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# Outcome of renal graft recipients with hepatitis C virus infection

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**Abstract** Hepatitis C virus (HCV) is a major cause of posttransplantation chronic liver disease. The aim of this study was to evaluate the prevalence of HCV in renal transplant recipients and to investigate risk and prognostic factors. Of 427 renal transplants carried out between July 1983 and January 1993, we retrospectively studied 66 (15.5 %) HBsAg-negative patients with anti-HCV detected by enzyme-linked immunosorbent assay (ELISA) and recombinant immunoblot assay (RIBA). Patient and graft survivals were estimated. Anti-HCV positive patients had more time on hemodialysis and pretransplant blood transfusions ($P = 0.0001$) than did the seronegative population. In a mean follow-up of 52.3 ± 27.7 months, 36 patients (54 %) had biochemical evidence of liver disease, predominantly with a persistently high pattern of serum alanine aminotransferase (ALT). Pretransplantation ALT elevation was associated ($P = 0.004$) with chronic liver disease (CLD) in the graft recipient. None of the other variables studied predicted posttransplantation CLD. Liver failure occurred in two (3 %) and was the cause of death in one of the patients. Death occurred in eight significantly more aged ($P = 0.0001$) patients, at 45.5 ± 28.8 months posttransplant. In 50 % of the cases, death was ascribed to sepsis. The biochemical pattern of HCV showed no predictive value for prognosis. The disease had no significant effect on the number of rejections or graft survival. The study revealed lower actuarial survival ($P = 0.004$) for HCV-positive patients in comparison with the seronegative population.

**Key words** Hepatitis C · Kidney transplantation

## Introduction

Hepatitis C virus (HCV) is the major cause of liver disease in patients on dialysis and awaiting renal transplantation [1–3]. The renal recipient is at increased risk of reactivation of the disease or infection acquired from blood products at the time of transplantation or from the graft [4]. The prevalence and the severity of HCV infection in this high risk population is underestimated with the current biochemical and serologic tests [4–7]. Liver failure is the cause of death in 8–28 % of long-term survivors after renal transplantation [4]. However, the impact of hepatitis C in patient and graft survival remains controversial. The current study evaluates the prevalence, the clinical expression, and the prognosis of hepatitis C in renal allograft recipients.

## Patients and methods

This study included 427 renal transplant recipients who were managed at Santo António General Hospital between July 1983 and January 1993. We have carried out a retrospective analysis of 66 HBsAg-negative patients, who were anti-HCV-positive on at

**Table 1** Characteristics of the anti-hepatitis C virus-positive *(anti-HCV⁺)* patients: comparison with the seronegative *(HCV⁻)* population. *(NS* Not significant)

| Characteristic | $HCV^+$ | $HCV^-$ | *P* value |
|---|---|---|---|
| Sex (male/female) | 43/23 | 151/127 | NS |
| Age (years) | 38.3 ± 11.8 | 35.1 ± 13.3 | NS |
| Timeonhemodialysis (months) | 76.3 ± 45 | 40.2 ± 35 | 0.0001 |
| Transfusion (units) | 11.5 ± 12.9 | 4.7 ± 6.5 | 0.0001 |
| Follow-up (months) | 52.3 ± 27.7 | 55.3 ± 28 | NS |

**Table 2** Chronic liver disease *(CLD)*. *(ATG* Anti-thymocyte globulin, *HLA* human leukocyte antigen, *NS* not significant)

| Characteristic | CLD ($n = 36$) | No CLD ($n = 30$) | *P* value |
|---|---|---|---|
| Sex (male/female) | 25/11 | 18/12 | NS |
| Age (years) | 40.7 ± 11.9 | 38.9 ± 9.8 | NS |
| Hemodialysis (months) | 89.5 ± 72.5 | 72.8 ± 62,8 | NS |
| Transfusions (units) | 12.4 ± 13.4 | 10.3 ± 12.5 | NS |
| Clinical hepatitis | 6 | 2 | NS |
| Immunosuppression with ATG | 14 | 13 | NS |
| HLA compatibility (< 3, = 3, > 3) | 22; 8; 6 | 17; 9; 4 | NS |
| Second graft | 5 | 4 | NS |
| Follow-up (months) | 56.7 ± 27.3 | 47.1 ± 27.9 | NS |

