Review

Treatment of Hepatitis C
A Systematic Review

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IMPORTANCE Hepatitis C virus (HCV) infects more than 185 million individuals worldwide. Twenty percent of patients chronically infected with HCV progress to cirrhosis. New, simpler therapeutics using direct-acting antivirals that target various stages of the HCV life cycle are in development to eradicate HCV without concomitant interferon.

OBJECTIVES To summarize published evidence on safety, efficacy (measured by a sustained virologic response [SVR], which is the treatment goal of undetectable plasma HCV RNA 12 or 24 weeks after therapy completion), and tolerability of current US Food and Drug Administration–approved interferon-based regimens and oral interferon-free regimens used for treating HCV infection and coinfection with human immunodeficiency virus (HIV) and HCV; to provide treatment recommendations for specialists and generalists based on published evidence.

EVIDENCE REVIEW A literature search of Web of Science, Scopus, Embase, Agricola, Cochrane Library, Cinahl Plus, ClinicalTrials.gov, Conference Papers Index, Gideon, PsycINFO, Google Scholar, and Oaister was conducted from January 1, 2009, to May 30, 2014. Publications describing phase 2, 3, and 4 studies evaluating the treatment of HCV were included. Forty-one studies involving 19 063 adult patients were included. Strength of clinical data and subsequent HCV treatment recommendations were graded according to the Oxford Centre for Evidence-Based Medicine.

FINDINGS Patients infected with HCV genotype 1 represent 60% to 75% of HCV infections in the United States. Hepatitis C virus genotype 1 is more difficult to cure than genotype 2 or genotype 3. Patients with HCV genotype 1 should receive treatment with sofosbuvir + pegylated interferon + ribavirin because of the shorter duration of therapy and high rates of SVR (89%-90%). Simeprevir + pegylated interferon + ribavirin is an alternative for patients with HCV genotype 1 (SVR, 79%-86%). Patients with HCV genotypes 2 and 3, representing 20% to 29% of US HCV infections, should receive therapy with sofosbuvir + ribavirin alone (SVR for genotype 2, 12 weeks' duration: 82%-93%; SVR for genotype 3, 24 weeks' duration, 80%-95%). Patients with HIV-HCV coinfection and patients with compensated cirrhosis (ie, cirrhosis but preserved synthetic liver function) should receive the same treatment as HCV-monoinfected patients.

CONCLUSIONS AND RELEVANCE New, short-duration, simpler therapies result in high SVR rates for HCV-infected patients. In conjunction with increased screening for HCV as suggested by recent Centers for Disease Control and Prevention guidelines, availability of new therapies may lead to the treatment of many more people with chronic HCV infection.

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Hepatitis C virus (HCV) infects an estimated 185 million individuals worldwide[1] and 3.4 million to 4.4 million people in the United States.[2] Approximately 80% of acutely infected HCV patients progress to chronic infection, 20% of whom develop cirrhosis within 25 years, with 25% of patients with cirrhosis developing hepatocellular carcinoma and/or decompensated liver disease.[3,4] Hepatitis C virus is the primary cause of liver transplantation in the United States.[5]

There are 6 known genotypes of HCV. The most common genotypes in the United States are genotype 1 (subtypes are 1a and 1b), genotype 2, and genotype 3, which together comprise 97% of all infections.[6] Although there is no difference in the risk of cirrhosis according to genotype, genotype 3 is associated with a higher rate of hepatic steatosis[7] and genotype 1b is associated with a higher rate of hepatocellular carcinoma.[8] The prevalence of hepatitis C is particularly high in subpopulations of incarcerated people, homeless people, veterans, and patients infected with human immunodeficiency virus (HIV) (**Table 1**). Since the discovery of HCV in 1989,[14] strategies to cure the infection have evolved dramatically. A cure is defined as a sustained virologic response (SVR) and consists of undetectable levels of plasma HCV RNA 12 or 24 weeks after therapy completion (**Box 1**).[16]

DAA *directly acting antiviral*
HCV *hepatitis C virus*
HIV *human immunodeficiency virus*
SVR *sustained virologic response*

Alfa interferons, which are immunomodulatory agents administered as subcutaneous injections, were the first to be used to treat HCV successfully (**Table 2**). Subsequently, ribavirin, an oral antiviral nucleoside analog, was added to improve cure rates.[17,18] More recently, oral directly acting antivirals (DAAs) that target various stages of the HCV life cycle have been developed (**Figure**).

The field of HCV therapeutics is evolving to develop strategies for eradicating HCV without using interferon formulations and/or ribavirin. This change simplifies treatment, improves tolerability, and decreases therapy duration, all while maintaining or increasing rates of SVR.

This review summarizes published data on interferon-based and oral interferon-free treatment regimens for patients infected with HCV genotypes 1, 2, or 3 from published phase 2, 3, and 4 randomized clinical trials (RCTs) and cohort studies of US Food and Drug Administration (FDA)–approved medications. We provide treatment recommendations for management of patients infected with HCV genotypes 1, 2, or 3.

