New drugs

Simeprevir

Approved indication: hepatitis C
Olysio (Janssen-Cilag)
capsules containing 150 mg
Australian Medicines Handbook section 5.4

There are six main genotypes of hepatitis C, genotypes 1–6. In Australia, genotype 1 accounts for 50% of cases, genotype 3 for 30% and genotype 2 for 5%. Most people with chronic hepatitis C are treated with a combination of peginterferon and ribavirin. Sofosbuvir (Aust Prescr 2014;37:172-9), a recently approved nucleotide polymerase inhibitor, can be added to this. Also, the protease inhibitors boceprevir (Aust Prescr 2012;35:102-3) or telaprevir (Aust Prescr 2012;35:128-35) can be added for people with genotype 1 disease. Simeprevir is another protease inhibitor approved as an adjunctive treatment for genotype 1 (and genotype 4) disease. It works by inhibiting the viral protease NS3/4A, which is required for replication.

Simeprevir has been tested in several trials of previously untreated[1,2] and treated[3,4] people with genotype 1 infection. Patients were excluded from the trials if they had decompensated liver disease or liver disease unrelated to hepatitis C, or co-infection with another hepatitis C genotype, hepatitis B or HIV. 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.

People who added simeprevir to peginterferon and ribavirin had significantly higher response rates compared to those who added placebo (see Table).[1-4] However, the presence of the naturally occurring viral NS3 Q80K polymorphism in people with genotype 1a infection was associated with lower response rates. For example in the QUEST-1 trial, the response rate to simeprevir was 52% (31/60) in people with the polymorphism compared to 85% (73/86) in those without it.[1] In an analysis of people who failed to respond to simeprevir or relapsed after treatment had finished, 92% (35/38) had one or more emerging

Table **Efficacy of daily simeprevir added to peginterferon and ribavirin in chronic hepatitis C genotype 1**

Trial name and design	Treatment (duration)	Patient response‡
QUEST-1[1] Randomised placebo-controlled phase III trial in treatment-naïve patients with genotype 1 disease	Simeprevir 150 mg (12 weeks)§	80% (210/264)
	Placebo (12 weeks)#	50% (65/130)
QUEST-2[2] Randomised placebo-controlled phase III trial in treatment-naïve patients§	Simeprevir 150 mg (12 weeks)	81% (209/257)
	Placebo (12 weeks)	50% (67/134)
PROMISE[3] Randomised placebo-controlled phase III trial in patients who had relapsed after previous treatment	Simeprevir 150 mg (12 weeks)§	79% (206/260)
	Placebo (12 weeks)#	36% (48/133)
ASPIRE[4] Placebo-controlled phase IIb trial in treatment-experienced patients#	Simeprevir 100 mg (12 weeks)	70% (46/66)
	Simeprevir 100 mg (24 weeks)	66% (43/65)
	Simeprevir 100 mg (48 weeks)	61% (40/66)
	Simeprevir 150 mg (12 weeks)	67% (44/66)
	Simeprevir 150 mg (24 weeks)	72% (49/68)
	Simeprevir 150 mg (48 weeks)	80% (52/65)
	Placebo (48 weeks)	23% (15/66)

‡ undetectable viral RNA (or less than 25 IU/mL) 12 weeks after the end of treatment in QUEST-1, QUEST-2 and PROMISE and 24 weeks after the end of treatment in ASPIRE
§ peginterferon and ribavirin were continued for a further 12 or 36 weeks depending on response to treatment
# peginterferon and ribavirin were continued for a further 36 weeks regardless of patient response

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.

amino acid substitutions in the viral protease.[1] Some of these mutations may also reduce the antiviral activity of telaprevir and boceprevir.

To assess long-term efficacy, 166 patients who had responded to simeprevir in the ASPIRE trial were followed up. After 16 months, all participants still had undetectable viral RNA.

The efficacy of simeprevir has also been tested in people co-infected with HIV and hepatitis C genotype 1 in an open-label, single-arm trial. HIV was well controlled in these patients. They received simeprevir 150 mg daily with peginterferon and ribavirin for 12 weeks followed by a period of continued peginterferon and ribavirin depending on their response. Twelve weeks after the end of treatment, 79% (42/53) of the treatment-naïve patients had responded compared to 87% (13/15) of those who had relapsed on previous treatment, 70% (7/10) of those who had partially responded and 57% (16/28) of those who had a null response to previous treatment.[5]

Another similarly designed open-label, single-arm trial assessed the simeprevir combination in 107 people with genotype 4 disease. Twelve weeks after the end of treatment, 83% (29/35) of treatment-naïve patients had undetectable viral RNA compared to 86% (19/22) of those who had previously relapsed, 60% (6/10) of those who had only partially responded to previous treatment and 40% (16/40) of those who had a null response to previous treatment. The study has not yet been published in full.

In a pooled safety analysis of placebo-controlled trials, discontinuation rates because of adverse events were low for both simeprevir and placebo (2.2%). Pruritus (23.8% vs 17.4%), rash (22.9% vs 16.7%) and photosensitivity (4.7% vs 0.7%) were more common with simeprevir than with placebo.[6] Patients should take appropriate precautions during sun exposure.

Simeprevir should only be used in combination with peginterferon and ribavirin. This combination is contraindicated (pregnancy category X) in women who are pregnant or may become pregnant and men whose partners are pregnant. Adequate contraception must be used by men and women during treatment and for six months afterwards.

Simeprevir should be taken once daily with food for 12 weeks with peginterferon and ribavirin. Viral RNA concentrations should be monitored at 4 and 12 weeks. The duration of continuing peginterferon and ribavirin depends on the patient's viral RNA results and on their previous response to treatment (as detailed in the product information). Treatment should be stopped if a patient is not responding after four weeks.

Following a daily oral dose, maximum plasma concentrations are reached after 4–6 hours and steady state is reached after seven days. Simeprevir is metabolised in the liver and is predominately eliminated by biliary excretion. Renal excretion is negligible. Its terminal half-life is 41 hours in people with hepatitis C. Simeprevir exposure may be increased in people with moderate to severe liver impairment, although these people were not included in the trials. Drug exposure was increased in East Asian people, so monitoring for adverse effects is particularly important in this population.

Simeprevir is metabolised by cytochrome P450 (CYP) 3A4 so there is potential for many interactions with other drugs. Moderate–strong CYP3A4 inhibitors (e.g. erythromycin, ketoconazole, darunavir/ritonavir, milk thistle) are not recommended as they may increase the adverse effects of simeprevir, while inducers (e.g. carbamazepine, efavirenz, etravirine, rifampicin, St John's wort) may lead to loss of efficacy. Simeprevir may also increase exposure of concomitant drugs such as amiodarone, amlodipine, digoxin and statins. Monitoring is recommended and dose adjustment may be needed.

Adding simeprevir to peginterferon and ribavirin seems to produce a sustained virologic response in approximately 80% of people with hepatitis C genotype 1 or 4 disease. It was also effective in people co-infected with HIV, but has not been studied in those co-infected with hepatitis B. Simeprevir is less effective in people carrying the NS3 Q80K viral polymorphism. Treatment resistance can also develop and is associated with emerging mutations in the viral protease. It is not known if simeprevir will be better than the other protease inhibitors, but patients may prefer its once-daily dosing compared to taking telaprevir or boceprevir three times a day. A preliminary study has shown promising efficacy of simeprevir given with sofosbuvir (with or without ribavirin) in an interferon-free regimen.[7]

☒ manufacturer did not supply data

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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)