

TREATMENT OF CHRONIC HEPATITIS B, DELTA RELATED LIVER DISEASE AND NON-A NON-B HEPATITIS

Pages with reference to book, From 162 To 167

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About 60-70% of patients infected with HBV (Hepatitis B virus) do not manifest clinical illness, but rather develop antibody and permanent immunity¹. For each case of Acute Hepatitis B, there are 2 or 3 cases of subclinical infection (Figure²).

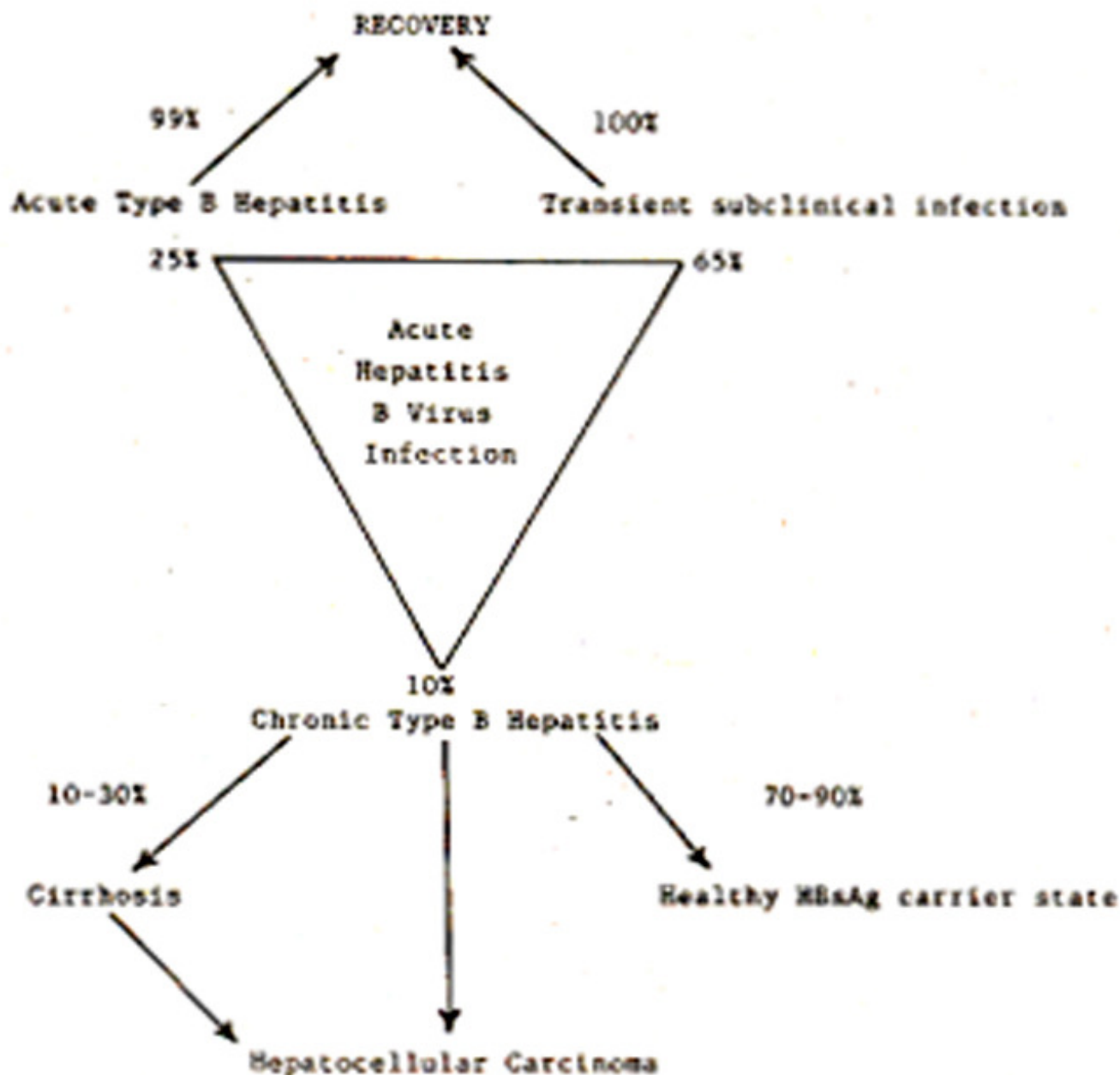


Figure: Sequelae of HBV infection in adults.

