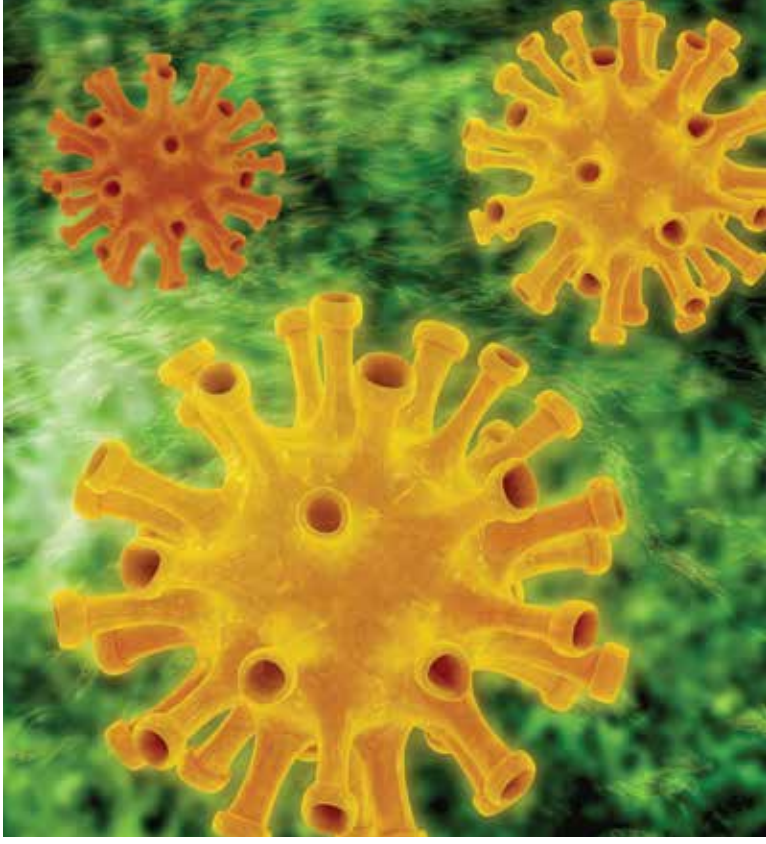
Direct-acting antiviral therapies for hepatitis C

The revolution is here



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New interferon-free treatments that cure hepatitis C in over 90% of patients were listed on the PBS on 1 March 2016. These therapies can be prescribed by GPs in consultation with a gastroenterologist, hepatologist or infectious diseases physician and will dramatically change the landscape of hepatitis C treatment in Australia.

In Australia, around 230,000 people are chronically infected with the hepatitis C virus (HCV). The primary aim of HCV therapy is cure, which is the achievement of a sustained virological response (SVR). Attaining an SVR decreases the risk of progression to cirrhosis, development of hepatocellular carcinoma and liver failure, and liver-related and overall mortality, as well as improving health-related quality of life. Interferon-based HCV treatment has been limited by significant toxicity, modest efficacy and poor treatment uptake. However, oral direct-acting antiviral (DAA) regimens are expected to deliver highly effective and safe therapeutic options across all HCV genotypes and stages of liver disease.

The new paradigm of HCV treatment

The past four years has seen a rapid evolution of therapies for HCV, with interferon-free DAA therapy now the standard of care for management of HCV infection in the USA and Europe. However, the higher cost of DAAs has had significant financial implications for healthcare budgets and has limited the wider availability of these drugs.

DAAs against HCV directly target proteins essential to the HCV life cycle. There are three major classes of DAA therapy for HCV infection:

- NS3/4A protease inhibitors – the first class of DAA drugs developed against HCV (e.g. boceprevir, simeprevir and telaprevir). NS3/4A protease inhibitors are most noted for their limited activity against HCV genotype 3 and their lower barrier to the development of resistance
- NS5A replication complex inhibitors
- NS5B polymerase inhibitors – nucleo(s)tide and non-nucleo(s)tide inhibitors. Nucleo(s)tide inhibitors are active against all HCV genotypes and have much higher barriers to the development of resistance than non-nucleo(s)tide inhibitors.