Methods

This systematic review was conducted according to PRISMA guidelines.[19] The National Library of Medicine through PubMed was searched for the hepatitis C (MeSH) filters *clinical trial, phase II*; *clinical trial, phase III*; and *clinical trial, phase IV*. The search was conducted for studies published between January 1, 2009, and May 30, 2014. In addition, we searched the following databases for the terms *hepatitis C* AND *clinical trial* AND *phase II* OR *phase III* OR *phase IV*: Web of Science, Scopus, Embase, Agricola, Cochrane Library, Cinahl Plus, ClinicalTrials.gov, Conference Papers Index, Gideon, PsycINFO, Google Scholar, and Oaister. Our search strategy included studies published in any language from 2009 to May 30, 2014. References of identified articles were searched for additional relevant articles. Randomized clinical trials and relevant cohort studies were included if they were published in English, used FDA-approved therapies that included SVR as a primary or secondary end point, and defined treatment-experienced patients using American Association for the Study of Liver Diseases definitions.[15] Studies presenting information exclusively about patients undergoing liver transplant, acute HCV, and HCV genotypes other than 1 through 3 and dose-finding studies were excluded. Data including study design, participant demographics, stage of liver disease, treatment regimens and durations, and SVR were extracted by coauthors and recorded on a standardized electronic data collection sheet. The strength of clinical data and subsequent recommendations for treatment of HCV-infected patients were graded according to the Oxford Centre for Evidence-Based Medicine levels of evidence[20] by 2 authors independently, with discrepancies resolved after joint article review and discussion. Levels of evidence are as follows: level 1A, systematic reviews (with homogeneity of randomized clinical trials); level 1B, individual randomized clinical trials (with narrow confidence intervals); level 2A, systematic reviews (with homogeneity of cohort studies); and level 2B, individual cohort studies (including low-quality randomized clinical trials). Grades of recommendation are as follows: A, consistent level 1 studies; B, consistent level 2 or 3 studies or extrapolations from level 1 studies; C, level 4 studies or extrapolations from level 2 or 3 studies; and D, level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

Results

Five hundred eighty relevant studies were screened and assessed for eligibility. After applying inclusion and exclusion criteria (eFigure in the Supplement), 41 studies (33 RCTs and 8 cohort studies) with 19 063 adult patients were selected for inclusion.

Table 3 summarizes included studies' findings and evidence levels. A full description of treatment regimens, duration, number of participants, demographics, SVR, and discontinuations for each study is available in eTables 1 through 3 in the Supplement.

Evidence for Use of Telaprevir or Boceprevir + Pegylated Interferon + Weight-Based Ribavirin for Patients With HCV Genotype 1

Boceprevir and telaprevir are selective HCV nonstructural protein (NS) 3/4A serine protease inhibitors. These drugs were the first DAAs developed and found to be effective in treating patients with HCV genotype 1. Based on the outcome of SVR, 7 evidence level 1B RCTs demonstrate the superiority of triple therapy using telaprevir[21-24,50] or boceprevir[25-27] with pegylated interferon + weight-based ribavirin (1 g/d for ≤75 kg and 1.2 g/d for >75 kg) for the treatment of HCV genotype 1 treatment-naive patients (SVR range, 61%-75%) compared with treatment with pegylated interferon + weight-based ribavirin (SVR range, 38%-49%).[21-26,28]

Shortened durations (24 weeks for telaprevir- and 28 weeks for boceprevir-containing regimens) for patients who achieve

Table 1. Prevalence of HCV Genotypes and of HCV Infection in the United States by Risk Factor

	Prevalence of HCV, %[a]
HCV genotype[6,9,10]	
1a	36-55
1b	25-23
2	13-16
3	8-13
4	1-2
Risk factors	
Race/ethnicity[2,b]	
White	2.8
Black	5.6
Hispanic	2.7
Sex[2,b]	
Male	3.9
Female	2.1
Birth cohort[2,11,b]	
1945-1949	1.58
1950-1965	3.61
1966-1970	1.97
HIV infection[12,13]	17-37
Intravenous drug user[2]	58
Homeless[2]	22-53
Prisoner[2]	23-41
Veteran[2]	3-18

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus.

[a] Ranges represent results from multiple studies. Estimated total number infected is 3.9 million (3.4-4.4 million)[2] from the National Health and Nutrition Examination Survey (NHANES) that excludes homeless and institutionalized (including prison) populations and therefore likely underestimates prevalence by 500 000 to 1 million persons.

[b] Data from NHANES; reports prevalence for birth cohort 1945-1970.

rapid viral load declines within the first 12 weeks of therapy are as effective as fixed-duration therapy of 48 weeks.[21,26]

Four evidence level 1B RCT and 2 level 2B studies evaluated telaprevir[29,30,32,33] or boceprevir[26,31] + pegylated interferon + weight-based ribavirin in treatment-experienced patients. Previous partial responders and patients who relapsed had significant improvement in SVR rates when treated with telaprevir- or boceprevir-containing regimens for up to 48 weeks (SVR range, 69%-83%) compared with pegylated interferon + weight-based ribavirin alone (SVR range, 20%-29%). Previous null responders had modest increases in SVR rates with telaprevir-based therapy (SVR range, 39%-56% vs 9%-17%) (Table 3).[29]

Evidence for Simeprevir + Pegylated Interferon + Weight-Based Ribavirin for Patients With HCV Genotype 1

