Poster #905

Baseline, Donor, and On-treatment Predictors of Sustained Virologic Response in Patients Treated for Recurrent Hepatitis C Following Orthotopic Liver Transplant: Subanalysis of the PROTECT Study

F. D. Gordon,[1] F. Poordad,[2] G. Neff,[3] S. Mukherjee,[4] G. Barnard,[5] D. Barnes,[6] A. Koch,[7] P. Hayashi,[8] M. R. Lucey,[9] L. Kulik,[10] A. D. Smith,[11] M. S. Olyaee,[12] P. Mantry,[13] E. Chaudhri,[14] L. D. Pedicone[14]

[1]Lahey Clinic Medical Center, Burlington, MA, USA; [2]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [3]University of Cincinnati, Cincinnati, OH, USA; [4]University of Nebraska Medical Center, Omaha, NE, USA; [5]University of Massachusetts, Worcester, MA, USA; [6]Cleveland Clinic, Cleveland, OH, USA; [7]University of Kentucky, Lexington, KY, USA; [8]University of North Carolina, Chapel Hill, NC, USA; [9]University of Wisconsin, Madison, WI, USA; [10]Northwestern University, Chicago, IL, USA; [11]Duke University, Durham, NC, USA; [12]University of Kansas Medical Center, Kansas City, KS, USA; [13]The Liver Institute at Methodist Dallas Medical Center, Dallas, TX, USA; [14]Schering-Plough Research Institute, now Merck & Co., Inc., Whitehouse Station, NJ, USA

Abstract

Aim: To identify baseline, donor, and on-treatment predictors of sustained virologic response (SVR) in patients (pts) receiving therapy for recurrent hepatitis C following orthotopic liver transplant (OLT).

Methods: Phase 3, single-arm, multicenter, open-label study. Adult pts with recurrent hepatitis C infection post-OLT received peginterferon (PEG-IFN) alfa-2b (1.5 µg/kg/wk) plus ribavirin (RBV, 400-1200 mg/day) for up to 48 weeks; then were followed for an additional 24 weeks. Primary end point was SVR (LLQ <25 IU/mL). This subanalysis examined baseline, donor, and on-treatment factors affecting SVR.

Results: 125 pts were enrolled at 24 US centers. Overall SVR was 28.8%. 80/80/80 adherent pts (80% of the assigned PEG-IFN dose, 80% of assigned RBV dose, and 80% of assigned treatment duration) were more likely to attain SVR than pts unable to maintain adequate dosing (odds ratio [OR] = 9.9, 95% confidence interval [CI] 4.1, 23.9, $P < .001$). Pts attaining complete EVR (undetectable HCV RNA at week 12) were more likely to attain SVR than those failing to attain EVR (OR = 110.0, 95% CI 16.4, 700.7; $P < .001$). The likelihood of SVR was also significantly higher in pts with partial EVR (≥2 $\log_{10}$ decline yet detectable HCV RNA at week 12) compared with those with no EVR (OR = 31.1, 95% CI = 4.8, 195.3, $P < .001$).

Conclusion: Dosing of at least 80/80/80, pEVR, and cEVR are significant positive predictors of SVR in pts receiving PEG-IFN alfa-2b plus RBV for recurrent hepatitis C post-OLT. Discontinuation of treatment may be considered in pts who fail to attain EVR.

Note: This abstract has been modified since submission.

Background

- Reinfection of liver allografts in hepatitis C virus (HCV)–infected transplant recipients begins immediately after transplantation in almost all patients[1-2]
  - Cirrhosis develops within 5 years in 10% to 30% of these patients, and the probability of decompensation within 12 months is 42% once cirrhosis is established[3]
- In the PROTECT study, sustained virologic response (SVR) was attained by 28.8% of post–orthotopic liver transplant (OLT) patients receiving peginterferon (PEG-IFN) alfa-2b plus ribavirin for 48 weeks[4]

