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Summary of the IX International Symposium on Viral Hepatitis☆

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1. New hepatitis viruses

Hepatitis non-A–E exists. It accounts for 25% of fulminant hepatitis, 3% of chronic liver disease and 20% of post-transfusion hepatitis. There are various candidate possibilities for the cause.

The TTV virus was originally described in 1997 in Japan as a transmissible agent associated with non-A–G hepatitis. It is now known to be worldwide including Shanghai, Mongolia and Columbia. Twenty percent of new-borns are infected within 1 year and carry the virus throughout life. Results depend on methodology.

M. Mizokami (Nagoya City) reported six genotypes. However, he found no association of any genotype with liver disease, transaminase levels or progression in man.

M. Mushahwar (Abbott Laboratories) reported on TTV virus, which he found by in situ hybridisation in the liver. It seems to be a circe-like virus affecting 33% of US blood donors. It is also found in domestic animals and patients may acquire the disease from their diet.

The GBV-C virus seems to have no relation to acute or chronic liver disease. However, M.P. Manns (Hannover) reported on interactions between GBV-C/HGV and human immunodeficiency virus and believed it may prolong survival. However, this could not be confirmed by S. Bagaglio (Milan).

C. Trepo (Lyons) discussed the significance of hepatitis B virus (HBV) in some apparently unexplained cryptogenic cases of viral hepatitis. He used a very sensitive method of measuring HBV DNA. He could detect HBV in 50% patients with non-A–E hepatitis. Mechanisms of these apparently silent HBV infections remain unknown; mutant viruses may be concerned.

2. Hepatitis delta virus

The course of chronic hepatitis delta virus (HDV) infection was discussed by P. Farci (Cagliari). This defective virus, dependent on its association with HBV, is decreasing with HBV vaccination. It is highly pathogenic. HBV sufferers superinfected with delta have a 70% chance of developing cirrhosis within 2 years. Spontaneous resolution is unusual. Patients treated with 9 million units interferon-alpha three time a week for 48 weeks had a 71% end of treatment response. However, follow-up showed no biochemical or virological improvement. Survival was increased and further observations of this important group are needed.

☆ This meeting was held in Madrid between 27 and 29 January 2000 under the Chairmanship of Vincente Carreno.

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3. Hepatitis B virus

3.1. Mechanisms of chronicity

Anexin V is a phospholipid-based hepatocyte surface protein, which is involved in the binding of the HBV to the hepatocyte. It is concerned particularly in the binding of small HBsAg (P.S.H. Yap, Leuven). Its identification opens possibilities in the therapy of hepatitis B by preventing the virus entering the hepatocyte.

D.R. Milich (La Jolla) investigated the T-helper response in acute and chronic HBV infection. This determines reaction to the virus and whether chronicity develops. He used T-cell specific transgenic mice and identified auto-reactive CD4 cells, which polarise the Th1 and Th2 responses.

M. Thursz (London) has investigated the genetic features influencing the outcome of HBV infection. He has identified specific HLA subtypes and related the outcome to MHC class 2 polymorphisms.

Core hepatitis B mutants have been described from most of the Mediterranean area, Japan, Israel and Hong Kong. They are responsible for late state re-activation in chronic hepatitis, cirrhosis and liver cancer. This late stage is associated with marked fluctuations in ALT and HBV DNA (S.J. Hadzyiannis, Athens).

3.2. Lamivudine

This nucleoside analogue is in general use for the treatment of HIV infections. It is safe and relatively inexpensive. It is now the treatment of choice for chronic HBV infections. Unfortunately, mutants of the virus develop in the later stages of treatment and the significance of these is under active investigation.

3.2.1. Long-term therapy in e antigen negative patients

E. Dimou and co-workers (Athens) followed 25 patients with e antigen negative chronic hepatitis B over a mean period of 2.3 years. They were probably all sufferers from the pre-core mutant. The initial biochemical response was 96% and the virological 64%. Treatment of mutants with clearance of HBV DNA by PCR was achieved in 20% for the first 6 months of therapy. However, sustained response rates tended to decrease with time. Reactions develop with HBV mutants and ALT increases even exceeded the baseline levels. These very high ALT levels are not associated with clinical features and can only be treated expectantly. Famcyclovir therapy may be useful.

3.2.2. Decompensated hepatitis B virus cirrhosis

Decompensated cirrhosis due to hepatitis B carries a dreadful prognosis with a 20% survival at 5 years once ascites has developed. J. Heathcote (Toronto) had treated 35 such patients with lamivudine. Twenty were alive 2 years later, they had improved markedly in their Child's score, albumin had risen and INR had fallen. Three developed YMDD polymerase HBV mutations. The clinical improvement in these patients made them better risk for subsequent liver transplantation if indicated. Lamivudine was better tolerated than interferon.