Two DAAs, simeprevir and sofosbuvir, were recently approved for treating HCV. Simeprevir, an HCV NS3/4 serine protease inhibitor, was evaluated in treatment-naive patients and patients who had relapsed in 4 evidence level 1B studies[34,35] and 1 level 2B study,[36] showing higher rates of SVR (79%-86%) using 12 to 24 weeks of simeprevir + 24 to 48 weeks of pegylated interferon + weight-based ribavirin compared with pegylated interferon + weight-based ribavirin alone (SVR range, 37%-65%). In one representative study, 88% of participants had an early viral load decline (HCV RNA less than quantifiable at weeks 4 and undetectable at week 12) and were eligible for a shortened total duration of therapy of 24 weeks, with 83% to 88% of patients achieving SVR.[35] Patients without an early viral load decline were less likely to achieve SVR (range, 22%-32%).[35]

One evidence level 1B study[37] of simeprevir in previous null and partial responders and relapsers showed that 12 to 48 weeks of simeprevir + pegylated interferon + weight-based ribavirin for 48 weeks resulted in high rates of SVR (67%-80%) compared with pegylated interferon + weight-based ribavirin alone (36%). Response rates to simprevir-containing therapy, however, were lower in null responders (41%-59% vs 19%) and partial responders (65%-86% vs 9%) than previous relapsers (76%-89% vs 37%) but higher compared with pegylated interferon + weight-based ribavirin. In both treatment-naive and treatment-experienced patients infected with HCV genotype 1a, those with a Q80K polymorphism in the NS3 region of hepatitis C virus responded less well to simeprevir-containing therapy (26%-31% difference in SVR).

Box 1. Definitions of Treatment Response to HCV Treatment[15]

Nonresponse: detectable HCV RNA after 12 weeks of HCV therapy

Partial response: >2 log decline in HCV RNA but detectable HCV RNA after 12 weeks of HCV therapy

Null response: ≤2 log decline in HCV RNA after 12 weeks of HCV therapy

Viral breakthrough: detectable HCV RNA after previously undetectable

Relapse: undetectable HCV RNA on therapy with detectable HCV RNA after stopping therapy

Sustained virologic response: undetectable HCV RNA 12 or 24 weeks after stopping therapy

HCV indicates hepatitis C virus.

Evidence for Use of Sofosbuvir + Pegylated Interferon + Weight-Based Ribavirin for Patients With HCV Genotype 1

Most recently, sofosbuvir, an HCV NS5b nucleotide polymerase inhibitor, has been approved for treating HCV infection. Two evidence level 1B studies[38,39] and 1 level 2B study[40] showed high SVR rates (89%-90%) after treatment with only 12 weeks of sofosbuvir + pegylated interferon + weight-based ribavirin in treatment-naive patients. There was no benefit to extending treatment duration to 24 weeks or use of response-guided therapy (SVR range, 89%-91%).[38,39]

Evidence for Use of an All-Oral Regimen of Sofosbuvir + Ribavirin in Patients With HCV Genotypes 1, 2, and 3

An evidence level 1B study[40] among patients with HCV genotypes 2 and 3 demonstrated improved response to sofosbuvir + weight-based ribavirin therapy for 12 weeks compared with pegylated interferon + weight-based ribavirin for 24 weeks (97% with sofosbuvir vs 78% with pegylated interferon) in treatment-naive patients with HCV genotype 2. This high SVR rate in patients with HCV genotype 2 treated with sofosbuvir + weight-based ribavirin was confirmed in another evidence level 2B study.[44] One level 1B study[43]

Table 2. Mechanism of Action, Activity, and Adverse Effects of HCV Therapies

Drug Class	Mechanism	Examples		Activity[b]	Resistance	Major Adverse Effects	Monitoring	Management of Adverse Effects
		FDA Approved	Not FDA Approved[a]					
Interferons	Induce specific and nonspecific immune response against HCV, which inhibits viral replication	Interferon alfa 2a, interferon alfa 2b, peginterferon alfa 2a, peginterferon alfa 2b		All HCV genotypes	No specific resistance mutations have been associated with treatment	Constitutional, neutropenia, thrombocytopenia, anemia, psychiatric, nausea, rash, cough, unmasking or worsening of autoimmune disease	Complete blood cell count with differential, physical examination	Neutropenia: treatment with G-CSF Anemia: treatment with erythropoietin
Ribavirin	Not fully understood; likely has both direct and indirect effects on HCV virus replication	Ribavirin		All HCV genotypes	No specific resistance mutations have been associated with treatment	Anemia, teratogenic	Complete blood cell count	Anemia: dose reduction of ribavirin or treatment with erythropoietin
Directly acting antivirals								
HCV protease inhibitors	Inhibit the HCV NS3/NS4 serine protease responsible for processing of HCV polyprotein and production of new infectious virions	Simperevir, boceprevir, telaprevir	Asunaprevir, ABT-450, faldaprevir, danoprevir, vaniprevir, MK5172	Genotypes 1a and 1b[c]	Low barrier to resistance	Anemia, pruritus, dysguesia, rash, photosensitivity, transient increased bilirubin[d]	Complete blood cell count, physical examination	
HCV NS5A inhibitors	Inhibit the HCV NS5A, whose function is not fully understood but may include modulation of viral RNA replication and assembly and regulation of endogenous interferon response		Daclatasvir, ledipasvir, ABT-267, MK8742	All HCV genotypes	Low barrier to resistance		Physical examination	
HCV NS5B polymerase inhibitors								
Nucleot(s)ide analogs	Inhibit RNA dependent RNA polymerase competitively by binding to the catalytic site of HCV polymerase	Sofosbuvir		All HCV genotypes	High barrier to resistance	Fatigue, headache, nausea	Physical examination	
Nonnucleos(t)ide analogs	Inhibit RNA dependent RNA polymerase by allosteric inhibition of the binding site of HCV polymerase		ABT-333, BMS-791325, ABT-072, deleobuvir	Genotypes 1a and 1b[c]	Low barrier to resistance			

Abbreviations: FDA, US Food and Drug Administration; G-CSF, granulocyte colony-stimulating factor; HCV, hepatitis C virus; NS, nonstructural protein.

