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 genotype-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.3 With a strategy of response-guided therapy (RGT) based on HCV genotype and treatment virological responses,4 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 relapers5 or for 24 weeks to HCV genotype-2 relapers6 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 peginterferon 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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**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, 28--48 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                           |
| §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.
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 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.
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 grazoprevir (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).

*HCV practice**

**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-naive 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 guideline6 with modification: treatment should be stopped for HCV-1 patients with HCV RNA decline < 1 log at W4 (interferon-norresponsiveness)11 and for HCV-2/3 patients without EVR.12

**Treatment-naive 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/IL28B-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 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/IL28B-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.

**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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