ARTICLE

Treating hepatitis C – what's new?

SUMMARY

Chronic hepatitis C infection causes cirrhosis, liver failure and hepatocellular carcinoma, and is the most common indication for liver transplantation.

Hepatitis C is curable and complications can be prevented. Until recently, treatment regimens involved peginterferon alfa. Although effective, their widespread use is limited by treatment-related toxicity.

A number of direct-acting drugs for hepatitis C, such as sofosbuvir, have recently been developed and target multiple steps in the viral life cycle. These drugs are used in combination in interferon-free regimens. Short courses are highly effective with minimal toxicity.

Alex J Thompson
Director of Gastroenterology[1]
Professor[1,2]

Jacinta A Holmes
Gastroenterologist[1]
PhD fellow[2]

[1] Department of Gastroenterology St Vincent's Hospital
[2] University of Melbourne Melbourne

Key words
asunaprevir, daclatasvir, hepatitis C, peginterferon, protease inhibitors, ribavirin, sofosbuvir

Aust Presc 2015;38:191–7
First published online 18 September 2015

CPD FOR PHARMACISTS

This article has a continuing professional development activity for pharmacists available at www.australianprescriber.com/continuing-professional-development

Introduction

It is estimated that more than 230 000 Australians are chronically infected with the hepatitis C virus.[1] The disease slowly progresses over decades. A significant minority of patients will develop cirrhosis (5–20% after 20 years) and be at risk of complications including liver failure and hepatocellular carcinoma.[2-4] Hepatitis C is the most common indication for liver transplantation in Australia. These complications may be prevented by viral eradication.

There are six main genotypes of hepatitis C virus – genotypes 1–6. Each of these can be further subdivided (e.g. 1a, 1b). Current Pharmaceutical Benefits Scheme (PBS)-subsidised treatment involves the combination of peginterferon alfa and ribavirin for all genotypes except genotype 1. First-line therapy for genotype 1 disease is triple therapy with peginterferon, ribavirin and a viral protease inhibitor. Overall cure rates are above 70%. However, many patients are ineligible for peginterferon or intolerant due to treatment-related toxicity.[5]

In 2015, several peginterferon-free treatments have been approved by the Therapeutic Goods Administration (TGA). They are simple, short regimens with high cure rates and minimal toxicity, and have received positive recommendations from the Pharmaceutical Benefits Advisory Committee (PBAC). They are currently being considered for PBS listing.

Diagnosis and assessment

Most patients with chronic hepatitis C are asymptomatic. Transmission of the virus is associated with identifiable risk factors, and most diagnoses result from screening at-risk individuals (see Box).

Testing for infection

The appropriate screening test for hepatitis C infection involves detection of specific antibodies to the virus in the blood. Their presence indicates exposure to hepatitis C virus from a current or past infection. Current infection is identified using a qualitative polymerase chain reaction (PCR) assay to detect viral RNA.

Approximately 25% of people with acute hepatitis C infection will clear it spontaneously within six months. These individuals continue to have anti-hepatitis C antibodies (positive screening test), but do not have detectable viral RNA in plasma (negative PCR test). In patients with recent exposure to hepatitis C virus, the

Box **Populations at increased risk of hepatitis C infection**

- People who inject drugs or have done so in the past
- Sex workers
- People in custodial settings
- People with tattoos or body piercings
- People who received a blood transfusion/organ transplant before 1990
- Children born to mothers with hepatitis C
- Sexual partners of people with hepatitis C
- People with HIV or hepatitis B
- People with liver disease (persistently elevated alanine aminotransferase)
- People who have had a needle-stick injury
- Migrants from high-prevalence regions (Egypt, Pakistan, Mediterranean and Eastern Europe, Africa and Southern Asia)

PCR test should be repeated after six months. There is no current recommendation for how frequently high-risk individuals should be screened, but annual serology is reasonable.

Assessing for liver disease

Once a patient has chronic infection, further investigation (Table 1) should assess the stage of liver disease. It is important to know whether a patient has advanced liver disease to determine the urgency for treatment, and also to screen for complications of cirrhosis such as portal hypertension and hepatocellular carcinoma.

