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Epidemiology and Outcome of Infections in 84 Spanish HCV/HIV-Coinfected Liver Transplant Recipients: A FIPSE/GESIDA Prospective Cohort Study

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ABSTRACT

Background: There are few published data on infections in HCV/HIV-coinfected recipients after liver transplantation (OLT). This study describes the incidence, clinical characteristics, time of onset, and outcome of bacterial, viral, and fungal infections in Spanish HCV/HIV-coinfected OLT recipients.
Methods: The study sample comprised 84 consecutive HCV/HIV-coinfected patients who underwent OLT at 17 Spanish centers between 2002 and 2006 and were followed until December 2007. Data were obtained from the FIPSE OLT-HIV-05-GESIDA 45-05 database. Each site used the same immunosuppressive regimens and antimicrobial prophylaxis protocols as for their HIV-negative patients. A descriptive analysis was performed.
Results: Median age was 42 y, 78% were men, and 73% were former drug users. Median follow-up was 2.6 y (IQR, 1.25-3.53 y), 54 recipients (64%) developed at least 1 infection. Thirty-nine patients (46%) had bacterial infections, 21 (25%) CMV infection (2 CMV disease), 13 (15%) Herpes-virus infection and 14 (17%) fungal infections (5 invasive cases). Two patients had tuberculosis and 1 had *P. jirovecii* pneumonia. Thirty patients (36%) had at least 1 infection within the first month after OLT, 14 (17%) between the first and sixth month, and 10 (12%) after the sixth month (late infections). There was a trend correlation between Herpes infection and acute rejection (p=0.07). Thirty (36%) patients died, and death was infection-related in 7 cases (23%). In the univariate analysis of mortality, invasive fungal infection was associated with death (p=0.03).
Conclusions: Infections are frequent and an important cause of morbidity and mortality after LT in HCV/HIV-coinfected recipients. Efforts to prevent fungal infections will improve outcome in this group of patients.

BACKGROUND AND OBJECTIVES

Liver transplantation is the best treatment option for HIV-infected patients with end-stage liver disease. Recent data suggest that the short-term prognosis of HIV-positive liver transplant recipients is similar to that of non–HIV-infected recipients. However, there are few published data on the incidence and severity of opportunistic and non-opportunistic infections in HCV/HIV-coinfected recipients after liver transplantation (OLT). This study describes the incidence, clinical characteristics, time of onset, and outcome of bacterial, viral and fungal infections in Spanish HCV/HIV-coinfected OLT recipients.

METHODS

The study sample comprised 84 consecutive HCV/HIV-coinfected patients who underwent OLT at 17 Spanish centers between 2002 and 2006 and were followed until December 2007. Data were obtained from the FIPSE OLT-HIV-05-GESIDA 45-05 database. Each site used the same immunosuppressive regimens and antimicrobial prophylaxis protocols as for their HIV-negative patients.
Definitions: The definitions of acute rejection, infectious episodes and post-transplant complications were defined based on clinical guidelines and previous studies.
Severe infections were defined as follows: any bacterial infection with bacteremia, pneumonia, intraabdominal and central nervous system bacterial infection, invasive fungal infection, CMV disease, any invasive viral infection, and mycobacterial disease.
Statistical analysis: Variables were compared using the chi-square test or Fischer's exact test. A Kaplan-Meier and Cox regression survival analysis was performed to evaluate the impact of infections on survival. All statistics were considered significant when a 2-tailed p value was less than 0.05.

RESULTS

Age	42 (39-45)
Male gender	64 (76%)
Caucasian race	82 (98%)
HIV risk factors	
IVDU	63 (75%)
Hemophiliac	4 (5%)
Heterosexual	10 (12%)
Others	7 (8%)
HBV coinfection	13 (15%)
HCV genotype	
1/4	58 (69%)
2/3	19 (23%)
Non-typable	7 (8%)
Plasma RNA-HCV viral load (U/mL)	466,000 (146,000-1,590,000)
Liver cancer (HCC)	14 (17%)
Child-Pugh class	
A	10 (12%)
B	38 (45%)
C	35 (42%)
MELD score	15 (11; 18)
Previous CDC C events	17 (20%)
Type of cART	
NRTI-based	11 (13%)
PI-based	20 (24%)
Efavirenz-based	37 (44%)
Other combinations	16 (19%)
CD4+ T cells	
Absolute number	296 (200; 420)
Percentage	26% (19%-33%)
Plasma RNA HIV-1 viral load	
<200 copies/mL	80 (95%)
Time on OLT waiting list (months)	4 (2; 7)
Type of donor	
Cadaveric	83 (99%)
Living-donor	1 (1%)
Follow-up	
Infections	54 (64%)
Acute rejection	32 (38%)
Crude mortality	30 (36%)

Table 1. Main characteristics of the cohort.

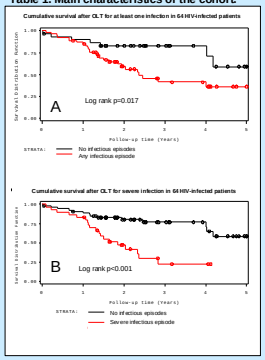

Figure 2. Kaplan.Meier survival analysis of HIV/HVC-coinfected liver transplant recipients according to the occurrence of any infectious episode (A) or serious infectious episodes (B).

