

Abstracts 2: Clinical Conditions

Conditions for Clinical Multicenter-Studies for the Treatment of Chronic Hepatitis C

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Antiviral therapy of chronic viral hepatitis has significantly improved in recent years. In contrast to many other viral infection therapies became available that not only suppress viral replication but can lead to sustained viral eradication. However, current antiviral therapies for chronic hepatitis C virus infection are based on treatment with interferon alpha which is associated with significant side-effects and costs. Thus for the clinician it is very important to identify patients prior to treatment or early during therapy who will not respond to therapy. Those patients may be considered for alternative treatment strategies to prevent progression of liver disease. In addition, still more than half of the patients infected with HCV-genotype 1 still do not achieve a sustained virological response requiring a search for alternative and improved treatment options.

The recent success in antiviral therapy of chronic hepatitis C has only been possible because several multi-center studies including 1000-1500 patients in each trial had been performed. From these studies we have learned several important issues that should be considered for the design of future trials in viral hepatitis. First of all, patients have to be informed very well about possible interferon related side-effects. Only well informed and motivated patients should be included into the study. Second, careful selection of patients is mandatory. This includes screening for contraindications for interferon alpha as well as careful evaluation of patients history and testing for autoantibodies. Meanwhile many patients have received antiviral therapy in previous trials and may not be considered for studies in treatment-naïve patients. We usually have to screen more than 50 patients to find 10

individuals being eligible to be included in a study. Third, the institution has to ensure that continuity of medical personal during the course of treatment should be provided. The factors "study nurse" and "treating physician" are more important for response to therapy than the question to use drug A or drug B. A good relation between the physician and the patient is an absolute prerequisite to keep the patients on therapy if interferon alpha is prescribed. Doctors should take time for their first contact to a patient to explain the course of the disease and treatment options. Patients have to have confidence in their treating doctor. Treatment adherence is among the most important factors predicting sustained response to antiviral treatment. Relatives of the patients should be aware of the fact that the patient might have to suffer for a whole year. We try to talk to the patient together with his/her partner before treatment is initiated. Patient compliance is much better if the patient knows in advance what he might expect. Fourth, the institution has recognize that the treating physician and the study nurse need time to ensure adequate and careful documentation of treatment response and side effects. Treating patients within protocols requires time and knowledge how to proceed in the case of adverse events.

The network of excellence for viral hepatitis "Hep-Net" offers to review study protocols. A statistician is checking each protocol for sample size and adequate power of the study. Five experienced experts of each model region are reviewing the scientific concept of each study. For more information on this review-process and on all ongoing trials within Hep-Net see <http://www.kompetenznetz-hepatitis.de>.

Conditions for Clinical Studies in Outpatients with Injection Drug Use

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Nearly all drug addicts in outpatient treatment are treated by general practitioners and doctors of internal medicine working in private practices. Most of those doctors are specialized in the treatment of addictive behaviour. In contrast, only very few are familiar with the treatment of drug related chronic infectious diseases as hepatitis C or HIV-infection. So the majority of the doctors are not used to be engaged in clinical trials on a higher scientific level.

The conditions for clinical trials are only given in specialised outpatient departments of universities or in private practices specialized in the treatment of chronic infectious diseases. That means, the number of qualified institutions is limited. To perform clinical trials with a medication which evokes severe psychiatric side effects as is the case in the treatment of hepatitis C you need a stable relationship between the doctor and the intravenous drug addict.

Conditions which qualify an institution for clinical studies in this field of outpatient treatment are the following:

Experience with addiction medicine, realization of a setting which meets the needs of drug addicts, possibility for methadone maintenance, experience in the treatment of hepatitis B, hepatitis C and HIV-infection, experience in treatment of the psychiatric and hematological complications occurring under HCV-therapy, experience with good clinical practice

for trials on medicinal products, data management and controlling of appointments by a study nurse, knowledge of immunological and virological laboratory methods and finally, the provider should not feel discomfort in treating IDUs.

Under these conditions clinical studies with IDUs are possible and discontinuation rates are not higher than in clinical studies with normal populations.

Management of Psychiatric Comorbidity under Antiviral Treatment of Hepatitis C

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Worldwide about 170 million people are chronically infected with the hepatitis C virus (HCV). Chronic hepatitis C can lead to cirrhosis, hepatocellular carcinoma, and the need for liver transplantation. Therefore, early intervention is required. While the seroprevalence in the general population ranges between 0.2 and 2%, the prevalence of HCV-infection in chronic drug abusers was estimated between 50-90%. Patients with psychiatric disorders were also shown to have a highly increased risk to be chronically infected with the hepatitis C virus with a prevalence between 8,5-19% [1].

