Ribavirin Dose Modification Based on Renal Function Is Necessary to Reduce Hemolysis in Liver Transplant Patients With Hepatitis C Virus Infection

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Hepatitis C virus (HCV) is currently the most common etiology for liver transplantation (LTx) in the United States. A significant number of patients develop recurrent HCV after LTx. Although there is no completely satisfactory treatment for recurrent HCV, a combination of interferon-α (INF) and ribavirin remains the most widely used. Ribavirin is eliminated through the kidneys and tends to accumulate in the presence of renal dysfunction. The primary side effect of ribavirin is hemolysis. The goal of the present study was to correlate the incidence of hemolysis with renal function in LTx patients with recurrent HCV who were being treated with ribavirin. The incidence of hemolysis and the renal function were examined in 72 liver transplant patients (58 male and 14 female patients) with recurrent HCV receiving INF (3 million units, three times per week) and ribavirin (initial dose of 400 mg twice daily). Patients were grouped according to the decrease in the percentage of hematocrit after the introduction of ribavirin, with their baseline serum creatinine and creatinine clearance calculated using the Cockcroft-Gault formula. The decrease in the percentage of hematocrit after ribavirin treatment was also examined with respect to creatinine clearance as a continuous variable. In addition, for purposes of presentation, patients were analyzed in three groups: creatinine clearance of ≥ 70 mL/min (group A), creatinine clearance < 70 mL/min and ≥ 40 mL/min (group B), and creatinine clearance < 40 mL/min (group C). Forty-five (62.5%) patients experienced a decrease in hematocrit (Hct) ≥15% after starting INF and ribavirin. The mean serum creatinine was 1.3 ± 0.5 mg/dL (median, 1.3) in this group, and the mean calculated creatinine clearance was 71 ± 29 mL/min (median, 66.47). In the 27 patients who did not show a significant decrease (< 15%) in hematocrit, the mean serum creatinine was 1.1 ± 0.3 mg/dL (median, 1.0) and the mean creatinine clearance was 95 ± 39 (median, 96) mL/min (*P* = .018). On continuous variable of calculated creatinine clearance, there was a trend in the decrease in hematocrit after ribavirin treatment compared with pretreatment (*P* = .09). However, the rate of hemolysis was significantly different in group A (53.7%), group B (70.8%), and group C (100%) (*P* = .042). Patients on INF and ribavirin therapy who experienced hemolysis had significantly higher serum creatinine levels and lower creatinine clearances compared with those who did not have hemolysis. The incidence of hemolysis was significantly associated with higher serum creatinine and decreased creatinine clearance. Because ribavirin is eliminated by the kidneys, this observation points to the need for adjustments in the dose of this agent in LTx patients, who tend to have some degree of renal dysfunction, to reduce the incidence of hemolysis. Further pharmacokinetic studies of ribavirin in LTx patients with varying degrees of renal function may allow the development of an algorithm for the safer use of ribavirin in HCV-positive LTx patients. (*Liver Transpl 2002;8: 1007-1013.*)

Hepatitis C (HCV) is the leading cause of end-stage liver disease in the adult population requiring liver transplantation (LTx).[1-5] This incidence is expected to increase further in the next decade. Liver transplantation in patients with HCV-related disease offers a good quality of life initially, with success rates comparable to those seen in non-HCV patients. However, the long-term results are significantly inferior[6-9] and are primarily the result of reinfection of the allograft. Currently, there is no satisfactory treatment or prophylaxis for HCV. Experience in using interferon-α (INF) with or without ribavirin, in the LTx population is limited. The rationale for the use of a combination of INF and ribavirin comes from the nonimmunosuppressed population, in which virologic clearance and biochemical and histologic improvement are seen in up to 40% of patients.[10-13] Ribavirin (1-β-dribofuranosyl-1, 2,4-trazole-3-carboxamide) is a synthetic nucleoside analog, structurally similar to guanosine and inosine. It seems to inhibit viral protein synthesis through its interface with the function of mRN.[14-16] The prin-

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cipal route of elimination of ribavirin is renal,[17-19]and renal dysfunction seems to affect the elimination of ribavirin. The area under the plasma concentration (AUC) versus time curve is three times higher in patients with a creatinine clearance of 10 to 30 mL/min compared with patients with a creatinine clearance of >90 mL/min. A fixed dosing regimen ranging from 400 to 600 mg twice per day is normally used in transplantation patients, without adjusting the dosage based on renal function.[10,15,20-25] There are several reports of hemolysis in patients on ribavirin therapy before and after LTx.[6,10,13,14,22,24,25] Recently, the multicenter trial for recurrent HCV infection in LTx patients reported a > 60% patient withdrawal rate from the trial mainly because of hemolysis.[23] In addition, data from the Mayo Clinic have shown the rate of hemolysis to be > 50.[22] No dosage adjustment of ribavirin was made according to renal function in these studies, despite the fact that a majority of LTx patients have renal dysfunction because of the effect of calcineurin inhibitors and cryoglobulinemia associated with HCV infection.[26-34] The goal of the present study was to examine the incidence of hemolysis (defined as a decrease in hematocrit [Hct] ≥ 15%) and its relationship to renal function in LTx patients with HCV infection who were treated with INF and ribavirin.

