Clinical Update of Viral Hepatitis A-G

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This discussion is a review and update on clinical information that will hopefully be useful in everyday practices and may provide some answers to most commonly asked question by the patients.

Hepatitis A

Hepatitis A (HAV) was identified in 1973 as a small non-enveloped single stranded RNA virus from the picornaviradae family. It is transmitted mainly fecal to oral but can occur from blood contact during the prodrome phase which is usually two weeks before the onset of jaundice. The incubation period is about 28 days and the HAV IgM is detectable 5-10 days after exposure and can persist up to six months. Most patients usually recover and develop life long immunity. However, there is about 12 % relapse and about 2% of the cases will develop into fulminant hepatic failure. The death rate is about 2% for some one over the age of 50 years but this fatality increases to 72 % when there is superinfection of HAV to a patient with HBV and a fatality rate of 40% when there is HCV. There is more than 50 times increase in mortality in patients with chronic hepatitis compare to patients with no history of liver disease. This leads to the importance of HAV vaccination in the Asian population with a high level of chronic hepatitis B.

HAV vaccinations are to be given to people traveling and working in country with high rate of infection, homosexual, intravenous drug users and people with chronic liver disease. The two vaccines that are available are Havrix(SKG) and Vaqta (Merck). There is almost 100% immunity and the vaccine should be injected intramuscularly two times over six month period. The vaccine must be given 3-4 weeks prior to visiting endemic areas. If there is not enough time for the vaccine, passive immunization should be administered. A 0.02 ml/kg of immune globulin should be given for post exposure and for less than three months stay and 0.06 ml/kg for up to six month stay. The vaccine is not recommended for any one younger than two years of age.

Hepatitis B

Hepatitis B (HBV) is the 9th leading cause of death worldwide and there are more than 300 million chronic HBV carriers worldwide. It affects 15-20% of the population in Asia. In United State it affects only 0.1% or 1.2 million people. The disease state is different in Asia and the U.S. This is due to the difference in the age of transmission. In Asia, HBV is vertically transmitted from mother to the infant. Placenta is a potent barrier and transmission occurs at the time of childbirth. Once the baby is infected, 30-90% will become a carrier. In the United State, transmission occurs later in life with experimentation with sex and drug. At this age, only 10% becomes a carrier. The difference in the carrier states may be due to immature immune systems. As a result there are more incidence of hepatocellular carcinoma and cirrhosis in the Asian population.

Hepatitis B can present as acute, fulminant and asymptomatic chronic carrier. There is no recommended therapy for acute hepatitis but Lamivudine has been used in some cases. The treatments that

are discussed are for chronic hepatitis B which by definition is persistently positive HBSAg for greater than six months.

Treatment is recommended for people with positive HBSAg, HBeAg with elevated ALT and viral DNA level. The treatment goal is to achieve seroconversion of HBSAg which is rare or loss of HbeAg which would mean less viral infectivity. Hopefully, this in turn would lead to less cirrhosis and liver cancer.

The two most commonly used treatments are Alfa Interferon (IFN) and Lamivudine. IFN is a family of naturally occurring small protein and glycoprotein which is a product of immune cell response to a viral infection. The mechanism of action is unknown. It is thought to inhibit viral replication, inhibit viral attachment, induce proteases or amplify cytotoxic T-cell. Therefore, people lacking a competent or under developed immune system does not response well to IFN. Patient with high ALT and low pre-treatment DNA level reflecting a good endogenous immune response has a good predictive outcome with IFN. It is given in 5 MU qd or 10 MU TIW for 16 weeks. There is a loss of eAg and DNA in 20-40% and loss of HBSAg in 5-10%.

The other main treatment of HBV consists of nucleoside analogues. They replace naturally occurring nucleoside such as adenosine, guanosine, cytidine, thymidine and uridine, and cause DNA chain termination. Besides Lamivudine, the other nucleoside analogues are Famciclovir(guanosine), Adefovir Dipivoxil(adenosine), Entecavir(guanosine) and Lobucavir(guanosine).These drugs suppress the replication but do not eradicate the HBV. As a result, stopping the medication may lead to relapse.

