Updates in the Treatment of Chronic Hepatitis C

Dr. James Fung
MBChB, FRACP, FHKCP, FHKAM (Medicine)
Teaching Consultant, Department of Medicine, University of Hong Kong, Queen Mary Hospital

Dr. Ching-lung Lai
MD, FRCP (Edin, Glasg & Lond), FRACP, FHKCP, FHKAM (Medicine)
Professor, Department of Medicine, University of Hong Kong, Queen Mary Hospital

Dr. Man-fung Yuen
MD, PhD, FRCP (Edin, Glasg & Lond), FRACP, FHKCP, FHKAM (Medicine)
Professor, Department of Medicine, University of Hong Kong, Queen Mary Hospital

Background

An estimated 170 million people worldwide are infected with the hepatitis C virus (HCV). The majority of these people will remain asymptomatic at the time of acute infection; therefore HCV infection is rarely diagnosed during the acute phase. In those subjects acutely infected with HCV, approximately 50-85% will become chronically infected, of which around 20% will progress to cirrhosis over the course of 15-20 years. In fact, HCV has become one of the major indications for liver transplantation in the Western world.

Currently Available Agents

The current standard treatment for chronic hepatitis C (CHC) is pegylated interferon (peg-IFN) α-2a or α-2b in combination with ribavirin (RBV). In a randomised trial (the IDEAL study) of these two forms of peg-IFN, efficacy and side-effect profiles were similar. The ultimate goal of antiviral therapy is the achievement of sustained virological response (SVR), which is defined by undetectable HCV RNA by a sensitive molecular assay at 6 months after the completion of antiviral therapy, and is considered as a cure. Achievement of SVR is associated with improvement of fibrosis stage, reduced incidence of hepatocellular carcinoma, and decreased morbidity and mortality. The exact antiviral mechanism of peg-IFN-α is not known. RBV is a guanosine analog with low antiviral potency against HCV when used alone. However, its antiviral effect is augmented when used together with IFN although the mechanism of this synergism is not known.

HCV can be divided into 6 major genotypes, numerically named from 1 to 6 according to their time of discovery. These genotypes display differences in their geographical distribution, with genotype 1 and 6 being the most prevalent in Hong Kong. The majority of genotype 1 patients are infected through the use of intravenous drug abuse. Apart from their differences in distribution, the other major difference between the genotypes is their responses to antiviral therapy.

Genotype 1

In patients infected with HCV genotype 1, the recommended duration of treatment is 48 weeks, with a SVR of approximately 50-55%. The level of HCV RNA is assessed at week 12 for early virological response (EVR), which can be defined as complete (undetectable HCV RNA) or partial (≥2 log decrease in HCV RNA from baseline). For those patients who cannot achieve EVR, the negative predictive value for treatment outcome is high at 97%, and the chance of going on to achieving SVR with 48 weeks of therapy is unlikely. In patients who fail to reach EVR at week 12, early treatment discontinuation is recommended as these patients are likely to be non-responders. For those patients who achieved EVR, an estimated 65-72% will go on to achieve SVR.

More recently, the use of rapid virological response (RVR), defined by undetectable HCV RNA at week 4 using sensitive molecular tests, has been evaluated to identify a subgroup of patients who may benefit from a shorter duration of therapy. Several trials have shown that in genotype 1 patients who achieve RVR, a high SVR rate of over 70% can be achieved with peg-IFN plus ribavirin with a shorter duration of treatment for 24 weeks, which was comparable to those that were treated for 48 weeks. The major factor determining the outcome in patients with RVR and shorter duration of therapy was the level of viraemia at baseline. However, there is currently no consensus as to the baseline cut-off HCV RNA level that can be adopted to select out those who will be sufficiently treated with 24 weeks, although various cut-offs of 400,000, 600,000, and 800,000 IU/mL have been evaluated. Further trials are needed to identify an optimal cut-off level before shorter duration of therapy can be implemented.

On the opposite end of the spectrum, there have been studies evaluating longer duration of treatment. In an earlier trial looking at 48 vs 72 weeks of treatment in genotype 1 patients, there was no significant difference observed in SVR rates, although a higher SVR rate was observed in those who failed to achieve complete EVR at 12 weeks with 72 weeks of treatment. Those patients who did not achieve RVR also had a higher SVR rate when treated for 72 weeks compared to 48 weeks. However, more recent trials have not shown the benefits of 72 weeks of treatment when compared with 48 weeks. In patients who achieve partial EVR (but not complete EVR), there was no significant increase in SVR observed with 72 weeks of therapy compared with 48 weeks. Another study also showed no significant difference in SVR rates between 48 and 72 weeks of therapy in patients with genotype 1/4 who achieved either partial or complete EVR.

