Hepatitis C drugs: The end of the pegylated interferon era and the emergence of all-oral, interferon-free antiviral regimens: A concise review

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Between 2001 and 2011, the standard of care for chronic hepatitis C virus (HCV) infection was a combination of pegylated interferon (PEG-IFN) and ribavirin (RBV). In May 2011, boceprevir and telaprevir, two first-generation NS3/4A protease inhibitors, were approved in combination with PEG-IFN and RBV for 24 to 48 weeks in hepatitis C virus genotype 1 infections. In December 2013, simeprevir, a second-generation NS3/4A protease inhibitor, was approved for use with PEG-IFN and RBV for 12 weeks in genotype 1, while sofosbuvir, a NS5B nucleotide polymerase inhibitor, was approved for use with PEG-IFN and RBV for 12 weeks in genotypes 1 and 4, as well as with RBV alone for 12 weeks in genotype 2 and for 24 weeks in genotype 3. Sofosbuvir combined with simeprevir or an NS5A replication complex inhibitor (ledipasvir or daclatasvir) with or without RBV for 12 weeks in genotype 1 resulted in a sustained virological response >90%, irrespective of previous treatment history or presence of cirrhosis. Similarly impressive sustained virological response rates have been shown with ABT-450/r (ritonavir-boosted NS3/4A protease inhibitor)-based regimens in combination with other direct-acting antiviral agent(s) with or without RBV for 12 weeks in genotype 1. The optimal all-oral interferon-free antiviral regimen likely entails a combination of an NS5B nucleotide polymerase inhibitor with either a second-generation NS3/4A protease inhibitor or an NS5A replication complex inhibitor with or without RBV. Further research is needed to determine the role of resistance testing, clarify the optimal follow-up duration post-treatment, and evaluate the antiviral efficacy and safety in difficult-to-cure patient populations.

Key Words: *All-oral; Hepatitis C; Interferon-free; Simeprevir; Sofosbuvir*

Les médicaments contre l'hépatite C : la fin de l'ère de l'interféron pégylé et l'émergence d'une posologie antivirale entièrement orale et sans interféron : une analyse concise

Entre 2001 et 2011, la norme des soins de l'infection par le virus de l'hépatite C (VHC) chronique était une polythérapie d'interféron pégylé (IFN-PEG) et de ribavirine (RBV). En mai 2011, le bocéprévir et le télaprévir, deux inhibiteurs de la protéase NS3/4A de première génération, ont été approuvés en combinaison avec l'IFN-PEG et la RBV pour un traitement de 24 à 48 semaines contre l'infection par le VHC de génotype 1. En décembre 2013, le siméprévir, un inhibiteur de la protéase NS3/4A de seconde génération, a été approuvé en combinaison avec l'IFN-PEG et la RBV pour un traitement de 12 semaines contre le génotype 1, tandis que le sofosbuvir, un inhibiteur nucléotidique de la polymérase NS5B, a été approuvé en combinaison avec l'IFN-PEG et la RBV pour un traitement de 12 semaines contre les génotypes 1 et 4, ainsi qu'avec la RBV seule pour un traitement de 12 semaines contre le génotype 2 et de 24 semaines contre le génotype 3. Le sofosbuvir en combinaison avec le siméprévir ou un inhibiteur du complexe de réplication NS5A (lédipasvir ou daclatasvir), accompagné ou non de RBV et administré pendant 12 semaines pour traiter le génotype 1, a suscité une réponse virologique soutenue de plus de 90 %, quels que soient les antécédents thérapeutiques et en présence ou en l'absence de cirrhose. De même, les posologies à base d'ABT-450/r (inhibiteur de la protéase NS3/4A rehaussé de ritonavir), combinées à d'autres antiviraux à action directe avec ou sans RBV pour un traitement de 12 semaines contre le génotype 1, entraînent un taux de réponse virologique soutenu impressionnant. La posologie antivirale entièrement orale et sans interféron optimale se compose probablement d'un inhibiteur nucléotidique de la polymérase NS5B combiné à un inhibiteur de la protéase NS3/4A de seconde génération ou à un inhibiteur du complexe de réplication NS5A, accompagné ou non de RBV. Il faudra mener d'autres recherches pour déterminer le rôle des tests de résistance, établir la durée de suivi optimale après le traitement et évaluer l'efficacité et l'innocuité antivirale au sein des populations de patients difficiles à soigner.

