TELAPREVIR WITH ADJUSTED DOSE OF RIBAVIRIN IN NAIVE CHC-G1: EFFICACY AND TREATMENT IN CHC IN HEMODIALYSIS POPULATION

TARGET C TRIAL- A PLACEBO RANDOMIZED CONTROL CLINICAL TRIAL

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Nothing to disclose for this study

- Gilead Science
- BMS
- ROMAX
- Geenetech
- Vertex
- Otsuka
- Takeda
- Three Rivers
- GI pathology
- Salix
- Ironwood
- MERK
OBJECTIVES

- Prevalence of CHC in hemodialysis (HD) patients is 3%\(^1\)
- CHC in ESRD has progressive fibrosis and high mortality
- Post organ transplant outcome is not favorable in ESRD
- CHC is an independent risk factor for death and graft failure in renal transplant patients
- Estimated relative risk of death 1.79% and graft failure 1.56%\(^2\)
- Traditional treatment with modified dose of Peg-IFN \(\alpha\) 2a, 135 mcg weekly and 400 mg of Ribavirin (RBV) in previous few trials had an SVR of approximately 27%

\(^{1}\text{Basu et al. 2013}\)
OBJECTIVES

- Protease inhibitors (PI) are now part of the SOC for the treatment of CHC in genotype I in US
- TPV is primarily metabolized in the liver and excreted in the feces, spares renal toxicity
- Higher RBV dose led to higher Viral Clearance with encouraging SVR (VIRID study 2008)
- Reduced doses of RBV (200 – 400 mg) with TPV showed equal efficacy in SVR and prevents viral breakthrough and relapses (Vertex trial)
- This pilot study evaluates the efficacy of respond guided therapy (RGT) of TPV with reduced doses of RBV with Peg-IFN α 2a, 135 mcg per week for ESRD patients on HD

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POPULATION ANALYSIS

- Total 79 patients 36 recruited from May 2010 until Nov 2012
- Male- 26, Female-10
- Mean age: 58 years
- Mean BMI: 26.6%
- Mean Viral load: 800K
- Genotype Ia 15/36 (41%) Genotype Ib 21/36 (58%)
- Black 23/36 (64%), Asian 4/36 (11%), Hispanic 6/36 (17%), White 3/36 (8%)
- IL28b: CC 10/36 (27%), TT 10/36 (27%), CT 16/36 (44%)
- Fibrosis score: F2 5/36 (14%), F3 26/36 (72%), F4 5/36 (14%)
- ESRD and Dialysis for mean 6 years from 6 centers.
- All liver biopsies were within 7 years in multiple centers,

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## DEMOGRAPHICS

<table>
<thead>
<tr>
<th>Mean</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56</td>
<td>53</td>
<td>58</td>
</tr>
<tr>
<td>Sex</td>
<td>Male- 8 Female- 4</td>
<td>Male- 9 Female- 3</td>
<td>Male- 8 Female- 3</td>
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<tr>
<td>Race</td>
<td>Caucasian- 1 Blacks- 7 Hispanics- 2 Asian- 2</td>
<td>Caucasian- 1 Blacks- 8 Hispanics- 2 Asian-1</td>
<td>Caucasian- 1 Blacks- 8 Hispanics- 2 Asian-1</td>
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<tr>
<td>Genotype</td>
<td>1a- 5 1b- 7</td>
<td>1a- 5 1b- 7</td>
<td>1a- 5 1b- 7</td>
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<tr>
<td>Viral Load</td>
<td>950</td>
<td>750</td>
<td>800</td>
</tr>
<tr>
<td>IL 28 beta</td>
<td>CC- 4   TT- 3 CT- 6</td>
<td>CC- 3 TT- 3 CT- 6</td>
<td>CC- 3 TT- 4 CT- 4</td>
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<tr>
<td>Fibrosis Score</td>
<td>F2- 2  F3- 9 F4- 2</td>
<td>F2- 2 F3- 8 F4- 1</td>
<td>F2- 1 F3- 9 F4- 2</td>
</tr>
</tbody>
</table>
BASELINE LABORATORY ANALYSIS