Risk factors for cirrhosis include:

- male gender
- older age at infection
- prolonged duration of infection (>20 years)
- comorbidities including excessive alcohol consumption, diabetes and metabolic syndrome
- coinfection with hepatitis B or HIV.

Clues to the presence of advanced liver disease include peripheral stigmata of chronic liver disease (e.g. leuconychia, spider naevi), splenomegaly and thrombocytopenia. Low albumin, raised bilirubin and raised INR are markers of reduced liver function and may reflect advanced liver disease.

All patients should have a liver ultrasound to examine for features of portal hypertension (e.g. splenomegaly, reversal of portal vein flow), and to screen for hepatocellular carcinoma. Transient elastography (FibroScan) is a non-invasive ultrasonic technique for measuring liver stiffness as a marker of the stage of liver fibrosis. It is widely available in specialist centres. A key question is what threshold of liver stiffness should be used to define cirrhosis, as this has implications for treatment duration. Thresholds have varied across clinical trials evaluating different regimens,[6,7] but a reasonable threshold for treatment decision making is 12.5 kPa. Serum biomarkers for liver fibrosis have also been developed, but are not currently reimbursed.

Liver biopsy is generally reserved for patients when there is a diagnostic query. Liver histology is no longer required for accessing antiviral therapy.

Table 1 **Diagnostic work-up for hepatitis C**

Diagnosis	Comment
Hepatitis C antibody positive (serology)	Indicates exposure to hepatitis C virus (past/current infection)
Hepatitis C viral RNA positive (qualitative PCR)	Indicates current infection
Post-diagnosis	
Hepatitis C genotype	Treatment regimens are genotype specific
Hepatitis C viral RNA level (quantitative PCR)	Predicts interferon responsiveness Establishes baseline for comparison once treatment has started
Full blood examination	Thrombocytopenia suggests portal hypertension
Markers of liver functional reserve: • liver function tests • INR	Low albumin, raised bilirubin and raised INR all suggest advanced liver disease
Liver ultrasound	Identify portal hypertension, screen for hepatocellular carcinoma
Hepatitis A, B serology, HIV serology	Important co-infections
Specialist	
Host IL28B genotype*	Predicts interferon responsiveness
Transient elastography* (FibroScan)/serum fibrosis biomarker (e.g. HepaScore, FibroTest, ELF test)	Non-invasive markers of liver fibrosis stage
± Liver biopsy	Infrequently performed No longer a requirement for treatment

PCR polymerase chain reaction
Alfa fetoprotein testing is no longer recommended as part of hepatitis C screening.
* Neither IL28B genotyping nor transient elastography are currently reimbursed. Both tests are widely available at specialist centres.

Viral genotyping

Approved treatment regimens for hepatitis C are genotype specific (Table 2). It is therefore important to find out which viral genotype the patient has in order to determine the most appropriate therapy. The common genotypes in Australia are genotype 1 (54%) and genotype 3 (37%).[8]

Other investigations

Before initiating antiviral therapy, the amount of viral RNA should be quantified by PCR. Testing the host IL28B genotype is also useful (Table 1).[9,10] Both of these predict a patient's response to peginterferon plus ribavirin therapy, particularly for genotype 1 infection.

Referral to a specialist

All patients with chronic hepatitis C should be considered for antiviral therapy and referred to a clinician with a specialist interest. Patients with clinical evidence of cirrhosis are the highest priority for referral.

Treatments for hepatitis C

The goal of treatment is a virological cure (sustained virological response). This is defined as undetectable viral RNA in plasma 24 weeks after treatment has finished. A sustained virological response prevents the development of cirrhosis. In patients who already have cirrhosis, a sustained virological response reduces the risks of liver failure and hepatocellular carcinoma.

The approved treatment combinations for hepatitis C in Australia are summarised in Tables 2 and 3. Currently, all PBS-subsidised regimens involve peginterferon plus ribavirin.

