Hepatitis C

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Hepatitis C virus (HCV) infection is a major health problem worldwide. The effects of chronic infection include cirrhosis, end-stage liver disease, and hepatocellular carcinoma. As a result of shared routes of transmission, co-infection with HIV is a substantial problem, and individuals infected with both viruses have poorer outcomes than do peers infected with one virus. No effective vaccine exists, although persistent HCV infection is potentially curable. The standard of care has been subcutaneous interferon alfa and oral ribavirin for 24–72 weeks. This treatment results in a sustained virological response in around 50% of individuals, and is complicated by clinically significant adverse events. In the past 10 years, advances in HCV cell culture have enabled an improved understanding of HCV virology, which has led to development of many new direct-acting antiviral drugs that target key components of virus replication. These direct-acting drugs allow for simplified and shortened treatments for HCV that can be given as oral regimens with increased tolerability and efficacy than interferon and ribavirin. Remaining obstacles include access to appropriate care and treatment, and development of a vaccine.

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Introduction

First discovered in 1989, hepatitis C virus (HCV) is a major health problem affecting more than 170 million people worldwide.[1] The percentage of people who are seropositive for anti-HCV antibodies worldwide is estimated to have increased from 2·3% to 2·8% between 1990 and 2005.[2] Central and east Asia, north Africa, and the Middle East have the highest prevalence (>3·5%), with moderate prevalence in eastern and western Europe (1·5–3·5%).[2] Most patients (80–85%) who become acutely infected cannot clear the virus and progress to chronic infection. This percentage is higher for patients who are co-infected with HIV, and is lower for women and children.[3,4] The severe results of chronic infection are cirrhosis, portal hypertension, hepatic decompensation, and the development of hepatocellular carcinoma, with HCV infection ultimately causing around 350 000 deaths per year.[5] In regions of high endemicity, chronic viral hepatitis usually accounts for more than 50% of hepatocellular carcinoma and cirrhosis.[6] 27% of cases of cirrhosis worldwide can be attributed to HCV, and 25% of hepatocellular carcinoma cases are attributable to HCV infection. Individuals chronically infected with HCV have a decreased quality of life compared with the general population.[7]

For many years, treatment for chronic HCV has been inadequate (success rates of ~50%, depending on genotype). The standard of care until 2011 was a combination of subcutaneous pegylated interferon (peginterferon) alfa and oral ribavirin. This combination can lead to a sustained virological response (SVR). Because SVR is regarded as a cure, chronic HCV can be cured by medical treatment, although this does not prevent future reinfection. However, treatment is associated with clinically significant adverse events, and is poorly tolerated and less efficacious in patients with advanced disease.[8] The introduction of direct-acting antiviral drugs (DAAs), with two protease inhibitor (PI) drugs licensed in 2011, has increased the number of patients who respond to treatment, and marks a new era of HCV treatment (figure 1).[9–12] New DAAs are in various stages of preclinical and clinical development, leading to optimism about future management of chronic HCV.[13]

Virology

HCV is a positive-sense, single-stranded 9600 kb RNA virus. A single HCV polyprotein of 3011 aminoacids is translated, and then cleaved by cellular and viral proteases into three structural proteins (core, E1, and E2) and seven non-structural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B).[14] Related viral sequences have been identified in dogs,[15] horses,[16] rodents, and bats.[17] HCV infections in human populations show extreme genetic diversity, which is partly explained by the long evolutionary association between the virus and human beings.[18] Most work has focused on genotypes 1–6 of the seven known HCV genotypes. Although all genotypes are distributed worldwide, genotypes 1, 2, 4, and 5 are endemic in Africa, whereas genotypes 3 and 6 evolved in Asia.[19] During the past century, medical interventions such as schistosomiasis eradication campaigns in Egypt have amplified specific strains to epidemic proportions, and many of these strains have subsequently spread internationally.[20] In the UK, genotype 3a is codominant with genotype 1—a feature that has implications for vaccines and therapy.

Additionally, HCV has enormous genetic diversity in infected hosts, existing in blood as a swarm of related quasispecies. This diversity is a result of the error-prone viral polymerase, and fast viral replication enables rapid adaptation to host antibody responses, cellular immune responses, and antiviral drugs.[21]

Search strategy and selection criteria

We searched Medline and PubMed with the search terms "HCV" and "hepatitis C virus", together with "epidemiology", "clinical manifestation", "virology", "diagnosis", "biopsy", "treatment", "drugs", "immunology", or "vaccines". We selected publications mostly from the past 5 years, but did not exclude commonly referenced and highly regarded older publications.