	Number of patients (%)	Acute rejection	Related-mortality
Any infection	54 (64)	24 (44%)	7 (13%)
Bacterial infection	39 (46)	17	1
With bacteremia	8 (9.5)	2	
Peritonitis	7 (8)	2	
Sepsis	5 (6)	4	1
Pneumonia	9 (11)	3	1
Fungal infection	14 (17)	8	
Invasive fungal infection	6 (7)	1	2
CMV infection	21 (25)	7	
CMV disease	2 (2)	1	1
Herpes simplex infection	13 (15.5)	8	
Disseminated	2 (2)	2	
Tuberculosis	2 (2)		1

Table 2. Incidence of infection in HIV/HVC-coinfected liver transplant recipients and incidence of acute rejection and related-mortality according to the type of infection.

	HR (95%CI)	p
Any infectious event	2.7 (1.2-6.2)	0.022
CMV disease	1.7 (0.2-12.7)	0.601
Any fungal infection	3.9 (1.9-8.3)	<0.001
Invasive fungal infection	4.0 (1.5-10.8)	0.006
Severe infection	3.6 (1.8-7.4)	<0.001
Bacteremic infection	4.7 (2.1-10.5)	<0.001

Table 5. Univariate analysis of the impact of infections on mortality in HIV/HVC-coinfected liver transplant recipients.

Microorganism	N (%)
Gram-positive	
Corynebacterium spp.	1 (1.7%)
Coagulase-negative staphylococci	6 (10.2%)
Staphylococcus aureus	5 (8.5%)
Streptococcus viridans	2 (3.4%)
Streptococcus pneumoniae	1 (1.7%)
Enterococcus faecalis	3 (5%)
Enterococcus faecium	1 (1.7%)
Clostridium difficile	4 (6.8%)
Rothia dentocariosa	1 (1.7%)
Gram-negative	
Escherichia coli	12 (20.3%)
Proteus mirabilis	1 (1.7%)
Citrobacter freundii	3 (5%)
Campylobacter jejuni	8 (13.6%)
Pseudomonas aeruginosa	8 (13.6%)
Acinetobacter baumannii	2 (3.4%)
Stenotrophomonas maltophilia	1 (1.7%)

Table 3. Microorganisms responsible for post-transplant bacterial infections in HIV/HVC-coinfected patients.

Source	N
Bacteremia of unknown origin	3
Catheter-related bacteremia	2
Upper respiratory tract	7
Lower respiratory tract	6
Intraabdominal	14
Surgical wound	2
Gastritis/Enteritis/Colitis	13
Urinary tract infection	12
Spontaneous bacterial peritonitis	7
Other	1

Table 4. Source of bacterial infections in HIV/HVC-coinfected patients.

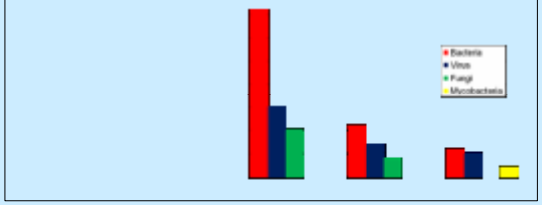

Table 1 summarize the main characteristics of the cohort. Most patients had a controlled HIV infection and only 20% had had C events. Almost 90% of patients were in Child-Pugh class B or C. HVC genotypes 1 and 4 predominated (69%). The most frequent cART regimens were those based on efavirenz. Median age was 42 years, 76% were men, and 75% were former drug users. Median follow-up was 2.6 y (IQR, 1.25-3.53 y), 54 recipients (64%) developed at least 1 infection. The incidence of infection and the relationship with acute rejection and related-mortality is summarized in Table 2. Thirty-nine patients (46%) had bacterial infections (isolates summarized in Table 3 and sources in Table 4); 21 (25%) had CMV infection (2 CMV disease), 13 (15%) Herpes simplex infection, and 14 (17%) fungal infections (5 invasive cases). Two patients had tuberculosis and 1 had *P. jirovecii* pneumonia (Table 2). Thirty patients (36%) had at least 1 infection within the first month after OLT, 14 (17%) between the first and sixth month and 10 (12%) after the sixth month (late infections). There was a trend correlation between Herpes infection and acute rejection (p=0.07). Figure 1 shows the distribution of infections during the post-transplant period. Thirty (36%) patients died, and death was infection-related in 7 cases (23%). Table 5 shows the univariate analysis of the impact of infections on mortality and Figure 2 the Kaplan-Meier survival analysis of mortality according to the development of infection over time.

CONCLUSIONS

1. Infections are frequent and an important cause of morbidity after LT in HCV/HIV-coinfected recipients.
2. Most infections occurred in the early post-transplant period.
3. The incidence of fungal infection was high (14 patients), and efforts to prevent fungal infections should be evaluated in HIV/HVC-coinfected patients undergoing liver transplantation.
4. Post-transplant infections, especially severe infections, had a significant impact on post-transplant survival.

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