Hepatitis B and C

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HBV

The Hepatitis B virus (HBV) genome has a circular, partially double stranded DNA. It belongs to the hepadnaviridae family of viruses and replicates within infected liver cells. The HBV is not a cytotoxic virus. Viral nucleocapsid antigens, HBeAg and/or HBcAg, expressed with HLA class I antigens on the hepatocytes plasma membrane are believed to be the major targets for activated cytotoxic T cells. The elimination of infected cells seems to be dependent on cellular immune responses and it is the immune response that causes the hepatitis. Host factors, mainly the immune system response, and intrinsic viral factors might play an important role in the viral escape from elimination in chronic disease. HBeAg seems to be important for the induction of T-cell tolerance to nucleocapsid antigens co-expressed with the major histocompatibility complex at the hepatocyte surface. HBV, by secreting the protein e, induces immunological tolerance in the host and causes chronic infection in 5-10% of acute hepatitis B cases. HBV is transmitted by the exchange of blood or body fluids. Many cases of acute hepatitis B occur sporadically with no known source and studies have shown that prior unrecognised infection is common.

Acute HBV infection may be differentiated from other causes of acute hepatitis by the assay of specific immunoglobulin M antibodies. A high titer of IgM antibody response to hepatitis B core antigen (anti-HBc IgM) is considered to be diagnostic of acute hepatitis B. A

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negative anti-HBc IgM test result in patients with acute or fulminant HBsAg positive or negative hepatitis points to a factor other than HBV as the cause of the liver damage.

However, IgM anti-HBc has been detected in many chronic carriers of HBsAg. A high cutoff can distinguish most of the time between acute and chronic HBV hepatitis. The distinction between chronic and acute HBV infection can be problematic if only qualitative results are obtained. Only quantitation of anti-HBc IgM can allow distinction of recent and chronic HBV infection. Quantitation of anti-HBc IgM was tried in undiluted sera in one run by applying the IMx analyser. Serum anti-HBc IgM levels have been found to correlate positively with HBV-induced chronic liver-cell damage. Remissions in liver damage are accompanied by decreases in levels of anti-HBc IgM. Testing of sequential serum specimens seems to be indicated for the follow-up of patients with chronic HBV infection.

Chronic infection is defined as the presence of hepatitis B for 6 months or more.

People with and chronic hepatitis infection are at risk of liver damage 20-30% of those will progress to cirrhosis. The natural history of chronic hepatitis B (HBV) infection can be divided mainly into three phases: a) a high replicative (immune tolerant) HBeAg positive phase, histologically and clinically mild, with HBcAg immunohistological distribution predominantly in the nuclei, with high levels of serum HBV-DNA (by dot-blot), b) the low replicative (immune clearance) phase which is characterized by acute exacerbations of transaminases, nuclear and cytoplasmic HBcAg expression, decreasing levels of serum HBV-DNA and HBeAg clearance with or without anti-HBe and c) the non-replicative HBeAg negative phase, during which there is no hepatitis activity, no HBcAg expression, but a potency for viral (wild or mutated strains) reactivation.

In general, HBeAg, which circulates in the serum, is a marker of HBV replication and infectivity and its presence is associated with active liver disease. HBeAg to anti-HBe seroconversion is usually associated with cessation of HBV replication and clinical and histological remission of chronic hepatitis. However, it has been demonstrated in various parts of the world that viral replication with continuous viremia and severe liver damage with cytoplasmic HBcAg expression exist in HBeAg negative patients. These patients are more frequently seen in the Far East and in the Mediterranean basin where they outnumber the HBeAg positive cases. In HBeAg negative patients with active liver disease, chronic hepatitis is often rapidly progressive with fluctuating HBV-DNA levels and transaminases. Moreover, these patients have a relatively higher risk of development of hepatocellular carcinoma.

