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ORIGINAL ARTICLE

Treatment of hepatitis C recurrence is less successful in female than in male liver transplant recipients

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Summary

It has been recently suggested that the risk of graft loss after liver transplantation (LT) may increase in female HCV patients. The aim of the study was to examine gender differences in HCV therapy tolerance and outcome in LT patients treated for HCV recurrence. A retrospective study was conducted on liver recipients with HCV recurrence, who were given antiviral therapy from 2001 to 2009 in 12 transplant centers in Italy. Sustained virological response (SVR), adherence-to-therapy, and side effects were evaluated. A multivariate logistic regression model was used after adjusting for possible confounders. The data regarding 342 treated patients were analyzed. SVR was reported in 38.8% of patients. At baseline, male and female did not differ in HCV viral load, histology, or rate of diabetes. SVR was lower in females than in males (29.5% vs. 42.1%; $P = 0.03$). Adherence-to-therapy was also lower in females than in males 43.4% vs. 23.8%; $P = 0.001$); anemia was the main reason for lower adherence. In a multivariate analysis in patients Genotype 1, female gender ($P < 0.04$), early virological response ($P < 0.0001$), and adherence to therapy ($P < 0.0001$) were independent predictors for SVR. In conclusion, female gender represents an independent negative prognostic factor for the outcome of HCV antiviral therapy after LT.

Introduction

Liver disease because of hepatitis C virus (HCV) is one of the main current indications for liver transplantation (LT) [1]. The recurrence of HCV after liver transplant is almost universal, with more severe disease progression and clinical outcome if compared with immunocompetent patients [2–4]. In LT recipients, chronic HCV infection leads to cirrhosis in up to 30% of individuals 5 years after LT [2,5]. In immunocompetent patients, there is

evidence supporting an effect of gender on the outcomes of patients infected with HCV [6,7]. In particular, studies regarding the natural history of hepatitis C in the general population have shown lower rates of progression to advanced liver disease, and higher rates of response to antiviral therapy in women [6,7]. Because of these and other favorable factors, women experience lower rates of hepatocellular carcinoma, and overall lower death rates for HCV-related liver disease [8].

Gender differences are still to be established in the natural history of patients who have undergone LT for HCV-related liver disease. In fact, there are few studies directly addressing this issue in the post-transplant setting [9,10]. Data from the United Network for Organ Sharing registry have indicated that HCV-positive female recipients have worse survival rates than males [7]. In recent large-cohort multicentre studies performed on LT patients, Lai *et al.* [11,12] found that the female gender is an under-recognized risk factor for advanced recurrent HCV disease and graft loss. Other studies evaluating the outcomes of HCV-infected LT recipients have suggested that female gender together with older donors are among the major risk factors for the development of a severe HCV recurrent liver disease [9].

To date no study has been performed in LT patients to elucidate whether there is a gender difference in the antiviral therapy response contributing to the poorer prognosis of female recipients.

The aim of our multicenter study was, therefore, to specifically examine gender difference in HCV therapy outcome in the post-transplantation setting.

Patients and methods

Patient population

This retrospective multicentre study included all patients undergoing transplantation for HCV-related liver disease who were consecutively evaluated for antiviral therapy from 2001 to 2009 in twelve Italian experienced LT centers (RECOLT-C group). Eligibility criteria for antiviral therapy were: being transplanted for at least 6 months, a positive test for anti-HCV and HCV RNA in serum, a liver biopsy demonstrating a recurrence of chronic hepatitis C and absence of contraindication. Patients who received antiviral treatment, but presented coexistent hepatitis B, or a diagnosis of cirrhosis (Ishak score < 5) were excluded from the analysis. To obtain a more homogeneous group of patients the study analyzed only patients treated with ribavirin (RBV) plus pegylated interferon (PEG-IFN). The treatment was scheduled for 48 weeks with no difference for genotype. Adverse events were recorded at each visit. A complete clinical history, physical examination, and biochemical and hematological work-up were performed every 4 weeks. RBV dose reduction was initiated for hemoglobin < 10g/dL and according to patient tolerability. Dose reduction of PEG-IFN was initiated for neutrophil count $<1000/mm^3$ or platelet count $<35{,}000/mm^3$. The use of the granulocyte colony-stimulating factor and erythropoietin were initiated if neutrophil counts were below $750–1000/mm^3$ and hemoglobin level <9 g/dL, respectively.