**Table 3** Pattern of serum transaminase levels: correlation with posttransplantation CLD. *(NS* Not significant)

| Pretransplantation profile | CLD ($n = 36$) | No CLD ($n = 30$) | *P* |
|---|---|---|---|
| Abnormal | 29 | 11 | 0.004 |
| Fluctuating | 11 | 0 | 0.004 |
| Occasional elevation | 10 | 6 | NS |

least one occasion, detected by enzyme-linked immunosorbent assay II and confirmed by recombinant immunoblot assay II (Ortho Diagnostics). Not until 1991 were the clinicians of this hospital able to have access to these serological tests.

There were 43 men and 23 women with HCV infection. The mean age of the patients was 38.3 ± 11.8 years and time on hemodialysis averaged 76 ± 45 months (Table 1). We evaluated the clinical history and the pretransplantation chemical profile. The immunosuppression included azathioprine and prednisolone in 4 (6 %) patients; cyclosporine and prednisolone in 32 (48.5 %) patients; cyclosporine, azathioprine, and prednisolone in 3 (4.5 %) patients; anti-thymocyte globulin (ATG), cyclosporine, and prednisolone in 11 (16.7 %) patients; ATG, cyclosporine, azathioprine, and prednisolone in 16 (24.3 %) patients.

Chronic liver disease (CLD) was defined by fluctuating or persistently elevated transaminases (ALT) for at least 6 months. Any value above normal, as defined by the local laboratory, was considered elevated. Liver failure was diagnosed by prothrombin activity > 70 %; hypoalbuminemia < 3 g/l; portal hypertension. The follow-up was of 52.3 ± 27.7 months. We evaluated the prevalence and the impact of hepatitis C in patient and graft survival.

Statistical analysis was performed using the chi-square test to determine the statistical differences between proportions by entered 2 × 2 contingency tables; Student's *t*-test was used to evaluate the differences between normally distributed continuous variables. Graft and patient actuarial survivals were calculated with the STAT (Statistics for Windows) software program. Results are expressed as mean ± SD. $P < 0.05$ was considered significant.

## Results

HCV serology was unknown in 134 (31 %) patients; 227 patients were seronegative. We verified a prevalence of HCV infection of 22.5 %.

Anti-HCV-positive patients had significantly more time on hemodialysis and pretransplant blood transfusions ($P = 0.0001$) than did the seronegative population (Table 1). Three infected patients have never been transfused. The lack of stored serum from the donors precluded us from implicating the role of donor organ transmission of HCV in this study.

Forty-one (60.6 %) patients had pretransplantation ALT elevation: 11 with a fluctuating profile; 16 with an occasional elevation; 12 with elevated ALT only detected at transplantation day; 2 with an unknown pretransplantation profile of elevated ALT. Eight (12 %) of these had clinical hepatitis. In 69.1 % of the patients the diagnosis of infection was done after transplantation, so we could not study the influence of immunosuppression on the sensitivity of serological tests for hepatitis C.

Thirty-six patients had posttransplantation fluctuating (41.7 %) or persistently elevated (58.3 %) ALT. Thirty maintained normal enzyme levels. None of the patients with pretransplantation CLD showed biochemical normalization under immunosuppression. Six renal allograft recipients who had never had elevated ALT showed at an average of 1 year (max. 2 years; min. 3 months) post-transplantation, a persistently elevated profile of ALT. One of these had liver disease and died of sepsis. All of these had perioperative transfusions. The HCV statuses of the donors are unknown.

