Chapter 9

Safety, Tolerability, and Associated Side Effects of Direct-Acting Antivirals

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Additional information is available at the end of the chapter

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Abstract

Hepatitis C virus (HCV) infection is one of the major reasons for causing chronic hepatic disease worldwide. Treatment options for patients infected with chronic hepatitis C (CHC) have effectually ameliorated over the last few years. Now, various novel antiviral drugs have been licensed for its treatment. Introduction of direct-acting antivirals (DAAs) for HCV therapy represents a major advancement with regard to sustained virologic response (SVR) rates and associated adverse effect (AEs) profiling. Systematically, DAAs specifically impede different nonstructural proteins of HCV including NS3/4A protease, NS5A protein, and NS5B polymerase. In spite of those DAAs, therapy is confronting multiple challenges such as possible drug-drug interactions and severe side effects including liver failure. This chapter discusses the safety and tolerability of DAAs relevant to associated side effects emphasizing their clinical pharmacology. Considering the increased HCV prevalence rate and interpreting safety data of DAA regimens approved in the USA, Europe, Russia, Australia, and Japan, this chapter also presents the pre- and post-marketing safety data. Eventually, the important safety issues of drug–drug interactions (DDIs) have also been discussed in brief.

Keywords: hepatitis C virus, direct-acting antivirals, safety, tolerability, side effects

1. Introduction

Hepatitis C virus (HCV) infection, one of the major elements of liver disease worldwide [1], can cause both acute and chronic infections. Acute infection may follow an asymptomatic condition as well as self-limited hepatitis. Almost 15–45% of HCV-infected patients impulsively clear out the virus within 24 weeks of infection without getting any treatment. The remaining 55–85% of patients develop chronic infection; out of them 15–30% come across the risk of liver

cirrhosis within 20 years [2, 3]. Hepatitis C infection may cause liver histological changes, pervasive fibrosis, and cirrhosis with or without hepatic carcinoma. Furthermore, HCV infection may be associated with higher risk of cardiovascular disease [4, 5]. Advanced liver disease may lead to liver transplantation worldwide predisposing patients to a wide variety of clinical manifestations, thus progressing to liver-related mortality in due sequel [6]. Viral genome sequences are highly variable. About 11 different genotypes have been discovered so far having 30–50% nucleotide sequence variation; however, six genotypes are more prevalent in different regions. HCV genotype 1 is the most common among them representing 46.2% of all HCV cases followed by genotype 3 (30.1% of all HCV cases). The rest of the genotypes including genotype 2 (9.1% of all HCV cases), genotype 4 (8.3% of all HCV cases), genotype 5 (5.4% of all HCV cases), and genotype 6 (<1% of all HCV cases) are less commonly found globally. All these genotypes also vary for their pathogenicity, virulence, and progression rate to severe clinical manifestations [7]. For example, HCV infection with genotype 1b is related to more aggressive course of hepatic disease while comparing with other genotypes [8]. Liver cirrhotic patients and those having decompensated liver disease requiring liver transplantation have more commonly found genotype 1b infection than patients exhibiting chronically active HCV [9]. However, rapid fibrosis progression is associated with HCV genotype 3 [10]. Furthermore, each genotype responds differently to pharmacological treatment. Higher resistance to interferon therapy was shown in patients having genotypes 1 and 4 than with genotypes 2 and 3 [7].

Chronic HCV treatment is undergoing a continuous dynamic change. Since 1991 interferon-based therapy for chronic hepatitis C (CHC) patients was used as the standard of care (SOC), but therapy had unresponsive cure rate of no more than 6% along with serious side effects that led to the discontinuation of treatment subsequently [11]. In the start of millennium, pegylated interferon (pegIFN) with guanosine analogue, ribavirin (RBV), replaced the standard interferon as a safer and well-tolerated therapy regardless of HCV genotypes [12, 13]. Therapeutic progress was limited due to substantial adverse event (AE) profile and minimal response rates particularly in HCV genotype 1-infected patients [14]. Side effects include bone marrow depression with lower content of granulocytes, neutropenia, and flu-like symptoms. Neuropsychiatric side effects such as irritability, severe fatigue, and apathy are extensive problems for patients and their families if not treated properly on time [15]. Furthermore, autoimmune diseases like rheumatoid arthritis, psoriasis, vitiligo, lichen planus, dermatitis herpetiformis, type 1 diabetes mellitus, and sarcoidosis can be enrooted or intensified during pegIFN therapy [15]. Therefore, therapy is advised with vigilance to patients having autoimmune disease. Thyroid dysfunction and RBV-associated side effects are also linked with pegIFN therapy. The abovementioned side effects, prolonged duration, high cost, and lesser adherence to therapy lead to the discontinuation of treatment.

A new era of HCV therapy was heralded with the emergence and approval of oral direct acting antiviral (DAA) agents. In comparison to nonspecificity of IFN-based therapy, DAAs directly intend to block various proteins involved in HCV replication pathways. Recently, available DAAs inhibit nonstructural proteins including NS3/4A protease, NS5A protein, and NS5B polymerase alone or in combination with other antiviral agents involved in blocking different stages of HCV replication [16]. Four main classes of DAAs used in multiple combinations for HCV treatment are described in **Table 1** [17]. First-generation protease inhibitors, telaprevir® and boceprevir®, were