5-10% of adults infected with HBV develop HBSAg carrier state and chronic infection, manifested by

the persistence of HBSAg and virus in serum and HBV DNA in liver³. When infection with HBV occurs in childhood during first few months of life, chronic HBSAg carrier state often results⁴. There are about 200 million carriers worldwide of HBV and it is the main cause of chronic liver disease⁵. The high risk groups include homosexuals, drug addicts, patients who receive multiple blood transfusions such as hemophiliacs and uraemics in haemodialysis centres. The persistence of hepatitis B virus may lead to the development of chronic active hepatitis, cirrhosis and hepatocellular carcinoma. Chronic Active Hepatitis is progressive in 20-70% of cases⁶ and the 5 year mortality may be as high as 50%⁷. It is very important indeed to institute treatment as early as possible in all infected patients in order to reduce morbidity and mortality and also for patients with chronic persistent hepatitis which was considered as a benign disease but is now proven to progress to chronic active hepatitis and cirrhosis. Aldershville et al⁸ reported in 1982 progression in patients with chronic persistent hepatitis, to chronic active hepatitis or cirrhosis in 5 of 14 patients with continued viral replication, compared with one of nine in whom viral replication had stopped and only 2 of 28 with chronic persistent hepatitis unrelated to hepatitis B virus infection. If the hepatitis Be antigen (HBeAg) a marker of active viral replication disappears from the serum and antibody against it is found, the patient usually enters remission⁹. Some patients who have anti HBe show continued activity of infection histologically, which could be due to auto immune reaction, superimposed Delta infection or continued replication of HBV which can be detected by the presence of hepatitis B DNA (Deoxyribonucleic acid) in serum. Patients who show active disease on biopsy specimens or show hepatitis B virus DNA in the serum or, in the absence of this investigation, if HBeAg and DNA polymerase is present, may be considered for treatment¹⁰. Since integrated viral sequences may be related to the development of hepatocellular carcinoma with the passage of time, treatment ideally should also aim at preventing integration and this would necessitate treatment as early as possible. Antiviral agents and interferons, either alone or in combination have been tried in several studies to identify the best treatment prospects for this infection. Infection acquired in neonatal life differs from early childhood or adult acquired infections, in addition homosexuals often exhibit secondary immunodeficiency state due to coincidental viral infections and behave differently.

ADENINE ARABINOSIDE AND ITS MONOPHOSPHATE DERIVATIVE

Adenine arabinoside is poorly water soluble and had to be administered intravenously whereas the monophosphate derivative (AraAMP) is highly water soluble and therefore can be administered intramuscularly. Bassendine and colleagues¹¹ showed definite benefits of Adenine Arabinoside therapy in HBSAg positive chronic liver disease in a controlled study with a significant effect on the rate of seroconversion from HBeAg to antibody. Majority of patients in this study acquired infection during childhood or adult life and there was no identification of heterosexuals or homosexuals. In a randomised study Hoofnagle and associates¹² showed a significantly increased rate of FBe antigen to antibody seroconversion observed at 1-year after one month therapy but 2 to 4 responders subsequently showed reactivation of virus; but in a different study Weller et al¹³ showed a significant rate of clearance of HBeAg with no evidence of viral replication. Trepo¹⁴ reported from France in a randomised placebo controlled study that repeated courses of Ara-Amp could convert 70% of patients with HBeAg to anti HBe. Homosexuals HBV carriers are noticeably non responders to a single course of Ara Amp, whereas in the heterosexuals infected in adults life response rates upto 45% can be obtained^{15,16}. This response rate is significantly different when judged against spontaneous seroconversion rate of 5-15% reported in several studies. The action of Ara A and Ara AMP (Monophosphate Derivative) is to inhibit the synthesis of HBV nucleic acid by acting as a faulty substrate¹⁸,

thus preventing DNA transcription. The long term benefits depend on recovery of the host immune response for continued inhibition of viral replication. During the 4 week period of treatment with Ara A or Ara AMP viral replication is inhibited and on stopping therapy, the host immune response is rapidly restored which results in lysis and elimination of infected cells. This would result in elevation of transaminases which is always seen after cessation of treatment if good therapeutic response is to be achieved. Patients who are infected in neonatal life may be tolerant of the virus, and homosexual patients who have a secondary immune deficiency do not respond¹⁵.

