Diagnosis and management of chronic hepatitis C

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A Pár. Diagnosis and management of chronic hepatitis C. Can J Gastroenterol 2000;14(Suppl B):83B-88B. This mini-review is devoted to the main questions of diagnosis, treatment and prevention of chronic hepatitis C (CHC). Diagnosis of CHC is based on virological, biochemical and histological findings. The etiology of CHC should be proven by the presence of antibody to hepatitis C virus (anti-HCV) and detection of viral nucleic acid (HCV RNA), using qualitative and quantitative polymerase chain reaction or branched chain DNA techniques. Serum aminotransferase levels can reflect the biochemical activity of liver disease, while biopsy is very important in the grading and staging of the pathological process. The generally accepted treatment of CHC is interferon (IFN); however, recently, the combination of IFN with the oral nucleoside analogue ribavirin has become the therapy of choice, not only for relapsers but also for naive patients. Prevention of hepatitis C by vaccination is not yet available. Screening blood donors and members of high risk groups, as well as ensuring good public health measures, are imperative to inhibit the spread of HCV.

Key Words: *Chronic hepatitis C; Diagnosis; Hepatitis C; Interferon; Prevention; Treatment*

Diagnostic et traitement de l'hépatite C chronique

RÉSUMÉ : Cette brève synthèse porte sur les principales questions relatives au diagnostic, au traitement et à la prévention de l'hépatite C chronique (HCC). Le diagnostic de l'HCC se fonde sur les résultats des analyses virologiques, biochimiques et histologiques. L'étiologie de l'HCC doit être confirmée par la présence de l'anticorps dirigé contre le virus de l'hépatite C (anti-HCC) et le dépistage de l'acide nucléique viral (ARN de l'HCV) par technique d'amplification génique qualitative et quantitative ou technique d'ADN à branches ramifiées. Les taux d'aminotransférase sérique peuvent refléter l'activité biochimique de la maladie hépatique, alors que la biopsie est très importante pour mesurer et stadifier le processus pathologique. Le traitement généralement accepté de l'HCC est l'interféron (IFN). Par contre, récemment, l'association d'IFN avec l'analogue nucléosidique oral ribavirine, est devenu le traitement privilégié non seulement chez les patients qui rechutent, mais également chez les patients qui n'ont encore jamais été traités. Nous n'avons pas encore accès à un vaccin contre l'hépatite C. Il est indispensable de procéder au dépistage auprès des donneurs de sang et des membres des groupes à haut risque, et d'instaurer des mesures visant à protéger la santé publique si l'on veut empêcher la propagation de l'HCV.

Chronic hepatitis C (CHC) infection is a major health problem; 150 million people may harbour hepatitis C virus (HCV) worldwide (1,2), and a significant number suffer from inflammatory liver disease that may lead to cirrhosis or hepatocellular carcinoma. Although screening programs and public health measures provide a certain degree of prophylaxis against HCV infection, there is no vaccination to prevent HCV spread. Thus, the early, correct diagnosis and

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effective treatment of chronic viral hepatitis C remains important (3). The aim of this paper is to outline briefly the up-to-date concepts on the diagnosis and management of CHC.

DIAGNOSIS

Diagnosis of CHC is based on virological, biochemical and histological evidence.

Virological evidence: There are two main types of virological diagnostic tests for HCV infection: serological assays and nucleic acid tests.

Serological assays: For detection of antibodies to hepatitis C virus (anti-HCV), ELISA tests have been developed. ELISA tests detect antibodies reactive for recombinant HCV antigens from the core (c22), nonstructural regions 3 (c33) and 4 (c-200), and 4 (c-100) proteins of the virus. The third-generation ELISA incorporates additional recombinant proteins from the NS5 region.

Anti-HCV ELISA tests may detect 85% to 90% of patients with HCV infection. Yet, their interpretation is limited because they do not detect anti-HCV in all infected persons and do not distinguish between acute and chronic or resolved infection, and there may be a long interval between onset of acute infection and seroconversion. In certain circumstances, the rate of false positivity may be high.

Anti-HCV test results may be falsely negative, eg, in hemodialysis patients or patients with humoral immunodeficiencies. Results may also be falsely positive in low risk groups or in those with autoimmune disease.

Anti-HCV is not an effective neutralizing antibody. Its presence only reflects the host's immune reactivity to HCV. Although anti-HCV positivity does not necessarily prove viremia, in patients with elevated alanine aminotransferase (ALT) levels and chronic hepatitis, it may suggest an ongoing viral infection (4).

