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Review article: safety and tolerability of direct-acting anti-viral agents in the new era of hepatitis C therapy

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SUMMARY

Background
Direct-acting anti-virals (DAAs) licensed to treat chronic HCV infection have revolutionised treatment algorithms by drastically mitigating side effects while enhancing efficacy relative to interferon-based therapy.

Aim
To review adverse events (AEs) uniquely associated with DAA therapy across a broad spectrum of patient populations.

Methods
Searches of PubMed and FDA surveillance studies were undertaken to complete an exhaustive review. Search terms included 'DAAs', 'safety', and 'tolerability'.

Results
While DAAs are remarkably well tolerated, they are accompanied by unique AEs. Simeprevir, an NS3/4A protease inhibitor, has been known, albeit infrequently, to cause mild hyperbilirubinemia and photosensitivity reactions; and paritaprevir boosted with ritonavir causes bilirubin and ALT elevations. Asunaprevir, another protease inhibitor, infrequently causes elevated transaminase levels. NS5A and NS5B inhibitors are well tolerated, although sofosbuvir is contraindicated in patients with severe renal impairment. Ribavirin co-administered in certain treatment regimens has been associated with cough, rash and haemolytic anaemia.

Conclusions
With the impending reality of a more tolerable interferon-sparing regimen, the future of DAA therapy offers shorter treatment duration, simplified disease management, and a patient-centred regimen. With advantages come drawbacks, including development of resistance to therapy and accessibility to this expensive treatment. DAA therapy continues to advance at a brisk pace with a promising trend for higher tolerability, even in difficult-to-treat subgroups such as those with cirrhosis, nonresponders to prior therapy, and transplant recipients. Subgroup-specific contraindications and safety-related limitations are active areas of research. Concerted research efforts and continuing advances lend hope to the goal of rendering HCV a routinely curable disease.

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INTRODUCTION

Formerly known as non-A, non-B hepatitis, Hepatitis C virus (HCV) infection has emerged as a modern-day pandemic, presently affecting upwards of 300 million people around the world.[1, 2] Advanced liver disease resulting from chronic HCV infection remains the leading indication for liver transplantation worldwide and predisposes patients to a range of clinical manifestations including cirrhosis, end-stage liver disease, and hepatocellular carcinoma, thus leading to liver-related mortality in due course.[3]

Treatment of chronic HCV is undergoing a revolution. Historically, the only therapy available for almost 25 years was interferon in combination with ribavirin, which yielded inconsistent results and elicited adverse events (AEs) that were at times quite severe.[4] The discovery and subsequent development of direct-acting anti-virals (DAAs) heralded a marked improvement in rates of sustained virological response as well as quality of life.[5–10] New anti-virals have been evaluated as add-on therapies to either pegylated interferon and ribavirin or, more recently, as all-oral DAA combination regimens, with interferon-based therapy now largely being eliminated from the armamentarium of HCV management.[11]

While efficacy of anti-virals on the market has been comprehensively evaluated, a broad review of the AE profiles produced by these agents is notably lacking. This review characterises the burden of the most clinically significant AEs associated with approved DAAs in combination therapy, either with or without interferon and ribavirin. Herein, the safety of DAA therapy will be reviewed for single DAAs and DAAs in combination therapy, as seen fit.

EVOLUTION OF TREATMENT

Since the early 1990s, standard interferon-based therapy via subcutaneous injection served as the standard of care (SOC) for patients with chronic hepatitis C; this therapy had a dismal cure rate of just 6% and was accompanied by serious side effects that frequently led to treatment discontinuation.[12] By the start of the millennium, pegylated interferon (peg-IFN) co-administered with a guanosine analogue called ribavirin (RBV) took the place of standard interferon as a safer and better tolerated regimen, and was routinely used to treat patients regardless of HCV genotype.[4, 8, 9] Progress was limited, however, as this dual therapy still produced a considerable AE profile and suboptimal response rates in patients infected with HCV genotype 1, the most common genotype in the USA and Europe.[8, 13]

The advent and subsequent approval of oral DAAs ushered in a new era of HCV treatment. In contrast to the nonspecific nature of interferon-based therapy, DAAs directly target various component proteins involved in the replication of HCV in the host.[14] The main classes of DAAs are NS3/4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors. The initial protease inhibitors approved for HCV therapy, telaprevir and boceprevir, led to an increase in efficacy when combined with peg-IFN and RBV, but also produced novel AEs in addition to side effects commonly associated with peg-IFN and RBV.[15, 16]

The next wave of approvals included the protease inhibitor, simeprevir, and the first NS5B nucleotide polymerase inhibitor, sofosbuvir.[17–19] Either simeprevir or sofosbuvir along with peg-IFN and RBV were indicated for therapy in patients with genotype 1 HCV infection, but again were accompanied by AEs related to the use of interferon and ribavirin.[20–26] These approvals were closely followed by several well tolerated interferon-free regimens, including sofosbuvir plus simeprevir, 3D regimen (paritaprevir/ritonavir/ombitasvir co-administered with dasabuvir with or without ribavirin), and ledipasvir plus sofosbuvir with the possible need for ribavirin in difficult-to-treat populations.[27–36] These combination therapies offered significant advantages, including higher cure rates, shorter treatment duration, and less severe side effects.[5, 22–25, 37–41] The last few years have witnessed an expansion within the classes of DAAs, with several new anti-virals currently populating the HCV drug development pipeline. Although great strides have been made for HCV therapy in this era of DAAs, many challenges remain; among these are drug–drug interactions, high-pill burden and strict dosing schedule, significant cost barrier, safety in all populations, variability in regimen and dosing duration across patient genotypes, and the development of viral resistance.[42–48]

HCV DRUG TARGETS IN THE CELL

Protease inhibitors (PIs)

The positive polarity of the HCV genome confers on the virus the ability to, with the aid of host-cell machinery, translate its genomic RNA into protein immediately upon cell entry.[49] However, this long polyprotein must be cleaved into single units to exert their necessary enzymatic activities, as each individual protein has an important structural role in viral progeny particles.[49] A number of proteases are responsible for cleavage of the unprocessed polyprotein, chiefly NS3/4A serine

protease.[50] PIs interfere with the essential role of NS3/4A in HCV self-cleavage during viral replication, and targeting this protease has been shown to restore responsiveness to interferon-based therapy as well as directly disrupt viral replication.[51] In the light of newer PIs (including simeprevir, paritaprevir, grazoprevir and asunaprevir), telaprevir and boceprevir have become obsolete and are no longer recommended by the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL), namely due to nonoptimal tolerability, restricted efficacy to genotype 1 disease, and a low barrier to resistance.[52, 53] As such, AEs associated with these two PIs will not be reviewed.

NS5A inhibitors

NS5A polymerase has a critical function in viral replication and assembly, though its mechanistic role in the HCV life cycle remains enigmatic.[54] Use of NS5A inhibitors, even at picomolar concentrations, has been associated with significant reductions in HCV RNA levels in cell culture-based models, producing the most rapid viral load declines of any anti-viral class in clinical monotherapy studies.[34] Ledipasvir, ombitasvir and daclatasvir are FDA-approved NS5A inhibitors, while elbasvir and velpatasvir show promise in phase II and III investigational trials.[55–57]

NS5B inhibitors

NS5B inhibitors fall into two classes: nucleos(t)ide and non-nucleoside inhibitors.[58] Nucleos(t)ide, RNA-dependent inhibitors act by way of competitive binding, have a high barrier to resistance, and are effective across a broad range of HCV genotypes.[59] In contrast, non-nucleoside allosteric inhibitors of RNA polymerase have a lower barrier to resistance and exhibit their effects only in specific strains of HCV.[60] Sofosbuvir is an example of a nucleotide analogue, while dasabuvir and beclabuvir comprise the current class of non-nucleoside analogues.[61]

Ribavirin

Several classes of DAAs are used in combination with the synthetic analogue, ribavirin.[62] Synthesised in 1970 as a first-in-class guanosine analogue against different RNA and DNA viruses, ribavirin still proves to be useful in HCV therapy four decades after its initial discovery and development.[62, 63] In spite of its longevity in clinical application, the precise mechanism of action by which ribavirin elicits its anti-viral effects has remained a scientific quandary.[7, 63–65]

The main toxicity observed with ribavirin is severe haemolytic anaemia.[13, 62, 66] Erythrocytes actively transport ribavirin into the cell; they have intracellular kinases that phosphorylate ribavirin into its triphosphate upon import, after which the triphosphate remains sequestered inside the cell. Erythrocytes lack the phosphatase enzymes necessary for converting ribavirin back to its dephosphorylated form, and consequently accumulate high levels of ribavirin triphosphate. High intracellular concentrations of the nucleotide deplete ATP reservoirs and lead to oxidative stress, ultimately resulting in lysis of the erythrocytes.[63, 67] The anaemia is further augmented when ribavirin is administered with interferon, a drug known to suppress bone marrow production and thus block a compensatory response to ribavirin-induced anaemia.[63, 66, 68] Other associated AEs include skin rash, cough and potential teratogenicity.[13, 63]

ADVERSE EVENTS OF DAA COMBINATION THERAPIES

Protease inhibitor (PI)-based regimen

Simeprevir-based regimens. Simeprevir is a macrocyclic protease inhibitor that exhibits its effects through reversible binding of the NS3 protease active site, thereby interfering with enzymatic cleavage of the HCV C-terminal polyprotein and precluding viral replication.[41] Patients on simeprevir frequently experience a variety of side effects including fatigue, headache, pruritus, influenza-like illness and neutropenia.[5, 69–71] The most clinically pertinent AEs uniquely associated with simeprevir-containing regimen are hyperbilirubinemia and photosensitivity reactions.[5, 23, 41] In addition, there is an augmented AUC for simeprevir in those with advanced liver disease, thus contraindicating its use in such patients (Child–Pugh class B and C).[24, 72, 73]