Classes of DAAs	Target proteins/enzymes	Dose/combination used/year of approval	Targeted genotypes	With or without cirrhosis	Cure rate/course of treatment	Cost of therapy ($)
NS3/NS4A protease inhibitors	NS3/NS4A inhibitors act to block viral protease that help virus in posttranslational processing and HCV replication	1. Glecaprevir (in combination with pibrentasvir) (2016) 2. Simeprevir (2014)	1. All six major genotypes 2. Genotypes 1a/b	1. Without cirrhosis 2. Without cirrhosis	1. 90–100%/8–12 weeks 2. 80–90%/12 weeks	$26,400/ treatment course $66,360/ treatment course
Nucleoside and nucleotide NS5B polymerase inhibitors	These inhibitors directly act to block viral replication by attaching to viral RNA polymerase enzyme	1. Epclusa (sofosbuvir and velpatasvir) (2016) 2. Sofosbuvir (2014)	1. All six major genotypes 2.Genotypes 1–4	1. Both 2. Without cirrhosis	1. 100% (some groups); 94% for decompensated cirrhosis/12 weeks 2. 30 –97%/12–24 weeks	$74,760 $84,000 in the USA
NS5A inhibitors	Block directly NS5A protein which is required for HCV reproduction	1. Zepatier (elbasvir/ grazoprevir) (2016) 2. Daclatasvir (2015) 3. Ombitasvir with paritaprevir and ritonavir (2015) 4. Ledipasvir with sofosbuvir (2014)	1. Genotypes 1 and 4 2. Genotype 3 3. Genotypes 1 and 4 4. Genotype 1	1. Both 2. Both 3. Without cirrhosis 4. Both	1. 94–97% (genotype 1); 97–100% (genotype 4)/12–16 weeks 2. 98% (treatment-naïve) and 58% (treatment experienced patients with cirrhosis)/12 weeks 3. 100% (treatment-naïve)/12 weeks 4. 93–99%/12–24 weeks	$54,600 for 12 weeks $63,000 in the USA $76,653 $94,500; 12 weeks
Non-nucleoside NS5B polymerase inhibitors	They work to block HCV from reproduction by inserting themselves into virus so that other viral pieces cannot attach to it	1. Dasabuvir (in combination with paritaprevir and ombitasvir) (2014)	1. Genotype 1a/1b	1. Both, for compensated cirrhosis (used with RBV)	1. >90%/12–24 weeks	$83,319 in the USA for 12 weeks

Table 1. List of direct acting antivirals (DAAs).

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approved in 2011 by the European Medical Academy (EMA) and Food and Drug Administration (FDA) for the treatment of CHC patients of genotype 1, but due to severe cutaneous AEs including diffuse rash or localized rash with pruritus and skin peeling, therapy was discontinued in 2012 [18, 19]. In 2014, the EMA approved four new polymerase/protease inhibitors (simeprevir®, sofosbuvir®, ledipasvir®, and daclatasvir®) having variable pharmacodynamic characteristics such as simeprevir® which inhibits NS3/4A protease, sofosbuvir® which blocks NS5B polymerase, and ledipasvir® and daclatasvir® which are HCV NS5A inhibitors. The Japanese Ministry of Health, Labor and Welfare approved an NS3/4A protease inhibitor, asunaprevir®, in 2014 for the treatment of genotypes 1 and 4. Combination of asunaprevir® with daclatasvir® is the first oral interferon and RBV-free treatment for CHC patients having genotype 1 infection. This combinatorial treatment is also approved in Australia and Russia. In the following year, the EMA and FDA approved a new combination of drugs ombitasvir®/paritaprevir®/ritonavir®. Among these, ritonavir® is not active against HCV infection; rather, it is a cytochrome P450 3A (CYP3A) inhibitor which increases systemic exposure of paritaprevir® (a CYP3A substrate). Ombitasvir® is an HCV NS5A inhibitor. In the same year, dasabuvir®, NS5B polymerase inhibitor, was also approved by the EMA. Combination of all these drugs with or without RBV can be used for the treatment of HCV genotypes 1a, 1b, and 4 [20]. In January 2016, the FDA approved zepatier® (grazoprevir®/elbasvir®) for marketing. In May 2016, the EMA also recommended the granting of marketing authorizations in the EU for zepatier® treatment [20]. In the same year, epclusa® (combination of sofosbuvir® and velpatasvir®) was approved for the treatment of all six major genotypes. Recently, in July 2017, Vosevi® (combination of sofosbuvir®/velpatasvir®/voxilaprevir®) was approved by the FDA in which each drug acts through a different mechanism [21]. Vosevi® includes combination of NS5B polymerase, NS3/NS4A, and NS5A inhibitors.

2. General safety and tolerability aspects of DAAs

The basic purposes of HCV pharmacological therapy are to eliminate viral infection and to prevent it from causing cirrhosis and associated complications. Alleviative effects of viral pharmacological therapies are estimated through the sustained virological response (SVR) which is defined as a viremia (undetectable HCV RNA in blood) 12 or 24 weeks after completion of anti-HCV therapy. In clinical trials, SVR is commonly used as primary efficacy end point and serves as the only factor linked with liver-associated events and all-cause mortality [22, 23].

2.1. Clinical efficacy and tolerability profile related to DAAs from premarketing studies

Fundamental characteristics of premarketing studies have been enlisted in **Table 2**. Antiviral drug's efficacy and tolerability profile of different DAA combinations are discussed below.