A supplemental confirmatory test for anti-HCV is the recombinant immunoblot assay (RIBA) (Ortho Diagnostic Systems, Raritan, New Jersey), which has greater specificity than ELISA. It is commercially available in different assay formats and with different antigen expression systems. RIBA 2 detects recombinant c-22, c23, c-100 and 5-1-1 antigens. The RIBA test may be useful to confirm indeterminate ELISA tests in persons at low risk (eg, blood donors).

Nucleic acid detection: For the direct detection of HCV viremia, HCV RNA assays have been developed that are widely applied. Serum HCV RNA determinations were earlier not routinely necessary to diagnose hepatitis C, although they can provide the most direct evidence of ongoing HCV infection. Determination of serum HCV RNA is of basic importance for the diagnosis of HCV infection and even determining the quantification has growing importance.

In the polymerase chain reaction (PCR) after reverse transcription, small amounts of viral RNA are amplified to levels that are detectable by standard techniques. HCV RNA PCR tests also have their limitations – frequently occurring false positive and false negative results (mostly due to improper collection, handling and storage of the test samples). In addition, detection of HCV RNA may be intermittent during the course of HCV infection, and a single negative PCR test result may not be conclusive.

Both qualitative and quantitative PCR assays are available. To quantify HCV RNA in serum, a quantitative PCR test has been developed by Roche (Roche Amplicor HCV Monitor, Nutley, New Jersey). Another method is the branched-chain DNA signal amplification technique. This, however, is a less sensitive test compared with standard PCR assay at lower levels of viremia. Serum HCV RNA load may be important in determining the treatment regimen during interferon (IFN) therapy.

HCV genotyping and serotyping: According to Simmonds' (5) nomenclature, there are six major HCV genotypes and 11 HCVsubtypes, based on the analysis of nucleotide sequences derived from the part of the gene encoding a nonstructural protein (NS5). Genotyping is not routinely done, but its use may gain significance if the treatment regimen changes to depend on the type of HCV.

There is an indirect method for serotyping using an ELISA system in which type-specific antibodies against the NS4 region are detected. The advantage of serotyping versus genotyping is that it can be performed even if no virus is detectable. Its disadvantage is that no subtyping is possible. Furthermore, this test is not suitable for studying sera of immunocompromised patients, eg, those who have antibody deficiency. Experiments by Pár et al (6) have showed that 85% of the Hungarian HCV carrier population is infected by HCV genotype 1 and that some carriers (eg, hemophiliacs) have HCV4 or mixed type infections (6).

Biochemical evidence: An important biochemical liver test that may suggest liver cell injury is serum ALT. ALT has been used for decades as a surrogate marker in post-transfusion hepatitis (non-A, non-B, ie, HCV). Although ALT is often helpful in clinical practice, it is an imperfect marker and may be misleading. It cannot predict liver histology because patients with normal ALT levels may have histologically advanced disease, although higher ALT levels often accompany more aggressive necroinflammatory activity in HCV infection. Because ALT levels often fluctuate during the course of CHC, there may be periods of normal enzyme levels.

In symptom-free individuals with normal ALT levels (eg, blood donors with anti-HCV positivity), an anti-HCV finding is not necessarily associated with HCV viremia, and in these cases an HCV RNA determination (via PCR) is crucial to establish or disclose an active virus infection. In chronic HCV infection, even the HCV RNA level can fluctuate. Persons with normal ALT levels who are anti-HCV positive but who repeatedly test negative for HCV RNA (via PCR) possibly have recovered from a previous HCV infection. (This is the situation for about 15% of symptom-free anti-HCV-positive blood donors with normal ALT levels [7].)

Another liver enzyme, gamma-glutamyl transpeptidase (an excretion marker), may also be elevated in patients with CHC, in accordance with bile duct injury, which is a typical histological abnormality of the disease.

Histological evidence: Liver biopsy is important in the diagnosis and the differential diagnosis of chronic hepatitis. Histology may be considered the most accurate measure of disease severity and stage, and thus it remains a gold standard in clinical assessment.

Biopsy is always desirable (except in hemophiliacs) because it reveals both the grade and the stage of the disease process, and discloses unsuspected other nonviral hepatic damages.