[a] Non–FDA approved drugs; adverse effects not reported in table.

[b] Antiviral activity of agents developed to date.

[c] More effective agaist genotype 1b than 1a.

[d] Reported for boceprevir, telaprevir, and simeprevir only.

and 1 level 2B[44] study showed a benefit in longer-duration therapy (12 weeks vs 16 weeks) with sofosbuvir + ribavirin for treatment-experienced patients with HCV genotype 3 (30% vs 62%) and an even larger benefit with 24 weeks of therapy in patients with HCV genotype 3 who were treatment experienced (80%) and treatment naive (95%) but not in patients with HCV genotype 2 (82% for treatment-experienced and 89% for treatment-naive).

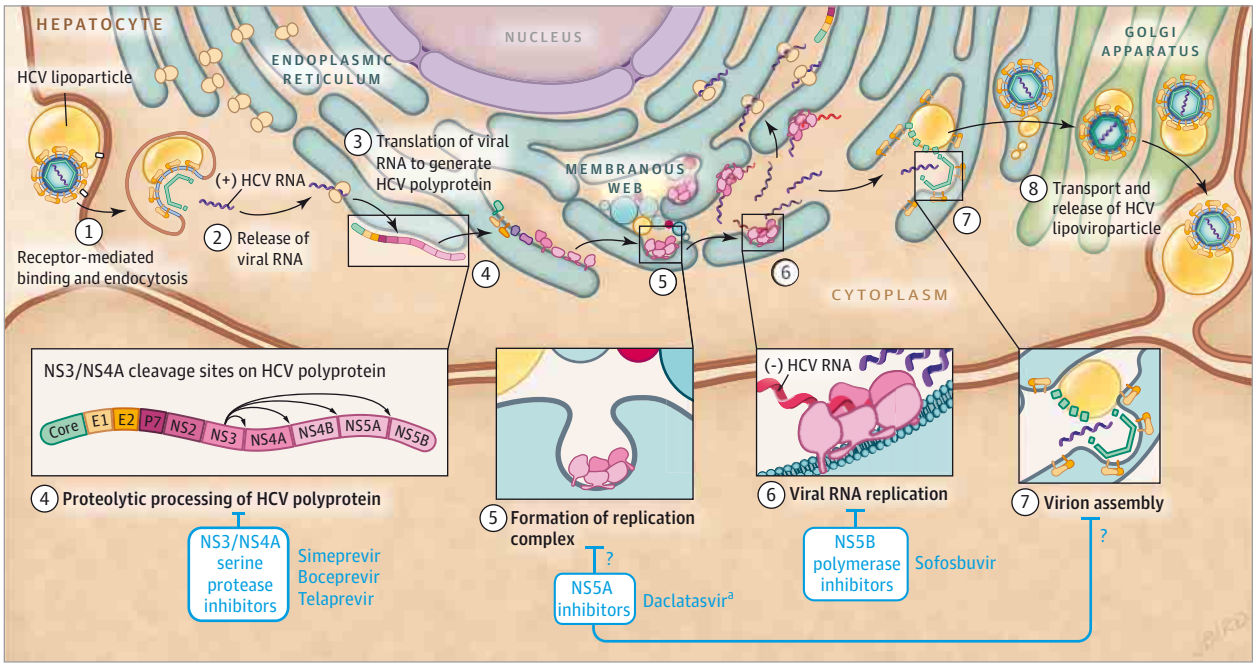
Sofosbuvir + ribavirin for 12 to 24 weeks in HCV genotype 1 was evaluated in 2 evidence level 2B studies.[41,42] Response to treatment in patients with HCV genotype 1 who were treatment naive was 68% to 84%.

Special Populations

Patients With Compensated Cirrhosis

Few patients with compensated cirrhosis (ie, without jaundice, ascites, encephalopathy, or variceal hemorrhage) have been included in clinical trials of regimens using new DAAs, and patients with signs of portal hypertension (as evidenced by a platelet count $<90\times10^3/\mu L$) are generally excluded. In 4 studies,[21,24-26] treatment-naive patients with cirrhosis treated with telaprevir-containing therapy (62%-63% vs 75%) or boceprevir-containing therapy (41%-52% vs 67%-76%) had lower response rates than patients without cirrhosis. In a subanalysis of 1 study[40] of sofosbu-

Figure. Steps in the Hepatitis C Virus Life Cycle Targeted by Directly Acting Antiviral Agents



Directly acting antiviral agents (DAAs; shown in cyan) disrupt hepatitis C virus (HCV) replication by targeting critical enzymatic steps in the HCV life cycle. Antiviral drug treatment with a DAA combined with ribavirin with or without pegylated interferon, depending on HCV genotype (see Table 4), increases suppression of HCV replication compared with interferon and ribavirin alone, leading to improved sustained virologic response rates. The illustration is schematic; structures are not to scale. Question marks indicate that mechanism of action is uncertain. Abbreviations: E, envelope glycoprotein; NS, nonstructural protein; + and −, positive and negative HCV RNA strands.

