Hepatitis C treatment: *In depth*

Introduction

In 2016, the first new direct acting antiviral (DAA) drugs to treatment hepatitis C were listed on the Pharmaceutical Benefits Scheme (PBS).

Since then new medications have been continued to be approved and listed, including pan-genotypic medications which can be used to treat all hepatitis C genotypes (subgroups of the hepatitis C virus).

Which medication is appropriate is determined predominantly by genotype, but also factors including, cirrhosis status and any previous treatment. Cirrhosis is severe and often irreversible liver scarring. The current medication regimes are:

- Sofosbuvir & velpatasvir **(Epclusa®)**
- Glecaprevir & pibrentasvir **(Mavyret®)**
- Elbasvir & grazoprevir **(Zepatier ®)**
- Sofosbuvir & ledipasvir **(Harvoni ®)**
- Sofosbuvir & daclatasvir *with or without ribavirin* **(Solvadi & Daklinza ®)**
- Sofosbuvir & velpatasvir & voxilaprevir (**Vosevi®)**

Pan genotypic medications

These medications can be used to treat all genotypes. Since these were made available, interferon is no longer used to treat hepatitis C and all treatments are tablets only.

Sofosbuvir & velpatasvir **(Epclusa®)**

This is a once daily, single tablet regime. It is usually taken for 12 weeks.

For most genotypes the cure rates are 95% or higher in clinical trials. Cure is defined as a blood test 12 weeks after finishing treatment in which the virus is undetected.

In the context of genotype 3 and cirrhosis and/or previously unsuccessful peginteferon treatment the success rate has been shown to be lower (89-93%). To this group, ribavirin may be added to the treatment regime.

Ribavirin

Ribavirin is an anti-viral drug. It has more severe side effects than DAA medications. Although no longer a first line treatment option, it is occasionally still used in conjunction with DAA's in the context of cirrhosis or previous treatment failure.

Side effects include anaemia, rash, cough, shortness of breath, insomnia and anxiety. Anaemia is common but usually only mild to moderate. Regular monitoring is important.

Ribavirin has severe effects on unborn children, cause malformation and birth defects. Both men and women taking Ribavirin must be told about the risks of pregnancy and require two forms of contraception to be used during and for six months after treatment.

Glecaprevir & Pibrentasvir **(Mavyret®)**

This regime is three tablets, taken together once daily with food.

For people who have never had any treatment before and who do not have cirrhosis, the treatment only needs to be taken for 8 weeks. For those with cirrhosis, it is 12 weeks.

cure rates above 95% have been seen for all genotypes.

Mavyret® is also approved for use in the context of most previous treatment regimens that have been unsuccessful. The length of treatment in this case can be up to 16 weeks.

Predominantly, Mavyret® is not excreted by the kidneys so it is the first line treatment for people with renal impairment, including those on dialysis. However caution must be taken in the setting of hepatic impairment the risk is increased for drug induced liver injury.

Sofosbuvir & velpatasvir & voxilaprevir (**Vosevi®)**

This is another pan-genotypic regime, **specifically designed for treatment of people who were not successful with first-line DAA's**. It is one tablet taken daily.

The recommended length of treatment is 12 weeks.

In clinical trials cure rates of more than 95% have been seen, including in the context of all prior treatment experiences, cirrhosis and all genotypes.

Genotype 1

Sofosbuvir & velpatasvir **(Epclusa®)**
Information as above.

Glecaprevir & Pibrentasvir **(Mavyret®)**
Information as above.

Elbasvir & grazoprevir **(Zepatier®)**

This is a once daily, single tablet regime.

The recommended length of time depends on genotype subtype (differences within genotypes) and is between 12 to 16 weeks.

Overall, SVR rates have been above 95% in phase 3 studies using the recommended length of time.

There is a risk of drug induced liver injury and is not recommended for those with decompensated liver injury.

Sofosbuvir & Ledipasvir **(Harvoni®)**

Harvoni is a once daily, single tablet. It is usually taken for 12 weeks, except for people who have cirrhosis and have previously been unsuccessful with the old pegylated interferon treatment. 24 weeks is recommended in this case. SVR rates above 95% have been seen in all patient groups.

Sofosbuvir & Daclatasvir *with or without ribavirin* **(Solvadi & Daklinza®)**

Although available as a first line treatment for genotype 1, this regime is becoming less common with the new single-tablet regimes.

Cure rates with this treatment are 95% and above. For people without cirrhosis, duration is 12 weeks and for those with cirrhosis is either 12 weeks including ribavirin or without ribavirin but for 24 weeks.

Genotype 2

The pan-genotypic regimes **Epclusa®** and **Mavyret®** are the recommended treatments for genotype 2. In clinic trials, cure rates above 95% were seen for both treatments in the context of genotype 2.

Medications for genotype 3

Sofosbuvir & velpatasvir **(Epclusa®)**
Information as above.

People with genotype 3 who also have cirrhosis have lower cure rates. (89%-93%). Ribavirin may be added in this context.

Glecaprevir & Pibrentasvir **(Mavyret®)**

Information as above.

Sofosbuvir & Daclatasvir *with or without ribavirin* **(Solvadi & Daklinza®)**

For people with genotype 3 and no cirrhosis, 12 weeks of this regime shows cure rates of 94%-97%.

It is lower for those with cirrhosis (58%-69%) so it is recommended that treatment be extended to 24 week or ribavirin is included and treatment is 12 weeks.