Grade (severity of the necroinflammation) may be minimal, mild, moderate or severe. Stage (or phase of disease) denotes the degree of fibrosis. Presence or absence of fibrosis is a key factor in determining the prognosis and response to treatment.

Lymphocyte aggregates, along with bile duct damage, strongly suggest HCV infection of the liver. Thrombocytopenia can indicate cirrhosis in HCV patients (7,8).

THERAPY

The goals of CHC treatment are to eradicate the virus, to normalize serum ALT levels, to improve necroinflammatory activity and to reduce fibrosis, thus preventing cirrhosis and hepatocellular carcinoma.

Following the first report of successful treatment with IFN of CHC (then known as chronic non-A, non-B hepatitis), several randomized, controlled trials confirmed the efficacy of IFN therapy. IFN became the only agent generally accepted for the treatment of CHC. IFN was used to treat hepatitis B as early as 1976, while for hepatitis C (then still named non-A, non-B hepatitis), IFN was applied first by Hoofnagle and co-workers (9) in 1986, before the etiological agent was identified. Since then, thousands of patients with chronic viral hepatitis have been treated with IFN. Unfortunately, however, IFN therapy resulted in limited therapeutic effects in chronic viral hepatitis C; fewer than half of HCV patients treated with IFN respond to the treatment, and half of those who respond relapse when the drug is stopped. Thus, the originally suggested standard IFN treatment regimen led to suboptimal results: a rate of sustained biochemical and virological remission of not more than 15% to 20% when a schedule of 3 MU IFN three times per week (TIW) for six months was applied (3,10-13).

Recently, more studies have attempted to define the optimum treatment regimen and to identify patients who will benefit most. It was suggested that the original moderate therapeutic results can be improved by using higher doses of IFN for longer duration or by combining IFN with other agents. However, IFN is costly and can cause side effects that may reduce compliance and decrease the patient's quality of life.

NEW DEVELOPMENTS IN TREATMENT MODALITIES

Because there are many HCV patients who do not benefit from standard IFN therapy, several attempts have been made to potentiate the effect of IFN.

High dose IFN: Iino et al (14) from Japan first recommended high dose induction therapy with IFN in CHC. They found the best results when 10 MU IFN was given six times a week for two weeks, followed by 10 MU TIW for an additional 12 weeks, for a cumulative total dose of 480 MU in 14 weeks. A sustained biochemical response (measured ALT level) was achieved in 54% of their patients, and HCV RNA clearance in 46%.

PEGylated IFN: Conjugation of IFN to polyethylene glycol prolongs plasma half-life of the agent and results in a protracted activity, thus allowing administration of larger doses and once-weekly dosing. In a recent study (15) that evaluated the pharmacokinetic/pharmacodynamic relationship of a PEGylated (PEG) IFN -2a, single doses of PEG IFN -2a 45, 135 and 270 µg, and IFN -2a MU and 18 MU were given. Blood samples were drawn for pharmacokinetic analysis. Pharmacodynamic analysis was evaluated by measuring serum 2 ,5 -oligoadenylate synthetase induction. Results indicated that the pharmacokinetics of both PEG IFN -2a and IFN -2a are linear. PEGylation of IFN -2a resulted in a slower absorption rate, decreased systemic clearance and increased serum half-life (about 10-fold), leading to longer circulation of PEG IFN -2a. In a phase II study of PEG IFN -2a in 155 patients with CHC treated for 48 weeks, a dose-dependent increase in virological sustained response rate was demonstrated. Tolerability of PEG IFN -2a was comparable with that of standard IFN in a program involving over 1500 patients (16).

Combination therapy with IFN plus ribavirin: The combination of IFN with the nucleoside analogue ribavirin has been used to treat chronic HCV infection. Ribavirin is a well known guanosine analogue with a broad spectrum of activity against RNA and DNA viruses. Several studies suggested that the combination of ribavirin with IFN might enhance the antiviral effect, even in those who do not achieve sustained response with IFN alone.

Reichard et al (17) first evaluated the efficacy of IFN and ribavirin combination therapy (versus IFN monotherapy) in naive patients in a double-blind trial. Following 24 weeks of therapy, the sustained virological response was significantly better in those receiving the combination than in patients receiving IFN alone (45% versus 23%). Both naive patients, partial responders and relapsers may benefit from the IFN plus ribavirin combination.

In a recent multicentre clinical trial, McHutchison et al (18) proved that, in naive patients, initial therapy with IFN and ribavirin was more effective than treatment with IFN alone; patients who received IFN monotherapy for 48 weeks showed a sustained response of 13%, while those treated with combination treatment achieved sustained virological remission in 38%.

