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Significant improvement in the outcome of HCV-infected transplant recipients by avoiding rapid steroid tapering and potent induction immunosuppression

Marina Berenguer[1,*], Victoria Aguilera[1], Martín Prieto[1], Fernando San Juan[2], José M. Rayón[3], Salvador Benlloch[1], Joaquín Berenguer[1]

[1]*HepatoGastroenterology Service, Servicio de HepatoGastroenterología, Hospital Universitario La Fe, Avenida Campanar 21, 46009 Valencia, Spain*
[2]*Liver Transplantation and Surgery Unit, Servicio de HepatoGastroenterología, Hospital Universitario La Fe, Avenida Campanar 21, 46009 Valencia, Spain*
[3]*Pathology Service, Servicio de HepatoGastroenterología, Hospital Universitario La Fe, Avenida Campanar 21, 46009 Valencia, Spain*

***Backgrounds/Aims*: Recurrent HCV-cirrhosis occurs in a substantial proportion of transplant recipients, with higher rates reported in patients who had recently received a transplant. Over-immunosuppression has been implicated in this more unfavorable outcome. To determine whether the implementation of specific measures aimed at reducing or avoiding negative predictive variables is associated with an improvement in the outcome of recurrent hepatitis C.**

***Methods*: Comparative study between a cohort of patients who had recently received a transplant (2001–2004) and a historical group of HCV-infected patients transplanted before the implementation of two simple measures (1999–2000): (i) use of dual initial immunosuppression (steroids + cyclosporine neoral or tacrolimus); (ii) slow steroid tapering (>6 months). Yearly biopsies were performed in these recipients, and only those with at least one protocol biopsy and those with cholestatic hepatitis (regardless of follow-up) were included in the study. End-point: rate of HCV-related severe disease (defined as bridging fibrosis, cirrhosis or fibrosing cholestatic hepatitis) within the first year post-transplantation.**

***Results*: Severe disease was significantly lower in this cohort compared to the historical group (26/90, 29% vs 25/52, 48%; $p = 0.02$). While other factors remained unchanged between the two cohorts, the proportion of patients on triple–quadruple regimes and the number of boluses of methyl-prednisolone were lower and the duration of prednisone therapy longer in more patients who had recently received a transplant.**

***Conclusions*: Improving the outcome of recurrent hepatitis C may be achieved by reducing overall immunosuppression and avoiding abrupt variations in immunosuppression.**

***Keywords*: Immunosuppression; Hepatitis C virus; Liver transplantation; Cirrhosis; Hepatocellular carcinoma; Donor age; Cyclosporine; Tacrolimus; Prednisone**

1. Introduction

Hepatitis C virus (HCV)-cirrhosis is the most frequent diagnosis in patients undergoing liver transplantation [1]. Viral recurrence occurs universally [2], with development of histologic hepatitis in the majority [3,4] and progression to cirrhosis in a substantial proportion of these [3–8]. In fact, recent data from our group [7] and from a large multicenter US study [9] show a significant negative impact of HCV infection on both graft and patient survival, an impact which appears to be more relevant in recent years [7]. Few simple variables, including the age of the donor and the immunosuppression utilized have been shown to be associated with the outcome [3–12]. In that sense, several studies have suggested that a more rapid progression to cirrhosis occurs in patients who receive organs from donors

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* Corresponding author. Tel.: +34 96 386 8792; fax: +34 96 398 7333.
E-mail address: mbhaym@teleline.es (M. Berenguer).

Abbreviations: HCV, Hepatitis C virus; HCC, hepatocellular carcinoma; HAI, histologic activity index; PCR, polymerase chain reaction; F, fibrosis; ALT, alanine aminotransferase; LT, liver transplantation; IS, immunosuppression.

