R E V I E W

Nanomedicines in the treatment of hepatitis C virus infection in Asian patients: optimizing use of peginterferon alfa

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Abstract: Asia is endemic for hepatitis C virus (HCV) infection, which is the leading cause of cirrhosis, hepatic decompensation, hepatocellular carcinoma , and liver transplantation worldwide. HCV has six major genotypes and each HCV genotype has its specific geographic distribution. HCV genotypes 1, 2, 3, and 6 are common in Asia. The aim of HCV treatment is to eradicate the virus by effective therapeutic agents; viral clearance is durable after long-term post-treatment follow-up. In most Asian countries, peginterferon alfa (PEG-IFN α) in combination with ribavirin remains the standard of care, and the overall sustained viral response (SVR) rate in Asian HCV patients is higher than that in Western patients. The differences are most significant in patients with HCV genotype 1 (HCV-1) infection, which is attributed to the higher frequency of IFN-responsive or favorable interleukin-28B (IL-28B) genotype in Asian populations than in other ethnic populations. In addition, the introduction of response-guided therapy, where the optimized treatment duration is based on the early viral kinetics during the first 12 weeks of treatment, increases the SVR rate. Recently, telaprevir or boceprevir-based triple therapy was found to further improve the SVR rate in treated and untreated HCV-1 patients and has become the new standard of care in Western and some Asian countries. Many novel direct-acting antiviral agents, either in combination with PEG-IFN α plus ribavirin or used as IFN-free regimens are under active investigation. At the time of this writing, simeprevir and sofosbuvir have been approved in the US. Because the SVR rates in Asian HCV patients receiving PEG-IFN α plus ribavirin therapy are high, health care providers should judiciously determine the clinical usefulness of these novel agents on the basis of treatment duration, anticipated viral responses, patient tolerance, financial burdens, and drug accessibility.

Keywords: PEG-IFN α, HCV, SVR, RGT, IL28B

Introduction

Hepatitis C virus (HCV) infection, the leading cause of cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), and liver transplantation, affects ~170 million people worldwide.[1] It is estimated that approximately 20% of individuals who are infected with HCV will develop cirrhosis within 20–30 years, and that the risk of HCC development in these patients is 1%–4% per annum.[2] The aim of HCV therapy is the eradication of HCV, and the current definition of successful treatment is sustained virologic response (SVR), referring to undetectable serum HCV RNA levels at 12 (SVR_{12}) or 24 (SVR_{24}) weeks after the cessation of antiviral therapy. The durability of viral response after achieving SVR has been confirmed by many observational studies, showing that over 98% of patients who achieve SVR can maintain non-viremic status after long-term post-treatment follow-up, regardless of HCV monoinfection, coinfection with hepatitis B virus

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(HBV) or human immunodeficiency virus (HIV), alanine aminotransferase (ALT) levels, or patient ancestry.[3,4] Compared to the development of conventional interferon alpha (IFN α) for the treatment of chronic HCV infection, which results in only 6%–19% of SVR after 24–48 weeks of treatment, the use of peginterferon alfa (PEG-IFN α) in combination with ribavirin (RBV) has greatly improved the overall SVR rate to 42%–52% in HCV genotypes 1/4 patients and 76%–82% in HCV genotype 2/3 patients, respectively.[5–7] In addition, the introduction of response-guided therapy (RGT), where the optimized treatment duration is on the basis of early viral kinetics during the first 12 weeks of treatment, has further increased the SVR rate to 70%–75%.[8,9] Interestingly, the SVR rates of Asian patients with HCV genotype 1 (HCV-1) infection receiving PEG-IFN α plus RBV combination therapy are higher than those of Western HCV-1 patients. In contrast, the response rates between Asian and Western non-HCV-1 patients are comparable. The higher response rate in Asian HCV-1 patients than in Western patients was explained by the discovery of human interleukin-28B (IL-28B) genetic polymorphisms (rs12979860 or rs8099917) that strongly affect the SVR rates in HCV-1 patients receiving dual therapy of PEG-IFN α plus RBV.[10,11] Recently, the development of telaprevir (TVR) or boceprevir (BOC)-based triple therapy with PEG-IFN α plus RBV further improved the SVR rate to 66%–76% in treated and untreated HCV-1 patients and has become the standard of care (SOC) for Western HCV-1 patients.[12–15] Many novel direct-acting antiviral agents (DAAs), either in combination with PEG-IFN α plus RBV or used as IFN-free regimens are under active investigation. This review will focus on the recent advances in the epidemiology, natural history, and therapy of Asian patients with HCV infection, with special attention on the role of PEG-IFN α.

Epidemiology

HCV infection remains a global health problem. It is estimated that approximately 3–4 million people are newly infected, and 170 million people (3% of the world's population) are chronically infected with HCV. The majority of chronic HCV-infected carriers come from East Asia (about 60 million) and Southeast Asia (30–35 million). The prevalence of the antibody to HCV (anti-HCV) in Asia varies widely by geographical area (Table 1). In general, East Asia and Southwest Asia are estimated to have a high prevalence (>3.5%), whereas South and Southeast Asia are estimated to have a moderate prevalence (1.5%–3.5%).[16] The distribution of HCV genotype/subtype also varies widely across different Asian regions. HCV genotype 1b

Table 1 Prevalence rates of HCV infection and distribution of HCV genotypes in Asia

Country	Prevalence (%)	Genotype/subtype
East Asia		
People's Republic of China	3.20	1b (42%–68%), 2a (10%–15%)
Taiwan	4.40	1b (46%–77%), 2a/2c (31%–65%)
Japan	0.49	1b (<85%)
Korea	1.30	1b (40%), 2a (40%)
South Asia		
India	0.87	3 (62%–80%)
Pakistan	5.31	3 (79%), 1 (7%)
Southeast Asia		
Cambodia	2.30	6 (56%), 1 (24%), 3 (20%)
Hong Kong	0.08	1b (61%), 6a (27%)
Indonesia	2.10	1 (58%–74%), 3 (11%–15%), 2 (4%–17%)
Laos	1.10	6 (<96%)
Myanmar	0.95	6 (21%–49%), 3 (39%–60%), 1 (11%–31%)
Philippines	0.47	1 (73%–82%), 2 (9%–26%)
Singapore	0.37	1 (43%), 2 (17%)
Thailand	2.20	3 (53%), 1 (33%), 6 (9%–17%)
Vietnam	6.10	1 (47%), 6 (47%)
Southwest and Cental Asia		
Iran	0.13	1a (70%), 3a (30%)
Iraq	7.10	1a/1b (2%–5%), 4 (>80%)
Jordan	3.45	–
Oman	0.90	4 (>80%)
Syria	0.95	1a/1b (25%), 4 (70%)
Saudi Arabia	1.10	4 (62%), 1 (24%), 2 (7%), 3 (6%),
Turkey	1.55	1b (80%), 1a (10%), 2 (10%)

Abbreviation: HCV, hepatitis C virus.

and genotype 2a (HCV-1b/HCV-2a) predominate in East Asia; HCV genotype 3 (HCV-3) predominates in South Asia; HCV genotype 6 (HCV-6) predominates in Southeast Asia.[17] Compared with HCV-1 patients in the US, where subtype 1a infection comprises more than 50% of the population, most Asian HCV-1 patients are infected with subtype 1b.[6]

Natural history

Since the identification of the HCV particle in 1989, the natural history of patients with HCV infection has been well documented in subsequent prospective and retrospective studies.[2] In patients with acute HCV infection, about 65%–80% of these patients without receiving effective antiviral treatment will evolve into chronic HCV infection. Most patients with chronic HCV infection will lead to hepatitis and hepatic fibrosis, which may be accompanied by non-specific symptoms, such as fatigue, anorexia, and right upper quadrant discomfort.[2,18] After 20–30 years of chronic infection, nearly 20% of these patients develop cirrhosis, which is followed by

the development of hepatocellular carcinoma (HCC) (1.5% per annum), variceal bleeding (1.1% per annum), hepatic encephalopathy (0.4% per annum), and ascites (2.5% per annum).[19] Many host and viral factors have been considered to adversely affect the progression of hepatic fibrosis (old age, HBV infection, HIV infection, and heavy alcohol consumption, etc), the development of HCC (high serum HCV RNA level and HCV genotype 1b), and hepatic or extrahepatic mortality (high serum HCV RNA level).[20–25]

With the use of IFN-based therapy to treat HCV infection, many studies have indicated that more than 98% of patients who achieve SVR have durable undetectable serum HCV RNA by long-term post-treatment follow-up.[3,4] Patients with SVR have improved liver histology on necroinflammation and fibrosis, as well as decreased liver-related mortality, hepatic decompensation, and HCC.[26,27] Furthermore, successful antiviral treatment may have beneficial clinical outcomes even for HCV-infected patients with decompensated cirrhosis.[28] These lines of evidence highlight that SVR is the closest to a life-long virologic cure for HCV infection possible and leads to the improvement of clinical outcomes.