Patients and Methods

The study involved a retrospective analysis of the electronic medical records and database of all LTx patients at a single institution who received INF and ribavirin combination therapy from August 1996 to July 2000 for recurrent HCV infection under a University of Pittsburgh IRB exempt protocol (IRB 00625). There were 72 patients, 58 male (80.5%) and 14 female (19.4%), with a mean age of 49.2 ± 8.2 years. The mean interval from LTx to INF and ribavirin therapy was 19.5 ± 17.9 months (range, 1 to 109; median, 14.9). INF was given subcutaneously at a dose of three million units three times per week, and ribavirin was administered orally at a dose of 400 mg twice per day. Biochemical indicators of the renal function (blood urea nitrogen and serum creatinine) were routinely measured serially in all patients. Changes in Hct were also recorded, and the decrease in Hct was described as a percentage using the formula:

$$\frac{\text{Preribavirin Hct} - \text{Postribavirin Hct}}{\text{Preribavirin Hct}} \times 100 = \%\,\Delta\,\text{Hct}$$

If the percent decrease in hematocrit is equal to or greater than 15%, these patients were considered to have hemolysis.

Creatinine clearance was calculated in all subjects using the Cockcroft-Gault formula. Patients were divided into two groups based on the percent decrease in hematocrit. Group I included patients with a decrease in Hct of ≥ 15%, and group II included patients with a decrease in Hct of < 15%. The baseline serum creatinine and creatinine clearance at the start of INF and ribavirin therapy were compared in both groups. The patient population was divided into three groups based on the creatinine clearance before ribavirin therapy. Group A included patients with a creatinine clearance ≥ 70 mL/min; group B patients had a creatinine clearance < 70 and ≥ 40 mL/min, and group C patients had a creatinine clearance < 40 mL/min.

Statistical Consideration

Continuous variables are reported as mean ± standard deviation; categorical variables are reported as proportions. For comparison of proportions between groups, a likelihood ratio Chi-squared test was used. The Mann-Whitney *U* test was used to compare creatinine clearance and baseline creatinine. The Spearman correlation coefficient was used to assess the correlation between continuous variables. *P* values of < .05 were considered significant.

Results

Incidence of Hemolysis and Renal Function

All patients were maintained on tacrolimus-based immunosuppression. All patients had histologic evidence of HCV recurrence on a liver biopsy and were positive for HCV by a polymerase chain reaction before treatment. Forty-five (62.5%) patients had hemolysis (group I), in which the decrease in Hct was ≥ 15%, and 27 (37.5%) had a decrease in Hct of < 15% (group II). The mean serum creatinine in group I was 1.3 ± 0.5 mg/dL, with a mean calculated creatinine clearance of 71 ± 29 mL/min (median, 66) compared with a serum creatinine of 1.1 ± 0.3 mg/dL (median, 1.0) and a calculated creatinine clearance 95 ± 39 mL/min (median, 96) in group II. This difference in creatinine clearance was statistically significant ($P = .018$). The mean Hct in group I before and after INF and ribavirin treatment was 39.6% ± 4.5% and 29.7% ± 5.3%, respectively, with a mean percent decrease in Hct of 24.8% ± 8.4%. The mean time to decrease in Hct was 122 ± 114 days (median, 90; range, 19 to 365) after initiation of ribavirin treatment. The mean Hct in group II was 38% ± 5.9% and 35.9% ± 5.3% before and after ribavirin therapy respectively, with a mean percent decrease of 5.5% ± 4.8% (Table 1). The percent decrease in Hct in group I and group II versus creatinine clearance is shown in Figure 1.

Renal Dysfunction and the Incidence of Hemolysis

The decrease in the percentage of hematocrit post-INF and ribavirin compared with pre-ribavirin treatment

was highly significant ($P = .011$). When patients were examined in three groups based on creatinine clearances, in group A (n = 41, 58.9%), group B (n = 24, 33%), and group C (n = 7, 9.7%), the rate of hemolysis was 53.7% in group A (22 of 41), 70.8% in group B (17 of 24), and 100% in group C (7 of 7). This difference was statistically significant ($P = .042$) (Table 2, Fig. 2). However, when creatinine clearance pretreatment was used as a continuous variable and compared with the percentage decrease in Hct after ribavirin treatment, although there was a trend, it did not reach statistical significance ($P = .09$).