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older than 50, those overimmunosuppressed and from those in whom steroids are withdrawn in a rapid and abrupt way [6,7,12–18]. The preferential use of organs from younger donors may hence become a strategy to improve the outcome of these patients. This strategy may, however, be unrealistic due to both ethical and 'practical' considerations. Alternatively, different schedules of immunosuppression should be performed in order to select a more rationale use of immunosuppression.

In a previous study from our group, we showed that the post-transplantation outcome of HCV-infected patients was substantially worse in patients transplanted recently compared to those transplanted years ago, with a lower survival and a higher rate of progression to cirrhosis [7]. In fact, in that study, the main cause of death was recurrent decompensated HCV-related graft cirrhosis with a probability of developing cirrhosis of 44% at 5 years. Reasons for the worse outcome were proposed and included older donor age, the use of stronger induction immunosuppression and an earlier and faster withdrawal of 'second-line immunosuppressive drugs' such as prednisone. Based on these findings, and in order to improve the outcome, we started implementing a few simple measures in 2001. These included: (i) the use of initial immunosuppression (during the first month) based on double therapy (calcineurin inhibitor + steroids) avoiding triple and quadruple regimes whenever possible; and (ii) a slow steroid tapering. We hypothesized that the implementation of these simple measures would lead to an improvement in outcome, measured as the proportion of patients developing severe recurrent disease within the first year post-transplantation. The aim of this study was therefore to determine whether the implementation of potential positive measures was associated with a reduction in the rate of severe disease. In order to test this, we compared the outcome of our study population to a historical group of patients transplanted between 1999 and 2000 just prior to the implementation of these measures. We present here the preliminary results, since this is an ongoing study that we plan to continue for two additional years.

2. Patients and methods

2.1. Patients

Study population (recent cohort): Between October 2001 and May 2004, 121 adult patients underwent primary liver transplantation at our institution for HCV-related cirrhosis ± hepatocellular carcinoma (HCC) without hepatitis B virus infection (HBV). The criteria used for selecting patients with cirrhosis and a localized HCC are those proposed previously [7]. Only HCV-RNA positive patients with at least one-year protocol biopsy performed in the absence of prior antiviral therapy and/or patients with an earlier clinical indicated biopsy showing severe recurrent disease (defined as cholestatic hepatitis and/or progression to bridging fibrosis) were included in this study. The follow-up of this preliminary analysis was terminated at the time of either the patient's death, retransplantation or at the end of the observation period (May 2005).

Control/historical group. This group consisted of patients undergoing liver transplantation for HCV-related liver disease between January 1999 and August 2000 before the implementation of simple measures to improve outcome ($n=78$) fulfilling the same criteria applied to the study cohort (i.e. patients with at least one-year protocol biopsy performed in the absence of prior antiviral therapy and/or a biopsy showing cholestatic hepatitis despite the lack of the one-year biopsy).

2.2. Histological assessment

Protocol liver biopsies were performed yearly (±4 months). Additional biopsies were performed when clinically indicated. All biopsy specimens were reviewed by a single pathologist (JMR) in a blinded fashion, and only those obtained before any antiviral therapy was instituted were evaluated in this study. Sections were stained routinely with hematoxylin-eosin, reticulin, Perls' and Orcein stains.

Liver biopsies classified as 'hepatitis' were scored evaluating both the stage of fibrosis and the degree of necroinflammatory activity, according to a slight modification of the histologic activity index (HAI) proposed by Knodell et al. [7]. The grade was determined by combining the HAI scores for periportal necrosis, lobular degeneration and necrosis and portal inflammation, and was defined as follows: 1–2, minimal; 3–6, mild; 7–10, moderate; 11–14, severe. The stage corresponded to the original HAI fibrosis score: 0, none; 1, fibrous portal expansion; 3, bridging fibrosis; and 4, cirrhosis.

Graft biopsy specimens were also examined for features of acute and chronic rejection. Cellular rejection was always based on histological findings, including mixed portal infiltrate, venous endothelitis and bile duct injury.

Cholestatic hepatitis was defined following recent recommendations[19].

