The Efficacy of Generic Daclatasvir-Sofosbuvir as Pan-Genotypic Regiment for Hepatitis C Virus (HCV) Infected Patients in Bandung Indonesia

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ABSTRACT

Background: *Direct-acting antivirals (DAAs) have altered the prognosis of hepatitis C virus (HCV) disease but its access is limited by socioeconomic factors. Generic DAAs with lower prices were available in Indonesia in 2016. The aim of this study was to determine the* efficacy of generic daclatasvir-sofosbuvir.

Method: *We performed an observational study from January to December 2016 in a tertiary care center in Bandung, Indonesia. Data were obtained from medical registry. All study subjects received* oral daclatasvir (60 mg, once daily) and sofosbuvir (400 mg, once daily) for 12 weeks for noncirrhotic chronic HCV patients and 24 weeks for cirrhotic chronic HCV patients. *The main endpoint criterion was sustained virologic response at post-treatment week 12 (SVR12).*

Results: *We enrolled 32 subjects (20 noncirrhotic, 12 cirrhotic). All noncirrhotic subjects (eighteen were previously untreated patients) and cirrhotic subjects (all were previously untreated patients) achieved SVR12 of 100%. These high rates of SVR12 were observed in all patients with HCV infection regardless of the genotype. ALT normalization was achieved in all patients 12 weeks after therapy. The most common adverse events were fatigue and nausea.*

Conclusion: *Once-daily oral generic daclatasvir-sofosbuvir showed good efficacy and safety. Furthermore, it yielded a high rate of SVR among patients infected with HCV of all genotypes.*

Keywords: *DAA; daclatasvir; sofosbuvir; HCV; pangenotypic regiment.*

ABSTRAK

Latar belakang: *Direct-acting antivirals (DAA) telah mengubah prognosis penyakit virus hepatitis C (VHC) tetapi akses obat terbatas oleh faktor sosial ekonomi. DAA generik dengan harga lebih murah tersedia di Indonesia pada 2016. Tujuan dari penelitian ini adalah untuk menentukan efikasi daclatasvir-sofosbuvir generik.*

Metode: *Kami melakukan penelitian observasional dari Januari hingga Desember 2016 di pusat perawatan tersier di Bandung, Indonesia. Data diperoleh dari rekam medis. Semua subjek penelitian mendapat daclatasvir oral (60 mg, sekali sehari) dan sofosbuvir (400 mg, sekali sehari) selama 12 minggu untuk pasien VHC kronis non-sirosis dan 24 minggu untuk pasien VHC kronis sirosis. Kriteria endpoint utama adalah sustained virologic response (SVR) pada minggu ke 12 pasca pengobatan (SVR12).*

Hasil: *Terdapat 32 subjek (20 nonsirosis, 12 sriosis). Semua subjek nonsirosis (delapan belas pasien yang sebelumnya belum diobati) dan subjek sirosis (semua pasien yang sebelumnya tidak diobati) mencapai SVR12*

100%. Tingkat SVR12 yang tinggi ini diamati pada semua pasien dengan infeksi VHC terlepas dari genotipe. Normalisasi ALT dicapai pada semua pasien 12 minggu setelah terapi. Efek samping yang paling umum adalah kelelahan dan mual.

Simpulan: *Daclatasvir-sofosbuvir generik oral sekali sehari menunjukkan efikasi dan keamanan yang baik. Lebih lanjut, terapi ini menunjukkan tingkat SVR yang tinggi di antara pasien yang terinfeksi VHC dari semua genotipe.*

Kata kunci: *DAA; daclatasvir; sofosbuvir; HCV; regimen pangenotipik*

INTRODUCTION

Hepatitis C virus infection affects 1-2.2% of the population worldwide.[1,2] Untreated chronic hepatitis C patient can progress to cirrhosis, end-stage liver disease, or hepatocellular carcinoma. Along with Hepatitis B, it accounts for 96% of hepatitis-related mortality.[2] Hepatitis C prevalence in Indonesia was around 0.8-1% in 2014 with the majority of the patients were around 20-29 years old.[3] The invention of DAAs for hepatitis C provide a recovery rate of more than 95%. While the combination of pegylated interferon with ribavirin for 24 to 48 weeks yields a cure rate of 40-50%[4], new DAAs for 12-24 weeks gives sustained virologic response 12 weeks post-treatment (SVR12) for up to 100%.[5–7]