Previous regimens for HCV infection include pegylated interferon plus the nucleoside analog ribavirin for 24 to 48 weeks, which for patients with HCV genotype 1 is combined with a protease inhibitor.

As of 1 March 2016, three novel DAAs for chronic HCV infection have been listed on the PBS. These are:

- daclatasvir, a pangenotypic NS5A inhibitor
- sofosbuvir, a pangenotypic NS5B nucleotide polymerase inhibitor
- ledipasvir, an NS5A inhibitor active against HCV genotype 1 but with limited activity against genotypes 2 and 3, which is coformulated with sofosbuvir.

In addition, the three DAA combination therapy paritaprevir/ritonavir/ombitasvir plus dasabuvir is TGA-listed for patients with chronic hepatitis C and has been recommended for PBS listing but is not currently listed. It is expected to be available for PBS prescription later in 2016. This therapy combines an NS3/4A

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TABLE 1. PBS-LISTED INTERFERON-FREE REGIMENS FOR PATIENTS WITH CHRONIC HCV INFECTION[2-7]

HCV genotype	Regimen	Treatment duration	SVR rate
HCV genotype 1*	Sofosbuvir – ledipasvir	• 12 weeks (8 weeks may be considered if treatment naïve with no cirrhosis and low baseline viral load) • 24 weeks if treatment experienced and cirrhosis present	>95%[2,3]
	Sofosbuvir + daclatasvir ± ribavirin	• 12 weeks (with ribavirin if cirrhosis present) • 24 weeks (without ribavirin) if cirrhosis present or if PI treatment experienced	>95%[4]
HCV genotype 2	Sofosbuvir + ribavirin	• 12 weeks	90 to 95%[5]
HCV genotype 3	Sofosbuvir + ribavirin	• 24 weeks (not recommended if cirrhosis present)	90 to 95%[5]
	Sofosbuvir + daclatasvir	• 12 weeks if no cirrhosis • 24 weeks if cirrhosis present	94 to 97%[6] 85 to 90%[7]

Abbreviations: DAA = direct acting antiviral; HCV = hepatitis C virus; PI = protease inhibitor; SVR = sustained virological response.
* The three DAA combination therapy paritaprevir/ritonavir/ombitasvir + dasabuvir ± ribavirin is also TGA-listed for patients with HCV genotype 1 and has an efficacy >95% but is not currently PBS-listed. It is expected to be available for PBS prescription later in 2016.

protease inhibitor (paritaprevir), NS5A inhibitor (ombitasvir) and non-nucleoside NS5B polymerase inhibitor (dasabuvir), boosted with the protease inhibitor ritonavir. The combination is active against HCV genotypes 1 and 4 and has limited activity against genotypes 2 and 3.

Interferon-free regimens containing these oral medications can be used to treat infection with any HCV genotype and have greater efficacy and shorter treatment duration than interferon-based therapies (Table 1).[2-7] However, for patients infected with HCV genotypes 4, 5 and 6, there are currently no PBS-listed interferon-free DAA therapies. Products and dose recommendations for the newly PBS-listed medications are shown in Table 2.

The coadministration of ribavirin is always required if sofosbuvir is the sole DAA used for treatment of patients infected with HCV genotypes 2 or 3 and may be required when cirrhosis is present.[1] Coadministration of ribavirin is also required with the three DAA combination therapy paritaprevir/ritonavir/ombitasvir plus dasabuvir for patients with HCV genotype 1a infection or cirrhosis. Ribavirin is given as a weight-based dosage (1000 mg daily if the patient weighs less than 75 kg, 1200 mg daily for 75 kg or over), in two divided doses.

