or subfulminat hepatic failure (9,10). In these patients an auxiliary liver transplant should be evaluated, as they might recover due to the response to immunosuppressive treatment with complete regeneration of the native liver (9).

Primary biliary cirrhosis (PBC)

Several survival models have been created retrospectively on data of large series of PBC patients (Table 1). Most of these studies have been published between 1983 and 1990. Nowadays controlled studies of the natural history vs. liver transplantation appear unethical based on the good results obtained with liver transplantation (11,12). It had been reported early that a serum bilirubin above 10 mg/dl is associated with a poor prognosis of PBC (13) before the first study using Cox multiple regression analysis (14) was published. In a group of 280 patients with PBC age, hepatomegaly, serum bilirubin exceeding 5 mg/dl and the presence of fibrosis in liver biopsy-specimens were found to correlate best with a decreased survival time. The European trial evaluating the effect of azathioprine on PBC has also established a survival model including the first formula for a prognostic index (PI) allowing to estimate the survival probability for a single patient based on age, serum level of bilirubin and albumin, and the histological presence of cirrhosis or centrilobular cholestasis (15) (Tab. 2). As for the following studies, the higher the value of PI, the shorter the expected survival. However, the calculation depends on the results of liver biopsy, an invasive procedure, being subject to sampling variability in PBC, where the liver tissue is not uniformly involved in the disease. Compared with the two former models the model calculated by the Mayo-clinic was independent of histology results (16). Five independent prognostic variables predictive of survival were identified in this model : serum levels of bilirubin and albumin, age, prothrombin time and the presence of peripheral oedema including response to diuretic therapy. The Mayo and the European model are used by most groups nowadays, as they are based on a big number of patients and as they seem to reflect the natural history of PBC quite well. Although not included in the Mayo and the European model, factors like bleeding from oesophageal and gastric varices, intractable ascites, portosystemic encephalopathy, bacterial peritonitis and hepatorenal syndrome are certainly predictors of poor survival, but they are rather presenting the very end stages of PBC, where OLT should be considered anyway. As already suspected (13) serum bilirubin is the most heavily weighted parameter in all formulas.

As the Mayo model (16) was not designed based on follow-up parameters, the European PBC study group calculated a new model for the use of follow-up values and found the following independent, but time dependent variables associated with a poor prognosis : High bilirubin, low albumin, ascites, variceal bleeding and

age (17). In contrast to the time fixed models, the PI can be estimated after each visit thereby reducing possible misinterpretation due to an uneven course of the disease (17).

An association of PBC with HLA DR8-DQB1* 0402 (18) and HLA DRB1*801-DQA1*0401/0601-DQB1*04 (19) has been reported, but no prognostic value of HLA typing in PBC has been established so far. The prognostic relevance for subtyping of the mitochondrial autoantibody response (20) has not been confirmed by other groups. As long-term ursodeoxycholic acid therapy seems to slow disease progression and referral to OLT (16) , the above models probably need to be corrected for this parameter.

In summary, taking into account all clinical parameters and the patients quality of life, transplantation for end stage PBC should be considered in patients with a Mayo Score of greater than 7.5 (corresponding to a median survival time below 18 month), progressive hyperbilirubinemia above 100 to 150 mol/l and or ascites (21,22). Intolerable and unmanageable pruritus or intractable fatigue is a highly subjective criterion and must remain an exception for the indication of liver transplantation. We have to emphasise that one should not stick to the predictive scores, and that transplantation could be advisable even earlier in the course of the disease.

