In Taiwan, interferon (IFN)-based therapy has long been used to treat chronic hepatitis C. Our earlier pilot study showed that naive patients with 3 MU of conventional IFN thrice weekly plus 1,200 mg of oral ribavirin daily for 24 weeks had a significantly higher sustained virologic response (SVR) rate than those with no treatment (43% vs. 6%). A randomized trial also suggested that more than one-third Taiwanese chronic hepatitis C patients who failed prior IFN monotherapy could achieve SVR after 24 weeks of retreatment with combination therapy, and the response rate was even higher (53%) in those with IFN 6 MU. A study from southern Taiwan also confirmed that 6 MU regimen has better efficacy than 3 MU regimen in terms of virologic and histological responses. In addition, sustained virologic response to interferon-based therapy can result in reducing HCC incidence and improving patient survival. Similar to Caucasian patients with chronic hepatitis C, a recent multicenter randomized study in Taiwan has confirmed that combination of PEG-IFN and ribavirin therapy for 24 weeks had significantly better SVR and lower relapse rate when compared to IFN and ribavirin therapy in our genotype 1 chronic hepatitis C patient, whereas both regimens can be recommended for genotype non-1 patients. Although the recurrent treated patients who achieve rapid virological response patients is peg-IFN plus ribavirin for 48 weeks, whether treatment duration of 24 weeks is as effective as standard treatment in genotype 1 patients with a rapid virological response (RVR; seronegative for HCV RNA at 4 weeks) remains unclear. Two large-scale randomized trials in Taiwan all showed that genotype 1 patients derive a significantly better SVR from 48 weeks versus 24 weeks of peginterferon/ribavirin even if they attain an RVR. Both 24 and 48 weeks of therapy can achieve high SVR rates in genotype 1 patients with low viral loads and an RVR. In addition, a randomized study showed that 16 weeks and 24 weeks of peg-IFN treatment with weight-based ribavirin at a dose of 1000–1200 mg/day provided equal efficacy in genotype 2 patients who achieved rapid virologic response (RVR) at 4 weeks.

Several specifically targeted antiviral therapies for hepatitis C (STAT-C) have been designed to directly inhibit the replication of HCV, and early preclinical data showed encouraging results. Therefore, combination therapy with a backbone of peg-IFN plus ribavirin, or perhaps using several of these small molecules with distinct modes of action and resistance profiles, will be proven useful in the future.

### Concurrent Session 10 – Management of Hepatitis C

#### I-53 Treatment of chronic hepatitis C in Taiwan

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Chronic hepatitis C virus (HCV) infection is a major health problem worldwide because of its potential adverse sequelae including cirrhosis-related complications and hepatocellular carcinoma (HCC). Taiwan is a country endemic for HCV infection, and 30% of Taiwanese patients with chronic liver diseases are attributable to this virus. The primary goal of treatment for chronic hepatitis C is to eliminate HCV replication and therefore reduce or prevent hepatic injury. Furthermore, the ultimate long-term goal of therapy is to prevent hepatic decompensation, to reduce or prevent disease progression to cirrhosis and/or HCC, and to prolong survival of patients.

#### I-54 Optimizing HCV antiviral treatment: reducing treatment duration

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The current ‘gold standard’ treatment for patients with chronic hepatitis C consists of pegylated interferon-alfa (PEG-IFN) + ribavirin, for a duration of 48 weeks for those with HCV genotype 1 and 4, and 24 weeks for genotypes 2 and 3. However, these rigid treatment durations are now being questioned in light of new information on viral kinetic responses during the early phase of treatment. In particular, those with a rapid viral response (RVR), defined as undetectability of HCV-RNA at 4wk after onset of treatment, may only need a shorter duration of treatment whereas they have genotype 1, 2, or 3. Evidence suggesting a shorter 24-wk course in genotype 1 RVR patients and 12–16 weeks in those with genotypes 2/3 will be presented. Although there are several pre-treatment baseline factors that may predict sustained virological response (SVR), such as genotype, viral load, presence of advanced fibrosis, body weight and ethnicity, one of the strongest predictors of SVR is the presence of RVR. Regardless of genotype (studied only for genotypes 1, 2, 3), the presence of RVR appears to improve the probability of achieving a sustained virologic response to interferon therapy. A recent randomized controlled trial showed that 48-week therapy was superior to 24-week therapy in terms of achieving sustained virologic response (SVR) in genotype 1 chronic hepatitis C patients. In conclusion, this randomized controlled trial showed that shorter duration therapy is effective for patients with chronic hepatitis C.
to be associated with approximately a 85–90% chance of SVR. There have also been concerns that RVR may differ depending on which assay is used. In other words, will using a very sensitive PCR assay with lower limit of detectability to approximately 10 IU/mL show the same predictability as the older assays with a detection limit of 50 IU/mL or those who use an assay with a limit of 500 IU/mL? Current evidence seems to suggest that no matter which assay is used, RVR holds its strong predictive value. While 24wk in genotype 1 RVR is now accepted and even recommended in some consensus guidelines, shortening treatment to 16 in those with RVR and genotypes 2 and 3 remains controversial. The largest study with nearly 1500 patients of genotypes 2 and 3 showed that even those who achieve RVR would benefit (slightly but significantly) from the full 24wk of treatment compared to only 16 wk. Further study is needed to better define those subgroups with genotype 2 and 3 who may be able to shorten duration of treatment without compromising the chance of achieving viral clearance. We also need to study increasing duration or intensifying treatment in those genotype 2 and 3 patients who do not achieve RVR (about 1/3 of genotype 2 and 3 patients do not achieve RVR), as their sustained virological response (SVR) rates are only approximately 50% with 24 wk of treatment. Finally, we should probably start considering genotypes 2 and 3 separately rather than lumping together as a single homogeneous entity. It is clear that they behave slightly differently in response to treatment.