INTERFERONS

Interferons consist of a group of secretory proteins and glycoproteins that are produced by human cells following an appropriate stimulation¹⁹. The interferons' antiviral, antiproliferative and immunomodulatory effects could be beneficial in a variety of clinical conditions. The effectiveness of alpha, beta and gamma interferons (IFN) are currently being evaluated in the treatment of chronic HBV infection. As the production of interferons is relatively easy through the recombinant DNA techniques and lymphoblastoid cell system several clinical trials are under study regarding its usefulness in a number of diseases. Greenberg and colleagues²⁰ demonstrated in 1976 the effectiveness in inhibiting viral replication by using leucocyte IFN in HBSAg positive CAH (Chronic active hepatitis). Scullard and associates²¹ showed a response of 25% in an uncontrolled study when IFN was administered for prolonged periods upto 6 months. Lymphoblastoid interferon IFN is the mixture of alpha interferons. Courses of alpha interferon given thrice weekly in doses of about 5×10^6 u/ml for 3 months favorably inhibit viral replication without significant toxicity²². The response was better in women and, unlike Adenine Arabinoside, both homosexuals as well as heterosexuals can respond. It was further noticed in other trials that Chinese were not good responders perhaps because the infection happened at birth. Further trials showed that increasing the dose or duration of treatment the response was not significantly altered^{23,24}. A hepatitis like illness occurs in some patients in the third month and is followed in most by seroconversion from I-rBeAg to anti HBe²⁵. Further work needs to be done before efficacy of Beta and Gamma interferons could be established. Kingham and associates²⁶ published in 1978 the use of human fibroblast interferon (IFNB) on hepatitis BVDNA in chronic active hepatitis claiming some success. It doesn't cause significant leukopenia which is an advantage over alpha IFN. Interferons inhibit viral protein synthesis and are immunostimulatory. It possibly enhances the host immune system which then destroys infected hepatocytes and this may result in long term improvement by inhibiting viral replication.

CLINICAL TOXICITY OF INTERFERONS

Acute symptoms include fever, chills, headache, malaise, myalgias, anorexia, fatigue and nausea. Weight loss may also be present. Other significant side effects include paresthesias, confusion, electroencephalographic abnormalities, arrhythmias, hyper and hypotension, syncope, coagulation defects, thyroid dysfunctions, electrolyte imbalances and azotemia. Taste disturbances and elevation of transaminases may be encountered. Anaemia, granulocytopenia, lymphopenia and thrombocytopenia maybe serious enough to necessitate cessation of therapy. Combination therapy with IFN and Ara A produces synergism and improvement in seroconversion but the incidence of side effects also increase significantly therefore this mode of treatment is unacceptable at present.

PREDNISONE WITHDRAWAL AND ANTI VIRAL AGENT

Scullard and associates²⁷, Rakela et al²⁸ and Weller²⁹ reported in 3 different studies that sudden withdrawal of corticosteroids may be associated with an increase in transaminases and clearance of HBV. A significant response was seen by Omata et al³⁰ when 9 of 14 patients who were treated with steroid withdrawal, followed by Ara A or IFN, responded whereas only 1 of 25 on anti-viral agents

alone showed seroconversion. The majority of these patients were thought to be infected at birth. In 1985 Perillo³¹ reported that after corticosteroid withdrawal followed by Ara-Amp, 73% of the patients treated in this fashion showed disappearance of HBV DNA polymerase from the sera. Most of these patients were adults. These two studies clearly demonstrate the efficacy of this mode of treatment on both the childhood infected or adult infected patients. However, corticosteroids withdrawal may precipitate fulminant hepatitis or hepatic decompensation specially in cirrhotics and should be avoided in this group. It has been further shown that anti-viral treatment may produce long term inhibition of viral replication, but HBS antigenemia persists³². Seroconversion from HBe antigen to antibody is beneficial as it reduces hepatic inflammatory response. If treatment is instituted within 12 to 24 months of infection, successful inhibition of viral replication may also result in clearance of HBS Ag and would prevent the development of cirrhosis and reduce the risk of development of hepatocellular carcinoma.