Primary sclerosing cholangitis (PSC)

The natural history of PSC is less clear than the one of PBC. Therefore models predicting the survival of patients with PSC have been developed later and have less predictive power (23). A first study from Yale identified serum bilirubin levels above 1.5 mg/dl and the presence of hepatomegaly as independent risk factors for a bad prognosis of the disease (24). While a subsequent study on a larger cohort of patients from the Mayo clinic found age, bilirubin, haemoglobin level, the histological stage and the presence of inflammatory bowel disease as independent risk factors (25), age, serum alkaline phosphatase, histological stage and presence of hepatomegaly and splenomegaly were identified in a study from the King's College (26) (Tab. 3). Both studies created a formula for calculating the individual risk score (PI) for individual patients (Tab. 4). Later the Mayo model was expanded and age, serum-bilirubin, presence of splenomegaly and the histological stage were identified as independent risk factors for disease progression (Tab. 3-4) (27). This was the only model which could differentiate between patient groups with and without need for OLT (27). Unfortunately the overlap between the two groups was large thereby reducing the usefulness of the index for individual patients. In contrast to the predictive value of Child-Pugh Score in AIH, this factors is not especially helpful in PSC, as liver function is often preserved when OLT is indicated.

The models were all done retrospectively and were not taking into account the beneficial effects of repeated endoscopic dilatation and stenting (28,29) in prolonging survival without OLT. Models of PSC taking into account the dynamic range at different disease stages might reveal alternative parameters for early stages of disease thereby hopefully predicting more precisely the outcome.

An association of PSC with HLA B8, HLA allele DR 3 (B1 locus of HLA DR) and possibly HLA DR52a (B3 locus of HLA DR) has been found, although the association of certain HLA-alleles with the prognosis of the disease is questionable.

Optimal timing of OLT for patients with PSC is complicated by the progressive risk of development of cholangiocellular carcinoma (CCC), incidentally found

Table 3. — **Prognostic models for PSC without OLT**

	Yale (24)	Mayo (25)	King's College (26)	Multicenter (27)
Patients	53	174	126	426
Year	1987	1989	1991	1992
Follow-up	4.7 y	6.0 y	5.8 y	3.0 y
Cross verified	no	no	no	yes
Prognostic index	no	yes	yes	yes
Independent risk factors	Bilirubin	Age Bilirubin Hemoglobin	Age Alkaline phosph.	Age Bilirubin
	Hepatomegaly		Splenomegaly Hepatomegaly	Splenomegaly
Histology		Histology stage	Histology stage	Histology stage

Table 4. — **Prognostic index formulas for PSC**

Mayo (25)	PI = 0.06*(Age yrs) + 0.85*$\log_e$(minimum Bilirubin mg/dl or 10) – 4.39*$\log_e$(minimum Hemoglobin g/dl or 12) + 0.51*(Histology stage) + 1.59*(IBD P/A)
King's College (26)	PI = 0.04*(Age yrs) + 2.66*log(Alkaline phosphatase U/l) + 0.58*(Histology stage) + 0.88*(Splenomegaly P/A) + 1.81*(Hepatomegaly P/A)
Multicenter (27)	PI = 0.41*(Age yrs) + 0.535*$\log_e$(Bilirubin mg/dl) + 0.486*(Histology stage) + 0.705*(Splenomegaly P/A)

P = 1 if present ; A = 0 if absent.

in up to 40% of patients at time of OLT (30,31). The 1 year survival of patients with occult carcinoma can be as low as 25-30% (30,31). Interestingly the multicentre-model (27) might help to identify patients with high risk for development of an occult carcinoma. In a cohort of 48 patients from our clinic the prevalence rate for a CCC was 14.3% in the low risk group compared to 33.3% in the moderate risk group. Similarly the seven year survival was 100% in the low risk, 68% in the moderate risk and 46.8% in the high risk group (30). Altogether, neither current imaging techniques, brush cytology by ERCP nor tumor markers or mathematical models can reliably predict the presence of occult CCC and it is therefore recommended to perform a liver transplantation rather earlier in the disease course. It can be seen that centres transplanting earlier in the disease course have a lower percentage of occult CCC and better survival (review in 30).

2) Outcome of autoimmune liver disease after liver transplantation

Autoimmune hepatitis (AIH)

It is very difficult to study the outcome of OLT for AIH, as immunosuppressive therapy is fortunately leading to remission in 85% of patients thereby avoiding subsequent transplantation in many of them. As AIH is a relatively rare disease, it is difficult to define subgroups of the different subtypes post-OLT (especially for type II and type III (anti-SLA positive)). The five year survival for a large group of patients with AIH type I from the Mayo-Clinic has been reported to be 92% thereby showing no difference to the numbers of patients being in remission under immunosuppression without need for OLT (32).