Chronic hepatitis C virus (HCV) infection has been estimated to affect 2% to 3% (170 million individuals) of the population worldwide (1) and 0.8% (275,000 individuals) of Canadians (2). In Canada, HCV-related morbidity and mortality increased by 15% to 18% annually between 1994 and 2004 (3). In response to the increasing medical and economic burden of HCV on the Canadian health care system, the landscape of HCV antiviral therapy has changed rapidly in the past three years (Table 1) (4). Between 2001 and 2011, the standard of care for chronic HCV infection was a combination of pegylated interferon (PEG-IFN) and ribavirin (RBV), with a sustained virological response (SVR) of up to 40% to 50% in genotype 1 (G1) and up to 70% to 80% in genotypes 2 and 3 (G2/3) (5,6). However, PEG-IFN is contraindicated in decompensated cirrhosis (7) and is associated with constitutional, neuropsychiatric, autoimmune and hematological side effects (8), whereas RBV is contraindicated in renal failure (9) and is associated with cough, rash, hemolysis and teratogenesis (8). Hence, many patients are ineligible for or intolerant to PEG-IFN and RBV therapy.

DIRECT-ACTING ANTIVIRAL AGENTS IN COMBINATION WITH PEG-IFN AND RBV: WHAT IS CURRENTLY AVAILABLE

The limited efficacy and tolerability of PEG-IFN and RBV have prompted the development of many direct-acting antiviral agents (DAAs) that target specific proteins involved in HCV replication (Table 2) (10). In May 2011, boceprevir (BOC) and telaprevir (TVR), two first-generation NS3/4A protease inhibitors, were approved for use in HCV G1, but must be used in combination with PEG-IFN and RBV to prevent the rapid emergence of resistance-associated variants (11-13). Although BOC and TVR have significantly improved the SVR to 60% to 75% in G1 treatment-naive patients (11-13), the SVR remained suboptimal (30% to 40%) in difficult-to-cure populations such as patients with cirrhosis (14), G1a (15), and previous null responders to PEG-IFN and RBV (defined as failure to achieve at least a 2 log reduction in HCV RNA at week 12 of therapy) (16,17). Moreover, protease inhibitors are associated with additional side effects including

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TABLE 1
Currently approved hepatitis C treatment regimens

Year	Treatment regimen	Genotype	SVR, %	Study (reference)
2001	PEG-IFN + RBV × 48 weeks	1 or 4	42–46	Manns et al (5), Fried et al (6)
2001	PEG-IFN + RBV × 24 weeks	2 or 3	76–82	Manns et al (5), Fried et al (6)
2011	PEG-IFN + RBV + BOC × 24–48 weeks	1	56–75	SPRINT-1 (11), SPRINT-2 (12)
2011	PEG-IFN + RBV + TVR × 24–48 weeks	1	69–75	ADVANCE (13)
2013	PEG-IFN + RBV + SMV × 12 weeks*	1	80–81	QUEST-1 (19), QUEST-2 (20), PILLAR (21)
2013	PEG-IFN + RBV + SOF × 12 weeks	1	89–91	NCT01188772 (25), ATOMIC (26), NEUTRINO (27)
2013	PEG-IFN + RBV + SOF × 12 weeks	4	96	NEUTRINO (27)
2013	RBV + SOF × 12 weeks	2	92–100	FISSION (27), POSITRON (35), VALENCE (36)
2013	RBV + SOF × 24 weeks	3	92–94	VALENCE (36)

**Followed by pegylated interferon (PEG-IFN) + ribavirin (RBV) for 12 weeks in treatment-naive or previous relapsers and 36 weeks in previous partial or null responders. Sofosbuvir (SOF) + RBV is recommended in hepatocellular carcinoma patients awaiting liver transplantation for up to 48 weeks or until transplant. BOC Boceprevir; SMV Simeprevir; SVR Sustained virological response in treatment-naive patients; TVR Telaprevir*

TABLE 2
General characteristics of direct-acting antiviral agents

Direct-acting antiviral agents	Antiviral efficacy	Resistance barrier	Genotypic coverage	Side effects	Drug interactions
NS3/4A protease inhibitor (first generation)	++	+	Genotype 1	+++	+++
NS3/4A protease inhibitor (second generation)	+++	++	Multiple genotypes	+	++
NS5A replication complex inhibitor	+++	++	Multiple genotypes	+	++
NS5B nucleotide polymerase inhibitor	+++	+++	All genotypes	+	+
NS5B non-nucleoside polymerase inhibitor	++	+	Genotype 1	++	++