2.1.1. Clinical tolerability analysis of sofosbuvir® treatment in different combinations

Clinical efficacy results of sofosbuvir pivotal studies including NEUTRINO, FISSION, POSITRON, and FUSION trials depicted that the most usual AEs were nausea, headache, fatigue,

and insomnia. In these trials more than 1000 patients of all six major HCV genotypes were treated with sofosbuvir® and RBV or PegIFN and RBV. Mostly, severe AEs were observed in patients treated with PegIFN and RBV as compared to sofosbuvir® [24, 25]. According to safety results of NEUTRINO and FISSION trials, fever, depression, and influenza-like symptoms were more common in PegIFN-treated patients as compared to those who received sofosbuvir®. Lastly, POSITRON safety data illustrated that gastrointestinal disorder, administration site reactions,

Treatment/study group/ year	Population	Adverse event (AE) profile	Overall SVR_{12} rate	Treatment status
SOF/RBV (n = 256) vs. PegIFNα-2a/RBV (n = 243) (2013) [23]	499 genotypes 2/3 HCV patients	More patients treated with PegIFNα-2a/RBV had AEs. Common AEs in patients treated with SOF/RBV and PegIFNα-2a/RBV were fatigue (36 vs. 55%), headache (25 vs. 44%), nausea (18 vs. 29%), insomnia (12 vs. 29%), anemia (8 vs. 12%), influenza-like symptoms (3 vs. 16%), fever (3 vs.18%), and depression (5 vs. 14%)	67%	26 patients treated with PegIFNα-2a/RBV and three patients treated with SOF/RBV discontinued their treatment
SOF/RBV/PegIFNα-2a (2013) [23]	327 genotypes 1, 4, 5, or 6 HCV patients	The most common AEs included fatigue (59%), headache (36%), nausea (34%), insomnia (25%), and anemia (21%)	90%	8 patients
SOF/RBV (n = 207) vs. placebo/RBV (n = 71) (2013) [24]	278 genotype 2 or 3 HCV patients	The most common AEs by SOC in SOF/RBV and RBV/placebo groups were general disorders and administration site reactions (57 vs. 36.6%), gastrointestinal disorders (43.5 vs. 39.4%), nervous system disorders (35.3 vs. 29.6%), musculoskeletal and connective disorders (18.8 vs. 7%), blood and lymphatic system disorders (14%vs.1.4%), complications (9.2 vs. 5.6%),and metabolism and nutrition disorders (7.2 vs. 12.7%)	78%	4 patients who received SOF/RBV and three patients who received placebo (4%)
SOF/RBV for 12 weeks (n = 103) vs. SOF/RBV for 16 weeks (n = 98) (2013) [24]	201 genotype 2 or 3 HCV patients	The most common AEs by SOC in SOF/RBV 12 weeks and SOF/RBV 16 weeks groups were general disorders and administration site reactions (58.3 vs. 60.2%), gastrointestinal disorders (47.6 vs. 46.9%), infections and infestations (31.1 vs. 23.5%), nervous system disorders (36.9 vs. 42.9%), musculoskeletal and connective disorders (28.2 vs. 34.7%), psychiatric disorders (34 vs. 41.8%), and skin and subcutaneous tissue disorders (33 vs. 31.6%)	50%	1 patient in SOF/RBV 12 weeks group

Treatment/study group/ year	Population	Adverse event (AE) profile	Overall SVR_{12} rate	Treatment status
DCV + SOF ± RBV for 12 weeks (n = 103) vs. 24 weeks (n = 302) (2017) [25]	617 HIV-/HCV-coinfected patients with genotype 1, 3, and 4	Common AEs associated with DCV + SOF ± RBV were decompensated cirrhosis/multi-organ failure, respiratory disorder, hepatic carcinoma, lymphopenia, and renal insufficiency	Overall 92%	7 patients discontinued
LDV/SOF for 12 weeks (n = 109) vs. LDV/SOF/RBV for 12 weeks (n = 111) vs. LDV/SOF for 24 weeks (n = 109) vs. LDV/SOF/RBV for 24 weeks (n = 111) (2014) [26]	440 genotype 1 HCV patients (20% with cirrhosis)	Six percent of patients in LDV/SOF for 24 weeks and 3% LDV/SOF/RBV for 24 weeks had a serious of AEs (P = 0.36) More patients in RBV groups had fatigue, nausea, insomnia, arthralgia, cough, rash, irritability, dyspnea, and anemia. Grade 1 or 2 hyperbilirubinemia occurred in more patients who received LDV/SOF/RBV for 12 and 24 weeks compared to patients who received LDV/SOF for 12 and 24 weeks (32 and 41% vs. 1 and 7%, respectively)	>90%	No AEs leading to treatment discontinuation
LDV/SOF for 8 weeks (n = 215) vs. LDV/SOF/RBV for 8 weeks (n = 216) vs. LDV/SOF for 12 weeks (n = 216) (2014) [27]	647 previously untreated patients with HCV genotype 1 infection	The most common AEs in LDV/SOF for 8 weeks, LDV/SOF/RBV for 8 weeks, and LDV/SOF for 12 weeks groups were fatigue (21 vs. 35 vs. 23%), headache (14 vs. 25 vs. 15%), nausea (7 vs. 18 vs. 11%), and insomnia (5 vs. 12 vs. 7%) Fatigue, headache, nausea, insomnia, irritability, rash, pruritus, cough, and anemia were more common in patients treated with RBV Three patients in the group LDV/SOF/RBV for 8 weeks had grade 3 hyperbilirubinemia	93–95%	1 patient in LDV/SOF/RBV for 8 weeks and two patients in LDV/SOF for 12 weeks
DCV/SOF for 23 weeks (groups A and B; n = 31) vs. DCV/SOF for 24 weeks (groups C and D; n = 28) vs. DCV/SOF/RBV for 24 weeks (groups E and F; n = 29) DCV/SOF, with or without RBV, for 12 weeks (group G; n = 41 or group H; n = 41) or 24 weeks (41 patients who did not have a response to prior treatment with HCV protease inhibitors, (n = 21) or J (n = 20) (2014) [28]	211 genotypes 1–3 HCV patients	Common AEs occurred in groups A and B; C and D; E and F; and G, H, I, and J were fatigue (29 vs. 50 vs. 31 vs. 39 vs. 37 vs. 29 vs. 45%), headache (16 vs. 29 vs. 38 vs. 34 vs. 22 vs. 33 vs. 35%), and nausea (16 vs. 32 vs. 31 vs. 20 vs. 20 vs. 10%)	>90%	1 patient in groups C and D (DCV/SOF) and one patient in groups E and F (DCV/SOF/RBV) discontinued the treatment