There has also been a controversy about recurrent disease, as many serological and histological changes reminiscent for AIH might be also caused by posttransplant complications. Similarly the observed decrease of ANA and anti-SMA titres post OLT might just reflect the higher doses of immunosuppression.

By using the diagnostic criteria of AIH and excluding other clinically relevant conditions recurrent AIH type I has been reported in 0 to 25% of cases (33-35) with 11% in the large Mayo clinic series (32), mostly occurring once immunosuppression has been reduced. The course of the recurrent disease is usually mild and responds well to an increase of immunosuppression. Moreover transplant recipients with former AIH type I experience more episodes of acute and chronic rejection the former ones being more often resistant to steroids (32,36). However there is also a recent report about an aggressive course of recurrent disease in 5/6 patients with early recurrence of cirrhosis in 3/7 (37). The few abstract reports of recurrent AIH type II seem to suggest even more episodes of prolonged rejection, also no definite conclusions can be drawn so far.

Primary biliary cirrhosis (PBC)

PBC is one of the three most common indications for OLT in most transplant centres. Five year survival can be as high 95% in some series (38) and is clearly superior to the estimated survival without OLT in several studies. Many surveys report about clear benefit for patients in quality of life despite bone disease, the main disease specific complication post OLT.

There has been a big controversy whether PBC recurs post-OLT (38-42) or not (43-45), but during the last few years there is growing evidence supporting the hypothesis of the recurrence of the disease.

The reason for the controversy may be, that many parameters used for establishing the diagnosis of PBC are not helpful in the posttransplant setting. Cholestatic liver enzymes and histologic damages to bile ducts can have multiple reasons after liver transplantation. Aetiologies like rejection, cholangitis, arterial hypoperfusion and drug treatment may cause similar changes as seen in PBC. Anti-mitochondrial antibody-titres (AMA) have been reported to stay elevated after OLT as well as to be decreased. Nevertheless AMAs are also found in asymptomatic relatives of PBC-patients and they are not even correlated with disease activity before OLT. The same holds true for IgM elevation, which rather seems to be an immunlogical B-cell defect, probably not cured by OLT, but masked by immunosuppression.

Therefore careful histologic evaluation seems to be the only method to prove disease recurrence. As many histologic lesions are not specific in the post-OLT setting, one has to look rather to the spectrum of changes and to exclude other reasons for the lesions by clinical means (39). Many groups reporting about disease recurrence between eight and 16% of patients within 5 years of follow-up (38-42) are supported by recent immunhistological findings of early PBC specific staining patterns in 73% of patients post OLT. Therefore disease recurrence might rather be the rule than the exception (46).

Nevertheless, just very little is known about the natural history of recurrent PBC. As expected from the long-lasting course of PBC before OLT, recurrence is unlikely to be important for the early graft loss (38,39,41,42), but with patients surviving longer post OLT it might become a future problem. There are even a few case reports indicating recurrent cirrhosis within 5 years (42), although it is unclear, if other factors might have contributed to this outcome. Different immunosuppressive regimens are likely to influence long-term outcome. Recurrence of PBC also stimulates the discussion about the pathogenesis of the disease.

Primary sclerosing cholangitis (PSC)

PSC accounts for 5.4 to 14.6% of all OLTs performed. OLT for end stage PSC gives excellent results with a 5 year survival rate up to 87% (47) and improved

quality of life thereby clearly exceeding predicted survival without OLT.

Disease recurrence of PSC is still controversial (48). Although most recent studies are suggestive of recurrent disease (47,49-53), definitive results will probably just obtained once we have a better understanding of the pathogenesis of the disease and once we will be able to find a disease specific criterion even for early stages of the disease.