+ Minimal; ++ Intermediate; +++ Significant; NS Nonstructural protein

anemia and dysgeusia for BOC and anemia, and rash and anorectal symptoms for TVR (18). Finally, the use of triple therapy is associated with a heavy pill burden, complex dosing schedule and numerous drug interactions, even though the treatment duration could be shortened from 48 weeks to 24 to 28 weeks through response-guided therapy.

Following the approval of BOC and TVR, second-generation NS3/4A protease inhibitors, such as simeprevir (SMV), were being developed. In December 2013, SMV was approved for use with PEG-IFN and RBV for 12 weeks in G1. The approval was based on data from the QUEST-1 (19), QUEST-2 (20) and PILLAR (21) clinical trials in which SMV in combination with PEG-IFN and RBV for 12 weeks followed by PEG-IFN and RBV alone for an additional 12 to 36 weeks produced an SVR of 80% to 81% in G1 treatment-naive patients. A similar SVR (79%) was shown with the same treatment regimen in G1 previous relapsers to PEG-IFN and RBV in the PROMISE study (22). This was further confirmed in the ASPIRE study, in which 12 weeks of SMV given with 48 weeks of PEG-IFN and RBV resulted in an SVR of 77% in previous relapsers; however, a lower SVR of 65% and 53% was found in previous partial and null responders, respectively (23). In all of these studies (19-23), the SVR in G1a was significantly lower (58% if Q80K positive, 75% if Q80K negative) than in G1b (>80%) due to the presence of the Q80K polymorphism, which is commonly found in 30% to 47% of G1a infections and significantly decreases susceptibility to SMV (24). This has strong clinical implications in North America, where G1a is the most prevalent HCV subgenotype and where Q80K polymorphism testing is recommended in G1a patients before treatment with SMV.

Because first- and second-generation protease inhibitors may develop cross-resistance, other classes of DAA, such as nucleotide NS5B polymerase inhibitors, which include sofosbuvir (SOF), were being developed. In December 2013, SOF was approved for use with PEG-IFN and RBV for 12 weeks in G1 and G4 infections. The approval was based on data from the NCT01188772 (25), ATOMIC (26) and NEUTRINO (27) clinical trials in which SOF in combination with PEG-IFN and RBV for 12 weeks produced an SVR of 89% to 91% in G1 treatment-naive patients. The NEUTRINO study also reported an SVR of 96% in G4 treatment-naive patients who received PEG-IFN, RBV and SOF for 12 weeks. G1a was present in 69% to 77% among these studies and cirrhosis was identified as a negative predictor of SVR (80% with cirrhosis, 92% without cirrhosis) in the NEUTRINO study. G2 and G3 treatment-naive patients also appear to benefit from the same treatment regimen, with an SVR of 92% to 96% in the NCT01188772 (25) and PROTON (28) studies. A similar SVR (83% to 96%) was demonstrated with this regimen in G2 and G3 treatment-experienced patients, in whom compensated cirrhosis was present in 50% of enrolled patients in the LONESTAR-2 study (29).

The addition of a DAA to the backbone of PEG-IFN and RBV has clearly improved the likelihood of achieving an SVR; however, SOF appears to be superior to BOC, TVR and SMV in enhancing antiviral efficacy. The first-generation protease inhibitors BOC and TVR are associated with significant adverse effects, which are in addition to those of PEG-IFN and RBV. The commercial availability of SMV and SOF offers patients a shortened treatment course and a lack of adverse effects experienced with BOC and TVR. The continued use of PEG-IFN and RBV in these new antiviral combinations, however, remains problematic because patients with decompensated cirrhosis and significant medical and/or psychiatric comorbidities are excluded from treatment. Moreover, the need for intensive monitoring of patients on PEG-IFN- and RBV-containing regimens imposes a heavy clinical burden on nursing care in chronic HCV.