Treatment was discontinued if anemia was symptomatic and refractory to RBV dose reduction/withdrawal and erythropoietin administration, if neutropenia was not improved by granulocyte colony-stimulating administration, in the case of a platelet count $<20{,}000/mm^3$, major depression, acute graft rejection, clinical decompensation (ascites, hepatic encephalopathy) occurring during antiviral therapy, or refusal of patients to complete the scheduled therapy. In patients, not matching early virological response the stopping rule was not applied, unless relevant side effects of therapy were reported.

Acute cellular rejection was based on the elevation of liver function test, and was confirmed by histology. Mild rejection episodes were treated by increasing the immunosuppressive drug dosage. Patients who experienced a moderate-severe rejection episode (Banff score, 4–9) discontinued interferon therapy and were usually treated with corticosteroid boluses.

Liver biopsy samples were scored according to the Ishak scoring system [13].

Adherence to therapy was considered such when patients completed at least 80% of therapy length with at least 80% of the intended dose of antiviral drugs [14].

Immunosuppression

Immunosuppression was not uniform among centers. Immunosuppressive regimen was based on calcineurin inhibitors (Tacrolimus and Cyclosporin) in the majority of patients. No patient was under corticosteroid therapy during the study.

Statistical analysis

For the statistical comparison, we used NCSS version 17.0 for Windows and R 2.11.1 for Linux. Data are expressed as percentages when categorical, median and range when there is no assumption of normality, and mean ± SD when the normality assumption is acceptable. Univariate relationships between gender and the other factors were assessed with Pearson's chi-squared test when the factor was categorical, and Mann–Whitney test when the factor was continuous. Univariate effects on the sustained viral response were assessed through simple logistic regression models.

To evaluate the effects of gender after adjusting for potential confounders, we also fit multivariate logistic regression models. For model choice, we used a backward strategy. As a result of the strong confounding effects of genotype, we conducted the same analysis stratified by genotype. ''$P < 0.05$'' was used for statistical significance.

Results

Of a total of 462 candidates for the study, 105 patients were excluded because they were receiving a nonstandard antiviral therapy (i.e. nonpegylated interferon or pegylated interferon alone without ribavirin), 5 for Ishak score >6 and 10 for coexistent HBV. The study cohort consisted of 342 liver transplant recipients, mostly males (74%). The median age, 54 years (range 19–68), was similar between females and males. At enrollment, the majority of women (85%) were menopausal. Males and females were homogeneous for donor age, previous antiviral treatment, baseline viral load, distance between LT, type of immunosuppressive therapy, BMI, and diabetes. Most patients were infected with HCV genotype 1, with a difference in gender prevalence rates (82% of females vs. 71% of males; $P = 0.01$) (Table 1).

Baseline histology showed mild to moderate liver fibrosis in most patients, and no gender difference in the fibrosis stage was found when considering the whole cohort of patients (Table 1).

The main characteristics of antiviral therapy are shown in Table 2.

Treatment response

Early virological response (EVR) was obtained in 51% of patients with no difference in gender prevalence ($P = 0.17$). End-of-treatment (EOT) virological response rate was 58.4% with a higher prevalence in males ($P = 0.08$). The relapse rate was similar in males and females ($P = 0.48$). A sustained virological response (SVR) was reported in 38.8% of treated patients. The rate of SVR showed a significant difference between males and females ($P = 0.03$) (Table 2).

As for the genotype 1 subgroup at univariate analysis SVR in male recipients was universally higher than in female recipients ($P = 0.05$) (Table 3). EVR and adherence to therapy were higher in SVR patients versus nonresponders (Table 3). No statistically significant association was found between therapy outcome and age of donor, gender mismatch, age of recipients, diabetes, HCV viral load, baseline fibrosis or the use of hematological growth factors (Table 3).