- Mean baseline Hemoglobin 11.8 g/dL
  All received EPO during HD per weekly schedule
- Mean MCV 76, Mean ALT 64, Mean Albumin 3.7
- Mean WBC 5700/ Platelet 203k
- Mean Haptoglobin 87
- Mean Ferritin 363
- Mean Hb A1c 5.9/ HOMA score 1.2
- All patients under went exclusion for sickle cell and any Hemoglobinopathies

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METHODS

• Viral load; HCV RNA PCR quant (Taqman Roche)
  • Taken at 0, 1, 2, 4, 12, 24, 36, 48, and 72 weeks

• CBC with ANC and Platelet count
  • Taken at 0, 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, and 72 weeks

• Reticulocyte count
  • Taken at 0, 1, 2, 4, 6, 8, 12, 24, 36, and 48 weeks

• TFT
  • Taken at 4, 12, 36, 48, and 72 weeks.

• Haptoglobin
  • Taken at 2, 4, 12, 24, 36, and 48 weeks
EXCLUSION CRITERIA

- Severe cardiovascular dysfunction (Grade 3-4 CHF, severe cardiomyopathy, pulmonary hypertension)
- Diabetic retinopathy, severe peripheral neuropathy
- History of severe skin reactions to drugs
- Decompensated cirrhosis
- Hemoglobinopathy
- HIV, HBV co-infections
- Severe depression, prior suicidal ideation
- Vasculitis, SLE, scleroderma, polyarteritis Nodosa

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(n= 36) treatment naïve CHC-GT1 with ESRD on HD were randomized into three groups ** Telaprevir 750mg two tablets – TID for four days and three tablets BID post dialysis for three days

<table>
<thead>
<tr>
<th>Group A (n=12)</th>
<th>Agents used</th>
<th>0-12 weeks</th>
<th>13-24 weeks</th>
<th>24-36 weeks</th>
<th>37-48 weeks</th>
<th>Comments</th>
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<tbody>
<tr>
<td>TPV</td>
<td>TPV</td>
<td></td>
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<td>ETVR at week 24 and SVR at week 48</td>
</tr>
<tr>
<td>RBV</td>
<td>200 mg/TIW</td>
<td>400 mg/TIW</td>
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<tr>
<td>Peg-IFN α 2a</td>
<td>135 mcg</td>
<td>135 mcg</td>
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<tr>
<td>Group B (n=12)</td>
<td>TPV</td>
<td>TPV</td>
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<td>ETVR at week 36 and SVR at week 60</td>
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<tr>
<td>RBV</td>
<td>Placebo</td>
<td>400 mg/TIW</td>
<td>400 mg/TIW</td>
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<tr>
<td>Peg-IFN α 2a</td>
<td>135 mcg</td>
<td>135 mcg</td>
<td>135 mcg</td>
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<tr>
<td>Group C (n=12)</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
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<td>ETVR at week 48 and SVR at week 72</td>
</tr>
<tr>
<td>RBV</td>
<td>400 mg/weekly</td>
<td>400 mg/weekly</td>
<td>400 mg/weekly</td>
<td>400 mg/weekly</td>
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<tr>
<td>Peg-IFN α 2a</td>
<td>135 mcg</td>
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<tr>
<td>RGT</td>
<td>Group A (24 weeks)</td>
<td>Group B (36 weeks)</td>
<td>Group C (48 weeks)</td>
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<tr>
<td>AVR (1st week)</td>
<td>4/12 (33%)</td>
<td>3/12 (25%)</td>
<td>3/12 (25%)</td>
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<tr>
<td>VRVR (2nd week)</td>
<td>5/12 (41%)</td>
<td>4/12 (33%)</td>
<td>3/12 (25%)</td>
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<tr>
<td>RVR (4th week)</td>
<td>6/12 (50%)</td>
<td>5/12 (42%)</td>
<td>3/12 (25%)</td>
<td></td>
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</tr>
<tr>
<td>EVR (12th week)</td>
<td>7/12 (63%)</td>
<td>6/12 (50%)</td>
<td>4/12 (33%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ETVR (24th week)</td>
<td>8/12 (67%)</td>
<td>6/12 (50%)</td>
<td>MTVR 3/12 (25%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ETVR (36th week)</td>
<td></td>
<td>6/12 (50%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ETVR (48th week)</td>
<td></td>
<td></td>
<td>3/12 (25%)</td>
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</tr>
<tr>
<td>SVR (48 weeks)</td>
<td>7/12 (63%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SVR (60th week)</td>
<td></td>
<td>6/12 (50%)</td>
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<tr>
<td>SVR (72 weeks)</td>
<td></td>
<td></td>
<td>3/12 (25%)</td>
<td></td>
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</tr>
<tr>
<td>Comments</td>
<td>1 relapser (8.5%)-G1a, AA, F4, CT1/16(6%)</td>
<td>No relapse</td>
<td>1breakthrough (8.5 %)-G1a, AA,F4,CT1/16(6%)</td>
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</tr>
</tbody>
</table>

