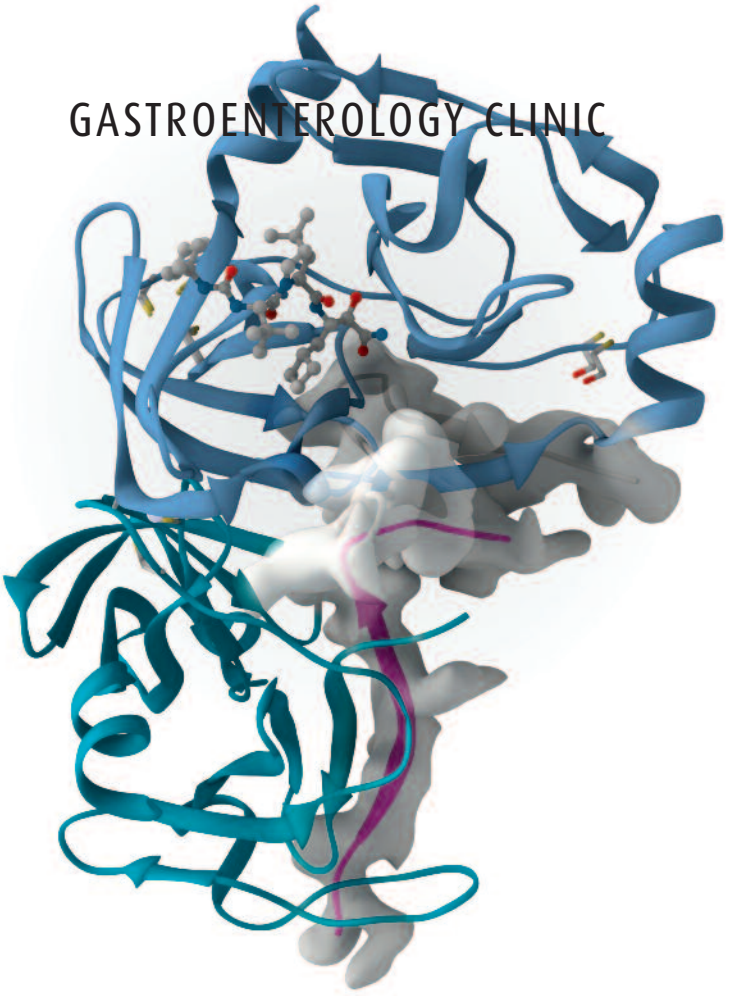

New treatments for hepatitis C
The protease inhibitors

MATTHEW T. KITSON BSc, MB BS(Hons), FRACP
STUART K. ROBERTS MB BS(Hons), MD, FRACP

The first-generation hepatitis C virus protease inhibitors telaprevir and boceprevir recently became available in Australia for treating chronic genotype 1 hepatitis C. They significantly improve treatment success rates.

MedicineToday 2012; 13(11): 73-75

Dr Kitson is a Gastroenterologist and Hepatologist, and Associate Professor Roberts is Director of Hepatology at The Alfred Hospital, Melbourne, Vic.
SERIES EDITOR: Associate Professor Simone Strasser, MD, FRACP, Clinical Associate Professor, Central Clinical School (Medicine), University of Sydney; and Senior Staff Specialist, AW Morrow Gastroenterology and Liver Centre, Royal Prince Alfred Hospital, Sydney, NSW.

The views published in this Series are those of the authors and not necessarily indicative of those held by all members of the Digestive Health Foundation or GESA.