DAAs WITHOUT PEG-IFN: EARLY CLINICAL TRIALS AND WHAT IS CURRENTLY AVAILABLE

The limited safety and tolerability of interferon (IFN)-based regimens (Table 3) have led to the development of IFN-free regimens that have been shown to have a superior impact on health-related quality of life and cost effectiveness (30-32). In 2010, Gane et al (33) published the first proof-of-concept study (INFORM-1) that demonstrated that potent viral suppression could be achieved with IFN-free DAA combination therapy whereby danoprevir (NS3/4A protease inhibitor) and mericitabine (NS5B nucleotide polymerase inhibitor) in combination for two weeks produced a 4.9 IU/mL and 5.1 $\log_{10}$ IU/mL decrease in HCV RNA in G1 treatment-naive and previous null responder patients, respectively. In 2012, Lok et al (34) published the first curative-intent study that showed that an SVR could be achieved with an IFN-free regimen whereby asunaprevir (NS3/4A protease

TABLE 3
Common adverse events of simeprevir (SMV)- and sofosbuvir (SOF)-based regimens

Treatment regimen	Adverse events
PEG-IFN + RBV + SMV	Anemia, fatigue, headache, hyperbilirubinemia, influenza-like illness, neutropenia, photosensitivity, pruritus, rash
PEG-IFN + RBV + SOF	Anemia, fatigue, headache, influenza-like illness, insomnia, nausea, neutropenia, rash, thrombocytopenia
RBV + SOF	Anemia, diarrhea, fatigue, headache, insomnia, nausea, pruritus, rash

PEG-IFN Pegylated interferon; RBV Ribavirin

inhibitor) and daclatasvir (NS5A complication complex inhibitor) given for 24 weeks to G1 previous null responders produced an SVR of 36%, which was interesting given the presence of G1a HCV subgenotype in 82% and non-CC IL28B genotype in 91%.

Subsequent clinical trials involving IFN-free regimens have shown more promising efficacy (Table 4). In December 2013, SOF was approved for use with RBV for 12 weeks in G2 and for 24 weeks in G3 based on results from the following studies. In G2 treatment-naive patients, SOF and RBV for 12 weeks produced an SVR of 92% to 97% in noncirrhotics and 94 to 100% in cirrhotics in the FISSION (27), POSITRON (35) and VALENCE (36) clinical trials. In G2 treatment-experienced patients, SOF and RBV for 12 weeks resulted in a SVR of 91% to 96% in noncirrhotics and 60% to 88% in cirrhotics in FUSION (35) and VALENCE (36). In G3 treatment-naive patients, SOF and RBV for 12 weeks produced a SVR of 68% in noncirrhotics and 21% to 56% in cirrhotics in FISSION (27) and POSITRON (35); however, extending the duration of SOF and RBV to 24 weeks improved the SVR to 94% in noncirrhotics and 92% in cirrhotics in VALENCE (36). In G3 treatment-experienced patients, SOF and RBV for 12 to 16 weeks resulted in an SVR of 37% to 63% in noncirrhotics and 19% to 61% in cirrhotics in FUSION (35). Extending the duration of SOF and RBV to 24 weeks improved the SVR to 87% in noncirrhotics but the SVR remained suboptimal (60%) in cirrhotics in VALENCE (36). However, the SVR did improve to 83% in G3 treatment-experienced cirrhotics when PEG-IFN was added to SOF and RBV for 12 weeks in LONESTAR-2 (29). In summary, an excellent SVR was demonstrated with SOF and RBV for 12 weeks in G2 and for 24 weeks in G3 irrespective of previous treatment history or presence of cirrhosis, with the exception of G3 treatment-experienced cirrhotics who required the addition of PEG-IFN to SOF and RBV for 12 weeks.