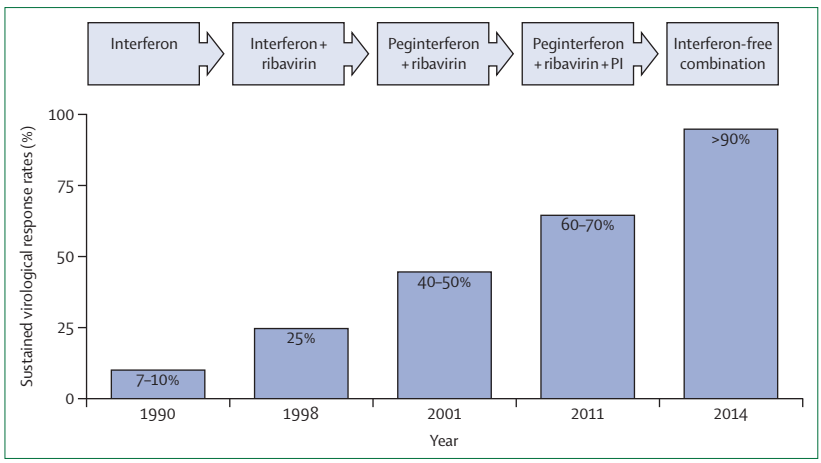

Figure 1: **Changes in standard of care for HCV, and improvements in numbers of sustained virological responses**
Data from references 9–12. PI=protease inhibitor.

Growth of HCV in tissue culture was not possible until the discovery of a specific strain of HCV genotype 2.[22] Culture of HCV has been used to identify a complex set of interactions with surface receptors, including CD81, SCARB1 (a scavenger receptor), and two tight junction proteins, OCLN and CLDN1.[23] These models have enabled crucial insights to be made into viral replication and host–virus interactions.[24] Electron microscopy has shown that mature virons have unusually irregular structures.[25] Most importantly, the ability to analyse HCV replication in tissue culture, coupled with structural analysis of key proteins, such as the NS3 protease and NS5B polymerase, has driven the development of novel specific DAAs.[26–28]

Immunology

Immune responses to HCV affect the outcome of acute disease and long-term disease progression. Acute responses to HCV include both innate and adaptive branches of the immune system. Polymorphisms in the region of the *IFNL3* (also known as IL28B) gene strongly affect spontaneous resolution of infection.[29] *IFNL3* codes for interferon, lambda 3, which has sustained antiviral activity similar to that of interferon, but with a more restricted receptor distribution. Whether the identified polymorphisms affect regulation of *IFNL3* itself or whether they affect a nearby gene, *IFNL4*, is yet to be clarified.[30] Similarly, associations between genes in the *KIR* locus and acute resolution of infection suggest that natural killer cell responses have a role in viral control.[31]

Adaptive responses mediated by CD8 and CD4 T cells are also involved in acute host defence, and strong associations with HLA class II alleles are reported in many studies, including a well powered genome-wide association study.[29] HLA class I associations have been identified in single-source outbreaks.[32] In chimpanzees, CD4 and CD8 T-cell responses are needed for full protection.[33] Results of such studies have prompted development of T cell-based preventive vaccines: a regimen based on two recombinant vectors expressing HCV non-structural genes—a novel adenovirus construct, followed by a modified vaccinia Ankara construct—is now in phase 2 clinical trials in the USA.[34]

B cell responses to HCV, which lead to generation of neutralising antibodies, have also been studied in detail.[35] The variability of regions such as the hypervariable regions of HCV E2 envelope protein within hosts is a result of antibody-driven immune selection. Nevertheless, broadly cross-reactive neutralising antibodies have been described,[36] and further work to characterise these antibodies, especially in the context of the recently described HCV E2 crystal structure, might lead to development of antibody-based vaccines.[37]

Epidemiology

HCV is an established parenteral cause of viral hepatitis.[38] Transmission via blood transfusion was a major route before universal screening of blood in the developed world, but this transmission route is a problem elsewhere.[39] Intravenous drug use, sharing of drug paraphernalia, and reuse of injection needles have become the major routes of HCV transmission.[40,41]

The natural history of HCV in pregnancy and in infants born to mothers with HCV is poorly understood, and thus effective methods for prevention of vertical transmission have not been developed. Mother-to-child transmission occurs in 2–8% of HCV monoinfected mothers, but might be more common in those co-infected with HIV.[42,43] No randomised controlled trials have been done to inform recommendations on caesarean section in this setting.[44] The efficiency by which HCV is sexually transmitted has been disputed; however, in monogamous heterosexual couples, transmission to a discordant partner is extremely rare.[45]

Since 2000, an epidemic of acute HCV infections has occurred in HIV-positive men who have sex with men (MSM).[46] Transmission seems to be permucosal rather than parenteral, and is associated with sexual practices (fisting and group sex) and intranasal and intrarectal drug use.[47] Results of molecular epidemiological and phylogenetic studies in several European countries have identified several transmission clusters in MSM networks.[46,48,49] Up to 25% of MSM treated for HCV will become reinfected within 2 years, highlighting the need for effective sexual health education and preventive interventions targeted at this group.[50] Moreover, natural immunity does not provide adequate protection against a subsequent infection.