DAAs target is specific non-structural proteins of the virus. It inhibits viral replication by inhibiting the protein replication.[8,9] There are more than 30 DAAs, with different mechanism of actions: NS3/4A protease inhibitor, NS5A protein inhibitor, NS5B nucleoside polymerase inhibitors (NPIs), and NS5B non-nucleoside polymerase inhibitor. DAAs were given in combination according to each mechanism of action.[10] There are several combinations of recommended DAAs, such as sofosbuvir–simeprevir, sofosbuvir–ledipasvir, sofosbuvir–daclatasvir, and grazoprevir–elbasvir. Among these combinations, sofosbuvir–daclatasvir showed one of the highest rates of SVR.[11] Sofosbufir is a *nucleotide analog* from HCV NS5B *polymerase inhibitor*, and daclatasvir is the first drug of HCV NS5A *replication complex inhibitor* with pangenotypic activity.[12] The superiority of this combination is the coverage of all genotypes of hepatitis C, high SVR in HCV patient with or without cirrhosis, and is a once-daily dose.[13,14]

Although the combination of sofosbuvir–daclatasvir had been introduced since 2014 worldwide, this drug was not available in Indonesia until 2015. Indonesia has one of the biggest population of hepatitis C patients but a limited access to the DAAs, as a consequences of its high cost.[3] In 2016, generic DAAs was available in Indonesia with a considerably lower cost. The data for successful treatment of sofosbuvir–daclatasvir had not been available in Indonesia. This study was the first study describing the successful treatment of daclatasvir-sofosbuvir in Bandung, Indonesia.

METHOD

This was a sigle-center, retrospective, observational study to all patients who received a combination of generic daclatasvir-sofosbuvir in Dr. Hasan Sadikin General Hospital in Bandung from January to December 2016. Data were obtained from the medical registry. Inclusion criteria were chronic hepatitis C with positive anti-HCV, positive HCV-RNA, and data of viral genotype. Exclusion criteria were patients with chronic CKD stage III–V, hepatocellular carcinoma, or undergoing hemodialysis. All patients fulfilled inclusion criteria will be recruited in the study, in which selection bias could be minimized.

Patients were divided into cirrhosis (if transient elastography result was F4) and non-cirrhosis group (if the result was F0, F2, or F3). Non-cirrhotic group received sofosbuvir 400 mg once daily and daclatasvir 60 mg once daily for 12 weeks. Cirrhotic group received sofosbuvir 400 mg once daily and daclatasvir 60 mg for 24 weeks. The treatment is according to Indonesia National Consensus of Hepatitis C treatment.

Serum ALT, AST, ureum, creatinin, transient elastography (fibroscan), HCV-RNA, and viral genotype were examined for baseline data. HCV-RNA measurement were repeated at week 12, and 24.

The primary outcome was SVR12, defined by the absence of HCV-RNA at week 12 after treatment SVR12 in both non-cirrhotic and cirrhotic group. Secondary outcome was normalization of ALT at the end of therapy. Side effects were also reported. Loss to follow up patient could be minimized through the study design used. Missing data will not be included in analysis. Statistical package for social sciences (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY, USA) were used for data analysis.

RESULTS

Baseline characteristics of patients are shown in table 1. From total 32 patients, 22 male and 10 females within the study, all of which were enrolled from the beginning to the end of study and no data was missing. There were twenty chronic hepatitis C patients with non-cirrhosis and twelve decompensated cirrhotic patients. From the 32 subjects, one patient had co-infection with HIV, one patient had undergone partial hepatectomy due to hepatocellular carcinoma, and one patient had undergone a kidney transplant. Majority of the subject had genotype 1 (19 patients), six patient with genotype 2, four patients with genotype 3, one patient with genotype 4, and six patients with undetermined genotype.