The widespread use of peginterferon-containing regimens has been limited by treatment-related toxicity, as well as disappointing efficacy in patients with advanced liver disease. Direct-acting antiviral drugs targeting multiple steps in the viral life cycle have been developed and used in combination to successfully treat hepatitis C infection. These interferon-free regimens have very high efficacy, short duration (8–12 weeks) and minimal toxicity. They are suitable for patients who

Table 2 **TGA-approved interferon-containing regimens for hepatitis C**

Viral genotype	Treatment regimen	Treatment duration	Response rates† ‡
1	Simeprevir + peginterferon + ribavirin	24–48 weeks§	>70%
	Telaprevir + peginterferon+ ribavirin	24–48 weeks§	>70%
	Boceprevir + peginterferon+ ribavirin	24–48 weeks§	>70%
	Asunaprevir + daclatasvir + peginterferon + ribavirin*	24 weeks	>90%
	Sofosbuvir + peginterferon + ribavirin*	12 weeks	90%
2 and 3	Peginterferon + ribavirin	24 weeks	>70%
	Sofosbuvir + peginterferon + ribavirin*	12 weeks	90%
4	Peginterferon + ribavirin	48 weeks	40–50%
	Simeprevir + peginterferon + ribavirin	24–48 weeks§	>70%
	Asunaprevir + daclatasvir + peginterferon + ribavirin*	24 weeks	>90%
	Sofosbuvir + peginterferon + ribavirin*	12 weeks	90%#
6	Peginterferon + ribavirin	48 weeks	70–80%
	Sofosbuvir + peginterferon + ribavirin*	12 weeks	>90%

TGA Therapeutic Goods Administration

* Not listed on the Pharmaceutical Benefits Scheme at the time of writing.

† Response rate was defined as proportion of patients with a sustained virological response (undetectable viral RNA in serum) measured at 3 or 6 months after the end of treatment. Results reflect the minimum overall response rate in published studies including non-cirrhotic and cirrhotic patients.

‡ Response rates were lower in patients with cirrhosis.

§ Response-guided therapy for protease inhibitors: treatment-naïve patients, and previous relapsers following peginterferon + ribavirin, are eligible for shorter treatment duration if serum viral RNA concentrations are undetectable after 4 weeks of treatment. Previous partial or null responders are not eligible for short-duration therapy. (Note: Previous relapsers are patients who had undetectable viral RNA concentrations following interferon-based therapy and detectable viral RNA during follow-up. Previous partial responders are patients with previous on-treatment ≥2 $\log_{10}$ IU/mL reduction in viral RNA from baseline at week 12 and detectable RNA at the end of previous therapy with peginterferon + ribavirin. Previous null responders are patients with previous on-treatment <2 $\log_{10}$ reduction in RNA from baseline at week 12 or <1 $\log_{10}$ reduction in RNA from baseline at week 4 during previous peginterferon + ribavirin therapy.)

The efficacy of sofosbuvir + peginterferon + ribavirin in patients who have previously been non-responders to peginterferon + ribavirin is not known.

Table 3 **TGA-approved interferon-free regimens for hepatitis C**

Viral genotype	Treatment regimen*	Patient characteristics			Response rates†
		No cirrhosis	Cirrhosis	Cirrhosis + treatment-experienced	
1a/b	Sofosbuvir + ledipasvir	12 weeks‡	12 weeks	24 weeks§	≥95%
1a	Paritaprevir + ritonavir + ombitasvir + dasabuvir	12 weeks + ribavirin	12 weeks + ribavirin	12 weeks + ribavirin#	≥95%
1b		12 weeks	12 weeks + ribavirin¶	12 weeks + ribavirin¶	
1a/b	Sofosbuvir + daclatasvir ± ribavirin	12 weeks	12 weeks + ribavirin OR 24 weeks**	12 weeks + ribavirin OR 24 weeks** ††	≥95%
1b	Asunaprevir + daclatasvir	24 weeks	24 weeks	24 weeks	90%
2	Sofosbuvir + ribavirin	12 weeks	12 weeks‡‡	12 weeks‡‡	F0-3 >90% F4 >80%
3	Sofosbuvir + ribavirin	24 weeks	24 weeks	24 weeks	F0-3 >80% F4 62-82%§§
3	Sofosbuvir + daclatasvir ± ribavirin	12 weeks	12 weeks + ribavirin OR 24 weeks##	12 weeks + ribavirin OR 24 weeks##	F0-3 >90% F4 >80%##

TGA Therapeutic Goods Administration F0-3 METAVIR fibrosis stage 0-3 F4 METAVIR fibrosis stage 4 (cirrhosis)

* Not listed on the Pharmaceutical Benefits Scheme at the time of writing.