Treatment/study group/ year	Population	Adverse event (AE) profile	Overall SVR_{12} rate	Treatment status
DCV 20 mg/PegIFN/RBV (n = 159) vs. DCV 60 mg/ PegIFN/RBV (n = 158) vs. placebo/PegIFN/RBV (n = 78) (2015) [29]	395 treatment-naïve patients with HCV genotype 1 or 4	A higher percentage of patients in placebo/PegIFN/RBV group had treatment failure compared to patients in DCV 20 mg or 60 mg groups (62.5 vs. 40.4 vs. 40.8%) Among the most common AEs in DCV 20, 60 mg, and placebo group, there were fatigue (55.3 vs. 54.4 vs. 59%), headache (42.8 vs. 43 vs. 46.2%), pruritus (35.2 vs. 39.9 vs. 33.3%), insomnia (30.8 vs. 33.5 vs. 38.5%), and rash (34 vs. 25.3 vs. 32.1%)	>90%	7 patients in DCV 20 mg group, seven patients in DCV 60 mg group, and eight patients in placebo group
DCV/SOF/RBV for 12 (n = 24) or 16 weeks (n = 26) (2016) [30]	50 treatment-naïve (n = 13) or treatment-experienced (n = 37) genotype 3 patients with advanced fibrosis (n = 14) or compensated cirrhosis (n = 36)	The most common AEs occurring in at least 10% of patients in DCV/SOF/RBV for 12 weeks or 16 weeks groups were insomnia (33.3 vs. 26.9%), fatigue (25 vs. 26.9%), headache (29.2 vs. 19.2%), irritability (20.8 vs. 7.7%), asthenia (8.3 vs. 19.2%), and diarrhea (4.2 vs.15.4%)	Overall 90%	No AEs leading to treatment discontinuation
SMV/PegIFN/RBV (n = 260) vs. placebo/ PegIFN/RBV (n = 133) (2014) [31]	393 genotype 1 HCV patients	Frequently associated AEs in SMV/PegIFN/RBV and placebo groups were fatigue (31.9 vs. 42.1%), headache (31.9 vs. 36.1%), and influenza-like symptoms (29.6 vs. 20.3%) 2 patients in SMV group had grades 2/3 photosensitivity events 6.2% of patients SMV/ PegIFN/RBV had grades 3/4 hyperbilirubinemia (the frequency in placebo group was 3.1%)	80–83%	0.4% of patients in SMV/PegIFN/RBV
SMV + SOF ± RBV for 12 weeks vs. 24 weeks (2014) [32]	167 genotype 1 chronic HCV patients	Most common AEs in pooled groups of patients treated with different simeprevir/sofosbuvir combinations included headache (20%), nausea (16%), and fatigue (31%). Grade 4 AEs were observed in one patient (2%) in each of groups 1 and 3, in three patients (10%) of group 2, while grades 3–4 AEs were scrutinized in less than 5% of the patients except the elevated level of blood amylase	92 and 94% for cohorts 1 and 2	4 patients (2%) had withdrawn from all study treatment due to AEs and three patients discontinued before week 12

Treatment/study group/ year	Population	Adverse event (AE) profile	Overall SVR_{12} rate	Treatment status
DCV 60 mg QD + ASV 200 mg BID × 24 weeks (group A1; n = 18) vs. DCV 60 mg QD + ASV 200 mg QD ×2 4 weeks (group A2; n = 20) vs. DCV 60 mg QD + ASV 200 mg BID + PegIFNα/RBV × 24 weeks (groupB1; n = 20) vs. DCV 60 mg QD + ASV 200 mg QD + PegIFNα/ RBV × 24 weeks (group B2; n = 21) vs. DCV 60 mg QD + ASV 200 mg BID + RBV × 24 weeks (group B3; n = 22) (2014) [33]	101 genotype 1a and 1b HCV patients	Frequently associated AEs in all groups were headache (44 vs. 40 vs. 60 vs. 48 vs. 46%), diarrhea (28 vs. 30 vs. 45 vs. 33 vs. 23%), fatigue 28 vs. 10 vs. 40 vs. 24 vs. 32%), asthenia (17 vs. 20 vs. 30 vs. 57 vs. 32%), myalgia (22 vs. 5 vs. 10 vs. 38 vs. 9%), and insomnia (17 vs. 15 vs. 45 vs. 14 vs. 41%)	Group A1 (78%), group A2 (65%), group B1 (95%), and group B2 (95%)	1 patient in B3 group
DCV/ASV/PegIFN/RBV for 24 weeks (2015) [34]	398 genotype 1 or 4 chronic HCV patients	Frequently associated AEs were fatigue (41.5%), headache (31.2%), pruritus (26.1%), asthenia (24.1%), influenza-like illness (22.4%), and insomnia (22.4%)	Genotype 1 (93%) and genotype 4 (98%)	18 patients
PrOD with RBV (group A) (n = 437) vs. matching placebos (group B) (n = 158) (2014) [35]	595 previously untreated genotype 1 HCV patients	Common AEs in groups A and B ($P < 0.05$ for each comparison) were fatigue (34.7 vs. 28.5%), headache (33.0 vs. 26.6%), nausea (23.7 vs. 13.3%), pruritus (16.9 vs. 3.8%), insomnia (14.0 vs. 7.6%), diarrhea (13.7 vs. 7.0%), and asthenia (12.1 vs. 3.8%)	Genotype 1a (95%) and genotype 1b (98%)	3 Patients in group A and 1 patient in group B
PrOD with RBV (n = 297) vs. placebo (n = 97) during the 12-week double-blind period/2014 [36]	394 Previously treated with PegIFN/RBV who had a relapse, a partial response, or a null response in patients with HCV genotype 1 infection without cirrhosis	Common AEs in active and placebo groups were headache (36.4 vs. 35.1%; P = 0.90), fatigue (33.3 vs. 22.7%; P = 0.06), and nausea (20.2 vs. 17.5%). More patients in the active-regimen group had anemia (P = 0.01), and vomiting (P = 0.006); while AEs with a higher frequency in the placebo group were constipation (P = 0.02), erythema (P = 0.05), neck pain (P = 0.05), and neutropenia (P = 0.01).	96.3% overall	3 patients in the active regimen group
86 patients were treatment-naïve (44 received PrOD and 42 received PrOD/RBV) and 49 treatment-experienced patients received the RBV-containing therapy/2015 [37]	135 genotype 4 chronic HCV	Most common AEs were headache (29% of treatment-experienced patients vs. 33% of 42 treatment-naïve patients), asthenia (24 vs. 33%), fatigue (7 vs. 18%), insomnia (5 vs. 16%), and nausea (9 vs. 17%)	100% RBV-containing regimen and 90.9% RBV-free regimen	No AEs leading to treatment discontinuation

