Clinical Performance of HBIg in Preventing Recurrent HBV After Liver Transplantation

David K. Imagawa, MD, PhD

Professor of Clinical Surgery

Department of Hepatobiliary and Pancreas Surgery

University of California, Irvine Medical Center

July 2006

Introduction

- Orthotopic liver transplantation (OLT) remains the primary curative modality for end-stage liver disease from chronic hepatitis B (HBV) infection

- Initial attempts at OLT without immunoprophylaxis in this patient population resulted in over 80% re-infection of the allograft followed by accelerated graft failure

Introduction

- Extra-hepatic reservoirs of HBV, such as peripheral blood mononuclear cells and various organs, likely contributed to the high rate of re-infection

- These disappointing results caused many centers to abandon transplantation as a treatment option for chronic HBV infection in the late 1980s

HBIg Immunotherapy

- A review of domestic and international reports on combination therapy with HBIg and a nucleoside analog after OLT reveals consistent results
- Low recurrence rates up to 5 years post-transplant
- Data covers all HBV patients, including patients with high viral loads

Large Studies and Long-term Follow-up for HBIg Combination Therapy

Author	Location	# of Patients	Follow-up	Recurrences
Roche 2003	France	24	60 months	2 (8.3%)
Aribizu 2003	Spain	14	58.8 (15-107) months	1 (7%)*
Honaker 2002	Univ. of Tenn, USA	9	4.2 +/- 1.0 yr	0 (0%)
Dumortier 2003	France	17	30 (12-48) months	0 (0%)
Marzano 2001	Italy	26	29 +/- 9 months	1 (4%)
Engler 2002	Germany	5	26.6 (20-36) months	1 (20%)*
Rosenau 2001	Germany	21	643 (73-1473) days	4 (19%)
Angus 2000	Australia-New Zealand	37	18.4 +/- 12.1 (5-45) months	0 (0%)

*recurrence occurred after deviation from HBIg protocol

Alternatives

There are no good alternatives to HBIg for preventing recurrent HBV after OLT

Lamivudine Monotherapy

- Not a viable solution for all patients
- Routine development of escape mutants/drug resistance
- Historically 24-67% recurrence rate across all patients undergoing OLT for HBV