† Response rate was defined as proportion of patients with a sustained virological response (undetectable viral RNA in serum) measured at 3 or 6 months after the end of treatment.

‡ 8 weeks may be considered in treatment-naïve patients with no cirrhosis and a baseline viral RNA concentration <6 x 10^6 IU/mL.

§ 24 weeks is recommended for patients who have failed treatment with peginterferon + ribavirin with or without a protease inhibitor.

24 weeks is recommended for patients who have had a previous null response to peginterferon + ribavirin, defined by a decrease in the viral RNA level of <2 $\log_{10}$ IU/mL at week 12 or <1 $\log_{10}$ IU/mL at week 4 during previous peginterferon + ribavirin treatment.

¶ Recent data suggest that ribavirin may not be necessary for patients with genotype 1b disease and cirrhosis.

** In patients with genotype 1 disease and cirrhosis, consider adding ribavirin to the sofosbuvir + daclatasvir 12-week regimen, or prolonging treatment duration to 24 weeks.

†† In patients with genotype 1 disease who have failed protease-based triple therapy, prolonging treatment to 24 weeks is recommended.

‡‡ In patients with genotype 2 disease and cirrhosis, consider prolonging treatment to 16–24 weeks.[11]

§§ Response rates are over 80% in all genotype 3 subgroups except treatment-experienced patients with cirrhosis (reported at 62–77%).[12,13]

In patients with genotype 3 disease and cirrhosis, consider adding ribavirin to the 12-week regimen, or prolonging treatment duration to 24 weeks. In a single phase III study evaluating 12 weeks of sofosbuvir + daclatasvir with no ribavirin, response rates were 96% in patients with no cirrhosis vs 63% in patients with cirrhosis.[14] The efficacy of sofosbuvir + daclatasvir + ribavirin for 12 or 16 weeks in patients with genotype 3 and cirrhosis is currently being evaluated. Preliminary data suggest response rates >85% in genotype 3 patients with cirrhosis who are treated with sofosbuvir + daclatasvir for 24 weeks.[15]

cannot tolerate interferon combinations or who are ineligible. These patients previously had no treatment options. The PBAC has recently made positive recommendations to list these regimens on the PBS.

Interferon-containing regimens

The combination of subcutaneous peginterferon plus oral ribavirin has been the backbone of treatment for hepatitis for the past decade.

Genotype 2 and 3 hepatitis C is treated with peginterferon plus ribavirin for 24 weeks (Table 2). Response rates are over 70%, but are lower in patients with cirrhosis.

Protease inhibitors

Treatment regimens for genotype 1 infection can include a protease inhibitor such as simeprevir, telaprevir or boceprevir (Table 2).

Simeprevir was approved in late 2014 and is now the first-line protease inhibitor for genotype 1 infections. It is also approved for genotype 4 infections. Compared to telaprevir or boceprevir, it offers the benefit of a single daily dose and an improved toxicity profile. Also, the majority of patients will qualify for shorter duration therapy (24 vs 48 weeks). Treatment-naïve patients are eligible for short-duration therapy if they have undetectable viral RNA at week four of treatment (Table 2).

In patients with genotype 1 infection, triple therapy with a protease inhibitor has been associated with response rates of over 70%. However, some patient subgroups remain harder to cure, including those with cirrhosis, and those who have previously failed treatment with peginterferon plus ribavirin. Cure rates are less than 50% in these patients.

A fourth protease inhibitor, asunaprevir, has been approved by the TGA in combination with daclatasvir (an inhibitor of the nonstructural protein NS5A). This is a quadruple therapy regimen with peginterferon and ribavirin for genotype 1 (and genotype 4) infections (Table 2). It has not yet been listed on the PBS.

