New drugs

Daclatasvir

Approved indication: hepatitis C
Daklinza (Bristol-Myers Squibb)
30 mg tablets
Australian Medicines Handbook section 5.5

Hepatitis C can be classified into six main genotypes (1–6). These can be further subdivided into subtypes (e.g. 1a, 1b). In Australia, genotype 1a and 1b account for 54% of hepatitis C cases and genotype 3a for 37%. Up until recently, patients were offered a combination of peginterferon and ribavirin and patients with genotype 1 disease could add a protease inhibitor. However, many people cannot tolerate interferon-based regimens or are not eligible because they have contraindications.

Several new drugs have been approved in Australia for hepatitis C.[1] Daclatasvir, a nucleotide polymerase inhibitor, adds to this list. It is a direct-acting antiviral that works by inhibiting the non-structural 5A protein involved in viral replication. Daclatasvir has been approved for use in combination with other drugs, such as sofosbuvir and asunaprevir, in patients with compensated liver disease (including cirrhosis).

The recommended dose of daclatasvir is 60 mg per day. After oral administration, daclatasvir is absorbed within 1–2 hours and steady state is reached after four days. Its terminal half-life is 12–15 hours and most of the dose is excreted in the faeces. Dose adjustment is not required in hepatic or renal impairment.

The safety and efficacy of daclatasvir in different treatment regimens have been studied in several trials (see Tables 1 and 2).

Daclatasvir and sofosbuvir

In an open-label trial of 211 patients, daclatasvir (60 mg daily) was assessed in combination with sofosbuvir (400 mg daily), with or without ribavirin.[2] Enrolled patients had genotype 1 (mostly subtype 1a), 2 or 3 disease with no evidence of cirrhosis. Most of them were treatment-naïve except 41 patients with genotype 1 infection who had not responded to, or had relapsed after, previous treatment with a protease inhibitor. These patients were treated for 24 weeks with the new regimen, whereas treatment-naïve patients were treated for 12 or 24 weeks. Almost all patients had a sustained response, which was defined as less than 25 IU/mL viral RNA in their serum 12 weeks after the end of treatment (see Table 1).[2]

Another study assessed 12 weeks of treatment with daclatasvir and sofosbuvir, but no ribavirin, in 152 patients with genotype 3 disease.[3] Of the participants, 34% had been previously treated for hepatitis C, and 21% had cirrhosis. Most patients had a sustained response to this regimen, but response rates were lower in those with cirrhosis (see Table 1).

Table 1 **Efficacy of daclatasvir and sofosbuvir in hepatitis C**

Study	Viral genotype	Treatment regimen	Sustained virological response‡	
			Treatment-naïve patients	Treatment-experienced patients
Sulkowski[2]	1	daclatasvir + sofosbuvir§	100% (70/70)	100% (21/21)
		daclatasvir + sofosbuvir + ribavirin§	98% (55/56)	100% (20/20)
	2 or 3	daclatasvir + sofosbuvir§	93% (28/30)	-
		daclatasvir + sofosbuvir + ribavirin§	93% (13/14)	-
Nelson[3]	3	daclatasvir + sofosbuvir#	Overall 90% (91/101)	Overall 86% (44/51)
			Patients with cirrhosis 58% (11/19)	Patients with cirrhosis 69% (9/13)

‡ Defined as proportion of patients with viral RNA less than the lower limit of quantification in serum, measured 12 weeks after the end of treatment.
§ Treatment given for 12 or 24 weeks in treatment-naïve patients and for 24 weeks in treatment-experienced patients.
# Treatment given for 12 weeks.

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.

NEW DRUGS

Table 2 **Efficacy of daclatasvir and asunaprevir in hepatitis C**

Study	Viral genotype	Treatment regimen (24 weeks)	Sustained virological response‡		
			Treatment-naïve patients	Treatment-experienced patient	Intolerant/ ineligible patients
Manns[5]	1b	daclatasvir + asunaprevir	90% (182/203)	82% (168/205)	82% (192/235)
Kumada[6]			-	80% (70/87)	88% (119/135)
Jensen[7]	1	daclatasvir + asunaprevir + peginterferon + ribavirin	-	Overall 93% (329/354) Patients with cirrhosis 90% (66/73)	-
	4		-	Overall 98% (43/44) Patients with cirrhosis 95% (19/20)	-

‡ Defined as proportion of patients with viral RNA less than the lower limit of quantification in serum measured 12 weeks after the end of treatment.

Daclatasvir combined with sofosbuvir has also been investigated in patients co-infected with HIV. Most of them had genotype 1a or 1b, and some had previously been treated for hepatitis C. After a 12-week course of daclatasvir and sofosbuvir, most of them (149/153) had a sustained virological response.[4]

Daclatasvir and asunaprevir

Daclatasvir has also been combined with asunaprevir (100 mg twice daily) in an open-label study of patients with genotype 1b infection.[5] Asunaprevir is another direct-acting hepatitis C drug. Although approved by the Therapeutic Goods Administration, it is not currently available on prescription in Australia. It selectively inhibits the viral non-structural protein 3/4A protease.

In the trial, participants were divided into three groups:

- treatment-naïve patients
- patients who had not responded or only partially responded to previous peginterferon and ribavirin
- patients intolerant to, and/or ineligible for, peginterferon and ribavirin (this included patients with depression, anaemia or neutropenia, or compensated advanced fibrosis or cirrhosis with thrombocytopenia).