Pharmacology of peginterferon
Process of pegylation

The process of pegylation was first developed in the 1970s. Pegylation involves attaching an inert polyethylene glycol (PEG) molecule to a core protein. It is now a well-established method to modify the pharmacological properties of proteins.[29] Pegylation involves the substitution of a PEG hydroxyl group with an electrophilic functional group that is covalently attached, via an amide or urethane bond, to a lysine (Lys) or histidine (His) residual or to the N-terminus of the proteins, and thus creates a larger molecule with an increased molecular weight and apparent Stokes radius. An alternative to attaching multiple PEG units is the use of a single branched PEG moiety. Compared with linear PEG conjugates, branched-chain PEG conjugates tend to have greater pH and thermal stability, as well as being resistant to proteolytic degradation.

The increase of drug size after pegylation prolongs the drug-absorption time and the half-life, which enables once weekly dosing. Several mechanisms are proposed to account for the increase in half-life, including interference with the interaction between the carbohydrate chains and the specific receptors, masking specific amino acid motifs for the corresponding cellular receptors, diminished proteolysis and antigenicity, and limiting the glomerular filtration. Furthermore, pegylation has been suggested to reduce the immunogenicity and antigenicity for the core protein, which

may decrease the possibility of a hypersensitivity reaction.[30] Despite the favorable pharmacologic properties, pegylation has been shown to reduce the activity of the original protein in an in vitro system, suggesting that pegylation may perturb the interaction between the original protein and the target receptor (Table 2).[31]

Chemical structure of peginterferon α
Peginterferon α-2a

Peginterferon α-2a (Pegasys, Hoffmann-La Roche, Basel, Switzerland) is formed by a covalent bond between a 40 kDa branched PEG moiety to IFN α-2a (Figure 1). The process of pegylation during drug manufacturing results in a mixture of four major positional isomers at Lys^{31}, Lys^{121}, Lys^{131}, and Lys^{134} and four minor positional isomers at Lys^{49}, Lys^{70}, Lys^{83}, and Lys^{112}. The antiviral activity of PEG-IFN α-2a is about 1% of IFN α-2a. The major positional isomers at Lys^{31} and Lys^{134} have greater antiviral activity than the other positional isomers and possess about 2% of the antiviral activity of IFN α-2a.[32]

Peginterferon α-2b

Peginterferon α-2b (Peg-Intron; Schering-Plough Group, Berlin, Germany) is formed by a covalent bond between a 12 kDa linear PEG moiety to IFN α-2b. The process of pegylation during drug manufacturing results in a mixture of mono-pegylated positional isomers.[31] The primary site of conjugation (>50% of all positional isomers) is located on the His^{34} amino acid residue. The sites of conjugation in the remaining positional isomers are distributed among the various Lys, His, cysteine, and serine residues. Compared with IFN α-2b, the antiviral activity of peginterferon α-2b is about 28% by weight of IFN α-2b core protein. However, the

Table 2 Advantages and disadvantages of pegylation

| Advantages	Disadvantages
Improved pharmacokinetics	Reduced in vitro activity
– Increased half-life	– Steric interference of core protein to the target receptor
– Reduced degradation	– Interference with protein binding site or conformation
– Reduced clearance	
– Reduced maximal drug concentration	
– Lower peak-to-trough ratio in plasma drug concentration	
– Restricted volume of distribution	
Decreased immunogenicity	
Decreased adverse effects	

PEG-IFN alfa-2a
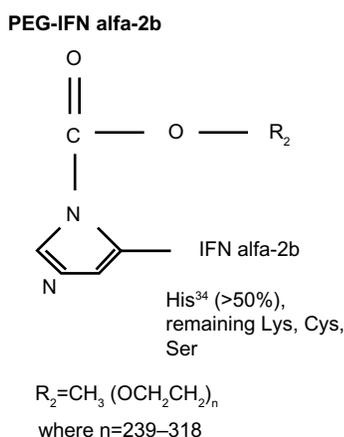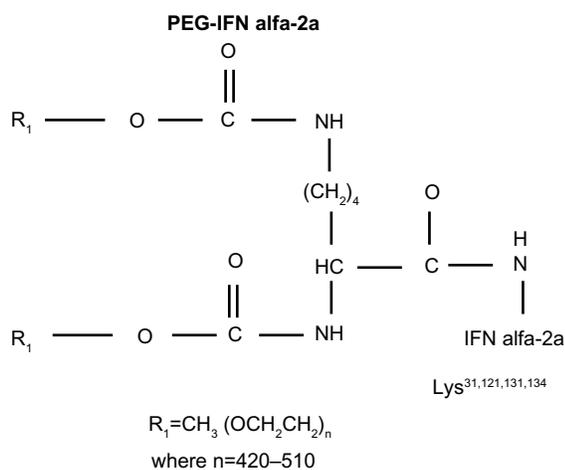
Figure 1 Chemical structure of peginterferon α-2a and α-2b.
Abbreviations: PEG-IFN, peginterferon; IFN, interferon; Lys, lysine; His, histidine; Cys, cysteine; Ser, serine.

positional isomer at His[34] has greater antiviral activity and possesses about 37% of the antiviral activity of IFN α-2b.

Pharmacokinetics of peginterferon α

PEG-IFN α-2a is absorbed at a sustained rate and has a prolonged absorption half-life ($t_{1/2abs}$, 50 hours) (Table 3 and Figure 2).[29,34] PEG-IFN α-2a at a single dose of 180 μg in healthy volunteers produces a mean time to maximum plasma drug concentration (t_{max}) of 72–96 hours. After multiple doses of PEG-IFN α-2a, the t_{max} value was about

45 hours. The mean elimination half-life ($t_{1/2β}$) is 65 hours. At the steady state, which is usually attained after 5–8 weeks of drug therapy, the serum peak-to-trough ratio of peginterferon α-2a is about 1.5, implying that the drug concentration can be sustained during the 1-week dosing interval. Furthermore, the serum PEG-IFN α-2a will be undetectable about 4–6 weeks after drug discontinuation.

Compared with PEG-IFN α-2a, the $t_{1/2abs}$ of PEG-IFN α-2b is much shorter (4.6 hours) and is about twice the $t_{1/2abs}$ of conventional IFN α-2a or α-2b (2.3 hours) (Table 3 and Figure 2).[29,33,35] Because of this rapid drug absorption, the t_{max} after a single dose or multiple doses of PEG-IFN α-2b is about 15–44 hours (mean 20 hours). The $t_{1/2β}$ of PEG-IFN α-2b (40 hours) is shorter than that of PEG-IFN α-2a. Although PEG-IFN α-2b can be used once per week, the serum peak-to-trough ratio is >10.

