CLINICAL CARE OPTIONS® HEPATITIS

High SVR Rates With 12-24 Weeks of Daclatasvir Plus Sofosbuvir With or Without RBV in Patients With Genotype 3 HCV and Advanced Liver Disease

Source: 2015 Annual Meeting of the American Association for the Study of Liver Diseases*

Capsule Summary

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- Interim analysis from multicenter, observational, compassionate use program[1]

Summary of Key Conclusions

- In patients with genotype (GT) 3 HCV and advanced liver disease, 12 weeks or 24 weeks daclatasvir (DCV) + sofosbuvir (SOF) ± ribavirin (RBV) resulted in high sustained virologic response (SVR) rates overall in real-world setting
- In cirrhotic patients, extended 24-week duration improved efficacy, use of RBV provided no additional benefit in patients treated for 24 weeks
  - Conclusions cannot be drawn regarding role of RBV in 12-week treatment groups because few patients treated with RBV
- In noncirrhotic patients (70% with F3 disease), 12-week regimens highly effective, no additional benefit of extending treatment to 24 weeks
  - Conclusions cannot be drawn regarding role of RBV in noncirrhotic patients because few patients treated with RBV
- Treatment generally well tolerated with few serious adverse events (AEs) or discontinuations for toxicity

Background

- GT 3 HCV infection associated with accelerated disease progression relative to other HCV genotypes[2]
  - Limited therapy choices available for GT 3 HCV, particularly in cirrhotic patients
- ALLY-3 study demonstrated higher SVR rate with 12 weeks DCV + SOF in noncirrhotic vs cirrhotic patients with GT 3 HCV (96% vs 63%)[3]
- Extended treatment and/or RBV utilization may improve outcomes in cirrhotic patients with GT 3 HCV
  - ALLY-3+ study reported SVR12 rates of 88% and 92%, respectively, with 12-week vs 16-week DCV + SOF + RBV in patients with GT 3 HCV and advanced fibrosis/cirrhosis[4] (Capsule Summary)
- Current study assessed safety, efficacy of 12-week vs 24-week DCV + SOF ± RBV in GT 3 HCV-infected patients as part of compassionate use program[1]

Summary of Study Design

- Patients enrolled in French DCV compassionate use program
- Inclusion criteria
  - GT 3 HCV infection
  - METAVIR score ≥ F3 or severe extrahepatic disease or HCV recurrence following liver transplantation or awaiting liver/kidney transplantation
- Study regimen
  - 24 weeks DCV 60 mg once daily + SOF 400 mg once daily
  - Use of RBV and/or 12-week regimen permitted by investigator choice
- Safety endpoints: AEs, serious AEs, discontinuation
  - Safety population includes all patients with HCV RNA detectable at baseline and ≥ 1 study visit (n = 468)
- Primary efficacy endpoint: SVR 12 weeks after treatment completion
  - Primary efficacy population includes all patients with posttreatment Week 12 HCV RNA data (n = 284)
- Treatment failure defined as any of the following:
  - HCV RNA ≥ lower limit of quantification at posttreatment Week 12
  - Death prior to posttreatment Week 12
  - Discontinuation for AEs in absence of SVR12

Baseline Characteristics

- Treatment groups generally well matched for age, sex, HCV RNA level, treatment experience, HIV/HBV coinfection, transplantation status

Characteristic	*DCV + SOF ± RBV* 12 Wks (n = 63)*	*DCV + SOF 24 Wks (n = 166)*	*DCV + SOF + RBV 24 Wks (n = 53)*	*All Patients† (N = 284)*
Median age, yrs (range)	53.4 (39-78)	55.0 (27-79)	53.2 (40-72)	54.1 (27-79)
Male, %	68.3	75.0	80.0	74.6
Median HCV RNA, log_{10} IU/mL (range)	5.99 (2.40-7.83)	6.00 (3.03-7.40)	5.60 (1.60-7.25)	5.94 (1.60-7.83)
F3 fibrosis,‡ %	30.2	12.7	3.8	14.8
Cirrhosis,‖ %	58.7	82.3	90.6	78.7
Child-Pugh stage, n (%)				
• A	83.3	85.2	76.7	82.7
• B	8.3	13.0	20.9	14.3
• C	8.3	1.7	2.3	3.1
Platelets < 100 ×10^9 cells/L, %	32.1	35.0	55.1	38.6
Albumin < 35 g/L, %	31.7	26.5	28.6	28.7
Liver transplant recipient, %	4.8	9.6	9.4	8.5
Awaiting liver or renal transplantation, %	6.3	9.6	9.4	8.8
Prior HCV treatment, %	60.3	76.2	75.5	72.7
Coinfection with HIV/HBV, %	11.3 / 0	18.7 / 3.0	5.7 / 3.7	14.4 / 2.5

*N = 5 patients received DCV + SOF + RBV.
†Includes 2 patients without regimen data.
‡Determined by biopsy, *FibroScan* ≥ 9.6 kPa, or *FibroTest* ≥ 0.59.