Patients with cirrhosis were present in all three groups (16%, 31% and 47%). After 24 weeks of daclatasvir and asunaprevir, most patients had a sustained virological response (see Table 2). Response rates were similar in patients with cirrhosis and without cirrhosis (84% vs 85%). A high viral titre at baseline (≥800 000 IU/mL) or the presence of viral variants associated with non-structural 5A protein resistance predicted a poor response to treatment.[5]

A Japanese trial also enrolled 222 patients with genotype 1b disease.[6] They were classified as non-responders to previous interferon and ribavirin or as intolerant to, or ineligible for, interferon-based treatment. Around 10% of patients had cirrhosis. They were given 24 weeks of daclatasvir and asunaprevir. Up to 88% of participants had a sustained viral response (see Table 2), including 20 of the 22 patients with cirrhosis.[6]

Another trial investigated daclatasvir and asunaprevir with peginterferon and ribavirin in 398 patients with genotype 1 or 4 infection.[7] Participants had been previously treated with peginterferon and ribavirin but had either not responded or had only partially responded. After 24 weeks of treatment with the new regimen, most of them had a sustained virological response (see Table 2).[7]

Safety and precautions

In the safety cohort of 1679 patients, the most common adverse events included fatigue, diarrhoea, nausea and headache. In one of the trials with daclatasvir and sofosbuvir, one patient discontinued because of fibromyalgia, and another because of a stroke. The ribavirin dose had to be reduced in five patients because of anaemia.[2] In a trial of daclatasvir and asunaprevir, 10 patients discontinued because of an adverse event. Reasons included increased liver enzymes (7 patients), prolonged QT interval (1), constipation (1), hypertransaminasaemia (1), brain cancer (1) and bronchiectasis (1).[5] In the

Japanese trial of patients who were intolerant to or ineligible for interferon, 10 patients discontinued because of elevations in liver enzymes and one because of myasthenia gravis.[6] When peginterferon and ribavirin were added to daclatasvir and asunaprevir, 18 patients discontinued. The most common reasons were rash, malaise, neutropenia and vertigo (2 cases of each).[7]

Cardiac arrhythmias, including severe bradycardia, have been reported in patients taking amiodarone with daclatasvir and sofosbuvir, so close monitoring is recommended with this combination.

Daclatasvir should not be used in pregnancy. In animal studies, it has been shown to cross the placenta, and maternal and embryofetal toxicity have been observed at high doses. Contraception should be used during treatment and for five weeks afterwards. Daclatasvir is also excreted in milk and breastfeeding is not recommended.

The safety and efficacy of daclatasvir in people who are co-infected with hepatitis B have not been established as these patients were generally excluded from the trials.

Resistance to daclatasvir can occur. If patients experience an increase in viral RNA during treatment, the regimen should be discontinued.

Drug interactions

Daclatasvir is mainly metabolised by cytochrome P450 (CYP) 3A4. It is contraindicated in combination with strong inducers of CYP3A4 (e.g. phenytoin, carbamazepine, rifampicin, dexamethasone and St John's wort), as these drugs may lower daclatasvir exposure. The daily daclatasvir dose should be increased to 90 mg with moderate CYP3A4 inducers. Conversely, the dose should be reduced to 30 mg per day with strong CYP3A4 inhibitors (e.g. clarithromycin, boceprevir, telaprevir, atazanavir, ritonavir, ketoconazole).

As daclatasvir inhibits P-glycoprotein, co-administered digoxin and other P-glycoprotein substrates with a narrow therapeutic index, such as dabigatran, should be used with caution. Care is also urged with the statins as rosuvastatin concentrations are increased with daclatasvir.

Conclusion

In general, daclatasvir-containing regimens were very effective at clearing hepatitis C virus in patients with chronic disease. This included those who had not adequately responded to previous treatments and patients who were co-infected with HIV. With the daclatasvir and sofosbuvir combination, adding ribavirin did not seem to give further benefit. Patients with genotype 3 infection who had cirrhosis were less likely to have a sustained response after 12 weeks of daclatasvir and sofosbuvir compared to those who did not have cirrhosis. This combination was not assessed in patients with genotype 1 disease and cirrhosis. The combination of daclatasvir and asunaprevir (with or without peginterferon and ribavirin) was effective in a range of patients with genotype 1 or 4 infection.

Daclatasvir regimens were generally well tolerated but prescribers should be mindful of adverse reactions to other drugs in the treatment regimen. As daclatasvir is metabolised by CYP3A4, there are numerous drug interactions that need to be considered. Most importantly, concomitant use of strong CYP3A4 inducers is contraindicated as this may reduce the efficacy of daclatasvir.

T T manufacturer provided additional useful information

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Ledipasvir with sofosbuvir

Approved indication: hepatitis C
Harvoni (Gilead)
90 mg/400 mg tablets
Australian Medicines Handbook section 5.5

Sofosbuvir (Aust Prescr 2014;37:177-8) is a nucleotide analogue antiviral drug that is used in combination with other drugs to treat chronic hepatitis C. As the effectiveness of regimens containing interferon can be limited by adverse effects, there is interest in studying other drugs to use in combination with sofosbuvir.

Ledipasvir is an antiviral drug aimed at a protein (NS5A) in the hepatitis C virus. As this protein is