Aim

- To identify baseline, donor, and on-treatment predictors of SVR in patients receiving therapy for recurrent hepatitis C following OLT

Patients and Methods

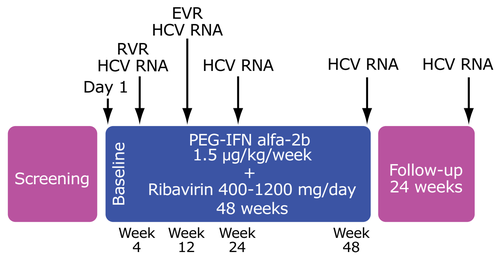
Patients

- Adult patients with a diagnosis of recurrent hepatitis C (any genotype) who had received a primary OLT from either a deceased or live donor
  - All patients had end-stage hepatitis C prior to transplantation and had persistent HCV viremia after OLT
  - Liver transplants were performed ≥3 months, but ≤3 years prior to screening
  - Patients were required to have been receiving stable doses of immunosuppressive therapy for at least 1 month
- All patients had compensated liver disease with hemoglobin ≥11 g/dL; neutrophil count ≥1000/mm^3; platelets ≥60,000/mm^3; direct, indirect, and total bilirubin ≤3 times the upper limit of normal; albumin ≥3.0 mg/dL; creatinine clearance >50 mL/min; and alpha-fetoprotein ≤250 ng/mL
- Patients with evidence of decompensated liver disease; coinfection with hepatitis B virus and/or human immunodeficiency virus; body weight >135 kg; or any cause of liver disease other than chronic hepatitis C were excluded
- Patients were not required to show any degree of fibrosis

Study Design

- This was a phase 3, single-arm, multicenter, open-label study
- All patients received PEG-IFN alfa-2b (1.5 µg/kg/week) plus ribavirin (400-1200 mg/day) for 48 weeks (**Figure 1**)
- All patients received ribavirin 400 mg/day during weeks 1 and 2 and 800 mg/day during weeks 3 and 4
  - Thereafter, among patients who tolerated treatment, ribavirin was administered according to body weight
  - Immunosuppressive therapy was administered according to the protocols at each center
  - Growth factors were permitted at the discretion of the treating physician
- Primary end point was SVR, defined as undetectable HCV RNA 24 weeks after completing treatment (lower limit of quantitation <25 IU/mL)
  - Relapse was defined as detectable HCV RNA during 24-week follow-up in patients with undetectable HCV RNA at the end of treatment

Figure 1. PROTECT study design.



Treatment week 1–2: RBV 400 mg/day
Treatment week 3–4: RBV 800 mg/day
Treatment week 5–48: RBV dose increased to max of 1200 mg/day (weight-based) if well tolerated

EVR = early virologic response; HCV = hepatitis C virus; PEG-IFN = peginterferon; RBV = ribavirin; RVR = rapid virologic response.

Results

Patients

- Most patients were white and male (**Table 1**)
- Tacrolimus and mycophenolate were the most frequently used immunosuppressive agents