Predominately seen with higher doses of the drug, hyperbilirubinemia typically manifests in patients as mild and transient increases in mean plasma bilirubin. Simeprevir is an inhibitor of bilirubin transporters OATP1B1 (influx) and MRP2 (efflux); OATP1B1 is principally responsible for transporting unconjugated (indirect) bilirubin into liver cells, while MRP2 mediates the efflux of conjugated (direct) bilirubin out of hepatocytes.[74] Results of biochemical assays have shown that simeprevir is a more potent inhibitor of OATP1B1 than MRP2, suggesting that an observed increase in unconjugated rather than conjugated bilirubin is the driving factor for systemic elevations in bilirubin.[75] Altogether, decreased clearance of bilirubin caused by inhibition of

these transporters is likely a reason for increased bilirubin levels in those treated with simeprevir. However, ribavirin-related haemolysis and the concomitant elevation in bilirubin is a confounder in the cause of hyperbilirubinemia in patients administered simeprevir in a ribavirin-containing regimen.[24]

As a sulphonamide, simeprevir is photodynamically active and may elicit unwelcome side effects through the absorption of UV light.[76] Photosensitivity reactions accompanying the administration of simeprevir have been noted over the course of its clinical development, observed from the first in-human studies through pivotal phase III clinical trials; pooled data from these studies have shown that the severity of these reactions increases in a dose-dependent manner.[76, 77] These reactions occur even in patients using sun-protective measures, and may lead to temporary or permanent treatment cessation.[73]

The action spectrum for simeprevir comprises the UV-B (290–320 nm) and UV-A (320–400) ranges, and the reported pattern of photosensitivity suggests phototoxicity rather than photoallergy.[77] *In vitro* studies present evidence in concert with the preponderance of free radical mechanisms mediated by absorption of UV light, but adequately attributing chemical structure to photobiological action is limited by the state of the science.[76] Furthermore, the agent causing the photosensitivity reaction could be unmetabolised simeprevir, or an excipient, metabolite or degradation product. As such, the precise pharmacologic actions of simeprevir that precipitate photosensitivity reactions are as yet unknown.[77, 78]

A number of phase III clinical trials evaluating the therapeutic value and safety of simeprevir in patients naïve to prior therapy for HCV infection have yielded consistent results; side effects associated with simeprevir were mild and easily managed, and occurred at low incidence.[20, 22, 23] In a randomised trial where patients received simeprevir (100 mg q.d.) or placebo in combination with peg-IFN and RBV, the incidence of mildly increased bilirubin (22.8% vs. 10.0%) and photosensitivity conditions (1.6% vs. 0%) was higher in the simeprevir group than in the placebo group, respectively. No AEs led to permanent discontinuation of simeprevir alone. The rate of SAEs was greater in the placebo group compared to the group receiving simeprevir-containing regimen (10.0% and 3.3%, respectively), suggesting that simeprevir was generally well tolerated.[20]

Even an increase in simeprevir dosage (150 mg q.d.) did not appear to alter its associated AE profile, as reported by two multinational trials that were similarly structured.[22, 23] Mild elevations in bilirubin, occurring in 9% of patients in the simeprevir group in one study[22] rapidly reversed after the end of simeprevir dosing, and were mainly attributed to increases in unconjugated (indirect) bilirubin. No concomitant increases in other laboratory markers of liver function were observed. One patient discontinued treatment according to protocol-defined toxicity management of elevated bilirubin levels; however, a lower number of patients in the simeprevir group discontinued treatment than did those in the placebo group. Photosensitivity reactions occurred in only 3% of those in the simeprevir group, none being grade 3 (severe: marked limitation in activity, some assistance usually required, medical intervention/therapy required, hospitalisations possible) or 4 (potentially life-threatening: extreme limitation in activity, significant assistance required, significant medical intervention/therapy required, hospitalisation or hospice care probable) in severity. Patients in the simeprevir group in a second study[23] reported AEs similar in frequency and severity with regard to hyperbilirubinemia and photosensitivity reactions; elevated bilirubin levels fell to baseline after therapy cessation, and, with the exception of a single grade 2 (moderate: mild-to-moderate limitation in activity, some assistance may be needed, no or minimal medical intervention/therapy required) reaction during the first 12 weeks of treatment, all reported photosensitivity reactions in the simeprevir group were grade 1 (mild: transient or mild symptoms/discomfort (<48 h), no medical intervention/therapy required) in severity.[22, 23]

Simeprevir was generally well tolerated in patients for whom prior treatment was unsuccessful; the drug was associated with a slightly higher incidence of AEs but little change in their severity. The tolerability profile associated with simeprevir was comparable in both those who have relapsed after prior therapy and in treatment-naïve patients. The most frequently reported AEs in all three trials included rash, pruritus, nausea, myalgia and dyspnoea.[22–24]

Safety data for patients who were null or partial responders to prior interferon-based therapy, however, were more variable. In a study investigating simeprevir (100 mg q.d.) for 12 weeks in those who relapsed, the majority of AEs were grade 1 or 2 in severity, with 34.7% of patients reporting grade 3/4 AEs and 2.0% reporting grade 4 AEs (AEs evaluated according to World Health Organization grading scale).[79] One patient permanently discontinued treatment due to a hematological AE.[21] In a randomised, double-blind, placebo-controlled study,[24] two relapsers receiving simeprevir-containing regimen reported grades 2/3 photosensitivity

reactions. After the first 12 weeks of simeprevir triple therapy, 5.8% of patients reported grades 1/2 while 6.2% reported grades 3/4 AEs. In all, less than half a percent of those receiving simeprevir or placebo with peg-IFN and RBV discontinued treatment due to AEs while no patients discontinued treatment with simeprevir or placebo alone, suggesting the observed AEs may have been due to the interferon and ribavirin components of the regimen. Elevations in bilirubin (direct, indirect, and total) reported in both trials were mild and reversible.[21, 24]

In a non-inferiority trial evaluating null or partial responders comparing simeprevir- and telaprevir-based regimens,[25] the safety profile of simeprevir reflected results observed in treatment-naïve patients: of the 2% of patients receiving simeprevir who experienced photosensitivity reactions, none discontinued treatment due to this AE or experienced side effects of grade 3/4 in severity; and 8% of those receiving simeprevir reported increased bilirubin levels. One phase III trial reported slightly different incidence rates of AEs in nonresponders.[21] A higher frequency of AEs occurred in nonresponders than in those who had relapsed after interferon-based treatment. The majority of AEs reported by nonresponders (26.4%) were grade 1 or 2 in severity, with 6.6% of patients reporting grade 4 AEs. Mild hyperbilirubinemia due to simeprevir was observed before week 4, but median bilirubin levels generally lowered after 2 weeks of treatment and subsequently returned to baseline levels after completion of the regimen.[21]

An interferon-free, simeprevir-containing drug combination initially used off-label to treat HCV received FDA approval in late 2014. Patients infected with genotype 1, the most prevalent genotype in the Western world and yet the most difficult-to-treat, responded favourably to simeprevir (150 mg q.d.) and sofosbuvir (400 mg q.d.) for 24 weeks with or without ribavirin.[27] The most common AEs patients experienced were fatigue (31%), headache (20%), nausea (16%), insomnia (14%), pruritus (11%), rash (11%) and photosensitivity reactions (7%), with the majority of AEs reported being grade 1 or 2 in severity (AEs evaluated according to World Health Organization grading scale).[79] Rash, pruritus, hyperbilirubinemia and anaemia were reported more commonly among patients receiving ribavirin compared to those not receiving ribavirin as part of their regimen. A higher proportion of those undergoing extended treatment for 24 weeks experienced additional AEs, including dizziness (16%) and diarrhoea (16%). Reported laboratory abnormalities correlated with the presence of ribavirin in the regimen; 75 (45%) patients experienced elevations in bilirubin levels, with 61 of 75 incidences reported in the groups receiving ribavirin. The frequency of AEs was similar in both treatment-naïve and treatment-experienced patients undergoing treatment, and AEs rarely led to treatment discontinuation (2% of patients). Furthermore, high-grade fibrosis did not pre-dispose patients to AEs. The results of two more recent trials reflected similar outcomes, showing that this regimen was well tolerated for eight or 12 weeks in those with and without compensated cirrhosis and regardless of past experience with interferon-based HCV therapy.[29, 30]

Simeprevir is primarily metabolised by cytochrome P450 isoform 3A4 (CYP3A4) enzymes, and its use can lead to unfavourable drug–drug interactions when co-administered with even moderate inhibitors or inducers of CYP3A enzymes (Table 1).[72, 75, 80] Concomitant use with CYP3A inducers leads to decreases in simeprevir exposure, potentially compromising its therapeutic effect. The increased systemic simeprevir concentrations observed when used with CYP3A inhibitors have been clinically shown to prolong therapeutic effects, but also increase the incidence of AEs.[81] Notably, simeprevir inhibits gut CYP3A4 but not hepatic CYP3A4 (Table 1), and simeprevir in combination with even with a low dose of a potent CYP3A inducer is known to lead to a moderate (48%) decrease in AUC24h with C_{max} increased by 31%.[80] Still, no dose adjustments are recommended when simeprevir is co-administered with CYP1A2, CYP2C9, or CYP2C19 substrates. In addition to its role in CYP and OATP transporter activity, simeprevir is also a mild inhibitor of intestinal efflux transporter P-glycoprotein (P-gp).[72, 75] At present, no dose adjustments are required in patients with moderate or severe renal impairment.[72, 82] Those of East Asian ancestry or patients with hepatic impairment experience increased exposure to simeprevir, but there is still insufficient data available to provide dose recommendations for individuals with moderate-to-severe hepatic impairment.[72, 81, 83, 84]