Anti-HBe positive chronic active hepatitis associated with pre-core HBV mutants is particularly common in Greece and Italy but is found in all parts of the world. It appears to represent a stage of chronic HBV infection which follows the HBeAg positive phase, rather than a disease entity distinct from the classical HBeAg positive chronic active hepatitis which is associated with non-mutated wild type HBV. This stage seems to occur rather late in the course of chronic HBV infection after HBeAg seronversion. However, a preceding HBeAg positive phase is not always seen. Liver enzyme activity indicated by ALT ant AST levels, is of the same magnitude as in HBeAg positive disease but seems to be more persistent and sustained. Spontaneous remissions are infrequent. Fluctuating enzyme activity resulting in an erratic pattern of ALT activity has been observed in about half the patients studied at our institute with a follow-up of two or more years. The level of serum HBV DNA is lower than in the HBeAg positive group and fluctuating levels are observed. Increases in serum HBV DNA and HBcAg in the liver usually precede flare-ups of enzyme activity during which serum HBV DNA sometimes drops dramatically and may even become undetectable. A progressive type of chronic liver disease with severe histology usually ensues and is frequently accompanied by well-established cirrhosis. Progression to hepatocellular carcinoma also occurs quite frequently.

These pre-core mutated strains are selected from the wild type virus around the time of seroconversion from HBeAg to anti-HBe in acute and chronic infection under the host immune selection pressure. These mutations, while prohibiting the synthesis of the protein e, still permit viral replication.[5]

HBV has a small genome and it makes very efficient use of its nucleic acids. The open reading frames are highly conserved, even between different hepadnaviruses. Yet, the potential for significant changes is also present. The most important selection pressure affecting HBV seems to be the immune response. G to A mutation in the pre-core region (mu-1896) of the HBV has been detected which results in a novel ATG translation stop codon that does not impair viral replication or infectivity but which prevents the production of secretory HBeAg peptide and consequently results in the non-appearance of HBeAg in the serum. Patients in whom the pre-core mutated strain becomes dominant usually have a second pre-core mutation (mu1899). The anti-HBe/HBV DNA-positive chronic hepatitis due to infection with a pre-core HBV mutant is a severe disease with immunologically induced liver cell damage carrying a bad prognosis and frequent progression to hepatocellular carcinoma. Precore mutations also arise during acute HBV infection and have been detected in association with fulminant and non-fulminant acute hepatitis. The pre-core mutated HBV seems to be particularly resistant to host immune mechanisms. This and/or other concomitant HBV mutations arising in the course of HBV infection may confer resistance to the virus against an immune attack by the host.

An HBV mutant unable to synthesize and secrete e protein because of a gouanidine (G) to adenosine (A) mutation at nucleotide 1896, creating a stop codon (TAG), was described (mu-1896). An additional mutation (G to A) at position 1899 can follow the first one (mu 1896/1899). These pre-core mutated strains are selected from the wild type virus around the time of seroconversion from HBeAg to anti-HBe in acute and chronic infection. The precore HBV mutant is identified by its phenotypic serological pattern in which HBsAg positive active liver disease is accompanied by negative tests for HBeAg in the presence of active HBV replication signaled by the detection of HBV DNA. It is more common in the Mediteranean basin. Clinical studies have demonstrated that the precore mutant is transmissible as a stable strain and is associated with an increased risk of fulminant hepatitis or rapidly progressive chronic hepatitis B. It is the host immune selection pressure which allows the emergence of the precore mutants. Other mutations in the pre-core/core region of the HBV genome have also described, including loss of the initial start codon, nucleotide insertions or deletion or a frame shift. These mutations, while prohibiting the synthesis of the protein e, still permit viral replication. Pre-core mutations, by preventing protein e production, might alter

the pathogenesis of chronic HBV infection. It has been suggested that HBeAg minus HBV strains might escape the immune system causing persisted disease. Those hepatocytes infected with precore mutated strains do not display on their surface HBeAg epitope and survive the immune elimination process. Moreover, HBeAg may distract the immune system from eliminating infected hepatocytes by down-regulating of the T-cells. Initially, it was thought that modification of HBV pathogeneity due to point-mutations in the pre-core region may be even more profound, resulting in direct cytotoxic effect of the pre-core peptide which is produced as a concequence of the novel stopo-codon. Liver-cell damage in HBeAg negative patients with active disease exhibits features of immunologically induced tissue injury. Increases in serun HBV-DNA usually precedes flare-ups of transaminase activity during which serum HBV-DNA drops dramatically. An anamnestic anti-HBc IgM response usually follows. Further studies will elucidate the mechanisms responsible for the liver damage.

