Pangenotypic Direct Acting Antivirals Treatment for Chronic Hepatitis C Infection

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Hepatitis C virus (HCV) is one of the major public health problems in the worldwide which can cause both acute and chronic infections.[1,2] Almost 15-45% of HCV-infected patients impulsively eradicate the virus without getting any treatment.[1,2,3] But the remaining 15-85% of patients develop chronic infection and is associated with a high level of morbidity and an elevated risk of developing potentially serious course like hepatocellular carcinoma, cirrhosis, pervasive fibrosis, and advanced liver disease which lead to the liver transplantation.[1,2,3] The Asia Pacific region has the largest share of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection in the world with largest number of global deaths from liver cancer reach which is reached 74%.[1] In Indonesia specifically, information about the data and prevalence of hepatitis infection is lacking for the general population because of several factors, including (1) inadequate disease surveillance system lead to underreporting of both acute and chronic infections; (2) geographical barriers with high number population who are distributed in more than 17.000 island; (3) lack of health facilities for testing, screening, and detecting HCV infection leading the difficulty to diagnose in this large population county.[1] For HCV infection, anti-HCV prevalence in Indonesia was 1,0% with peak incidence in subjects aged 60 years and older. In 2014, an estimated 9% of the viremic population develop cirrhosis and HCC and it is projected to increase to 15% by 2030.[1]

HCV has 6 different genotype which are prevalent in different regions, varying from genotype 1 to 6. All the genotype has different nucleotide sequence that lead to vary for pathogenicity, virulence, progression rate to severe clinical manifestation, and would respond differently to pharmacological treatment.[2,3,4] By 1991 up to early 2014, chronic treatment of HCV infection using interferon-based therapy with generally has low cure rated, long duration of therapy, and several side effect due to its substantial toxicity.[2,3,4] Over the last 5 years, direct-acting antiviral agents (DAAs) have revolutionized the treatment of HCV infection with their specific mechanism of action disturbing the HCV life cycle an able to target the viral proteins implicated in replication of the virus such as NS3/4A protease, NS5B polymerase, and multifunctional NS5A replication complex. The first-generation of protease inhibitor improved the sustained virologic complex (SVR), but it still required the use of PEGylated interferon (PEG-IFN).[2,3,4] The second-generation of DAAs was introduced in 2014, provided effective interferon-free therapy combinations for all HCV genotype. Oral IFN-free combinations containing at least two DAAs enable less complex dosing with high SVR, tolerable side effect, and fewer drug-drug interactions.[2,3,4]

The first pan genotypic DAA regiment for HCV is Sofosbuvir which is a nucleotide polymerase NS5B inhibitor combined with Daclatasvir, first in class HCV NS5A replication complex inhibitor. Recent study about the efficacy and safety Daclatasvir/Sofosbuvir showed that the overall SVR for HCV patients among all major six genotypes was 92% and 95% in non-cirrhotic patient.[5,6,7] Daclatasvir/Sofosbuvir with or without ribavirin (RBV) achieved high twelve week of SVR (SVR12) and was well tolerated, including in special HIV/HCV coinfected and patient with advanced liver disease. Specifically, the Daclatasvir/Sofosbuvir twelve weeks SVR was 89% in patients infected with genotype 3 and only 62.5% in cirrhotic patient.[5,6,7] Therefore, additional evaluation to optimize the treatment outcome with combination Daclatasvir and Sofosbuvir in genotype 2-infected patients with cirrhosis was adding ribavirin for 12 weeks or extension the treatment up to 24 weeks.[5,6,8] Another study from a French multicenter analyzed that 12 weeks of Daclatasvir/Sofosbuvir was not an optimal way to treat cirrhotic patient with HCV genotype 3 with SVR12 was only 76%.[5,6,7]

A once daily, single-tablet, pangenotypic regiment, Sofosbuvir/Velpatasvir, which has similar mechanism of action to disturb viral replication in HCV, was recently developed. ASTRAL studies demonstrated

the highly effective Sofosbuvir/Velpatasvir for treating Hepatitis C infection across all genotype and different stage of liver damage.[4,8,9,10] Especially in ASTRAL-3 with subject population including patient with chronic HCV infection caused by genotype 3 HCV showed that the SVR patients treated with Sofosbuvir/Velpatasvir for twelve weeks reached 95%, 91% SVR in patient with compensated cirrhosis. [4,7,9,10] Sofosbuvir/Velpatasvir is a RBV-free regimen and in naïve non-cirrhotic patients attains SVR rates up to 100% in all genotypes.[4,9,10] In decompensated cirrhotic patients, Sofosbuvir/Velpatasvir, with the addition of RBV, resulted in 94% of SVR. As a pangenotypic and pan-fibrosis regimen, it is conceivable that Sofosbuvir/Velpatasvir will simplify, or perhaps eliminate, the pre-treatment assessments and on treatment monitoring that represent a barrier to treatment access in several countries. [4,9,10] Considering the characteristics of Sofosbuvir/Velpatasvir, this regimen can be considered the ideal partner in the path to HCV eradication.[4,9,10] Beside combination regimen Sofosbuvir/Velpatasvir, another combination pangenotypic regiment Glecaprevir/Pibrentasvir (GLE/PIB) is quite promising. Especially for HCV genotype 3, in recent study showed that patient with HCV genotype 3 treated with GLE/PIB for twelve weeks achieved 95% SVR with and without cirrhosis.[4,7,11]

The availability of pangenotypic DAA regiment in Indonesia for right now is only combination Sofosbuvir/Daclatasvir regiment for chronic HCV infection with and without compensated and decompensated cirrhosis.[12]

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