Sofosbuvir

More recently, sofosbuvir, an NS5B nucleotide polymerase inhibitor, has been approved for use by the TGA but is not yet listed on the PBS. For patients with genotypes 1, 4, 5 or 6, sofosbuvir plus peginterferon and ribavirin for 12 weeks is associated with response rates of approximately 90%. Response rates among patients with cirrhosis are 80%.

For genotype 3 infections, sofosbuvir can be added to peginterferon and ribavirin in a 12-week regimen or to ribavirin alone in a 24-week regimen. The response rate for 12 weeks of triple therapy was higher than for 24 weeks of sofosbuvir plus ribavirin (93% vs 84%).[12] For genotype 2 infections, sofosbuvir without ribavirin for 12 weeks is associated with response rates over 90%.

Interferon-free regimens

Multiple interferon-free treatment regimens have recently been approved for genotype 1, 2 and 3 hepatitis C infections (Table 3). The first-line regimens for genotype 1 include:

- sofosbuvir and ledipasvir (an NS5A inhibitor)[6,7]
- paritaprevir (a protease inhibitor that requires ritonavir boosting), ombitasvir (NS5A inhibitor) and dasabuvir (NS5B polymerase non-nucleoside inhibitor) with or without ribavirin.[16-18]

For both regimens, response rates are over 95% across all patient groups including those with cirrhosis and those who have previously failed on peginterferon plus ribavirin. Treatment duration is 12 weeks for most patients. The pill burden is low and the regimens are well tolerated.

A third regimen, sofosbuvir plus daclatasvir, was very effective in a phase II study of patients with genotype 1 infection who had previously failed protease inhibitor-based triple therapy.

Interferon-free treatment regimens for genotype 3 infection include sofosbuvir plus ribavirin for 24 weeks, and the combination of sofosbuvir plus daclatasvir for 12 weeks[12-14] (Table 3). These regimens are very effective in patients who do not have cirrhosis.

Genotype 3 remains harder to cure in patients with cirrhosis, particularly in those who have previously failed peginterferon and ribavirin. In this subgroup, triple therapy with sofosbuvir plus peginterferon and ribavirin for 12 weeks produces better response rates than sofosbuvir plus ribavirin for 24 weeks. A prospective study is evaluating the benefit of adding ribavirin to the 12-week regimen of sofosbuvir plus daclatasvir versus prolonging treatment duration of sofosbuvir plus daclatasvir. Preliminary data from an early-access program in Europe suggest that sustained virological response rates are over 85% among cirrhotic patients treated with sofosbuvir plus daclatasvir for 24 weeks.[15]

The approved interferon-free treatment regimen for genotype 2 infection is sofosbuvir plus ribavirin for 12 weeks (Table 3). The combination of sofosbuvir plus ledipasvir is effective for genotype 4 and 6 infections. Paritaprevir/ritonavir plus ombitasvir plus ribavirin is effective for genotype 4 infections.

Adverse reactions

Adverse reactions to hepatitis C treatments can be a problem. Interferon-based regimens are associated with considerable morbidity, and many patients are intolerant to or ineligible for peginterferon. Intensive monitoring is required during treatment. In contrast, interferon-free regimens are well tolerated with fewer adverse effects and very low discontinuation rates.

Interferon-based regimens

The most common adverse effects of peginterferon include systemic symptoms (flu-like illness with fevers, lethargy and myalgias), fatigue, bone marrow suppression, mood disturbance (irritability, depressed mood, insomnia) and alopecia. Severe cytopenias, major depression and psychosis occur less frequently. Peginterferon should be used with caution in patients with a history of depression. Untreated major depression or psychosis is a contraindication to therapy.

Autoimmune complications are uncommon and include thyroid disturbance and exacerbation of psoriatic and rheumatoid arthritis. Interferon-based regimens may precipitate hepatic decompensation in patients with advanced liver disease. Treatment may be contraindicated and should only be considered within a specialised hepatitis C centre. Patients with a platelet count below 100 x 10^9/L and albumin below 35 g/L have been identified as a high-risk population.