[a] Not approved by the US Food and Drug Administration.

vir + pegylated interferon + weight-based ribavirin for 12 weeks, patients with cirrhosis responded less well than patients without cirrhosis (80% vs 92%). Similarly, response to sofosbuvir + weight-based ribavirin alone for 24 weeks in patients with HCV genotype 1 was lower in patients with stage 3 or 4 liver disease (54% vs 79% with stage 2 or lower diease).[42] Response to treatment with simeprevir + pegylated interferon + weight-based ribavirin was lower in patients with bridging fibrosis or cirrhosis compared with those with less liver fibrosis for both treatment-naive patients (68% vs 84%) and treatment-experienced patients (73% vs 82% in previous relapsers, 67% vs 79% in partial responders, and 33% vs 66% in null responders).[35,37]

These differences were not observed among patients with HCV genotype 2 who were treated with 12 weeks of sofosbuvir + weight-based ribavirin (83%-94% with fibrosis vs 92%-97% without fibrosis). Extending the duration of sofosbuvir + weight-based ribavirin combination therapy for treatment-naive patients with HCV genotype 3 from 12 weeks to 24 weeks improved SVR rates for patients with cirrhosis (21% vs 92%). This extended duration also resulted in a higher response rate in treatment-experienced patients with cirrhosis (SVR, 60%); however, this rate is still lower than that seen in treatment-experienced patients without cirrhosis (SVR, 85%) who were treated for the same duration.[40,43,44]

Patients With HIV-HCV Coinfection

About one-third of all HIV-infected patients are also coinfected with HCV.[12] Response rates to pegylated interferon + weight-based ribavirin in 2 evidence level 2B studies[47,48] were poor in treatment-naive and treatment-experienced coinfected patients (36%-15%). Two evidence level 1B studies[45,46] showed that the addition of telaprevir or boceprevir to pegylated interferon + weight-based ribavirin (SVR rates, 74% and 63%) was superior to pegylated interferon + weight-based ribavirin alone (SVR rates, 30% and 45%). However, sofosbuvir + weight-based ribavirin therapy for 24 weeks resulted in high response rates in patients with HCV genotypes 1, 2, and 3 (SVR range, 76%-92%) in 1 evidence level 2B study.[44]

In summary, the addition of DAAs to pegylated interferon + ribavirin leads to significant improvements in SVR rates. The regimen of sofosbuvir + ribavirin has high SVR rates in small studies of patients with HIV-HCV coinfection.

Minorities

Limited data have been published regarding treatment of African American and Hispanic patients using regimens that include sofosbuvir or simeprevir. One study, however, included a subanalysis of 159 African American patients and showed an improvement in SVR with boceprevir + pegylated interferon + weight-based ribavirin (SVR, 53%) over pegylated interferon + weight-based ribavirin alone (SVR, 23%).[27]

Recently, polymorphisms in the upstream promoter region of the *IL28B* gene were described that partially explained differential response rates to interferon-containing therapy for HCV genotype 1 infection among races, with individuals who carry the CC genotype (enriched in Asians or whites) more likely to respond to therapy than those with a TT genotype (enriched in African American populations).[4] Subanalyses of studies in treatment-naive patients

Table 3. Studies Evaluating Hepatitis C Treatment Using SVR as Outcome, 2000-2013: Summary of Systematic Review and Findings