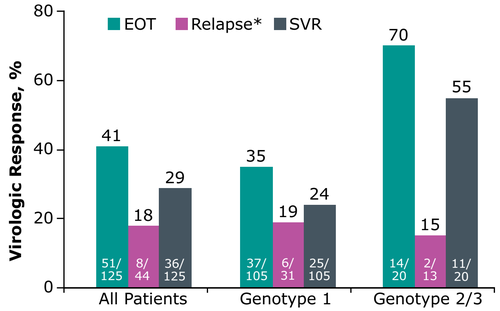
Table 1. Patient Characteristics

	All Patients (N = 125)	Genotype 1 (n = 105)	Genotype 2/3 (n = 20)
Male, n (%)	106 (85)	92 (88)	14 (70)
Race, n (%)			
White	101 (81)	82 (78)	19 (95)
Black	14 (11)	14 (13)	0
Age, mean, y	54.2	54.5	52.2
Weight, mean, kg	86.5	86.0	89.2
Baseline viral load >600,000 IU/mL, n (%)	111 (89)	95 (90)	16 (80)
Donor age, mean, y	40.4	39.4	45.2
Donor deceased, n (%)	108 (86)	90 (86)	18 (90)
Transplant–treatment interval, mean ± SD, days	477.6 ± 240	467.0 ± 235	533.7 ± 266
Primary immunosuppressive therapy, n (%)			
Tacrolimus	104 (83)	87 (83)	17 (85)
Cyclosporine	18 (14)	16 (15)	2 (10)
Sirolimus	9 (7)	8 (8)	1 (5)
Mycophenolate	70 (56)	60 (57)	10 (50)
Prednisone	16 (13)	15 (14)	1 (5)
Methylprednisolone	2 (2)	1 (1)	1 (5)
Antithymocyte immunoglobulin	1 (1)	1 (1)	0

Virologic Response

- In total, 29% of patients attained SVR (**Figure 2**)
  - 52 of 125 (41.6%) patients discontinued treatment early
  - Reasons for discontinuation were adverse events (n = 38), treatment failure (n = 7), did not wish to continue (n = 5), noncompliant (n = 2)

Figure 2. Virologic response rates in the PROTECT study.



*Relapse rate calculation includes patients with undetectable HCV RNA at EOT who were not missing follow-up visit data.
EOT = end of treatment; SVR = sustained virologic response.

- Predictors of SVR:
  - 80/80/80-adherent patients were more likely to attain SVR than patients unable to maintain adequate dosing (odds ratio [OR] 9.9, 95% confidence interval [CI] 4.1-23.9, $P < .001$) (**Table 2**)
  - Early virologic response (EVR) was a significant predictor of SVR
    - Patients attaining complete EVR (undetectable HCV RNA at week 12) were more likely to attain SVR than those failing to attain EVR (OR 110.0, 95% CI 16.4-700.7, $P < .001$)
    - Patients attaining partial EVR (≥2-$\log_{10}$ decline yet detectable HCV RNA at week 12) were also significantly more likely to attain SVR than those with no EVR (OR 31.1, 95% CI 4.8-195.3, $P < .001$)

Table 2. SVR in Patient Subgroups

Variables, % (n/N)	All Patients (N = 125)	Genotype 1 (n = 105)	Genotype 2/3 (n = 20)
Patient			
Genotype	28.8 (36/125)	23.8 (25/105)	55.0 (11/20)
Gender			
Male	33.0 (35/106)	27.2 (25/92)	71.4 (10/14)
Female	5.3 (1/19)	0 (0/13)	16.7 (1/6)
Race			
White	29.7 (30/101)	24.4 (20/82)	52.6 (10/19)
Non-White	25.0 (6/24)	21.7 (5/23)	100 (1/1)
Age, y			
<50	42.3 (11/26)	31.6 (6/19)	71.4 (5/7)
≥50	25.3 (25/99)	22.1 (19/86)	46.2 (6/13)
Bodyweight, kg			
<75	19.2 (5/26)	22.7 (5/22)	0 (0/4)
≥75	31.3 (31/99)	24.1 (20/83)	68.8 (11/16)
Baseline viral load, IU/mL			
≤600,000	46.2 (6/13)	44.4 (4/9)	50.0 (2/4)
>600,000	27.0 (30/111)	22.1 (21/95)	56.3 (9/16)
Baseline hemoglobin, g/dL			
≤14	13.6 (9/66)	10.3 (6/58)	37.5 (3/8)
>14	45.8 (27/59)	40.4 (19/47)	66.7 (8/12)
Baseline serum glucose, mmol/L			
<5.6	31.1 (19/61)	26.9 (14/52)	55.6 (5/9)
≥5.6	26.6 (17/64)	20.8 (11/53)	54.5 (6/11)
Donor			
Status			
Deceased	32.4 (35/108)	27.8 (25/90)	55.6 (10/18)
Living	11.1 (1/9)	0 (0/8)	100 (1/1)
Donor age, y			
≤50	32.9 (26/79)	30.4 (21/69)	50.0 (5/10)
>50	25.8 (8/31)	13.0 (3/23)	62.5 (5/8)
On-treatment			
RVR			
Yes	83.3 (5/6)	100 (3/3)	66.7 (2/3)
No	25.7 (29/113)	20.8 (20/96)	52.9 (9/17)
EVR[a]			
cEVR	66.7 (22/33)	60.0 (12/20)	76.9 (10/13)
pEVR	36.1 (13/36)	37.5 (12/32)	25.0 (1/4)
No EVR	1.8 (1/56)	1.9 (1/53)	0 (0/3)
Nadir hemoglobin, g/dL			
<10	26.4 (23/87)	23.0 (17/74)	46.2 (6/13)
≥10	34.2 (13/38)	25.8 (8/31)	71.4 (5/7)
Cyclosporine use[b]			
Yes	29.4 (5/17)	33.3 (5/15)	0 (0/2)
No	28.7 (31/108)	22.2 (20/90)	61.1 (11/18)
Tacrolimus use[b]			
Yes	30.4 (31/102)	23.5 (20/85)	64.7 (11/17)
No	21.7 (5/23)	25.0 (5/20)	0 (0/3)
80:80:80 compliant[a]			
Yes	61.5 (24/39)	57.1 (16/28)	72.7 (8/11)
No	14.0 (12/86)	11.7 (9/77)	33.3 (3/9)