2.3. Immunosuppression

During the study period, all patients undergoing liver transplantation at our institution were prospectively randomized to receive cyclosporine neoral + steroids vs tacrolimus + steroids. Additional therapies were used in cases of early calcineurin-related post-transplantation complications that required a substantial reduction in calcineurin inhibitor doses. Initial doses were as follows: methylprednisolone given intravenously with tapering of the dose from 200 to 20 mg at day 6, at which time 20 mg/day of prednisone were administered orally; cyclosporine (trough levels of 250–350 ng/ml the first month, 150–250 ng/ml the second and third months, 100–150 ng/ml until the end of the first year and around 100 ng/ml thereafter); tacrolimus (trough levels of 5–15 ng/ml the first 3 months, 5–10 ng/ml thereafter). Prednisone dose was started at 20 mg one week after transplantation and tapered down at a slow rate with final withdrawal after 9–12 months from transplantation. Only in cases where cholestatic hepatitis was diagnosed or in patients with severe side-effects related to the use of corticosteroids, prednisone was tapered down more rapidly.

Histologically confirmed episodes of moderate to severe rejection were treated with boluses of corticosteroids (1 g of methyl-prednisolone/day during three consecutive days) ± introduction of mycophenolate mofetil. Increase in baseline immunosuppression was the standard of care for mild episodes of rejection that otherwise were left untreated. Empiric treatment for suspected rejection was never done. The same criteria to treat rejection episodes was used during the two periods.

2.4. Cytomegalovirus (CMV) prophylaxis

Ganciclovir, either administered intravenously for 14-21 days or orally (1 gm/8 h for 90 days) was given under the following circumstances: (1) positive donor and negative recipient; (2) retransplantation; (3) use of monoclonal or policlonal antibodies; (4) surgery complicated with high blood-product requirements.

2.5. Outcome variables

Progression to severe disease within the first year (bridging fibrosis, cirrhosis, cholestatic hepatitis, death due to recurrent hepatitis) was used as the primary end-point. Secondary end-points included: (i) progression to fibrosis ≥ 1 in the first-year liver biopsy, (ii) percentage of patients

developing acute hepatitis and time to hepatitis, (iii) percentage of patients developing cholestatic hepatitis and (iv) graft/patients survival.

Factors analysed as potential predictors of severe disease were compared between the two cohorts. These included: (1) *Demographics*. age at transplantation and sex distribution; (2) *Pre-transplantation variables*. Presence of HCC, Child-Pugh classification, history of significant alcohol consumption, history of failed interferon therapy in the past; (3) *Donor-related variables*. Age and sex; (4) *Surgical-related variables*. Duration of cold preservation and rewarming time, duration of intervention, initial graft function; (5) *History of acute recurrent hepatitis* evidenced histologically and time to acute hepatitis. An initial liver biopsy was typically performed when liver enzymes rose to twice the upper limit of normality. If, in these cases, changes compatible with HCV-related acute hepatitis were present, the patient was included in the group of patients with a history of 'acute hepatitis C'; (6) *Immunosuppression-related variables*. Histologically diagnosed rejection episodes requiring methylprednisolone boluses, use of additional immunosuppressive drugs either for induction immunosuppression and/or rejection treatment, and prednisone doses at 1, 3 and 6 months post-transplantation; (7) *biochemical-related variables*. Alanine aminotransferase levels at 1, 6 and 12 months; (8) Genotype (1 vs non-1).

Pre-transplantation viral load was only available in a percentage of patients transplanted in the most recent cohort, and hence was only included in the analysis of prediction of severe disease but not in the comparison between the two cohorts.