‖Determined by biopsy, *FibroScan* ≥ 14.6 kPa, or *FibroTest* ≥ 0.75.

Main Findings

- Treatment duration, use of RBV had no significant impact on SVR rates in overall population
  - DCV + SOF: 87%
  - DCV + SOF + RBV: 83%
  - DCV + SOF ± RBV for 12 weeks: 83%
  - DCV + SOF ± RBV for 24 weeks: 87%
- In patients without cirrhosis, SVR12 rates similar with 12 vs 24 weeks treatment
  - Few patients received RBV
- In patients with cirrhosis, SVR12 rates did not differ by RBV use in patients receiving 24 weeks treatment
  - In 12-week treatment groups, SVR12 rate lower without vs with RBV
    - Difference greater in treatment-experienced vs treatment-naive patients
- SVR12 rates lower in patients with Child-Pugh B or C disease vs A even with extended treatment duration

SVR, n/N (%)	*DCV + SOF 12 Wks*	*DCV + SOF + RBV 12 Wks*	*DCV + SOF 24 Wks*	*DCV + SOF + RBV 24 Wks*
All patients	47/58 (81.0)	5/5 (100)	147/166 (88.6)	43/53 (81.1)
Patients without cirrhosis	24/25 (96.0)	1/1 (100)	29/29 (100)	4/5 (80.0)
Patients with cirrhosis	23/33 (69.7)	4/4 (100)	116/135 (85.9)	39/48 (81.3)
• Treatment naive	7/9 (77.8)	2/2 (100)	25/29 (86.2)	9/11 (81.8)
• Treatment experienced	16/24 (66.7)	2/2 (100)	89/103 (86.4)	28/35 (80.0)
Child-Pugh A		24/30 (80.0)	90/100 (90.0)	28/33 (84.8)
Child-Pugh B or C		2/6 (33.3)	12/17 (70.6)	7/10 (70.0)

- 3 patients (0.6%) discontinued for AEs
- Most serious AEs considered unrelated to treatment

AEs, %	*All Patients (N = 468)*
Death	1.5
Serious AEs	9.4
• Related to treatment*	0.4
• Unrelated to treatment†	9.0
Discontinuation for AEs‡	0.6
AEs occurring in ≥ 3% of patients	
• Asthenia	10.5
• Sleep disorder	6.4
• Headache	5.6
• Diarrhea	3.8
• Fatigue	3.2

*Includes hepatic decompensation (n = 1), allergic dermatitis (n = 1).
†Includes hepatic decompensation (n = 8), severe infection (n = 6), hepatocellular carcinoma (n = 7), renal impairment (n = 2), liver transplantation (n = 1), blood/vascular disorders (n = 4), medical procedures (n = 5), general disorders (n = 3), neoplasm (n = 1), respiratory distress (n = 2), alcoholic hepatitis (n = 1), urinary retention (n = 1).
‡Includes allergic dermatitis (n = 1), neutropenia (n = 1), unspecified medical decision (n = 1).

References

1. Hezode C, de Lendinghen V, Fontaine H, et al. Daclatasvir plus sofosbuvir with or without ribavirin in genotype 3 patients from a large French multicenter compassionate use program. Program and abstracts of the 2015 Annual Meeting of the American Association for the Study of Liver Diseases; November 13-17, 2015; San Francisco, California. Abstract 206.

2. Ampuero J, Romero-Gómez M, Reddy KR. Review article: HCV genotype 3 – the new treatment challenge. Aliment Pharmacol Ther. 2014;39:686-698.

3. Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology. 2015;61:1127-1135.

4. Leroy V, Angus PW, Bronowicki J-P, et al. All-oral treatment with daclatasvir (DCV) plus sofosbuvir (SOF) plus ribavirin (RBV) for 12 or 16 weeks in HCV genotype (GT) 3-infected patients with advanced fibrosis or cirrhosis: the ALLY-3+ phase 3 study. Program and abstracts of the 2015 Annual Meeting of the American Association for the Study of Liver Diseases; November 13-17, 2015; San Francisco, California. Abstract LB-3.