Paritaprevir/ritonavir in combination with ombitasvir. Paritaprevir (ABT-450) is a protease inhibitor that has been evaluated when administered with other DAAs and ribavirin, as well as in ribavirin-free regimens.[32, 85–90] As paritaprevir is metabolised by CYP3A, it can be boosted with ritonavir (ABT-450/r).[47] When used with peg-IFN and RBV, ABT-450/r produces an AE profile similar to that observed in patients solely administered the then traditional SOC (peg-IFN and RBV).[32] In contrast, anti-viral

Table 1 | Metabolism of DAAs and ritonavir by CYP enzymes[80, 139–141]

DAA	CYP3A4	CYP3A5	CYP2C8	CYP2C19	CYP2D6	CYP1A2
Simeprevir*,†,‡	↓§	–	–	–	–	↓
Paritaprevir*,¶	–	–	↓	–	–	–
Asunaprevir	↑	–	–	–	↓↓	–
Grazoprevir*	↓		↓			
Ombitasvir*	–	–	↓	–	–	–
Dasabuvir**	–	–	–	–	–	–
Ritonavir††,‡‡	↓↓↓	–	–	–	–	–
Sofosbuvir	–	–	–	–	–	–
Daclatasvir*	–	–	–	–	–	–
Ledipasvir	–	–	–	–	–	–
Elbasvir*	–	–	–	–	–	–

↑DAA induces enzyme: dose of co-administered CYP inducer should decrease or may remain the same. ↓DAA suppresses enzyme: dose of co-administered CYP inhibitor should increase or may remain the same

* Metabolised by CYP3A4.

† Metabolised by CYP2C8.

‡ Metabolised by CYP2C19.

§ Inhibits intestinal CYP3A4 transporters, but not hepatic CYP3A4 transporters.

¶ Metabolised by CYP3A5.

** Metabolised by CYP2C8 > CYP3A4 > CYP2D6.

†† Metabolised by CYP2D6.

‡‡ Metabolised by CYP3A.

regimens using paritaprevir concurrently with other DAAs that employ a multi-targeted approach towards HCV clearance appear to be better tolerated.[33, 89] Ombitasvir is an HCV NS5A inhibitor with pangenotypic picomolar anti-viral activity that is commonly co-administered with paritaprevir, along with the NS5B RNA non-nucleoside polymerase inhibitor, dasabuvir.[31–33, 87]

Treatment-emergent AEs uniquely associated with paritaprevir are elevated bilirubin and alanine aminotransferase (ALT) levels. One trial evaluated ombitasvir plus paritaprevir/ritonavir with or without ribavirin in patients with genotype 1 and 4 HCV infection.[32] The regimen appeared to be well tolerated, with the most commonly reported AEs being headache (29–33%), asthenia (24–33%), fatigue (7–18%), insomnia (5–16%), and nausea (9–17%); no patient discontinued treatment due to AEs. Elevated ALT and aspartate aminotransferase (AST) concentrations improved from baseline in week 1 and persisted through to the last protocol-indicated laboratory assessment 4 weeks after treatment cessation. 7% of patients experienced AEs that led to ribavirin dose reduction, but none required blood transfusion or erythropoietin.[32]

Paritaprevir and ritonavir are primarily metabolised by enzymes constituting the CYP3A pathway, while CYP enzymes play a minor role in the metabolism of ombitasvir (Table 1). However, all drugs are substrates of P-gp. As such, co-administration of this regimen with strong inhibitors of CYP3A or P-gp is contraindicated; concomitant use of CYP3A inhibitors may increase paritaprevir and ritonavir concentrations, while use with P-gp inhibitors may lead to spikes in systemic concentrations of all three medications. Adjustments in dosage should be made for concomitantly administered medications, as changes in dosage of paritaprevir/ritonavir and ombitasvir are usually not recommended.[47]

Paritaprevir/ritonavir/ombitasvir with dasabuvir. Coined the '3D regimen', fixed-dose paritaprevir/ritonavir/ombitasvir combination tablets co-packaged with dasabuvir taken with or without ribavirin is indicated for patients with HCV genotype 1 in many countries, including the USA.[31, 33, 86–89, 91] The most clinically significant AEs associated with this regimen are PI-associated hyperbilirubinemia due to competitive binding of bilirubin transporters, and self-limiting elevations of aminotransferase (ALT and AST) levels.

Phase III clinical trials evaluating ombitasvir/paritaprevir/ritonavir (25/150/100 mg q.d.) with dasabuvir (250 mg b.d.) and weight-based ribavirin in patients with genotype 1 HCV infection for 12–24 weeks have shown a

favourable AE profile in both treatment-experienced and treatment-naïve populations.[85–87] The most frequent clinically significant abnormality was grade 3-elevated (more than 3–10 times the upper limit of the normal range) total bilirubin levels, predominantly reflecting increased indirect bilirubin, with improvement or resolution without discontinuation of therapy (Table 2). Less than 1% of patients displayed elevated ALT levels of grade 3 (more than 5–20 times the upper limit of the normal range) or 4 (more than 20 times the upper limit of the normal range), with peak values generally occurring within the first 2 weeks of treatment and subsequently declining to normal range or grade 1 with ongoing treatment. Notably, the observed trends in bilirubin levels did not cause concomitant abnormalities in aminotransferase levels of grade 3 (more than 5–20 times the upper limit of the normal range) or 4 (more than 20 times the upper limit of the normal range). The AE profile for this active regimen compares favourably with that for a protease inhibitor plus peg-IFN and RBV.[85–87]

Noncirrhotic patients previously treated with peg-IFN and RBV who had a background of prior relapse, nonresponse, or null response most frequently experienced grade 3- or 4-elevated total bilirubin (2.4%), with increased levels resolving by post-treatment week 4. None of these patients went on to develop concomitant grade 3- or 4- elevations in ALT levels, and no patient discontinued treatment owing to hyperbilirubinaemia. Elevations of ALT levels of grade 3 or 4 occurred in 1.7% of patients in the active regimen group (Table 2).[88]

Table 2 | Adverse events experienced by patients treated with ritonavir-boosted paritaprevir, ombitasvir and dasabuvir with or without ribavirin therapy for at least 12 weeks in Phase III clinical trials (SAPPHIRE-1,[77] SAPPHIRE-II[80] and TURQUOISE-II[78])

	SAPPHIRE-1 (n = 473)	SAPPHIRE-II (n = 297)	TURQUOISE-II 12 weeks (n = 208)	TURQUOISE-II 24 weeks (n = 172)
Any AE	414 (87.5)	271 (91.2)	191 (91.8)	156 (90.7)
Patients with SAEs	10 (2.1)	6 (2.0)	13 (6.2)	8 (4.7)
Discontinuation	3 (0.6)	3 (1.0)	4 (1.9)	4 (2.3)
Deaths	0	0	1 (0.5)	0
Common AEs				
Fatigue	164 (34.7)	99 (33.3)	68 (32.7)	80 (46.5)
Headache	156 (33.0)	108 (36.4)	58 (27.9)	53 (30.8)
Nausea	112 (23.7)	60 (20.2)	37 (17.8)	35 (20.3)
Pruritus	80 (16.9)	41 (13.8)	38 (18.3)	33 (19.2)
Insomnia	66 (14.0)	42 (14.1)	32 (15.4)	31 (18.0)
Diarrhoea	65 (13.7)	39 (13.1)	30 (14.4)	29 (16.9)
Asthenia	57 (12.1)	47 (15.8)	29 (13.9)	22 (12.8)
Rash	51 (10.8)	72 (24.2)	23 (11.1)	25 (14.5)
Irritability			15 (7.2)	21 (12.2)
Anaemia	30 (6.3)	29 (9.8)	16 (7.7)	18 (10.5)
Dyspnoea		37 (12.5)	12 (5.8)	21 (12.2)
Grade 3 or 4 chemical or hematological abnormality*				
ALT	4/469 (0.9)	5/296 (1.7)	6 (2.9)	0
AST	3/469 (0.6)	3/296 (1.0)	1 (0.5)	0
AP	0	0	0	0
Bilirubin	13/469 (2.8)	7/296 (2.4)	28 (13.5)	9 (5.2)
Haemoglobin	0	1/296 (0.3)	3 (1.4)	1 (0.6)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase.

Common AEs are those that occurred in at least 10% of patients in any study group.

* An aminotransferase (ALT or AST) level of grade 3 was defined as a level that was more than 5–20 times the upper limit of the normal range, and grade 4 as the elvel that was more than 20 times the upper limit of the normal range. An AP level of grade 3 was defined as a level that was more than 5–20 times the upper limit of the normal range, and grade 4 as a level that was more than 20 times the upper limit of the normal range. A total bilirubin level of grade 3 was defined as a level that was more than 3–10 times the upper limit of the normal range, and grade 4 as a level that was more than 10 times the upper limit of the normal range. A haemoglobin level of grade 3 was defined as a level that was less than 8.0–6.5 g/dL, and grade 4 as a level that was less than 6.5 g/dL.