The cytokine interferon-alpha (IFN- α) is still the only effective treatment for patients with chronic hepatitis C. However, there is some evidence that immunotherapy with interferon-alpha (IFN- α) can significantly increase the severity of pre-existing depressive disorders and therefore treatment for chronic hepatitis C is contraindicated for patients with drug abuse and psychiatric disorders. As a consequence HCV-treatment is at present only offered to about 50% of all HCV-infected patients who require treatment. In recent years, at least the consequences that result from the exclusion of the highly affected group of drug addicts have been critically discussed and new treatment guidelines suggest to also treat drug users. However, Pariente et al. demonstrated that also patients with mood disorders do not have an increased risk for the development of IFN- α -associated depression compared to non psychiatric controls [2]. We recently reported, that patients with psychiatric disorders and hepatitis C did not differ in adherence and sustained response to combined treatment with IFN- α and ribavirin, if antidepressants

were given in case of IFN-induced depressive mood changes [3]. Musselmann and colleagues provided evidence that pre-emptive antidepressive therapy with paroxetine, a selective serotonin reuptake inhibitor (SSRI), given to patients who received standard IFN- α because of malignant melanoma reduced significantly the incidence of major depression [4]. Taking together, the available data suggest that HCV-infected patients with psychiatric disorders and/or drug addiction can safely and successfully be treated with interferon-alpha if it is performed in an interdisciplinary setting. Psychiatric contraindications to IFN- α treatment have to be critically discussed and patients with psychiatric disorders should not longer be excluded from the only effective treatment for chronic hepatitis C.

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Treatment of Hepatitis C in Injection Drug Users under Methadone Maintenance (PERMIT-Study)

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Injection drug use (IDU) is regarded as the most important risk factor for transmission of the hepatitis C virus (HCV) in industrialized countries, and prevalence rates in IDUs are between 40% and 90%. Implications for the individual's health as for the public are considerable. Chronic infection with the virus may lead to liver cirrhosis in 20% – 30% of patients within 2 or 3 decades, which consecutively may translate into end stage liver failure or hepatocellular carcinoma. Treatment of chronic HCV-infection has improved significantly due to introduction of antiviral combination therapy with pegylated interferon and ribavirin. Rates of inactivation of disease (sustained viral response, SVR) exceed the 50%-limit, in detail – depending on the genotype – SVR can be achieved in between 40% and 85%. However, treatment access for IDUs is limited, and current treatment guidelines are controversial as to treatment of IDUs. The guidelines of the European Association for the Study of the Liver (EASL 1999) recommend not to treat active IDUs, whilst Consensus Conference statements from France or the US do not regard IDU per se as exclusion criterion from antiviral therapy (<http://www.anaes.fr>, http://consensus.nih.gov/cons/116/116cdc_intro.htm). Meanwhile, some evidence has been produced to support feasibility of antiviral therapy in IDUs. Antiviral treatment may successfully be conducted after detoxification therapy in a specialised in-patient/out-patient setting by staff trained in hepatology and addiction medicine. Relapse may not automatically predict poor viral outcome, but adherence to appointments may (Backmund et al. 2001). Even patients with psychiatric comorbidity may be treated safely and successfully in a specialised setting including psychiatrists and hepatologists (Schaefer et al. 2003). Treatment is also successful in IDUs in methadone maintenance, despite (moderate) alcohol consumption or cannabis use (Sylvestre 2002). Re-infection rates in IDUs may not necessarily be higher than in non-IDUs (Dalgard et al. 2002). Yet, a large number of HCV-infected IDUs experience lack of treatment access. This disparity calls for evaluation and outreach implementation of treatment programs. Therefore, the PERMIT-study (Psychoeducation Reaches HCV-infected Methadone Substituted Patients in Antiviral Treatment) was initiated. It will be conducted in substitution offices throughout Germany, and treatment will be offered to stable substituted patients. Additionally to antiviral treatment by pegylated

interferon (-2a and ribavirin, every second patient will take part in a specialised psychoeducational program. Psychoeducation is a systemic, cognitive-behavioral psychotherapeutic approach to model behavior, which starts from the level of individual experience and transfers of knowledge about an illness. Psychoeducation is a group therapy with homogenous clients with specific problems, who take part in a specifically designed program and who are participated in definition of aims and processing. It has been shown to be beneficial in terms of reduction of illicit drug use, relapse and social integration (e.g. McLellan et al. 1993). Within PERMIT, psychoeducation takes place in closed groups with 8 – 12 patients, will be conducted by trained staff, and different media will be supplied (papers, overhead, flipcharts, tv/video). Outcome parameters of PERMIT include feasibility, efficacy, mental health and course of addictive disorder. In the context of HCV-therapy in IDUs, it is expected that PERMIT contributes to the evaluation of the adequate treatment setting and facilitates treatment access.

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