

PRESENTACIONES DE INVITADOS EXTRANJEROS

New drugs in the treatment of hepatitis C

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Treatment of hepatitis C has greatly progressed in recent years with the appropriate use of pegylated compounds of interferons-alpha in combination with ribavirin. It has become individualized in terms of drug doses and duration of therapy, and with increasing experience and knowledge of treating physician and proper education of nurses and patients its compliance has also increased. Treatment of hepatitis C initially restricted to compensated chronic liver disease is now extended to acute hepatitis C, patients with HCV infection with normal and nearly normal aminotranfeases, to re-treatment of non-responders and relapses to a first course of therapy, to patients with overt and even decompensated cirrhosis, to HIV co-infected individuals and others difficult to treat subsets of HCV-infected patients. However combination therapies are far from optimal except in genotype 2 and 3 patients. Therefore there is a pressing need for novel therapeutic approaches. In this context a number of new drugs acting stronger and /or at different levels and pha-

ses of the replicative cycle of HCV and on immune mechanism are under development.

• New drugs can be grouped in the following five broader categories:

1. With activities similar to those of already approved therapies: Albuferon, other forms of interferon, viremagine

2. Drugs for possible combination with existing therapies: AMA, histamine. Thymosin, NM283 (valopicitabin)

3. Purely antiviral agents: Inhibitors of the enzymes of HCV, mostly of the NS3 serine protease (IRBM, WO-9950230, WO0102424, WO-00009543, BILN 2061, US6187905, WO01/77113 A2 and peptide aptamers), glycosidase inhibitors, oligonucleotides, ribozymes

4. Immunotherapeutic agents: Therapeutic vaccines, monoclonal antibodies

5. Antifibrotic agents: Interleukins, IFN α and miscellaneous other

The results of recently communicated phase I and II trials with several of these compounds alone or in combination with approved anti-HCV therapies will be presented in brief and discussed in relation to the future of therapy of chronic hepatitis C and its complications.

Management of acute hepatitis B. Should it ever be treated?

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In the management of patients with typical acute hepatitis B, antiviral treatment is not currently recommended. However approximately 1% of symptomatic patients with acute hepatitis B run a fulminant/fatal course while a varying percentage of others, particularly immune-suppressed ones or of very young age and with mild disease develop chronic HBV infection. The benefits of treatment in these two subsets of patients at risk for developing fulminant/subfulminant hepatic failure or for transition of acute HBV infection B to chronicity respectively, are largely unknown.

Treatment of acute icteric hepatitis B has been attempted with interferon-alpha (IFN- α) in a relatively large randomized controlled trial of adult patients conducted in Greece in the 1990s (J Viral Hepatitis 4:387-394) as well as in smaller uncontrolled studies. None of the IFN-treated patients, but also of the untreated controls, developed fulminant hepatitis or chronic hepatitis B. The interferon-treated group tolerated therapy without severe side-effects, symptoms ameliorated and the duration of illness was shortened significantly.

Following the introduction of nucleos(t)ide analogues in the treatment of chronic hepatitis B several reports have also appeared in the literature on their use in patients with de novo severe acute hepatitis B as well as in severe episodes of acute exacerbation of chronic hepatitis B virus infection. Most are small, observational, retrospective, uncontrolled studies or case reports concluding that

such a treatment of acute hepatitis B is safe well tolerated of benefit to the patients. The need for large RCTs is stressed by most authors of these reports although there appears to exist a general consensus that n. analogue therapy reduces the risk of fulminant/fatal course. In a recent publication (Liver 2004 (Dec) 24:547-51) lamivudine was reported to prevent in selected patients progression of de novo severe acute hepatitis B to fulminant or

chronic liver disease and a similar benefit of lamivudine treatment on the clinical outcome of spontaneous severe acute exacerbations of chronic HBV infection was also reported from Japan (Intervirolgy, Dec 2004;47:335-41).

In this presentation data from the literature and from personal observations on antiviral treatment of acute hepatitis B will be critically reviewed and discussed.