Treatment	No. of Studies by Evidence Level[20]	Findings[a]
Genotype 1		
Evidence for use of telaprevir or boceprevir in combination with pegylated interferon and weight-based ribavirin for patients with HCV genotype 1	11 1B studies[21-31] 2 2B studies[32,33]	Telaprevir + pegylated interferon + ribavirin is superior to pegylated interferon + ribavirin in treatment-naive, null, nonresponder, and relapse patients[21-24,28-31,33] In treatment-naive patients, shortened durations of telaprevir + pegylated interferon + ribavirin therapy based on early viral decline were equivalent to fixed duration therapy[21] In partial-responder and relapse patients, a shortened duration of telaprevir + pegylated interferon + ribavirin for 24 weeks or guided by virologic response was effective (based on evidence level 2B cohort study data only)[33] In null responders, SVR rates after 48-week regimens of telaprevir + pegylated interferon + ribavirin were higher then after 24-week regimens (based on evidence level 2B cohort study data only)[33] Boceprevir + pegylated interferon + ribavirin is superior to pegylated interferon + ribavirin in treatment-naive, partial responder, and relapse patients with HCV genotype 1[25-27] In treatment-naive patients, shortened durations of boceprevir + pegylated interfron + ribavirin were similar to fixed-duration therapy[27] In partial responders and relapsers, shortened duration of boceprevir + pegylated interferon + ribavirin based on virologic response were similar to a 48-week regimen[26]
Evidence for use of simeprevir in combination with pegylated interferon and weight-based ribavirin for patients with HCV genotype 1	4 1B studies[34-37]	Pegylated interferon + ribavirin + simeprevir resulted in higher SVR rates than pegylated interferon + ribavirin alone in treatment-naive, relapse, and null and partial responder patients[34-37] Shortened duration of simeprevir + pegylated interferon + ribavirin based on virologic response resulted in higher SVR rates than pegylated interferon + ribavirin for 48 weeks in relapse patients[35]
Evidence for use of sofosbuvir in combination with pegylated interferon and weight-based ribavirin for patients with HCV genotype 1	3 1B studies[38-40]	The combination of pegylated interferon + ribavirin + sofosbuvir resulted in higher SVR rates than pegylated interferon + ribavirin alone in treatment-naive patients[38-40] Extending therapy to 24 weeks and use of response-guided therapy did not improve outcomes[38,39]
Evidence for use of all-oral regimen of sofosbuvir and ribavirin for patients with HCV genotype 1	2 2B studies[41,42]	The combination of sofosbuvir + ribavirin for 12 to 24 weeks resulted in moderate rates of SVR in treatment-naive patients (based on cohort study and evidence level 2B randomized clinical trial data only)[41,42] Sofosbuvir + ribavirin for 12 weeks was not effective in treatment-experienced patients (based on evidence level 2B cohort study data only)[41]
Genotypes 2 and 3		
Evidence for use of all-oral regimen of sofosbuvir and ribavirin for patients with HCV genotypes 2 and 3	2 1B studies[40,43] 1 2B study[44]	Sofosbuvir + ribavirin for 12 weeks was better than pegylated interferon + ribavirin for 24 weeks in patients with HCV genotype 2[40] Sofosbuvir + ribavirin for 12 and 24 weeks in treatment -naive and treatment-experienced patients with HCV genotype 2 and HCV genotype 3, respectively, resulted in high SVR rates (based on randomized clinical trial and cohort study data)[43,44]
Special Populations		
Patients with cirrhosis	7 1B studies[21,24-26,35,37,40] 1 2B study[42]	Patients with HCV infection and cirrhosis had lower response rates to telaprevir-, boceprevir-, sofosbuvir-, and simeprevir-containing therapy (based on subanalysis of randomized clinical trial and cohort study data)[21,24-26,35,37,40,42-44]
Patients coinfected with HIV and HCV	2 1B studies[45,46] 2 2B studies[44,47,48]	Response to pegylated interferon + ribavirin in patients with HIV and HCV is poor[47,48] Boceprevir + pegylated interferon + ribavirin was superior to pegylated interferon + ribavirin alone, and telaprevir + pegylated interferon + ribavirin resulted in higher SVR rates than pegylated interferon + ribavirin in treatment-naive patients with HIV-HCV genotype 1 coinfection[45,46] Patients coinfected with HIV and HCV genotypes 1 or 3 treated for 24 weeks and with HIV and HCV genotype 2 treated for 12 weeks with sofosbuvir + ribavirin had similar SVR rates as HCV-monoinfected patients in previous studies[44]
Minorities	2 1B studies[34,35] 1 2B study[49]	Pegylated interferon + ribavirin was more effective for HCV genotype 1 infection in white patients than in Hispanic patients (based on cohort study data only)[49] Patients with a non-CC genotype (enriched in African Americans) were less likely to respond to simeprevir + pegylated interferon + ribavirin[34,35]

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; SVR, sustained virologic response.

[a] Findings with level 1 evidence unless otherwise specified.

using simeprevir have shown this regimen to be more effective in patients carrying the *IL28B* CC polymorphism compared with those without the CC genotype (94%-97% vs 68%-58%[34,35]). The predictive ability of *IL28B* in patients treated with sofosbuvir + pegylated interferon + weight-based ribavirin or sofosbuvir + weight-based ribavirin is unclear.[38-40]

Other Populations

Few data are available regarding the use of DAAs in patients with impaired renal function (ie, glomerular filtration rate <50) or end-stage renal disease. This group may be at an increased risk of adverse events, particularly anemia in regimens containing ribavirin, and may require dose reductions in medications. No DAAs have been studied or are approved for use in children.

Safety and Adverse Events

A major deterrent for wide use of interferon alfa + ribavirin in the treatment of HCV has been the spectrum of adverse events associated with them (Table 2). The addition of boceprevir to pegylated interferon + ribavirin regimens is further associated with an increased incidence of anemia, dysgeusia, and neutropenia compared with pegylated interferon + ribavirin alone.[25,26] The addition of telaprevir to pegylated interferon + ribavirin is associated with increased fatigue, pyrexia, nausea, diarrhea, hemorrhoids,