ERCP just defines the progressed stages of the pre-transplant disease and "typical findings" might be also due to arterial stenosis, cold ischemia time, ABO incompatibility, CMV-infection, rejection or secondary sclerosing cholangitis post OLT. Histological diagnosis of recurrent PSC might mislead because of the same reasons. Although some histological findings like fibroobliterative lesions are thought to be disease specific, they are just found in 12 to 40% of PSC patients pre-OLT (54). Cholestatic liver enzymes and pANCAs are non-specific and insensitive as well. By trying to exclude above disease conditions recurrence rates of 8 to 12% are suggested by histological criteria during the first years of follow-up. In one series the histological lesions are quantitatively and qualitatively different to a control group with Roux-Y anastomosis without PSC (53). Recurrent disease does not seem to have a significant impact on short term survival, although the natural history for longer periods is not known. The optimal treatment regimen for recurrent disease is not known at all. One group assuming an autoimmune aetiology suggests increased immunosuppression, while another group assuming possibly enteral derived pathogens might favours low immunosuppression and antibiotic treatment (55).

Inflammatory bowel disease (IBD), present in 60 to 80% of PSC patients, usually returns after OLT with 60% of patients experiencing a more benign course under immunosuppression, but 20% might even deteriorate (56). Taken together concomitant PSC and IBD seems to predispose for a higher rate of rejections, retransplantations (47,57) and there are even hints for an increased rate of colorectal cancer in this setting (58,59).

De-novo autoimmune hepatitis after OLT

Recently a syndrome of late graft dysfunction has been reported in children (60) and adults (61,62) closely resembling autoimmune hepatitis, which was rather responding to immunosuppression schemes used in AIH than to those used for treating rejection. The syndrome consists of elevated IgG, high titres of autoantibodies and typical histologic lesions and has been observed in about 4% of liver transplant recipients with different pretransplant liver diseases. As some of these patients already had elevated IgG levels and insignificant autoantibody titres pre-OLT, the significance of this entity still needs to be established. So far all patients seem to respond to classical immunosuppressive therapy used for AIH.

Conclusions

Orthotopic liver transplantation is good a treatment option for end stage autoimmune liver disease with favourable 5 year survival. Medical treatment can prevent or delay the need for liver transplantation in autoimmune hepatitis and primary biliary cirrhosis and probably also in primary sclerosing cholangitis. Although the time point for liver transplantation can be roughly estimated for AIH by failure of immunosuppressive therapy and for PBC by prognostic models, the prediction of survival in patients with PSC is more difficult, and further complicated through the risk of developing cholangiocellular carcinoma. Better models of predicting disease progression will certainly be available in the future, as multicentre analysis with more patients are currently investigated. The risk of disease recurrence has been recognised for each of these entities although its clinical relevance is controversial and not exactly determined today. As survival after liver transplantation is steadily increasing, recurrent autoimmune liver disease may become a clinical problem in the future. Recently, de novo autoimmune hepatitis after liver transplantation has been reported from several transplant centres, although its importance still needs to be established.