Efficacy

HCV genotype 1

- For patients with HCV genotype 1 infection without hepatic cirrhosis, 12 weeks of treatment with either the sofosbuvir–ledipasvir coformulation or sofosbuvir plus daclatasvir leads to virological cure in both treatment-naïve and treatment-experienced patients in 95 to 99% of cases.[2,4]
- For patients with HCV genotype 1 who have cirrhosis and are treatment-naïve, 12 weeks of treatment with sofosbuvir–ledipasvir achieves cure rates of more than 95%.[2]
- For those with cirrhosis who are treatment-experienced, 24 weeks of treatment with sofosbuvir–ledipasvir achieves cure rates of more than 95%.[3]
- For all previous nonresponders to PI triple therapy, 24 weeks of sofosbuvir plus daclatasvir achieves a cure rate of around 95%.[4]
- Treatment with paritaprevir/ritonavir/ombitasvir and dasabuvir is given in combination with ribavirin for patients with HCV genotype 1a but without ribavirin for those with HCV genotype 1b. Duration of therapy is 12 weeks in all patients except those with genotype 1a, cirrhosis and prior nonresponse to therapy, who should receive 24 weeks of therapy. All groups achieve SVR rates of more than 95%.[8]

HCV genotype 2

- In patients with HCV genotype 2 infection, 12 weeks of treatment with sofosbuvir plus ribavirin achieves cure rates of 90 to 95% in those

TABLE 2. NOVEL HCV DAA PRODUCTS LISTED ON THE PBS*

Product	Presentation	Administration
Sofosbuvir	Tablet 400 mg	One tablet once daily
Sofosbuvir/ledipasvir coformulation	Tablet 400 mg/90 mg	One tablet once daily
Daclatasvir	Tablet 30 mg or 60 mg	60 mg daily

Abbreviations: DAA = direct acting antiviral; HCV = hepatitis C virus.
* The three DAA combination therapy paritaprevir/ritonavir/ombitasvir + dasabuvir has been recommended for PBS listing but is not currently listed. It is presented as tablets 75 mg/50 mg/12.5 mg (dose, two tablets once daily) plus 250 mg (dose, one tablet twice daily).

without cirrhosis.[5]
- In those with cirrhosis, extension of treatment to 24 weeks increases SVR rates, but this regimen is not listed on the PBS.

HCV genotype 3

- For patients with HCV genotype 3 infection and no cirrhosis, treatment with either sofosbuvir plus ribavirin for 24 weeks or sofosbuvir plus daclatasvir for 12 weeks achieves cure rates of around 90 to 97%.[5,6]
- Patients with HCV genotype 3 and cirrhosis require treatment with either sofosbuvir plus daclatsavir and ribavirin for 12 weeks or with sofosbuvir plus daclatasvir for 24 weeks, to achieve cure rates of 85 to 90%.[7]

HCV genotypes 4 to 6

- Data on treatment outcomes of interferon-free DAA therapy for patients with the less common HCV genotypes 4 to 6 are limited. The current recommendation for these patients, including those with cirrhosis, is treatment with sofosbuvir plus pegylated interferon and ribavirin for 12 weeks. This regimen achieves SVR rates of 96 to 100%.

TABLE 3. PHARMACOKINETICS AND DRUG INTERACTIONS FOR SOFOSBUVIR, LEDIPASVIR, DACLATASVIR AND RITONAVIR[1]

Medication	Primary route of excretion	Major drug interactions
Sofosbuvir	Renal	Amiodarone, carbamazepine, phenytoin, rifampicin, St John's wort,
Ledipasvir	Biliary	Amiodarone, proton pump inhibitors, rosuvastatin
Daclatasvir	Faecal	Amiodarone, carbamazepine, dexamethasone, phenytoin, rifabutin, rifampicin, St John's wort
Ritonavir	Faecal	Alfuzosin, amiodarone, astemizole, atorvastatin, carbamazepine, cisapride, ergot derivatives, ethinyl oestradiol-containing contraceptives, gemfibrozil, some HIV antiretrovirals, lovastatin, phenobarbital, phenytoin, quetiapine, quinidine, rifampicin, St John's wort, salmeterol, sildenafil, simvastatin, terfenadine

