New drugs

Sofosbuvir

Approved indication: hepatitis C
Sovaldi (Gilead)
400 mg tablets
Australian Medicines Handbook section 5.4

There are six major types of hepatitis C – genotypes 1–6. In Australia, about half of cases are caused by genotype 1, a third by genotype 3 and 5% by genotype 2. Until recently, standard treatment for chronic hepatitis C infection was with peginterferon and ribavirin. Protease inhibitors boceprevir (Aust Prescr 2012;35:102-3) and telaprevir (Aust Prescr 2012;35:128-35) were approved in 2012. Adding either of these to peginterferon and ribavirin seems to improve the response rates in people with genotype 1 disease.

Sofosbuvir is another antiviral drug that can be added to combination treatment for chronic hepatitis C. It is a direct-acting nucleotide polymerase inhibitor. The prodrug is converted to a nucleotide analogue in hepatocytes. This active analogue then binds to RNA polymerase which terminates RNA synthesis and inhibits viral replication.

Sofosbuvir 400 mg/day has been investigated in four pivotal phase III hepatitis C trials (see Table).[1,2] One trial enrolled people with genotypes 1, 4, 5 or 6 and the others enrolled those with genotypes 2 or 3. Some patients in the trials had evidence of liver cirrhosis (15–35%). The primary outcome was the proportion of patients who had achieved a sustained virologic response, defined as undetectable viral RNA 12 weeks after the end of treatment. The highest rate of response to treatment was seen when sofosbuvir was added to peginterferon and ribavirin (90%) in previously untreated patients with genotypes 1, 4, 5 or 6. Response rates were high with all genotypes although there were only seven people with serotypes 5 or 6.[1] When sofosbuvir was added to ribavirin in patients with genotypes 2 or 3, response rates in genotype 3 infections were considerably lower than those in genotype 2 infections.[1,2] Liver cirrhosis was also associated with lower response rates, particularly in those with genotype 3 disease (see Table).

Another trial found that extending sofosbuvir plus ribavirin treatment from 12 to 24 weeks improved response rates in people with genotype 3 infection from 27% (3/11) to 85% (213/250).[3] However, as the trial design was changed during the study, there was no hypothesis testing or statistical comparisons and results were only descriptive. Other trials have found that patients co-infected with HIV[4] and those with hepatocellular carcinoma awaiting liver transplant benefit from treatment with sofosbuvir added to ribavirin.

Treatment discontinuation because of an adverse event occurred in 2% or less of patients taking sofosbuvir-containing regimens. The most common adverse events with sofosbuvir added to ribavirin were fatigue (30–38%), headache (24–30%), nausea (13–22%) and insomnia (15–16%). These events occurred more frequently in patients who were also receiving peginterferon. This was also the case for anaemia and neutropenia.

Absorption is rapid after an oral dose of sofosbuvir with peak plasma concentrations reached after 0.5–2 hours. After metabolism in the liver, most of the dose is excreted in the urine (80%) and faeces (14%). The mean terminal half-life of the main metabolite is 27 hours.

Sofosbuvir is a substrate of P glycoprotein so potent inducers of this transporter, such as rifampicin and St John's wort, should be avoided as they may decrease sofosbuvir's therapeutic effect. Other drugs that may reduce sofosbuvir exposure and are not recommended include modafinil, carbamazepine, phenytoin, phenobarbitone and tipranavir in combination with ritonavir.

Sofosbuvir should always be used in a combination regimen. As ribavirin is teratogenic, adequate contraception must be used during and for six months after treatment in men and women.

Sofosbuvir is effective and well tolerated when added to current therapy for people with chronic hepatitis C. The main predictors of response are viral genotype and liver cirrhosis. Response rates in people with genotype 3 infection are lower than with other genotypes and these people may need to take treatment for longer. Sofosbuvir also provides an alternative for people who have relapsed, cannot tolerate or do not want to take interferon-containing regimens.

T manufacturer provided the product information

REFERENCES *†A

1. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013;368:1878-87.

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

2. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 2013;368:1867-77.
3. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med 2014;370:1993-2001.
4. Sulkowski MS, Naggie S, Lalezari J, Fessel WJ, Mounzer K, Shuhart M, et al. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. JAMA 2014;312:353-61.

Table **Efficacy of sofosbuvir in chronic hepatitis C infection**

Trial name and details	Treatment arms (including duration)	Proportion of patients with a sustained virologic response ‡
NEUTRINO[1] Single arm, open-label trial in treatment-naïve patients with genotypes 1, 4, 5 and 6 §	Sofosbuvir plus peginterferon and ribavirin (12 weeks)	Overall: 90% (295/327) liver cirrhosis: 80%
FISSION[1] Non-inferiority, randomised, open-label trial in treatment-naïve patients with genotypes 2 or 3 §	Sofosbuvir plus ribavirin (12 weeks)	Overall: 67% (170/253) liver cirrhosis: 47% genotype 2: 97% genotype 3: 56%
	Peginterferon plus ribavirin (24 weeks)	Overall: 67% (162/243) liver cirrhosis: 38% genotype 2: 78% genotype 3: 63%
POSITRON[2] Randomised, placebo-controlled trial in patients with genotypes 2 or 3 who were intolerant or had refused interferon-containing regimen, or had contraindicated comorbidities §	Sofosbuvir plus ribavirin (12 weeks)	Overall: 78% (161/207) genotype 2: 93% genotype 2/liver cirrhosis: 94% genotype 3: 61% genotype 3/liver cirrhosis: 21%
	Placebo (12 weeks)	Overall: 0% (0/68)
FUSION[2] Randomised, actively-controlled trial in patients with genotypes 2 or 3 who had relapsed or not responded to previous interferon-containing regimen #	Sofosbuvir plus ribavirin (12 weeks) then placebo (4 weeks)	Overall: 50% (50/100) genotype 2: 86% genotype 2/liver cirrhosis: 60% genotype 3: 30% genotype 3/liver cirrhosis: 19%
	Sofosbuvir plus ribavirin (16 weeks)	Overall 73% (69/95) genotype 2: 94% genotype 2/liver cirrhosis: 78% genotype 3: 62% genotype 3/liver cirrhosis: 61%

‡ undetectable viral RNA 12 weeks after the end of treatment
§ up to 21% of enrolled patients had liver cirrhosis
# 35% of enrolled patients had liver cirrhosis

The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov)

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu)

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)