Protease Inhibitors in Hepatitis C: From Chronic Disease to Cure

The recent publication of two controlled trials on boceprevir and three on telaprevir heralds a new era for hepatitis C therapy[1-6]. Bocreprevir and telaprevir are protease inhibitors which act directly on the hepatitis C virus to inhibit replication and are referred to as direct acting antiviral agents (DAAâ s). They are the first 2 such agents to be licensed but it is hoped that many more will soon follow[7]. These are very important studies and represent a major advance in treatment for patients with chronic hepatitis C virus infection. To appreciate their significance it is important to be aware of some of the clinical features of hepatitis C virus infection. Firstly, hepatitis C exposure leads to chronic infection in approximately 70% of patients. Over time (years or decades) this may lead to chronic hepatitis, cirrhosis, liver failure and hepatocellular carcinoma. The speed of progression depends on a number of co-factors. Patients who are male, drink alcohol, are overweight, diabetic or co-infected with HIV have more rapid progression to cirrhosis[8]. In contrast young, non-drinking females progress more slowly[9].

The second important point is that there are 6 main genotypes of hepatitis C. These genotypes vary in geographical distribution and response to anti-viral therapy. In common with most western countries genotype 1 is dominant in Ireland. The third important feature is that sustained virological response (SVR) appears to equate to viral cure[10]. Sustained virological response means the patient has no detectable circulating hepatitis C virus (PCR negative) six months after finishing antiviral therapy. True late relapse occurs in less than 1% although re-infection is always possible as viral clearance does not provide protective immunity. Sustained virological response is associated with a significant reduction in overall mortality[11].

Given this background, what do these new studies tell us about hepatitis C treatment. Firstly, both protease inhibitors act primarily against HCV genotype 1. This is fortunate as this is the dominant genotype in Irish patients. Until now the standard treatment for HCV genotype 1 was pegylated interferon and ribavirin for 48 weeks with sustained virological response rates of 35%-50%[12]. Because of the rapid development of viral resistance with monotherapy both boceprevir and telaprevir are used in combination with pegylated interferon and ribavirin, although the dosage schedules and duration of treatment vary. In naˆflve patients sustained virological responses of between 67% and 75% were reported with both drugs compared to 40% and 44% in the standard treatment arms. In patients who had previously not responded to standard therapy, or who had relapsed, SVRâ s of 60% to 66% were reported. This improvement in SVR is very impressive but comes at the expense of an increased side effect profile. Significant anaemia and dysgeusia were common with boceprevir whereas rashes and pruritus were frequent with telaprevir. Both are powerful drugs with complex dosing schedules and stopping rules and should not be prescribed without appropriate expertise and support systems in place. For the patients these are demanding treatment regimens but early stopping rules may mean shorter treatment courses for some individuals.

These new drugs clearly represent a major therapeutic advance in the treatment of chronic hepatitis C. As one would expect the improved efficacy comes with an economic price tag. The price of therapy is not yet fixed but estimates vary from 20,000 to 30,000 for a treatment course. These estimates donâ t include the ancillary costs including pegylated interferon, ribavirin, erythropoietin, viral assays, clinic visits etc. In the current economic situation, can the Irish public health service afford to provide these new treatments? Given the striking improvements in cure rates for a chronic, and potentially life threatening condition, it would be unfortunate if these drugs were not made available to Irish patients. Consideration of innovative funding models and/or changes in resource allocation may be required. One option would be to consider some form of risk sharing with the pharmaceutical companies concerned[13]. For example the state could consider paying only for successful viral eradication and agree an appropriate price based on this outcome. From the stateâ s point of view this would have the advantage of paying only for patients who were cured. From the pharmaceutical industry point of view revenue could be maximised by optimising the number of patients with sustained viral clearance.

In terms of resource allocation we may have to look at how resources are spent in the management of hepatitis C. To date most resources are concentrated on chronic follow up and monitoring for complications. Perhaps it is time to focus on early identification, treatment and eradication rather than long term care. If patients achieve SVR, have normal liver function tests, normal liver imaging (ultrasound scan and/or Fibroscan), they shouldnâ t need long term follow up and could be discharged from the liver clinics. Similarly patients who spontaneously clear the virus should not require long-term follow-up, in the absence of cirrhosis or significant fibrosis. Many patients with hepatitis C attend drug treatment clinics. This group rarely receive anti-viral therapy but represents the bulk of the population at risk for complications of chronic hepatitis C[14,8]. It has been shown that antiviral treatment in drug treatment centres, linked to methadone treatment, is very effective in ensuring compliance[15]. As the drug treatment infrastructure already exists, widening its remit to include hepatitis C treatment should be cost effective. A recent large study from the United States confirmed that it is possible to provide effective anti-viral therapy for hepatitis C in primary care settings, provided there is appropriate back-up[16].

In addition to more effective therapy we now also have tools to improve prediction of response to treatment. It has been discovered that patients homozygous for a single nucleotide polymorphism upstream of gene IL-28B on chromosome 19 (CC) have high rates of sustained virological response to treatment for hepatitis C genotype 1 with standard antiviral therapy. In a large US study CC was observed in 37% of Caucasian patients and was associated with an SVR of 69%[17]. Early results indicate that addition of protease inhibitors may improve these results significantly[18]. It is a clinical and economic question whether the increment is worth the additional cost. An alternative view could be that protease inhibitors should be reserved for genotype 1 patients without this favourable response genotype as the cost-benefit ratio may be higher in these patients. Debates about who should receive the new direct acting anti-virals are not limited to Ireland and require consideration of medical need and social justice[19]. On a lighter note a recent study suggests that drinking 3 or more cups of coffee a day significantly increases SVR rates with standard anti-viral therapy[20]. If confirmed this may offer an additional, low cost, method of boosting viral clearance rates.

The new protease inhibitors present the Irish health service with new opportunities and challenges. The challenge is to cure the maximum number of patients using the resources available. We may need to re-orientate our treatment delivery model from chronic disease surveillance to infectious disease eradication. In particular we need to effectively target the â hard to treatâ patients, who are at most risk of developing end stage liver disease and the associated complications.

Conflict of interest

PA McCormick reports receiving consultancy fees from Merck Sharp & Dohme, Janssen-Cilag Ltd and Bayer Ltd has received funding for clinical research studies from Astellas Ltd, Novartis Ltd and Bayer Ltd.

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