[a]Highlighting denotes variables that were significantly associated with SVR (cEVR, pEVR, vs no EVR; 80:80:80 vs no 80:80:80; $P < .001$ for all comparisons). All other variables failed to show a significant association with SVR ($P > .05$). Analysis was performed only for the "all-patient" population.
[b]Use of immunosuppressive agent during screening and/or treatment.
cEVR = complete early virologic response; EVR = early virologic response; pEVR = partial early virologic response; RVR = rapid virologic response.

Conclusions

- Dosing of at least 80/80/80 and partial and complete EVR are significant positive predictors of SVR in patients receiving PEG-IFN alfa-2b plus ribavirin for recurrent hepatitis C post-OLT
- Discontinuation of treatment may be considered in patients who fail to attain EVR

Acknowledgments

Study investigators: Graham Barnard, David Barnes, Kim Brown, Robert Brown, Jeffrey Crippin, Reem Ghalib, Fred Gordon, Paul Hayashi, Alvaro Koch, Laura Kulik, Paul Kwo, Michael Lucey, Parvez Mantry, Sandeep Mukherjee, Guy Neff, Mojtaba Olyaee, Fred Poordad, Nikolaos Pyrsopolous, Thomas Schiano, Alastair Smith, Lewis Teperman, Hugo Vargas.

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1. Ballardini G, et al. *Liver Transpl.* 2002;8(1):10-20.
2. Guerrero RB, et al. *Mod Pathol.* 2000;13(3):229-37.
3. Berenguer M. *Liver Transpl.* 2002;8(10):S14-8.
4. Gordon FD, et al. Presented at the 45th Annual Meeting of the European Association for the Study of the Liver; April 14–18, 2010; Vienna, Austria.

Disclosures

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Supported by Schering-Plough Corporation, now Merck & Co., Inc., Whitehouse Station, NJ, USA.

Poster #905

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F. D. Gordon,[1] F. Poordad,[2] G. Neff,[3] S. Mu

[1]Lahey Clinic Medical Center, Burlington, MA, USA; [2]Cedars-Sinai Me
[7]University of Kentucky, Lexington, KY, USA; [8]University of No
1

Abstract

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Methods: Phase 3, single-arm, multicenter, open-label study. Adult pts with recurrent hepatitis C infection post-OLT received peginterferon (PEG-IFN) alfa-2b (1.5 µg/kg/wk) plus ribavirin (RBV, 400-1200 mg/day) for up to 48 weeks; then were followed for an additional 24 weeks. Primary end point was SVR (LLQ <25 IU/mL). This subanalysis examined baseline, donor, and on-treatment factors affecting SVR.