Treatment/study group/ year	Population	Adverse event (AE) profile	Overall SVR_{12} rate	Treatment status
PrOD with RBV (group 1) vs. PrOD (group 2)/ 2014 [38]	179 patients with HCV genotype 1b infection, without cirrhosis, previously treated with PegIFN/RBV	The most frequently reported AEs in groups 1 and 2 were fatigue (31.9 vs. 15.8%), headache (24.2 vs. 23.2%), and nausea (20.9 vs. 6.3%). Patients treated with RBV had more commonly insomnia, anemia, rash, and increased blood bilirubin levels	Group 1 97% and group 2 100%	1 patient in group 1 and 1 patient in group 2
GZP/EBR (immediate treatment group) (n = 111) vs. placebo (deferred treatment group) (n = 113)/2015 [39]	224 patients with HCV genotype 1 infection and chronic kidney disease	Common AEs occurred in patients in immediate treatment and deferred treatment groups were headache (17.1 vs. 16.8%), nausea (15.3 vs. 15.9%), fatigue (9.9 vs. 15%), insomnia (6.3 vs. 10.6%), dizziness (5.4 vs. 15.9%), and diarrhea (5.4 vs. 13.3%)	99%	5 patients in deferred treatment group
GZP/EBR/ 2015 [40]	218 treatment-naïve patients with chronic HCV genotype 1, 4, or 6 infection and HIV co-infection, with or without cirrhosis	The most frequent AEs were fatigue (13%), headache (12%), and nausea (9%).	96%	There were no AEs leading to treatment discontinuation

Table 2. Clinical efficacy and tolerability of direct acting antivirals (DAAs).

and nervous system disorders were mostly found in sofosbuvir®/RBV-treated patients as compared to the placebo group [24, 25]. Efficacy and safety of daclatasvir®/sofosbuvir® with or without RBV was assessed in more than 600 patients with advanced HCV disease. Population was mostly cirrhotic (72%, of whom 18% were decompensated), HCV treatment-experienced (82%), and infected with genotypes 1 (69%), 3 (12%), or 4 (19%). Most of them were treated for 24 weeks and 14% received RBV. Twelve weeks of SVR was 92% overall, 90% in cirrhotic patients, and 95% in non-cirrhotic patients. Twelve weeks of SVR (SVR12) remained constant among all major six genotypes and antiretroviral regimens. Among 617 patients with safety data, seven patients discontinued due to adverse events and ten died. About three out of seven reported discontinuation as AEs were consequently found fatal (decompensated cirrhosis/multi-organ failure, respiratory disorder, hepatic carcinoma) and for the remaining four were nonfatal (treatment-associated lymphopenia, renal insufficiency) [26]. Daclatasvir®/sofosbuvir® with or without RBV achieved high SVR12 and was well tolerated in this large real-world cohort of HIV-/HCV-coinfected patients with advanced liver disease. Conclusively, it is found that daclatasvir®/sofosbuvir® with or without RBV is well tolerated in real-world HIV-/HCV-coinfected cohort with advanced hepatic disease, and treatment is more suitable in this perspective [26].

Safety profile of sofosbuvir®/ledipasvir® combination with or without RBV was evaluated in pivotal study trials including ION-1, ION-2, and ION-3. In these clinical trials, 2000 HCV-infected

patients (cirrhotic and non-cirrhotic) with genotype 1 were treated with ledipasvir®/sofosbuvir® or ledipasvir®/sofosbuvir® plus RBV. Ledipasvir® was found to be associated with the occurrence of headache, insomnia, nausea, and asthenia. In data obtained from ION-2 and ION-3 trials, AEs such as cough, rash, grade 1 or 2 hyperbilirubinemia, arthralgia, anemia, irritability, and dyspnea were found frequently among patients treated with RBV [27, 28]. Furthermore, outcomes of treatment combinations like daclatasvir®/pegIFN/RBV vs. placebo, daclatasvir®/sofosbuvir®, and with or without RBV, were evaluated in ALLY-3+, AI444040, and AI444010 clinical studies, respectively, in more than 650 patients having genotype of 1, 2, 3, or 4. Like other DAAs symptoms like asthenia, headache, and nausea were more frequently observed [29–31]. AI444040 study illustrated discontinuation of therapy in two patients, one having stroke with history of hyperlipidemia, smoking, and myocardial infarction and the other having fibromyalgia exacerbation with history of fibromyalgia [29]. According to another efficacy study, in placebo group a large number of patients had grade 3–4 AEs when compared with patients who received daclatasvir® 20 or 60 mg (23.1 vs. 20.1 vs. 14.6%). In 3.8% of patients receiving 60 mg daclatasvir®, an increased alanine aminotransferase (ALT) level was observed vs. 1.3% of patients in placebo group, while patients receiving 20 mg daclatasvir® did not experience this side effect. However, both groups of drug dosage experienced the symptoms of influenza-like syndrome, nausea, and dry skin [30]. In ALLY-3+ phase III study trial, no AEs were observed in patients receiving daclatasvir®/sofosbuvir®, with RBV which led to discontinuation of therapy. The most common treatment-associated general side effects including irritability, insomnia, asthenia, fatigue, dyspnea, and diarrhea were observed in 10% of the patients. The high level of safety and clinical efficacy was demonstrated in patients having challenging viral 3a genotype who were administered with this combination for 12 or 16 weeks [31].