Results have been reported from a randomized double-blind, placebo controlled trial of IFN -2b with and without ribavirin for CHC (19,20). The ribavirin-IFN combination has been proven beneficial, mostly in patients who relapsed following an IFN-induced remission or in naive patients (19,20).

Poynard et al (21) performed an international, multicen-

tre, placebo controlled trial to assess the value of combination therapy in naive patients with chronic HCV infection. In this study, when 3 MU IFN -2b TIW was given with 1000 to 1200 mg/day ribavirin for 48 weeks, the sustained virological remission rate was 43% versus 19% for those receiving 3 MU IFN TIW monotherapy for 48 weeks. The adverse effect rate was 19% versus 8%, respectively.

Independent factors associated with good response were HCV genotype 2 or 3, low viral load (less than 2 million copies/mL), age younger than 40 years, minimal fibrosis and being female. The combination therapy was effective even in patients with few favourable predictor factors.

Other potential therapeutic approaches: The inhibitors of viral enzymes, including NS3 proteinase and helicase, are highly awaited, but these agents are at least two years away from development (8,22).

Alternative modalities: To enhance the efficacy of IFN there have been other several attempts at combinations, for example with phebotomy, nonsteroidal anti-inflammatory drugs, vitamin E, amantadine or ursodeoxycholic acid. These combinations should be regarded as nonconventional, and their use is discouraged outside of controlled trials (8).

RECOMMENDED TREATMENT REGIMENS

Combination therapy with IFN plus ribavirin dramatically improves the sustained remission rate and seems to be the future standard treatment for CHC. According to the Consensus Statement of EASL International Consensus Conference on Hepatitis C (held in February 1999) (23), the recommended treatment regimens can be summarized as follows.

Naive patients: In naive patients with no contraindication to ribavirin, the combination of IFN and ribavirin seems adequate. Duration of therapy may depend on the HCV genotype and level of viremia. In patients with genotype 2 or 3, the duration is six months regardless of the viral load. In patients with genotype 1, six months may be sufficient if the HCV RNA load is low (less than 2 million copies/mL), but 12 months of therapy is recommended if the level is higher than that. The dosage of IFN is 3 MU TIW; ribavirin is given orally 1000 to 1200 mg/day, depending on body weight (1000 mg/day for those weighing 70 kg or less; 12,000 mg/day for those weighing 70 kg or more).

In naive patients in whom ribavirin is contraindicated, IFN monotherapy at a dosage of 3 MU TIW should be administered for 12 months. Serum HCV RNA should be tested after three months of therapy, and therapy should be continued only in patients in whom HCV RNA has disappeared.

Relapsed patients: In patients who relapse after IFN therapy, two options may be considered: combination therapy for six months if there are no contraindications to ribavirin; or IFN monotherapy with higher dose (more than 3 MU TIW or 9 g TIW) for 12 months. In both options, HCV RNA levels should be checked after three months, and therapy should be discontinued if HCV RNA remains positive.

In patients who have failed to respond to therapy, there are no data to indicate that retreatment will be beneficial.

MONITORING PATIENTS DURING TREATMENT

The following steps are recommended to monitor patients during CHC treatment.

During treatment, patients should have complete blood counts (including platelet count) checked regularly – weekly for the first four weeks, then monthly.

Regular tests for thyroid function should be performed every three to six months during therapy and then six months after therapy ends. Emotional status, in particular depression, also must be regularly assessed.

Men and women with reproductive potential must practise strict contraception during and for six months after IFN plus ribavirin combination therapy.

As a biochemical marker of liver disease activity, serum ALT is generally being used in follow-ups. Although its normalization within two months may be a good prognostic feature, it does not disclose continuous viral replication. Thus, ALT measurements are of limited value in disease monitoring. Testing ALT is important for determining the biochemical end-of-treatment response (checked before stopping therapy) and the sustained response (checked six months after the cessation of treatment).

The most important tool in the follow-up of chronic hepatitis C is serum HCV RNA determination by sensitive PCR. If HCV RNA promptly (within two to four weeks) disappears from the serum and levels remain negative even six to 12 months after the end of therapy, this signifies a real efficacy of therapy and is predictive of a sustained remission (24,25).