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Presented at the 61st Annual Meeting of the American Association for the Study of Liver Diseases, Oc

On-treatment Predictors of S
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ukherjee,[4] G. Barnard,[5] D. Barnes,[6] A. Koch,[7] P. Hayashi

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- This was a phase 3, single-arm, multicenter, open-label study
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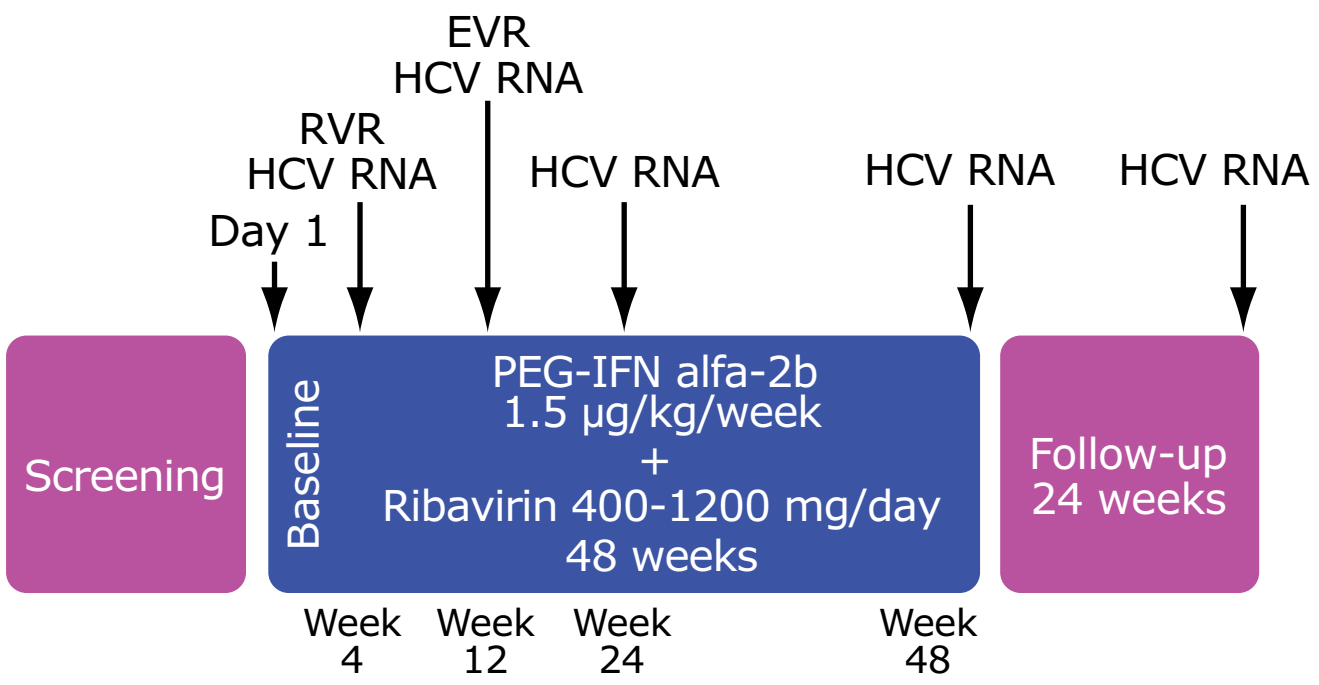