2.1.2. Efficacy and safety analysis of simeprevir® in different combinations

Simeprevir® in combination with PegIFNα and RBV was assessed in more than 1000 patients using QUEST-1, QUEST-2, and PROMISE clinical trials. AEs associated with simeprevir® included rash, increased bilirubin level, pruritus, and photosensitivity events as compared to the placebo group. No differences were found in PROMISE trial between simeprevir®/PegIFN/RBV and placebo groups for frequency of grades ¾ AEs [32]. Simeprevir® in combination with sofosbuvir® was approved by the FDA in 2014 for chronic patients of genotype 1. In COSMOS randomized study, patients were grouped in ratio of 2:1:2:1 who received simeprevir® (150 mg) and sofosbuvir® (400 mg) for 24 weeks with (group 1) or without (group 2) RBV and for 12 weeks with (group 3) or without (group 4) RBV, in two different cohorts: previously nonresponders having METAVIR[1] scores of F0–F2 and treatment-naïve patients and previously nonresponders with F3–F4 scores of METAVIR [33]. In cohorts 1 and 2, 92 and 94% of patients achieved SVR12, respectively. Most common AEs in pooled groups of patients treated with different simeprevir®/sofosbuvir® combinations included headache (20%), nausea (16%), and fatigue (31%). Grade 4 AEs were observed in one patient (2%) in each of groups 1 and 3 and in three patients (10%) of group 2, while grades 3–4 AEs were scrutinized in less than 5% of the patients except the elevated level of blood amylase. Serious

[1]Scoring system used to assess the extent of inflammation and fibrosis via histopathological evaluation in liver biopsy of HCV patients.

AEs were observed in four patients (2%); four patients (2%) had withdrawn from all study treatment due to AEs, and three patients discontinued before week 12 [33].

2.1.3. Tolerability analysis of asunaprevir® combinations

In a randomized phase 2a open-label study, safety and tolerability of asunaprevir®/daclatasvir® combination therapy was assessed in 100 patients of genotype 1a and 1b. Patients received five different regimens including daclatasvir® and asunaprevir® alone, at different dosages, or plus PegIFN/RBV. Efficacy data depicted that asthenia, headache, and diarrhea were more common and that serious hematological side effects were found in patients who received PegIFN and/or RBV. Correspondingly, flu-like illness, alopecia, and rash were observed in patients treated with PegIFN and/or RBV compared to those who treated with daclatasvir® and asunaprevir® [34]. During trials six severe AEs were analyzed: one patient got panic attack, one case of forearm fracture, one case of prostate cancer found in patients who received asunaprevir®/daclatasvir® combination, two over dosage cases, and one case of squamous cell carcinoma in patients treated with daclatasvir®/asunaprevir®/ PegIFN/ RBV [33]. In phase 3 study of HALLMARKQUAD trial, patients with genotype 1 (n = 354) or genotype 4 (n = 44) (partial or nonresponders to PegIFN/ RBV) were treated daily with daclatasvir®/asunaprevir® combination and weekly with PegIFN and/or RBV. In serious AEs (5.5% of patients), grade ¾ clinical manifestations included lymphopenia, thrombocytopenia, neutropenia, anemia, and elevated level of ALT/aspartate transaminase (AST) were found in the treated patients. Fatigue, pruritus, influenza-like symptoms, rash, asthenia, and insomnia were common AEs observed during study. Negligible difference was found in ALT and AST elevation among patients with or without cirrhosis [35]. Drug combination was well tolerated, and no additional safety concerns were identified in comparison to pegIFN/RBV regimens.

2.1.4. Efficacy study of ombitasvir®/paritaprevir®/ritonavir®

Safety analysis of ombitasvir®/paritaprevir®/ritonavir® in combination with dasabuvir® was analyzed among 1025 patients during clinical trials of SAPPHIRE-I and SAPPHIRE-II. Clinical efficacy data depicted that headache and fatigue were the most frequent AEs. In comparison to placebo group, patients treated with ombitasvir®/paritaprevir®/ritonavir®, dasabuvir®, and RBV were found to exhibit asthenia, diarrhea, pruritus, nausea, and insomnia as the most common AEs. On the other hand, placebo group patients were confronted to have erythema, neck pain, and constipation. Ventricular extra systoles, sinus tachycardia, acute respiratory failure, and acute transient stroke were reported as severe AEs in study treatment [36, 37]. In PEARL-I and PEARL-II trials, safety results in HCV-infected patients of genotypes 1 and 4 who were treated with combination of ombitasvir®/paritaprevir®/ritonavir®, with or without dasabuvir®, and RBV® illustrated that insomnia, nausea, asthenia, and headache were the most common AEs [38, 39].