The UC Irvine Experience

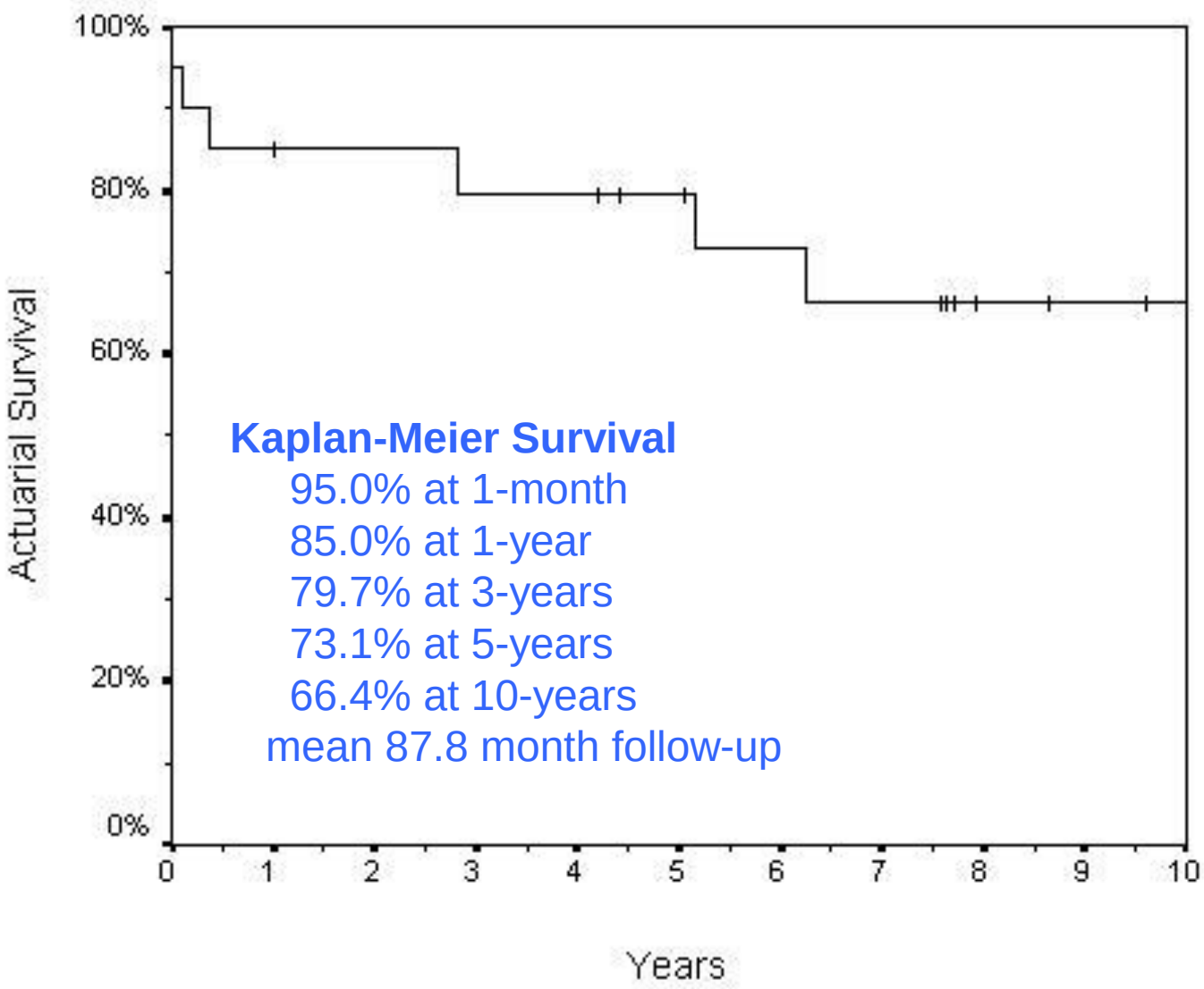
- Patients with HBV-related end-stage liver failure, followed at our institution
- Transplanted between 1993 and 2001 to ensure long-term follow up
- After OLT, all patients received combination therapy with HBIg and lamivudine

The UC Irvine Experience

HBIg Protocol

- During the anhepatic phase, 10,000 IU of HBIg was given intravenously (IV) followed by 10,000 IU of HBIg IV daily for 6 days
- Administration of HBIg was then changed to the intramuscular (IM) route and the frequency of doses was adjusted to maintain HBsAb titers above 150 IU/L
- Patients were evaluated on a monthly basis for the presence of HBV DNA and HBsAg until the HBsAb titers stabilized at therapeutic levels
- Thereafter, serology and HBsAb titers were checked every 2 months.

The UC Irvine Experience



The UC Irvine Experience

Overall Results

# of Patients	# DNA + prior to OLT	Continued HBIg	Recurrent HBV	Follow-up months
10	2	Yes	0 (0%)	80.2 (range 34-115)
6	0	No	3 (50%)	100.6 (range 36.3-148.7)

The UC Irvine Experience

- 3 patients experienced recurrent HBV after cessation of HBIg and institution of lamivudine monotherapy
- Retrospectively, laboratory data demonstrates a marked increase in viral replication as HBsAb titers were depleted

Conclusions

- Published data strongly supports the use of combination therapy with HBIg and a nucleoside analog to prevent recurrent HBV after OLT
- There are no viable alternatives at this time