References

1. MANNS M.P. Recent developments in autoimmune liver diseases. *J. Gastroenterol. Hepatol.*, 1997 Oct, **12** (9-10) : S256-S271
2. PERSON J.L., MCHUTCHISON J.G., FONG T.L., REDEKER A.G. A case of cyclosporine-sensitive, steroid-resistant, autoimmune chronic active hepatitis. *J. Clin. Gastroenterol.*, 1993, **17** : 317-320.
3. SCHÜLER A., MANNS M.P. Treatment of autoimmune hepatitis. *In* : ARROYO V., BOSCH J., RODEZ J. (eds). Treatment in Hepatology. 1995, 375-383.
4. COOK G.C., MULLIGAN R., SHERLOCK S. Controlled prospective trial of corticosteroid therapy in active chronic hepatitis. *Q.J.Med.*, 1971, **40** : 159.
5. COMBES B., MADDREY W.C. Therapy of idiopathic autoimmune chronic active hepatitis. *In* : MEYER ZUM BÜSCHENFELDE K.H., HOOFNAGLE J., MANNS M.P. (eds). Immunology of the liver : Proceeding of the Falk Symposium 1970 held in Basel, Switzerland. pp. 250-256. Kluwer Academic Publishers 1993. Dordrecht.
6. CZAJA A.J., STRETTELL M.D.J., THOMSON L.J., SANTRACH P.J., MOORE S.B., DONALDSON P.T., WILLIAMS R. Association between a alleles of the major histocompatibility complex in autoimmune hepatitis. *Hepatology*, 1997, **25** : 317-323.
7. VENTO S., CAINELLI F., RENZINI C., GHIRONZI G., CONCIA E. Resolution of autoimmune hepatitis after bone marrow transplantation. *Lancet*, 1996, **348** : 544-545
8. LUCEY M.R., BROWN K.A., EVERSON G.T., FUNG J.J., GISH R., KEEFFE E.B., KNETEMAN N.M., *et al.* Minimal criteria for placement of adults on the liver transplant waiting list : A report of a national Conference organized by the American Society of Transplant Physicians and the American Association of the Study of Liver Disease. *Liver Transplant and Surgery*, 1997, **3** : 628-637.
9. CHENARD-NEU M.P., BOUDJEMA K., BERNUAU J., DEGOTT C., BELGHITI J., CHERQUI D., COSTES V. *et al.* Auxilliar liver transplantation : Regeneration of the native liver and outcome in 30 patients with fulminant hepatic failure — a multicenter European study. *Hepatology*, 1996, **23** : 1119-1127.