Treatment of precore mutant chronic hepatitis B

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Mutations at the precore and core promoter regions of the HBV genome, most commonly a G to A mutation at nt 1896 creating a novel translational stop codon, abolish or reduce the formation of HBeAg. They become selected in the natural course of HBeAg-positive HBV infection and are implicated for the development of the majority of HBeAg-negative cases of chronic hepatitis B (CHB) also referred as "precore mutant CHB". They are also linked with HBV genotypes B and D and less so with genotype C (harboring T at 1858) and with their geographical distribution being common in the Mediterranean Area and in Asia. Precore mutant and in general HBeAg-negative chronic hepatitis B, is characterized by persistent or intermittent HBV replication with increased ALT activity, liver necroinflammation and fibrosis, with frequent development of cirrhosis, liver failure and hepatocellular carcinoma. Effective treatment of HBeAg-negative CHB without development of viral resistance or relapses after discontinuation of therapy represents an undisputed need and major challenge in clinical practice.

Interferon-alfa based therapies applied to HBeAg-negative chronic hepatitis B in finite courses give promise of achieving the goal of sustained off-therapy response in a number of patients. In this context the use of pegylated interferon-alfa-2a looks superior to conventional compounds, while nucleos(t)ide analogues rarely if ever can achieve such a goal when applied in finite courses of therapy. Long-term/indefinite nucleoside analogue therapy, can achieve powerful suppression of HBV replication with biochemical and histological remission of hepatitis, maintained by continuous long-term/indefinite treatment. However, in the case of lamivudine it faces the problem of progressively decreasing efficacy because of high

rates of development of HBV resistance. Thus effective HBV suppression with biochemical remission for more than 3 years can be maintained in less than 50% of treated patients. Virological and biochemical breakthroughs of response during long-term LAM treatment in HBeAg-negative chronic hepatitis B, result in loss of the benefit gained during the earlier period of such treatment. Moreover, breakthroughs and relapses can be quite severe and even life threatening, particularly in patients with advanced liver disease and overt cirrhosis, thus raising major concerns on the suitability of long-term LAM therapy in such clinical settings. Long-term monotherapy with adefovir dipivoxil (ADV, Hepsera), the second nucleoside analogue approved for the treatment of hepatitis B, is effective in more than two thirds of HBeAg-negative patients with chronic hepatitis B at least for the period of the first 3 years with rare (6%) and delayed appearance of HBV resistance. Moreover it has proved to be effective against both wild type and LAM-resistant HBV strains as well as against all HBV genotypes either with a positive or negative HBeAg phenotype. However efficacy may cover only three quarters of treated patients, HBV resistance-though limited- is nevertheless existent and may further increase with the duration of therapy while the high cost of ADV remains a major drawback. Entecavir is a most potent anti-HBV compound promising almost 100% efficacy under therapy of one year duration without viral resistance but no data are yet available in long-term treatment of HBeAg-negative patients. On the other hand, it is well appreciated, that going "monotherapy", with any nucleoside analogue, may not be the best way for a long-term/indefinite suppression of HBV replication. Combinations of agents with complementary mechanisms of antiviral activity and different profiles of HBV resistance (like adefovir or tenofovir in combination with telbivudine or entecavir or lamivudine or emtricitabine) may soon prove successful in preventing the development of HBV resistance and/or in inducing sustained/indefinite virological responses.

Hepatitis B virus and hepatitis C virus infections in health care workers: guidelines for prevention of transmission of HBV and HCV from HCW to patients

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Background: The transmission of viral hepatitis from health care workers (HCW) to patients is of world-wide concern. Since the introduction of serologic testing in the 1970s there have been over 45 reports of hepatitis B virus (HBV) transmission from HCW to patients, which have resulted in more than 400 infected patients. In addition there are six published reports of transmissions of hepatitis C virus (HCV) from HCW to patients resulting in the infection of 14 patients. Additional HCV cases are known of in the US and UK, but unpublished. At present the guidelines for preventing HCW to patient transmission of viral hepatitis vary greatly between countries. It was our aim to reach a Europe-wide consensus on this issue. In order to do this, experts in blood-borne infection, from 16 countries, were questioned on their national protocols. The replies given by participating countries formed the basis of a discussion document. This paper was then discussed at a meeting with each of the participating countries in order to reach a Europe-wide consensus on the identification of infected HCWs, protection of susceptible HCWs, management and treatment options for the infected HCW. The results of that process led to the formulation of a proposal for guidelines published in *J Clin Virol* 2003;27:213-230 as follows:

Evaluation, Prevention and Treatment of HBV in infected HCWs: All HCWs should apply standard precautions to every patient. It is highly recommended that all HCWs in contact with patients, blood or other body secretions should be vaccinated for HBV and have their response checked within a month after the final dose. Initial non-responders should be given one to three more doses of vaccine and have their response determined. Non-responders should have an individual risk assessment based on job description to determine whether they will be investigated for persistent HBV infection. All HCWs who perform Exposure Prone Procedures (EPP), including dental, medical and nursing students, should provide proof of anti-HBs response before starting a post. If negative/or unavailable then the HCW should receive a booster dose of vaccine and have their response determined at least 1 month after. Continued non-responders should be investigated for persistent HBV infection (presence of HBsAg or anti HBe in the absence of HBsAg). Those found to be HBsAg negative should be allowed to perform EPP but should be tested regularly (frequency to

be decided by each individual country) and after any significant exposure. All HCWs who refuse to be vaccinated must understand the implications of his/her actions. The implication of the anti-HBs response differs between non-EPP and EPP HCWs. In non-EPP HCWs: Anti-HBs levels >100 IU/l are desirable. HCWs with anti-HBs levels between 10 and 100 IU/l should have their response confirmed using another assay. A further dose should be given. HCWs with anti-HBs levels <10 IU/l should be given up to three additional boosters and have their response re-checked. HCWs with anti-HBs levels <10 IU/l (non-responder) should consult a specialist advisory group to assess risk. In EPP performing HCWs: Anti-HBs levels >100 IU/l are preferred. HCWs with anti-HBs levels 10–100 IU/l should be given a booster and have their response re-checked using another assay. All HCWs with a confirmed anti-HBs level between 10 and 100 IU/l should be tested for HBsAg. However, it is not imperative that anti-HBs titres reach a level of >100 IU/l. Those HCWs who have anti-HBs levels <10 IU/l (non-responders) should be tested for HBsAg. Those found to be negative should consult a specialist advisory group to assess risk. All HBV infected HCWs with HBeAg should not perform EPP. If HBeAg positive HCWs wish to have their HBV DNA level determined they will first have to be referred to an expert panel. If the panel recommends testing and HBV DNA is below that country's cut off, a HCW can perform EPP. However, the HBV DNA level should be examined every 3 months. All HBV infected HCWs negative for HBeAg who are performing EPP should have their HBV DNA level determined. At present the consensus panel recommends a cut off level of 10⁴ genome equivalents/ml. However, the consensus panel agreed that each country could determine the HBV DNA level cut off on an individual basis based on risk to patients and loss of experienced HCWs. All HCWs with HBV DNA levels above the determined cut off level should not perform EPP. All those equal to or below this level are allowed to practice EPP. All HCWs with HBV DNA levels equal to or below their country's cut off should be annually tested for HBV DNA and managed as above. All HCWs shown to be a source of transmission to patients, regardless of HBV profile, should not perform EPP. All infected HCWs should be referred to a hepatologist for specialist advice. Some HCWs may elect to take treatment. In order to return to performing EPP, infected HCWs receiving treatment should demonstrate that their HBV DNA levels have fallen below the 10⁴ genome equivalents cut off level, 4. Each HCW who has successfully reduced the HBV DNA level to below the cut off should be retested every 3 months. HCWs who default on mono-therapy should have their HBV DNA level tested immediately and then retested every 3 months. All HCWs with HBV DNA levels above this cut off should not perform EPP. All those below this level are

allowed to practice EPP. All HCWs with HBV DNA levels above the chosen cut off level should be given the option of disclosure to their patient in order to continue practising EPP. HCWs should ensure that the patient is given accurate and understandable data on the risk of being operated on by an infected HCW. Alternatives should be offered to the patient e.g. HBV vaccination

Infected HCWs with hepatitis C: No consensus was reached as to how to manage HCV infected HCWs who perform EPP. On balance it is not recommended that EPP be forbidden for the HCV infected HCW. However, as a minimum, it is recommended that all HCWs performing EPP know their HCV status as it may have implications for their future career. Those found to be infected with HCV should be referred to a hepatologist, as successful treatment will reduce the risk

of transmission of HCV to patients. If there is a substantial blood letting into a patients body cavity, then the status of the HCW should be made known to occupational health and the patient informed, and treated if infection occurs; or referred to a hepatologist.

Summary: The guidelines produced aim to reduce the risk of transmission from infected HCWs to patients. The document is designed to complement existing guidelines or form the basis for the development of new guidelines. This guidance is applicable to all HCWs who perform EPP, whether newly appointed or already in post.

**On behalf of the authors of the manuscript - J Clin Virol 2003;27:213*