New Treatments for HCV: Perspective From Asia

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Introduction

The prevalence and number of people with antibodies to hepatitis C virus (anti-HCV) globally are estimated to be 2.8% and 185 million respectively, with two-thirds (124 million) in Asia.[1]

HCV genotype distribution varies greatly in the Asian regions, with estimated populations of 54, 12, 48, 7.5, and 9.7 million, respectively, for HCV genotype 1 (HCV-1), HCV-2, HCV-3, HCV-4, and HCV-6, respectively (Table 1).[2]

More than 80% of Asian persons infected with HCV have a more favorable host genotype (either interleukin-28B (IL28B) rs12979860 CC versus CT or TT or IL28B rs8099917 TT versus GT or GG). These innate immune genotypes are associated with a higher rate of sustained virological response (SVR) to treatment with pegylated interferon and ribavirin. For example, 80% of Asian HCV gentotype- 1 patients with lower baseline viral loads (LVL) and the IL28B CC host genotype can expect to achieve an SVR after a 24-week course of peginterferon/ribavirin.

Peginterferon/Ribavirin for Asian Patients

For Asian patients infected by HCV genotype 1 or 4, the SVR rates in response to peginterferon/ribavirin for 48 weeks and 24 weeks are 60% and 75%, whereas for patients with genotype 2 or 3 virus the rates of SVR rise to 80% and 90% respectively.[5] With a strategy of response-guided therapy (RGT) based on HCV genotype and treatment virological responses,[6] treatment duration could be abbreviated to 24 weeks for HCV-1/4 patients with a low viral load (LVL) (ie less than one million IU/mL) and rapid virological response (RVR) (undetectable HCV RNA at treatment week 4 [W4]) and to 16 weeks for HCV-2 patients with RVR. Treatment should be stopped for those not achieving an early virological response (EVR) (HCV RNA decline < 2 logs at W12). Extending treatment to 72 weeks is recommended for HCV-1 patients with partial EVR (HCV RNA detectable at W12 with EVR).

Among treatment-experienced patients in Asia, the administration of peginterferon/ribavirin for 48 weeks to HCV genotype-1 IL28B CC relapsers[7] or for 24 weeks to HCV genotype-2 relapsers[8] achieved an SVR in greater than 60% of cases.

Perspective of Directly-Acting Antiviral Agent in Asia

The progress of directly-acting antiviral agent (DAA) in HCV treatment is moving from interferon-containing regimens in 2011 to interferon-free regimens, which are the current standard of care in most Western countries.[9] Table 2 and Figure 1 demonstrate the timeline and expected indications of DAA regimens in Asia-Pacific countries. Unfortunately, the variety and uncertainty of the timeline for DAAs in Asia-Pacific make it difficult to develop a universal HCV practice guideline appropriate for the whole Asian population.

Interferon-Containing Regimens

The first wave of NS3/4A protease inhibitors, boceprevir and telaprevir, in combination with peginterferon/ribavirin for between 24 and 48 weeks based on RGT, was approved for HCV-1 treatment-naïve and experienced patients in several Asian countries. However, adding a first generation protease inhibitor had no benefit for HCV-1 treatment-naïve patients with LVL and RVR compared with a 24-week course of peginteferon and ribavirin.[10] Japan approved 24-week telaprevir triple therapy for HCV-2 in September 2014.

Simeprevir, a second wave protease inhibitor, has recently been approved in Japan and Australia, for use in

Abbreviations: DAA, directly-acting antiviral agent; EVR, early virological response; HCV, hepatitis C virus; HVL, high viral load ; IL28B, interleukin-28B; LVL, low viral load; RGT, response guided therapy; RVR, rapid virological response; SVR, sustained virological response; W, week.

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Potential conflict of interest: Nothing to report.