10. HERZOG D., RASQUIN-WEBER A.M., DEBRAY D., ALVAREZ F. Subfulminant hepatic failure in autoimmune hepatitis type 1 : An unusual form of presentation. *J. Hepatol.*, 1997, **27** : 578-582.
11. KNOOP M., BECHSTEIN W.O., SCHREM H., LOBECK H., HOPF U., NEUHAUS P. Clinical significance of recurrent primary biliary cirrhosis after liver transplantation. *Transpl. Int.*, 1996, **9** (Suppl 1) : S115-S119.
12. KEIDING S., ERICZON B.G., ERIKSSON S., FLATMARK A., HOCKERSTEDT K., ISONIEMI H., KARLBERG I. *et al.* Survival after liver transplantation of patients with primary biliary cirrhosis in the Nordic countries. Comparison with expected survival in another series of transplantations and in an international trial of medical treatment. *Scand. J. Gastroenterol.*, 1990, **25** : 11-18.
13. SHAPIRO J.M., SMITH H., SCHAFFNER F. Serum bilirubin : a prognostic factor in primary biliary cirrhosis. *Gut*, 1979, **20** : 137-140.
14. ROLL J., BOYER J.L., BARRY D., KLATSKIN G. The prognostic importance of clinical and histologic features in asymptomatic and symptomatic primary biliary cirrhosis. *N. Engl. J. Med.*, 1983, **308** : 1-7.
15. CHRISTENSEN E., NEUBERGER J., CROWE J., ALTMAN D.G., POPPER H., PORTMANN B., DONIACH D., RANEK L., TYGSTRUP N., WILLIAMS R. Beneficial effect of azathioprine and prediction of prognosis in primary biliary cirrhosis. Final results of an international trial. *Gastroenterology*, 1985, **89** : 1084-1091.
16. DICKSON E.R., GRAMBSCH P.M., FLEMING T.R., FISHER L.D., LANGWORTHY A. Prognosis in primary biliary cirrhosis : model for decision making. *Hepatology*, 1989, **10** : 1-7.
17. CHRISTENSEN E., ALTMAN D.G., NEUBERGER J., DE STAVOLA B.L., TYGSTRUP N., WILLIAMS R. Updating prognosis in primary biliary cirrhosis using a time-dependent Cox regression model. PBC1 and PBC2 trial groups. *Gastroenterology*, 1993, **105** : 1865-1876.
18. UNDERHILL J., DONALDSON P., BRAY G., DOHERTY D., PORTMANN B., WILLIAMS R. Susceptibility to primary biliary cirrhosis is associated with the HLA-DR8-DQB1*0402 haplotype. *Hepatology*, 1992, **16** : 1404-1408.
19. BEGOVICH A.B., KLITZ W., MOONSAMY P.V., VAN DE WATER J., PELTZ G., GERSHWIN M.E. Genes within the HLA class II region confer both predisposition and resistance to primary biliary cirrhosis. *Tissue Antigens*, 1994, **43** : 71-77.
20. KLEIN R., KLOPPEL G., GARBE W., FINTELMANN V., BERG P.A. Antimitochondrial antibody profiles determined at early stages of primary biliary cirrhosis differentiate between a benign and a progressive course of the disease. A retrospective analysis of 76 patients over 6-18 years. *J. Hepatol.*, 1991, **12** : 21-27.
21. WIESNER R.H., PORAYKO M.K., DICKSON E.R., GORES G.J., LARUSSO NF, HAY J.E., WAHLSTROM H.E., KROM R.A. Selection and timing of liver transplantation in primary biliary cirrhosis and primary sclerosing cholangitis. *Hepatology*, 1992, **16** : 1290-1299.
22. Consensus statement on indications for liver transplantation : Paris, June 22-23, 1993. *Hepatology*, 1994, **20** : 63S-68S.
23. BROOME U., ERIKSSON L.S. Assessment for liver transplantation in patients with primary sclerosing cholangitis. *J. Hepatol.*, 1994, **20** : 654-659.
24. HELZBERG J.H., PETERSEN J.M., BOYER J.L. Improved survival with primary sclerosing cholangitis. A review of clinicopathologic features and comparison of symptomatic and asymptomatic patients. *Gastroenterology*, 1987, **92** : 1869-1875.
25. WIESNER R.H., GRAMBSCH P.M., DICKSON E.R., LUDWIG J., MACCARTY R.L., HUNTER E.B., FLEMING T.R., FISHER L.D., BEAVER S.J., LARUSSO N.F. Primary sclerosing cholangitis : natural history, prognostic factors and survival analysis. *Hepatology*, 1989, **10** : 430-436.
26. FARRANT J.M., HAYLLAR K.M., WILKINSON M.L., KARANI J., PORTMANN B.C., WESTABY D., WILLIAMS R. Natural history and prognostic variables in primary sclerosing cholangitis. *Gastroenterology*, 1991, **100** : 1710-1717.
27. DICKSON E.R., MURTAUGH P.A., WIESNER R.H., GRAMBSCH P.M., FLEMING T.R., LUDWIG J., LARUSSO N.F., MALINCHOC M., CHAPMAN R.W., KAPLAN M.M. *et al.* Primary sclerosing cholangitis : refinement and validation of survival models. *Gastroenterology*, 1992, **103** : 1893-1901.
28. STIEHL A., RUDOLPH G., SAUER P., BENZ C., STREMMEL W., WALKER S., THEILMANN L. Efficacy of ursodeoxycholic acid treatment and endoscopic dilation of major duct stenoses in primary sclerosing cholangitis. An 8-year prospective study. *J. Hepatol.*, 1997, **26** : 560-566.
29. WAGNER S., GEBEL M., MEIER P., TRAUTWEIN C., BLECK J., NASHAN B., MANNS M.P. Endoscopic management of biliary tract strictures in primary sclerosing cholangitis. *Endoscopy*, 1996, **28** : 546-551.