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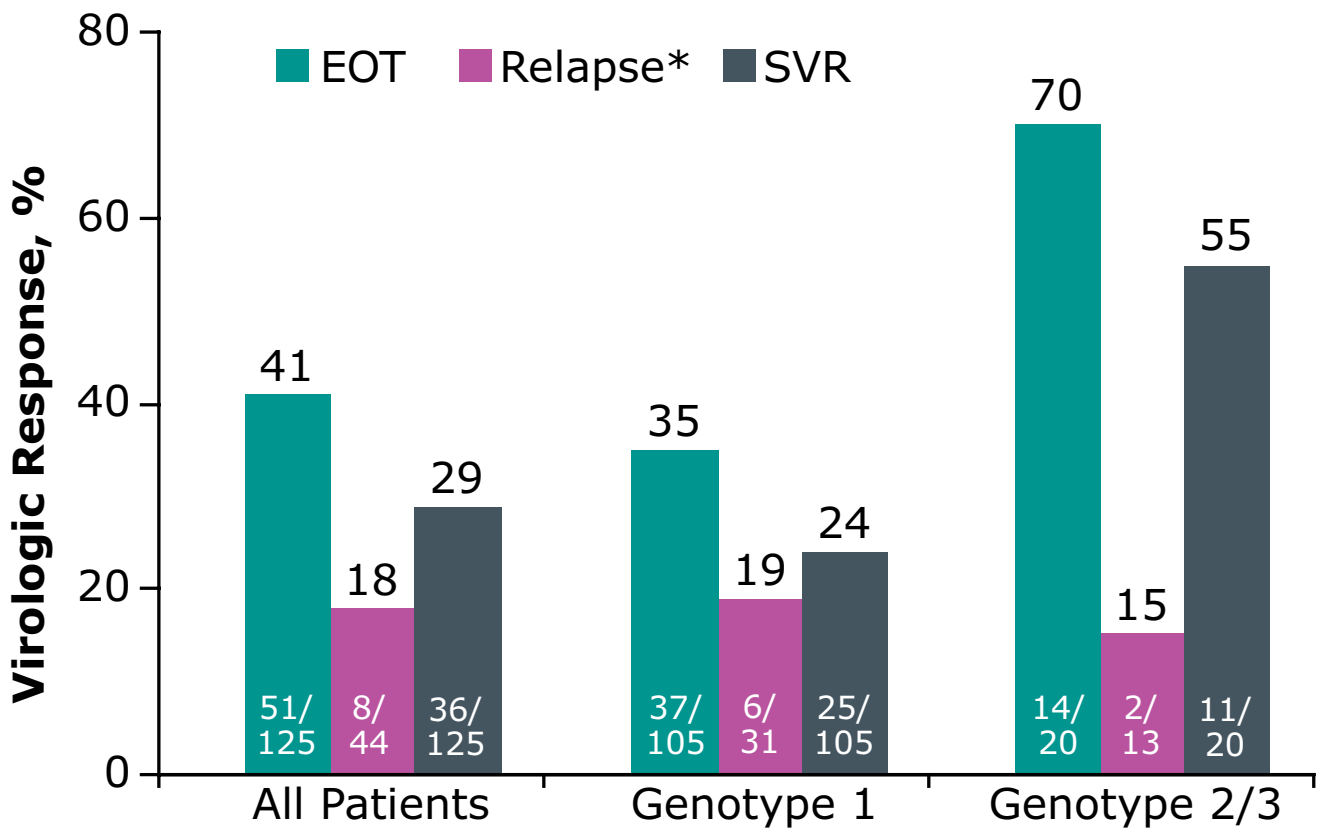
Virologic Response

- In total, 29% of patients attained SVR (**Figure 2**)
  - — 52 of 125 (41.6%) patients discontinued treatment early
  - — Reasons for discontinuation were adverse events (n = 38), treatment failure (n = 7), did not wish to continue (n = 5), noncompliant (n = 2)

Figure 2. Virologic response rates in the PROTECT study.