The highest degree of hemolysis (56%) was observed in the patient who had the worst serum creatinine, 2.6 mg/dL, and a calculated creatinine clearance of only 14 mL/min (case 67). Within 14 days of treatment (400 mg twice per day) her hematocrit decreased from 38% to 26.1%, and the dose of ribavirin was reduced by 50%. Five days later (19th postribavirin day), hematocrit decreased further to 17.4%, at which point ribavirin was discontinued, and the patient received three units of packed red blood cells. Based on this experience, lower doses of ribavirin were used (200 to 400 mg/d) in the patients with a serum creatinine $\geq$ 2.0 mg/dL, which avoided the need for the transfusion or the use of erythropoietin in most cases.

Table 1. Creatinine Clearance in Relation to Hemolysis

	Decrease in Hct(%)	n(%)	Creatinine Clearance mL/min Mean ± SD(Median)	Serum Creatinine Mean ± SD(Median)	Hct Before INF ± Ribavirin Mean ± SD(Median)	Hct After INF ± Ribavirin Mean ± SD(Median)	Mean % Decrease in Hct Mean ± SD(Median)	Use of Erythropoetin for Anemia n(%)
Group I	≥15	45 (62.5)	71.35 ± 29.29 (66.47)*	1.33 ± 0.45 (1.3)	39.57 ± 4.49 (40.0)	29.73 ± 5.33 (31)	24.75 ± 8.39 (23.3)	16 (34.8)
Group II	<15	27 (37.5)	94.61 ± 39.08 (96.11)*	1.09 ± 0.32 (1.0)	38.13 ± 5.87 (37.73)	35.93 ± 5.3 (35.42)	5.53 ± 4.8 (5.91)	5 (19.2)

*P-Value, .02

Liver Function in Response to Anti-HCV Therapy

The mean changes in total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and gamma glutamyl transferase before starting INF and ribavirin and at 1, 3, 6, and 12 months posttreatment are shown in Table 3. There was an overall improvement in all the biochemical parameters.

Use of Erythropoietin

Twenty-one patients received erythropoietin to treat their decreasing hematocrit levels. Twelve patients in group A (29.3%) and 8 in group B (33.3%) required erythropoietin. In group C, all patients had a > 15% decrease in hematocrit. Four patients received lower doses of ribavirin (200 to 400 mg/d) and did not require erythropoietin. In the other three patients who received a standard dose of ribavirin, one required a blood transfusion (described above) and one needed erythropoietin therapy.

Discussion

The combination of INF and ribavirin seems to be beneficial in the treatment of HCV. After oral admin-