30. NASHAN B., SCHLITT H.J., TUSCH G., OLDHAFER K.J., RINGE B., WAGNER S., PICHLMAYR R. Biliary malignancies in primary sclerosing cholangitis : timing for liver transplantation. *Hepatology*, 1996, **23** : 1105-1111.
31. DELCORE R., EISENACH J.B., PAYNE K.M., BHATIA P., FORSTER J. Risk of occult carcinomas in patients undergoing orthotopic liver transplantation for end-stage liver disease secondary to primary sclerosing cholangitis. *Transplant Proc.*, 1993, **25** : 1883-1884.
32. SANCHEZ-URDAZPAL L., CZAJA A.J., VAN HOEK B., KROM R.A.F., WIESNER R.H. Prognoszic features and role of liver transplantation in severe corticosteroid-treated autoimmune chronic active hepatitis. *Hepatology*, 1991, **15** : 215-22.
33. SEMPOUX C., HORSMAN Y., LERUT J., RAHIER J., GEUBEL A. Acute lobular hepatitis as the first manifestation of recurrent autoimmune hepatitis after othotopic liver transplantation. *Liver*, 1997, **17** : 311-315.
34. DEVLIN J., DONALDSON P., PORTMANN B., HEATON N., TAN K.C., WILLIAMS R. Recurrence of autoimmune hepatitis following liver transplantation. *Liver Transpl. Surg..*, 1995, **1** : 162-165.
35. NEUBERGER J. Recurrence of primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune hepatitis. *Liver Transpl. Surg.*, 1995, **1** (Suppl. 1) : 109-115.
36. HERRERA J., MARTIN P., SHACKLETON C., GOLDSTEIN L., SHAKED A., BUSUTTIL R.W. Acute cellular rejection of liver allografts is increased in frequency in patients with autoimmune idiopathic chronic active hepatitis. *Hepatology AASLD*, 1995.
37. BIRNBAUM A.H., BENKOV K.J., PITTMAN N.S., MCFARLANE-FERREIRA Y., ROSH J.R., LELEIKO N.S. Recurrence of autoimmune hepatitis in children after liver transplantation. *J. Pediatr. Gastroenterol. Nutr..*, 1997, **25** : 20-25.
38. KNOOP M., BECHSTEIN W.O., SCHREM H., LOBECK H., HOPF U., NEUHAUS P. Clinical significance of recurrent primary biliary cirrhosis after liver transplantation. *Transpl. Int.*, 1996, **9** (Suppl. 1) : S115-S119.
39. HUBSCHER S.G., ELIAS E., BUCKELS J.A.C., MAYER A.D., MCMASTER P., NEUBERGER J.M. Primary biliary cirrhosis : Histological evidence for disease recurrence after liver transplantation. *J. Hepatol.*, 1993, **18** : 173-184.
40. NEUBERGER J., PORTMANN B., MACDOUGALL B.R.D., CALNE R.Y., WILLIAMS R. Recurrence of primary biliary cirrhosis after liver transplantation. *N. Engl. J. Med.*, 1982, **306** : 1-4.
41. POLSON R.J., PORTMANN B., NEUBERGER J., CALNE R.Y., WILLIAMS R. Evidence for disease recurrence after liver transplantation for primary biliary cirrhosis. *Gastroenterology*, 1989, **97** : 715-25.
42. DIETZE O., VOGEL W., MARGREITER R. Primary biliary cirrhosis after liver transplantation. *Transpl. Proc.*, 1990, **22** : 1501-2.
43. ESQUIVEL C.O., VAN THIEL D.G., DEMETRIS A.J. *et al.* Transplanation for primary biliary cirrhosis. *Gastroenterology*, **94** : 1207-16.
44. HAAGSMA E.B., MANNS M., KLEIN R. *et al.* Subtypes of antimitchondrial antibodies in primary biliary cirrhosis before and after liver transplantation. *Hepatology*, 1987, **7** : 129-33.
45. DEMETRIS A.J., MARKUS B.H., ESQUIVEL C. *et al.* Pathologic analysis of liver transplantation for primary biliary cirrhosis. *Hepatology*, 1988, **8** : 939-47.
46. VAN DE WATER J., GERSON L.B., FERREL L.D., LAKE J.R., COPPEL R.L., BATTS K.P., WIESNER R.H., GERSHWIN M.E. Immunohistochemical evidence of disease recurrence after liver transplantation for primary biliary cirrhosis. *Hepatology*, 1996, **24** : 1079-1084.
47. NARUMI S., RIBERTS J.P., EMOND J.C., LAKE J., ASCHER N.L. Liver transplantation for sclerosing cholangitis. *Hepatology*, 1995, **22** : 451-457.
48. BOYER T.D. Does primary sclerosing cholangitis recur after liver transplantation ? No ! *Liver Transpl. Surg.*, 1997, **3** (5 Suppl 1) : S24-25.
49. HUNTER E.B., WIESNER R.H., MACCARTY R.H., LARUSSO N.F., PORAYKO M.K., EID A., KROM R.A.F. Does primary sclerosing cholangitis recur after liver transplantation ? *Gastroenterology*, 1989, **96** : A610.
50. LERUT J., DEMETRIS A.J., STIEBER A.C., MARSH J.W., GORDON R.D., ESQUIVEL C.O., IWATSUKI S. *et al.* Intrahepatic bile duct strictures after human othotopic liver transplantation : recurrence of primary sclerosing cholangitis or unknown presentation of allograft rejection ? *Transplant. Int.*, 1988, **1** : 127-130.
51. HARRISON J., MCMASTER C. The role of orthotopic liver transplantation in the management of sclerosing cholangitis. *Hepatology*, 1994, **20** : 14S-19S.
52. GOSS J.A., SHACKLETON C.R., FARMER D.G., ARNAOUT W.S.,