Lau et al (13) emphasized that when IFN eradicates HCV infection, patients may be cured of the liver disease, and that with virus eradication, even liver fibrosis can regress. Thus, the aforementioned lack of HCV RNA in serum six months after stopping therapy may indicate cure of disease. On the other hand, a persistent HCV viremia may indicate treatment failure of treatment.

Response to IFN monotherapy should be assessed by retesting HCV RNA after three months of treatment, and therapy should be interrupted if HCV RNA remains positive. Response to combination therapy (in patients with HCV genotype 1 and high pretreatment levels of viremia) should be assessed by retesting HCV RNA after six months of therapy, and treatment should be continued for an additional six months only if HCV RNA is undetectable.

End-of-treatment response should be determined by ALT and qualitative HCV RNA testing at the end of treatment, while sustained response should be assessed by ALT and HCV RNA testing six months after the cessation of treatment.

Liver biopsy is important to confirm CHC diagnosis and to determine the activity and stage of the disease. It may be essential for evaluating the effect of therapy too; a control histology performed 12 months after the end of IFN treatment could prove or rule out sustained

remission. However, follow-up biopsies are recommended only in prospective controlled studies and are unnecessary for individual patients outside clinical trials.

TYPES OF RESPONSE

The different responses to IFN treatment are listed below (26).

Early response: No detectable HCV RNA by PCR four to eight weeks after starting treatment during IFN monotherapy.

End of treatment response: Complete response, with normalization of serum ALT activity and disappearance of HCV RNA at the end of treatment.

Sustained response: A long-lasting (for at least six months after the end of treatment) loss of HCV RNA viremia and normalization of serum ALT level.

Nonresponse: Failure to achieve normal ALT level regardless of HCV RNA status after either three months of IFN monotherapy or six months of IFN plus ribavirin combination treatment.

Relapse: ALT levels returning to levels above normal and reappearance of HCV RNA after complete remission (usually occurs within six months of stopping therapy).

Breakthrough: Re-elevation of ALT and reappearance of HCV RNA after a complete response or even during the therapy (relapse during treatment). IFN antibodies and the development of HCV mutants are possible causes.

Paradoxical response: Serum ALT level does not decrease, but sharply increases, suggesting activation of autoimmune reaction. This response can be found soon after beginning IFN therapy.

FEATURES ASSOCIATED WITH RESPONSE: PREDICTORS

The optimum treatment schedule in an individual patient relies on predictors, ie, pretreatment variables associated with IFN response. Several such variables that are commonly associated with beneficial effects of IFN include viral and host factors (eg, low pretreatment serum HCV RNA level and HCV genotype other than HCV genotype 1b), shorter disease duration, young age of the patient, absence of cirrhosis, absence of human immunodeficiency virus or hepatitis B virus infection, being female, and low pretreatment serum iron and ferritin (27-29).

While these predictors have been shown to correlate with the response rate, none has a real predictive value high enough to be used for a yes or no decision. Predictors are only in statistical association with response and are not the same as outcome analysis in that they do not determine appropriateness of therapy. Patients with negative predictors and low probability of good response must also be treated (with a therapy of longer duration or with combination treatment) to avoid progression to cirrhosis and the need for organ transplantation. (27,29).

COMPLICATIONS OF IFN THERAPY

IFN therapy may be hindered by various complications, including neuropsychiatric complications (fatigue or depression). These complications may occur in 10% to 20% of treated patients, more commonly in the elderly or in cirrhotics. (Note: there is a risk for psychiatric complication of IFN therapy if delirium tremens or attempted suicide is found in the patient's medical history.)

Other complications are neutropenia and thrombocytopenia autoimmune hepatitis. In the latter, an increase of serum ALT to more than 10 times the upper limit of normal is suspicious for flare of autoimmunity and requires cessation of IFN.

Further complications include autoimmune thyroid disease (thyroid-stimulating hormone changes and autoantibodies to thyroid antigens must be checked), diabetes mellitus (if this develops or worsens during IFN treatment, therapy should be stopped), cardiac failure, pulmonary infiltrates, bacterial infection, sepsis, and visual and hearing loss.

Ribavirin may cause hemolytic anemia.

Contraindications to IFN treatment: Contraindications to IFN treatment include autoimmune disease (thyroiditis, inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, autoimmune hepatitis, diabetes mellitus), decompensated liver disease, present or past psychiatric disorders (depression), uncontrolled seizures, alcoholism, infection (tuberculosis), myelosuppression, and cardiac and renal failure.