The use of SOF and RBV for 24 weeks could also be considered in G1 patients who are ineligible for PEG-IFN, although the efficacy appears to be more limited (Table 4). In G1 treatment-naive patients, SOF and RBV for 12 weeks produced an SVR of 84% in noncirrhotics in ELECTRON (37), but only 56% in a patient population consisting of 4% to 8% cirrhotics in QUANTUM (38). Extending the duration of SOF and RBV to 24 weeks in QUANTUM did not improve the SVR which remained suboptimal at 52% (38). However, combination DAA with SMV and SOF with or without RBV for 12 weeks produced a SVR of 67% to 100% in G1 treatment-naive cirrhotics in COSMOS (39-41). In G1 previous null responders, SOF and RBV for 12 weeks resulted in a disappointing SVR of 10% in noncirrhotics in ELECTRON (37). However, combination DAAs with SMV and SOF with or without RBV for 12 weeks in G1 previous null responders produced an impressive SVR of 93% to 96% in noncirrhotics and 80% to 100% in cirrhotics in COSMOS (39-41). In summary, a modest SVR was demonstrated with SOF and RBV for 12 weeks in G1 treatment-naive noncirrhotics, whereas a combination os DAAs with SMV and SOF with or without RBV for 12 weeks was required for G1 treatment-naive cirrhotics and G1 prior null responders with or without cirrhosis. It appears that the addition of RBV may not be needed to achieve a SVR when two potent DAAs are used in combination, as shown in COSMOS (39-41); however, RBV appears to be necessary when a single DAA is used as shown in ELECTRON (37), in which SOF with and without RBV for 12 weeks produced an SVR of 100% and 60%, respectively, in G2/3 treatment-naive noncirrhotics. It has been postulated that RBV may accelerate viral clearance and, thereby, suppress the emergence of DAA resistance (42).

DAAs WITHOUT PEG-IFN: RECENT CLINICAL TRIALS AND WHAT MAY BE AVAILABLE IN THE FUTURE

Following the success of SMV and SOF in COSMOS (39), several other SOF-based regimens in combination with another DAA have also shown impressive results (Table 4). In G1 treatment-naive noncirrhotic patients, SVR with ledipasvir (LDV) (NS5A replication complex inhibitor) and SOF with or without RBV for eight weeks was 93% to 100% in ION-3 (43) and LONESTAR (44); daclatasvir (DCV) (NS5A replication complex inhibitor) and SOF with or without RBV for 12 weeks was 95% to 100% in AI444040 (45); and GS-9669 (NS5B non-nucleoside polymerase inhibitor) and SOF with RBV for 12 weeks was 92% in ELECTRON (46). In G1 treatment-naive patients in whom cirrhosis was present in 16%, LDV and SOF with or without RBV for 12 weeks resulted in a SVR of 97% to 99% in ION-1 (47). In G1 previous null-responders to PEG-IFN and RBV, an SVR of 100% was produced with GS-9669, SOF, and RBV for 12 weeks in noncirrhotic patients and with LDV, SOF and RBV for 12 weeks in noncirrhotics and cirrhotics in ELECTRON (46). In G1 patients with previous virological failure to protease inhibitor-based regimens (ie, BOC or TVR), DCV and SOF with or without RBV for 24 weeks produced a SVR of 95 to 100% in noncirrhotics in AI444040 (45), whereas LDV and SOF with or without RBV for 12 weeks resulted in a SVR of 94% to 100% in a patient population consisting of cirrhosis in 20% in ION-2 (48) and in 55% in LONESTAR (44). Importantly, these findings demonstrated that failing the protease inhibitor class of DAAs does not preclude treatment success with another class. Finally, the AI444040 (45) study showed that DCV and SOF with or without RBV for 24 weeks produced a SVR of 92% in G2 and 89% in G3 treatment-naive noncirrhotic patients. In summary, an impressive SVR >90% was demonstrated in G1 with SOF in combination with LDV or DCV or GS-9669 with or without RBV for 12 weeks irrespective of treatment history or the presence of cirrhosis. Furthermore, the majority of patients in these studies had unfavourable characteristics including G1a HCV subgenotype and non-CC IL-28B genotype, which strongly suggest that their relevance in IFN-free regimens is minor.

Aside from SOF, another NS5B nucleotide polymerase inhibitor, mericitabine (MCB), was also evaluated in clinical trials although results were less encouraging. In G1 treatment-naive noncirrhotic patients, MCB in combination with ritonavir-boosted danoprevir (NS3/4A protease inhibitor) and RBV for 24 weeks produced a SVR of only 41% which was significantly lower in G1a at 26% compared with G1b (71%) in INFORM-SVR (49). In G1b treatment-experienced noncirrhotics, the same treatment regimen resulted in a SVR of 39% in previous partial responders and 55% in previous null responders in MATTERHORN (50). Based on these disappointing results, MCB is unlikely to be selected as an optimal candidate in DAA combination therapy.