Extrahepatic manifestations reflecting an immune-complex mediated serum sickness-like syndrome are seen in fewer than 10% of patients with acute hepatitis B. Onset of the serum sickness-like typically occurs during the prodromal phase and symptoms recede with the development of jaundice. In some patients with chronic hepatitis B, serologic (HBsAg and HBeAg) and biochemical features of persistent hepatitis B virus (HBV) infection (increased aminotransferases) are accompanied by signs of generalised vasculitis of medium and small arteries (polyarteritis nodosa) or membranous (most common), mesangiocapillary or mesangial proliferative glomerulonephritis. Spontaneous recovery due to seroconversion (HBeAg to anti-HBe) has been reported and a slow relentless progressive course is observed in one third of cases.

20 - 40% of patients with chronic hepatitis B develop cirrhosis or hepatocellular carcinoma. Management of chronic hepatitis B depends on the level of virus replication. There is a need for treatment during the highly viraemic phases of the disease. Bed rest is not helpful. Physical fitness is encouraged. Diet should be normal. Alcohol excess to be avoided. The majority of patients lead normal lives. No treatment is indicated for asymptomatic non replicative hepatitis B "carriers". The treatment options of therapy are to use IFN for antiviral and immunomodulating activity to increase the immune response and to use antiviral drugs (nucleoside analogues). Immunosuppressives are not helpful and potentially hazardous. Treatment goals of any chronic viral hepatitis are to relieve symptoms, to ameliorate biochemistries, to improve histology, to change the natural course of the disease, to increase survival and finally, if possible, to cure[1].

The initial aims of therapy of chronic hepatitis B are the suppression and possibly the sustained loss of viral replication and this can be achieved by negative HBV DNA and seroconversion HbeAg to anti-HBe, the long-term improvement of histology with the corresponding normalisation of ALT levels, reduction in the diminishment of infectivity. The ultimate aims of therapy are the eradication of the virus as this can be achieved by negative HBV DNA in the liver and the seroconversion from HbsAg to anti-HBs, to prevent the development of cirrhosis and hepatocellular carcinoma and to improve survival.

Interferon-alpha (IFN-α) recombinant or lymphoblastoid, has antiviral and immunoregulatory activities and pushes the balance towards the host immune system. IFN-a increases the helper/suppressor ration, induces the expression of MHC class I antigen along with viral antigen on the hepatocyte membrane, stimulates the NK response and has a direct antiviral action by interfering in the replication. Nevertheless, IFN-α therapy is expensive, poorly tolerated, limited in effectiveness especially in immunosuppressed patients and contraindicated in decompensated cirrhosis. Side effects occur early: (influenza-like syndrome-fatigue, muscle pain, headache, nausea, diarrhea, weight loss, hair loss), or late: (depression, infections, autoimmune diseases, myelotoxicity). They are usually reversible.

Randomized prospective controlled trials have established that HBeAg positive patients respond to antiviral therapy with IFN-α. Definition of complete response is the loss of HBV DNA, the loss of HBeAg and normal ALT[2]. The optimal regimen is 4,5-9 MU thrice weekly for 4-6 months. The response rate (seroconversion HBeAg to anti-HBe) is approximately 40%. Liver histology improves and 10-20% of patients lose HBsAg[3]. Seroconversion is accompanied by an acute hepatitis -like elevation in ALT activity which is believed to represent an immunostimulatory effect of IFN-α. The likehood of losing HBsAg increases when the duration of the disease is less than 2 years. The main criteria for successful therapy are the persistently elevated ALT levels (>2X), HBV-DNA < 100 pg/ml, active histology, the well compensated disease and no other complicating immunosuppressive illnesses. IFN-a can be given to children with the same reults. However, a high percentage of patients don't respond to IFN-α treatment or relapse after stop

of therapy. In addition, decompensated cirrhotics and immunocompromised transplanted patients are not treated with IFN-α.

Treatment of chronic HBV infection caused by the pre-core mutated strain with a-interferon, 3-5 MU thrice weekly for 6-12 months, is accompanied by a suppression of HBV repliication and a return of ALT to normal values in approximately two-thirds of cases. However, relapses occur frequently[1]. Despite the high relapse rate after discontinuation of therapy, at least one fourth of treated patients remain in sustained remission. The frequency of long-term remissions in IFN-α treated anti-HBe/HBV DNA positive patients is comparable to that in other forms of chronic viral hepatitis.