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doi: 10.1002/cld.442

TABLE 1 Estimated Prevalence of HCV Infection in Asia-Pacific Countries

HCV Population	Asia-Pacific Countries (million)	Global Estimation (million)	Percentage
Anti-HCV seropositive population	> 124	184	67%
HCV genotype population			
HCV genotype 1*, widely in Asia-Pacific	54	83	65%
HCV genotype 2, East, Southeast and South Asia	12	16.5	72%
HCV genotype 3, South and Southeast Asia	48	54	88%
HCV genotype 4, Middle East	> 7.5	15	> 50%
HCV genotype 5, rare	0.1	1.5	6.7%
HCV genotype 6, Southeast Asia	9.7	9.8	99%

Asian countries included all Asia and Australia/New Zealand
Prevalence of anti-HCV in Asian countries, data derived from Hanafiah et al.[1]
Distribution of HCV genotype in Asia-Pacific countries, data derived from Messina et al.[2]
*More than 90% of infected individuals in East Asia are infected by HCV subtype 1b

TABLE 2 Expected Indications of DAA Regimens in Asia-Pacific Countries

DAA Regimen	Treatment Duration	HCV Genotype	Decompensated Liver Diseases
Interferon-Containing Regimens			
*Boceprevir + PR, RGT (Boceprevir 800 mg every 8 hr, 24--44 wk)	28--48 weeks	G1	No
*Telaprevir + PR, RGT (Telaprevir 1125 mg every 12 hr, 12 wk)	24--48 weeks	G1/2	No
*Simeprevir + PR (Simeprevir 150 mg daily, 12 wk)	24--48 weeks	G1/4	No
*Sofosbuvir + PR (Sofosbuvir 400 mg daily, 12 w)	12 weeks	G1/3--6	No
*Daclatasvir + PR, RGT (Daclatasvir 60 mg daily, 24 wk)	24--48 weeks	G4	No
Interferon-Free Regimens			
*Sofosbuvir + RBV	12--24 weeks	G1--6	Yes
†Sofosbuvir + Simeprevir ± RBV	12 weeks	G1	No
*Daclatasvir + Asunaprevir	24 weeks	G1b	No
*Daclatasvir + Sofosbuvir ± RBV	12--24 weeks	G1--4	Yes
*Sofosbuvir + Ledipasvir ± RBV	8--24 weeks	G1/3/4	Yes
‡Ritonavir ± Ombitasvir + Dasabuvir ± RBV	12--24 weeks	G1	Yes
§Daclatasvir + Asunaprevir + BMS-791325	12 weeks	G1	No
§Grazoprevir + Elbasvir ± RBV	12 weeks	G1--6	No

DAA, directly-acting antiviral agent; RGT, response-guided therapy; G, genotype; P, peginterferon; R or RBV, ribavirin.
*Approved regimens in the United States, European Union, or Japan.
†Off-label regimen.
‡Regimen awaiting approval.
§Regimens of ongoing phase 3 trials.
Underlining indicates fixed-dose combination.