**I-55 Management of chronic hepatitis B and C in HIV-co-infected patients**

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Due to sharing the same route of transmission, co-infection of HIV-HBV or HIV-HCV can occur in some patients. Co-infection with HBV or HCV accelerates liver disease progression and increases the risk of liver-related mortality in HIV-infected patients.

Due to low baseline ALT, high baseline HBV DNA and decreased HBV-specific T-cell response in HBV-HIV co-infected patients, treatment with IFN has low efficacy with HBeAg loss in 0–20% and less tolerability. IFN treatment should be considered only in patients with ALT more than 2 times ULN, HBV DNA less than 7 logs copies/ml and CD4 count greater than 500 cells/mm². Anti HBV agents without effect on HIV such as adefovir dipivoxil or telbivudine is the treatment of choice for patients who do not require HAART. Lamivudine and tenofovir plus other anti HIV agent are recommended in patients with CD4 more than 200 cells/mm² whom HAART is indicated. In order to prevent immune reconstitution induced-hepatitis flare, patients with advanced liver disease and low CD4 count should be initially treated with lamivudine plus tenofovir until HBV DNA become undetectable before adding the third agent of HAART.

Peg-IFN plus ribavirin treatment is the standard treatment for both HCV mono-infection and HCV-HIV co-infection. As in mono-infected patients, HCV genotype 2, 3 have better sustained virological (SVR) than genotype 1 (44–69% vs 11–38% in HIV-coinfected patients treated with Peg-IFN plus ribavirin). Drug interaction and mitochondrial toxicity must be carefully monitored through out treatment period in patient receiving HAART. Didanosine should be avoided in patients receiving ribavirin. On treatment virological response have a good predictive of response and may be used to guide treatment decision.

**I-56 Death and severity of meningococcal disease – influence of microbial phenotype, host genotype and environment**

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Across Europe the incidence of meningococcal disease varies from between 1 per 100,000 up to 14.3 per 100,000 population per annum. The case fatality rate overall is approximately 8%, but amongst survivors there is a relatively high frequency of severe sequelae including hearing impairment, neuro-cognitive abnormalities, severe skin and soft tissue abnormalities including loss of limbs, and renal failure. Physicians and paediatricians who treat meningococcal disease observe a range of severity from relatively benign disease to severe physiological disruption leading to death. In general terms, those who present with meningitis tend to have a better prognosis, whilst those who present with severe sepsis syndrome have the worst prognosis. Study of factors associated with the severity of meningococcal disease is difficult and confounded by factors such as the sporadic nature of the disease and marked differences in access to health systems between individuals. Many studies have shown that the outcome of meningococcal disease is associated with the phenotype of the infecting organism. The odds of death from disease are highest for certain sequence types, for example ST-11/ET-37 complex and ST-32/ET-5 complex. The precise phenotypes responsible for the enhanced virulence of these sequence types has not been precisely defined. The major virulence determinants of *Neisseria meningitidis* include the polysialic capsule, LPS immunotypes, sialylation, and outer membrane proteins including Opa and Opc. Whilst there is no consistent segregation of virulence determinants in clonal groups associated with the most severe disease, organisms expressing serogroup C have been associated with fatal outcome. A number of host factors have been identified as important in determining severity of disease. Chief amongst these is age at presentation, with the worst prognosis being associated with adults. Some of this may be explained by the increasing sophistication of paediatric intensive care. Twin studies have indicated that death from severe infectious disease has a familial component and in the case of meningococcal disease a large number of studies have been conducted to investigate the role of genes encoding components of the immune system, the inflammatory response and coagulation pathways. The difficulty faced by geneticists is that death is the most easily verifiable end point for the purpose of studying genetic modifiers of severity of disease. Because of the death rate of only 8% this means that very small cohorts are available for study. However, association studies have revealed a relationship between a number of genes and the likelihood of death in meningococcal disease. These include Fc receptors, polymorphisms of plasminogen activator inhibitor type 1, prooprin deficiencies, and polymorphisms within interleukin 1 and the interleukin 1 receptor antagonist. In several countries, there have been increasing reporting of isolates of *Neisseria meningitidis* with reduced sensitivity to penicillin. Treatment failure has been reported extremely rarely and studies have failed to demonstrate any association between reduced penicillin susceptibility and fatal outcome. Most doctors consider that emergency treatment of newly-presenting cases with penicillin in the community is mandatory. Controversially, a recent study has suggested that treatment in the home with injected penicillin may be associated with increased severity of disease. This will be discussed.