HIV/HCV co-infection

HIV and HCV share routes of transmission, and therefore co-infection with both viruses is a common problem affecting an estimated 20–30% of the world's 34 million individuals with HIV.[51] HCV-related liver disease has become a leading cause of morbidity and

death in patients with HIV.[50,51] Development of chronic HCV is more common in patients with HIV, and is associated with higher HCV viral loads than in patients infected with HCV alone.[51] Co-infected patients progress faster to cirrhosis and end-stage liver disease (although early highly active anti-retroviral therapy [HAART] might attenuate this effect),[52–54] and respond less well to interferon and ribavirin treatment regimens than do patients with HIV monoinfection.[55] An SVR substantially reduces liver-related morbidity and mortality in co-infected patients.[56]

Initiation of HAART in co-infected patients might be associated with a higher risk of hepatotoxicity than in those without HCV. However, this benefit is outweighed by the potential advantages of immune restoration that might lessen disease progression, and thus, initiation of HAART is generally recommended early in co-infected patients.[57] Both HIV and HCV infections are associated with disorders of multiple systems. In addition to the effect of HIV infection on HCV-related liver pathology, patients who have HIV/HCV co-infection are more likely to have HIV-related kidney disease,[58] have more global neurocognitive dysfunction,[59] and have a higher prevalence of cardiovascular disease and bone disease, than patients with HCV mono-infection.[60–62]

Diagnosis

Diagnosis of HCV relies on detection of antibody to the virus and nucleic acid amplification tests to detect HCV RNA. Antibody tests have improved substantially since their approval by the US Food and Drug Administration in 1990.[63] HCV RNA is detected early in infection (~2 weeks), and will be followed by antibody seroconversion days to weeks later (~6 weeks), although development of detectable antibody can be delayed, or might not occur at all in immunocompromised patients.[64] HCV-specific antibodies are detected by an enzyme immunoassay or chemiluminescence immunoassay.[63] Presence of anti-HCV antibody in the absence of detectable RNA indicates spontaneously resolved or treated infection but, in the presence of RNA, HCV antibody indicates current HCV infection. Therefore, a positive anti-HCV test should be followed by a sensitive test for HCV RNA. In acute infection, HCV RNA might be present before seroconversion. Accurate genotyping of chronic infections is important. Hybridisation assays might not be specific enough, and more accurate results could be obtained from molecular sequence data.[65,66]

HCV genotypes respond differently to, and need different durations of, treatment with peginterferon and ribavirin.[11,12,67] Quantification of HCV RNA at predetermined timepoints can be used to measure response to therapy.[68] The lower limits of detection and sensitivity of quantification of HCV RNA have improved. Resistance testing might become more important than it has previously been.[68]

Acute HCV

Most acute infections are asymptomatic and anicteric.[69] Typically, 10–14 weeks after infection, an increase in serum aminotransaminases occurs.[70] The early peak in HCV viral RNA load is sometimes followed by a transient decline,[69] and approximately 15–20% of patients will clear acute infection.[3,69,71] Factors that have been shown to be associated with spontaneous clearance of HCV infection include being female, *IFNL3* polymorphisms, high alanine aminotransferase concentrations, presence of jaundice, speed of decline of HCV RNA, and high blood IP-10 concentrations.[72] A balance has to be made between early treatment in patients who might spontaneously clear infection and delaying treatment, which will result in reduced treatment efficacy. A positive HCV RNA test 12 weeks into the course of acute HCV infection is an indication for treatment.[73]

Early treatment is more effective than delayed treatment in patients with and without HIV co-infection.[74] The optimal treatment regimen for acute HCV infection with peginterferon has not been established, but 24 weeks or 48 weeks of peginterferon with ribavirin is recommended.[73] The proportion of patients who have an SVR ranges from 65% to more than 85%.[75,76] Peginterferon alfa alone for up to 24 weeks might be sufficient to cure up to 98% of patients without HIV co-infection.[77,78] Optimal treatment regimens for DAAs have not yet been defined.

Natural history

HCV infection causes chronic hepatitis, potentially leading to cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma. The onset and accumulation of hepatic fibrosis is clinically silent in the early stages of disease, and identification of disease progression is therefore difficult.[79,80] The yearly incidence of progression of hepatic fibrosis from minimal disease to cirrhosis has been modelled and estimated. The prevalence of biopsy-proven cirrhosis after 20 years of infection has varied between 7% (in retrospective studies) and 18% (in clinical referred settings). The risk of cirrhosis is increased in individuals abusing alcohol, in those who acquire the disease at an older age, in those with concomitant obesity, in men, in immunosuppressed HIV-positive patients, and in those with recurrent HCV after liver transplantation.[81,82]

Patients with minimal fibrosis have a low risk of development of complications of liver disease during the subsequent two decades; conversely, patients with bridging fibrosis or cirrhosis have a higher risk. Repeat liver biopsy samples might be needed to detect progression. Alternatively, and more practically, non-invasive blood tests, fibroelastography, and hepatic imaging can be used to identify patients with advanced fibrosis to gauge indications for treatment.[83] Extrahepatic manifestations of HCV, such as cryoglobulinaemia or HCV-associated splenic lymphoma, are also indications

for antiviral therapy. Treatment reduces infectivity and transmission, and thus incident chronic disease, in individuals using intravenous drugs.