SEU P., MARKOWITZ J.S., MARTIN P., STRIBLING R.J., GOLDSTEIN L.I., BUSUTTIL R.W. Orthotopic liver transplantation for primary sclerosing cholangitis. A 12-year single center experience. *Ann. Aurg.*, 1997, **225** : 472-481.

53. HARRISON R.F., DAVIES M.H., NEUBERGER J.M., HUBSCHER S.G. Fibrous and obliterative cholangitis in liver allografts : Evidence of recurrent primary sclerosing cholangitis ? *Hepatology*, 1994, **20** : 356-361.
54. MCSWEEN R.N.M. Primary sclerosing cholangitis. Recent advances in histopathology, 1984, **12** : 158-167.
55. KAPPLAN M.M. Toward better treatment of primary sclerosing cholangitis. *Lancet*, 1997, **336** : 719-721.
56. STEPHENS J., GOLDSTEIN R. CRIPPIN J., HUSBERG B., HOLMAN M., GONWA T.A., KLINTMALM G. Effects of orthotopic liver transplantation and iimunosuppression on inflammatory bowel disease in primary sclerosing cholangitis. *Transpl. Proc.*, 1993, **25** : 1122-1123.
57. MIKI C., HARRISON J.D., GUNSON B.K., BUCKELS J.A., MCMASTER P., MAYER A.D. Inflammatory bowel disease in primary sclerosing cholangitis : An analysis of patients undergoing liver transplantation. *Br. J. Surg.*, 1995, **82** : 1114-1117.
58. HIGASHI H., YANAGA K., MARSH J.W., TZAKIS A., KAKIZOE S., STARZL T.E. Development of colon cancer after liver transplantation for primary sclerosing cholangitis associated with ulcerative colitis. *Hepatology*, 1990, **11** : 477-480.
59. BLEDAY R., LEE E., JESSURUN J., HEINE J., WONG W.D. Increased risk of early colorectal neoplasms after hepatic transplant in patients with inflammatory bowel disease. *Dis. Colon Rectum*, 1993, **36** : 908-912.
60. KERKAR N., HADZIC N., DAVIES E.T., PORTMANN B., DONALDSON P.T., RELA M., HEATON N.D., VERGANI D., MIELI-VERGANI G. De-novo autoimmune hepatitis after liver transplantation. *Lancet*, 1998, **351** : 409-413.
61. HERANDEZ A.A., ALVAREZ E., SALCEDO M. *et al.* Autoimmune mediated liver disease after liver transplanation. *J. Hepatol.*, 1997, **26** (Suppl.) 152.
62. CONTI F., DOUSSET B., LEVILLAYER H., GRUSKA J., WEILL B., CALMUS Y. Autoantibodies after liver transplantation : a marker of allograft disease. *J. Hepatol.*, **26** (Suppl) : 150.