The volume of distribution (V_d) is affected by the size of the PEG-protein conjugate. The V_d of PEG-IFN α-2a is 8–12 L, which is 4–6-fold less than that of conventional IFN α-2a (31–73 L), suggesting that the drug is mainly distributed in the intravascular compartment. However, the V_d of PEG-IFN α-2b is 0.99 L/kg, which is slightly less than that of conventional IFN α-2b (1.4 L/kg). PEG-IFN α-2a may be given as a single fixed dose, whereas PEG-IFN α-2b should be administered by weight-based dosing.

The clearance (CL) of PEG-IFN α-2a and PEG-IFN α-2b are about one-hundredth and one-tenth that of conventional IFN α, respectively. Both types of PEG are metabolized by the liver and cleared by the kidneys. No dose adjustments are needed for PEG-IFN α-2a and PEG-IFN α-2b in patients with creatinine clearance above 20 mL/minute and 50 mL/minute, respectively. In patients with end-stage renal disease, PEG-IFN α-2a at a dose of 135 μg per week produces a similar pharmacokinetic profile to 180 μg per week in patients with normal renal function.[36]

Pharmacodynamics of peginterferon α

The activity of 2′5′-oligoadenylate synthetase (OAS), the key effector protein stimulated in response to IFN, is

Table 3 Pharmacokinetics of interferon α and peginterferon α

	IFN α-2a	IFN α-2b	PEG-IFN α-2a	PEG-IFN α-2b
V_d	31–73 L	1.4 L/kg	8–12 L	0.99 L/kg
CL	6,600–29,200 mL/h	231.2 mL/h/kg	60–100 mL/h	22.0 mL/h/kg
$t_{1/2abs}$ (hours)	2.3	2.3	50	4.6
t_{max} (hours)	7.3–12	7.3–12	80	15–44
$t_{1/2β}$	3–8	~4	65	~40
Peak-to-trough ratio	∞	∞	1.5	>10

Abbreviations: V_d, volume of distribution; CL, clearance; $t_{1/2abs}$, absorption half-life; t_{max}, time to maximum plasma drug concentrations; $t_{1/2β}$, elimination half-life.
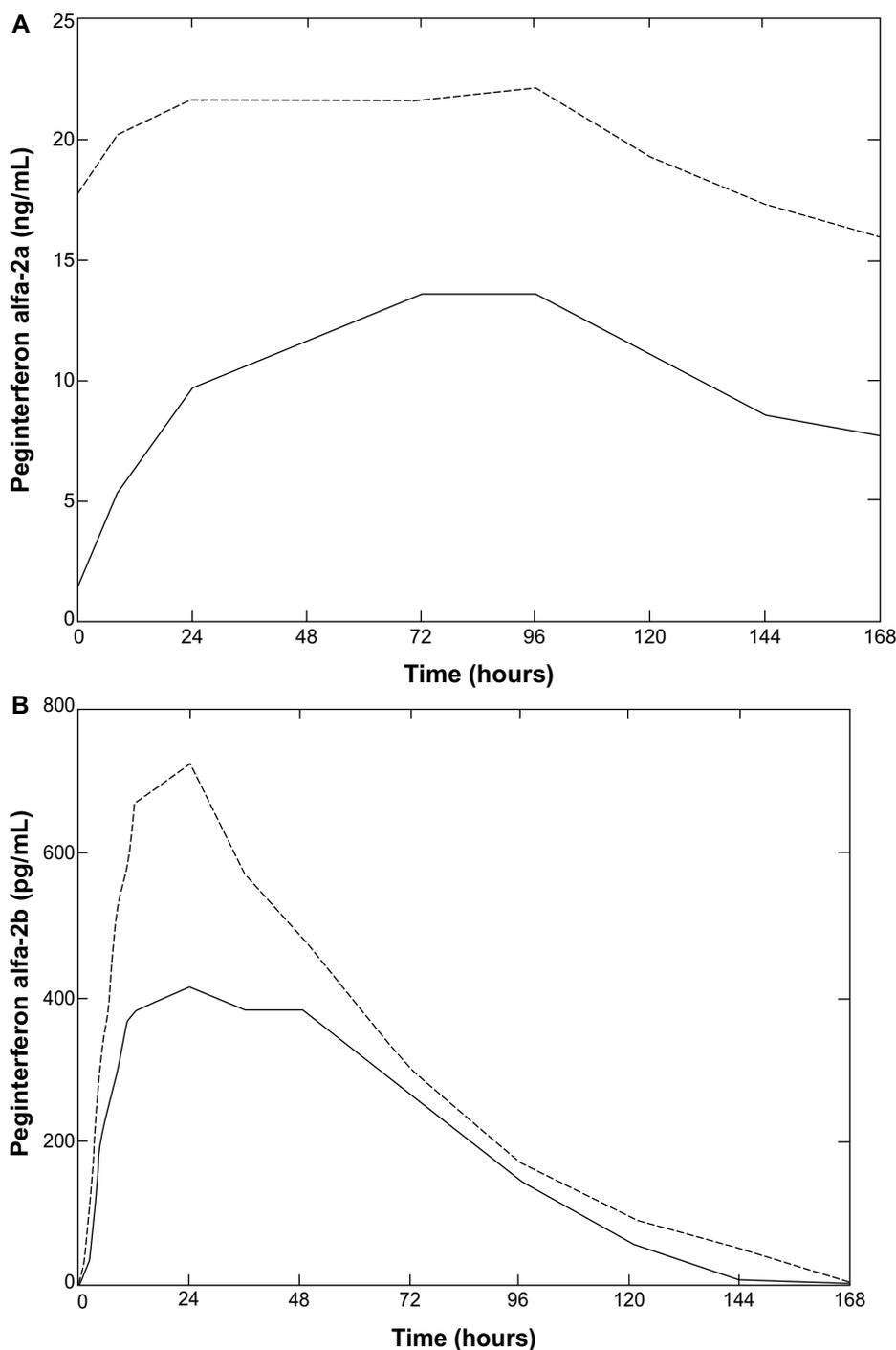
Figure 2 Mean peginterferon α-2a (**A**) or α-2b (**B**) concentration–time profiles.
Notes: Week 1 (solid line) and week 4 (dashed line) were in non-cirrhotic patients with chronic hepatitis C treated with peginterferon α-2a 180 μg per week (adapted from peginterferon α-2a product monograph)[34] or peginterferon α-2b 1.0 μg per kilogram of body weight per week. Data from Glue et al[33] and package inserts.[34,35]

involved in the inhibition of viral function and replication. Serum OAS levels increase rapidly after the administration of conventional IFN α-2a or PEG-IFN α-2a, and the peak OAS levels occur at 24 and 48 hours after the administration. Although the OAS levels decline within 24 hours after IFN α-2a administration, they remain near the peak level for up

to 168 hours after PEG-IFN α-2a administration, which is consistent with the pharmacokinetic profiles as described above.[37] The pharmacodynamics assessment of PEG-IFN α-2b shows dose-related increases of serum neopterin, which is synthesized by macrophages in response to IFN stimulation and serves as a marker for cellular immune

system activation, and non-dose-related increases of serum OAS levels.[33]

Treatment of hepatitis C virus infection
Overview

The goal of treating HCV infection is sustained virologic response (SVR), defined as undetectable serum HCV RNA levels at 12 weeks (SVR_{12}) or 24 weeks (SVR_{24}) after the cessation of therapy.[38,39] The durability of viral response is supported by many observational studies, showing that over 98% of patients who achieve SVR can maintain non-viremic status after long-term post-treatment follow-up, regardless of HCV monoinfection, HBV or HIV coinfection, ALT levels, or patient ancestry.[3,4] Furthermore, patients with SVR are shown to have decreased liver and non-liver related morbidity and mortality.[27,28,40–42] SVR is thus the short-term surrogate marker to predict long-term viral suppression and improved clinical outcome.