3.3. Combination therapy for chronic hepatitis B virus infection

V. Carreno (Madrid) had used combined interferon/ribavirin therapy for chronic hepatitis B. He noted that interferon alone produced a 25% sustained response, and lamivudine alone a 11% response after 52 weeks, but mutations developed in 20–30%.

He had treated 24 interferon non-responders with additional ribavirin. HBV DNA fell at 6 months: 50% had cleared HBV. ALT normalised. There was no loss of HBsAg. Hepatic histology showed improved appearances. One patient had an exacerbation. The development of pre-core mutants was the same whether the response was sustained or not. Those responding showed a proliferative cellular response in liver histology and an improved Th1 immunological profile.

S.W. Schalm and the Eurohep group (Rotterdam) had combined lamivudine with interferon in a 48 weeks course. A sustained antiviral effect was seen in 29%, HBV DNA becoming negative and HBeAb appearing. The role of enhanced immunity relating to the interferon was discussed. Du-

ration of treatment was also undecided and might have to be life long. Interferon may block the re-infection hepatitis, which has been related to lamivudine.

4. Hepatitis C virus

Hepatitis C virus (HCV) is the major cause of chronic liver disease, cirrhosis and hepatocellular carcinoma in most countries of the world. It affects approximately 170 million individuals world-wide. It is more common than HIV. It exists within the individual as a mixture of closely related, yet heterogeneous, viral sequences known as quasi-species. It shows considerable heterogeneity, particularly in the viral envelope. Variants of HCV collected from different parts of the world can be divided into six main genotypes. There are at least 50 more closely related variants. Genotype 1b is particularly serious, as is genotype 4.

S.R. Lemon (Galveston) had developed an infectious molecular clone of genotype 1b of the hepatitis C virus. This came from the 3 NTR region. The clone was related to increased viraemia, but not to severity of liver damage.

M.U. Mondelli (Pavia) investigated the role of immune responses in the selection of HCV variants. He had identified hypervariable region 1 (HVR1) and E 2 glycoprotein as increasing the immune response in genotype 2. He described an antibody-driven variant selection related to HVR1. Unfortunately he had not investigated lymphocytes responses, which are probably more important than the antibody-related ones.

W. Sallberg and co-workers (Huddinge) had measured the T-cell responses to the hepatitis C virus NS3 protein, which was largely conserved and was a specific T-cell activator. It proved immunogenic in mice and raised the possibility of an ultimate development of a HCV vaccine.

The NS5A protein of HCV was investigated by J.M. Pawlotsky (Creiteil). This is conserved and phosphorylated and is a transcription activation domain. In patients, who are genotype 1, it is an interferon-alpha sensitive area, but not in genotype 3. NS5A region interacts with protein kinase (PKR). Identification of the NS5A domain raises the possibility of antiviral therapy and of the production of a vaccine.

Hepatic fatty change was described by Negro (Geneva) and this was more marked than usually associated with HCV infections. It returned in the donor liver after transplantation. It seems to be virus-related as it is unaffected by ribavirin therapy, but improves with interferon-alpha. The clinical significance is uncertain.

4.1. Therapy of chronic hepatitis C virus

Factors predicting response include age, gender, alcohol consumption, genotype, viral load and the extent of quasi-species.

There was much discussion concerning the management of patients carrying HCV, but with persistently normal ALT and only minor liver biopsy changes. The EASL hepatitis C Consensus meeting in Paris, held in the spring of 1999 concluded that such patients should not receive therapy, but should be followed closely. At this Madrid meeting, N.C. Tassopoulos (Athens) had given 5 million units interferon three times a week for 6 months with a follow-up of 1 year. A sustained antiviral effect was shown in 21.6 versus 5.1% control patients. In contrast, L. Castera and co-workers (Creteil) found results of treatment of such patients did not differ from those observed in those with histologically more severe disease. Moreover, the evolution of hepatic histology did not differ between treated and untreated groups.

The decision to treat patients with HCV depends on the possibility that fibrosis will increase. This predicts the development of cirrhosis and ultimately of hepatocellular cancer. E. Marcellin (Clichy) had studied the natural progression of fibrosis by serial biopsies. After 3 years, the necro inflammatory activity was similar. Fibrosis in 50% was stable, only one patient showed significant increases. He recommended follow-up of those with initial mild fibrosis and if possible, a second biopsy at 3 years to determine whether the patient was going to progress or would remain stable. Prediction of progressive fibrosis is impossible without liver biopsy.

T. Poynard (Paris) had studied the effect of combined interferon/ribavirin therapy on the progression of fibrosis. In those showing a sustained response, fibrosis progression was reduced, and even in non-responders the progression was halted. Consequently, Poynard believed that therapy should be given even in those, who do not show a sustained response.