Treatment

The main goal of treatment for chronic HCV is cure, and thus prevention of disease progression. SVR (defined as HCV RNA <15 IU/mL 12–24 weeks after completion of antiviral therapy) is associated with reduction of both all-cause and liver-related mortality from HCV.[84,85] A combination of peginterferon and ribavirin, given for up to 48 weeks, was previously the mainstay of treatment for all genotypes of HCV, but is being superseded by DAAs (figure 2). No prophylactic vaccine exists, but several are in development and in early-stage clinical trials.[14]

Indications for treatment

Patients with cirrhosis are at more immediate risk of complications of liver disease. Favourable responses to interferon-based treatments are less common in patients with cirrhosis compared with those without cirrhosis, but can be improved by addition of first-generation PIs. Furthermore, the potential risks of adverse events are increased in patients with cirrhosis. Additionally, treatment might be given to patients to prevent development of advanced fibrosis and cirrhosis, for extrahepatic symptoms, and to prevent transmission of infection. The high costs of newer DAA-including treatment regimens might necessitate stratification of patients for treatment.

Treatment for genotype 1

First-generation PIs increase the number of patients with genotype 1 infection who respond to treatment. Previously untreated and treated patients who are given a combination of telaprevir or boceprevir plus peginterferon and ribavirin are more likely to achieve SVR than are those treated with peginterferon and ribavirin alone.[11,12] Around 50–60% of PI recipients achieve a rapid virological response (defined as HCV RNA <15 IU/mL 4 weeks into treatment), meaning that treatment duration can be reduced to 6 months; however, this percentage is reduced for patients with cirrhosis and patients with a previous null response to peginterferon and ribavirin (ie, those with a <2 log10 IU/mL decline in HCV RNA by treatment week 12). Patients with cirrhosis need a longer duration (48 weeks) of peginterferon and ribavirin treatment than do those without cirrhosis.[86] Treatment with first-generation PIs can be complex, and can cause clinically significant adverse events. The safety profile of prolonged interferon and first-generation DAA treatment in patients with advanced cirrhosis is poor.[87]

High response rates have been reported in patients inheriting the *IFNL3* rs12979860 CC genotype—a polymorphism upstream of the *IFNL3* gene—compared with individuals without the polymorphism.[88] Several drug–drug interactions can occur.[89] Resistance-associated viral variants with substitutions located in the catalytic site of the NS3 protease have been described after telaprevir and boceprevir treatment. Stopping rules to avoid acquisition of more complex mutations are recommended.[90–92]

The most common side-effects of telaprevir are anaemia, pruritis, nausea, diarrhoea, and anorectal discomfort. Around 4% of patients develop severe dermatitis, necessitating cessation of treatment. Drug reactions with eosinophilia and systemic symptoms or Stevens-Johnson syndrome are rare, but have been reported. Boceprevir causes dysguesia and anaemia.[93]

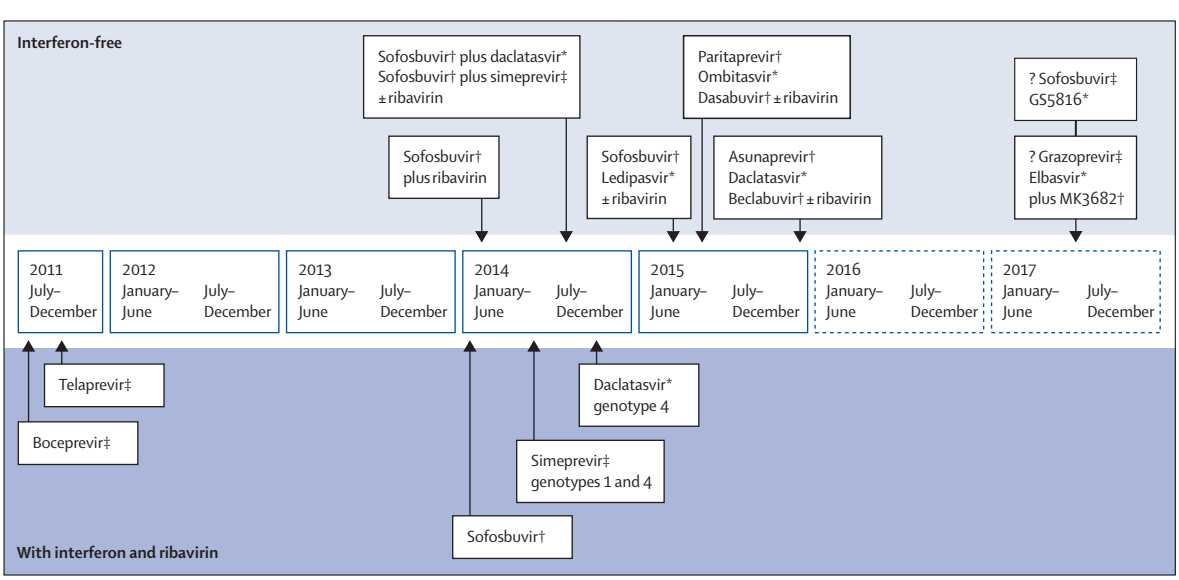

Figure 2: **Treatment of HCV in 2015 (including protease, NS5B, and NS5A inhibitors that are approved or are about to be approved)**
*NS5A inhibitor. †NS5B inhibitor. ‡Protease inhibitor.