2.6. Description of 'measures' aimed at improving outcome:

- *Avoidance of 'potent immunosuppression'*. Potent immunosuppression was defined by the use of triple and/or quadruple immunosuppressive drugs. During the study period, dual therapy with either cyclosporine–prednisone or tacrolimus–prednisone was used unless there were complications (particularly renal insufficiency or severe neurotoxicity) that led to the addition of other immunosuppressive agents while lowering the dose of calcineurin inhibitors.
- *Avoidance of 'rapid steroid withdrawal'*. The term 'rapid steroid withdrawal' was used when steroids were used for a period shorter than 6 months.

2.7. Statistical analyses

Categorical data were compared using a x^2 test or Fisher's exact test when indicated. When categorical variables were ordered, comparisons were done using a x^2 test for trend. Continuous variables were expressed as median and range and compared by the Mann-Whitney test. Multivariate analysis was performed to identify independent predictors of severe disease using logistic regression. A P value of <0.05 was considered statistically significant. HCV-related severe disease was defined by the presence of bridging fibrosis, cirrhosis or fibrosing cholestatic hepatitis occuring within the first year post-transplantation. All statistical analyses were performed with SPSS 9.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Patient demographics

Study cohort. Ninety patients out of the 121 patients transplanted between October 2001 and May 2004, fulfilled the inclusion criteria (Table 1). The remaining 31 liver transplant recipients were excluded due to: negativity of HCV RNA following transplantation ($n=1$); associated medical conditions (Budd-Chiari post-transplantation, $n=2$; biliary and/or arterial complications, $n=3$; recurrence of HCC, $n=1$); lack of adequate first-year liver biopsy ($n=3$); and death within the first year ($n=21$, none related to HCV). The causes of death included: sepsis ($n=13$), cardiovascular complications ($n=3$), de novo tumor ($n=2$), neurological complications ($n=1$) and surgical-related complications ($n=2$). Excluded patients were similar to those included in the study in terms of demographics, donor and surgical-related variables, genotype distribution and initial immunosuppression (data not shown).

Table 1
Baseline features of the two cohorts of patients

Variables/year of LT	1999–2000 ($n=52$)	2001–2004 ($n=90$)	P value
Sex (% male)	35 (67%)	64 (71%)	0.6
Age at transplantation	54 (38–67)	58 (28–67)	0.3
Alcohol pre-transplantation (%)	8 (15%)	18 (20%)	0.5
HCC at transplantation (%)	21 (40%)	37 (41%)	0.9
Child classification (% C)	23 (44%)	42 (47%)	0.9
Genotype 1 (%)[a]	41 (93%)	66 (87%)	0.3
IFN pre-transplantation (% yes)	5 (9.5%)	27 (30%)	0.006
Donor			
Sex[a] (% male)	32 (61.5%)	55 (61%)	0.9
Age[a] (years)	51 (16–77)	57 (12–83)	0.07
Cold ischemia (min)	300 (45–760)	295 (115–685)	0.5
Rewarming time (min)	35 (15–255)	40 (15–80)	0.08

HCC, hepatocellular carcinoma; LT, liver transplantation; IFN, interferon; IS, immunosuppressive

[a] Available in 120 patients.

Historical cohort. Fifty-two of the 78 patients undergoing transplantation between January 1999 and August 2000 fulfilled the inclusion criteria (Table 1). The remaining 26 liver transplant recipients were excluded due to: negativity of HCV RNA following transplantation ($n=1$); associated medical conditions (Budd-Chiari post-transplantation, $n=2$; biliary and/or arterial complications, $n=1$; recurrence of HCC, $n=4$); lack of adequate first-year liver biopsy ($n=2$); and death within the first year ($n=16$, none related to HCV). Excluded patients were similar to those included in the study in terms of demographics, donor and surgical-related variables, genotype distribution and initial immunosuppression (data not shown).