Genotypes 2 and 3

In patients infected with HCV genotype 2 or 3, the recommended treatment length is 24 weeks, with a...
SVR rate of 70-75%. Given that most patients will achieve EVR, and coupled with a shorter duration of therapy (compared to genotype 1), the use of EVR at week 12 to determine treatment outcome has not been adopted. Similar to the recent approaches for genotype 1 patients, both shortening and extending the duration of therapy have been evaluated in patients infected with genotype 2/3.

In the ACCELERATE trial comparing 16 vs 24 weeks of therapy, those treated for 16 weeks resulted in a lower SVR rate. For patients with HCV genotype 2/3 (the NORDynamiC study), treatment length of 12 weeks was inferior to 24 weeks of therapy. However, in patients who achieved RVR at week 4, 12 weeks of therapy was shown to be as effective as 24 weeks of therapy. Another study showed similar results with 16 weeks of therapy, although those patients infected with HCV genotype 3 and a high baseline viral load (>800,000 IU/mL) showed a lower SVR with 16 weeks of therapy compared with 24 weeks. Patients infected with HCV genotype 2 who achieved RVR appeared to show equal efficacy when treated for either 16 or 24 weeks. A meta-analysis of trials evaluating shorter duration of 12-16 weeks in genotype 2/3 patients with RVR showed an association with a lower SVR rate and higher relapse rates. Given the heterogeneity of these studies it is difficult to recommend a shorter duration of therapy for patients infected with genotype 2/3, although those who achieve RVR would appear to benefit most.

Genotype 6
There is currently no randomised controlled trial for genotype 6, therefore the recommendation is to treat these patients for 48 weeks. In retrospective studies comparing genotypes 6 and 1, the SVR rates were significantly higher in genotype 6 compared to genotype 1 when treated for 48 weeks. However, another retrospective study showed that 24 weeks of treatment was inferior to 48 weeks of treatment for genotype 6.

Non-responders to Therapy
In patients who do not respond to peg-IFN plus RBV therapy, the HALT-C study showed that further prolonged maintenance therapy with low-dose peg-IFN did not significantly reduce the rate of disease progression despite significant decline in HCV RNA. However, studies of re-treatment with a limited duration have shown some benefits. In the REPEAT study, re-treatment with peg-IFN-a2a + RBV for 72 weeks achieved a higher SVR rate compared to 48 weeks, although the SVR rate was still low at 16%. The EPIC3 study also showed a SVR of 22% in patients re-treated for 48 weeks with peg-IFN-a2b + RBV. Therefore, re-treatment appears to be beneficial in subgroups of patients who have failed previous treatments with peg-IFN. However, there is no current recommendation for retreatment of patients who have completed a full course of peg-IFN + RBV therapy.

Side-effects of Current Therapy
Prior to commencing antiviral therapy, a full medical history and examination must be obtained as there can be potential for serious adverse effects. Since immune stimulation by peg-IFN may induce severe liver injury, treatment for patients with established cirrhosis should be considered carefully, and is contra-indicated in those with decompensated cirrhosis. The side-effects of hepatitis C therapy are summarised in table 1. Because of the possible serious adverse events, patient selection is of utmost importance, and the decision to treat requires a careful assessment of the risk to benefit ratio for each individual patient. Patients should also be aware of the possible worsening of their quality of life during the course of the treatment.

| Table 1. Common side effects of pegylated interferon and ribavirin therapy |
|-------------------------|---------------------------|
| Flu-like symptoms | Haematological |
| Fatigue | Anaemia |
| Myalgia | Leucopenia |
| Pyrexia | Thrombocytopenia |
| Rigours | Autoimmune |
| Headache | Thyroid disorder |
| Arthralgia | Other autoimmune disorders |
| Mood disturbances | Dermatological |
| Depression | Rash |
| Irritability | Exacerbation of psoriasis |
| Memory loss | Injection site reaction |
| Mood swings | Alopecia |
| Insomnia | |

Interferon
Patients who experience flu-like symptoms may respond to treatment with acetaminophen or non-steroidal anti-inflammatory drugs, whereas those with insomnia may be treated with sleeping medications. Although neutropenia is commonly observed in patients treated with IFN, the risk of infection is low, and careful monitoring usually suffices. The use of granulocyte colony-stimulating factor is only rarely considered. Thrombocytopenia is commonly observed in patients with liver disease secondary to both hypersplenism and insufficient hepatic production of thrombopoietin. This can be further compounded by the administration of IFN-based therapy, which is associated with a rapid and sustained reduction in peripheral platelet count. Currently there is no approved agent available for the treatment of thrombocytopenia, although thrombopoietin-mimetic agents such as eltrombopag may become available in the near future.