Decompensated cirrhotics and immunocompromised patients are not treated with IFN-α. HBV, although a DNA virus, replicates via a pre-genomic RNA and by reverse transcription, mimicking the retroviruses and can be inhibited by nucleoside analogs like in HIV infection. Several oral, second-generation, nucleoside analogues (which encompasses lamivudine, famciclovir, ganciclovir, adefovir dipivoxil and lobucavir) have been developed with potent activity against HBV, acting on the reverse transcriptese/polymerase gene as chain terminators. They are reverse transcriptase/DNA polymerase inhibitors and were first administered to patients with Human Immunodeficiency Virus, Varizzella-Zoster Virus and cytomegalovirus infection respectively. They are widely tried in clinical phase III studies. These drugs are used mainly for patients resistant to IFN-α, with decompensated cirrhosis or pre- and post-transplantation. The drugs are safe even when they are given long term. They are taken oraly and they don't affect the immune system. The development of resistance due to viral mutations mainly observed in the immunosuppressed individuals is worring. The optimal duration of the treatment is still unclear since most of the patients relapse after discontinuation.

Lamivudine is a nucleoside analog with potent antiviral effects against hepatitis B. Lamivudine is used in post transplant patient to prevent reinfection of the graft, decrease the necroimflammatory activity and prevented the development of fibrosis. 100 mg are enough for long term therapy. Famciclovir therapy may lead to 3 mutation at the B region of polymerase gene resulting in amino-acid change. The HBV DNA viraemia disappeared but relapsed after discontinuation. Chronic infection is sustained by multiple copies of covalently closed sircular DNA in the nucleus which act as a template for viral replication.

There is a need for a long therapy. In a comparisons of viral dynamics kinetics of HBV and HIV, the total daily production of plasma virus is higher in HBV carriers and the half life of virus producing cells is much shorter in HIV. The minimun half life of infected cells may exceed 100 days.

Lamivudine, in single daily doses of 100 mg results in inhibition of HBV DNA levels in more than 80% of HBeAg positive patients and improvement in serum aminotransferases and hepatic histology in the majority of patients. Lamivudine is equally effective in HBeAg negative highly viraemic patients harboring the precore mutated HBV, in immunosuppressed patients and as a prophylaxis or treatment of HBV reinfection before or after orthotopic liver transplantation. When lamivudine is stopped, however, most patients relapse. The shortcomings of long-term therapy have been the development of viral resistance in up to one-quarter of patients within a year and up to 70% within 4 years and a higher percentage with more prolonged therapy due to the development of a point mutation within the YMDD motif of the HBV DNA-polymerase. In conclusion, future successful approaches of therapy of chronic hepatitis B may well be long-term combination therapy of nucleoside analogues (lamivudine, ganciclovir, adefovir dipivoxil, entecavir etc) with or without several immunomodulating (like IFN-a or other cytokines) agents.

For patients with end-stage chronic hepatitis B liver transplantation is the only potential lifesaving intervention. Reinfection of the new liver is universal. An unpredictable proportion of patients experience severe hepatitis B related liver injury. Reinfection is related to the presence of HBV replication prior to transplantation. Long-term passive anti-HBs immunoprophylaxis and nucleoside analogues with antiviral activity have been used to prevent reinfection of the graft. The frequnecy of HBV reccurence is higher in HBV cirrhosis (<30%) than in HBV-HDV cirrhosis (13%) and in fulminant HBV hepatitis (0%).

To prevent lived fibrosis long-term suppression of HBV is needed. To prevent liver cancer initiaion of treatment before viral DNA has been integrated into the majority of hepatocytes is likely to be necessary. To achieve these ends Lamivudine is a safe drag siutable for long-term use. New types of drug that might suppress lamivudine resistant strains may be required. Prophylaxis against the latter possibility can be provided by anti-hepatitis B virus (HBV), immunoglobulin and synthetic nucleosides.

In conclusion, antiviral nucleoside analogs represent a real improvement in the treatment of chronic hepatitis B therapy and their use is going to be widely applied in the near future.