The results from univariate analysis for the genotype 2/3 showed a lower response to therapy in the subjects with diabetes or with a lower adherence to therapy. Gender of recipients, age of recipients, age of donor, gender mismatch, and the use of hematological growth factors were not associated with SVR (Table 4).

Results from the final multivariate analysis, chosen by stepwise selection and stratified for genotype are shown in Table 5. In the group of genotype 1 recipients, female gender was a significant independent predictor of SVR

Table 1. Baseline characteristics of the liver recipients included in the study.

Variables	Males (254)	Females (88)	*P*
Age (years)	52 (19–68)	56 (22–67)	0.07
Donor Age (years)	49 (13–80)	49 (12–84)	0.99
Genotype 1 (*n* of patients)	181/254	71/88	0.01
HBV co-infection (*n* of patients)	6/254	4/88	0.47
Naive to treatment (*n* of patients)	109/254	31/88	0.61
Diabetes (*n* of patients)	79/254	26/88	0.42
BMI (kg/m^2)	24.4 (15–34)	24.48 (17–36)	0.43
Distance LT-therapy (months)	12 (6–70)	15 (6–68)	0.28
HCV-RNA level (IU/ml)	9.8×10^6	9.95×10^6	0.91
Range	3×10^5–4×10^7	3.5×10^5–3.8×10^7	
Fibrosis stage (S-Ishak)			
F1-2 (% of patients)	65	63	0.47
F3-4 (% of patients)	30	33	
F5 (% of patients)	5	4	
Inflammation grade (G-Ishak)	6.2 (2–15)	6 (2–13)	0.62
Recipient-donor gender mismatch (%)	28	47	0.001

Data are expressed as median (range) unless otherwise specified.

Table 2. Characteristics of antiviral therapy and virological response.

Variables	Males (254)	Females (88)	*P*
Pegylated Interferon (μg/kg/week)	1.33 (SD 0.5)	1.29 (SD 0.9)	0.82
Ribavirin (mg/kg/day)	8.24 (SD 4.6)	8.2 (SD 3.9)	0.64
Interferon therapy duration (weeks)	42.2 (SD 4.1)	37.4 (SD 2.5)	0.03
Ribavirin therapy duration (weeks)	43.8 (SD 23.3)	27.8 (SD 26)	0.08
Adherence to at least 80% of Interferon intended therapy dose (% of patients	61.4	54.3	0.26
Adherence to at least 80% of Ribavirin intended therapy dose (% of patients)	47.5	43.4	0.32
Adherence to at least 80% of total therapy duration (% of patients)	51.7	33.8	0.003
Adherence to 80/80/80 (% patients)	43.4	23.8	0.001
Anemia (% of patients)*	31	43	0.005
Hematological growth factors (% of patients)	25.8	40	0.09
Erythropoietin (% of patients)	18	28	0.08
Early virological response (% of patients)	53.5	44.3	0.17
End-of-treatment virological response (% of patients)	56	46	0.08
Sustained virological response (% of patients)	42.1	29.5	0.03
Relapser (% of patients)	14	16.5	0.48

Data are expressed as a mean ± standard deviation unless otherwise specified.
*Anemia which required therapy dose reduction despite the use of growth factor.

Table 3. SVR-related variables: results from univariate analysis in genotype 1 patients.

Variable	SVR	Non-Responders	*P*
Male/female (% of patients)	29.9/18.3	70.1/81.7	0.05
Age of donor ≥60 years (% of patients)	22.6	28.6	0.38
Median time from LT to therapy (months)	18.0 (7–70)	16.0 (8–68)	0.93
Gender mismatch (% of patients)	34.5	37.1	0.77
Age of recipient in years (median)	56.1 (29–68)	55 (24–64)	0.51
Diabetes (% of patients)	34.2	41.6	0.34
Mean viral load (IU/ml) at baseline	7.1×10^6	1.05×10^7	0.23
	3×10^5–2.8×10^7	5×10^5–3.8×10^7	
Fibrosis stage at baseline (% of patients)			
F1-2	68.6	64.2	0.62
F3-4	27.1	30.5	0.74
F5	4.2	5.3	0.51
Early virological response (% of patients)	85.9	26.6	<0.0001
Use of growth factors (% patients)	34.1	37.1	0.75
Adherence to therapy 80/80/80 (% of patients)	53.3	29.3	0.0001

Table 4. SVR-related variables: results from univariate analysis in genotype 9+2/3 patients.