3.2. Factors associated with severe disease

Variables associated with severe disease by univariate analysis were: acute hepatitis post-transplantation (63 vs 28.5%, $P=0.0001$), use of additional immunosuppressive drugs for induction immunosuppression (27.5 vs 9%, $P=0.003$); MMF induction (14 vs 3%, $P=0,03$); infection with HCV genotype 1 (100 vs 83%; $P=0.004$); donor age [58 (17–79) vs 48 (12–83), $P=0.001$] and prednisone duration {278 (22–953 vs 343 (25–710) $P=0.007$). A history of significant alcohol consumption prior to transplantation was found to be protective against severe disease (8% vs 24%; $P=0.02$). Of all these variables, those retained in the model by multivariate analysis were: donor age {RR:0.96 (95% CI: 0.94–0.99), $P=0.03$}; acute hepatitis {RR 4.78 (95% CI: 1.8–12), $P=0.001$); use of additional immunosuppressive

drugs for induction {RR 0.11 (95% CI: 0.3–0.43), $P=0.001$); and a history significant consumption of alcohol pre-transplantation {RR 0.13 (95% CI: 0.029–0.64), $P=0.012$}.

3.3. Comparison of outcome with a previous cohort of patients who were transplant recipients in 1999–2000 before the implementation of simple measures

Patient histology at one year was compared between the two cohorts of patients. The percentage of patients with severe disease within the first year was significantly lower in those transplanted in the most recent cohort (26/90, 29%) compared to those transplanted in the historical cohort (25/52, 48%; $P=0.02$). Among the historical cohort, 12 patients (23%) had no fibrosis in the first year liver biopsy compared to 33 (37%) in the study cohort ($P=0.1$). The comparison of the stage of fibrosis in the first year between the two cohorts is shown in Fig. 1. The percentage of patients diagnosed with cholestatic hepatitis was also lower in the study cohort ($P=0.01$) (Table 2).

Both cohorts were not different in terms of baseline characteristics (Table 1). As expected: (i) a history of interferon therapy in the past was more common in those transplanted in the most recent cohort ($P=0.006$); (ii) The immunosuppression utilized was also different in both cohorts (Table 3). In the most recent cohort: (a) the duration of prednisone was longer ($P=0.004$); (b) the percentage of patients receiving combination of different immunosuppressive drugs (in addition to calcineurin inhibitors ± steroids) was lower ($P=0.0017$); and (c) the number of patients treated with boluses of corticosteroids for cellular rejection was lower ($P=0.002$) compared to the historical cohort. By multivariate analysis, the same variables were found to be significantly different between the two cohorts.

Since immunosuppression-related variables were found to be strongly related with the change in outcome, a second analysis was carried out to determine the specific effect of immunosuppression-related variables on the outcome in the two cohorts of patients (Table 4). Use of additional immunosuppressive agents was the only variable statistically related with the outcome in both cohorts.

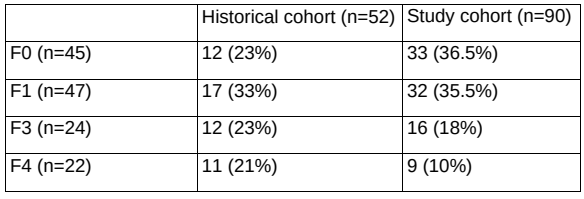

Fig. 1. Stage of fibrosis in the first-year liver biopsy $P=0.04$.

Table 2
Outcome comparison between the two cohorts of patients

Variables/year of LT	1999–2000 ($n=52$)	2001–2004 ($n=90$)	P value
History of acute hepatitis[a]	28 (54%)	30 (33%)	0.017
Cholestatic hepatitis	12 (23%)	7 (7.5%)	0.01
Time to acute hepatitis (days)	79 (11–404)	65 (35–395)	ns
ALT at 1 month post-LT (IU)	108 (16–743)	58 (9–609)	0.002
Fibrosis ≥1	40 (77%)	57 (63%)	0.09
Severe disease in 1 year	25 (48%)	26 (29%)	0.02
Graft loss	23 (44%)	16 (18%)	0.001

ALT, alanine aminotransferase levels.
[a] Acute hepatitis was evidenced histologically and based on an initial liver biopsy performed when liver enzymes rose to twice the upper limit of normality.