Ribavirin

Ribavirin commonly causes haemolytic anaemia, which may precipitate or exacerbate symptoms of ischaemic heart disease. Dose reduction may be necessary. Although erythropoietin may be used to maintain haemoglobin concentrations during ribavirin therapy, it is not PBS-listed for this indication.

Ribavirin is teratogenic so is contraindicated in pregnancy. Two forms of contraception are recommended for men and women during treatment and for six months afterwards.

Ribavirin is renally excreted so dose reduction is required in patients with significant renal impairment. Treatment should occur in a specialist centre.

Protease inhibitors

The protease inhibitors present new challenges, with additional adverse effects and drug–drug interactions.[19-22] Telaprevir and boceprevir both need to be taken three times a day, and are associated with anaemia and gastrointestinal disturbance.

Telaprevir is commonly associated with a rash, which may be severe and life-threatening. Simeprevir has largely replaced telaprevir and boceprevir for use with peginterferon plus ribavirin for genotype 1 infections. It seems to have better tolerability[11,23] and only needs to be taken once a day. Common adverse effects are mild and include photosensitivity and transient hyperbilirubinaemia due to inhibition of bilirubin transporters.

Interferon-free regimens

The most common adverse effects with sofosbuvir plus ledipasvir are mild fatigue, headache, nausea and insomnia. This combination is safe and effective even in patients with decompensated liver disease. Sofosbuvir is not recommended in combination with amiodarone as symptomatic bradycardia has been reported. Sofosbuvir is renally excreted and should not be used in patients with an estimated glomerular filtration rate below 30 mL/min pending further studies.

The combination of paritaprevir/ritonavir, ombitasvir and dasabuvir is also well tolerated. Paritaprevir causes a transient hyperbilirubinaemia due to inhibition of biliary transporters. Approximately 1% of patients in the phase III clinical trials experienced increases in serum alanine aminotransferases. This was most common in women taking concomitant ethinyloestradiol. It is recommended that ethinyloestradiol-containing drugs are stopped before starting treatment.

Studies are currently evaluating the safety of paritaprevir/ritonavir, ombitasvir and dasabuvir in patients with decompensated liver disease. Patients with decompensated liver disease should not be treated with this regimen until there are more data.

Pregnancy

There are no safety data for interferon-free regimens in pregnancy. Ribavirin is contraindicated in pregnancy and requires contraceptive precautions.

Drug interactions

Drug–drug interactions may occur with all interferon-free treatment regimens, and relevant drugs include proton pump inhibitors, statins and common antibiotics. Concomitant medicines should be reviewed before starting any patient on treatment. An independent resource is available from the University of Liverpool (www.hep-druginteractions.org).

Treat now or wait?

In the context of such dramatic therapeutic developments, it is important for clinicians and patients to decide whether to pursue treatment now with current PBS-subsidised regimens, or to defer treatment until interferon-free regimens become available. Combinations listed in Table 3 have been recommended by the PBAC, but PBS listing has not been confirmed. In light of this, we currently advocate for treatment deferral with monitoring every six months.

Post-treatment care

Patients with early-stage fibrosis who achieve a sustained viral response do not require long-term follow-up. They should be advised that hepatitis C serology tests will remain positive, but that it is not protective and repeat exposure may lead to reinfection.

Patients with cirrhosis do need to remain in long-term follow-up to monitor for complications including portal hypertension and hepatocellular carcinoma. This is best coordinated by a gastroenterologist. Patients with comorbid liver disease, such as non-alcoholic steatohepatitis, will also require specific management.

Treatment of hepatitis C in the future – new models of care

Treatment of hepatitis C currently occurs in specialist liver clinics, typically within tertiary hospitals. This system is very effective and necessary to manage the complexities of interferon-based treatment. However, capacity is limited. Patients with advanced fibrosis and cirrhosis will need to remain in the tertiary system for management of their liver disease. However, patients who do not have cirrhosis may not need to be managed in a specialist clinic if they can be treated with simple interferon-free regimens. This will allow new models of care involving GPs, nurse practitioners, opioid-substitution therapy clinics and the custodial system. The PBAC has recommended that newer hepatitis C therapies are listed on the general schedule to promote treatment in primary care.