The evolution of treatment for chronic HCV infection has greatly improved over the past 20 years (Figure 3). Ever since early 1990 when conventional IFN α monotherapy was used to treat chronic HCV infection with a SVR rate of about 6%–19%, PEG-IFN α in combination with RBV for 24–48 weeks has achieved an overall SVR rate of about 54%–63% across various HCV genotypes.[5–7] The introduction of TVR and BOC, the first-generation DAA in May 2011, in combination with PEG-IFN α and RBV has further improved the SVR rates to 68%–75%.[12–15] The newer generation of DAA, simeprevir or sofosbuvir, in combination with PEG-IFN α and RBV has an overall SVR rate of >80%, and the regimen has recently been approved by the US Food and Drug Administration (FDA) to treat HCV-1 patients in December 2013.[43,44]

Although PEG-IFN α-2a or PEG-IFN α-2b in combination with RBV is effective in treating patients with chronic HCV infection, controversies have been raised with regard to the antiviral responses between the two formulas of PEG-IFN α. Two recent meta-analyses which directly compared the safety and efficacy of PEG-IFN α-2a and PEG-IFN α-2b indicated that compared with patients who received PEG-IFN α-2b plus RBV, those who received PEG-IFN α-2a plus RBV tended to have greater SVR rates. Furthermore, the safety profiles were comparable between the two formulas of PEG-IFN α.[45,46] In Asian patients with chronic HCV infection, Miyase et al also demonstrated that the SVR rate was statistically greater in patients with PEG-IFN α-2a plus RBV therapy than those with PEG-IFN α-2b plus RBV therapy.[47] The more favorable pharmacokinetic profile of PEG-IFN α-2a than that of PEG-IFN α-2b may account for the superior antiviral effects of PEG-IFN α-2a when compared to PEG-IFN α-2b.

Combination therapy of peginterferon α and ribavirin in Asian patients with chronic HCV infection
HCV genotype 1 infection

In Western patients with HCV-1 infection, the overall SVR rates were far from satisfactory, ranging from 39%–52% by 48 weeks of PEG-IFN α-2a plus weight-based RBV (daily 1,000 mg for patients with body weight <75 kg; daily 1,200 mg for patients with body weight ≥75 kg).[5–7,48] However, the SVR rates of Asian HCV-1 patients receiving 48 weeks of PEG-IFN α-2a plus weight-based RBV were higher than those of Western patients.[49–55] Two studies enrolling East Asian HCV-1 patients in Taiwan indicated that combination
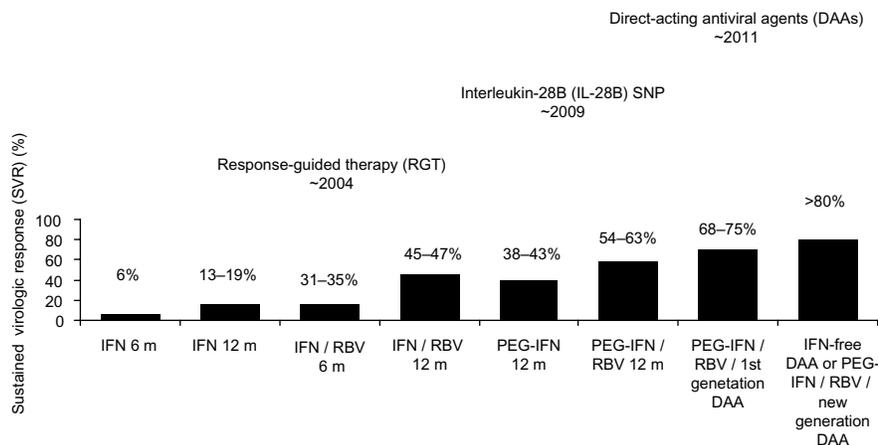

Figure 3 Milestones of therapy for chronic HCV infection.
Abbreviations: HCV, hepatitis C virus; PEG-IFN, peginterferon alfa; IFN, interferon alfa; SNP, single nucleotide polymorphism; RBV, ribavirin; m, months.

therapy with PEG-IFN α-2a plus RBV for 48 and 24 weeks had SVR rates of 76%–79% and 56%–59%, respectively.[53,54] With regard to PEG-IFN α-2b plus weight-based RBV for Asian HCV-1 patients, the SVR rates of 48 weeks of treatment were 44%–51%, which was similar to the response rates for Western HCV-1 patients.[47,56,57] One study in the US which enrolled HCV patients from different ethnic groups (Asian, White, Hispanic, and African-American) confirmed that Asian HCV-1 patients had the highest response rates to IFN-based therapy (Table 4).[58]

Table 4 Treatment responses to peginterferon α plus ribavirin in Asian patients with chronic HCV infection

HCV genotype	Peginterferon	Treatment duration (weeks)	Country	Year	Patient number	Authors	SVR rate	Reference
1	α-2a	48	People's Republic of China	2007	41	Yu et al	44	49
	α-2a	48	Japan	2007	201	Kuboki et al	61	50
	α-2a	48	Japan	2007	100	Kuboki et al	54[a]	50
	α-2a	48	Japan	2012	101	Miyase et al	65	47
	α-2a	48	Korea	2006	29	Lee et al	55	51
	α-2a or α-2b	48	Korea	2012	461	Park et al	54	52
	α-2a	48	Taiwan	2008	100	Yu et al	79	53
	α-2a	48	Taiwan	2008	154	Liu et al	76	54
	α-2a	48	Taiwan	2009	110	Liu et al	77	55
	α-2a	24	Taiwan	2008	100	Yu et al	59	53
	α-2a	24	Taiwan	2008	154	Liu et al	56	54
	α-2b	48	Japan	2008	120	Kogure et al	51	56
	α-2b	48	Japan	2011	87	Hashimoto et al	44[b]	57
	α-2b	48	Japan	2012	100	Miyase et al	51	47
2/3	α-2a	24	People's Republic of China	2007	61	Yu et al	75	49
	α-2a	24	Korea	2006	46	Lee et al	80	51
	α-2a or α-2b	24	Korea	2012	283	Park et al	71	52
	α-2a	24	Taiwan	2009	50	Liu et al	84	55
	α-2a	24	Taiwan	2008	100	Yu et al	95	59
	α-2a	16	Taiwan	2008	50	Yu et al	94	59
	α-2b	16	Japan	2011	21	Kanda et al	67	60
	α-2b	24	Japan	2011	97	Kanda et al	87	60
	α-2b	48	Japan	2011	20	Kanda et al	80	60
	α-2b	24	Japan	2012	151	Sato et al	78	61
	α-2b	24	Japan	2012	118	Kagawa et al	75	62
4	α-2a	48	Kuwait	2009	30	Varghese et al	63	63
	α-2a	48	Qatar	2008	84	Derbala et al	68	64
	α-2b	48	Saudi Arabia	2003	180	Shobokshi et al	50	65
	α-2b	48	Saudi Arabia	2004	48	Alfaleh et al	44[c]	66
	α-2b	48	Kuwait	2004	66	Hasan et al	45	67
6	α-2a or α-2b	24	People's Republic of China	2011	22	Zhou et al	82[d]	68
	α-2a	48	Hong Kong	2008	21	Fung et al	86	69
	α-2a or α-2b	48	Hong Kong	2013	60	Seto et al	70[d]	70
	α-2a	24	Thailand	2012	25	Tangkijvanich et al	88[e]	71
	α-2a	48	Thailand	2012	9	Tangkijvanich et al	44[e]	71
	α-2a	24	USA	2010	27	Lam et al	70[f]	72
	α-2a	48	USA	2010	33	Lam et al	79[f]	72
	α-2a	24	Vietnam	2012	35	Thu Thuy et al	60	73
	α-2a	48	Vietnam	2012	70	Thu Thuy et al	71	73

Notes: [a]Enrolling non-responders or relapsers to previous treatment; [b]enrolling patients receiving full dose of therapy and without premature treatment discontinuation; [c]enrolling patients receiving flat dose ribavirin (800 mg/day); [d]86% and 72% of the patients received PEG-IFN α-2a plus RBV by Zhou et al and Seto et al, respectively; [e]24 weeks of treatment for patients who achieved RVR; 48 weeks of treatment for patients who failed to achieve RVR; [f]enrolling Southeast Asians in CA, USA and TX, USA.
Abbreviations: HCV, hepatitis C virus; SVR, sustained viral response; RVR, rapid virologic response.