REMEMBER

- Over 200,000 people in Australia are infected with the hepatitis C virus (HCV), which is a leading cause of hepatic cirrhosis and liver cancer, and the most common indication for liver transplantation in Australia.[1]
- To date, standard of care therapy for chronic hepatitis C in Australia is peginterferon plus ribavirin. Treatment duration depends on viral genotype: HCV genotype 1, the most common genotype, requires 48 weeks of treatment, and HCV genotypes 2 and 3 require 24 weeks of treatment.
- Sustained virological response, which is defined as a negative HCV RNA result on polymerase chain reaction (PCR) testing six months after therapy, is associated with a reduced risk of disease progression and improved survival.
- Currently only about 2% of people with chronic hepatitis C seek treatment. This figure is low because of concern over medication side effects and suboptimal rates of sustained virological response (around 50%), especially for HCV genotype 1.[2]
- The HCV life cycle depends on the activity of HCV protease (NS3/4A) and polymerase (NS5B) enzymes, and the replication complex (NS5A) protein. Direct-acting antiviral drugs that specifically inhibit these targets have recently been developed and are rapidly changing the paradigm of HCV management.
- In particular, the first-generation protease inhibitors telaprevir and boceprevir are both now available in Australia. They can be used as part of triple therapy regimens, in combination

TABLE 1. RESPONSE-GUIDED THERAPY WITH TELAPREVIR IN TREATMENT-NAIVE GENOTYPE 1 CHRONIC HEPATITIS C

Response	Regimen		Treatment duration
	Telaprevir plus peginterferon–ribavirin	Peginterferon–ribavirin	
HCV RNA undetectable at weeks 4 and 12 (60% of patients)	First 12 weeks	Additional 12 weeks	24 weeks
HCV RNA detectable at week 4 but undetectable at week 12 OR Hepatic cirrhosis	First 12 weeks	Additional 36 weeks	48 weeks

HCV = hepatitis C virus.

TABLE 2. RESPONSE-GUIDED THERAPY WITH BOCEPREVIR IN TREATMENT-NAIVE GENOTYPE 1 CHRONIC HEPATITIS C

Response	Regimen		Treatment duration
	Peginterferon–ribavirin	Boceprevir plus peginterferon–ribavirin	
HCV RNA undetectable at weeks 8 and 24 (40% of patients)	First 4 weeks	Additional 24 weeks	28 weeks
HCV RNA detectable at week 8 but undetectable at week 24 OR Hepatic cirrhosis	First 4 weeks	Additional 44 weeks	48 weeks

HCV = hepatitis C virus.

with peginterferon–ribavirin, for treating genotype 1 chronic hepatitis C (Tables 1 and 2). Both telaprevir and boceprevir are taken orally.

ASSESSMENT

- Most (85%) adults exposed to HCV develop chronic hepatitis C, which is frequently asymptomatic. As HCV antibodies develop within six months of infection and may persist for life, PCR testing for HCV RNA is necessary to distinguish past from active infection (the latter indicated by detectable HCV RNA).
- Recently identified genetic poly - morphisms associated with the human interleukin-28B gene (IL28B genotype) are an important pre-treatment pre - dictor of sustained virological response in HCV genotype 1 infection.[3,4]
- When assessing response to direct-acting antiviral therapy, it is important to consider fibrosis stage, patient IL28B genotype and HCV subtype. Notably, HCV genotype 1b responds better to treatment with protease inhibitors and/or NS5A inhibitors than HCV genotype 1a.[5-8] In addition, in treatment-experienced patients the previous response to peginterferon–ribavirin (null response or partial response and relapse) has predictive value for the success of direct-acting antiviral therapy.[9,10]
- Several noninvasive measures of liver fibrosis in chronic hepatitis C have recently been developed, including serum markers (e.g. Hepascore) and liver stiffness measurement (with transient elastography or acoustic radiation force impulse imaging).[11,12] Of these measurement methods, ultrasound-based transient elastography is the most widely used. It can assess a volume of liver 100-times greater than biopsy and has largely eliminated the need for liver biopsy.[13]

MANAGEMENT

- Telaprevir for 12 weeks combined with peginterferon–ribavirin for up to 48 weeks improves sustained virological response rates in HCV genotype 1 infection – to about 80% in treatment-naïve patients and prior relapsers, and to about 40% in prior nonresponders.[5,9] Therapy can be shortened to 24 weeks without sacrificing efficacy in about 60% of those treated (see Tables 1 and 3).[5]
- Boceprevir is added after a four-week lead-in of peginterferon–ribavirin