DELTA HEPATITIS AND ITS TREATMENT PROSPECTS

The hepatitis Delta virus is an incomplete RNA virus which produces disease in patients who are hepatitis surface antigen positive. This is a highly pathogenic virus and is responsible for both acute and chronic liver disease³³. Hepatitis Delta virus infection in patients with chronic hepatitis B is associated with a more rapid progression to cirrhosis compared with hepatitis B surface antigen carriers with chronic hepatitis and no evidence of HDV infection³⁴. The incidence of HDV infection in HBSAg positive carriers is 12.3% to 51% reported in different series from Italy^{34,35}. This high degree of prevalence of HDV certainly warrants treatment programmes to eliminate the delta virus. Lymphoblastoid human alpha interferon does inhibit delta virus replication and in some cases this effect is long lasting. Further trials need to be conducted to prove the definite efficacy of this agent.

NON-A NON-B HEPATITIS AND PROSPECTS OF ITS TREATMENT

Albert and associates reported in 1987 from Mayo Clinic the benefits of corticosteroid therapy in achieving sustained remission in severe hepatitis B surface antigen negative chronic active hepatitis³⁶. Twenty four of 66 patients (36%) sustained remission for at least 5 years (mean 11 ± 0.6 yr) after initial therapy and 42 (64%) relapsed and were retreated; of the 42 patients who relapsed 9 (21%) ultimately entered a sustained remission after retreatment. Remission for at least 5 years was possible in 33 of 66 patients (50%). The usefulness of alpha interferon in the treatment of NANB was demonstrated by Thomson and colleagues³⁷; Non-A Non-B hepatitis is commonly the cause of hepatitis following transfusion of blood and its products as HB surface antigen screening is commonly used on donated blood 5-15% of post transfusion hepatitis is caused by an unidentified virus NANB. NANB hepatitis occurs after infusion of fibrinogen, factor VIII, factor IX concentrates and cryoprecipitates and has been reported after IV gammaglobulin in hypogammaglobulinaemic patients. NANB hepatitis commonly progresses to chronic active hepatitis and cirrhosis. Steroids and acyclovir therapies have been unsuccessful in the treatment of post-transfusion hepatitis. The success that Thomson and associates have shown is quite promising in the treatment of short incubation period NANB hepatitis. Further trials will be very helpful as evidence is accumulating that NANB hepatitis is quite prevalent in our country with all its sequelae and complications.

CONCLUSION

Chronic infection as a result of neonatal exposure is the most difficult to treat. Interferons have no value, the carrier status is the result of immunologic tolerance to part of the antigenic structure of the virus. Carrier status in adults may be the result of defect in IFN production on administration of deficient IFN, lysis of infected cells would result in elimination of the virus. Up to 60% of Northern

European patients respond to lymphoblastoid IFN with clearance of HBV DNA and HBeAg. Some of the non responders have a coexisting deficiency of gamma interferon and associated HTV III infection. In these patients combined alpha and gamma IFN treatment may be effective. Ara-AMP was found to be non-effective in treating patients infected in neonatal life and homosexual group of adult carriers; however, a single course of Ara-AMP proved to be effective in 45% of adult heterosexual carriers, IFN because of immunostimulatory effect is beneficial for both homosexual and heterosexual patients. Neither Ara AMP, nor IFN are found to be effective in carriers resulting neonatal infection. Steroid withdrawal followed by anti-viral therapy maybe the only hope of treating these patients at present or early vaccination of these infants who are predisposed to this infection from their hepatitis B surface antigen positive mothers would be most beneficial.

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