HCV genotype 2/3 infection

In contrast to HCV-1 patients, where racial differences may affect the SVR rates to combination therapy, the overall SVR rates in HCV-2/3 patients who received PEG-IFN α-2a or PEG-IFN α-2b plus flat-dose RBV (daily 800 mg) for 24 weeks were similar in different ethnic groups (Western versus [vs] Asian patients: 70%–82% vs 71%–95%).[5–7,48,49,51,52,55,59–62] In East Asian HCV-2 patients treated with PEG-IFN α-2a plus weight-based RBV, the SVR rates were comparable for those receiving 24 or 16 weeks of treatment (95% vs 94%, respectively).[59]

HCV genotype 4 infection

Three studies are available with regard to the efficacy of PEG-IFN α-2a plus RBV for 48 weeks in Southwest Asian HCV-4 patients.[63–65] The overall SVR rate was 50%–68%, which was higher than that for HCV-4 patients receiving PEG-IFN α-2b plus RBV (44%–45%).[66,67]

HCV genotype 6 infection

Several studies have indicated that the SVR rates in HCV-6 patients receiving 48 weeks of PEG-IFN α-2a or PEG-IFN α-2b plus weight-based RBV were superior to those in HCV-1 patients receiving the same treatment regimen. The SVR rates were 70%–86% and 60%–82% for HCV-6 patients with 48 and 24 weeks of treatment, respectively.[68–73] Two randomized studies for Southeast Asian HCV-6 patients indicated that 24 weeks of treatment can achieve comparable response rates to 48 weeks of treatment.[72,73]

Response-guided therapy for Asian patients with chronic HCV infection

In early 2000, the HCV viral kinetic models found for PEG-IFN α-based therapy showed two phases of early viral decline: the first phase has a rapid viral decline within the first 48 hours, indicating an effect of the direct inhibition of viral replication; the second phase has a slower viral decline after 48 hours, indicating the elimination of the infected virus in hepatocytes.[74] Patients with good viral declines at both phases are rapid responders; those with good first phase but with poor second phase declines are slow responders; those with poor or no viral declines at both phases are null responders. Numerous studies in the following 5–10 years have confirmed that the measurements of serum HCV viral load during the first 12 weeks of treatment may help determine the optimized treatment duration in HCV-infected patients receiving PEG-IFN α-based therapy. The notion of response-guided therapy (RGT) for HCV infection is based on the dogma that the more rapidly the viral load declines, the shorter the duration of treatment can be.

The viral responses during the 12 weeks of treatment are defined and the clinical implications of early viral responses are described in the next sections "Rapid virologic response", "Week 8 virologic response", and "Early virologic response".[8,38]

Rapid virologic response

Rapid virologic response (RVR), which is the key determinant for SVR, is defined as undetectable serum HCV RNA level at week 4 of treatment. Patients who achieved RVR had high SVR rate (88%–100%) by PEG-IFN α-2a plus RBV therapy across various HCV genotypes.[75] Baseline factors predictive of RVR included HCV genotype, age, viral load, ALT levels, and hepatic fibrosis. The RVR rates in patients with HCV genotypes 1, 2, 3, and 4 receiving PEG-IFN α-2a plus RBV were 16%, 71%, 60%, and 38% in the large international trials.[6,7,76] Furthermore, RVR outweighed other baseline factors to predict SVR. Therefore, patients with HCV-2/3 infection can have greater SVR rates than those with HCV-1/4 infection.

Although the standard duration of PEG-IFN α plus RBV therapy was 48 weeks for HCV-1 patients, two meta-analysis studies indicated that patients with low baseline viral load (HCV viral load <400,000 IU/mL) and with RVR had comparable SVR rates by 24 or 48 weeks of PEG-IFN α plus RBV therapy.[9,77] In East Asian HCV-1 patients who achieved RVR, two independent studies indicated that the SVR rate for 24 weeks of PEG-IFN α-2a plus RBV therapy is similar to 48 weeks of combination therapy in HCV-1 patients with baseline viral load <400,000 IU/mL (94%–96% vs 100%, respectively).[53,54] In contrast, patients who failed to achieve RVR or patients who achieved RVR but had high viral load (>400,000–800,000 IU/mL) should receive 48 weeks of therapy to secure the SVR rates.[53,54]

In HCV-2/3 patients who achieved RVR after PEG-IFN α plus RBV therapy, a meta-analysis study indicated that treatment for 24 weeks achieved greater SVR rates than treatment for 12–16 weeks.[9] However, the overall SVR rates were similar in these patients if they received PEG-IFN α plus weight-based RBV therapy. Compared with HCV-3 patients, the beneficial effects of 24 weeks over 12–16 weeks of treatment were limited in HCV-2 patients.[9] In East Asian HCV-2 patients who achieved RVR, Yu et al showed that the SVR rates were 98%–100% if they received PEG-IFN α-2a plus weight-based RBV therapy for 16–24 weeks.[59] In addition, Sato et al showed that the SVR rates were 94% and

93% if East Asian HCV-2 patients achieved super-rapid virologic response (defined as undetectable HCV RNA at week 2 of treatment) and RVR by PEG-IFN α-2b plus weight-based RBV therapy for 12 and 24 weeks, respectively.[61]

In HCV-4 patients who achieved RVR after PEG-IFN α plus RBV therapy, the international expert panel from the European Association for the Study of Liver Diseases (EASL) recommends that patients can receive 24 weeks of PEG-IFN α plus weight-based RBV therapy only if they do not have poor response predictors (high baseline viral load >800,000 IU/mL, advanced hepatic fibrosis, and high basal insulin resistance).[78] In contrast, patients who achieve RVR but have poor predictors of response should receive 48 weeks of treatment.

In Southeast Asian HCV-6 patients, PEG-IFN α-2a plus weight-based RBV for 24 weeks achieved a comparable SVR rate to 48-week treatment if they achieved RVR (75% vs 85%, respectively).[73]

Week 8 virologic response

Week 8 virologic response (Wk-8R) is defined as undetectable serum HCV RNA level at week 8 of treatment in the absence of RVR. Mangia et al conducted individualized treatment for HCV-1 patients who received 24, 48, or 72 weeks of PEG-IFN α-2a or PEG-IFN α-2b plus weight-based RBV if the serum HCV RNA level first became undetectable at weeks 4, 8, or 12 weeks of treatment, taking the standard 48 weeks of combination as the control group.[79] The SVR rates were similar in patients who achieved Wk-8R and those with a standard duration of treatment (72% vs 70%, respectively). In contrast, for patients who failed to achieve Wk-8R but who achieved first undetectable HCV RNA level at week 12 of treatment, treatment for 72 weeks showed a superior response to treatment for 48 weeks (63% vs 38%, respectively). Liu et al conducted a randomized trial to compare the efficacy of 48 and 72 weeks of PEG-IFN α-2a plus weight-based RBV in East Asian HCV-1 patients. In patients who achieved Wk-8R, the SVR rates were similar for those receiving treatment for 72 and 48 weeks (84% vs 85%, respectively); patients who failed to achieve Wk-8R, extending the treatment duration of therapy to 72 weeks, had greater SVR rates than at 48 weeks of treatment (50% vs 26%, respectively).[80]

Early virologic response

Early virologic response (EVR) is defined as ≥2-log reduction of serum HCV RNA from baseline to week 12 of treatment. In patients who achieve EVR, the viral responses are further classified into complete early virologic response

(cEVR), which is defined as undetectable serum HCV RNA at week 12 of treatment in the absence of RVR, and partial early virologic response (pEVR), which is defined as detectable viremia at week 12 but ≥2-log reduction of serum HCV RNA from baseline to week 12 of treatment in the absence of RVR.[8,38,81]

The absence of EVR is a robust negative predictor of non-response to IFN-based therapy. Data from a large-scale international trial in HCV patients with genotypes 1–4 infection receiving PEG-IFN α-2a plus RBV therapy showed that as low a percentage as 3% of patients who failed to achieve EVR achieved SVR. Because of the low chance of viral response, non-EVR patients should discontinue treatment beyond week 12.[6] None of the East Asian HCV-1 patients achieved SVR by 24 or 48 weeks of PEG-IFN α-2a plus RBV therapy if they did not have EVR.[54] The utility of EVR is relatively less helpful in HCV-2/3 patients because few patients fail to clear the virus at week 12 of treatment.