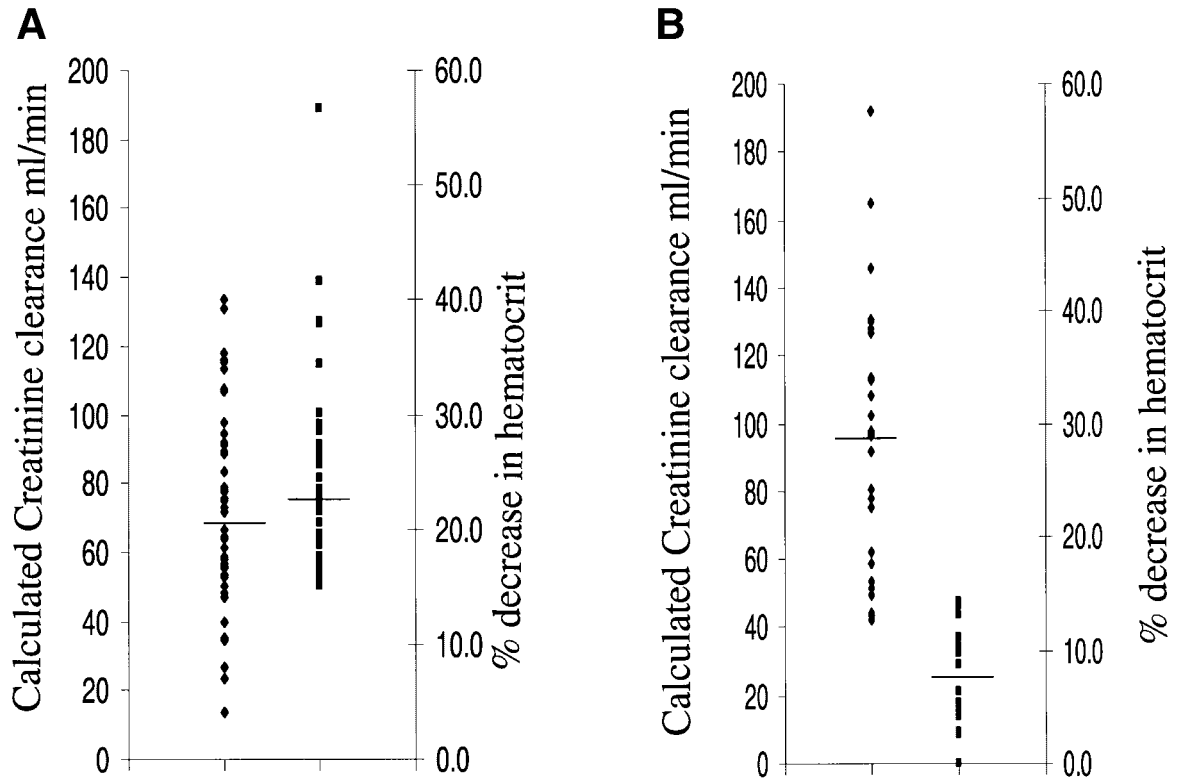

Figure 1. Percentage decreases in hematocrit versus creatinine clearance (solid horizontal bar represents mean value). (A) Group I: decrease in hematocrit ≥15% versus creatinine clearance mL/min. (B) Group II: decrease in hematocrit <15% versus creatinine clearance mL/min.

istration, the mean systemic bioavailability of ribavirin is 32 to 42.[35,36] The half-life of ribavirin is 19 to 20 hours.[35,37,38] Ribavirin accumulates in the red blood cells but is not bound to plasma proteins. The concentration of the ribavirin in erythrocytes is 100 times greater than that in the plasma, and the half-life of ribavirin in the red blood cells is approximately 40 days. After multiple dosing, there is an accumulation of ribavirin in plasma. The steady-state plasma concentrations are achieved in about four weeks.[17] The longer half-life and the correspondingly longer time to achieve a steady-state concentration may be responsible for the observation of hemolysis only after a few weeks of therapy. Ribavirin is phosphorylated into ribavirin triphosphate, which is the active form of the drug against the broad spectrum of DNA, RNA, and retroviruses. Red blood cells lack a dephosphorylating pathway, which affects the metabolism of ribavirin diphosphatase and triphosphatase. This accumulation of phosphorylated ribavirin may alter oxidative respiration in red blood cell membranes by directly competing with adenosine triphosphate and lead to hemolysis.[39]

Ribavirin is excreted by the kidneys, and renal impairment is known to reduce the renal clearance and increase the AUC of the drug.[17] In patients with impaired renal function, ribavirin will accumulate at higher levels in the red blood cells, resulting in a greater risk of hemolysis. This is consistent with reports of a higher incidence of hemolysis in patients who are in renal failure and who cannot eliminate the drug even by hemodialysis.[40] Most liver transplantation patients are maintained on calcineurin inhibitors. One of the known side effects of these agents is nephrotoxicity.[30-34] Furthermore, many patients with HCV infection have cryoglobulinemia, which can further impair renal function.[26-29]

It is possible that other factors, such as low endogenous levels of erythropoietin and marrow suppression in this group of patients, could have contributed to the observed decrease in hematocrit. Erythropoietin levels were not measured in this group of patients, and we have not observed such a marked reduction in hematocrit in other transplantation patients who were immunosuppressed but not treated with ribavirin. Erythro-

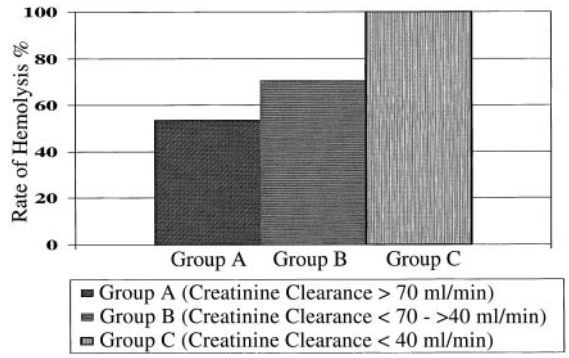

Figure 2. Rate of hemolysis with respect to renal dysfunction.

poietin was used in 21 patients, and this might have counterbalanced the risks of ribavirin-induced hemolysis associated with renal dysfunction. McHutchison et al,[41] in nontransplantation patients, reported dose reduction in 7% to 10% of the patients treated with ribavirin and INF to treat hemolysis. However, they also reported a decrease in hemoglobin of up to 2 g/d in 75% of patients. The rate in the posttransplantation population may be higher because of impaired renal function with the use of calcineurin inhibitors.

