They are effective in the treatment of candidaemia, esophaegeal candidaisis, and aspergillus infections. Selected agents can also be used for prophylaxis in stem cell transplant recipients and other candida infections. Currently, there are 3 echinocandins available, caspofungin, micafungin and anidulafungin. No dosage adjustment is required for renal impairment. Only caspofungin requires adjustment in liver insufficiency. Pharmacokinetic-pharmacodynamic studies have identified that these agents are concentration dependent with post-antifungal effect. Therefore a single daily dosing regimen is usually sufficient. In addition, novel dosing regimen such as extended interval dosing (alternate day or even weekly) may be possible as demonstrated in animal models. While these agents have demonstrated similar efficacy, patients' comfort would be another considerations in the choice of anti-infective agents. Possibility on extended interval dosing, and drug cost would impact on the hospital decision on their formulary placement.

Concurrent Session 4 − HCV Development and Strategies

CS4-01 **Response-guided Therapy for Chronic Hepatitis C**

Stefan Zeuzem*. *Professor of Medicine, Chief, Department of Medicine, Goethe University Hospital, Frankfurt a.M., Germany*

Pegylated interferon alfa in combination with ribavirin administered for 48 and 24 weeks has been approved as standard antiviral treatment in patients with HCV genotype 1 (4-6) and 2/3 infection, respectively, in many countries. Different virus- and host-related baseline parameters are known to predict the probability of sustained virologic response including HCV genotype, HCV viral load, gamma glutamyltranspeptidase (GGT) levels, age and liver fibrosis. While HCV genotype 2, 3 infected patients are generally treated for 24 weeks, management of therapy is based on early discontinuation rules in HCV genotype 1 infected patients with a low or no chance of further sustained virologic response. Thereby, a decline of less than 2 log10 steps at week 12 in comparison with baseline (early virologic response, EVR) and detectable HCV RNA at week 24 by a sensitive assay (detection limit $\leq$50 IU/ml) can be safely used as stopping rules with predictive values of 98-100% for virologic non-response. Future developments are aiming for individualization of treatment duration based on HCV RNA concentrations before initiation of therapy and decline early during therapy. Rapid virologic response (RVR) defined as undetectable HCV RNA at week 4 of therapy ($\leq$50 IU/ml) together with low baseline viral load ($\leq$600.000 IU/ml) were introduced as parameters for shortening of treatment duration in HCV genotype 1 infected patients without a loss of the probability of sustained virologic response. Vice versa in patients with a slow virologic response which become HCV RNA negative at the first time at week 24 of therapy prolongation of treatment duration to 72 weeks seems to be associated with increased sustained virologic response rates. Similar in HCV genotype 2, 3 infected patients reduction of treatment duration from 24 to 12-16 weeks was investigated in different clinical trials. However, in several studies shortening therapy to 12-16 weeks higher relapse rates were reported and future trials are needed to define subgroups of patients with specific baseline parameters (e.g. genotype, viral load, degree of fibrosis) and RVR at week 4 for a safe reduction of treatment duration.

Basic to the development of new specific anti-HCV drugs is the understanding of the viral life cycle, in particular the genomic organization and the polyprotein processing. Major progress in this field was achieved due to the development of sub-genomic and more recently full-genomic replicon systems. The HCV genome is a single-stranded RNA molecule that contains a single open reading frame encoding a polyprotein of about 3000 amino acids. The polyprotein is subsequently processed at the level of the endoplasmic reticulum (ER) by cellular and viral proteases to yield 4 structural and 6 non-structural proteins. The open reading frame is flanked by 5' and 3' untranslated regions. Each single HCV structure represents a potential antiviral target. Antisense oligonucleotides, ribozymes, siRNA, and small molecules have been targeted in particular against the 5'-noncoding region with substantial success in vitro but not yet in vivo. Inhibition of nucleocapsid formation to the icosahedral viral coat is an attractive target, however, no specific molecules have yet been developed. Envelope proteins HCV E1 and E2 are the basis for the development of prophylactic and/or therapeutic vaccines.

NS3 and NS4A are cleaved by the catalytic activity of the NS3 protease domain. In addition to the protease domain located in the 189 aminoterminal amino acids, NS3 also possesses a helicase domain located in the 442 carboxyterminal amino acids. The NS3 protease domain is responsible to complete the polyprotein processing down to NS4B, NS5A, and NS5B. Despite the fact that the catalytic site is a shallow and largely hydrophobic groove and therefore very difficult to target several compounds have been successfully designed (BILN 2061, VX-950, SCH503034, etc.). The NS5B RNA-dependent RNA polymerase is the key enzyme for synthesis of a complementary minus-strand RNA using the genome as template, and the subsequent synthesis of genomic plus-strand RNA from this minus-strand RNA template. The active site of the enzyme is a target for nucleoside/nucleotide analogue inhibitors. Nonnucleoside inhibitors, reported to bind at various sites, may act by blocking the enzyme in the initiation mode through inhibition of a conformational change needed to proceed with elongation.

CS4-02 **Treatment of Different Genotypes in Chronic Hepatitis C**

James Y.Y. Fung*. *Department of Medicine, University of Hong Kong, Hong Kong*

Hepatitis C virus (HCV) affects an estimated 175 million people worldwide. Up to 4 million people will be newly infected each year, and the majority of these will progress to chronic infection. There are currently six major genotypes, with geographical differences in the distribution of these different genotypes. In China, the predominant genotypes are 1b and 2a, compared to Hong Kong, where the predominant genotypes are 1b and 6.

The most important clinical implication of HCV genotypes lies in the differences in response to antiviral therapy between the different genotypes, and HCV genotypes is the strongest predictor of treatment response. Therefore, the determination of HCV genotype has become an essential part in the treatment of chronic hepatitis C. The exact mechanism of why some genotypes are more difficult to treat than others remains unknown, and is likely to involve both host and viral factors. With our current knowledge, patients infected with genotype 1 and 4 have an inferior response to interferon-based therapy compared to patients with genotypes 2, 3, 5 and 6.

CS4-03 **Mechanism of IFN-gamma in Anti-HCV Infection**

Xuefan Bai*. *Department of Infectious Diseases, Tangdu Hospital, Fourth Military Medical University, Xi'an, China*

CS4-04 **The Impact of Lipid Profiles on HCV RNA Levels in Patients with Genotypes 1 and 2**

Chen-Hua Liu*. *Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan*

Chronic hepatitis C virus (HCV) infection, a leading cause of cirrhosis, hepatocellular carcinoma (HCC) and liver failure, affects more than 170 million people worldwide. Despite the improving