4.2. Therapeutic strategies for chronic hepatitis C virus

Classical treatment is 3 million units interferon three times a week for 6 months. The sustained antiviral and biochemical response 6 months after stopping therapy is 10–30%. The estimated half-life of free HCV virions is 2.7 h (10/virions/day). Interferon has a short serum half-life, disappearing from blood between the dose administrations. The troughs between doses allow the virus to recover and so facilitate the emergence of resistant forms.

Treatment based on relatively low doses of interferon administered three times a week is associated with viral replication rebounds at post-injection day followed by a subsequent HCV resistance. There are various strategies to reduce this effect. The interferon may be combined with ribavirin. Therapy should continue for 1 year, particularly in those who are genotype 1 or 4. The sustained antiviral response is 36%.

Another strategy is to use large daily doses of intravenous interferon. D. Vandelli and co-workers (Modena) had used 6 million units interferon intravenously daily to patients, who were non-responsive to prior therapy. Six million units daily were given for 1 month followed by subcutaneous 6 million units every other day for 12 months. The end of treatment response was HCV RNA negative in 23 patients (74%). The trial is ongoing.

O. Weiland (Huddinge) had used large dose intravenous interferon induction therapy in patients non-responsive to interferon. He recommended 10 million units daily for 1 month, followed by combination standard interferon ribavirin management.

Pegylated interferon (PEG INF) is interferon covalently bound to a large branched polyethylene glycoprotein. It provides sustained drug exposure thus eliminating large peak-to-trough fluctuations. Sustained serum concentrations last more than one full week (168 h). It has the advantage of convenient once weekly dosing.

M.L. Shiffman has shown that PEG IFN results in a 36% sustained response in patients with chronic hepatitis C compared with 41% for the ribavirin/interferon combination therapy.

J. Heathcote (Toronto) had used PEG 1FN to treat patients with compensated cirrhosis due to HCV. One hundred and eight mcg were given and results compared to thrice weekly interferon. Thirty percent showed a sustained response compared with 15% of those randomised to standard interferon. Side effects include falls in absolute neutrophil count and platelets, which may lead to dose modification.

G.R. Foster (London) reported liver biopsy findings from patients receiving PEG IFN. Four percent showed improved liver histology particularly in inflammatory activity. Fibrosis showed mild reduction.

B. Soriano (Madrid) had given IFN therapy to patients with HIV/HCV co-infection. HIV accelerates the progression of HCV to cirrhosis. The hepatitis C infection is often fatal in HIV infected patients. Interferon reduces the lymphocyte CD4 count. Nevertheless, sustained results are obtained, when interferon is given to HIV sufferers.

S. Zeuzem (Frankfurt) had used interleukin 12 in the treatment of chronic hepatitis B and C. This promotes the Th1 immunological response. However, once weekly administration led to only transient rises in IL12 and Th1 cytokines. Other studies are necessary.

4.3. Conclusions: hepatitis C virus infection

Current therapies with standard interferon with or without ribavirin offer a 20–50% chance of a sustained response virologically and biochemically. PEG INF will probably replace the standard drug.

The cost and availability makes all these treatments out of reach of sufferers world-wide. The impact of HCV (especially of hepatocellular cancer) on world health in the 21st century is awesome and at present insoluble.

5. Hepatocellular cancer

M. Colombo (Milan) discussed the natural history. Cancer develops usually on the basis of an underlying cirrhosis and its probability depends on the extent of hepatocyte proliferation. Proliferative cell nuclear antigen (PCNA-1), performed on liver biopsies, may be used as a predictor of hepatocellular cancer and hence as a screening tool.

Multicentric type must be distinguished from the intra-hepatic metastatic type, which has a worse prognosis.

The doubling time for tumour is 6 months and this is the period used between screening with ultrasound and alpha-fetoprotein.

A patient with a 5 cm tumour and grade Child's A or B has a 50% chance of being alive at 5 years. The prognosis for HCV-related HCC is probably better than for HBV.

Death is usually due to tumour progression, hence any local method of reducing tumour size (such as alcohol injection) can be useful although not curative.

P. Benvegnu and A. Alberti (Padua) discussed the patterns of hepatocellular carcinoma development. They noted the marked recent increase, particularly in women and in the HCV infected. They had followed up 400 cirrhotic patients. Development of HCC was related to the patient's age and the duration of infection. They distinguished the nodular from the infiltrative types. The nodular affected older people with longstanding disease, often HCV infected. The infiltrative was more serious and largely involved the HBV patients.

The role of previous antiviral, especially interferon, in preventing the development of HCC is undecided. In the case of HBV, it remains uncertain, in the case of HCV prior therapy is probably beneficial, but this must be confirmed by longer follow-up.