Table 4. Recommended Therapy for Hepatitis C

Recommendation Based on This Review	Grade of This Review's Recommendation[a]	Comparison With Current AASLD/IDSA Guidelines[54]
Genotype 1		
Therapy for treatment-naive patients with HCV genotype 1 should include sofosbuvir (400 mg/d) in combination with pegylated interferon + weight-based ribavirin	A	Same except no recommendation included in this review for combination of sofosbuvir + simeprevir given lack of published data for that regimen
An alternative for treatment-naive patients with HCV genotype 1b or 1a without a baseline Q80K mutation is simeprevir (150 mg/d) for 12 weeks in combination with pegylated interferon + weight-based ribavirin for 24 weeks	A	
All therapy for patients who receive simeprevir-containing regimens should be stopped for patients with an inadequate on-treatment virologic response (ie, quantifiable HCV viral load at week 4, 12, and/or 24)	B	
For interferon-intolerant or -ineligible patients, therapy with sofosbuvir + ribavirin for 24 weeks can be considered	B	
This combination may not be as effective in patients with advanced liver disease (metavir fibrosis stage 3-4)	C	
Therapy for treatment-experienced patients with HCV genotype 1 should include sofosbuvir (400 mg/d) in combination with pegylated interferon + weight-based ribavirin	B	Same except no recommendation included in this review for combination of sofosbuvir + simeprevir given lack of published data for that regimen
An alternative for treatment-experienced patients with HCV genotype 1b or 1a without a baseline Q80K mutation is simeprevir (150 mg/d) in combination with pegylated interferon + weight-based ribavirin for 48 weeks	A	
Previous relapsers with HCV genotype 1b or 1a without a baseline Q80K mutation should be treated with a shorter duration of simeprevir (150 mg/d) for 12 weeks in combination with pegylated interferon + weight-based ribavirin for 24 weeks	A	
All therapy should be stopped for patients with an inadequate on-treatment virologic response (ie, quantifiable HCV viral load at week 4, 12, and/or 24)	B	
In treatment-experienced patients, therapy with sofosbuvir + ribavirin alone should not be used	B	
Genotypes 2 and 3		
Therapy for treatment-naive or treatment-experienced patients with HCV genotype 2 should consist of sofosbuvir + weight-based ribavirin for 12 weeks	A	Same except no recommendation included in this review for use of combination of sofosbuvir + pegylated interferon + ribavirin given lack of published data for that regimen
Therapy for treatment-naive or treatment experienced patients with HCV genotype 3 should consist of sofosbuvir + weight-based ribavirin for 24 weeks	B	
HIV-HCV Coinfection		
Therapy for HCV in patients coinfected with HIV and HCV genotypes 1, 2, or 3 should be with the same regimens recommended for patients without HIV after careful evaluation of drug-drug interactions by a specialist in this field	B	Same except no recommendation included in this review for combination of sofosbuvir + simeprevir given lack of published data for that regimen
Cirrhosis[b]		
Patients with cirrhosis should be treated with the same regimen and duration as patients without cirrhosis	B	Same

Abbreviation: AASLD, American Association for the Study of Liver Diseases; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDSA, Infectious Diseases Society of America.

[a] Grades of recommendation: A, based on consistent level 1 studies; B, based on consistent level 2 or 3 studies or extrapolations from level 1 studies; C, based on level 4 studies or extrapolations from level 2 or 3 studies; D, based on level 5 evidence or inconsistent or inconclusive studies of any level (levels of evidence for individual studies in this review are described in Table 3 and definitions of levels of evidence are described in Box 2).

[b] Compensated with no or minimal portal hypertension.

pruritus, rashes, alopecia, insomnia, and anemia.[22,24] Given the diversity in adverse events reported, no formal statistical comparison of adverse events on various treatment regimens was performed in this review, but the rates of discontinuation of medications were higher in treatment groups containing telaprevir or boceprevir than pegylated interferon + ribavirin alone (ranges, 9%-26% vs 8%-25% vs 2%-16%, respectively). The addition of sofosbuvir to pegylated interferon + ribavirin is associated with increased fatigue, nausea, anemia, pyrexia, and neutropenia, with the range of patients who discontinued therapy increasing with treatment duration from 12 weeks (range, 2%-6%) to 24 to 48 weeks (range, 2%-14%).[38-40] During therapy with sofosbuvir + ribavirin alone, fatigue, headache, nausea, insomnia, irritability, and pruritus were the most common adverse events. Anemia occurred in up to 10% of patients receiving sofosbuvir + ribavirin; however, discontinuations of this regimen were rare (range, 0%-1%).[40,41] The addition of simeprevir is associated with increased rash, transient hyperbilirubinemia, pruritus, nausea, myalgia, and dyspnea; however, discontinuation rates for simeprevir-containing regimens were similar to those seen with pegylated interferon + ribavirin (range, 2%-11% vs 1%-13%).[34,35,37] Drug interactions between DAAs and other medications or other

Box 2. Key Points

1. Pegylated interferons with ribavirin and sofosbuvir or simeprevir should be used to treat patients infected with HCV genotype 1.
2. Sofosbuvir with ribavirin alone should be used to treat patients infected with HCV genotypes 2 and 3.
3. Patients coinfected with human immunodefiency virus and HCV genotype 1 should be treated for HCV with pegylated interferons, ribavirin, and sofosbuvir by a physician with experience in treating this particular group of patients and familiar with potential drug interactions.

HCV indicates hepatitis C virus.

DAAs are of particular concern with the use of the protease inhibitors boceprevir and telaprevir and, to a lesser extent, simprevir and should be reviewed prior to the initiation of HCV therapy.[51] Finally, no data are available regarding the teratogenicity of DAA agents, while ribavirin is a known teratogen. All patients should be counseled to use one form of contraception and those receiving ribavirin to use 2 forms of contraception during therapy and for 6 months following completion given the teratogenic effect of ribavirin.[52,53] In summary, the addition of boceprevir or telaprevir to pegylated interferon + ribavirin increased overall adverse effects, while the addition of simeprevir or sofosbuvir reduced the total duration and pill burden of therapy and maintained or decreased adverse events. Sofosbuvir + ribavirin alone is well tolerated and shows promise to improve the adverse effect profile and tolerability of HCV treatment.

Discussion

Treatment of HCV has evolved rapidly and has led to improved rates of SVR. Improvement in HCV therapy began with the addition of the protease inhibitors telaprevir and boceprevir to pegylated interferon + weight-based ribavirin for patients with HCV genotype 1. These have now been replaced by sofosbuvir and simeprevir, with improved efficacy and safety for treating HCV genotype 1. Sofosbuvir + weight-based ribavirin alone has replaced interferon-containing therapy for HCV genotypes 2 and 3.