This study is the first to quantify the risk of hemolysis in LTx patients on ribavirin, and shows a statistically significant impact of ribavirin with renal dysfunction on hemolysis. It is possible that dose adjustments of ribavirin, based on renal function, may reduce the rate and severity of hemolysis and thereby improve the tolerance of the drug. If this results in a lower percentage of patients who need to discontinue the drug, there may be a corresponding improvement in the overall success rate of the combination of INF and ribavirin in LTx patients with recurrent HCV. Our observations also point to the need to develop newer agents such as Levovirin (ICN Pharmaceuticals Inc, Costa Mesa, CA) and Viramidine (ICN Pharmaceuticals Inc) that may cause lower incidences of hemolysis.

This is a retrospective study, and is based only on the serum creatinine and calculated creatinine clearance. It is known that serum creatinine is a poor indicator of renal function in patients,[42] attributed to lack of muscle mass and other factors. In our population, however, the nutritional status was satisfactory in most patients. Additional studies must evaluate this phenomenon using 24-hour urinary creatinine clearance or other functional assessments of glomerular filtration, renal plasma flow, and glomerular filtration fractions. The findings in this study point to the need for prospective studies to evaluate the relationship between the severity

Table 2. Hemolysis in Relation to Renal Function

Group	Creatinine Clearance mL/min	n(%)	Mean + SD(Median) Creatinine Clearance mL/min	Serum Creatinine Mean + SD(Median)	Rate of Hemolysis n(%)*	Hct Before Ribavirin Mean + SD(Median)	Hct After Ribavirin Mean + SD(Median)	Mean % Decrease in Hct Mean + SD(Median)	Use of Erythropoetin for Anemia n (%)
A	≥70	41 (56.9)	104 + 26 (98)	1.02 + 0.22 (1.0)	22 (53.7)	41.3 + 3.93 (41.0)	34.5 + 6.31 (5.31)	14.94 + 9.66 (15.0)	12 (29.3)
B	<70-≥40	24 (33.3)	54 + 7 (55)	1.36 + 0.31 (1.35)	17 (70.8)	36.6 + 5.8 (38.0)	29.55 + 5.39 (30)	19.56 + 12.11 (21.51)	8 (33.33)
C	<40	7 (9.7)	30 + 9(34)	2.03 + 0.4 (2.1)	7 (100)	35.66 + 2.9 (35.2)	26.29 + 5.76 (27.0)	26.28 + 14.3 (23.3)	†

*P-Value, .042;
†Four patients on reduced dose of ribavirin, of remaining three patients, one required blood transfusion and another erythropoetin (see text).

Table 3. Liver Functions

	Before	Months Post INF + Ribavirin 1	3	6	12
Bili mg/dL (mean + SD)	1.2 ± 0.5	1.7 ± 4.2	1.4 ± 1.6	1.1 ± 0.7	1.1 ± 0.8
AST u/L (mean + SD)	119 ± 137	91 ± 145	69 ± 88	57 ± 46	56 ± 46
ALT u/L (mean + SD)	150 ± 143	101 ± 158	76 ± 71	65 ± 53	76 ± 83
ALKPo4 u/L (mean + SD)	156 ± 123	143 ± 135	133 ± 132	93 ± 58	104 ± 80
GGTP u/L (mean + SD)	402 ± 532	333 ± 470	278 ± 496	233 ± 402	197 ± 358

Abbreviations: Bili, Bilirubin; AST, aspartate amino transferase; ALT, alaninine amino transferase; GGTP, gamma glutamyl transferase; ALKPo4, Alkaline phosphatase.

of hemolysis and renal dysfunction in more detail. Future studies should help to develop an algorithm of ribavirin dosage with drug level monitoring to the calculated creatinine clearance to further improve the management of recurrent HCV hepatitis with INF and ribavirin.

Conclusion

Progressively higher rates of hemolysis were observed in relation to the increasing severity of renal dysfunction in liver transplantation patients treated with ribavirin. Use of lower doses of ribavirin in patients with impaired renal function was associated with a reduced severity of hemolysis, and the need for erythropoietin was avoided. Further kinetic studies of ribavirin in transplantation patients in relation to glomerular filtration rate are needed to design an appropriate algorithm for the dosage schedule to reduce toxicity and improve the tolerance of the drug. This should improve the overall response to INF and ribavirin therapy in LTx patients with recurrent HCV.

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