*Relapse rate calculation includes patients with undetectable HCV RNA at EOT who were not missing follow-up visit data.
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in Patients Treated for the PROTECT Study

[2] P. Mantry,[13] E. Chaudhri,[14] L. D. Pedicone[14]

achusetts, Worcester, MA, USA; [6]Cleveland Clinic, Cleveland, OH, USA; SA; [12]University of Kansas Medical Center, Kansas City, KS, USA; USA

Table 2. SVR in Patient Subgroups

Variables, % (n/N)	All Patients (N = 125)	Genotype 1 (n = 105)	Genotype 2/3 (n = 20)
Patient			
Genotype	28.8 (36/125)	23.8 (25/105)	55.0 (11/20)
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Female	5.3 (1/19)	0 (0/13)	16.7 (1/6)
Race			
White	29.7 (30/101)	24.4 (20/82)	52.6 (10/19)
Non-White	25.0 (6/24)	21.7 (5/23)	100 (1/1)
Age, y			
<50	42.3 (11/26)	31.6 (6/19)	71.4 (5/7)
≥50	25.3 (25/99)	22.1 (19/86)	46.2 (6/13)
Bodyweight, kg			
<75	19.2 (5/26)	22.7 (5/22)	0 (0/4)
≥75	31.3 (31/99)	24.1 (20/83)	68.8 (11/16)
Baseline viral load, IU/mL			
≤600,000	46.2 (6/13)	44.4 (4/9)	50.0 (2/4)
>600,000	27.0 (30/111)	22.1 (21/95)	56.3 (9/16)
Baseline hemoglobin, g/dL			
≤14	13.6 (9/66)	10.3 (6/58)	37.5 (3/8)
>14	45.8 (27/59)	40.4 (19/47)	66.7 (8/12)
Baseline serum glucose, mmol/L			
<5.6	31.1 (19/61)	26.9 (14/52)	55.6 (5/9)
≥5.6	26.6 (17/64)	20.8 (11/53)	54.5 (6/11)
Donor			
Status			
Deceased	32.4 (35/108)	27.8 (25/90)	55.6 (10/18)
Living	11.1 (1/9)	0 (0/8)	100 (1/1)
Donor age, y			
≤50	32.9 (26/79)	30.4 (21/69)	50.0 (5/10)
>50	25.8 (8/31)	13.0 (3/23)	62.5 (5/8)
On-treatment			
RVR			
Yes	83.3 (5/6)	100 (3/3)	66.7 (2/3)
No	25.7 (29/113)	20.8 (20/96)	52.9 (9/17)
EVR[a]			
cEVR	66.7 (22/33)	60.0 (12/20)	76.9 (10/13)
pEVR	36.1 (13/36)	37.5 (12/32)	25.0 (1/4)
No EVR	1.8 (1/56)	1.9 (1/53)	0 (0/3)
Nadir hemoglobin, g/dL			
<10	26.4 (23/87)	23.0 (17/74)	46.2 (6/13)
≥10	34.2 (13/38)	25.8 (8/31)	71.4 (5/7)
Cyclosporine use[b]			
Yes	29.4 (5/17)	33.3 (5/15)	0 (0/2)
No	28.7 (31/108)	22.2 (20/90)	61.1 (11/18)
Tacrolimus use[b]			
Yes	30.4 (31/102)	23.5 (20/85)	64.7 (11/17)
No	21.7 (5/23)	25.0 (5/20)	0 (0/3)
80:80:80 compliant[a]			
Yes	61.5 (24/39)	57.1 (16/28)	72.7 (8/11)
No	14.0 (12/86)	11.7 (9/77)	33.3 (3/9)

[a]Highlighting denotes variables that were significantly associated with SVR (cEVR, pEVR, vs no EVR; 80:80:80 vs no 80:80:80; $P < .001$ for all comparisons). All other variables failed to show a significant association with SVR ($P > .05$). Analysis was performed only for the "all-patient" population.

[b]Use of immunosuppressive agent during screening and/or treatment.

cEVR = complete early virologic response; EVR = early virologic response; pEVR = partial early virologic response; RVR = rapid virologic response.

Conclusions

- Dosing of at least 80/80/80 and partial and complete EVR are significant positive predictors of SVR in patients receiving PEG-IFN alfa-2b plus ribavirin for recurrent hepatitis C post-OLT
- Discontinuation of treatment may be considered in patients who fail to attain EVR

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