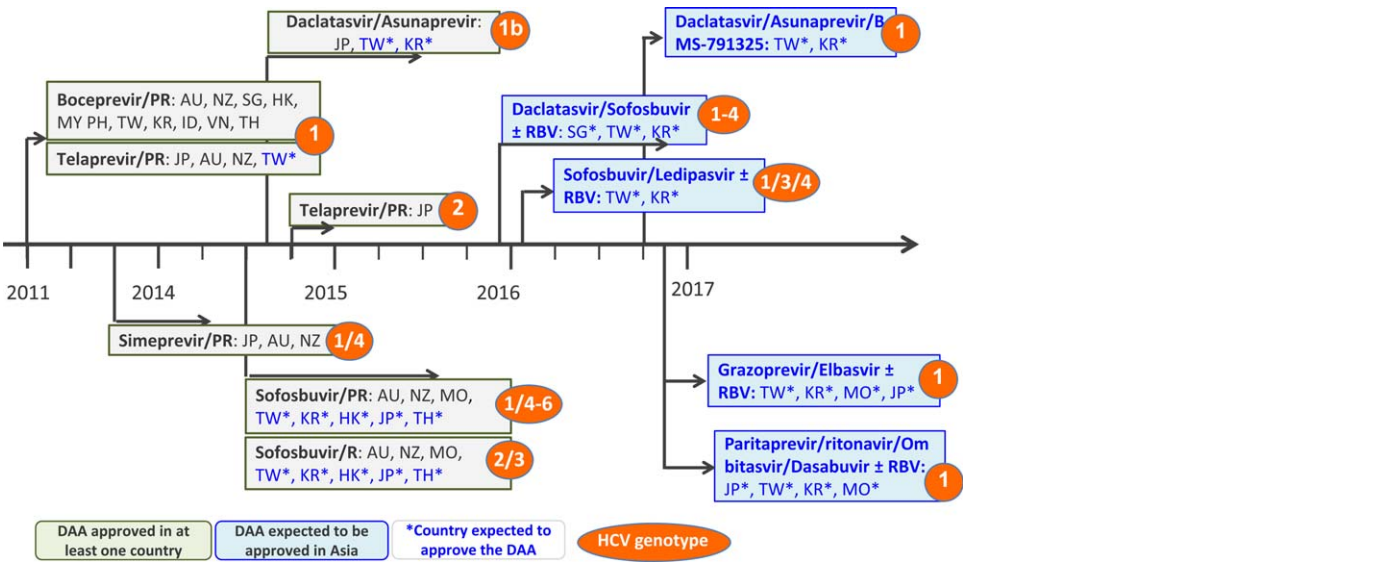

Figure 1 DAA landscape in Asian countries. AU, Australia; DAA, directly-acting antiviral agent; HK, Hong Kong; ID, Indonesia; JP, Japan; KR, Korea; MO, Macau; MY, Malaysia; NZ, New Zealand; P, peginterferon; PH, Philippines; R, ribavirin, SG, Singapore; TH, Thailand; TW, Taiwan; VN, Vietnam; HCV, hepatitis C virus.