Elevations in total bilirubin levels occurred at a higher frequency in treatment-experienced patients with Child–Pugh class A cirrhosis than in noncirrhotic patients. Six patients exhibited post-baseline elevations in ALT levels of at least grade 3 during treatment or within 30 days after the end of treatment, with two patients discontinuing therapy.[86]

Ribavirin confers additional benefits for patients with genotype 1a infection, but is accompanied by an additional AE profile. One phase III, placebo-controlled trial on noncirrhotic, treatment-naïve patients with genotype 1 HCV infection[87] showed that groups receiving ribavirin-containing regimen exhibited a higher frequency of AEs compared to their counterparts receiving ribavirin-free regimen. Regardless of genotypic subtype, a higher proportion of patients receiving the ribavirin-containing regimen had elevated serum bilirubin levels compared to their counterparts, with mean levels peaking 1 week after the start of treatment and normalising thereafter. The maximum observed bilirubin levels were 6.5 mg per decilitre (110 μmol/L) in the genotype 1a patients and 9.4 mg/dL (160 μmol/L) in genotype 1b patients. Elevations in bilirubin levels were not associated with elevations in aminotransferase levels; these abnormalities appeared to affect neither the likelihood of treatment success nor rate of treatment discontinuation. Overall, the observed AEs were consistent with those reported in past trials evaluating these regimens.

Providers should take into consideration known drug–drug interactions relevant to paritaprevir/ritonavir and ombitasvir regimen when assessing co-administration of drugs with the 3D regimen. In addition to existing contraindications, providers must also account for the presence of dasabuvir, primarily metabolised by CYP2C8 enzymes, as co-administration with CYP2C8 inhibitors may lead to increased dasabuvir plasma concentrations (Table 1). Adjustments in dosage should be made for concomitantly administered medications, as modifications in the fixed-dose 3D regimen components are usually not possible or recommended.[47, 92, 93]

Asunaprevir-containing regimens. Asunaprevir is a highly selective anti-viral that directly inhibits HCV NS3/4A protease.[94] Significant safety issues associated with asunaprevir are generally limited to mild increases in aminotransferase levels, occasionally accompanied by elevations in mean plasma bilirubin. The precise mechanisms by which these hematological alterations occur have yet to be elucidated.[11, 94–97]

In a large global phase III trial that evaluated asunaprevir (100 mg b.d.) and daclatasvir (60 mg q.d.) for 24 weeks in patients with HCV genotype 1b,[98] the associated AE profile was similar in treatment-naïve patients treated with combination therapy and in those receiving placebo, and AEs precipitating treatment discontinuation were rare (1–3% across all arms). Across all groups, 2–3% of patients experienced an increase in ALT greater than fivefold, and only 0–1% of patients observed increases in total bilirubin greater than 2.5-fold. This regimen in patients with comparable HCV subtype demographics produced similar results in an open-label phase III trial in Japan.[95] Elevations in ALT and AST were the most frequent AEs, leading to 10 of 222 patients prematurely discontinuing treatment. Elevations in bilirubin and transaminases rapidly corrected in most patients after 2–4 weeks while on treatment. In addition, elevations rapidly reversed post-treatment for eight of ten patients who discontinued treatment.[95]

Hepatotoxicity of asunaprevir has led to a decrease in dosage (to 100 mg b.d.) in several studies; however, based on reassuring results from the most recent phase III trials, the potential risk of hepatic flare does not present a substantial obstacle to using asunaprevir in combination DAA therapy.[95, 98] Notwithstanding, decompensation in patients with liver disease is a clear contraindication for therapy with asunaprevir due to its highly impaired pharmacokinetics and dramatically increased risk for hepatic flare in this setting.[11, 95, 98]

Finally, asunaprevir has modest potential for drug–drug interactions via its role in CYP metabolism (Table 1), P-gp transport and OATP receptor saturation.[94, 99]

Daclatasvir-containing regimens. As a first-in-class inhibitor of a protein implicated in several key steps of the HCV replication cycle, daclatasvir is believed to possess potent anti-viral activity and has shown significant promise in clinical trials.[46, 97, 98, 100–103]

Administration of daclatasvir in combination with peg-IFN and RBV or with other DAAs (such as asunaprevir or sofosbuvir), is accompanied by clinically unremarkable side effects. The anti-viral appears to be well tolerated across multiple genotypes, and severe adverse events (SAEs) exclusively related to daclatasvir are not widely known. The most commonly observed side effects in patients administered daclatasvir in combination with peg-IFN and RBV are fatigue (43–45%) and headache (33–41%), occurring with equal frequency in both treatment and placebo groups.[46]

When opting for daclatasvir plus asunaprevir therapy in several phase II and III clinical trials, self-limiting elevations of serum ALT in approximately 5–29% of patients have been reported. Incidence of ALT elevations was highest at doses >200 mg b.d., or when asunaprevir was co-administered with peg-IFN and RBV. However, findings from several studies implicate asunaprevir as the more attributable cause for elevated ALT levels.[46, 95, 98]

Investigating a 12-week regimen of a fixed-dose combination of co-formulated daclatasvir/asunaprevir/beclabuvir (30/200/150 mg b.d.) with or without ribavirin in a broad range of patients with genotype 1 HCV infection, two trials provide compelling results for the safety of this all-oral regimen.[97, 101] Patients with genotype 1 HCV infection reported seven SAEs, all considered unrelated to study treatment, with three SAEs leading to treatment cessation.[97] One of the trials evaluating the regimen in cirrhotic patients offered favourable results, reporting three treatment-related SAEs and four AEs leading to therapy discontinuation.[101] The most common AEs from both trials were headache (25.8% and 19.8%) and fatigue (16.6% and 19.8%).[97, 101] Daclatasvir has a potential for modest drug–drug interactions with other medications. Metabolised by hepatic CYP3A4, daclatasvir is a mild inhibitor of P-gp and OATP1B1. When co-administered with drugs that strongly activate CYP3A4 and P-gp, the drug is metabolised more quickly thereby reducing daclatasvir exposure; in such cases, the dose of daclatasvir must be increased from 60 to 90 mg. Conversely, daclatasvir dosage must be decreased from 60 to 30 mg when co-administered with strong inhibitors of CYP3A4.[46, 100, 104]

Ledipasvir-containing regimens. As a small molecule inhibitor of HCV-encoded NS5A polymerase, ledipasvir is one of the most potent and well tolerated anti-virals on the market. Across three studies evaluating investigational fixed-dose ledipasvir/sofosbuvir (90/400 mg q.d.) with and without ribavirin for eight, 12, or 24 weeks in genotype 1 treatment-naïve, treatment-experienced, non-cirrhotic, and patients with compensated cirrhosis,[105–107] those who received the ribavirin-containing regimen had higher rates of common AEs associated with ribavirin therapy including fatigue, headache, nausea, insomnia and diarrhoea, the majority of which were mild-to-moderate in severity (Table 3).[108] Likewise, mean decreases in the haemoglobin levels reported by these patients were greater in magnitude than experienced by patients in parallel treatment duration groups receiving ledipasvir plus sofosbuvir alone, and thus were consistent with ribavirin-mediated haemolysis. Furthermore, those receiving the ribavirin-containing regimen suffered from increased incidence of hyperbilirubinemia (reported in 1–41% of patients in each group), while no such effect was observed in their ribavirin-free counterparts.[106] Less than 1% of patients discontinued therapy due to treatment-emergent AEs, though medical intervention to address treatment-emergent AEs (such as dose modification or use of additional medications) were more common in patients receiving the ribavirin-containing regimen.[108] The high SVR rates and favourable safety profile reported with use of this regimen across a variety of genotype 1 populations suggest that a simple, short course of single tablet ledipasvir/sofosbuvir is broadly well tolerated and thus eliminates the need for both ribavirin and interferon.

NS5b inhibitor-based regimen

Sofosbuvir-containing regimens. Sofosbuvir, a prodrug of a uridine nucleotide analogue inhibitor of NS5B polymerase, became one of the first commercially available NS5B inhibitors in early 2014. While the drug is quite effective, has pangenotypic activity, and a high barrier to resistance, its one limitation is in those with advanced renal disease. Sofosbuvir is primarily eliminated from the body through filtration in the kidney after first being converted to GS-331007, an inactive nucleoside metabolite.[109] Studies investigating the pharmacokinetics of single- or multi-dosing reported that no dosage modifications were required for patients with mild-to-moderate renal impairment. However, for patients with creatinine clearance less than 30 mL/min including those on haemodialysis, no dosage recommendation for sofosbuvir has been established.[6, 61, 110] Single-dose pharmacokinetics demonstrated the area under the curve (AUC) of the sofosbuvir metabolite GS-331007 and, to a lesser extent, sofosbuvir itself, increased with worsening renal status. Patients with mild, moderate and severe renal impairment displayed approximately 56%, 90% and 456% higher GS-331007 metabolite AUC, respectively, relative to subjects with normal renal function.[109]

Several trials evaluated sofosbuvir (400 mg q.d.) administered to nearly 1000 treatment-naïve and treatment-experienced patients with genotypes 2 and 3 chronic HCV infection as part of an all-oral treatment.[26, 111, 112] The regimen was administered in combination with weight-based ribavirin for 12 or 16 weeks in patients with genotypes 2 and 3, or with peg-IFN and weight-based RBV for 12 weeks in patients with genotypes 1, 4, 5 and 6.[26, 111] Sofosbuvir was associated

Table 3 | Adverse events experienced by patients treated with sofosbuvir and ledipasvir with ribavirin for at least 8 weeks in Phase III clinical trials (ION-1,[93] ION-2[94] and ION-3[95])