Variable	SVR	Non-Responders	*P*
Male/female (% of patients)	69.2/77.7	30.8/22.3	0.46
Age of donor ≥60 years (% of patients)	29.1	22.5	0.98
Median time from LT to therapy (months)	15.9 (6–68)	13 (7–56)	0.71
Gender mismatch (% of patients)	28.5	31.2	0.81
Age of recipient in years (median)	54 (30–65)	54 (28–67)	0.58
Diabetes (% of patients)	19.2	63.2	0.001
Median viral load (IU/ml) at baseline	4.43×10^6	2.41×10^7	0.008
	2×10^5–1.8×10^7	1.7×10^5–4.2×10^7	
Fibrosis stage at baseline (% of patients)			
F1-2	67.5	64.3	0.31
F3-4	28.1	30.8	0.23
F5	3.4	4.7	0.25
Early virological response (% of patients)	90.2	9.8	<0.0001
Use of growth factor (% patients)	26.5	38.4	0.61
Adherence to therapy 80/80/80 (% of patients)	46.2	23.3	0.05

Table 5. Prognostic variables on SVR: results from multivariate analysis in genotype 1 and genotype 2/3 patients.

Prognostic factor in genotype 1 pts	OR	95% CI	*P*
Female gender	0.51	0.02–0.4	0.04
Early virological response	34.5	2.01–13.4	<0.0001
Adherence to therapy 80/80/80	8.15	2.38–27.8	<0.0001
Prognostic factor in genotype 2/3 pts			
Diabetes	0.1	0.03–0.34	<0.0001
Early virological response	38	1.10–10.2	<0.0001
Female gender	1.1	0.21–3.87	0.83
Adherence to therapy 80/80/80	3.7	1.13–12.65	0.03

failure ($P = 0.04$), whereas adherence to therapy ($P < 0.0001$) and EVR ($P < 0.0001$) were associated with a better response to therapy. In the genotype 2/3 group, adherence to therapy ($P = 0.03$), EVR ($P < 0.0001$) and absence of diabetes ($P < 0.0001$) were significant predictors of SVR. No prognostic value of gender was found in this group.

Treatment compliance

Although the intended treatment protocol did not differ between males and females, we found out that there had been a difference in the actual dose of antiviral therapy. The actual length of therapy was longer in males than in females, i.e., 42 ± 25 vs. 37 ± 25 weeks, respectively ($P = 0.03$). Premature discontinuation of therapy was recorded in 51.7% of treated females versus 33.8% of males ($P = 0.003$; Table 2) despite the wider use of growth factors in female recipients (40% vs. 25.8% in males; $P = 0.09$, Table 2). Support with EPO was needed in 25% of females versus 17.9% of males ($P = 0.08$). Adherence to therapy was much lower in females than in males: 23.8% vs. 43.4% ($P = 0.001$). The main reason for their low adherence to therapy was anemia secondary to ribavirin administration, which was higher among females (43%) than in males (31%) ($P = 0.005$). No difference in gender distribution was found for the other reasons of treatment discontinuation, such as neutropenia, neuropsychiatric conditions, thyroid abnormalities, poor tolerability, and rejection episodes.

Recipient–donor gender mismatch, although more frequent in females than in males (47% vs. 28%; $P = 0.001$), was not found to be a significant predictor of SVR at univariate and multivariate analysis.

Discussion

In this retrospective multicentre study of 342 patients with a recurrence of HCV after LT, we found that female gender is independently associated with a lower likelihood of achieving SVR. Recipient female gender was consistently associated with a lower adherence to therapy as well.

In the post-transplant setting, female gender has already been identified as an independent factor for a more advanced recurrent disease and a higher mortality. Our results seem to support the findings of previous studies that reported an influence of recipient gender in HCV disease progression [9,11,12]. Our large multicentre study describes a worse therapy compliance and outcome for female recipients and offers one of the potential explanations for this gender difference in disease progression and mortality: women have a more aggressive recurrence of HCV secondary to a lower response to antiviral therapy.