Lamivudine, an analogue of dideoxycytidine is the nucleoside which has been tested in patients with chronic HBV in long-term trials. There are now data using Lamivudine up to four years. In the initial study, Lamivudine 100 mg per day was given for one year. There was 72% normalization of ALT, 16% HbeAg loss or conversion and 55% improvement in histology. Two-year study revealed 27-38% eAg loss with 52% undected DNA. Three-year study revealed 40% eAg loss and four-year study revealed 47% eAg loss. The seroconversion of HbeAg increases if ALT is >2X normal. The side effects are minimal with reports of pancreatitis and lactic acidosis.

Resistance is a problem with nucleoside analogue and can be seen as elevation of DNA level. This occurs only after 9-12 months use of medication and occurs at a rate of 10-15% per year. With Lamivudine there is a mutation at the YMDD locus with a substitution of either valine or isoleucine for methionine at residue 552. Substitution of this smaller amino acid side chain may enlarge the nucleotide-binding pocket, reducing its affinity for lamivudine. YMDD variants continue to replicate at low level and often induce little or no liver injury. Lamivudine should be continued despite the mutant since there is still evidence of improved biochemical and histological improvement. In the 4-year data consisting of 58 patients, 39 or 69% of the patients developed YMDD mutation. With continued treatment, 13 out of 39 patient loss their eAg.

Lamivudine should be given 100 mg qd with laboratory testing of DNA, ALT, eAg/eAb every month. Medication should be discontinue when there is an eAg loss and recheck labs in 3-6 months. Lamivudine should be restarted if there is an elevation of DNA.

The other area of research has been immunomodulatory therapy where the main focus is activation of T-cell. Thymosin alpha1(Zadaxin) which is a thymic derived peptides to stimulate T cell function. Interleukin-

12 has been used to promote T-helper cell. The use of DNA vaccine as oppose to peptide vaccines can stimulate not only B cell but also T cell response. This can lead to prolong expression of viral proteins.

Hepatitis C

The hepatitis C virus was discovered and named in 1989 by Choo et al. It has long been a cause of post-transfusion hepatitis and was known as non-A, non-B hepatitis.

Chronic hepatitis C effect 170 million people worldwide and 3.9 million people in the United States. It is the main reason for liver transplantation in the United States. Like HBV, it is transmitted via blood and sex. However, the U.S. Public Health Department did not suggest any change in the sexual practice in monogamous relationship. There is a 3% chance of sexual transmission in a monogamous relationship while there is a 10 % chance with high-risk behavior. Homosexual transmission is about 7%. Perinatal transmission is about 5% and increase to about 10-15% when the mother is co-infected with HIV. Like other viruses, the level of viremia dictates the incidence of transmission.

It is a hepacivirus which is a RNA virus with an envelope. It has 9400 base pair and has been difficult to study the virus due to the lack of cell culture and due to the genetic variations. There are six genotypes with many subtypes which will be important for duration of treatment. Genotypes 1-3 occurs through out the world but genotype 4 is found in Egypt while genotype 5 in South Africa and genotype 6 in Asia. This genetic variability has made it difficult to develop a vaccine and there is no treatment for HCV post-exposure since the immune globulin is not effective.

When acute infection occurs, approximately 85% of the patients become a carrier. The incubation period is 2 to 30 weeks and the symptoms can be wide range. The diagnosis can be made with several tests which include the HCV antibody, recombinant immunoblot assay(RIBA) or measurement of HCV viral level. The HCV antibody test is an ELISA and the first generation test only has a sensitivity of 70-80%. There is many false positive and the confirmatory testing such as RIBA and HCV PCR are done.

Current therapy consists of Rebetron, combination Interferon and Ribavirin. The NIH consensus suggests treatment for patient with elevated ALT and RNA with moderate to severe histology with or without fibrosis. Patient with mild histology and cirrhosis should be evaluated in individual cases. Patient with normal ALT and decompensated cirrhosis should not be treated. The best predictors of response are hepatic histology, genotype and pre-treatment viral load.

Randomized trials have shown that Interferon alone for 24 and 48 weeks lead to a sustained response of 6% and 16% respectively. Rebetron for 24 and 48 weeks lead to a sustained response of 33% and 41%. The recommendation is treatment for six months for genotype 2,3 and type 1 with viral load less than 2 million copies/ml. Treatment of 12 months for genotype 1,4 and high viral load greater than 2 million copies/ml.