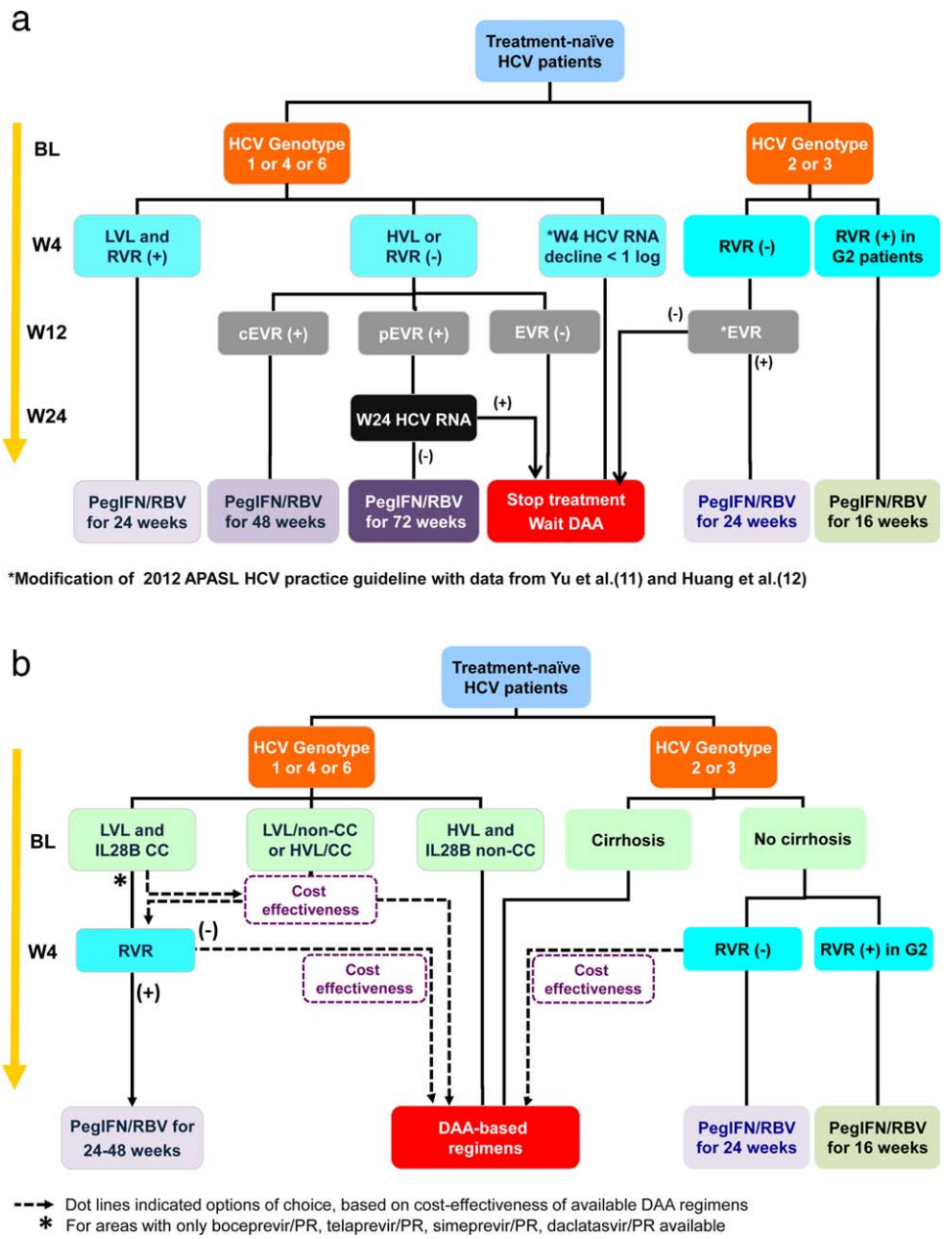

Figure 2 HCV Practice Recommendations in the transition era of DAA in Asian countries. (2a) IFN-eligible naïve patients without DAA available; (2b) IFN-eligible naïve patients with DAA available; (2c) IFN-eligible experienced patients without DAA available; (2d) IFN-eligible experienced patients with DAA available. Abbreviations: RVR, rapid virological response, HCV RNA undetectable at week 4; EVR, early virological response, HCV RNA decline > 2 logs at week 12; cEVR, complete EVR, no RVR, but HCV RNA undetectable at week 12; HCV RNA decline > 2 logs but detectable at week 12. BL, baseline; IL28B CC, interleukin-28B CC genotype; PegIFN, peginterferon; RBV, ribavirin; W, treatment week; G2, HCV genotype 2; DAA, directly-acting antiviral agent.

concert with peginterferon and ribavirin for HCV genotype 1 and 4 patients, both treatment-naive and treatment experienced.

Sofosbuvir, a pangenotypic NS5B nucleotide polymerase inhibitor with high efficacy (SVR rates > 90%) has recently received approval in Australia and Macau for use in conjunction with with pegylated interferon and ribavirin for 12 week course of therapy in HCV genotypes 1, 3-6.

Daclatasvir, a NS5A inhibitor, in combination with peginterferon/ribavirin based on RGT, was approved for HCV-4 patients in Europe in October 2014.

Interferon-Free Regimens

Sofosbuvir plus a weight-based dose of ribavirin, was approved for all HCV genotypes in Australia and 2014, thereby becoming the first interferon-free regimen approved