Treatment monitoring

Ribavirin may cause anaemia, necessitating four-weekly monitoring of the haemoglobin level and dose reduction if anaemia becomes significant (haemoglobin level less than 100 g/L). No dose reduction of DAAs is allowed. Hepatitis C viral load

INFORMATION SOURCES ON THE NOVEL PBS-LISTED HEPATITIS C DRUGS

Information for clinicians

- Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement 2016 (www.gesa.org.au)[9]
- University of Liverpool. Hepatitis drug interactions (www.hep-druginteractions.org)

Information for patients

- PBS. New hepatitis C medicines – factsheet for patients and consumers (www.pbs.gov.au/info/publication/factsheets/hep-c/factsheet-for-patients-and-consumers)
- PBS. New hepatitis C medicines – frequently asked questions (www.pbs.gov.au/info/publication/factsheets/hep-c/frequently-asked-questions)

testing can be considered at week 4, mainly to document compliance in patients whose adherence is of concern, and at the end of treatment (week 12 or 24). HCV load testing should also be performed at the 12-week follow-up to assess for an SVR.

Adverse effects

DAAs are well tolerated, with the most common side effects being fatigue, headache and nausea, which are usually mild and rarely require discontinuation of therapy. Ribavirin is highly teratogenic (Australian Drug Evaluation Committee category X), and women of child-bearing potential and/or their male partners must use an effective form of contraception while receiving ribavirin-containing treatment and for six months after completion of treatment.

Precautions

Sofosbuvir is cleared by the kidneys, and its safety in patients with severe renal impairment (estimated glomerular filtration rate less than 30 mL/min) is yet to be determined. Coadministration of amiodarone with sofosbuvir in combination with either ledipasvir or daclatasvir is contraindicated because of the risk of symptomatic bradycardia. Ritonavir is a potent cytochrome P450 inhibitor with multiple interactions. Some significant drug interactions are listed in Table 3. This list is not exhaustive, and the website www.hep-druginteractions.org is a valuable online tool.

GP's role in prescribing

The PBS listing of the three novel DAAs is on the General Schedule (Section 85) and allows them to be prescribed by GPs in consultation with a gastroenterologist, hepatologist or infectious diseases physician who is experienced in the treatment of chronic HCV infection. However, a noninvasive assessment for the presence of cirrhosis by either liver elastography (e.g. transient elastography [FibroScan], acoustic radiation force impulse [ARFI] or shear wave elastography) or measurement of a serum biomarker (e.g. aspartate aminotransferase to platelet ratio index [APRI] and Hepascore) is essential before commencing any therapy, and patients with cirrhosis should be managed by a gastroenterologist or hepatologist. Furthermore, patients with HCV–HIV or HCV–hepatitis B virus coinfection, acute HCV infection, renal impairment or extrahepatic manifestations of HCV should be referred for specialist management.

Australian guidelines on the use of the new DAAs have been prepared by the Gastroenterological Society of Australia (GESA)–Australian Liver Association in partnership with other expert bodies and the RACGP. These guidelines are available online (www.gesa.org.au).[9]

Sources of information on the new drugs for clinicians and patients are shown in the Box.

Conclusion

Highly effective, well-tolerated all-oral therapies for chronic HCV infection are available through the PBS in Australia as of 1 March 2016. Most patients with chronic hepatitis should be suitable for therapy, with the notable exceptions of those with severe renal disease and those infected with HCV genotypes 4 to 6. Prescribers need to be aware of the infecting HCV genotype, any previous hepatitis C treatment, whether cirrhosis is present and any concomitant medications to identify the appropriate treatment regimen and duration, and potential drug interactions. Clinical trials of several other DAAs are in progress, and these agents should become available in Australia in the next few years. MT

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COMPETING INTERESTS: Dr Kitson: None. Associate Professor Roberts sits on advisory boards for Roche Australia, Bristol-Myers Squibb, Janssen and Merck Sharp and Dohme.