It is difficult to account for female disadvantage in the antiviral treatment response, so much so in view of the scarcity of literature on the topic, and the fact that several studies regarding HCV treatment in immunocompetent patients have shown an association of female gender with a better outcome [6,7]. Nevertheless, recent studies suggest that menopausal women may have an accelerated progression to fibrosis and a higher rate of no response to antiviral therapy, especially in genotype 1 HCV patients [15,16]. Although these studies were not designed to identify the pathogenesis of this association, they found a profound change in TNF-α and IL-6 levels, which were significantly increased after the occurrence of menopause. Various lines of evidence support a link between TNF-α high levels and resistance to IFN. In this scenario menopause seems to determine a switch toward a pro-inflammatory state in which increased TNF-α and IL-6 levels contribute to the resistance to IFN-based therapy [17].

Indeed, in our cohort of female patients because of the median age the prevalence of menopause was $\approx$85%, which is about 20% higher as compared with data from the literature regarding nontransplanted women who underwent antiviral treatment [15,16]. Although, we found no significant gender difference in the prevalence of several baseline characteristics known to be predictive of SVR, such as viral load, diabetes, and fibrosis stage, a higher prevalence of genotype 1 subjects in the female group was evidenced from our data. The stratified analysis confirmed, however, that the female gender was also associated with a greater resistance to antiviral therapy when compared with males genotype 1 carriers.

Another relevant finding of our study is that female gender coincided with a lower adherence to therapy, which has been identified as a negative prognostic factor for SVR [14]. We also found that in many cases the use of erythropoietin in women did not prevent the need of ribavirin/interferon tapering. As a point of fact, in spite

of the increased use of the hematological growth factor, females exhibited a higher incidence of *refractory* anemia secondary to ribavirin exposure which was the most common reason for the shorter length of therapy and the reduced adherence in women. Our findings may reflect a gender-specific sensitivity to ribavirin and interferon side effects, which entailed a qualitative and quantitative difference in the given antiviral therapy.

In any case, when we performed a multivariate analysis to examine the influence of gender on the response to antiviral therapy, we found that the female gender was independently correlated with SVR.

Based on our data, the influence of baseline fibrosis on the efficacy of the hepatitis C antiviral therapy is called into question. Baseline fibrosis is recognized as a predictor of successful therapy in immunocompetent HCV patients [15]. In the post-transplant setting, however, the role of fibrosis as a predictor of SVR is still a matter of debate. In two large, systematic reviews on the treatment of recurrent hepatitis C after liver transplantation, baseline fibrosis was found to be associated with SVR in the univariate analysis only in 2 of 10 studies, and in the multivariate analysis the association was not found at all [18,19].

There are some limitations to our study: a multicenter retrospective study is not the best to establish associations or to investigate the causes of the intrinsic disadvantage for females in HCV antiviral therapy outcome. We cannot rule out that the lack of data on IL-28 polymorphism [20,21] and on vitamin D serum levels [22] which are considered influencing factors on therapy response- could bias our interpretation of results.

In any case, our retrospective study is the first study directly addressing the issue of the influence of gender on HCV-treatment outcome in the post transplant setting. Female liver recipients with HCV recurrence were less responsive to antiviral treatment and showed a lower adherence-to-therapy and a higher rate of therapy discontinuation mostly because of ribavirin-induced anemia. The identification of this gender difference opens up the possibility of devising gender-specific models for antiviral therapy follow-up and for post-transplant care of HCV-infected liver recipients. According to our finding, an increased vigilance or a closer follow-up seems to be advisable in female recipients to prevent the hematological side effects that can negatively affect the patient's adherence-to-therapy.

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Authorship

VG, MG and MM: participated in the research work, its design and the writing of the paper. FRP, MP, RV, RMI, MFD, MR, PT, LP, MCM, EDM, LM, DDP and SF: collected the data from the other centers and participated in the design of the study. AF: contributed for the statistical analysis.

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