Two meta-analyses showed that extending treatment duration from 48 weeks to 72 weeks could improve the SVR rates in HCV-1 patients who have slow responses to PEG-IFN α plus RBV therapy.[9,82] The beneficial effect of extending treatment duration is maintained, regardless of the use of weight-based or flat-dose RBV. Among HCV-1 patients with cEVR, there were no differences in terms of SVR rate for patients receiving 48 or 72 weeks of therapy.[9] Liu et al further examined Wk-8R in East Asian HCV-1 patients who achieved cEVR, and found that if these patients achieved Wk-8R, extending treatment duration to 72 weeks did not offer any beneficial effect on the SVR rate over 48 weeks of therapy (84% vs 85%, respectively). However, treatment for 72 weeks had a greater SVR rate than treatment for 48 weeks if these cEVR patients failed to achieve Wk-8R (50% vs 26%, respectively).[80] For patients with pEVR, the SVR rates for 72 and 48 weeks of treatment were 26% and 17%, respectively.[80]

Until now, limited data are available with regard to the optimized treatment duration in HCV-2/3 patients with slow viral responses to PEG-IFN α plus RBV therapy. Cheinquer et al randomly assigned Western HCV-2/3 patients who failed to achieve RVR but who achieved cEVR or pEVR to receive PEG-IFN α-2a plus RBV therapy for 48 or 72 weeks.[83] The SVR rates of 72 and 48 weeks of treatment were similar by intention-to-treat (ITT) and per-protocol (PP) analyses (61% vs 52%; 63% vs 52%, respectively). However, the SVR rate was improved if patients completed the extended duration of therapy (73% vs 54%, respectively, *P*=0.02). In Asian HCV-2/3 patients who failed to achieve RVR, Sato et al showed that PEG-IFN α-2b plus RBV therapy for 48 weeks

had higher SVR rates than treatment for 24 weeks (77% vs 51% , respectively).[61]

The RGT for HCV-4 patients with slow viral responses was similar to that for HCV-1 patients.[78] Limited data are available for Asian HCV-4 slow responders.

One study for Southeast Asian HCV-6 patients with cEVR or pEVR showed that these patients had poor responses to 24 or 48 weeks of PEG-IFN α-2a plus RBV therapy (0% vs 8%, respectively).[73]

Impact of interleukin-28B genotype on viral responses in Asian HCV patients receiving peginterferon α and RBV therapy

The racial factors affecting the treatment responses in HCV-1 patients remained elusive until four independent genome-wide association studies from America, Europe, and Japan reported that the single nucleotide polymorphisms at the loci of rs12979860 and rs8099917 near the IL-28 gene strongly predicted the SVR rates in HCV-1 patients receiving PEG-IFN α plus RBV therapy in 2009–2010.[84–87] Patients with a favorable IL-28B genotype (rs12979860 CC or rs8099917 TT) had significantly higher SVR rates than those with unfavorable IL-28B genotypes (rs12979860 CT/TT or rs8099917 GT/GG) by PEG-IFN alfa plus RBV therapy. In the 5 years after the publication of these landmark articles, hundreds of studies have further examined the role of IL-28B genotyping in the treatment responses across various HCV genotypes.

Recent meta-analysis studies indicated that IL-28B genotypes strongly affect the SVR rates in HCV-1/4 patients, but only marginally affect the SVR rates in HCV-2/3 patients receiving PEG-IFN α plus RBV therapy.[88–90] Among HCV-1 patients, IL-28B genotypes are highly associated with SVR rates, regardless of ethnicity or HIV coinfection.[88,89] The allele frequencies of IL-28B (rs12979860 C/T or rs8099917 T/G) vary in different ethnicity. The Asian population have the greatest frequency of the favorable IL-28B allele (rs12979860 C/T or rs809917 T/G =0.92/0.08), followed by the European–American population (rs8099917 T/G =0.83/0.17), the Hispanic population (rs12979860 C/T =0.56/0.44; rs8099917 T/G =0.69/0.31), and the African population (rs8099917 C/T =0.40/0.60; rs8099917 T/G =0.93/0.07).[91,92] Furthermore, IL-28B genotypes are associated with the RVR rates in HCV-infected patients, especially in those with HCV-1 infection.[78,80,91,93–97] Because the favorable IL-28 genotype highly predicts RVR and SVR in HCV-1 patients, Asian HCV-1 patients, who carry the highest frequency of the favorable IL-28B genotype, have greater SVR rates than HCV-1 patients of other ethnicities.

Based on the important role of IL-28B genotyping in the treatment responses to PEG-IFN α plus RBV therapy, the interplay of early viral kinetics and IL-28B genotypes on SVR rates was further examined. Thompson et al evaluated the effect of RVR and IL-28B genotypes from a large-scale international trial in HCV-1 patients receiving 48 weeks of PEG-IFN α plus RBV therapy. In patients who achieved RVR, the IL-28B genotypes did not predict the SVR rates; in patients who failed to achieve RVR, the SVR rates were greater in those with a favorable IL-28B genotype than those with unfavorable IL-28B genotypes.[93]

In East Asian HCV-1 patients who received 24 weeks of PEG-IFN α-2a plus RBV therapy, the IL-28B genotypes played a minor role to affect the overall SVR rates if they achieved RVR.[80,94,95] In line with the report by Thompson et al, IL-28B genotypes strongly affected the SVR rates in East Asian HCV-1 patients if they failed to achieve RVR.[96,98] However, the role of IL-28B genotypes was limited in East Asian HCV-1 patients who failed to achieve RVR if Wk-8R was taken into consideration.[80] In Asian HCV-1 patients who relapsed to 24 weeks of PEG-IFN α-2a plus RBV therapy, patients with a favorable IL-28B genotype achieved greater SVR rates than those with unfavorable genotypes by 48 weeks of retreatment (67% vs 14%, respectively).[99] With regard to the determination of the early stopping rule at week 4 of treatment in Asian HCV-1 non-responders, Yu et al and Huang et al evaluated patients receiving PEG-IFN α-2a plus RBV therapy for 48 weeks. In patients with HCV RNA >10,000 IU/mL or <3 log HCV viral decline at week 4 of treatment, patients with unfavorable IL-28B genotypes had low SVR rates (0%–18%) and should stop further treatment beyond week 4.[100,101]

In the era of RGT, the role of IL-28B genotypes in HCV-2/3 patients treated with PEG-IFN α plus RBV therapy has been evaluated in three independent studies from Europe and Asia.[97,102,103] All HCV-2/3 patients who achieved RVR had similar SVR rates, regardless of IL-28B genotypes or the duration of therapy. However, there were controversies with regard to the role of IL-28B genotypes on the SVR rates in HCV-2/3 patients who failed to achieve RVR. Furthermore, IL-28B genotypes played no role to predict SVR in East Asian HCV-2 relapsers or non-responders who received 48 weeks of retreatment with PEG-IFN α-2a plus RBV.[104]

In line with HCV-1 patients, the role of IL-28B genotypes in HCV-4 patients who received PEG-IFN α plus RBV by RGT

was limited, and may not select patients with the abbreviated duration of therapy.[105] The role of IL-28B genotypes in the treatment of Asian HCV-4 patients remains largely unclear.