Conclusion

The clinical complications of hepatitis C can be prevented by viral eradication. All patients should be considered for treatment and actively engaged in care. Current subsidised regimens continue to include peginterferon. Although their efficacy is good, the associated toxicity means that only a minority of patients start antiviral therapy.

The introduction of interferon-free therapies in the near future will increase treatment efficacy, tolerability and uptake. These regimens will play a front-line role in tackling the hepatitis C epidemic, with expanded models of care as well as treatment prevention programs to reduce transmission. <

Alex Thompson is supported by a National Health and Medical Research Council fellowship (1053344). He has received research support and consulting fees from Abbvie, Bristol-Myers Squibb, Gilead, MSD and Roche, and speaker fees from Abbvie, Bristol-Myers Squibb, Gilead, Janssen, MSD and Roche.

Jacinta Holmes is supported by a postgraduate scholarship from the Gastroenterological Society of Australia. She has received research support from MSD and Roche.

REFERENCES

1. Sievert W, Razavi H, Estes C, Thompson AJ, Zekry A, Roberts SK, et al. Enhanced antiviral treatment efficacy and uptake in preventing the rising burden of hepatitis C-related liver disease and costs in Australia. J Gastroenterol Hepatol 2014;29 Suppl 1:1-9.
2. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 1997;349:825-32.
3. Seeff LB. Natural history of chronic hepatitis C. Hepatology 2002;36 Suppl 1:S35-46.
4. Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA 2000;284:450-6.
5. Grebely J, Bryant J, Hull P, Hopwood M, Lavis Y, Dore GJ, et al. Factors associated with specialist assessment and treatment for hepatitis C virus infection in New South Wales, Australia. J Viral Hepat 2011;18:e104-16.
6. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al.; ION-2 Investigators. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014;370:1483-93.
7. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al.; ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014;370:1889-98.
8. Bowden DS, Berzsenyi MD. Chronic hepatitis C virus infection: genotyping and its clinical role. Future Microbiol 2006;1:103-12.
9. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009;461:399-401.
10. Thompson AJ, Muir AJ, Sulkowski MS, Ge D, Fellay J, Shianna KV, et al. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. Gastroenterology 2010;139:120-9.e18.
11. European Association for Study of Liver. EASL recommendations on treatment of hepatitis C 2015. J Hepatol 2015;63:199-236.
12. Foster GR, Pianko S, Cooper C, Brown A, Forton D, Nahass RG, et al. Sofosbuvir plus Peg-IFN/RBV for 12 weeks vs sofosbuvir/RBV for 16 or 24 weeks in genotype 3 HCV-infected patients and treatment-experienced cirrhotic patients with genotype 2 HCV: The BOSON Study. J Hepatol 2015;62 Suppl 2:S259-60.
13. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al.; VALENCE Investigators. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med 2014;370:1993-2001.
14. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al.; ALLY-3 Study Team. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology 2015;61:1127-35.
15. Hezode C, De Ledinghen V, Fontaine H, Zoulim F, Lebray P, Boyer N, et al. Daclatasvir plus sofosbuvir with or without ribavirin in patients with HCV genotype 3 infection: interim analysis of a French multicenter compassionate use program. J Hepatol 2015;62 Suppl 2:S265-6.
16. Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1594-603.
17. Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourlière M, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1604-14.
18. Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014;370:1973-82.
19. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al.; SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195-206.
20. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al.; HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1207-17.
21. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al.; ADVANCE Study Team. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364:2405-16.
22. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al.; REALIZE Study Team. Telaprevir for retreatment of HCV infection. N Engl J Med 2011;364:2417-28.
23. Manns MP, Fried MW, Zeuzem S, Jacobson IM, Forns X, Poordad F, et al. Simeprevir with peginterferon/ribavirin for treatment of chronic hepatitis C virus genotype 1 infection: pooled safety analysis from Phase IIb and III studies. J Viral Hepat 2015;22:366-75.