References

- Anselmo DM, Ghobrial RM, Busuttil RW., et al. New era of liver transplantation for hepatitis B: a 17-year single-center experience. Ann Surg. 2002 May;235(5):611-9; discussion 619-20.
- Todo S, Demetris AJ, Van Thiel D, et al. Orthotopic liver transplantation for patients with hepatitis B virus-related liver disease. Hepatology 1991;13:619-626.
- O'Grady JG, Smith HM, Davies SE, et al. Hepatitis B virus reinfection after orthotopic liver transplantation. Serological and clinical implications. J Hepatology 1992;14:104-111.
- Omata M. Significance of extrahepatic replication of hepatitis B virus. Hepatology 1990;12:364-366.
- Perillo RP, Mason AL. Hepatitis B and liver transplantation. Problems and promises. N Engl J Med 1993;329:1885-1887.
- Lok AS. Prevention of recurrent hepatitis B post-liver transplantation. Liver Transplantation 2002;8:S67-73.
- Roche B, Feray C, Samuel D, et al. HBV DNA persistence 10 years after liver transplantation despite successful anti-HBS passive Immunoprophylaxis. Hepatology 2003;38:86-95.
- Chu CJ, Fontana RJ, Moore C, et al. Outcome of liver transplantation for hepatitis B: report of a single center's experience.
  Liver Transpl. 2001 Aug;7(8):724-31.
- Han SH, Ofman J, Martin P, et al. An efficacy and cost-effectiveness analysis of combination hepatitis B immune globulin and lamivudine to prevent recurrent hepatitis B after orthotopic liver transplantation compared with hepatitis B immune globulin monotherapy. Liver Transplantation 2000;6:741-748.
- Honaker MR, Shokouh-Amiri MH, Vera SR, et al. Evolving experience of hepatitis B virus prophylaxis in liver transplantation. Transpl Infect Dis. 2002 Sep;4(3):137-43.
- Perillo RP, Wright T, Rakela J, Levy G, et al. A multicenter United States-Canadian trial to assess lamivudine monotherapy before and after liver transplantation for chronic hepatitis B. Hepatology 2001;33:424-432.
- Mutimer D, Dusheiko G, Barrett C, Grellier et al. Lamivudine without HBIg for prevention of graft reinfection by hepatitis B: long-term follow-up. Transplantation 2000;70:809-15.

References

- Malkan G, Cattral MS, Humar A, et al. Lamivudine for hepatitis B in liver transplantation: a single-center experience. Transplantation 2000;69:1403-7.
- Mutimer D, Pillay D, Dragon E, et al. High pre-treatment serum hepatitis B virus titre predicts failure of lamivudine prophylaxis and graft re-infection after liver transplantation. J Hepatology 1999;30:715-721.
- Marzano A, Salizzoni M, Debernardi-Venon W, et al. Prevention of hepatitis B virus recurrence after liver transplantation in cirrhotic patients treated with lamivudine and passive immunoprophylaxis. J Hepatol. 2001 Jun;34(6):903-10.
- Angus PW, McCaughan GW, Gane EJ, et al. Combination low-dose hepatitis B immune globulin and lamivudine therapy provides effective prophylaxis against posttransplantation hepatitis B. Liver Transpl. 2000 Jul;6(4):429-33.
- Neff GW, O'Brien CB, Nery J, et al. Outcomes in liver transplant recipients with hepatitis B virus: resistance and recurrence patterns from a large transplant center over the last decade. Liver Transpl 2004;10:1372-1378.
- Albeniz Arbizu E, Barcena Marugan R, Oton Nieto E, et al. Use of combined treatment of hepatitis B immune globulin and lamivudine as prevention of hepatitis B virus recurrence in liver allograft. Transplant Proc. 2003 Aug;35(5):1844-5.
- Engler S, Sauer P, Klar E, et al. Prophylaxis of hepatitis B recurrence after liver transplantation with lamivudin and hepatitis B immunoglobulin. Transplant Proc. 2002 Sep;34(6):2285-7.
- Dumortier J, Chevallier P, Scoazec JY, et al. Combined lamivudine and hepatitis B immunoglobulin for the prevention of hepatitis B recurrence after liver transplantation: long-term results. Am J Transplant. 2003 Aug;3(8):999-1002.
- Rosenau J, Bahr MJ, Tillmann HL, et al. Lamivudine and low-dose hepatitis B immune globulin for prophylaxis of hepatitis B reinfection after liver transplantation possible role of mutations in the YMDD motif prior to transplantation as a risk factor for reinfection. J Hepatol. 2001 Jun;34(6):895-902.