Many new therapeutic strategies are the subject of experimental and/or clinical trials. Immunomodulatory approaches, aim at the improvement of the immune responsiveness of the host, with agents like thymosine-a, cytokines a.o., passive transfer of immunity or therapeutic vaccines. There are three types of therapeutic vaccines: vaccine containing viral proteins, lipopeptide CTL epitope vaccine and DNA vaccine. Gene therapy includes therapeutic stagies directed against the virus itself try to block the viral DNA expression at different levels. In conclusion there is an extensive experience today with new emerging agents for the therapy of chronic hepatitis B. Unfortunately none of them is absolutely efficient, most of them are still experimental and their safety has yet to be proved. The future challenge for chronic hepatitis B treatment seems to be the combination therapy.[8,9]

HCV

The cloning and sequencing of hepatitis C virus (HCV) and the development of serological assays to detect antibodies to epitopes of both structural and non-structural regions of the viral genome have been major breakthroughs in the search for the agent of non-A, non-B (NANB) hepatitis. HCV is the major cause of post-transfusion, community-aquired and cryptogenic NANB hepatitis. HCV is a 9401 base, lipid-enveloped, single-stranded, polyadenylated RNA virus with one reading frame and an unknown physical structure. The viral genome encodes for a 3011 amino acids polyprotein. HCV is distantly related to the family Flaviviridae. The structure of the HCV RNA and the encoded polyprotein has properties similar to flaviviruses and pestiviruses. Genetic heterogeneity characterises the virus. Comparison of the nucleic acid sequences from different isolates of HCV have shown considerable variability throughout the genome but mostly at the envelope region where the immune pressure exists. The virus is global in distribution with a prevalence of 0,3 to 1,5%. 500.000 persons worldwide appear to have been infected with HCV. Only 25% of infected persons give a history of blood transfusion. Body secretions do not seem to contain the virus. Heterosexual spread is possible but sexual and house hold contact rarely lead to anti-HCV seroconversion. Perinatal spread does not seem to occur frequently. The mechanism of transmission of HCV in 50% of infected patients as well as those used by the virus to escape the host's immune elimination remain unknown. HCV is much less infectious than HBV and HIV and large quantities of infective material seems to be needed to transmit the virus. Hepatic histology shows a characteristic, albeit not diagnostic, picture with prominent lymphoid follicles. Diagnosis relies on anti-HCV detection by a second or a third generation ELISA assays containing structural and non-structural antigens. Antigens corresponding to the structural components of the virus (C22) are more sensitive and specific for the early detection of viral antibodies than those to non-structural epitopes (C100-3, 5-1-1, C33, NS5). Second and third generation assays have a sensitivity of 95% to detect HCV infection. A comfirmatory radioimmunoblot assay (RIBA) is needed to exclude false-positive results. Anti-HCV can be regarded as an indirect marker of viral replication and infectivity. Adding the anti-HCV testing by the most sensitive assay to the blood donor-screening process has substantially diminished but not eliminated the risk of post-transfusion hepatitis. HCV-RNA detection by the "nested" polymerase chain reaction after reverse transcription (RT/PCR) is the gold standard for diagnosis and following the course of disease and therapy. The method however is unsuitable for diagnostic laboratories because of the complexities and pitfalls of cDNA synthesis and "nested" PCR amplification. Although acute HCV infection usually evolves as a subclinical or mild hepatitis, the condition may in some cases have a fulminant course. 30% of the patients make a complete recovery and the remainder progress to chronic liver disease. HCV causes cirrhosis in 20% of chronic hepatitis cases and hepatocellular carcinoma in a substantial number of patients. Autoantibodies can be found in some patients with chronic HCV infection due to cross-recognition of viral and host epitopes. Antibodies against a host-derived protein (anti-GOR) have been proposed for early diagnosis of acute HCV hepatitis. There is a strong association of liver cirrhosis due to HCV infection and the development of hepatocellular carcinoma. Knowledge of the natural history of chronic hepatitis C and its sequelae is not yet complete. The onset of the disease is undetected in the majority of cases, since less than 10% of acute cases are icteric. Fulminant hepatitis C is very rare. About 85% of patients with acute HCV hepatitis develop chronic hepatitis and 20-30% of these eventually develop cirrhosis with the associated risk of hepatocellular carcinoma (HCC). The factors that lead to chronicity in hepatitis C are not well defined. Age, male gender, immunodeficiency, high viral load and high HCV RNA titer are thought to be important for chronic progression. Chronic hepatitis C seems to be an indolent, slowly progressive dis-