	ION-1* 12 weeks (*n* = 217)	ION-1* 24 weeks (*n* = 217)	ION-2* 12 weeks (*n* = 111)	ION-2* 24 weeks (*n* = 111)	ION-3† 8 weeks (*n* = 216)	ION-3†‡ 12 weeks (*n* = 216)
Any AE	185 (85)	200 (92)	96 (86)	100 (90)	165 (76)	149 (69)
Patients with SAEs	7 (3)	7 (3)	0	3 (3)	1 (<1)	5 (2)
Discontinuation	0	6 (3)	0	0	1 (<1)	2 (1)
Common AEs						
Fatigue	79 (36)	82 (38)	45 (41)	50 (45)	75 (35)	49 (23)
Headache	49 (23)	65 (30)	26 (23)	35 (32)	54 (25)	33 (15)
Insomnia	45 (21)	47 (22)	18 (16)	19 (17)	26 (12)	15 (7)
Nausea	37 (17)	32 (15)	20 (18)	25 (23)	38 (18)	24 (11)
Diarrhoea	18 (8)	14 (6)	5 (5)	17 (15)	13 (6)	9 (4)
Rash	21 (10)	27 (12)	11 (10)	16 (14)	19 (9)	5 (2)
Irritability	17 (8)	24 (11)	13 (12)	12 (11)	29 (13)	9 (4)
Cough	21 (10)	25 (12)	16 (14)	16 (14)	12 (6)	7 (3)
Anaemia	25 (12)	22 (10)	9 (8)	12 (11)	17 (8)	2 (1)
Hematological abnormality						
Decreased haemoglobin <10 g/dL	20 (9)	16 (7)	2 (2)	9 (8)	11 (5)	1 (<1)
Lymphocyte count <500 per mm^3	1 (<1)	0	2 (2)	4 (4)	1 (<1)	0

* Common AEs are those that occurred in at least 10% of patients in any study group.

† Common AEs are those that occurred in at least 5% of patients in any study group.

‡ Regimen without ribavirin.

with no clinically significant AEs beyond headache, fatigue, nausea, insomnia, pruritus, anaemia and dizziness (Table 4). A consistently lower incidence of AEs associated with organ systems was reported among patients receiving sofosbuvir plus ribavirin compared to their counterparts receiving peg-IFN and RBV, and less than 2% of patients discontinued treatment due to AEs. The most common AEs included flu-like symptoms and were consistent with the safety profiles of peg-IFN and RBV used with sofosbuvir in genotype 1 patients. Notably, presence of cirrhosis had no additive effect on the AE profile of patients treated with interferon-free regimen. In the absence of any substantial differences in AEs during treatment with sofosbuvir plus ribavirin, adjustments in treatment duration to 24 weeks for genotype 3 HCV-infected patients appeared to provide an additional benefit for clearing the virus without compromising overall safety.[112] These studies demonstrated excellent tolerability of sofosbuvir-based HCV therapy without compromising efficacy, while mitigating the need for interferon injections to just 12 weeks or otherwise completely eliminating interferon from the regimen when treating patients infected with genotypes 1, 4, 5 and 6.

SPECIAL POPULATIONS

The substantial AE profile of interferon-based regimen limits the utility of these therapeutic agents for treating recurrent HCV infection in historically difficult-to-treat populations. Concerted research efforts are being made to evaluate second-generation DAAs in patient populations for whom treatment options are limited.

HCV/HIV co-infected patients

Patients co-infected with HCV and HIV are at an increased risk for developing liver cirrhosis and hepatic decompensation. One trial evaluated interferon-free ombitasvir/paritaprevir/ritonavir (25/150/100 mg q.d.) and dasabuvir (250 mg b.d.) regimen for 12 or 24 weeks in patients with HCV-1/HIV-1 co-infection.[89] The 3D-plus-ribavirin regimen was generally well tolerated in this study population that included cirrhotic and noncirrhotic patients, and treatment-naïve and treatment-experienced patients. Although the majority of patients experienced AEs (89%), most were mild-to-moderate in severity. One patient reported a treatment-emergent SAE, while no patients discontinued treatment due to AEs. The most common side effects were fatigue (48%), insomnia (19%), nausea (17%) and headache (16%). Laboratory abnormali-

Table 4 | Adverse events experienced by patients treated with sofosbuvir and ribavirin with or without pegylated interferon for at least 12 weeks (NEUTRINO,[25] FISSION,[25] POSITRON,[99] FUSION,[99] VALENCE[100])

	NEUTRINO* 12 weeks (*n* = 327)	FISSION* 12 weeks (*n* = 256)	POSITRON† 12 weeks (*n* = 207)	FUSION† 12 weeks (*n* = 103)	FUSION† 16 weeks (*n* = 98)	VALENCE† 12 weeks (*n* = 84)	VALENCE† 24 weeks (*n* = 250)
Any AE	310 (95)	220 (86)				72 (86)	229 (92)
Patients with SAEs	4 (1)	7 (3)	11 (5)	5 (5)	3 (3)	0	10 (4)
Discontinuation	5 (2)	3 (1)	4 (2)	1 (1)	0	1 (1)	1 (<1)
Common AEs							
Fatigue	192 (59)	92 (36)	91 (44)	46 (45)	46 (47)	19 (23)	75 (30)
Headache	118 (36)	64 (25)	43 (21)	26 (25)	32 (33)	24 (29)	74 (30)
Insomnia	81 (25)	31 (12)	39 (19)	21 (20)	28 (29)	9 (11)	41 (16)
Nausea	112 (34)	46 (18)	46 (22)	22 (21)	20 (20)	26 (31)	33 (13)
Diarrhoea	38 (12)	23 (9)	19 (9)	15 (15)	6 (6)	4 (5)	30 (12)
Rash	59 (18)	23 (9)	18 (9)	7 (7)	12 (12)		
Irritability	42 (13)	25 (10)	19 (9)	15 (15)	11 (11)	4 (5)	26 (10)
Pruritus	54 (17)	19 (7)	23 (11)	12 (12)	7 (7)	20 (24)	67 (27)
Hematological abnormality							
Decreased haemoglobin level							
<10 g/dL	74 (23)	23 (9)	15 (7)	10 (10)	5 (5)	5 (6)	15 (6)
<8.5 g/dL	8 (2)	1 (<1)	2 (1)	2 (2)	0	1 (1)	1 (<1)
Platelet count <50 000 per mm^3	1 (<1)	0	0	2 (2)	0	0	3 (1)
Decreased lymphocyte count <500 per mm^3	17 (5)	0	1 (<1)	6 (6)	0	1 (1)	5 (2)
Decreased neutrophil count 500 to <750 per mm^3	49 (15)	0	0	0	0	1 (1)	0
Decreased white-cell count 1000–1500 per mm^3	18 (6)	0	0	0	0	0	0

* Common AEs are those that occurred in at least 15% of patients in any study group.

† Common AEs are those that occurred in at least 10% of patients in any study group.

ties were infrequent, with the most commonly observed being PI-mediated elevated bilirubin (predominately indirect) and reduced haemoglobin. No patients required erythropoietin or transfusion. HCV/HIV co-infected patients treated with ledipasvir (90 mg q.d.) and sofosbuvir (400 mg q.d.) for 12 weeks reported mild-to-moderate AEs (77%), the most common being headache (25%), fatigue (21%), and diarrhoea (11%).[113] Again, no patient discontinued treatment due to AEs. Laboratory abnormalities reported by >1% of patients included elevations in lipase, creatinine kinase (none study-related), and serum glucose (all in patients with known diabetes or abnormal baseline glycosylated haemoglobin levels). This regimen showed limited potential for clinically significant drug–drug interactions with most co-administered antiretrovirals, except with tenofovir disoproxil fumarate.[113]

Patients with decompensated cirrhosis

In the era of conventional interferon-based regimens, treatment options for patients with decompensated liver disease were limited and prognosis was poor due to suboptimal response, tolerability, and high potential for worsening hepatic impairment.[114, 115] Although interferon-free DAA combination therapy circumvents the adverse effects of interferon and several studies have thus evaluated this treatment modality in the setting of compensated cirrhosis, there is still limited experience of its use in those with advanced cirrhosis (Child–Pugh class B or C). Several predictors of treatment complications in those with cirrhosis have been identified as they relate to DAA-based treatment, including low albumin at baseline and increased age.[116–118] In several studies, older patients with a greater degree of liver decompensation and more severe cirrhosis faired worse than their younger counterparts, presumably due to reduced drug delivery resulting from shunting within and around the liver that is caused by cirrhosis.[116–118] In accord with these findings, it has been suggested that anti-viral therapy may bring about more AEs and lower efficacy through local direct hepatoxicity or more general systemic toxicity in patients with cirrhosis.[116] Use of several DAAs has also resulted in dose-related toxicity. Grazoprevir dosage was reduced

when administered in patients with cirrhosis to mitigate the increased risk of AEs, but this compromised its pangenotypic coverage.[119] In contrast, dose adjustment of elbasvir and ribavirin led to high rates of cure and minimal reports of increased transaminase levels.[56] Asunaprevir has also been associated with hepatoxicity, including biochemical elevations and augmented exposure in patients with moderate-to-severe hepatic impairment. However, accompanying AEs (including elevations in INR, bilirubin, and ALT) resolved with drug discontinuation in patients with cirrhosis.[101] Poor outcomes in those with cirrhosis have even led to changes in SOC in the present era of DAAs. Real-world data of triple therapy consisting of telaprevir or boceprevir with peg-IFN and RBV revealed incidence of profound systematic toxicity particularly in patients with cirrhosis, resulting in contraindication of these protease inhibitors to treat HCV infection.[120] Finally, low albumin levels, usually a proxy for liver dysfunction and commonly observed in those with decompensated cirrhosis, may have a direct relationship with infectious complications, possibly through prostaglandin E2 inhibition of macrophages.[121]

In spite of treatment data for these patients being sparse, results of recent clinical trials with DAA combination therapy show promise for sofosbuvir-containing intervention in this target population. In one study, all-oral sofosbuvir (400 mg q.d.) and ledipasvir (90 mg q.d.) plus variable-dose ribavirin regimen was administered for 12 or 24 weeks in patients with advanced cirrhosis.[35] Though most patients experienced AEs, 4% of patients had to discontinue treatment prematurely due to treatment-related AEs, most often due to sepsis, acute renal failure, dyspnoea, and gastrointestinal haemorrhage. The most common cause of death in 13 patients was septic shock accompanied by multi-organ failure, but none of the deaths were assessed as being treatment-related. Pre-transplantation patients most frequently experienced increased bilirubin levels followed by lymphopenia, while post-transplantation patients most commonly reported decreased haemoglobin and lymphocyte levels. Ribavirin-induced haemolysis accounted for hyperbilirubinemia and observed decreases in haemoglobin levels.