None of the variables studied was associated with posttransplantation CLD (Table 2). Pretransplantation, however, abnormal ALT levels were correlated with CLD in the renal graft recipients (Table 3).

Two patients (3 %) had liver failure. Eight patients, significantly more aged ($P = 0.0001$), died at 45.5 ± 28.8 months posttransplantation. They did not differ from the HCV-positive survivors in time on hemodialysis, number of transfusions of follow-up (Fig. 1). Four patients died with functioning grafts. In four (50 %) of the cases, death was ascribed to sepsis; two patients died of cardiovascular accident, one had fatal liver failure, and one died at home, of unknown cause.

We verified no significant differences in the number of rejection episodes [17/66 (25 %) in HCV-positive patients versus 92/275 (33 %) in seronegatives] or graft actuarial survival in the HCV-positive group. HCV-positive patients with CLD had a similar actuarial survival when compared with the infected patients who main-

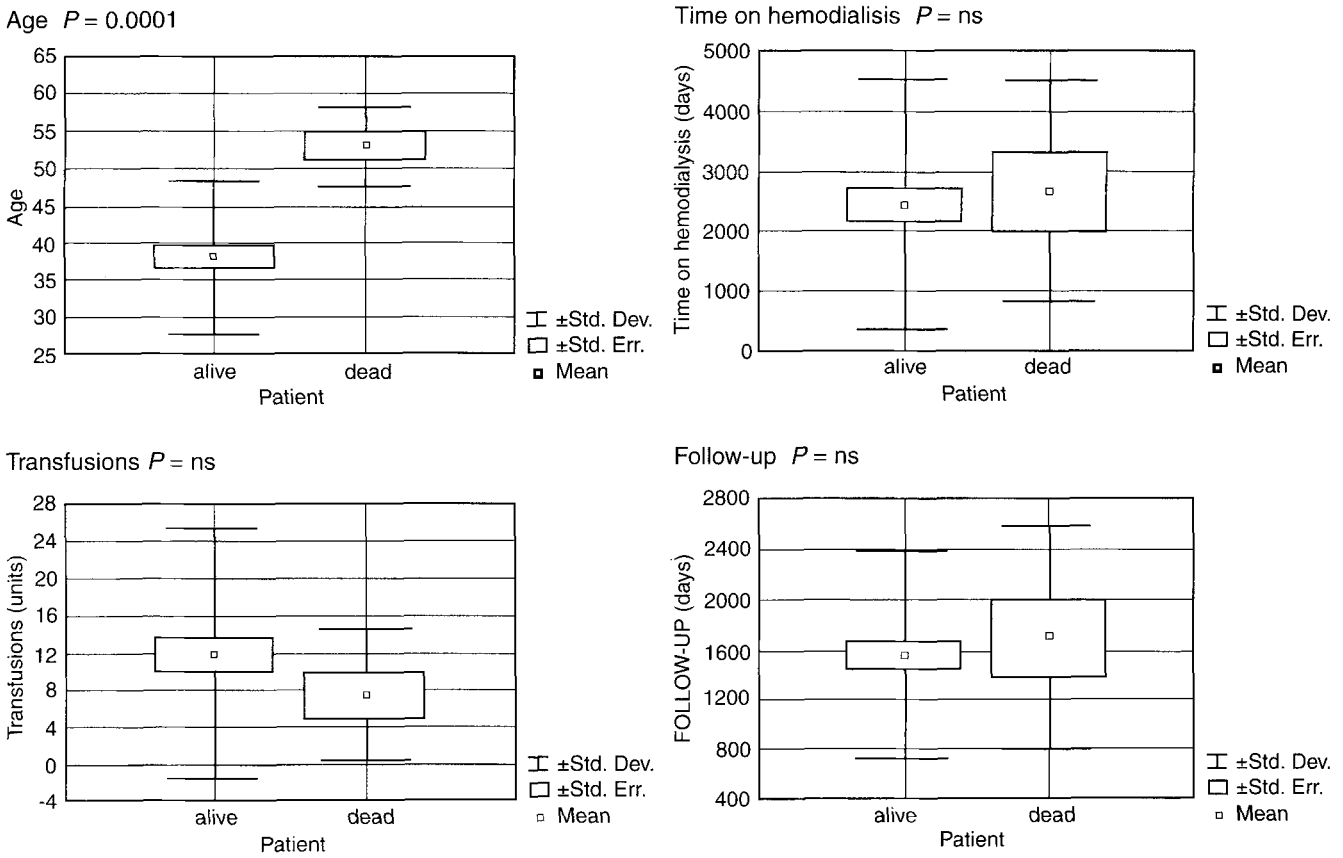


**Fig. 1** Mortality ($n = 8$) in the hepatitis C virus-positive ($HCV^+$) group. Comparison with the $HCV^+$ survivors

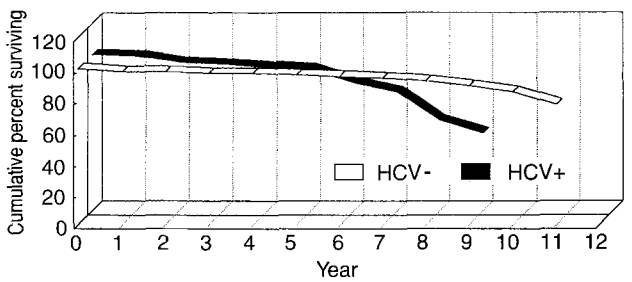


**Fig. 2** Impact of HCV infection on patient survival (log rank $P = 0.004$)

tained normal enzyme levels. The actuarial HCV-positive patient survival differed significantly from that of the seronegative group. The results were: 99 %, 91 %, 58 % and 98 %, 96 %, 92 % at 1, 5, and 8 years, respectively, for HCV-positive and -negative groups (log-rank test $P = 0.004$, Fig. 2).

## Discussion

The prevalence of HCV infection in our renal transplant population is similar to those of other series [2–7]. Time on hemodialysis and number of transfusions were risk factors for acquisition of the infection. Because of the lack of stored serum from the donors, we