ease, usually accompanied by little if any clinical evidence of illness or death during the first two or three decades after initial infection. Spontaneous regression of chronic HCV infection is very rare (<2%). If progression occurs, it usually requires the passage of 3 to 4 decades before end-stage liver disease evolves. The yearly rate of HCC development in HCV cirrhosis is approximately 1-3%. Serum ALT levels tend to fluctuate over months or years. The appearance of jaundice characterises the advanced disease. It is most likely that both viral and host factors contibute to HCV persistence and progression. Old age at the time of infection; duration of infection; concomitant alcohol abuse; concurrent HBV and HIV infection and the immunocompetence of the infected person are aggravating factors causing more rapid progression of the disease. It has been suggested that HLA class II alleles and haplotypes may be associated with an accelerated or slower progression of chronic hepatitis C towards cirrhosis and eventually to HCC. The degree of hepatic inflammation as assesed by liver biopsy may be a predictor of progression; the stage of hepatic fibrosis may be an even better predictor. The importance of viral load (high serum HCV RNA titer), specific HCV genotypes and the development and complexity of closely related HCV quasispecies remains uncertain. Predicting progression in the individual patient is not yet possible. HCV has been proposed to be a co-factor in the pathogenesis of cirrhosis in patients with chronic alcoholism. HCV is the main cause of acute and chronic liver disease in hemodialysis patients and of chronic liver disease in kidney allograft recipients. Nearly all the recipients of organs from anti-HCV positive donors become infected with HCV but chronic HCV infection does not influence the survival of the allograft nor that of the patients. HCV is associated with membranoproliferative glomerulonephritits, as is the hepatitis B virus, which can be related to deposition within glomeruli of immune complexes. Chronic HCV infection can be a cause of essential mixed cryoglobulinaemia type II which is frequently associated with chronic liver disease. The therapeutic use of interferon can be of some help in chronic HCV infection. A 6-12 month course of low-dose (3-6 MU) a-interferon therapy is effective in controlling the disease activity in about 50% of the patients, although relapse after the cessation of treatment is common. Sustained remission occurs in 25% of treated patients. Hepatic transplantation is followed by reinfection of the graft with the virus probably due to extrahepatic replication of the virus in the monocytes.

Interferon-α (IFN-α) in a dose of 3MU, thrice weekly, for 12 months, has a limited (around 20%), sustained virologic response in naive patients with chronic hepatitis C. The aim of this review is to discuss therapy options of patients with hepatitis C virus who relapsed after a previous virologic response to treatment. In patients who have relapsed after IFN-α monotherapy two option can be considered: to treat with a combination of IFN-α 3MU thrice weekly and ribavirin 1000-1200mg daily for 6 months if there are no contraindications to ribavirin, or to treat with a high dose (more than 3MU or 9μg thrice weekly) of IFN-α for 12 months. In both options, HCV RNA should be checked after 3 months and therapy should be discontinued if HCV RNA remains positive. The above retreatment gives a 50% general sustained viral response. Histologic improvement occurs in nearly two thirds of patients retreated with combination therapy and is most pronounced in those who lose serum HCV RNA. Viral genotype and HCV RNA levels influence the rate of response to retreatment. The sustained viral response in genotype 1 patients is 29% using combination therapy for 6 months and is thought to be better with longer therapy. The presence of fibrosis or cirrhosis does not appear to decrease the response to combination therapy. 6% to 9% of patients discontinue combination therapy because of an adverse event. In conclusion, IFN-a is used in combination with ribavirin or in high doses in patients who relapsed after initial treatment with IFN-α. For patients who relapse after combinantion therapy, high dose IFN-α or combination of pegylated IFN-α and ribavirin, with or without induction therapy, can possibly offer a sustained virologic response.

Patients with chronic hepatitis C who are considered as belonging to "special" groups are numerous and possibly represent the majority. These patients have differences in the natural history of the disease and/or the response to therapy. Patients with HCV viremia and normal aminotransferase levels are asymptomatic and usually have mild liver histology. For the time being, they should be followed but not treated. Co-infections with HCV and HBV are frequent due to common routes of transmission. Co-infection is associated with more severe histological changes, increased hepatocarcinogenicity, poor response to interferon-α (IFN-α) therapy and high relapse rate. Haemodialyzed patients develop HCV cirrhosis quite rapidly. In these patients, ribavirin is containdicated but IFN-α therapy is well tolerated and is as efficient as in the general population. HCV is a major cause of chronic hepatitis post-renal transplantation and contributes to the long-term (more than 20 years) morbidity and mortality of renal transplant recipients. IFN-α therapy of renal allograft recipients is contraindicated