In another trial, this regimen was administered in those with advanced cirrhosis with impressive results.[122] Of the cohort of patients with decompensated cirrhosis, 24% reported SAEs but no deaths were assessed as being related to treatment. Most notably, approximately one-third of patients with Child–Pugh class B cirrhosis improved to Child–Pugh class A, while approximately one half of patients with Child–Pugh class C cirrhosis improved to Child–Pugh class B.

Finally, a third multicenter, prospective trial investigating this regimen in patients with decompensated cirrhosis reported ledipasvir co-formulated with sofosbuvir with ribavirin was generally safe and well tolerated.[123] While almost all patients experienced AEs, grade 3-4 AEs were more frequently reported by patients on 24 weeks of treatment compared to their counterparts on 12 weeks of treatment (28% vs. 7% for patients with Child–Pugh class B cirrhosis, 42% vs. 26% for patients with Child–Pugh class C cirrhosis). Of 128 patients on treatment, 30 experienced SAEs, with four assessed as being related to the active regimen: anaemia (2), hepatic encephalopathy, and peritoneal haemorrhage. Three patients had to discontinue treatment due to sepsis, hepatic encephalopathy, and peritoneal haemorrhage. Six patients died during the course of treatment due to septic shock (2), multi-organ failure and septic shock (2), oliguric renal failure, and cardiac arrest.

An investigational daclatasvir-based regimen showed promise in a recent phase III trial to effectively treat those with HCV decompensated cirrhosis.[124] No SAEs related to study medications occurred during the course of treatment. AEs experienced by greater than 10% of patients were headache (15%), fatigue (18%), anaemia (20%), diarrhoea (8%) and nausea (17%).

Transplant recipients

HCV-related liver disease invariably occurs in patients following liver transplantation, and has a rapidly progressing course in some. Almost half the patients who require a liver transplant are infected with HCV, and viraemia prior to transplantation is currently an absolute predictor of HCV recurrence post-transplantation. Second-wave DAA therapy has the potential to circumvent the use of interferon-based treatment and improve long-term, post-transplantation outcomes. In this nascent field of research, clinical trials evaluating interferon-sparring regimen administered to this subgroup of patients are few in number. Most notably, DAA treatment has led to drug–drug interactions with immunosuppressive agents, particularly with ciclosporinand tacrolimus. Since both immunosuppressants are substrates of CYP3A and P-gp, therapy should be limited to agents that are neither inhibitors nor inducers of these molecules. One recent trial evaluated an all-oral regimen consisting of ombitasvir/paritaprevir/ritonavir (25/150/150 mg q.d.) combination tablets with dasabuvir (250 mg b.d.) and variable-dose ribavirin for 24 weeks in transplant recipients with recurrent HCV

genotype 1 infection and without advanced fibrosis.[90] Patients reported clinically manageable AEs associated with the regimen, regardless of prior interferon-based therapy. The most common side effects were fatigue, headache and cough. Transient, low-grade aminotransferase and bilirubin elevations were observed in two patients (6%), and nine patients (26%) reported decreased haemoglobin with one patient requiring erythropoietin. All laboratory abnormalities were similar to those reported in patients who had not undergone transplantation. A single patient discontinued treatment after 18 weeks due to rash, memory impairment and anxiety, but still cleared the virus. A major limitation of this regimen was the need to modify the dose of tacrolimus and cyclosporine, as close monitoring of the levels of the calcineurin inhibitor drugs was necessary due to substantial drug–drug interactions.

Another trial evaluated sofosbuvir (400 mg q.d.) and ribavirin (starting at 400 mg q.d.) for 24 weeks in patients with a broad range of demographics including genotypes 1, 3 and 4 genotypes, cirrhosis or lack thereof, and no exposure or prior exposure to treatment.[125] Six study participants reported ten SAEs and the same number reported AEs, but only a single AE was deemed to be study-related. In addition, the two AEs that led to treatment discontinuation were not associated with the regimen. The incidence of laboratory abnormalities mirror that observed in the other trial evaluating ombitasvir/paritaprevir/ritonavir with dasabuvir and ribavirin, the most frequent being lymphopenia (35% of patients).[90, 125] Decreases in haemoglobin were consistent with the safety profile of ribavirin, with eight (20%) patients receiving erythropoietin and/or blood products at the discretion of the investigator. Eight patients required increased tacrolimus dosing during therapy, five patients required decreases in tacrolimus during the treatment course, and four patients required reductions in ciclosporin, although sofosbuvir was not thought to have interacted with any concomitant immunosuppressants (tacrolimus, cyclosporine, mycophenolate, prednisone and azathioprine).

Patients with HCV genotype 3

Additional studies with all-oral daclatasvir in combination with sofosbuvir have been conducted in patients with a high unmet need, including post-transplantation patients, those co-infected with HCV/HIV, and patients with genotype 3 HCV infection.[102, 103] Daclatasvir plus sofosbuvir was well tolerated, with no AEs leading to clinically significant bleeding, pancreatitis, or treatment discontinuation. The most common AEs (in >10% of patients) were headache, fatigue and nausea. Treatment-emergent grade 3 AEs (2%) and laboratory abnormalities occurred in no greater than 2% of patients and were reversible, with hematological deviations in absolute lymphocytes, platelets, INR and lipase.[103]

CLINICAL DEVELOPMENT OF OTHER SECOND-GENERATION DAAs

The HCV therapy development pipeline is currently populated by several second-wave anti-virals, with many of them proving their utility in clinical evaluation. Among these trials are grazoprevir co-administered with elbasvir, and velpatasvir plus sofosbuvir.[55, 126, 127] Preliminary results are promising, as these interferon-sparing regimens are very well tolerated and are favourable also due to their once-daily dosing potential. Very few SAEs have been reported with the use of elbasvir and grazoprevir with or without ribavirin. The most frequently experienced AEs were fatigue, headache and nausea, and occurred at comparable rates in patients on

Table 5 | Major adverse events of novel direct-acting anti-virals at-a-glance

Anti-virals	Unique adverse events or limitations
Protein inhibitors	
Simeprevir	Hyperbilirubinaemia Photosensitivity Contraindicated in those with Child–Pugh class B or C cirrhosis
Paritaprevir (boosted with ritonavir)	Hyperbilirubinaemia Elevated ALT (drug–drug interactions due to ritonavir) Contraindicated in those with Child–Pugh class B or C cirrhosis
Asunaprevir	Elevated aminotransferase levels and infrequently elevated bilirubin levels
Grazoprevir	Well tolerated
NS5A inhibitors	
Ledipasvir	Low barrier to viral resistance, well tolerated (drug–drug interactions with acid suppressants)
Ombitasvir	Low barrier to viral resistance, well tolerated
Daclatasvir	Low barrier to viral resistance, well tolerated
Elbasvir	Low barrier to viral resistance, well tolerated
NS5B inhibitors	
Sofosbuvir	No dosage recommendation for those with severe renal impairment (estimated GFR less than 30 mL/min)
Dasabuvir	No unique AEs, thus far well tolerated
Beclabuvir	No unique AEs, thus far well tolerated

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the active regimen and in those on placebo.[128] ALT elevations from normal levels occurred in just 0.8% of patients receiving treatment, often resolving with continuing therapy or scheduled cessation of therapy. Tolerability was not impacted by treatment duration or presence of compensated cirrhosis.[128] Time will tell whether these favourable clinical profiles will translate into widely reproducible results.

POSTMARKETING REPORTS OF APPROVED DAAS

Post-marketing surveillance studies refining the safety profile of DAA regimens approved for clinical use are few and far between. Investigating altered drug metabolism in patients undergoing HCV treatment with other comorbidities and drug–drug interactions among DAAs and concomitantly administered medications remain at the forefront of optimising DAA therapy. A case concerning DAA/non-DAA drug interaction suggested simeprevir administered with peg-IFN and RBV therapy may augment the risk of interstitial pneumonitis caused by interferon-based therapy, as evidenced by earlier onset of the condition compared to conventional peg-IFN and RBV therapy.[129] Another case concerning DAA/non-DAA drug interaction in a patient with recurrent HCV

Table 6a | Serious or severe AEs and mortality associated with simeprevir-based therapy

Regimen	Patient population	Duration (weeks)	Number of SAEs/total treated	Number of deaths
SIM 100 mg q.d. PR	Treatment-naïve, GT 1[20] Treatment-experienced nonresponders and relapsers, GT 1[21]	24 or 48 24 or 48	4/123 11/155	0 0
SIM 150 mg q.d. PR	Treatment-naïve, GT 1[22, 23] Treatment-experienced relapsers and nonresponders, GT 1[24]	24 or 48 24 or 48	26/521 13.4/639	2 (none study-related) 1
SIM 150 mg q.d. SOF 400 mg q.d.	Treatment-naïve and treatment-experienced, noncirrhotic and compensated cirrhotic[27–29]	8–24	13/580	3 (1 study-related)

SIM, simeprevir; SOF, sofosbuvir; PR, pegylated interferon and ribavirin.