Contraindications to ribavirin: Contraindications to ribavirin comprise end-stage renal disease, anemia, hemoglobinopathia, severe heart disease, pregnancy, no reliable method of contraception, uncontrolled arterial hypertension and old age. Because of the risk of teratogenicity with ribavirin, women with reproductive potential should have a negative pregnancy test before treatment.

Decompensated cirrhosis: Once decompensated liver cirrhosis has developed, there is only one therapeutic modality: liver transplantation. Worldwide, more than 30% of liver transplantation is performed for HCV cirrhosis patients. Recurrent HCV infection in new graft occurs, but usually is mild. The five-year survival rate for patients receiving a liver transplant for HCV cirrhosis is 65%, which is similar to that for other diagnoses (30).

PREVENTION

Due to the genetic diversity of HCV, there is no vaccination to prevent hepatitis C, and immunoglobulin is ineffective for postexposition prophylaxis. Both vaccines and hyperimmune anti-HCV immunoglobulin have been intensively studied in order to develop effective prophylactic measures (8).

Experimental data suggested that a low dose rechallenge with HCV may be blocked by an 'envelope' vaccine in a chimpanzee model (31). Pooled plasma studies demon-

strated that mixtures of antibodies to HCV neutralized diverse HCV strains. Mapping of the diversity of these strains may lead to a polyvalent vaccine (32).

Screening blood and organ donors for anti-HCV and using virus-inactivated plasma pools for coagulation factor supplements have reduced the incidence of post-transfusion hepatitis C. Post-transfusion HCV hepatitis may show a more aggressive course than disease acquired from injection use, possibly due to the larger size of viral inoculum that occurs in the former case (33).

During medical examination, it is important to obtain a history of high risk exposures associated with the transmission of HCV and other blood-borne pathogens in order to identify asymptomatic persons who should be offered HCV screening. HCV-infected persons should be evaluated for liver disease and possible treatment, in addition to being counselled on avoiding alcohol and on how to reduce their risk of transmitting HCV.

Routine screening for HCV infection is recommended only for persons who are at high risk of HCV infection, including those who received blood transfusions before 1991, hemophiliacs, chronic hemodialysis patients or intravenous drug users. Sexual partners of HCV-positive patients, infants 12 months or older who were born to HCV-infected women and health care workers with needlestick injury should also be screened.

Injection drug use is the most frequently identified risk factor for acquiring hepatitis C in the western world. HCV transmission associated with drug injection can be prevented by using new, disposable sterile syringes and needles, not only for every injection, but also to prepare and distribute dissolved drug solutions.

Anti-HCV-positive persons should refrain from donating blood, organs, tissues or semen, but there are no specific recommendations for changes in sexual practices with steady partners. There are also no recommendations against pregnancy or breastfeeding (8).

Health care workers should use hygienic measures when handling any body fluids, especially potentially infective materials. On the other hand, medical staff with needlestick injury should be followed for HCV RNA and undergo PCR testing. Although there is no formal recommendation for postexposure prophylaxis, the newly infected HCV RNA-positive person should consider starting IFN therapy (8).