High rates of SVR have also been shown without using NS5B nucleotide polymerase inhibitors as backbone in ABT-450/r (ritonavir-boosted NS3/4A protease inhibitor) -based regimens (Table 4). In G1 treatment-naive noncirrhotic patients, ABT-450/r in combination with ombitasvir (ABT-267) (NS5A replication complex inhibitor) for 12 weeks produced a SVR of 95% in G1b in PEARL-I (51) but only 60% in M12-998 (52) in which G1a was present in 80% of enrolled patients. The decrease in SVR in G1a was also observed in previous clinical trials with protease inhibitor-based regimens. However, the SVR improved to 100% with the addition of RBV in M12-998 (52) and to

TABLE 4
Sustained virological response (SVR) of sofosbuvir (SOF)- and ABT-450/r-based regimens

Genotype (%)	Treatment history	Cirrhosis status	Antiviral regimen	SVR, %	n	Study (reference)
G1a (88)	TN	NC	SOF + RBV x 12 weeks	84	25	ELECTRON (37)
G1a (80)	TN	NC	SOF + LDV ± RBV × 8 weeks	93–94	431	ION-3 (43)
G1a (88)	TN	NC	SOF + LDV ± RBV × 8 weeks	95–100	41	LONESTAR (44)
G1a (82)	TN	NC	SOF + DCV ± RBV × 12 weeks	95–100	82	AI444040 (45)
G1a (84)	TN	NC	SOF + GS-9669 + RBV × 12 weeks	92	25	ELECTRON (46)
G1b (100)	TN	NC	ABT-450/r + ABT-267 × 12 weeks	95	42	PEARL-I (51)
G1a (80)	TN	NC	ABT-450/r + ABT-267 × 12 weeks	60	10	M12-998 (52)
G1a (73)	TN	NC	ABT-450/r + ABT-072 + RBV × 12 weeks	91	11	PILOT (55)
G1a (80)	TN	NC	ABT-450/r + ABT-267 + RBV × 12 weeks	100	10	M12-998 (52)
G1a (85)	TN	NC	ABT-450/r + ABT-333 + RBV × 12 weeks	93–95	33	CO-PILOT (56)
G1a (66)	TN	NC	ABT-450/r + ABT-267 + ABT-333 × 12 weeks	89	79	AVIATOR (53)
G1a (100)	TN	NC	ABT-450/r + ABT-267 + ABT-333 × 12 weeks	90	205	PEARL-IV (54)
G1a (60)	TN	C (6%)	SOF + RBV × 12–24 weeks	52–56	50	QUANTUM (38)
G1a (68)	TN	C (16%)	SOF + LDV ± RBV × 12 weeks	97–99	431	ION-1 (47)
G1a (81)	TN	C	SOF + SMV ± RBV × 12 weeks	67–100	9	COSMOS (39-41)
G1a (67)	TN	C	ABT-450/r + ABT-267 + ABT-333 + RBV × 12 weeks	94	86	TURQUOISE-II (58)
G1a (90)	TE	NC	SOF + RBV × 12 weeks	10	10	ELECTRON (37)
G1a (89)	TE	NC	SOF + LDV + RBV × 12 weeks	100	9	ELECTRON (46)
G1a (81)	TE	NC	SOF + DCV ± RBV × 24 weeks	95–100	41	AI444040 (45)
G1a (90)	TE	NC	SOF + GS-9669 + RBV × 12 weeks	100	10	ELECTRON (46)
G1a (76)	TE	NC	SOF + SMV ± RBV × 12 weeks	93–96	41	COSMOS (39-41)
G1b (100)	TE	NC	ABT-450/r + ABT-267 × 12 weeks	90	40	PEARL-I (51)
G1a (94)	TE	NC	ABT-450/r + ABT-333 + RBV × 12 weeks	47	17	CO-PILOT (56)
G1a (62)	TE	NC	ABT-450/r + ABT-267 + ABT-333 + RBV × 12 weeks	93	45	AVIATOR (53)
G1a (58)	TE	NC	ABT-450/r + ABT-267 + ABT-333 + RBV × 12 weeks	96	297	SAPPHIRE-II (57)
G1a (79)	TE	C (20%)	SOF + LDV ± RBV × 12 weeks	94–96	220	ION-2 (48)
G1a (85)	TE	C (55%)	SOF + LDV ± RBV × 12 weeks	95–100	40	LONESTAR (44)
G1a (78)	TE	C	SOF + LDV + RBV × 12 weeks	100	9	ELECTRON (46)
G1a (81)	TE	C	SOF + SMV ± RBV × 12 weeks	80–100	9	COSMOS (39-41)
G1a (67)	TE	C	ABT-450/r + ABT-267 + ABT-333 + RBV × 12 weeks	87–97	122	TURQUOISE-II (58)
G2	TN	NC	SOF + RBV ×12 weeks	92	92	POSITRON (35)
G2	TN	NC	SOF + RBV × 12 weeks	97	30	VALENCE (36)
G2	TN	NC	SOF + DCV ± RBV × 24 weeks	92	26	AI444040 (45)
G2	TN	NC	ABT-450/r + ABT-267 + RBV × 12 weeks	80	10	M12-998 (52)
G2	TN	C (20%)	SOF + RBV × 12 weeks	97	70	FISSION (27)
G2	TN	C	SOF + RBV × 12 weeks	94	17	POSITRON (35)
G2	TN	C	SOF + RBV × 12 weeks	100	2	VALENCE (36)
G2	TE	NC	SOF + RBV × 12 weeks	91	33	VALENCE (36)
G2	TE	NC	SOF + RBV × 12 weeks	96	26	FUSION (35)
G2	TE	C	SOF + RBV × 12 weeks	60	10	FUSION (35)
G2	TE	C	SOF + RBV × 12 weeks	88	8	VALENCE (36)
G3	TN	NC	SOF + RBV × 12 weeks	68	84	POSITRON (35)
G3	TN	NC	SOF + RBV × 24 weeks	94	92	VALENCE (36)
G3	TN	NC	SOF + DCV ± RBV × 24 weeks	89	18	AI444040 (45)
G3	TN	NC	ABT-450/r + ABT-267 + RBV × 12 weeks	50	10	M12-998 (52)
G3	TN	C (20%)	SOF + RBV × 12 weeks	56	183	FISSION (27)
G3	TN	C	SOF + RBV × 12 weeks	21	14	POSITRON (35)
G3	TN	C	SOF + RBV × 24 weeks	92	13	VALENCE (36)
G3	TE	NC	SOF + RBV × 12 weeks	37	38	FUSION (35)
G3	TE	NC	SOF + RBV × 16 weeks	63	40	FUSION (35)
G3	TE	NC	SOF + RBV × 24 weeks	87	100	VALENCE (36)
G3	TE	C	SOF + RBV × 12 weeks	19	26	FUSION (35)
G3	TE	C	SOF + RBV × 16 weeks	61	23	FUSION (35)
G3	TE	C	SOF + RBV × 24 weeks	60	45	VALENCE (36)