In Southeast Asian HCV-6 patients, a recent report evaluated the role of IL-28B in 60 patients treated with PEG-IFN α plus RBV therapy for 48 weeks. Compared with patients with unfavorable IL-28B genotypes, those with a favorable IL-28B genotype had greater SVR rates (96% vs 63%, respectively). Data are scarce on the role of IL-28 genotypes with regard to RGT in HCV-6 patients.[70]

BOC or TVR-based triple therapy in Asian patients with chronic HCV infection

In May 2011, two first-generation DAAs (BOC and TVR), which target the HCV NS3/4A serine protease, in combination with PEG-IFN α plus weight-based RBV were approved for use in treatment-naïve and treatment-experienced HCV-1 patients. In treatment-naïve HCV-1 patients, the SVR rates of BOC- or TVR-based triple therapy were higher than in PEG-IFN α plus RBV therapy patients (63%–66% vs 38%, respectively for BOC; 69%–76% vs 44%, respectively for TVR).[12,14] In treatment-experienced HCV-1 patients, the SVR rates of BOC- or TVR-based triple therapy were also higher than for PEG-IFN α plus RBV therapy (59%–66% vs 21%, respectively for BOC; 64%–66% vs 17%, respectively for TVR).[13,15]

Although BOC- or TVR-based triple therapy has greatly improved overall SVR rates, data on the efficacy of BOC-based triple therapy in Asian patients are limited (Table 5). Hu et al retrospectively evaluated Asian HCV-1

patients who participated in three Phase II and Phase III BOC-based trials. Compared to patients receiving PEG-IFN α-2b plus RBV for 48 weeks, patients receiving BOC-based triple therapy for 24–48 weeks had a slightly higher SVR rate (79% vs 67%, respectively).[106]

At the time of this writing, almost all studies on TVR-based triple therapy were from Japan, and PEG-IFN α-2b was universally included in their treatment regimens. Data from these studies showed that the SVR rates of TVR-based triple therapy for 12 weeks were only 45% in treatment-naïve patients.[107,108] The SVR rates increased to 70%–82% with an additional 12 weeks of PEG-IFN α plus RBV, except for one small trial[112] enrolling the most difficult-to-treat partial responders and nonresponders, which showed an SVR rate of 27%.[107,109–115]

In line with Western reports, IL-28B genotypes and RVR strongly affected the SVR rates in Asian HCV-1 patients receiving BOC- or TVR-based triple therapy.[107,109,115] Because the numbers of Asian HCV-1 patients who received BOC were low, and no studies were designed for TVR-based RGT in Asian HCV-1 patients, the optimized strategies for shortening treatment duration on the basis of early viral kinetics and IL-28B genotypes have not yet been determined.

Implications of personalizing management of HCV in Asian patients

Epidemiologically, HCV-1 is dominant in most regions of Asia; while HCV-2, 3, 4, and 6 are common in East Asia, South Asia, Southwest Asia, and Southeast Asia, respectively. Currently, PEG-IFN α plus RBV is the SOC for the treatment

Table 5 Treatment responses to boceprevir or telaprevir in combination with peginterferon α plus ribavirin in Asian patients with chronic HCV genotype 1 infection[a]

Protease inhibitor	Peginterferon	Treatment duration (weeks)	Country	Year	Patient number	Authors	SVR rate	Reference
Boceprevir	α-2b	24–48	International	2012	24	Hu et al	79[b]	106
Telaprevir	α-2b	12	Japan	2010	201	Akuta et al	45	107
	α-2b	24	Japan	2010	100	Akuta et al	67	107
	α-2b	12	Japan	2013	20	Suzuki et al	45	108
	α-2b	24	Japan	2011	94	Chayama et al	73	109
	α-2b	24	Japan	2012	126	Kumada et al	73[c]	110
	α-2b	24	Japan	2012	141	Hayashi et al	76[d]	111
	α-2b	24	Japan	2012	15	Akuta et al	27[e]	112
	α-2b	24	Japan	2013	120	Furusyo et al	80	113
	α-2b	24	Japan	2013	102	Ogawa et al	70[f]	114
	α-2b	24	Japan	2013	137	Tsubota et al	82	115

Notes: [a]Telaprevir was administered for 12 weeks; [b]SVR was achieved in 8 of 12 (67%) patients receiving PEG-IFN α-2b plus RBV for 48 weeks; subgroup analysis in Asian HCV-1 patients; [c]SVR was achieved in 31 of 63 (49%) patients receiving PEG-IFN α-2b plus RBV for 48 weeks; [d]SVR was achieved in 96 of 109 (88%) relapsers, and in 11 of 32 (34%) non-responders; [e]eight patients were partial responders and 7 patients were null-responders to previous PEG-IFN plus RBV therapy; [f]patients with advanced hepatic fibrosis or cirrhosis.
Abbreviations: HCV, hepatitis C virus; SVR, sustained viral response; RBV, ribavirin; PEG-IFN, peginterferon.

of patients with all HCV genotypes in most Asian countries. Although BOC- or TVR-based triple therapy has become the SOC for HCV-1 patients since 2011, the recent approval of simeprevir-based and sofosbuvir-based triple therapy may change the landscape of HCV therapy in the coming years. However, few Asian countries have gained access to BOC and TVR. In addition, a recent cost-effectiveness study for BOC and TVR-based triple therapy indicated that such treatments would only be cost-effective in patients with advanced hepatic fibrosis who received IL-28B guided therapy.[116]

Asian populations tend to have higher frequencies of favorable IL-28B genotypes than other ancestries. In Asian HCV-1/4/6 patients, those with a favorable IL-28B genotype have higher SVR rates when treated with PEG-IFN α plus RBV. Moreover, Asian HCV-1/4 patients with low baseline viral load can further truncate the treatment duration to 24 weeks without compromising the SVR rate. In Asian HCV-1/4 patients who fail to achieve RVR, Wk-8R and EVR (including cEVR and pEVR), rather than IL-28B genotypes, are the key to determine the optimal treatment duration.

In line with HCV-1 patients, Asian HCV-2/3 patients with a favorable IL-28B genotype also tend to have a higher RVR rate in response to PEG-IFN α plus RBV therapy than those with unfavorable IL-28B genotypes. A truncated duration of PEG-IFN α plus RBV therapy from 24 weeks to 12–16 weeks may be considered in Asian HCV-2 patients with RVR, regardless of IL-28B genotypes. In contrast, Asian HCV-3 patients still require 24 weeks of PEG-IFN α plus RBV therapy even if they achieve RVR. Although existing evidence is limited, HCV-2/3 patients who fail to achieve RVR may extend the treatment duration to 48 weeks if they have unfavorable IL-28B genotypes.

In HCV-1 patients who have unfavorable factors to achieve RVR and SVR, including advanced hepatic fibrosis or cirrhosis, unfavorable IL-28B genotypes, high pretreatment viral load, or previous non-response to PEG-IFN α plus RBV therapy, the health care providers should allocate these patients to receive BOC or TVR-based triple therapy or novel DAA therapies on a case-by-case basis according to the anticipated RVR rate, SVR rate, patient tolerance, treatment duration, financial burdens, and drug accessibility.

Peginterferon α with or without RBV therapy in a special population of Asian patients with chronic HCV infection

In addition to ordinary patients with HCV infection, patients with HBV co-infection and patients with end-stage renal

diseases are also at high risk of HCV infection. This is of particular importance because Asian people have high prevalence rates of HBV infection and end-stage renal disease (Table 6).