Group A- triple therapy for 24 weeks  
Group B- Dual therapy, without RBV for 12 weeks, total 36 wk  
Group C- Traditional SOC- dual therapy for 48 weeks
## SIDE EVENTS

<table>
<thead>
<tr>
<th>Side events</th>
<th>Group A (24 weeks)</th>
<th>Group B (36 weeks)</th>
<th>Group C (48 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>7/12 (58%)</td>
<td>6/12 (50%)</td>
<td>4/12 (33%)</td>
</tr>
<tr>
<td>Neutropenia &lt; 750 ANA</td>
<td>6/12 (50%)</td>
<td>6/12 (50%)</td>
<td>3/12 (25%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5/12 (42%)</td>
<td>4/12 (33%)</td>
<td>3/12 (25%)</td>
</tr>
<tr>
<td>Skin rash/Puritus</td>
<td>6/12 (50%)</td>
<td>4/12 (33%)</td>
<td>2/12 (17%)</td>
</tr>
<tr>
<td>Anorectal dysfuunction</td>
<td>4/12 (33%)</td>
<td>4/12 (33%)</td>
<td>None</td>
</tr>
<tr>
<td>Dysguisea</td>
<td>6/12 (50%)</td>
<td>4/12 (33%)</td>
<td>2/12 (17%)</td>
</tr>
<tr>
<td>Depression</td>
<td>3/12 (25%)</td>
<td>3/12 (25%)</td>
<td>2/12 (17%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2/12 (17%)</td>
<td>2/12 (17%)</td>
<td>1/12 (8%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6/12 (50%)</td>
<td>4/12 (33%)</td>
<td>4/12 (33%)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>4/12 (33%)</td>
<td>4/12 (33%)</td>
<td>2/12 (17%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2/12 (17%)</td>
<td>1/12 (8%)</td>
<td>2/12 (17%)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>1/12 (8%)</td>
<td>None</td>
<td>2/12 (17%)</td>
</tr>
</tbody>
</table>

**Total Procrit use - in all groups:** 50%

**Total Romilopostim use:** 20%

**Total Neulasta (Pegalyted Filgastrim) use:** 12%

For myalgia, neuropathy and depression - Pregabalin used: 30%

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CONCLUSIONS

• Triple therapy: In special hemodialysis population with CHC has SVR of 63% in 24 weeks
• Traditional SOC: For 48 weeks- SVR was 25%
• Dual therapy with Placebo followed by reduced dose of RBV- yield SVR of 50%
• 24 weeks of triple therapy in ESRD on hemodialysis have substantial efficacy over 63%
• This study postulates truncated triple therapy with optimal retention, the efficacy and cost, demonstrated definite benefit in treating ESRD.
• Large prospective trial will validate

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LIMITATIONS

- Small cohort
- Multiple dialysis centers
- Multiple liver biopsy centers
- Time of biopsy mean 5-7 years
- RBV serum levels not measured.
- Generous use of growth factors
- Total cost index

ADVANTAGE

- FREQUENT FOLLOW UP AS PER DIALYSIS SCHEDULE
- LESS FREQUENT NEEDLE STICKS
- OPTIMAL RETENTION
REFERENCES

- These are the most recent peer reviewed on HCV in ESRD and Dialysis; Doses variations and Pharmaco Kinetics of RBV
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- All the staff of dialysis centers.
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