2.1.5. Safety analysis of grazoprevir®/elbasvir® combination

According to C-SURFER safety study data, in which 244 patients of viral genotype 1 along with chronic kidney disease (CKD) were included, grazoprevir®/elbasvir® combination was

associated with AEs like nausea, headache, and fatigue. In two patients cardiac arrest and myocardial infarction were observed, while in placebo group, three patients were reported with serious cardiac events. Though the severities and frequencies of liver-associated events were comparable between groups, elevation in ALT and AST levels were more frequent in placebo group. In grazoprevir®/elbasvir®-treated group of patients, a low hemoglobin level (24.3 vs. 16.8%) was recorded [40]. In single-arm C-EDGE COINFECTION phase 3 study, safety of grazoprevir®/elbasvir® was assessed in patients (n = 218) of genotype 1, 4, or 6 coinfected with HIV. Related to the previous study, the most frequent AEs were nausea, fatigue, and headache [41].

2.2. Post-marketing safety reports of DAAs

Post-marketing survey studies scrutinizing the efficacy profile of clinically approved DAAs are very limited. Probing the altered drug metabolism among patients receiving HCV treatment with other clinical manifestations, drug-drug interactions and concurrently administered medications remain at the front position for optimizing DAA regimen. A study regarding DAA/non-DAA drug interaction recommended that simeprevir®/pegIFN/RBV may increase the risk of interstitial pneumonitis due to IFN as evinced by earlier onset of condition while comparing to conventional pegIFN/RBV treatment [42]. Another study regarding DAA/non-DAA drug interaction in a patient with recurrent HCV and cirrhosis first reported the case of seizures, possibly participated by simeprevir®/sofosbuvir®/RBV therapy [43]. Whereas risk of interstitial pneumonitis and seizures is still being evaluated, extensive cases of cardiac events in patients who received simeprevir®/sofosbuvir® and amiodarone®, an anti-arrhythmic medication having long half-life, led to extra care on the account of prescribing providers and an appendix on labels of antiviral drugs. Most cases of liver decompensation or hepatic failure from the post-approval use of simeprevir®/pegIFN/RBV or with sofosbuvir® were recorded by patients of advanced cirrhosis who were formerly at high risk for deteriorating liver function. Due to limited data available, simeprevir® is contraindicated in patients with severe cirrhosis or decompensated liver disease [44, 45]. Due to potent toxicity, the three-dimensional (3D) therapies are contraindicated in patients suffered from severe liver impairment [46, 47]. A total of 26 cases globally were significantly found to be related to 3D therapy administration with liver disorder occurring within 1–4 weeks of starting treatment [48, 49]. Moreover, it was revealed from real-world data that high incidence of primarily hypersensitivity reactions and immune system disorders may often lead to liver failure [49].

Post-marketing data obtained from HCV-/HIV-coinfected patients led to commendations for patients to stay on suppressive antiretroviral regimen while on 3D therapy due to the presence of ritonavir® (HIV-1 protease inhibitor) that can select for HIV-1 protease inhibitor resistance-associated substitutions [46–49]. Very low treatment discontinuation and AE rates were found in phase II–III study regarding sofosbuvir®-containing regimen as compared to IFN-based therapy while analyzing real-world results [50, 51]. Data depicted that two patients had to stop anti-HCV therapy earlier due to variceal bleeding and nonmedical reasons. However, therapy was well tolerated for majority of the patients (97%) [52]. Overall, Child-Pugh[2] and

[2]Score used to analyze prognosis of chronic hepatic disease, specifically cirrhosis.

Model for End-Stage Liver Disease[3] (MELD) classifications improved for majority of HCV-infected patients, therefore lessening the need for transplantation of the liver. Post-marketing data obtained from CHC patients with renal disease depicted that same treatment was safe and tolerable regardless of baseline kidney function, yet patients who received sofosbuvir®-containing regimen seemed to have higher incidence of anemia [50].

3. Anti-HCV drug combinations tolerability in distinctive population

Significant AE profile of IFN-based therapy confines the applicability of these regimens for treating recurrent hepatitis C infection in difficult-to-treat population. Intensive research struggles are being done to assess DAAs in different populations of CHC patients for whom therapeutic options are limited.

3.1. Elderly CHC patients

Recently, evidence-based retrospective cohort studies have been reported regarding safety and tolerability analysis of DAAs in elderly CHC patients. Patients (n = 244) were categorized into two groups: individuals aged under 65 years (n = 156) and patients equal to or elder than 65 years (n = 84). Treatment recommendations during the late 2012 and early 2013 were protease inhibitors in combination with pegIFN and RBV. During years of 2014 and 2015, the rest of the therapies were given to patients as approved in succession by the FDA. Different treatment combinations used were sofosbuvir®/pegIFN/RBV, sofosbuvir®/ledipasvir®/RBV, ombitasvir®/paritaprevir® /ritonavir®/dasabuvir® ± RBV, and simeprevir®/sofosbuvir®. Just three patients received telaprevir®/pegIFN/RBV, and one patient each was treated with boceprevir®/pegIFN/RBV, sofosbuvir®/ledipasvir®/RBV, and simeprevir®/sofosbuvir®/RBV combinations in cohort study [53]. With all regimen combinations, the overall end-of-treatment (EOT) response rate, defined as undetectable HCV RNA transcript after the completion of treatment, was 98.2% (n = 233) and SVR12 was 94% (n = 191). Statistically, no significant difference was found with EOT (98.8 vs. 98%) and SVR12 (93.1 vs. 94.1%) between patients aged 65 years or older and those younger than 65 years. SVR12 for DAAs/pegIFN/RBV was 98% higher than that (91.4%) obtained from IFN-free DAA regimen but was statistically insignificant. Analogous response rate was seen in patients aged 65 or older with 100% of the patients on IFN-based therapy attaining an SVR compared with only 91.07% SVR with IFN-free therapy [53]. No serious AEs were reported except two patients suffered from severe anemia. Common AEs observed in elder patients were fatigue (32.5%), anemia (19.6%), and leukopenia (11.7%) followed by thrombocytopenia (10%), skin rash (8.3%), and headache (7.9%). Leucopenia, thrombocytopenia, and anemia were observed in almost half of the patients treated with IFN/RBV. By reducing RBV dose, all patients achieved SVR12. Treatment discontinuation of RBV dose reduction did not attain statistical significance among both groups. Conclusively, on the basis of cohort studies, we can say that age is not a major factor to have an