In twenty non-cirrhotic patients, after having a combination of DAAs sofosbuvir-daclatasvir, 100% achieved SVR12 at the end of therapy for all genotypes, as shown in table 2. Likewise, in twelve chronic hepatitis C with cirrhosis of all genotype, 100% of the patients had SVR12 at the end of therapy. Normalization of ALT at the end of therapy was achieved in all subjects receiving a combination of daclatasvir-sofosbuvir for 12 and 24 weeks.

Observed side effect of daclatasvir-sofosbuvir were nausea and fatigue in 1 noncirrhotic and 3 in cirrhotic patients. No major side effect or serious adverse event occurred.

DISCUSSION

Our study showed an SVR12 rate of 100% in patients of all HCV genotype with or without cirrhosis receiving generic daclatasvir-sofosbuvir. We identified that this DAAs combination was well tolerated in both cirrhotic and non-cirrhotic patients. Minor adverse events were nausea and vomiting, no adverse event leading to discontinuation of the drugs was reported. Patients with pre-existing HIV, post-renal transplant, and post-hepatectomy showed good response and tolerability to daclatasvir-sofosbuvir treatment.

Non-cirrhotic patients were treated for 12 weeks, in contrast to 24 weeks-treatment for cirrhotic patients. Our national consensus recommended 12 weeks daclatasvir-sofosbuvir regiment for all genotype

Table 1. Baseline characteristics

	Total (n = 32)	Non-cirrhosis (12 weeks) All Genotype (n = 20)	Cirrhosis (24 weeks) All Genotype (n = 12)
Age (years)			
Mean ± SD	57 ± 16	52 ± 17	65 ± 10
Sex, n (%)			
Male	22	17 (85.0)	5 (41.7)
Female	10	3 (15.0)	7 58.3)
HCV-RNA (x10^5)			
Median (min-max)	9.65 (0.007 – 212)	10.00 (0.007 – 212)	8.58 (2.00 – 16.1)
Genotype, n (%)			
Genotype 1	19	12	7
Genotype 2	4	1	3
Genotype 3	2	2	0
Genotype 4	1	1	0
Undetermined	6	4	2
AST (IU/dL)			
Median (min-max)	63 (14 – 572)	51 (14 – 572)	75 (25 – 211)
ALT (IU/dl)			
Median (min-max)	58 (15 – 942)	50 (15 – 942)	69 (25 – 96)
Metavir			
Median (min-max)	18.2 (2.7 – 67.8)	14.0 (2.7 – 67.8)	26.0 (4.8 – 45.7)
Hb (g/dL)			
Median (min-max)	11.9 (10.6 – 16.9)	14.6 (11.4 – 16.9)	11.4 (10.6 – 14.8)
Comorbid			
Post kidney transplant	1	1	0
Post hepatectomy	1	1	0
HIV coinfection	1	1	0

HCV-RNA: hepatitis C virus-ribonucleic acid, AST: aspartate aminotransferase, ALT: alanine aminotransferase, Hb: hemoglobin, HIV: human immunodeficiency virus

Table 2. Therapeutic outcomes

	Non-cirrhosis (12 weeks) All Genotype (n = 20)	Cirrhosis (24 weeks) All Genotype (n = 12)
Pre-treatment HCV-RNA (x10^5)	10.0 (0.007 – 212.0)	8.57 (2.0 – 16.1)
Post-treatment HCV-RNA (x10^5)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)
SVR12	20 (100%)	12 (100%)
ALT baseline (IU/dL)	50 (15 – 942)	69 (25 – 96)
ALT at end of treatment (IU/dL)	26.5 (5 – 124)	25.5 (13 – 55)

HCV-RNA: hepatitis C virus-ribonucleic acid, SVR 12: sustained virologic response rates at 12 weeks, AST: aspartate aminotransferase, ALT: alanine aminotransferase

hepatitis C without cirrhosis.[3] Daclatasvir-sofosbuvir can be used in both compensated and decompensated cirrhosis. Recommended duration of treatment is 24 weeks or 12 week with additional Ribavirin.[3,11]