ABT-267 Ombitasvir; ABT-333 Dasabuvir; C Cirrhotic; DCV Daclatasvir; G Genotype; LDV Ledipasvir; NC Noncirrhotic; r Ritonavir; RBV Ribavirin; SMV Simeprevir; TE Treatment experienced; TN Treatment naive

89% to 90% with the addition of dasabuvir (ABT-333) (NS5B non-nucleoside polymerase inhibitor) in AVIATOR (53), in which G1a was present in 61% to 68%, and in PEARL-IV (54), in which G1a was present in 100%. Similarly, ABT-450/r and RBV in combination with ABT-072 (NS5B non-nucleoside polymerase inhibitor) for 12 weeks produced a SVR of 91% in PILOT (55) in which G1a was present in 73%, whereas ABT-450/r and RBV in combination with dasabuvir for 12 weeks produced a SVR of 93% to 95% in CO-PILOT (56) in which G1a was present in 79% to 90%. Importantly, one patient experienced a late relapse at 36 weeks post-treatment in PILOT (55), raising the concern that longer follow-up beyond 24 weeks may be needed with IFN-free regimens. In G1 treatment-experienced noncirrhotic patients, ABT-450/r and ombitasvir given for 12 weeks resulted in an SVR of 90% in G1b in PEARL-I (51), whereas ABT-450/r, dasabuvir and RBV given for 12 weeks produced a relatively disappointing SVR of 47% in CO-PILOT (56), in which G1a was present in 94% of study patients. However, when ombitasvir was added as a third DAA, the SVR improved significantly to 93% in AVIATOR (53), in which G1a was present in 62% and to 96% in SAPPHIRE-II (57), in which G1a was present in 58%. In G1 treatment-naive and experienced cirrhotic patients (Child-Pugh class A), ABT-450/r, ombitasvir, dasabuvir and RBV given for 12 weeks produced an SVR of 94% and 87% to 97%, respectively, in TURQUOISE-II (58). Finally, the M12-998 study (52) showed that 12 weeks of ABT-450, ombitasvir and RBV produced an SVR of 80% in G2 but only 50% in G3 treatment-naive non-cirrhotic patients. In summary, an SVR >90% was demonstrated in G1b noncirrhotics regardless of treatment history with ABT-450/r and ombitasvir for 12 weeks; in G1a treatment-naive noncirrhotics with ABT-450/r combined with either another DAA and RBV or two other DAAs for 12 weeks; and in G1a treatment-experienced noncirrhotics and G1 cirrhotics irrespective of treatment history with ABT-450/r, ombitasvir, dasabuvir and RBV for 12 weeks. Treatment was well tolerated in all of these clinical trials.