TABLE 3. FEATURES OF TELAPREVIR AND BOCEPREVIR THERAPY IN TREATMENT-NAIVE GENOTYPE 1 CHRONIC HEPATITIS C

Feature	Telaprevir	Boceprevir
Stopping rules	• HCV RNA >1000 IU/mL at week 4 • Detectable HCV RNA at weeks 12 or 24 • Discontinuation of peginterferon–ribavirin for any reason	• HCV RNA ≥100 IU/mL at week 12 • Detectable HCV RNA at week 24 • Discontinuation of peginterferon–ribavirin for any reason
Improvement in SVR	30% higher than peginterferon–ribavirin	30% higher than peginterferon–ribavirin
Adverse events	Rash, pruritus, anaemia, anorectal problems, nausea, diarrhoea	Anaemia, altered taste (dysgeusia)
Drug–drug interactions	Multiple because of: • high dependence on CYP3A enzymes for clearance • strong induction of CYP3A enzymes	Multiple because of: • high dependence on CYP3A4/5 enzymes for clearance • strong induction of CYP3A4/5 enzymes

ABBREVIATION: SVR = sustained virological response.

and continues as triple therapy for up to 44 weeks. Response rates are similar to those for telaprevir, while treatment shortening to 28 weeks is possible in approximately 40% of patients (see Tables 2 and 3).[6,10]

- Several nucleoside and nonnucleoside HCV polymerase inhibitors, second-generation HCV protease inhibitors and NS5A inhibitors are currently in advanced stages of clinical development. Many of these newer direct-acting antiviral drugs have pan-genotypic activity, higher genetic barriers to antiviral resistance and/or improved efficacy. The most promising of these offer the potential for interferon-free oral regimens that cure hepatitis C with high efficacy (>90%), minimal side effects and a treatment duration as short as 12 weeks.[7,8,14]
- Many patients with chronic hepatitis C and early stage liver disease who wish to avoid interferon-based therapy can safely wait for interferon-free regimens, because disease progression is usually slow, particularly in those who do not consume excessive alcohol. However, serial noninvasive assessment of liver fibrosis should be considered in these patients to monitor for disease progression and help guide the timing of therapy. MT

REFERENCES

1. Law MG, Dore GJ, Bath N, et al. Modelling hepatitis C virus incidence, prevalence and long-term sequelae in Australia, 2001. Int J Epidemiol 2003; 32: 717-724.
2. Roberts SK, Weltman MD, Crawford DHG, et al. Impact of high-dose peginterferon alfa-2A on virological response rates in patients with hepatitis C genotype 1: a randomized controlled trial. Hepatology 2009; 50: 1045-1055.
3. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009; 461: 399-401.
4. Suppiah V, Moldovan M, Ahlenstiel G, et al. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. Nat Genet 2009; 41: 1100-1104.
5. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011; 364: 2405-2416.
6. Poordad F, McCone J, Bacon BR, et al. Boceprevir for previously untreated chronic HCV genotype 1 infection. N Engl J Med 2011; 364: 1195-1206.
7. Lok AS, Gardiner DF, Lawitz E, et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. N Engl J Med 2012; 366: 216-224.
8. Chayama K, Takahashi S, Toyota J, et al. Dual therapy with the nonstructural protein 5A inhibitor, daclatasvir, and the nonstructural protease inhibitor, asunaprevir, in hepatitis C virus genotype 1b-infected null responders. Hepatology 2012; 55: 742-748.
9. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med 2011; 364: 2417-2428.
10. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011; 364: 1207-1217.
11. Adams LA, Bulsara M, Rossi E, et al. Hepascore: an accurate validated predictor of liver fibrosis in chronic hepatitis C infection. Clin Chem 2005; 51: 1867-1873.
12. Sandrin L, Fourquet B, Hasquenoph JM, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003; 29: 1705-1713.
13. Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology 2008; 134: 960-974.
14. Gane EJ, Stedman CA, Hyland RH, et al. Once daily PSI-7977 plus RBV: pegylated interferon-alfa not required for complete rapid viral response in treatment-naïve patients with HCV GT2 or GT3. Hepatology 2011; 54(Suppl 1): S377A.

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