Current evidence indicates that treatment for HCV genotype 1 should consist of sofosbuvir + pegylated interferon + weight-based ribavirin for 12 weeks (treatment-naive patients: grade A recommendation; treatment-experienced patients: grade B recommendation) (**Table 4**) because of the short duration of overall therapy. A second-line alternative in treatment-naive patients and previous relapsers is pegylated interferon + weight-based ribavirin for 24 weeks along with simeprevir for the first 12 weeks (grade A recommendation). Partial and null responders can be treated with pegylated interferon + weight-based ribavirin for 48 weeks along with simeprevir for the first 12 weeks (grade A recommendation). All therapy in patients who receive simeprevir-containing regimens should be stopped for patients with an inadequate on-treatment virologic response (ie, quantifiable HCV viral load at week 4, 12, and/or 24) (grade B recommendation). Prior to treatment with simeprevir-containing regimens, patients with HCV genotype 1a should be tested for the presence of a Q80K mutation, which reduces the likelihood of treatment success.

Patients infected with HCV genotype 2 can be treated with sofosbuvir + weight-based ribavirin for 12 weeks (treatment-naive patients: grade A recommendation; treatment-experienced patients: grade B recommendation). Patients infected with HCV genotype 3 can be treated with sofosbuvir along with weight-based ribavirin for 24 weeks (treatment-naive and -experienced patients: grade B recommendation).

Sofosbuvir + weight-based ribavirin had SVR rates similar in patients with HIV-HCV coinfection to those seen in patients with HCV monoinfection for genotype 1 (76%), genotype 2 (88%), and genotype 3 (92%); however, few patients with HCV genotypes 2 and 3 were included in initial studies. The use of sofosbuvir and, to a larger extent, simeprevir, telaprevir, and boceprevir in HIV-infected patients is complicated by extensive drug interactions with HIV antiretrovirals.[55,56] Hence, patients with HIV-HCV coinfection should be treated only by an experienced physician after careful assessment for potential drug interactions and using the same recommended regimens for HCV monoinfection (grade B recommendation).

Prior to HCV treatment, the stage of liver fibrosis should be assessed by liver biopsy or noninvasive markers. Patients with cirrhosis should be referred to a specialist for evaluation of sequelae (ie, hepatocellular carcinoma, hepatic decompensation)[46] and HCV treatment using the same regimens for patients with compensated cirrhosis as patients without cirrhosis (grade B recommendation).

Given the prevalence of neutropenia and anemia for patients receiving interferon-containing therapy, patients should be monitored for 2 weeks after starting treatment and at least monthly thereafter for the duration of therapy.

Limitations of this review include that study populations included in RCTs of sofosbuvir and simeprevir as well as newer DAAs are not demographically reflective of all patients with HCV. In particular, only small numbers of patients with cirrhosis, patients previously treated, minority patients, and patients coinfected with HIV were included, limiting the generalizability of recommendations. Further studies are warranted to evaluate the optimal combinations of DAAs and treatment duration that maximize treatment efficacy and minimize adverse effects for all subgroups of HCV-infected patients, to assess for potential for drug interactions between DAAs and concomitant medications, and to elucidate the implications of antiviral resistance.

Changes to guidelines for treatment of HCV can be expected as new regimens, many of which do not include interferon and are not included in this review, are developed and receive FDA approval. These interferon-free regimens have shown high SVR rates with few adverse events in phase 3 trials.[53,57,58] In response to these rapidly emerging results, the Infectious Diseases Society of America and the American Association for the Study of Liver Diseases jointly released in 2014 a dynamic online clinical guidance that accommodates rapid updates, which should be used as a reference.[54] In addition, given the recently published Centers for Disease Control and Prevention guidelines recommending birth cohort screening for HCV infection, many new HCV diagnoses can be expected in the United States.[11] The burden of care in

HCV treatment will likely overwhelm the capacity of US hepatologists and infectious disease physicians. Hepatitis C virus–positive patients without cirrhosis who have few comorbidities may be treated in a primary care setting using interferon-free therapy. Primary care physicians will need to be familiar with potential adverse effects of new regimens. Patients with cirrhosis, decompensated liver disease, renal insufficiency, multiple concomitant medications or comorbidities, or HIV coinfection, as well as pediatric patients, should be referred to a subspecialist for evaluation of liver disease as well as potential drug-drug interactions prior to HCV treatment. An important aspect of HCV not covered in this review is the cost of emerging DAAs. At the moment, the cost of treatment for a patient with HCV genotype 1 may be as high as $150 000, which will likely restrict wide use of novel agents.

Conclusions

Recent therapeutic advances are transforming chronic HCV into a routinely curable disease. Increased HCV detection combined with the availability of simple, well-tolerated treatment regimens can potentially reduce the need for liver transplantation and reduce HCV-related mortality. For patients needing treatment, there is strong evidence for the use of sofosbuvir + pegylated interferon + ribavirin for patients with HCV genotype 1 and for sofosbuvir + ribavirin alone for patients with HCV genotypes 2 and 3 (**Box 2**). Further studies are required to better characterize the utility of sofosbuvir and simeprevir in patients with HIV-HCV coinfection. Treatment of patients with HIV-HCV is best carried out by a specialist.

ARTICLE INFORMATION

Author Contributions: Drs Kohli and Kottilil had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
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