could not verify the role of the graft in the HCV transmission [4, 8–15]. The majority of the patients had CLD following renal transplantation, with no correlation with the type of immunosuppression. We found a poorer survival rate of the HCV-positive group. In agreement with several other published series, Morales et al. [2] and Pereira et al. [4] had suggested that HCV hepatitis is more aggressive in renal allograft recipients [16–19]. In a previous study of mortality in our renal transplant population [20] cardiovascular disease was the main cause of death. In this HCV-positive group, 50 % died of sepsis. In fact, hepatitis C has been incriminated in increasing the risk of infectious death [21].

Although hepatitis C is said to contribute to the long-term morbidity and mortality of renal transplant recipients, many studies were unable to demonstrate any significantly adverse effect on patient and graft survival [22–25]. The prognosis of these patients depends on the histological severity of hepatitis [17]. Those who died in

our series had probably had a long-term infection. More severe liver disease, with a higher Knodell index, is said to exist as a function of time [26]. These patients were also more aged at transplantation day and hepatitis under immunosuppression may be more aggressive in the aged.

The prognostic importance of HCV genotypes is currently under investigation. From the several isolated strains, type 1, principally type 1b, seems to be associated with a worse prognosis [27]. Coinfection of 1b-HCV virus with other HCV strains is said to occur frequently in the hemodialyzed, which may justify a more aggressive pattern of disease. This may correlate with the severity of liver disease, cirrhosis in particular. Furthermore, HCV infection is associated with persistent viremia in the immunosuppressed renal allograft recipients [4].