The long-term prognosis of patients with HBV and HCV co-infection is inferior to those with HBV or HCV mono-infection.[21,117] However, data on the efficacy of PEG-IFN α plus RBV on HCV treatment in HBV and HCV co-infected patients were limited in Asian patients. Liu et al evaluated the efficacy of SVR rates in HBV/HCV dually infected East Asian patients with HCV-1 or HCV-2/3 who received 48 and 24 weeks of PEG-IFN α-2a plus RBV therapy, taking HCV-1 or HCV-2/3 mono-infected patients as the reference controls. The overall SVR rates in HCV-1 and HCV-2/3 patients were 72% and 83% in dually infected patients, respectively, and were comparable to mono-infected patients (77% and 84%), suggesting that dually infected patients can be treated as effectively as HCV mono-infected patients.[55] Because PEG-IFN α-2a is also effective in the treatment of HBV infection, dually infected patients also had improved HBV seroclearance after long-term follow-up. In addition, the HCV viral clearance was durable in these patients who achieved SVR.[3]

Because of high rates of nosocomial transmission, patients with end-stage renal disease who are on maintenance dialysis are at an increased risk of HCV infection. The natural history of HCV-infected dialysis patients showed that their long-term prognosis was worse than non-HCV-infected dialysis patients. It is estimated that the prevalence rate of HCV infection in dialysis patients is about ten times that in the general population. Therefore, the treatment of HCV infection in this special population is important, and it is relevant in Asian patients where the prevalence rates of end-stage renal disease are high.[118] Diabetes, hypertension, hyperlipidemia, cardiovascular disease, obesity, smoking, and probably the use of herbal medicines are attributed to the development of end-stage renal disease. Based on the pharmacokinetics studies, the optimal dose of PEG-IFN α-2a and PEG-IFN α-2b for patients with end-stage renal disease who are on hemodialysis is 135 µg per week and 0.75–1.0 µg per kilogram of body weight per week, respectively.[36,119]

Many Asian experts treated dialysis patients with HCV infection by using PEG-IFN α-2a or PEG-IFN α-2b monotherapy for 24–48 weeks.[120–129] However, the SVR rates varied widely (from 0%–100%) because of small sample size, heterogeneous population, and divergent regimens. Recently, two large-scale trials evaluated East Asian HCV-1 and HCV-2 hemodialysis patients receiving PEG-IFN α-2a for 48 and 24 weeks, and the SVR rates

Table 6 Treatment responses to peginterferon α with or without ribavirin in special Asian populations with chronic HCV infection

Patient group	HCV genotype	Peginterferon	Ribavirin (mg/day)	Treatment duration (weeks)	Country	Year	Patient number	Authors	SVR rate	Reference
HBV co-infection	1	α-2a	1,000–1,200	48	Taiwan	2009	97	Liu et al	72	54
	2/3	α-2a	800	24	Taiwan	2009	64	Liu et al	83	54
End-stage renal disease[a]	1	α-2a	0	48	Hong Kong	2007	2	Chan et al	50	120
	2	α-2a	0	48	Hong Kong	2007	3	Chan et al	0	120
	3	α-2a	0	48	Hong Kong	2007	1	Chan et al	100	120
	1	α-2a	0	10–48	Japan	2013	8	Kojima et al	13	121
	2	α-2a	0	4–48	Japan	2013	10	Kojima et al	50	121
	1	α-2a	0	48	Saudi Arabia	2011	4	Alsaran et al	50	122
	4	α-2a	0	48	Saudi Arabia	2011	9	Alsaran et al	89	122
	1	α-2a	0	48	Turkey	2006	12	Kokoglu et al	75	123
	1	α-2a	0	48	Turkey	2008	22	Ayaz et al	65[b]	124
	1	α-2a	0	48	Turkey	2009	33	Kose et al	46	125
	1	α-2a	0	24	Taiwan	2008	20	Liu et al	45	126
	2	α-2a	0	24	Taiwan	2008	5	Liu et al	60	126
	1/2	α-2a	0	24	Taiwan	2010	35	Liu et al	89[c]	127
	1	α-2b[d]	0	48	Malaysia	2010	24	Tan et al	38	128
	3	α-2b[d]	0	24	Malaysia	2010	10	Tan et al	80	128
	1/2	α-2b[e]	0	24 or 48	Taiwan	2013	26	Tseng et al	27	129
	1	α-2a	0	48	Taiwan	2013	102	Liu et al	33	130
	2	α-2a	0	24	Taiwan	2013	86	Liu et al	44	131
	1	α-2a	200	48	Taiwan	2013	103	Liu et al	64	130
	2	α-2a	200	24	Taiwan	2013	86	Liu et al	74	131
	1/2	α-2b[e]	100[f]	24 or 48	Taiwan	2013	26	Tseng et al	62	129
	1	α-2a	200	48	Taiwan	2009	25	Liu et al	52[g]	136
	2	α-2a	200	24	Taiwan	2009	10	Liu et al	80[g]	136

Notes: [a]PEG-IFN α-2a at a dose of 135 μg per week (Kojima et al:[121] dose from 45 μg every 2 weeks to 135 μg per week); PEG-IFN α-2b at a dose of 0.5–1.0 μg per kilogram of body weight per week; [b]three patients were non-HCV 1 infection; [c]enrolling end-stage renal disease with acute HCV infection; [d]escalating dose of PEG-IFN α-2b from 0.5 to 1.0 g per kilogram of body weight per week; [e]PEG-IFN α-2b at a dose of 1.0 g per kilogram of body weight per week; [f]RBV at a dose of 200 mg three times per week; [g]enrolling relapsers to IFN α-2a or PEG-IFN α-2a monotherapy.
Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; SVR, sustained viral response.

were 34% and 44%, respectively, which was similar to the results from the meta-analysis.[130–133] RBV has been considered contraindicated for treating dialysis patients because of concerns of life-threatening hemolytic anemia. However, the pharmacokinetics study of RBV in hemodialysis patients showed that the daily dose of 200 mg may be suitable for these patients.[134,135] Liu et al further evaluated PEG-IFN α-2a at a dose of 135 μg per week plus RBV at a dose of 200 mg per day for 48 and 24 weeks in treatment-naïve and -experienced East Asian HCV-1 and HCV-2 patients on hemodialysis.[130,131,136] The SVR rates for treatment-naïve HCV-1 and HCV-2 patients were 64% and 74%, respectively; those for treatment-experienced HCV-1 and HCV-2 patients were 52% and 80%, respectively. Furthermore, Tseng et al evaluated PEG-IFN α-2b at a dose of 1.0 μg per kg of body weight per week plus RBV at a dose of 200 mg three times per week for 48 and 24 weeks in treatment-naïve East Asian HCV-1 and non-HCV-1 patients on hemodialysis, and the overall SVR rate was 62%.[129] Compared to PEG-IFN α monotherapy, combination therapy had higher SVR rates.

Furthermore, the safety profiles were comparable between monotherapy and combination therapy groups.[129–131] Two recent pilot studies used TVR in combination with PEG-IFN α plus low-dose RBV to treat Western HCV-1 patients on hemodialysis, and the SVR rates were superior to those using PEG-IFN α plus low-dose RBV.[137,138] Whether triple therapy or all oral DAA regimen could benefit Asian patients on hemodialysis deserves further investigation.

Conclusion

HCV infection is prevalent in Asia, and the distribution of HCV genotypes varies across different Asian regions. Currently, PEG-IFN α plus RBV therapy remains the SOC in most Asian countries. PEG-IFN α-2a seems to have superior pharmacokinetics profiles to PEG-IFN α-2b, and therefore has better response rates than PEG-IFN α-2b to treat HCV infection. The optimized dose and duration of PEG-IFN α plus RBV therapy for Asian HCV patients should consider HCV genotypes, baseline viral load, and the early viral decline during the first 12 weeks of treatment.

Although IL-28B genotyping is an important baseline predictor of SVR, its role in predicting SVR and determining the optimized treatment duration is less mandatory when on-treatment viral kinetics are taken into consideration. More studies are needed to personalize HCV treatment in Asian patients in terms of the use of IFN-containing triple therapy and IFN-free all oral regimens.

Disclosure

The authors report no conflicts of interest in this work.

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