Table 3
Immunosuppression in both cohorts

Variables/year of LT	1999–2000 ($n=52$)	2001–2004 ($n=90$)	P value
Immunosuppressive regime			
CYC+P	3	39	
FK+P	36	41	
FK/CYC+P+Atgam	2	0	
FK/CYC+P+Il2R-Ab	7	3	
FK/CYC+P+MMF	3	5	
Others			
FK+MMF	0	1	
FK+MMF+Il2R-Ab	1	0	
CYC+P+R	0	1	
Additional IS drugs (% yes)[a]	13 (25%)	9 (10%)	0.0017
Duration prednisone (days)	249 (25–470)	350 (22–953)	<0.0001
Prednisone duration > 1 year (% yes)	10 (21%)	39 (46%)	0.004
Prednisone duration >6 months (% yes)	31 (65%)	69 (81%)	0.03
Boluses of MP	11 (21%)	4 (4.5%)	0.002
First month[a]	10	3	
>first month	1	1	

CS, cyclosporine; FK, tacrolimus; P, prednisone; IL2R-Ab, interleukin 2 receptor antibodies; MMF, mycophenolate mofetil; MP, methylprednisolone; R, rapamycin.
[a] Additional IS drugs were those added to the immunosuppressive regime in addition to calcineurin inhibitors ± steroids or MMF.

Table 4
Immunosuppression and severe disease in the historical and most recent cohorts

	Severe disease ($n=25$)	Benign disease ($n=27$)	P value
(a) Historical cohort			
MP boluses	5 (20%)	6 (22%)	0.6
Use of additional IS drugs	9 (36%)	4 (15%)	0.07
Prednisone duration	243 (163–466)	249 (25–470)	0.4
(b) Recent cohort			
MP boluses	1 (4%)	3 (4.5%)	0.5
Use of additional IS drugs	5 (19%)	4 (6%)	0.06
Prednisone duration (days)	296 (22–953)	364 (154–710)	0.005

MP, methyl-prednisolone; IS, immunosuppressive.

4. Discussion

Recurrent hepatitis C is a major problem in liver transplant units, due to both its high frequency and aggressivity, particularly in recent years [1,6,7]. In the recent consensus conference on this topic held in Phoenix in March 2003, the experts raised the need to further explore the effect of immunosuppression on the severity of recurrent hepatitis C [19]. Indeed, there are several indirect findings that suggest that immunosuppression is likely the major factor in determining variations in clinical outcome: (1) the higher rate of HCV-related fibrosis progression in immunosuppressed populations, such as liver transplant recipients or HIV-coinfected patients, compared to immune competent patients [5,20]; (2) the higher aggressivity of compensated cirrhosis in transplant recipients compared to non-immunosuppressed patients with HCV-cirrhosis [21]; (3) the known detrimental effect of high methyl-prednisolone boluses on the severity of recurrent hepatitis C [1,3,4,10,12–19,22,23] and (4) the potential implication of more potent immunosuppressive drugs in the recent worsening of recurrent hepatitis C [6,7,23].

The effect of additional viral, donor and/or external factors on recurrent hepatitis C is also under investigation. It is established that the use of organs from old donors is associated with a worse outcome [6,7,13–15]. In contrast, the data are controversial regarding the effect of steroid tapering, with some retrospective studies suggesting that a rapid steroid tapering may be deleterous for hepatitis C progression in liver transplant recipients [6,7,12,16,17,23].