We did not find more rejection episodes or worse graft survival in the HCV-positive patients. The infection may immunologically protect the graft, although recent results are contradictory [21]. The understanding of the natural history of hepatitis C in renal allograft recipients will grow with longer follow-up of these patients. The prevalence of infection is underdiagnosed by clinical and serological parameters, therefore, the detection of HCV by the polymerase chain reaction (PCR) is important for diagnosis [28–30]. Neither viremia nor the serological and biochemical profiles can accurately predict the severity of liver disease [26], although persistent elevations in alanine aminotransferase may be associated with more severe liver histology [31]. Liver biopsy is needed for definitive diagnosis of hepatitis in pretransplantation evaluation [21, 26, 32]. Milder histological abnormalities such as chronic persistent hepatitis are associated with a minor risk of mortality or morbidity in renal transplant recipients. Those with chronic active hepatitis and liver fibrosis often progress to micronodular cirrhosis, which may be a contraindication for isolated renal transplantation [17, 32]. Older patients are at an increased risk [17]. The better quality of life of the transplant patient should be weighed against the low but definite risk of development of chronic liver failure.

The results of this study emphasize that HCV hepatitis is a frequent complication that may have an adverse impact in morbidity and mortality of renal transplant recipients. It was associated with death from sepsis in 50 % of cases. The infection did not affect the number of rejection episodes or graft actuarial survival. It is important to obtain histological data to better understand the natural progression of hepatitis in the immunosuppressed host. Liver biopsy should be incorporated into the pretransplantation evaluation of hepatitis C.

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# Pharmacokinetics and immunodynamics of chimeric IL-2 receptor monoclonal antibody SDZ CHI 621 in renal allograft recipients

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**Abstract** SDZ CHI 621 is a murine-human chimeric monoclonal antibody (mAb) to the interleukin-2 (IL-2) receptor (CD25) intended for prophylactic immunosuppression against acute rejection in the first several weeks following kidney transplantation. A multicentre, prospective, dose-finding study was conducted in 37 primary, mismatched cadaver kidney transplant patients to assess its tolerability, pharmacokinetics and immunodynamics. Successive cohorts of patients were stratified to receive total doses of 20, 30, 40 or 60 mg ($n$ = 4, 4, 14, 15, respectively) administered as 15- or 20-mg intravenous infusions with the first dose given preoperatively and subsequent doses within the first 10 days posttransplant. Daily mAb serum concentrations were analysed by a radioimmunoassay method and the percentage of peripheral T-lymphocytes expressing CD25 from serial blood samples was determined by FACScan. Intravenous administrations were well tolerated. mAb concentration profiles exhibited a biphasic decline with an initial $t_{1/2}$ of 14.4 ± 14.2 h, terminal $t_{1/2}$ of 13.4 ± 6.0 days, distribution volume ($V_{ss}$) of 6.9 ± 3.3 l and clearance of 17.4 ± 7.8 ml/h. The concentration-effect (mAb-CD25) relationship indicated that mAb concentrations exceeding a threshold of about 0.7 μg/ml corresponded to complete suppression of CD25 (≤ 3 % $CD25^+$ T-cells). The threshold mAb concentration was exceeded at all dose levels, whereas the duration above the threshold (and thus of CD25 suppression) rose with increasing dose: 20 mg, 20 ± 7 days; 30 mg, 32 ± 6 days; 40 mg, 37 ± 10 days; and 60 mg, 53 ± 17 days. As mAb concentrations declined below the threshold following the last dose, CD25 expression returned to baseline (18–44 % $CD25^+$ T-cells) within a few days.