Genotype 4

Sofosbuvir & velpatasvir **(Epclusa®)**
Information as above.

Glecaprevir & Pibrentasvir **(Mavyret®)**
Information as above.

Elbasvir & grazoprevir **(Zepatier®)**
Information as above.

Genotype 5 & 6

Sofosbuvir & velpatasvir **(Epclusa®)**
Information as above.

Glecaprevir & Pibrentasvir **(Mavyret®)**
Information as above.

Side effects of medications

Headache, fatigue and nausea are uncommon and usually mild side-effects of many DAA's including Epclusa®, Mavyret®, Zepatier®, Harvoni® and Solvadi & Daklinza®.

People on Epclusa® have also experienced cold symptoms, however this is also mild and uncommon.

For both Epclusa® & Zepatier®, rates of headache, fatigue and nausea were seen to be similar to those in the placebo groups (and cold symptoms with Epclusa®).

For some people, Vosevi®, can also cause diarrhoea as well as headache fatigue and nausea.

Drug interactions

There are some potential drug interaction issues with DAA treatment. These may include drugs to treat acid reflux called proton –pump inhibitors, cholesterol lowering drugs, St John's Wort, drugs to treat epilepsy, antivirals and antimicrobials, immunosuppressive drugs and the cardiac drug amiodarone. However these are not complete contraindications and most issues will be able to be managed through appropriate drug selection, modifying other medications or careful monitoring.

For some DAA's concomitant use of contraception containing the hormone ethinyloestradiol may increase the risk of a rise in liver enzymes and in these cases an alternative form of contraception should be considered.

It is important to discuss any prescribed, over the counter or alternative medications with your doctor. Medications should be reviewed prior to hepatitis C treatment commencing.

The University of Liverpool's Hepatitis Drug interactions website can be used for review and working with an experienced pharmacist is also recommended. It is strongly suggested to seek advice before starting a new medication whilst on hepatitis C treatment.

Preparing for treatment

Prior to commencing treatment, a blood test is required.

This will confirm your hepatitis C status, genotype and viral load as well as your liver function. The blood tests can be used to gain an indication of how much scarring your liver has. If this shows there is more significant scarring and a chance you have cirrhosis you may need to get a FibroScan®.

This is a non-invasive, painless test which measures liver stiffness giving an indication of how much scarring your liver has. It uses transient elastography which is a technique that generates a vibration on the skin and then measures how long that vibration takes to

move through the liver to a certain depth. Scarred tissue is harder than healthy liver tissue, therefore the degree of liver scarring can be established. It takes only minutes and is completely pain free, it feels similar to getting an ultrasound.

Monitoring whilst on treatment

High level monitoring whilst on treatment is no longer necessary due to the high efficacy of these new regimes and the reduction of significant side effects compared to previous treatments.

Most people require no monitoring during treatment and can be reviewed at 12 weeks after finishing treatment to check for SVR and cure. However this decision will be made on a case by case basis. People whose treatment includes ribavirin and those with liver disease will likely require more regular blood tests and monitoring. People living with chronic hepatitis B are at risk of hepatitis B reactivation during hepatitis C treatment so will require monitoring for this.

No treatment restrictions

All Australian adults who have been diagnosed with chronic hepatitis C and who hold a Medicare Card are eligible to access the new DAA treatments, regardless of their stage of disease, co-morbidities, if they are using and/or injecting drugs and whether or not they are in prison. DAA treatment is funded and available in Victorian prisons. This is co-ordinated by the state-wide hepatitis service based at St Vincent's hospital.

If you are denied access to treatment and believe it is due to being in prison or your drug use you can call the *Hepatitis Infoline* on 1800 703 003 for support and information.

The PBS listing of DAA's is for adults over 18 only. However children with hepatitis C should be seen and assessed by a paediatrician experienced in viral hepatitis.

To find out more, contact the gastroenterology unit at The Royal Children's Hospital in Parkville on 9345 5060.

Who can prescribe them?

The PBS listing means that general practitioners who are experienced at prescribing DAA's can initiate treatment in primary care settings. GP's who are not as experienced can prescribe in consultation with a specialist gastroenterologist, hepatologist or infectious diseases physician. There is no official or formal accreditation process needed for GP's to prescribe DAA's.

Appropriate nurse practitioners are also able to prescribe the DAA treatment.

There are reasons for which you may need to be referred to and treated by a specialist. These include if you have cirrhosis, have

previously had treatment that has been unsuccessful or are living with chronic hepatitis B or HIV.

Getting scripts filled

If a person's prescription is written as an S.100 HSD public hospital item (HSD PUB) it will need to be dispensed in a public hospital pharmacy. If the script is written as an S.100 HSD private hospital item (HSD PTE) it can be dispensed in a private hospital pharmacy or community pharmacy.

If the script is written as a S.85 General Schedule streamlined approval (by a GP) it can be dispensed at a community pharmacy. Community pharmacies may have to order medicines before being able to fill prescriptions. There have been reports of delays of several days. This is an important consideration when filling repeats, so ensure you have a discussion with your pharmacist about ensuring continuity of supply. If you are having difficulty finding a pharmacist to fill your prescription, call the Hepatitis Infoline on 1800 703 003.

Treatment costs

Each script costs $6.40 with a healthcare card or $39.50 without. Usually one script covers a duration of one month. Treatments usually range between two to three and rarely up to 6 months.

To find out more, please call the Hepatitis Infoline on **1800 703 003**