SAEs indicated for the entire treatment period, not just the regimen period. Serious AEs reported may have resulted in poor outcomes, including death. The total number treated does not include the number of patients on placebo in the respective studies reviewed.

Table 6b | Serious or severe AEs and mortality associated with OBV/PTV/ritonavir with or without DSV and RBV

Regimen	Patient population	Duration (weeks)	Number of SAEs/total treated	Number of deaths
OBV 25 mg q.d. PTV 150 mg q.d. ritonavir 100 mg q.d. with or without RBV	Treatment-naïve GT 4, noncirrhotic[32]	12	1/86 (without RBV)	*
OBV 25 mg q.d. PTV 150 mg q.d. ritonavir 100 mg q.d. RBV	Treatment-experienced GT 4, noncirrhotic[32]	12	0/49	0
OBV 25 mg q.d. PTV 150 mg q.d. ritonavir 100 mg q.d. DSV 250 mg b.d. RBV b.d.	Treatment-naïve, GT 1[80, 85] Treatment-naïve and treatment-experienced, GT 1, cirrhotic[86] Treatment-experienced relapsers, noncirrhotic[88] Treatment-naïve and treatment-experienced, HCV-1/HIV-1, noncirrhotic and cirrhotic[89] Post-liver transplant, no fibrosis or mild fibrosis[90]	12 12 or 24 12 12 or 24 24	31/1197 21/380 6/297 2/63 2/34	0* 1 0 0 0

OBV, ombitasvir; PTV, paritaprevir; DSV, dasabuvir; RBV, ribavirin.

SAEs indicated for the entire treatment period, not just the regimen period. Serious AEs reported may have resulted in poor outcomes, including death*. The total number treated does not include the number of patients on placebo in the respective studies reviewed.

and cirrhosis was the first report of seizures, potentially precipitated by simeprevir-containing therapy (simeprevir was co-administered with sofosbuvir, although its use was contraindicated in this patient as he required lifelong itraconazole treatment).[130]

While risk of interstitial pneumonitis and seizures is still being assessed, more widespread cases of cardiac and hepatobiliary events in patients treated with sofosbuvir-based regimens co-administered with another DAA, including simeprevir, and amiodarone, an anti-arrhythmic medication with a markedly long half-life, have led to increased vigilance on the part of prescribing providers and an addendum on labels of these anti-viral agents.

Cardiac events included symptomatic bradycardia, pacemaker intervention, and fatal cardiac arrest. Six patients experienced symptoms of bradycardia within 24 hours of the first dose of therapy, while symptoms developed over two to 12 days in the remaining three patients.[131] While all patients were on amiodarone and sofosbuvir, five also received daclatasvir, three ledipasvir and one simeprevir. Notably, seven of the nine patients were concurrently taking a beta-blocker. One patient died of cardiac arrest, three patients required placement of a pacemaker to regulate heart rhythms, and the remaining patients recovered after discontinuing either DAA therapy or amiodarone. Several evidences suggest a causal link between DAA therapy and development of symptomatic bradycardia in these patients concomitantly receiving amiodarone: (i) rechallenge with therapy resulted in recurrence of symptomatic bradycardia in three patients who continued on amiodarone, (ii) a patient who had stopped amiodarone treatment 8 weeks prior to rechallenge with therapy was asymptomatic for bradycardia and (iii) symptoms occurred within hours to

Table 6c | Serious or severe AEs and mortality associated with DCV- and ASV-containing regimen

Regimen	Patient population	Duration (weeks)	Number of SAEs/total treated	Number of deaths
DCV 60 mg q.d. ASV 100 mg b.d.	Treatment-naïve, GT1b, noncirrhotic and compensated cirrhotic[98]	24	12/205	0
	IFN-intolerant/ineligible, treatment-experienced, GT1b, noncirrhotic and compensated cirrhotic[86, 98]	24	40/662	0
DCV 30 mg b.d. ASV 200 b.d.	Treatment-naïve and treatment-experienced, GT 1, noncirrhotic[97]	12	7/415 (none study-related)	1 (not study-related)
BCV 75 mg b.d.	Treatment-naïve and treatment-experienced, compensated cirrhotic[101]	12	3/202	0

DCV, daclatasvir; ASV, asunaprevir; BCV, beclabuvir.

SAEs indicated for the entire treatment period, not just the regimen period. Serious AEs reported may have resulted in poor outcomes, including death. The total number treated does not include the number of patients on placebo in the respective studies reviewed.

Table 6d | Serious or severe AEs and mortality associated with DCV and SOF regimen

Regimen	Patient population	Duration (weeks)	Number of SAEs/total treated	Number of deaths
DCV 60 mg q.d. SOF 400 mg q.d. with or without RBV	Treatment-naïve, GT 1-3[102]	12 or 24	2/70 (with RBV), 7/100 (without RBV) 1/82 (12 weeks of treatment), 8/88 (24 weeks of treatment)	*
	Treatment-experienced, GT 1-3[102]	24	1/20 (with RBV), 0/21 (without RBV)	*
DCV 60 mg q.d. SOF 400 mg q.d.	Treatment-naïve and treatment-experienced, GT 3[103]	12	1/152	0

DCV, daclatasvir; SOF, sofosbuvir; RBV, ribavirin.

SAEs indicated for the entire treatment period, not just the regimen period. Serious AEs reported may have resulted in poor outcomes, including death*. The total number treated does not include the number of patients on placebo in the respective studies reviewed.

days of therapy initiation in those taking amiodarone.[132] Many mechanisms explaining the clinical manifestations of amiodarone drug–drug interaction have been hypothesised: amiodarone mediates P-gp inhibition, which leads to increases in plasma concentrations of sofosbuvir (a P-gp substrate); or co-administration of daclatasvir, ledipasvir or simeprevir may inhibit CYP3A drug transporter, thereby leading to acute toxicity.[132] The most plausible explanation may lie in the high protein-binding tendency of daclatasvir, ledipasvir, simeprevir and amiodarone. Addition of DAAs may displace amiodarone from its binding site, releasing the free active form of the drug into the bloodstream, potentially leading to more potent slowing of heart rate as was reported by these cohorts.[131, 132] The role of beta-blockers in this regimen was difficult to assess, but drug–drug interactions of beta-blockers with DAAs may also increase the risk of bradycardia by their known mechanism of action.[132]

Most cases of hepatic decompensation or hepatic failure from post-approval use of simeprevir with peg-IFN and RBV or with sofosbuvir were reported by patients with advanced cirrhosis who were already at an increased risk for worsening liver function. Due to the minimal data available, simeprevir is contraindicated in patients with decompensated liver disease or severe cirrhosis.[72, 73]

The 3D regimen is contraindicated in patients with severe hepatic impairment due to potential toxicity.[92, 93] A total of 26 cases worldwide were considered to be potentially related to administration of the 3D regimen, with liver injury occurring within one to 4 weeks of starting treatment.[133, 134] Furthermore, real-world data revealed increased incidence of immune system disorders, primarily hypersensitivity reactions including angioedema, and hepatobiliary disorders often leading to liver failure.[134] Such AEs were reported mostly in patients with cirrhosis or underlying advanced liver disease, with several cases leading to accelerated liver failure and indication for orthotopic liver transplantation.

Table 6e | Serious or severe AEs and mortality associated with LDV and SOF regimen

LDV 90 mg q.d. SOF 400 mg q.d. with or without RBV b.d.	Treatment-naïve, GT 1[96, 105]	8–24	44/1512	*
	Treatment-experienced[106]	12 or 24	9/440	*
	Treatment-naïve and treatment-experienced, HCV-1/HIV-1, noncirrhotic and cirrhotic[113]	12	8/335 (without RBV, due to anti-retroviral regimen)	1
	Pre/post-liver transplant, GT 1 or 4, advanced cirrhotic (Child–Pugh class B or C)[35]	12 or 24	77/337 (with RBV, majority associated with hepatic decompensation)	13 (none study-related)

LDV, ledipasvir; SOF, sofosbuvir; RBV, ribavirin.

SAEs indicated for the entire treatment period, not just the regimen period. Serious AEs reported may have resulted in poor outcomes, including death*. The total number treated does not include the number of patients on placebo in the respective studies reviewed.

Table 6f | Serious or severe AEs and mortality associated with SOF-based regimen

Regimen	Patient population	Duration (weeks)	Number of SAEs/total treated	Number of deaths
SOF 400 mg q.d. PR or RBV	Treatment-naïve[26]	12	4/327 (with PR), 7/256 (with RBV)	*
SOF 400 mg q.d. RBV b.d.	Treatment-naïve GT 2 or 3[111]	12	11/207	*
	Treatment-experienced GT 2 or 3, compensated cirrhotic[111]	12 or 16	8/201	*
	Treatment-naïve and treatment-experienced, GT 2 or 3[112]	12 or 24	10/334	0*
	Post-liver transplant, no fibrosis or mild fibrosis[125]	24	10/40	0

SOF, sofosbuvir; PR, pegylated interferon and ribavirin; RBV, ribavirin.

SAEs indicated for the entire treatment period, not just the regimen period. Serious AEs reported may have resulted in poor outcomes, including death*. The total number treated does not include the number of patients on placebo in the respective studies reviewed.