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Interferon-sparing regimens with new agents for genotype 1

Treatment for genotype 1 HCV infection is changing rapidly. Key viral replication targets have been identified: the NS3 protease, NS5A, and the NS5B RNA polymerase. In 2014, other potent antiviral inhibitors targeting these proteins have been licensed with once-daily dosing, and the possibility of a shorter duration of treatment with peginterferon and ribavirin. These interferon-sparing regimens include the addition of simeprevir (a second-generation PI), daclatasvir (an NS5A inhibitor), and sofosbuvir (a uridine nucleotide prodrug NS5B polymerase inhibitor), in combination with peginterferon and ribavirin for 12–24 weeks.[94–97] 80–90% of previously untreated patients infected with HCV genotype 1 responded to treatment with simeprevir, sofosbuvir, or daclatasvir, in combination with peginterferon.

150 mg of simeprevir daily for 12 weeks, with peginterferon and ribavirin for 24 weeks, in previously untreated patients infected with genotype 1 resulted in SVR in 80% of patients in the QUEST-1 study,[98] and 81% of patients in the QUEST-2 study.[99] A rapid virological response occurs in 85% of patients, 91% of whom subsequently achieve SVR at 12 weeks. Fewer patients with stage F3–F4 fibrosis were reported to respond. A Gln80Lys mutation detectable at baseline in the NS3 sequence impairs the response to simeprevir. Simeprevir with peginterferon and ribavirin resulted in SVR in 79% of patients who previously relapsed compared with 36% of peginterferon-retreated controls.[100]

Sofosbuvir together with peginterferon and ribavirin has been given for 12 weeks in previously untreated patients with genotypes 1, 4, 5, and 6. SVR was reported in 89% of patients infected with genotype 1 and in 82–100% of patients infected with genotype 4.[97,101] Few patients with genotypes 5 and 6 were treated in these studies. Previous non-responders were not included in these clinical trials, and only a small number of patients with cirrhosis were included.

In a dose-finding study, 332 patients were treated with grazoprevir, a PI, (MK-5172; Merck & Co., NJ, USA; 100 mg, 200 mg, 400 mg, or 800 mg) once-daily for 12 weeks together with peginterferon and ribavirin. A control group received boceprevir plus peginterferon and ribavirin. 89–91% of patients given grazoprevir were reported to achieve SVR compared with 61% of patients in the control group. Increases in alanine aminotransferase concentration were not observed with the 100 mg dose.[102]

Interferon-free regimens for genotype 1

Interferon-sparing regimens will probably be replaced in 2015 by interferon-free regimens with improved efficacy and tolerability for both previously untreated patients and previous interferon non-responders. These regimens comprise the following: a PI or an NS5A inhibitor plus a nucleoside NS5B inhibitor, with or without ribavirin; a PI, an NS5A inhibitor and an NS5B non-nucleoside inhibitor, with or without ribavirin; or a PI and an NS5A inhibitor, with or without ribavirin.[103] Updated guidelines are published by the European Association for the Study of the Liver and the American Association for the Study of Liver Disease.

Sofosbuvir can also be used in combination with ribavirin in patients with genotype 1 infection who are intolerant to interferon, particularly in non-cirrhotic patients, and responses can be achieved in up to 72% of patients.[104] Sofosbuvir plus daclatasvir[105] or sofosbuvir plus ledipasvir, an NS5A inhibitor, (without ribavirin) are highly effective regimens for previously untreated patients with HCV genotype 1 and previous interferon non-responders (including telaprevir and boceprevir non-responders).[103] SVR was achieved in 97% of previously untreated patients (ION-1),[106] 93% of treatment-experienced patients (ION-2) treated with sofosbuvir and ledipasvir without ribavirin for 12 weeks, and 94% of treatment-naive patients with genotype 1 infection treated for 8 weeks (ION-3);[107] ION-1 and ION-2 included 15–20% of patients with cirrhosis. Anaemia was rare in the ribavirin-free groups. Clinical resistance is extremely rare, although a Ser282Thr mutation in a replicon model confers resistance to sofosbuvir.[108] However, resistant NS5A variants are detected in patients who relapse after sofosbuvir in combination with an NS5A inhibitor.

The European Medicines Agency recommendation for sofosbuvir and ledipasvir in combination for patients without cirrhosis is 8 weeks for treatment-naive patients with genotype 1 or 4 infection; 24 weeks should be considered for treatment-experienced patients with uncertain subsequent retreatment options. For patients with compensated cirrhosis, 24 weeks of treatment is recommended, but 12 weeks could be considered for patients who are thought to be at low risk for clinical disease progression and who have subsequent retreatment options. For patients who have decompensated cirrhosis, those who are yet to receive a liver transplant, or have received a liver transplant, 24 weeks of treatment plus ribavirin is recommended. However, the combination of sofosbuvir and ledipasvir plus ribavirin for 12 weeks was equally as efficacious as sofosbuvir plus ledipasvir for 24 weeks in patients with well compensated cirrhosis (Childs-Pugh-Turcotte [CPT] class A)—96% of patients achieved SVR with sofosbuvir and ledipasvir plus ribavirin for 12 weeks, and 97% of patients achieved SVR with sofosbuvir and ledipasvir for 24 weeks.[109]