**Key words** Immunosuppression · Monoclonal antibodies · Renal transplantation · Pharmacokinetics · Pharmacodynamics

## Introduction

The development of antibody therapy in the prophylaxis against acute rejection in transplantation has progressed from aspecific polyclonal antisera to increasingly selective monoclonal antibodies, which have the potential to regulate specific immunological responses via functional receptors. In this context, rat and mouse monoclonal antibodies to the interleukin-2 receptor (IL-2R) have shown promise in preventing acute rejection in renal allograft recipients [1, 2]. However, their clinical use has been limited by the rapid development of neutralising antibodies. In an attempt to reduce immunogenicity, a chimeric mouse-human anti-IL-2R monoclonal antibody has been developed. SDZ CHI 621 contains a murine variable region (RFT5) and a human constant

region (IgG1$\varkappa$) and demonstrates high affinity for the CD25 activation antigen on the IL-2R$\alpha$ chain. An investigation was designed to characterise the pharmacokinetics and immunodynamics of SDZ CHI 621 in renal allograft recipients.

## Methods

A multicentre, open-label dose-finding study was undertaken in recipients of primary, mismatched cadaver kidneys. Successive cohorts of patients were stratified to receive total SDZ CHI 621 doses of 20, 30, 40 or 60 mg. Total doses were administered as 15- or 20-mg intravenous infusions delivered over 30 min. The first infusion was given prior to transplant surgery, with subsequent administrations within the first 10 postoperative days. Blood samples were collected daily for the determination of serum SDZ CHI 621 concentrations by a radioimmunoassay (RIA) method. For pharmacokinetic analysis, concentration-time data were fitted to a two-compartment, open model with first-order elimination from the central compartment. Blood samples were obtained twice weekly over the study duration for pharmacodynamic measurements. Specifically, lymphocyte subpopulations were analysed by FACScan flow cytometry (Becton-Dickinson) and the percentage of CD25A$^+$ T-cells was quantified.

## Results and discussion

### Patient population and clinical observations

Thirty-nine patients were enrolled in this investigation; data from the 37 who provided evaluable pharmacokinetic profiles are presented. There were 23 men and 14 women aged 48 ± 14 years (range 18–71 years) and weighing 74 ± 16 kg (range 46–103 kg). They were stratified as follows among the dose levels: 4 (20 mg), 4 (30 mg), 14 (40 mg), 15 (60 mg). The infusions of SDZ CHI 621 were safe and well-tolerated and no cytokine-release syndrome or hypersensitivity reactions were observed.

### Pharmacokinetics

Peak serum SDZ CHI 621 concentrations at the end of the infusion ranged between 5 and 10 μg/ml; the distribution volume ($V_{ss}$) was 6.9 ± 3.3 l. Concentrations subsequently declined in a biphasic manner with a prolonged terminal disposition half-life of 13.4 ± 6.0 days. The total body clearance was 17.4 ± 7.8 ml/h; the between-subject variability in clearance was not influenced by body weight, supporting dosing on a milligram basis in adults.

### Immunodynamics

The baseline percentage of CD25A$^+$ T-cells from pretreatment blood samples ranged from 18 % to 44 %. In the presence of SDZ CHI 621, CD25A was continuously suppressed, with the percentage of T-cells expressing this activation marker below 3 %. Clinically relevant suppression was maintained until SDZ CHI 621 concentrations declined to a threshold region around 0.7–1.0 μg/ml (as determined by RIA) following the last administration. At this point, CD25A counts returned to baseline within a few days. The concentration-effect relationship was also explored by plotting the paired determinations of SDZ CHI 621 concentration versus the percentage of CD25A$^+$ T-cells, pooling the data pairs from all study patients. Again, concentrations exceeding approximately 0.7–1.0 μg/ml were associated with CD25A suppression ($\leq$ 3 % CD25A expression), while concentrations below this threshold region were associated with the pre- and post-treatment baseline values (> 3 % CD25A expression). All cumulative dose levels assessed in this investigation yielded CD25A suppression; however, the duration of suppression increased with increasing total dose. Specifically, at total doses of 20, 30, 40 and 60 mg, the duration was 20 ± 7, 32 ± 6, 37 ± 10 and 53 ± 17 days, respectively. These data were used as a basis for dose selection in the indication of immunosuppressive prophylaxis following kidney transplantation.

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