because it gives very poor results and can lead to chronic rejection. Thus, patients should be treated before renal transpalntation. IFN-α therapy represents a useful therapeutic option for patients with transfusion-dependent thalassemia, mild or moderate secondary hemochromatosis and chronic hepatitis C. Haemophilia patients with chronic hepatitis C have an icreased morbidity and mortality related to a possible co-infection with HIV. Therapy is effective but development of a factor VIII inhibitor can occur. Alcohol consumption induces an increase in HCV RNA vireamia, a more rapid and severe clinical and histologic evolution of chronic HCV infection and may play a role in hepatocarcinogenesis. Response to therapy is decreased. Chronic HCV infection is mild in children. Co-infection of HCV with HIV is frequent due to common routes of transmission. The immunodeficiency accelerates the course of chronic hepatitis C, as vireamia and fibrosis increase. IFN-α therapy of chronic hepatitis C in HIV-positive patients with normal CD4 count can be successful. In patients transplanted for HCV cirrhosis, reinfection by the virus is universal. Short term survival is satisfactory but the long-term prognosis is questionable. IFN-α therapy in liver transplant recipients has poor antiviral effect. Preliminary results of prophylaxis against HCV recurrence after liver transplantation or treatment of recurrent hepatitis C with combination ribavirin/IFN-a are encouraging. In patients with primary hypogammaglobulinemia, rapidly progressing liver disease to liver failure may occur and response to IFN-α therapy is poor. Patients with chronic hepatitis C can develop several extrahepatic manifestations like mixed cryoglobulinemia or membranoproliferative glomerulonephritis, thrombocytopenic purpura, leucocytoclastic vasculitis, Mooren's corneal ulcer, porphyria cutanea tarda, lichen planus.

Interferon-α (IFN-α) or -β treatment of patients with acute hepatitis C is recommended. Patients with HCV viremia and normal aminotransferase levels should be followed but not treated. Patients with cirrhosis can respond to IFN-a therapy at a low response rate and can be protected from the development of hepatocellular carcinoma. Only patients with compensated or mildly decompensated cirrhosis should be given IFN-α therapy. For severe decompensated cirrhosis with manifestations of hepatic failure, liver transplantation should be offered. Patients with co-existing psychiatric illness and chronic HCV infection can be treated successfully with IFN-α with the active participation of a psychiatrist and the maintenance of psychotropic drugs. Alcohol decreases the response to IFN-a therapy. The use of IFN-a in the elderly is safe and efficient. IFN-α represents a useful therapeutic option for patients with transfusion-dependent thalassemia, mild or moderate secondary hemochromatosis and chronic hepatitis C. IFN-α is effective in haemophilia patients with chronic hepatitis C, but development of a factor VIII inhibitor can occur. Co-infections with multiple hepatitis viruses (HCV, HBV, HDV) is associated with poor response to IFN-α therapy and high relapse rate. Patients with autoimmune hepatitis can exhibit a severe worsening under IFN-α therapy. It is appropriate to try a course of corticosteroids before trying IFN-α in patients with cryptogenic hepatitis in whom a specific diagnosis cannot be made. IFN-α has been given with success in patients with several extrahepatic manifestations of chronic HCV infection like porphyria cutanea tarda, lichen planus, thrombocytopenic purpura, Mooren's corneal ulcer, leucocytoclastic vasculitis, mixed cryoglobulinemia or membranoproliferative glomerulonephritis. IFN-α therapy of HCV infection in haemodialyzed patients is well tolerated and is as efficient as in the general population. IFN-α therapy of renal allograft recipients can lead to chronic rejection. Generally speaking, immunosuppressed patients do not respond to IFN-α therapy. IFN-α therapy of chronic hepatitis C in HIV-positive patients with normal CD4 count can be successful. IFN-α therapy in liver transplant recipients has poor antiviral effect. Preliminary results of prophylaxis against HCV recurrence after liver transplantation or treatment of recurrent hepatitis C with combination ribavirin/IFN-a are encouraging. In patients with primary hypogammaglobulinemia, response to IFN-α therapy is poor.[10-16]

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