[3]Classification used to categorize liver dysfunction in preparation for liver transplantation.

impact on SVR during treatment. Older patients did not attain higher frequency of AEs while comparing with younger patient group. Some other clinical manifestations like fibrosis, cirrhosis, ALT/AST, hemoglobin, and platelet levels may disturb the SVR in the elderly [53, 54].

3.2. Transplant recipients with chronic hepatitis C infection

HCV-related hepatic disease generally arises in patients following liver transplantation. Nearly half of the patients who have the need of liver transplant are also infected with hepatitis C infection. Viremia before transplantation is a strong predictor of virus recurrence post-transplantation. IFN-free DAA therapy has improved the long-term, posttransplantation sequel. Preeminently, DAA therapy leads to drug-drug interaction with different immunosuppressants, mainly with cyclosporine and tacrolimus. As both are substrates of CYP3A and P-glycoprotein (P-gp), treatment should be restricted to agents that are neither inducers nor inhibitors of these molecules. Currently, in a recent trial, combination of antiviral drugs (ombitasvir®/paritaprevir®/ritonavir® (25/150/150 mg q.d[4])/dasabuvir® (250 mg b.d[5])/variable RBV dose) was given for 24 weeks to transplant recipients having recurrent viral genotype 1 infection and without advanced stages of fibrosis [55]. Clinically, manageable AEs such as headache, cough, and fatigue were found to be associated with therapy. Momentarily, elevated levels of ALT and bilirubin were noticed in two patients, and nine patients were reported to have a reduced level of hemoglobin with one patient requiring erythropoietin. No significant treatment-associated abnormalities were observed in transplant recipients while comparing with those who had not undergone transplantation. Only one patient quitted treatment after 18 weeks due to memory impairment, anxiety, and rash but still cleared out the virus. Major limitation of this therapy was the need to improve tacrolimus and cyclosporine dosage [55].

In another trials, efficacy and safety of IFN-free sofosbuvir®/RBV therapy to treat CHC infection in kidney transplant recipients (n = 10) were evaluated. The effect of sofosbuvir®/RBV therapy upon calcineurin inhibitor (CNI) drug levels was also assessed. SVR12 was seemed to be maintained in all patients (100%) [56, 57]. Acute rejection graft loss was not detected during antiviral therapy. Among ten patients, seven did not exhibit significant AEs. Only one patient had symptoms of fatigue, muscle cramps, headache, and anorexia during therapy. Acute gastroenteritis was observed in one patient who recovered after 5 days. Another patient was found to have hyperuricemia with gout, but its association with sofosbuvir/RBV treatment was not recognized. All patients completed the course of treatment, and none of the patients discontinued their antiviral treatment. Significant reduction in CNI drug exposure was found during anti-HCV treatment, but none of the patients required having dose modification of CNIs [56].

3.3. HCV-/HIV-coinfected patients

HCV-/HIV-coinfected patients are at high risk for progression of liver cirrhosis and hepatic decompensation. One study assessed IFN-free ombitasvir®/paritaprevir®/ritonavir® (25/150/100 mg q.d.) and dasabuvir® (250 mg b.d.) regimen in HCV-/HIV-coinfected patients for 12 or 24 weeks [58]. This therapy was found well tolerated in study population including

[4]One tablet per day orally (Latin: quaque die).
[5]Twice a day (Latin: bis in die).

treatment-experienced and treatment-naïve patients and cirrhotic and non-cirrhotic patients. Mild-to-moderate AEs were experienced by majority of the patients (89%); however, one patient was found to have severe AEs, but none of the patients discontinued their therapy due to AEs. Along with infrequent laboratory abnormalities, no erythropoietin or transfusion was required by any patient. Ledipasvir® (90 mg q.d.) and sofosbuvir® (400 mg q.d.) treatment to HCV-/HIV-coinfected patients for 12 weeks stated mild-to-moderate AEs (77%) including fatigue, headache, and diarrhea [59]. Less than 1% of the patients were reported for laboratory abnormalities including increased levels of creatinine kinase (non-study-related), lipase, and serum glucose (in those patients who had history of diabetes or abnormal baseline glycosylated hemoglobin levels). However, no patient was reported to discontinue therapy due to AEs. Consequently, this therapy displayed less potential for clinically significant drug-drug interactions with coadministration of antiretrovirals except with the drug, tenofovir disoproxil fumarate [59].

4. Conclusion

The last few years evidently made the progress in development of successful HCV therapeutic regimens with higher clinical efficacy and inconsiderable side effects except some with severe AEs, but negligible treatment discontinuation rate was reported. Likewise, therapy duration with DAAs is markedly reduced from 6 to 12 months (pegIFN/RBV) to 3–6 months. So, development of DAAs has remarkably changed the disease management. Despite various advantages of DAA therapy, their safety profile is albeit not absolutely known. Indeed, interpreting the constraints of premarketing studies like population size and short duration trials, only during the post-approval level, it is probable to ascertain and apprehend the safety matters linked with the utilization of DAAs in real conditions. As a result, pharmacovigilance activities portray the main gadget to promote patient care and safety in comparison to the use of any medication.

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