REFERENCES

1. Alter MJ. Epidemiology of hepatitis C. Hepatology 1997;26(Suppl 1):62-5.
2. World Health Organization. Hepatitis C. Wkly Epidemiol Rec 1997;72:65-9.
3. Hoofnagle JH. Therapy of viral hepatitis. Digestion 1998;59:563-78.
4. Alter MJ, Mast EE, Moyer LA, Margolis HS. Hepatitis C. Infect Dis Clin North Am 1998;12:13-26.
5. Simmonds P. Variability of hepatitis C virus. Hepatology 1995;21:570-83.
6. Pár A, Gervain J, Gógl Á. Hepatitis C virus infection: pathogenesis, diagnosis and treatment. Scand J Gastroenterol 1998;33(Suppl 228):107-14.
7. Hoofnagle JH. Hepatitis C. The clinical spectrum. Hepatology 1997;26:15S-20S.
8. Gordon SC, Schiff ER. Hepatitis C virus. Curr Pract Med 1999;2:935-42.
9. Hoofnagle JH, Mullen KD, Jones DB, et al. Treatment of chronic non-A non-B hepatitis with recombinant human alpha interferon. N Engl J Med 1986;315:1575-8.
10. Poynard T, Bedossa P, Chevallier M and the Multicentre Study Group. A comparison of three interferon alpha-2b regimens for the long term treatment of chronic non-A, non-B hepatitis. N Engl J Med 1995;332:1457-62.
11. Chemello L, Bonetti P, Cavaletta L. Randomized trial comparing three different regimes of alpha-2a interferon in chronic hepatitis C. Hepatology 1995;22:700-6.
12. Niederau C, Heintges T, Haussinger D. Treatment of chronic hepatitis C with alpha-interferon: an analysis of the literature. Hepatogastroenterology 1996;43:1544-56.
13. Lau DTY, Kleiner DE, Chang MG, Park Y, Schmid P, Hoofnagle JH. 10-year follow-up after interferon alpha therapy for chronic hepatitis C. Hepatology 1998;28:1121-7.
14. Iino S, Hino K, Kuroki T, Suzuki H, Yamamoto S. Treatment of chronic hepatitis C with high-dose alpha-2b. Dig Dis Sci 1993;38:612-8.
15. Hu Z-X, Hoffman J, Patel I, Joubert P. Single-dose safety, tolerability and pharmacokinetic/pharmacodynamics (PK/PD) following administration of ascending subcutaneous doses of pegylated-interferon (PEG-IFN) and interferon -2a (IFN -2a) to healthy Subjects. Hepatology 1998;28:702A.
16. Lindsay KL. Different types of interferon. EASL International Consensus Conference on Hepatitis C. Paris, February 26-27, 1999.
17. Reichard O, Norkrans G, Fryden A. Interferon alpha and ribavirin vs interferon alone as therapy for chronic hepatitis C. Hepatology 1996:24:356A.
18. McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 1998;339:1485-92.
19. Reichard O, Norkrans G, Fryden A, Braconier J-H, Sonnerborg A, Weiland A. Randomised, double blind, placebo controlled trial of interferon alpha- 2b with and without ribavirin for chronic hepatitis C. Lancet 1998;351:83-7.
20. Davis GL, Esteban-Mur R, Rustgi VK, et al. Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. N Engl J Med 1998;339:1493-9.
21. Poynard T, Marcellin P, Lee SS, et al. Randomised trial of interferon alphas2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. Lancet 1998;352:1426-32.
22. Love RA, Parge HE, Wichersham JA. The crystal structure of hepatitis C virus NS3 proteinase reveals a trypsine-like fold and a structural zinc binding site. Cell 1996;87:331-42.
23. EASL International Consensus Conference on Hepatitis C. Paris, February 26-27, 1999. Consensus Statement. J Hepatology 1999;30:956-61.
24. Kakumu S, Aiyama T, Okumara A, Iwata K, Ishikawa T, Yoshioka K. Earlier loss of hepatitis C virus RNA in interferon therapy can predict a long term response in chronic hepatitis C. J Gastroenterol Hepatol 1997;12:468-72.
25. Lee WM, Redd KR, Tong MJ, et al, and Consensus Interferon Study Group. Early hepatitis C virus RNA responses predict interferon treatment outcomes in chronic hepatitis C. Hepatology 1998;28:1411-5.
26. Craxi A, Camma C, Giunta M. Definition of response. EASL International Consensus Conference on Hepatitis C. Paris, February 26-27, 1999.
27. Alberti A. Long-term effects of extended duration of interferon treatment for chronic hepatitis C. International Symposium on Hepatitis C at AASLD Annual Meeting, Chicago, November 8-12, 1996.
28. Davis GL, Lau JYN. Factors predictive of beneficial response to therapy of hepatitis C. Hepatology 1997;26:112S-21S.
29. Pár A, Paál M, Horányi M, et al. Role of viral and host factors in the pathogenesis of hepatitis C virus infection and in the response to interferon treatment. Period Biol 1998;100:515-9.
30. Samuel D. Viral recurrence and liver transplantation. EASL International Consensus Conference on Hepatitis C. Paris, February 26-27, 1999.
31. Farci P, Shimodo A, Wong D, et al. Prevention of hepatitis C virus infection in chimpanzees by hyperimmune serum against the hypervariable region 1 of the envelope 2 protein. Proc Natl Acad Sci USA 1996;93:15394-9.
32. Purcell R. The hepatitis C virus: Overview. Hepatology 1997;26(Suppl 1):1-14.
33. Gordon, SC, Bayati N, Silverman AL. Clinical outcome of hepatitis C as a function of mode of transmission. Hepatology 1998;28:562-7.