The SVR12 rate of daclatasvir-sofosbuvir combination in this study was consistent with previous studies. Evaluation of daclatasvir-sofosbuvir combination was first done by Sulkowski et al. They assessed the SVR12 in patients with HCV genotypes 1, 2, and 3. They observed SVR12 rate of 89-98%, depend on viral genotypes, previous treatment, or additional ribavirin.[13] Pol et al evaluating the combination of daclatasvir-sofosbuvir in HCV genotipe 1 patients in France. In noncirrhotic patient, SVR12 of 100% was achieved.[15]

For the pan-genotypic activity of daclatasvir-sofosbuvir combination, our study was parallel with the study by Nair *et al*. in India. In thirty HCV patients of all genotypes treated with daclatasvir-sofosbuvir combination, they achieved an SVR of 100%. The SVR achieved not only in naïve, but also in post-therapy patients with interferon. Six patients with undetermined genotype also showed high SVR indicating that daclatasvir-sofosbuvir combination was effective in undetermined genotype of HCV.[14]

In our study, HCV genotype 1 patients were the most frequent. This was consistent with epidemiologic data in Indonesia that HCV genotype 1 is the most prevalent.[3]

Genotype 3 is a risk factor for DAAs treatment failure.[6] Furthermore, it poses patients to greater risk of progression to cirrhosis or hepatocellular carcinoma.[9,16] The ALLY-3 and a French Early Access Programme studies assessed the combination of daclatasvir-sofosbuvir regimen in genotype 3 patients. They demonstrated that the combination lead to achievement of SVR of 96-98% in non-cirrhotic patients, but the SVR decline to 63-86% in cirrhosis.[9] Our study demonstrated that patients with genotype 3 achieved SVR. However, these patients were non-cirrhotic, so we were not able to observe the efficacy of daclatasvir-sofosbuvir combination in genotype 3 HCV with cirrhosis.

Treating Hepatitis C with DAA requires a comprehensive assessment of the patients. Genotype 3 and cirrhosis status were associated with an increased rate of failure of DAAs treatment and lower SVR12.[5,17] Some studies recommended adding other DAAs over existing treatment or triple therapy in HCV patients with cirrhosis.[5,11] Ribavirin is a preferred DAA to be given in addition to daclatasvir-sofosbuvir to treat HCV patients with cirrhosis. Ribavirin has been shown to increase SVR12 in HCV patients receiving a combination of DAAs.[15] Alternatively, daclatasvir-sofosbuvir combination in cirrhosis patients was given longer than non-cirrhosis patient.[17] National consensus gives recommendation of 24 weeks treatment with daclatasvir-sofosbuvir regimen or 12 weeks if adding ribavirin.[3] Daclatasvir-sofosbuvir in cirrhosis patients for 24 weeks of treatment yielded SVR12 of 95.7% if ribavirin was added to the regimen, and 92.5% without ribavirin.[5,15] In our study, ribavirin was not given due to its anaemia side effect which may worsen patients condition, particularly cirrhotic patients. A Study by Welzel et al. showed an increased risk of anaemia with sofosbuvir-daclatasvir-ribavirin combination, compared with daclatasvir-sofosbuvir only.[5] However, all patients achieved 100% SVR in genotype 1, 2, and undetermined. Since no genotype 3 and 4 patients with cirrhosis in our study with, the efficacy of daclatasvir-sofosbuvir combination could not be observed in these subgroups.

All subjects in this study showed tolerance to the combination of the drugs. This is consistent with studies by Nair et al and Welzel et al, daclatasvir-sofosbuvir combination were well tolerated.[5,14] Minor side effect reported were fatigue and nausea. Nair *et* al. reported headache, nausea, and fatigue symptoms occurred in 5% of subjects.[14]

This observational study demonstrated that combination of daclatasvir-sofosbuvir was effective in achieving SVR in all HCV patients, with or without cirrhosis. However, limitation of this study were retrospective design, small subject size, and non-blinding treatment that may lead to biases. Further observational prospective study is needed to evaluate the long-term side effect, viral reactivation, and efficacy of using DAAs in some population such as hepatitis B co-infection, HIV co-infection, or hemodialysis patients.