Ribavirin
The most significant adverse effect of ribavirin is haemolytic anaemia, which is commonly observed in patients undergoing treatment. Management includes reducing the dose of ribavirin if the haemoglobin level falls below 10 g/dL, or stopping therapy if it falls below 8.5 g/dL. Ribavirin may need to be avoided in patients who cannot tolerate anaemia, such as those with pre-existing cardiovascular or cerebrovascular diseases. The use of erythropoietin is effective in treating anaemia and ameliorating the need for dose reduction of ribavirin, and in improving the quality of life of patients. However, the effect on improved SVR is yet to be demonstrated. As there is associated teratogenicity with ribavirin, it is contra-indicated during pregnancy, and adequate contraception must be adopted for both male and female patients.
Future Therapeutic Agents in HCV Treatment

As described previously, with the current standard of care using peg-IFN and ribavirin, only around 50% of patients with genotype 1 may achieve SVR. Newer agents are much anticipated to improve the modest cure rate. Newer types of IFN are undergoing evaluation, including consensus IFN and albuferon. Novel deliveries of IFN include controlled release formulations and the uses of nanoparticle delivery systems are also being explored.

Currently, there are many promising agents known as specifically targeted antiviral therapy for hepatitis C (STAT-C) compounds which target the HCV replication cycle are undergoing phase I to III trials. Two of these STAT-C agents, telaprevir and boceprevir, are in advance stages of development, and should become available in the following 1-2 years.

Telaprevir
Telaprevir is an oral NS3 protease inhibitor currently undergoing phase III evaluation. In the initial phase I studies, an optimal dose of 750mg q8h following an initial loading dose of 1250mg was identified. Selection of telaprevir-resistant mutations was observed with telaprevir monotherapy, although the rate was significantly lower when combined with peg-IFN. In the phase II trial of treatment-naive genotype 1 patients (PROVE 1 study in USA and PROVE 2 study in Europe), those treated with 12 weeks of telaprevir had a significantly higher SVR rate when treated with 24 or 48 weeks or Peg-IFN + ribavirin compared to standard therapy of 48 weeks of peg-IFN + ribavirin without telaprevir. These two trials also showed that 12 weeks of therapy using telaprevir, peg-IFN, and ribavirin was associated with a high relapse rate. The PROVE 2 trial also showed that those treated without ribavirin was associated with a lower SVR rate. In the trial of treatment-experienced patients (the PROVE 3 study), re-treating non-responders with 12 weeks of telaprevir + peg-IFN + ribavirin for 12 weeks followed by a further 12 weeks of peg-IFN + ribavirin resulted in a SVR rate of 51%, compared to 14% in patients retreated with peg-IFN + ribavirin without telaprevir. A number of phase III trials are currently in progress for treatment-naive patients (the ADVANCE and ILLUMINATE study) and for patients with previous treatment failure (the REALISE study). The most common side effects of telaprevir include rash, gastrointestinal disorders, and anemia.

Boceprevir
Boceprevir is a NS3 protease inhibitor, another STAT-C compound that is currently undergoing phase III evaluation. In the phase II trial (the SPRINT 1 study) of treatment-naive genotype 1 patients, those patients receiving boceprevir had higher rates of SVR compared to patients treated with peg-IFN + ribavirin without boceprevir. Common side-effects included anaemia and gastrointestinal symptoms. Boceprevir is currently being evaluated in phase III trial of treatment-naive genotype 1 patients (the SPRINT 2 study) using boceprevir 800mg tds + peg-IFN α-2b + ribavirin for 28/48 weeks versus standard treatment with peg-IFN α-2b + ribavirin for 48 weeks. The other phase III trial is on relapers and non-responders (the RESPOND-2 study) using boceprevir 800mg tds + peg-IFN α-2b + ribavirin for 36/48 weeks versus standard treatment with peg-IFN α-2b + ribavirin for 48 weeks. Similar to telaprevir, there are also mutations associated with boceprevir treatment.

Apart from telaprevir and boceprevir, there are currently a host of other NS3/4A protease inhibitors undergoing phase I and II evaluations. In addition to the NS3/4A protease inhibitors, other classes of antiviral compounds undergoing phase I and II development include the NS5B polymerase inhibitors and NS5A inhibitors.

Summary
Over the recent years, there has been a shift towards individualisation of treatment according to their initial responses to therapy. There have been many studies evaluating shortening of therapy in patients who achieve RVR and also those with lower baseline viral load. However, further studies are still needed to clarify the optimal modified duration of therapy and also the optimal baseline viral load at which these truncated treatment regimens can be implemented. For those patients who do not respond to therapy, extending the duration of therapy may not improve the chance of achieving SVR. Fortunately there are now many newer agents in various stages of development to treat patients infected with genotype 1 and those patients who have failed peg-IFN + RBV therapy. Both telaprevir and boceprevir are undergoing phase III evaluation and should become available in the very near future. Because of the high risk of resistant mutations when used as monotherapy, these newer agents will be used in combination with peg-IFN + RBV or with other newer STAT-C compounds as they become available.

References