Other studies are examining the efficacy of sofosbuvir in combination with either ledipasvir and a non-nucleoside HCV NS5B inhibitor (GS-9669; Gilead Sciences, Foster, CA, USA) at 500 mg per day, or a PI (GS-9451; Gilead Sciences) at 80 mg per day in previously untreated patients without cirrhosis, and further reduction of treatment to 4 weeks or 6 weeks.[110] Phase 3 studies examining the efficacy of sofosbuvir and GS-5881 (Gilead Sciences)—a

next-generation NS5A inhibitor—are in progress, on the basis of the pangenotypic efficacy of this combination in preliminary studies.[111]

Other potentially effective, short-duration, oral combinations for genotype 1 infection include ritonavir-boosted PI paritaprevir (ABT-450; AbbVie, Chicago, IL, USA), 150 mg paritaprevir and 100 mg ritonavir, co-formulated with an NS5A inhibitor, ombitasvir (ABT-267; AbbVie), 25 mg once-daily, and a non-nucleoside NS5B polymerase inhibitor, dasabuvir (ABT-333; AbbVie), 250 mg twice-daily with ribavirin (weight-based; SAPPHIRE I). 96% of treatment-naive patients with genotype 1 infection achieved SVR,[112] and in the SAPPHIRE-II study, 96% of non-cirrhotic previous non-responders to peginterferon and ribavirin, 49% of whom were previous null responders, achieved SVR.[113]

Similar results have been obtained in patients with cirrhosis: 191 (92%) of 208 treatment-naive or treatment-experienced patients with compensated cirrhosis treated for 12 weeks achieved SVR, compared with 165 (96%) of 172 patients treated for 24 weeks (TURQUOISE-II).[114] Virological failure was rare, but the emergence of NS3, NS5A, and NS5B resistance-associated viral variants means that an appropriate salvage therapy is needed. Results of other linked studies have shown that ribavirin should only be used if needed, and that ribavirin is not needed in previously untreated non-cirrhotic patients with genotype 1b infection.[115] A longer duration of treatment (24 weeks) with ribavirin is advisable for patients with genotype 1a infection who have cirrhosis and a previous non-response or other adverse factors.[116] Licensing information is awaited.

400 mg of sofosbuvir and 150 mg of simeprevir once-daily have been assessed in previously untreated cirrhotic and non-cirrhotic patients and previous non-responders. In the COSMOS study,[117] two cohorts were studied: F0–F2 null responders, and F3–F4 previously untreated patients or null responders. 92–96% of patients responded, without an apparent need for ribavirin with this combination of a PI and an NS5B polymerase inhibitor. Previous Gln80Lys mutations in patients with genotype 1a infection had little effect on treatment. Data obtained from large observational databases have likewise confirmed the efficacy of simeprevir and sofosbuvir in patients with genotype 1 infection (TARGET and TRIO cohorts).[118,119] Responses have been recorded in 80–94% of patients, although this percentage could be 10–15% lower in patients with cirrhosis. A combination of daclatasvir and asunaprevir (a PI) is effective in patients with genotype 1b infection (HALLMARK DUAL).[120]

New DAA regimens, including sofosbuvir plus 100 mg of GS-5816 (Gilead Sciences) for 12 weeks without ribavirin,[121] grazoprevir and elbasvir, an NS5A inhibitor, (MK8742; Merck & Co.) with or without ribavirin,[122] or asunaprevir, daclatasvir, and beclabuvir (a non-nucleoside NS5B polymerase inhibitor) are similarly encouraging and result in cures in more than 87–93% of patients.[123,124]

These interferon-free regimens are remarkably effective in patients with genotype 1 infection. Further analysis is needed, but baseline factors, including baseline resistance-associated viral variants, unfavourable *IFNL3* genotype, viral load, subtype, and cirrhosis can affect response to potent multiple DAA regimens. Refinements of treatment for decompensated cirrhosis will be ascertained in further phase 3 trials. Ultrashort regimens of 4–6 weeks are being studied with several combinations of next-generation PIs, NS5A inhibitors, and polymerase inhibitors. Factors acting together, such as baseline viral load or baseline NS5A mutations, could affect response to NS5A inhibitors, although their detection does not preclude a response. In some patients, multidrug-resistant viruses will be encountered after treatment failure or relapse.[125]

The dose of sofosbuvir in patients with an estimated glomerular filtration rate (eGRF) <30 mL/min per 1·73 m² is not yet established. No dose adjustment of daclatasvir is needed for renal or hepatic impairment.

Treatment for genotypes 2–6

Peginterferon and ribavirin are effective against genotypes 2–6. 48 weeks of peginterferon and ribavirin are generally needed for genotypes 4, 5, and 6, although rapid virological responders might be successfully treated within 24 weeks. Peginterferon and ribavirin are given for 24 weeks to patients with genotypes 2 and 3. The percentage of patients who achieve SVR is highest in patients with genotype 2 infection (85–90%). 43–70% of patients with genotype 4 infection and 60–85% of patients with genotype 6 infection treated with peginterferon and ribavirin have been reported to achieve SVR.[126] Patients with genotype 3 infection and cirrhosis have higher risk of relapse than do patients infected with other genotypes, and thus fewer patients with genotype 3 have been reported to achieve SVR.

