WE HAVE PERFECTOVIR- DO WE NEED ANYTHING ELSE?

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Chronic hepatitis C virus (HCV) infection is a global epidemic with more than 110 million infected, including 300,000 in Australia and New Zealand. The proportion of the HCV infected population with hepatocellular carcinoma and liver failure will treble by 2030. Because attempts to develop an effective vaccine have been unsuccessful, the only means of reducing the health burden associated with hepatitis C is through increased treatment uptake and success of antiviral therapy. However, poor efficacy and tolerability current antiviral therapies have limited treatment uptake to <1%.

The discovery of HCV in 1989 led to better understanding of the HCV lifecycle which provided new therapeutic targets for inhibition by direct acting antivirals (DAAs). More than 100 DAAs have entered clinical development allowing DAA combinations which increase viral suppression, prevent the emergence of resistance and also remove the need for interferon. Sofosbuvir was the first DAA to exhibit potent activity and a very high barrier to resistance, paving the way towards the first approved 12 week DAA combination of HARVONI for HCV GT 1 and 4. Two other combinations are now approved for treatment of GT 1 and 4 – VIEKIRA PAK (ombitasvir/ritonavir/paritaprevir plus dasabuvir) and ZEPATIER (elbasvir/grazoprevir). All 3 all-oral regimens can now cure >95% of patients infected with HCV GT 1, including cirrhotics and treatment experienced.

The next waves of HCV treatment are oral pangenotypic regimens (HCV GT 1 – 6). The results from the Phase III ASTRAL studies demonstrated that Gilead combination of sofosbuvir plus pangenotypic NS5A inhibitor velpatasvir for 12 weeks cured overall 99% of patients infected with GT 1-6. The only remaining difficult-to-treat population with <90% SVR rate was the treatment-experienced GT 3 patients with cirrhosis.

The AbbVie fixed dose combination of the next generation protease inhibitor ABT-493 () and NS5A inhibitor ABT-530 (Pibrentasvir) provides the first pangenotypic regimen without a NUC. In the Phase II studies, only 8 weeks GLE/PIB achieved SVR in 99% of noncirrhotic patients infected with GT 1-3 whilst 12 weeks duration achieved SVR in >99% cirrhotic patients infected with GT 1-6.

DAA triplets are being developed to shorten treatment duration and salvage DAA failure patients. In Phase II studies, 8 weeks of sofosbuvir/velpatasvir plus the pangenotypic protease inhibitor GS-9857 achieved SVR in 100% HCV GT1 and GT 3 patients with cirrhosis. SVR rates were lower in DAA failures, suggesting that these patients will require longer than 8 weeks.

These pangenotypic and ultrashort regimens represent the final phase of HCV drug development, with SVR rates above 99% across all patient populations. Future studies will focus on how to ensure maximum benefits from these advances in therapy, how to address the challenges of low diagnosis rates, high rates of new infections, poor access to and high costs of treatment. There is a need to prioritise treatment in people who inject drugs to stop transmission (TasP). But the benefits are huge in terms of reducing the huge health burden associated with HCV in most high income and low income countries. Combined with DAA access programs, public awareness and community-based targeted testing campaign, elimination of HCV from ANZ should be feasible within the next 10 years and global eradication within the next 30 years.