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HBsAg level at time of liver transplantation determines HBsAg decrease and anti-HBs increase and affects HBV DNA decrease during early immunoglobulin administration☆

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***Background/Aims*: Administration of hepatitis B immunoglobulin (HBIG) initially after liver transplantation of hepatitis B patients is considered important to prevent reinfection reliably. However, dosing schedules differ considerably between centers. We measured HBsAg, anti-HBs and HBV DNA kinetics to create a rational basis for dosing schemes.**

***Methods*: Thirteen patients (group A) received 10,000 IU HBIG in the anhepatic phase followed by 10,000 IU daily until HBsAg became negative, whereas five patients (group B) received 20,000 IU followed by 5000 IU every 30 min.**

***Results*: HBsAg levels at time of transplantation ranged from 0.12 to 12,990 IU/ml. Correlations between initial HBsAg and HBIG required to decrease HBsAg below 1 IU/ml were high in groups A and B ($r = 0.97$, $p < 0.001$; $r = 1.00$, $p < 0.001$), as were correlations between initial HBsAg and HBIG required to raise anti-HBs above 1000 IU/l ($r = 0.94$, $p < 0.001$; $r = 1.00$, $p < 0.001$). In 11 HBV DNA-positive patients, DNA levels became negative in seven, and dropped by 2.5 $\log_{10}$ (mean) in the other four patients during immunoglobulin administration.**

***Conclusions*: In conclusion, required HBIG doses to decrease HBsAg and raise anti-HBs are determined by HBsAg levels at time of transplantation, not by HBV DNA levels. Shortened HBIG dosing intervals accelerate HBsAg decrease and anti-HBs increase. HBV DNA decreases rapidly during HBIG administration in most patients.**

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***Keywords*: Reinfection; Prophylaxis; Surface antigen; Kinetic**

1. Introduction

Hepatitis B recurrence was frequent in absence of hepatitis B reinfection prophylaxis after liver transplantation (OLT), resulting in considerably reduced graft and patient survival [1,2]. Reinfection rates dropped and survival improved significantly with the use of hepatitis B immunoglobulin (HBIG) prophylaxis [3–19]. High viral replication at time of transplantation was shown to be the key risk factor for reinfections in patients receiving HBIG mono-prophylaxis

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[7,12,20,21]. A quantitative relation between HBsAg level at time of transplantation and HBIG dose required for HBsAg elimination was assumed but not verified [22,23].

Early reports on antiviral mono-prophylaxis with lamivudine were encouraging [24]. Disappointingly, reinfections occurred more frequently in following studies, particularly in patients with high viral replication prior to lamivudine initiation [25–31]. Not all reinfections could be attributed to lamivudine resistance [25,28–31], and even with adefovir as salvage therapy, single patients did not clear HBsAg during follow up [32].

Therefore, combined administration of nucleoside and/or nucleotide analogs and HBIG remains the gold standard of reinfection prophylaxis [33–42].

In all these studies, regardless whether HBIG was administered as mono-therapy or in combination with antiviral drugs, different dosing phases can be discriminated. In the initial period, i.e. the anhepatic phase and the first days after transplantation, HBIG is mostly administered in high doses [32–34,36,39,41–46]. During follow up HBIG doses are lowered. However, HBIG dosing in the peri-transplant period differs considerably between transplant centers (Table 1). In most protocols, early HBIG dosing is invariable [31–33,35,39,40,43–46]. In some protocols, every individual receives HBIG amounts of 70,000 or 80,000 U [33,39,44,45]. In contrast, other centers propagate low-dose administration schemes, even in early postoperative phase [31,35,40]. In some centers HBV DNA-positive patients are treated with higher HBIG doses than HBV DNA-negative patients [36,42]. Most German centers administer high-dose HBIG until HBsAg becomes undetectable [34,41].

In this study, quantitative kinetics of HBsAg, anti-HBs and HBV DNA during HBIG administration in the initial phase after transplantation were measured. The study was initiated to establish a rational basis for parameter-oriented cost-effective dosing schemes in reinfection prophylaxis protocols.

Table 1
Reinfection prophylaxis protocols: initial HBIG dosage (days 0–28 after liver transplantation)

Reference	Transplant center	Publ. year	Route of HBIG administration	day 0	day 1	day 2	day 3
Markowitz [33]	USA, Los Angeles	1998	IV	10	10	10	10
Yoshida [35]	Canada, Brit. Columbia	1999	IM	2	2	2	2
Yao [36]	USA, San Francisco	1999	IV	10	10 daily only in HBV DNA-pos. pat.		
Angus [40]	Australia, Melbourne	2000	IM	0.4/0.8	0.4/0.8	0.4/0.8	0.4/0.8
Rosenau [34]	Germany, Hannover	2001	IV	10	10 daily until HBsAg negative		
Lo [25]	China, Hong-Kong	2001	No HBIG	–	–	–	–
Perrillo [30]	USA, New Orleans	2001	No HBIG	–	–	–	–
Seehofer [41]	Germany, Berlin	2002	IV	10	10 daily until HBsAg negative		
Buti [43]	Spain, Barcelona	2003	IV/IM[a]	10	10	5	5
Roche [44]	France, Paris	2003	IV	10	10	10	10
Dumortier [39]	France, Lyon	2003	IV	10	10	10	10
Ferretti [42]	Italy, Rome	2004	IV	10	10	10	10
Marzano [46]	Italy, Turin	2005	IV	10	10	5	5
Zheng [31]	China, Hang Zhou	2006	IM	2	0.8	0.8	0.8
Dickson [45]	USA multicentre	2006	IV	20	10	10	10

Reference	Transplant center	Publ. year	Route of HBIG administration	day 4	day 5	day 6	day 7	day 8–28
Markowitz [33]	USA, Los Angeles	1998	IV	10	10	10	–	10
Yoshida [35]	Canada, Brit. Columbia	1999	IM	2	2	2	–	14
Yao [36]	USA, San Francisco	1999	IV	10 daily only in HBV DNA-pos. pat.				
Angus [40]	Australia, Melbourne	2000	IM	0.4/0.8	0.4/0.8	0.4/0.8	0.4/.08	0.4/0.8
Rosenau [34]	Germany, Hannover	2001	IV	10 daily until HBsAg negative				o.d.
Lo [25]	China, Hong-Kong	2001	No HBIG	–	–	–	–	–
Perrillo [30]	USA, New Orleans	2001	No HBIG	–	–	–	–	–
Seehofer [41]	Germany, Berlin	2002	IV	10 daily until HBsAg negative				o.d.
Buti [43]	Spain, Barcelona	2003	IV/IM[a]	5	5	5	4[a]	
Roche [44]	France, Paris	2003	IV	10	10	10	–	o.d.
Dumortier [39]	France, Lyon	2003	IV	10	10	10	10	
Ferretti [42]	Italy, Rome	2004	IV	10[b]	10[b]	10[b]	10[b]	o.d.
Marzano [46]	Italy, Turin	2005	IV	5	5	5	5	1.5
Zheng [31]	China, Hang Zhou	2006	IM	0.8	0.8	0.8	–	2.4
Dickson [45]	USA multicentre	2006	IV	10	10	10	10	10

IV, intravenous; IM, intramuscular; o.d., on demand; –, no HBIG.
[a] Intramuscular HBIG administration.
[b] Only HBV DNA-positive patients.

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