Newer drugs consist of pegylated interferon which is IFN conjugated one to one with a 12,000 dalton polyethylene glycol molecule. This reduces the clearance of interferon and can be given subcutaneous one time a week as oppose to three times a week. Monotherapy offers a sustain response of 36% which is still not as

good Rebetron. The combined Pegylated interferon and Ribavirin has the best-sustained response rate of about 52-56%.

The future treatment will focus on stopping the viral cycle. They are model after HIV treatment and are inhibitor of protease, helicase and ribozyme. Serine protease inhibitor would block cleavage of non-structural proteins while Helicase inhibitor would stop viral replication and transcription by not allowing the RNA to unwind. The ribozyme cleaves target RNA in specific manner to stop replication.

There are also researches on gene therapy, which is being directed to block protein synthesis by preventing translation. CDNA, a synthetic complementary DNA is made to bind to initiation site of messenger RNA to stop translation. However, there are no adequate delivery systems of the CDNA since the body has many nucleases to breakdown the CDNA.

Current therapy for both hepatitis B and C is adequate for select patients but with newer treatments and combination treatment the future hold optimism for possible eradication of the disease.

Hepatitis D

Hepatitis D (HDV) was first describes in 1977 in Italy and is a defective 36 nm particle with an envelope, HD Ag and single stranded circular RNA. The infections occurs mainly via blood but can be sexually transmitted with a require presence of hepatitis B. It can be a coinfection where the HBV and HDV are simultaneous contracted or superinfection where a HBV carrier is infected with HDV. The clinical importance of coinfection is that it rarely leads to chronic HDV since it depends on the concurrent activity of HBV. In superinfection the hepatitis D is saved by the pre-existing HBSAg and usually leads to chronic hepatitis D. Due to coinfection of two or even three viruses(B,C,D), chronic hepatitis D can result in severe disease and can progress to cirrhosis in 70% of the patients. Hepatitis D is more prevalent among intravenous drug user.

Diagnosis is made by finding HDV antibody in the serum or by finding the HDV RNA or HDV Ag in the liver cells. The treatment consists of Interferon or by treating the HBV.

Hepatitis E

Hepatitis E (HEV) was cloned and sequenced in 1990 and was initially named enterically transmitted non-A, non-B hepatitis. It was first detected in 1983 in feces collected from a patient who was suspected of having enteric non-A, non-B. It is a small non-enveloped 34 nm particle with a single stranded RNA. The gene has been sequenced but the many aspects of the viral life cycle such as attachment, entry, transcription, assembly and release are still unclear. It is endemic in Mexico, India, Southeast and central Asia and there have only been two reported cases in the United States. There are two distinct strains (Asian and Mexican) with a 75% homology of the gene. It is transmitted fecal-oral route with an incubation period of about two to ten weeks. Diagnosis is usually made by checking for Anti-HEV IgM and IgG. Clinical presentation is similar to other viral hepatitis and is a self-limiting disease which last 1-4 weeks. The mortality rate is low(0.07-0.6%) except in a pregnant woman in her third trimester, where there is a 25% mortality rate. There is no

associated chronic hepatitis, cirrhosis or liver cancer. Passive immunity is not useful and vaccine is in the works for traveler going to endemic area

Hepatitis G

After the discovery of HCV, there were still cases of unexplained post transfusion hepatitis. This led to looking for non-A,B,C hepatitis and the initial interest was sparked by the serum of a surgeon who acquired hepatitis which was non-A, B or C. Hepatitis G (HGV) is a virus that is similar to the Flaviviridae family with a single stranded RNA(+) virus. The gene was sequenced in 1997 and is detected by ELISA for theE2 envelope or by PCR assay. It was discovered in 24% of intravenous drug user and in 2% of blood donor in the United States. Due to the self-limiting nature and acquisition of immunity, the research in HGV has slowed down. The most interesting to have come out in the past five years is that it does not cause major liver disease. It is equally present in post transfusion blood tests of patients with elevated transaminases or with normal transaminases.

This has lead to a decision not to screen the worldwide blood supply since there is not enough evidence to suggest any benefits to the recipients. To screen for a new agent it has to be transfusion related transmission, must cause an adverse reaction in the recipient and a screening test must be available. In the meantime, the search continues for other viral hepatitis.

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