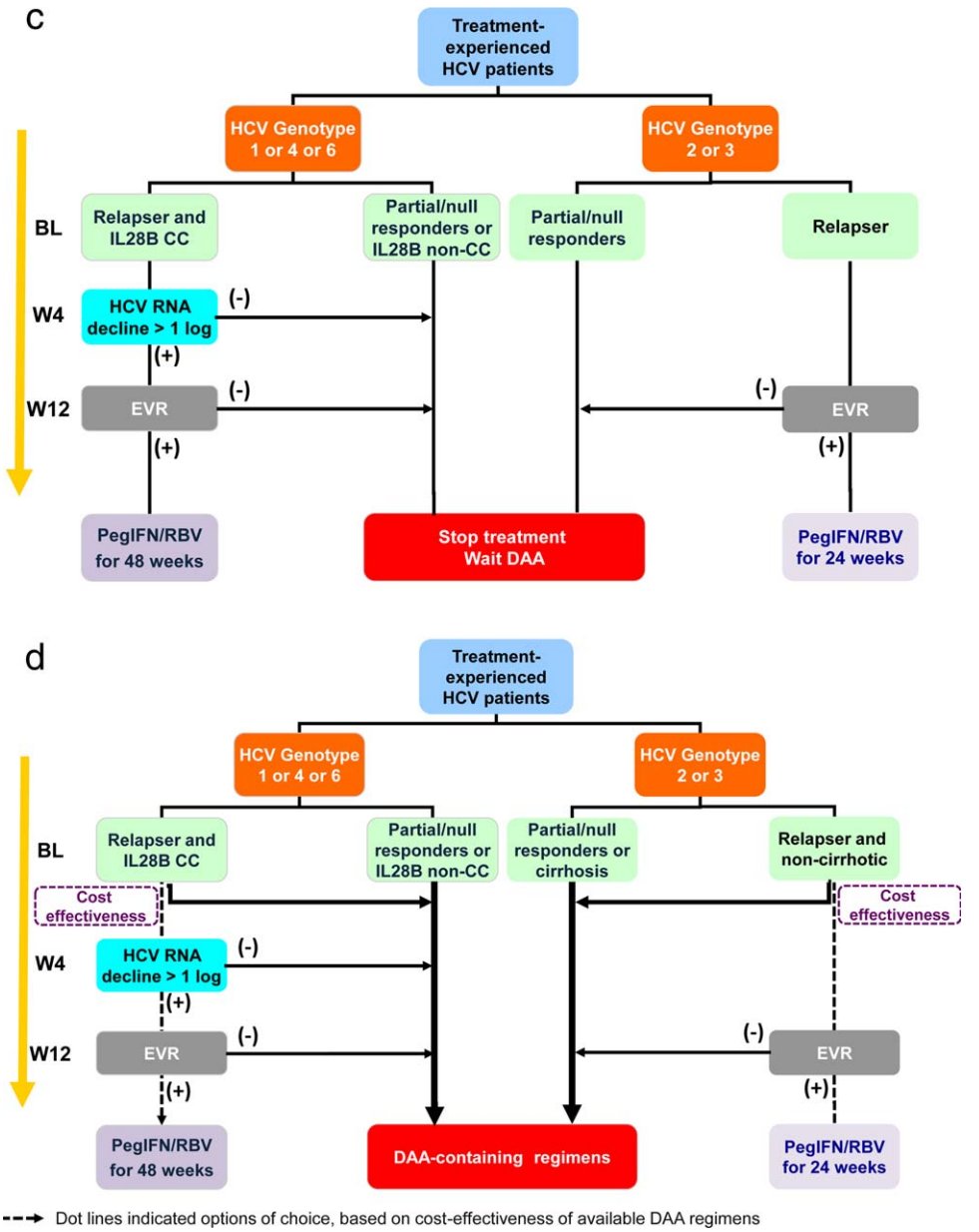

Figure 2 Continued

for use in Asia. A 12-week and 24-week regimen is recommended for HCV-2 and HCV-3 patients, respectively, with SVR rates of > 90%. However, 24 weeks of sofosbuvir/ribavirin, with SVR rate of 60% to 70% for HCV-1 patients, is an alternative recommendation for interferon-ineligible patients.

Instead, 12 weeks for sofosbuvir plus simeprevir, with high SVR rates (> 90%) in phase 2 COSMOS trial, is an off-label recommendation for HCV-1/interferon-ineligible patients.

The first approved interferon-free regimen for HCV-1b, 24-week daclatasvir plus asunaprevir (NS3/4A protease inhibitor), was approved in Japan in July 2014 for interferon-ineligible/intolerant and treatment-experienced patients with SVR rates of 85% to 90%.