Interferon-sparing regimens for genotypes 2–6

Daclatasvir has been given with peginterferon and ribavirin for 12 or 16 weeks to previously untreated patients with genotype 2 or 3 infection. Around 83% of patients infected with genotype 2 and 70% of patients with genotype 3 infection have been reported to achieve SVR.[127] Similar encouraging results were reported in patients infected with genotype 4.[128] Simeprevir, a second-generation PI, is active against genotype 4, particularly in treatment-naive and relapsed patients.[129] As noted, sofosbuvir given with 12 weeks of peginterferon and ribavirin is active against all genotypes. In the LONESTAR-2 study,[130] sofosbuvir given to treatment-experienced patients in combination with peginterferon and ribavirin for 12 weeks resulted in SVR in 96% of patients infected with genotype 2 and 83% of patients infected with genotype 3. Although the numbers of patients with cirrhosis were small, cirrhosis did not affect the response.[130] Thus at present,

genotype 3 treatment-experienced patients with cirrhosis might need peginterferon, sofosbuvir, and ribavirin for 12 weeks to achieve the highest response.

Interferon-free regimens for genotypes 2 and 3

A 12 week combination of sofosbuvir and ribavirin is highly efficacious (97% of patients) in genotype 2, but a longer treatment period of 24 weeks is needed for patients infected with genotype 3. Responses are lower among those with cirrhosis than among those without cirrhosis, and are reduced to 62% in treatment-experienced patients with genotype 3 infection and cirrhosis treated with sofosbuvir and ribavirin for 24 weeks.[131,132] However, SVR occurred in 94% of previously untreated, non-cirrhotic patients with genotype 3 infection who were treated for 24 weeks.[132] High numbers of patients with genotype 2 infection responded to treatment. Virological failures are usually due to relapse with wild-type HCV, and discontinuations for drug-related adverse events are rare.

In previously untreated patients infected with genotypes 2 or 3, SVR was reported in 94–100% of patients treated with the combination of daclatasvir plus sofosbuvir. In the ALLY-3 study,[133] in which previously treated and untreated patients with genotype 3 infection were treated for 12 weeks with 400 mg of sofosbuvir and 60 mg of daclatasvir (without ribavirin) for 12 weeks, 92 (91%) of 101 previously untreated patients had an SVR compared with 44 (86%) of 51 treatment-experienced patients. Overall, 105 (96%) of 109 patients without cirrhosis responded, compared with 20 (63%) of 32 with cirrhosis. The European Medicines Agency recommends sofosbuvir plus daclatasvir and ribavirin for 24 weeks for patients with genotype 3 infection with compensated cirrhosis, those who are treatment-experienced, or both.[104] Similarly, preliminary results of a 12 week combination of sofosbuvir and ledipasvir for patients with genotype 3 infection showed that fewer patients had an SVR (16 [64%] of 25) with sofosbuvir plus ledipasvir compared with 26 (100%) of 26 of those treated with sofosbuvir, ledipasvir, and ribavirin.[134] The European Medicines Agency recommendation for patients with genotype 3 infection with cirrhosis, previous treatment failure, or both is sofosbuvir, ledipasvir, and ribavirin for 24 weeks.

Sofosbuvir plus GS-5816 and other combinations, including grazoprevir and elbasvir (or next-generation NS5A inhibitors), plus next-generation polymerase inhibitors are being studied to increase the number of patients with genotype 3 infection who respond to therapy. High numbers of patients with genotype 3 infection without cirrhosis have been reported to respond to 100 mg of GS-5816. Fewer treatment-experienced patients with genotype 3 infection and cirrhosis were reported to respond if ribavirin was not used.[121] More than 90% of patients with genotype 4 infection have been reported to have an SVR when treated with sofosbuvir and ribavirin for 24 weeks. By extrapolation, the combination of sofosbuvir and simeprevir or daclatasvir should be active against genotype 4.[135] A 12 week dual regimen of ritonavir-boosted paritaprevir–ombitasvir, with or without ribavirin in treatment-naive patients (treatment-experienced patients all received ribavirin) showed excellent response rates,[136] as did all-oral therapy with daclatasvir plus asunaprevir and beclabuvir for previously untreated patients with chronic genotype 4 infection.[137]