Other treatment regimens that included three DAAs (NS3/4A protease inhibitor, NS5A replication complex inhibitor and NS5B non-nucleoside polymerase inhibitor) also appeared to improve SVR. Asunaprevir (NS3/4A protease inhibitor) in combination with DCV (NS5A replication complex inhibitor) for 24 weeks in G1 previous null responder noncirrhotic patients produced an SVR of 65% to 100% in G1b (59-61) but only 36% in a patient population in which G1a was present in 82% (34). The SVR remained suboptimal (23%) with the addition of RBV (61). However, ASV, DCV and BMS-791325 (NS5B non-nucleoside polymerase inhibitor) given for 12 to 24 weeks in G1 treatment-naive noncirrhotic patients resulted in a SVR of 89% to 94% in NCT01455090 (62), in which G1a was present in 72% to 75% of patients. On the other hand, unexpectedly disappointing results have been recently published involving G1 treatment-naive noncirrhotics whereby vedroprevir (VDV) (NS3/4A protease inhibitor), LDV (NS5A replication complex inhibitor), tegobuvir (NS5B non-nucleoside polymerase inhibitor) and RBV for 12 to 24 weeks produced a surprisingly low SVR of only 54 to 63% in the QUAD trial (63) in which G1a was present in 67% to 76% of patients. Finally, MK-5172 (NS3/4A protease inhibitor), MK-8472 (NS5A replication complex inhibitor), and RBV for 12 weeks resulted in a remarkable SVR of 96% to 100% in C-WORTHY trial (64) in which G1a was present in 70% to 76% of patients.

CONCLUSION

As the present brief review indicates, there are many DAAs that have been through clinical trials, both currently and in the recent past, that seek to provide an efficacious, IFN-free treatment for the long-term clearance of HCV. Clearly not all of these agents will survive to licensure and the marketplace. It is commonly accepted that the ideal DAA combination should include such primary characteristics as potent antiviral efficacy, high genetic barrier to resistance, broad genotypic coverage, minimal side effects and favourable safety profile, whereas secondary characteristics should include low pill burden, short treatment duration, no dietary restriction, few drug interactions and affordable drug cost (10). The optimal antiviral regimen likely entails combination of an NS5B nucleotide polymerase inhibitor with either a second-generation NS3/4A protease inhibitor or a NS5A replication complex inhibitor. The role of RBV requires further clarification but appears to be unnecessary when two DAAs with potent antiviral efficacy and high genetic barrier to resistance are used. Although it is too early to declare that PEG-IFN is 'dead', clearly in the near future, its role in HCV treatment will continue to diminish. Despite the recent advances in DAA drug development, many questions remain unanswered. Whether resistance testing is warranted before treatment initiation or in virological failure to IFN-free regimens remains to be elucidated. It is also unclear whether prolonged follow-up beyond 24 weeks post-treatment is necessary with IFN-free regimens. Finally, more data from future research are needed in HCV G4, G5 and G6, and in difficult-to-cure patient populations, which include decompensated cirrhosis, renal failure, HIV coinfection, solid organ transplantation, and pre- and post-liver transplantation. The most important question of whether long-term HCV clearance will also result in clinical improvement in patients with early decompensated cirrhosis, as has been the situation in hepatitis B, remains unknown and awaits further experience with IFN-free DAAs.

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