We recently showed that recurrent hepatitis C is more aggressive in patients transplanted in recent years [6,7]. Reasons that explain this change in the natural history of recurrent hepatitis C, at least in some centers are unknown, but likely involve the increasing age of the donor [6,7,13–15] and changes in immunosuppression [7,23]. In our prior study, we hypothesized that the use of newer and more potent immunosuppressive drugs together with a shorter prednisone duration might have negatively impacted outcome [7]. Hence in 2001, and in order to improve the outcome, two simple measures were undertaken in our center: the use of less potent immunosuppression avoiding triple and quadruple regimes and a slow steroid tapering over at least 6 months following surgery. During the last few years, these measures have been implemented in our center. We report here the preliminary results in a population of liver transplant recipients mainly infected with HCV genotype 1b. The major conclusions is that a significant reduction in the rate of severe hepatitis C in the first year may be achieved by implementing simple measures basically related to immunosuppression.

This is the first study to show that simple changes in immunosuppression based on observations from retrospective studies have an actual positive impact on outcome. We chose to evaluate the outcome at only the first year, since it has become increasingly common to start antiviral therapy based on the results of the first-year protocol liver biopsy [4,18,19]. In addition, we chose as a 'historical cohort', the group of patients who were transplant recipients in the prior two-year cohort (1999–2000) just prior to the implementation of 'positive measures'. As we showed in a previous study [7], this is the two-year cohort of patients with the worse results obtained in one decade of transplant activity. In that sense, we must emphasize that the two groups are not comparable in the year of transplantation nor in numbers and both these circumstances might bias the results. The worsening in disease outcome though, was not a specific event that was only observed during the years 1999–2000 but rather a trend that started approximately in 1995 and has continued until we changed our policy regarding immunosuppression.

We had hypothesized that the use of additional immunosuppressive agents besides calcineurin inhibitors $\pm$ steroids had a negative effect on recurrent hepatitis C. Based on this hypothesis, we decided to use only dual therapy with either cyclosporine neoral or tacrolimus in combination with steroids. We had also hypothesized that a rapid steroid tapering was also, in part, responsible for the recent worsening in disease progression due to 'partial immune reconstitution'. Based on this hypothesis, we decided to taper steroids at a lower rate, with reduction to 5 mg over the first 6 months with subsequent withdrawal during the following 3–6 months. Interestingly, the number of patients treated with boluses of steroids, a factor consistently associated with severe recurrence [1,3,8,11,12,17–19,22,23], was higher in the historical group compared to the most recent cohort, a finding that by itself could also explain the improvement in outcome. While we have no clear explanation for this finding, it may have resulted from the prolonged use of steroids. Boluses though, were typically administered in the first month post-transplantation. Although this suggests that it is very unlikely that we were treating recurrent hepatitis C, it also points towards additional causes explaining the lower rate of rejection treatment in the recent cohort. Interestingly, our protocol regarding treatment of rejection did not change in the two cohorts, and only moderate to severe rejection episodes were treated with boluses. In fact, the rate of treated rejection episodes is similar in the two cohorts (11/19 in the historical cohort vs 4/8 in the study cohort). In order to further speculate and understand the complex relationship between immunosuppression and outcome, we carefully analysed the effect of immunosuppression-related variables on outcome in the two cohorts of patients (see Table 4). The results from this second analysis further suggest that the main factors impacting outcome are induction therapy and prednisone duration, results not substantially different from those recently reported by Samonakis et al. [23]. No additional differences that could potentially explain our results were noted between the two cohorts except for a higher rate of 'past interferon therapy' recorded in patients transplanted more recently. In most of

these cases, therapy had been used several years before transplantation and frequently consisted of interferon monotherapy or thereby in combination with ribavirin. In addition, while donor age was not statistically different in the two cohorts, the improvement in outcome happened in an era where older donors were used (see Table 1).

The study clearly demonstrates that there is a potential to reduce HCV-disease progression in liver transplant recipients through a better management of immunosuppression, in particular by avoiding overall excess immunosuppression and abrupt changes in immunosuppression with a slow steroid tapering and absence of methylprednisolone boluses.

In conclusion, the results from this study confirm previous assumptions, that is, the detrimental effect of excess immunosuppression on HCV-related disease progression following liver transplantation; and as a consequence, the possibility of improving outcome by modifying immunosuppression in these patients.

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