Patients with HIV/HCV co-infection

Telaprevir and boceprevir have both been assessed in patients with chronic co-infection.[138–141] Although promising numbers of patients have achieved SVR, drug–drug interactions can be problematic. Telaprevir can be given for 12 weeks in combination with peginterferon and ribavirin to treat acute genotype 1 co-infection.[142] Several promising interferon-sparing and interferon-free regimens have been tested in patients with HIV/HCV co-infection.[138] These regimens include simeprevir together with peginterferon and ribavirin, sofosbuvir plus ribavirin, or sofosbuvir plus ledipasvir for 12 weeks,[143] or grazoprevir plus elbasvir with or without ribavirin in the C-WORTHY study.[144] In the PHOTON study,[145] co-infected genotype 1, 2, and 3 previously untreated patients were treated with 400 mg of sofosbuvir daily and ribavirin for 24 weeks (for genotype 1) or 12 weeks (for genotypes 2 and 3). 87 (76%) of 114 patients with genotype 1 infection (treated for 24 weeks), 23 (88%) of 26 patients with genotype 2 infection (treated for 12 weeks), and 28 (67%) of 42 patients with genotype 3 infection (treated for 12 weeks) achieved SVR. Among the patients who were previous non-responders, 92% with genotype 2 infection and 94% with genotype 3 infection achieved SVR after 24 weeks of treatment. Patients who are co-infected with HIV and HCV now have similar treatment outcomes to those with HCV monoinfection.[146] However, appropriate dose modifications or changes in HAART regimens might be needed in co-infected patients. Efavirenz, etravirine, and nevirapine are not recommended with daclatasvir, simeprevir, or sofosbuvir. The dose of daclatasvir should be reduced from 60 mg to 30 mg if ritonavir-boosted atazanavir is used, but increased to 90 mg if dosed together with efavirenz, nevirapine, or etravirine. Coadminstration of ritonavir-boosted atazanavir, or darunavir with simeprevir is not recommended.

Patients with decompensated cirrhosis or undergoing liver transplantation

Decompensated cirrhosis

Patients with decompensated cirrhosis are not candidates for interferon therapy. Before transplantation, a preliminary report of sofosbuvir and ribavirin for up to 48 weeks, stopping on day of transplantation for patients with HCV and hepatocellular carcinoma (within Milan criteria), showed a post-transplantation SVR in 64% of patients. The duration of undetectable HCV RNA before

transplantation was the best predictor of response.[147] Several clinical trials are now in progress. Results of studies in which ledipasvir and sofosbuvir plus ribavirin given for 12 weeks or 24 weeks in patients with CPT class B or C cirrhosis suggest that 86–90% of previously treated or untreated patients with genotype 1 or 4 infections respond. An improvement in the model for end-stage liver disease (MELD) score has been recorded.[148] Definitive guidance about the optimum duration of therapy in this group is crucial.

HCV after transplantation

Telaprevir and boceprevir have been used to treat post-transplantation recurrent HCV.[149] Preliminary reports indicated that more patients achieved SVR with these treatments than with peginterferon and ribavirin alone. However, toxicity, particularly anaemia and sepsis, and drug–drug interactions with calcineurin inhibitors complicate treatment.[150] Fortunately, these treatments are beginning to be replaced by better tolerated and more effective DAA therapies. Sofosbuvir and ribavirin have been used for treatment of recurrent post-transplantation HCV infection (all genotypes). Virological responses were reported in 77% of patients after 24 weeks of treatment.[151] These landmark treatments have already been improved. Reponses have been reported in high numbers of patients (>90% of patients with CPT class A cirrhosis with sofosbuvir and ledipasvir,[152] or sofosbuvir plus simeprevir, with or without ribavirin).[153] Excellent SVR results after a transplantation were reported in a small group of patients with genotype 1 infection without advanced fibrosis, who were treated with ombitasvir, paritaprevir, ritonavir, and dasabuvir. This combination increases the half-lives of both tacrolimus and ciclosporin, but this is manageable by varying dose and dose interval of each.[154]

Conclusions

Improved, efficacious and simplified interferon-free and, for most patients, ribavirin-free treatments for HCV infection are now available. Detailed guidelines, treatment algorithms, and licensing information, which will be updated at frequent intervals, are being published to guide clinicians. Simple all-oral regimens of short duration have become a reality. Treatment can now be given to groups of patients for whom interferon was contraindicated. Evidence is emerging that patients on stable opioid replacement therapy are also good candidates for DAA regimens.[155,156]

However, next-generation DAA treatments are costly. Meeting demand for therapy of a common disease with these breakthrough therapies is concerning for policy makers because of the immediate budgetary effect. The high cost might reduce access, thus restricting societal benefit. Stratification and prioritisation of patients on the basis of cost-effectiveness, stage of disease, and potential gain from treatment might be needed. Prices might decrease as several effective drugs offering a cure are licensed. Major obstacles at present are the identification and appropriate referral of people in need of treatment and widespread delivery in primary care. Treatment will form part of the control of the disease; however, successful treatment of an infection has never led to eradication. The search for an effective prophylactic vaccine should continue, and advances in molecular vaccinology will enable progress in the coming years.

Contributors

All authors contributed equally in writing sections of the manuscript that suited their expertise. All authors reviewed the final manuscript. DPW and GMD designed the figures.

Declaration of interests

DPW has received travel grants or lecture fees from Bristol-Myers Squibb, Gilead, Janssen, Viiv, and Abbott Molecular. PK declares no competing interests. GMD has acted as an adviser for Janssen, Gilead Sciences, AbbVie, Merck, and Bristol-Myers Squibb.

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