CONCLUSION

Combination of generic daclatasvir-sofosbuvir in the treatment of hepatitis C patients showed SVR12 of 100% in all genotypes, with or without cirrhosis. The optimal duration of treatment was 12 weeks in noncirrhotic and 24 weeks in compensated cirrhosis patients, with tolerable side effects.

CONFLICT OF INTEREST

None to declared.

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REFERENCES

1. Hutin Y, Kitler ME, Dore GJ, Perz JF, Armstrong GL, Dusheiko G, et al. Global Burden of Disease (GBD) for Hepatitis C. J Clin Pharmacol 2004;44:20–9.
2. World Health Organization. Global Hepatitis Report, 2017 [serial online] World Health Organization 2017.p.62 [cited 2017 December 10]. Available from: http://www.who.int/hepatitis
3. Hasan I, Gani RA, Sulaiman AS. Konsensus Nasional Penatalaksanaan Hepatitis C di Indonesia. Perhimpunan Peneliti Hati Indonesia; 2017.
4. Dresch KFN, de Mattos AA, Tovo CV, de Onofrio FQ, Casagrande L, Feltrin AA, et al. Impact of the pegylated-interferon and ribavirin therapy on the treatment-related mortality of patients with cirrhosis due to hepatitis C virus. Rev Inst Med Trop Sao Paulo 2016;58:1–6.
5. Welzel TM, Petersen J, Herzer K, Ferenci P, Gschwantler M, Wedemeyer H, et al. Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort. Gut 2016;65:1861–70.
6. Hézode C, Lebray P, De Ledinghen V, Zoulim F, Di Martino V, Boyer N, et al. Daclatasvir plus sofosbuvir, with or without ribavirin, for hepatitis C virus genotype 3 in a French early access programme. Liver Int Off J Int Assoc Study Liver 2017;37:1314–24.
7. Shiha G, Soliman R, ElBasiony M, Hassan AA, Mikhail NNH. Sofosbuvir plus Daclatasvir with or without ribavirin for treatment of chronic HCV genotype 4 patients: real-life experience. Hepatol Int 2018;12:339-47.
8. Poordad F, Dieterich D. Treating hepatitis C: Current standard of care and emerging direct-acting antiviral agents. J Viral Hepat 2012;19:449–64.
9. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, 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;61:1127–35.
10. Jakobsen JC, Nielsen EE, Feinberg J, Katakam KK, Fobian K, Hauser G, et al. Direct-acting antivirals for chronic hepatitis C. Cochrane Database Syst Rev 2017;6:x.
11. Omata M, Kanda T, Wei L, Yu ML, Chuang WL, Ibrahim A, et al. APASL consensus statements and recommendation on treatment of hepatitis C. Hepatol Int 2016;10:702–26.
12. Gao M, Nettles RE, Belema M, Snyder LB, Nguyen VN, Fridell RA, et al. Chemical genetics strategy identifies an HCV NS5A inhibitor with a potent clinical effect. Nature 2010;465:96–100.
13. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus Sofosbuvir for Previously Treated or Untreated Chronic HCV Infection. N Engl J Med 2014 Jan 16;370:211-21
14. Nair AS, Ramachandran TM, Prasad GP. Pan genotypic response to combination treatment with Sofosbuvir and Daclatasvir in chronic Hepatitis C patients. Int J Biomed Res 2017;8:333–8.
15. Pol S, Corouge M, Valet-Pichard A. Daclatasvir–sofosbuvir combination therapy with or without ribavirin for hepatitis C virus infection: from the clinical trials to real life. Hepatic Med Evid Res 2016;8:21–6.
16. Sperl J, Frankova S, Kreidlova M, Merta D, Tothova M, Spicak J. Combination of sofosbuvir and daclatasvir in the treatment of genotype 3 chronic hepatitis C virus infection in patients on maintenance hemodialysis. Ther Clin Risk Manag 2017;13:733-738.
17. Sundaram V, Kowdley K V. Dual daclatasvir and sofosbuvir for treatment of genotype 3 chronic hepatitis C virus infection. Expert Rev Gastroenterol Hepatol 2016;10:13–20.