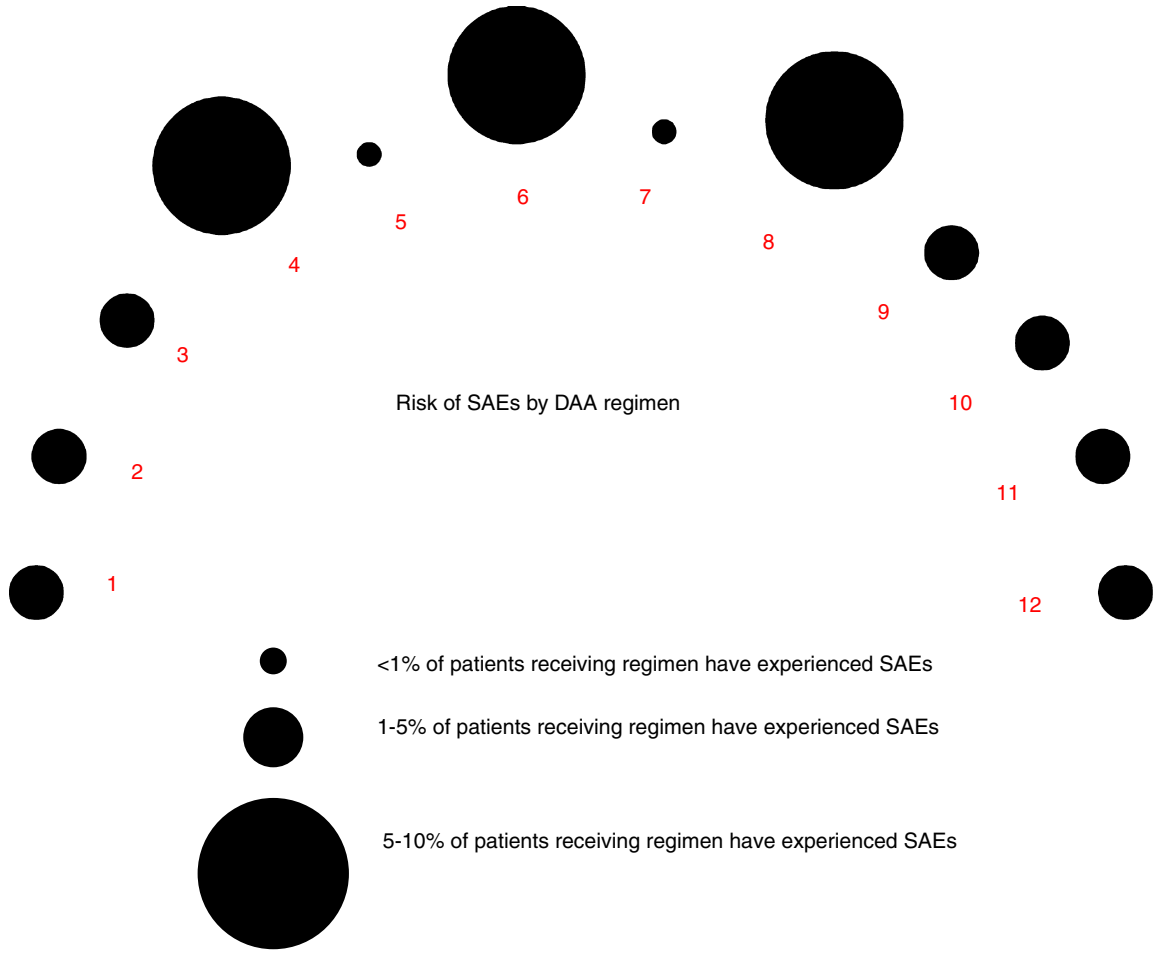

Figure 1 | Visual representation of the risk of SAEs attributed to each DAA regimen evaluated in phase II/III clinical trials. Risk of SAEs measured by percent of patients who have experienced SAEs while receiving treatment. Findings are limited to treatment-naïve and treatment-experienced populations, and those without cirrhosis or with compensated cirrhosis; data is not generalisable for special populations. Some SAEs reported were not deemed regimen-related. 1: SIM 150 mg q.d., PR; 2: SIM 150 mg q.d., SOF 400 mg q.d.; 3: OBV 25 mg q.d., PTV 150 mg q.d., ritonavir 100 mg q.d., DSV 250 mg b.d., RBV b.d.; 4: SIM 100 mg q.d., PR; 5: OBV 25 mg q.d., PTV 150 mg q.d., ritonavir 100 mg q.d., with or without RBV; 6: DCV 60 mg q.d., ASV 100 mg b.d.; 7: DCV 60 mg q.d., SOF 400 mg q.d.; 8: DCV 60 mg q.d., SOF 400 mg q.d., with or without RBV; 9: DCV 30 mg b.d., ASV 200 mg b.d., BCV 75 mg b.d.; 10: SOF 400 mg q.d., PR; 11: SOF 400 mg q.d., RBV; 12: LDV 90 mg q.d., SOF 400 mg q.d., with or without RBV

Post-marketing results in HCV/HIV co-infected patients have led to recommendations for patients to be on suppressive anti-retroviral therapy while on 3D regimen due to the presence of an HIV-1 protease inhibitor (ritonavir) that can select for HIV-1 protease inhibitor resistance-associated substitutions.[92, 93, 134, 135] A preliminary analysis of real-world HCV treatment in a German HCV/HIV co-infected cohort showed most who were treated with sofosbuvir/ledipasvir for 8 weeks were cured with minimal accompanying AEs and no treatment discontinuations, including those who were advised to continue treatment for 12 weeks due to factors including cirrhosis, prior treatment experience, or high viral load.[136] The most common AEs reported were headache (10%), fatigue (7%), nausea (3%) and joint pain (2%).

Real-world results of sofosbuvir-containing regimens, including treatment of patients with decompensated cirrhosis, were generally consistent with phase II-III data, with very low discontinuation and SAE rates and the incidence of AEs being much lower for the all-oral regimen of sofosbuvir and simeprevir with or without

ribavirin compared to interferon-based therapy.[117, 118] Anti-viral therapy had to be stopped prematurely for two patients, the first due to variceal bleeding and the second due to nonmedical reasons. However, the treatment was tolerable for the majority of patients, as suggested by the completion of 97% of the intended treatment period and the low rate of treatment discontinuation.[137] Altogether, MELD and Child–Pugh classifications improved for the majority of patients, thereby reducing the need for liver transplantation. Post-marketing data from HCV-infected patients with reduced renal function showed that the same regimen was effective and tolerable independent of baseline renal function, though patients on sofosbuvir-containing regimen experienced a higher incidence of anaemia.[117]

CONCLUSION

The last few years have witnessed the development of several direct-acting anti-viral agents that has led to a new treatment paradigm for HCV-infected patients. Landmark clinical trials have demonstrated that NS3/4A protease inhibitors, NS5A inhibitors and NS5B inhibitors used in combination with each other greatly attenuate AEs associated with peg-IFN and RBV dual therapy and shorten the duration of treatment by as much as four-fold. Side effects unique to different DAAs have been enumerated in Table 5.

Simeprevir is generally well tolerated by patients, is a photosensitiser, but consequent adverse skin reactions rarely lead to withdrawal from therapy. In addition, elevated bilirubin levels, often of the unconjugated type, routinely return to baseline following completion of simeprevir triple therapy in most patients. The 3D regimen is generally well tolerated by both treatment-naïve and treatment-experienced patients. Hyperbilirubinaemia, presumably due to transient elevated unconjugated (indirect) bilirubin, has been most frequently reported alongside reversible increases in aminotransferase levels. Elevated bilirubin has a higher incidence in treatment-experienced patients with Child–Pugh class A cirrhosis compared to patients without cirrhosis, but rarely leads to treatment cessation. The most frequent use of asunaprevir is in combination with daclatasvir, which has a favourable AE profile in patients with genotype 1 HCV infection. Drawbacks of asunaprevir include risk of elevated liver enzymes and other limitations characteristic of PIs. No AEs unique to daclatasvir have been reported in clinical trials, but dose modifications may be required due to drug–drug interactions, based on the use of concomitant therapies. Ledipasvir co-administered with sofosbuvir is generally well tolerated, and results of clinical trials implicate a diminishing role of ribavirin with this regimen. Those on additional ribavirin have an increased incidence and severity of AEs without any concomitant increase in efficacy. While sofosbuvir possesses pangenotypic activity, has a high barrier to resistance, and is very effective in a variety of combination therapies, no dosage recommendation has been established for its use in those with severe renal impairment. Preliminary results of elbasvir and grazoprevir are promising, as this regimen was effective and tolerable with no unique AEs reported regardless of treatment duration or setting of compensated cirrhosis.

Altogether, data collated from several phase II and III clinical trials show that various DAA therapies are well tolerated in both treatment-naïve and treatment-experienced patients with compensated or decompensated cirrhosis, with no more than 10% of patients undergoing treatment experiencing SAEs (Tables 6a–f, Figure 1).

The safety of DAAs has yet to be extensively assessed in special populations, including pregnant women, those with advanced-stage liver disease, children, patients post-transplantation, and those who have failed DAA therapy. Further clinical trials and real-world data are likely to shed light on the newer AEs, and their frequency, that have thus far not been observed in clinical trials where patients are often well selected. Attempts are also being made to eliminate ribavirin from HCV therapy due to its dose-limiting toxicity.[138]

AUTHORSHIP

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Author contributions: D. Banerjee conceptualised, reviewed the literature, created the tables and figure, and drafted the manuscript. K. R. Reddy conceptualised, provided guidance, and critically reviewed the paper.

Both authors approved the final version of the manuscript.

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