Sofosbuvir plus daclatasvir with/without ribavirin for 12 to 24 weeks was approved for naïve or experienced HCV1-4 patients in Europe in August 2014. A fixed-dose combination of sofosbuvir/ledipasvir, a NS5A inhibitor, for 8 to 12 weeks with SVR rates of > 92% for HCV-1 treatment-naïve and experienced patients was approved in the United States in October 2014. Both regimens are expected to be available in Asia before 2016.

A 3-DAA (coformulated paritaprevir [NS3/4A protease inhibitor boosted by ritonavir]/Ombitasvir [NS5A inhibitor] and Dasabuvir [NS5B nonnucleoside analogue]) plus ribavirin for 12 weeks achieved high SVR rates (90%-95%) for naïve and experienced, cirrhotic and noncirrhotic HCV-1 patients in phase 3 trials.

Recently, two fixed-dose combinations, 12-week daclatasvir/asunaprevir/BMS-791325 (NS5B nonnucleoside analogue) and 12-week grazooprevir (NS3/4A protease inhibitor)/elbasvir (NS5A inhibitor) could attain SVR rates of > 90% for HCV-1 and HCV1-6, respectively. The phase 3 studies are ongoing now.

HCV Practice Recommendation in Asia-Pacific

Lacking a one-size-fits-all regimen increases HCV treatment complexity and barriers. The current recommendations should be based on the availability, indication, and cost-effectiveness of DAAs in Asia (Table 2).

Treatment-naïve interferon-eligible patients without DAA available (Fig. 2a)

The treatment algorithm is based on the 2012 Asian Pacific Association for the Study of the Liver (APASL) HCV practice guideline[6] with modification: treatment should be stopped for HCV-1 patients with HCV RNA decline < 1 log at W4 (interferon-nonresponsiveness)[11] and for HCV-2/3 patients without EVR.[12]

Treatment-naïve interferon-eligible patients with DAA available (Fig. 2b)

1. HCV-1, 4, 6:
   - DAA-containing regimens for patients with high viral load (HVL) and IL28B-non-CC genotype.
   - Either peginterferon/ribavirin dual therapy or DAA-containing regimens for patients of LVL/IL28B-CC without rapid virological response (RVR), LVL/IL28B-non-CC, or HVL/IL28-CC, based on cost-effectiveness.
   - Twenty-four weeks of peginterferon/ribavirin for patients with LVL and IL28B-CC genotype if only boceprevir/peginterferon/ribavirin, telaprevir/peginterferon/ribavirin, simeprevir/peginterferon/ribavirin, or daclatasvir/peginterferon/ribavirin are available.
2. HCV-2/3:
   - Sixteen to 24 weeks of RGT with peginterferon/ribavirin for noncirrhotic patients.
   - DAA-containing regimens for cirrhotic patients, and for non-RVR patients if cost-effective.

Treatment-experienced interferon-eligible patients without DAA available (Fig. 2c)

- Forty-eight weeks of peginterferon/ribavirin for HCV-1,4,6 prior relapsers with IL28B-CC genotype; 24 weeks of peginterferon/ribavirin for HCV-2/3 prior relapsers.
- Treatment should be stopped for patients without EVR and for HCV-1 with HCV RNA decline < 1 log at W4.
- Deferring treatment for all prior partial/null responders and for HCV-1 IL28B-non-CC patients.

Treatment-experienced interferon-eligible patients with DAA available (Fig. 2d)

- DAA-containing regimens for all patients.
- Alternatively, 48 weeks of peginterferon/ribavirin for HCV-1,4,6 prior relapsers with IL28B-CC genotype, and 24 weeks of peginterferon/ribavirin for HCV-2/3 prior relapsers, if cost-effective.

Interferon-ineligible/intolerant patients

- Interferon-free DAA regimens according to viral genotypes.

Conclusion

In the emerging era of DAA, treatment should weigh the benefit/risk and cost-effectiveness, especially in lower socioeconomic areas of Asia. Before the availability of interferon-free DAA regimens, peginterferon/ribavirin will hang around years in a number of Asian countries. ■

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