Treatment for chronic hepatitis B: interferon What we have learned after so many years ?

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Several controlled clinical trials have proved that therapy with Interferon-alfa (INFα) reduced the level of viral replication and inflammatory activity in patients with chronic hepatitis B (1). This favourable effect of INFα occurs especially in patients who benefit most from treatment : patients with active liver disease including cirrhosis. Indeed, in this situation a high level of inflammatory activity and a low viral replication rate are found ; these are independent factors predicting a good response to INFα (2). However, in case of decompensation, lethal complications have been reported (3). In general, interferon therapy accelerates HBe antigen clearance in the first year of therapy compared with spontaneous HBe antigen seroconversion with an additional 20% (4). Interesting to note is that in almost all the treated patients the hepatitis Be antigen seroconversion is associated with normalisation of aminotransferase levels, whereas in about one third of the patients with spontaneous hepatitis Be antigen clearance aminotransferase levels remain elevated and persistent hepatitis B viral DNA can be documented in a considerable part of the patients (4). In addition, cumulative rates of hepatitis B surface antigen clearance are higher in treated than in untreated patients, which suggests that INFα therapy offers a more efficient eradication of the hepatitis B virus infection.

Later on, several authors confirmed that the seroconversion was sustained over years in the majority of patients (5-8).

Since chronic hepatitis B is a slowly progressive disease and clinical complications of the disorder occur only late in the evolution, data became only recently available which suggest that the drug diminished the frequency of death or the need for liver transplantation and induced a reduction in several clinical complications of cirrhosis in comparison with untreated patients (9,10,11).

This positive effect was most obvious in patients with cirrhosis at the moment of enrolment in the follow-up studies. However, some controversy still exists whether INFα really changes the natural history of the disease. In most of the studies, untreated patients served as controls and a selection bias can not be rulled out because they were not randomized. This issue will probably not be definitively settled because it is unethical to withhold patients from treatment during a long period of time with INFα, only for the purpose of having a placebo treated group.

Whether INFα therapy diminishes the risk of progression to hepatocellular cacinoma in HBV infected patients is also still under debate. This is not surprising, taking into account that HBV can be oncogenic, also in anti HBc positive patients without HBsAg. Integrated HBV-DNA sequences have been detected in such patients. Integrated HBV-DNA can result in chromosomal rearrangement and deletion, which, in turn, can result in the expression of oncogenes or deletion of genes regulating hepatocyte growth (suppressor genes) (12). Several retrospective and non-randomized trials reported a beneficial effect of INF on the progression to HCC in HBV patients (13-14). This was confirmed by the results of a recent long-term follow-up study (11). In most of the studies cancer prevention could be achieved even in case of cirrhosis. On the other hand there are also studies, although fewer in number, which have not shown this link (15).

Improved survival after INFα is particularly associated with ALT normalisation (4). Indeed, even after sero- conversion, progress of liver disease can occur e.g. in case of precore mutation development. Furthermore, recent data show that seroclearance of HBs Ag in chronic carriers not always confers a favorable response. This is seen especially in those who are aged, male or cirrhotic (16). Several studies have pointed out that hepatitis B-DNA persists in the liver after loss of hepatitis B surface antigen ; the extra-chromosomal localisation of hepatitis B-DNA suggest the persistence of low level hepatitis B replication even after loss of hepatitis B surface antigen (17).

Although the effect of INFα in chronic hepatitis B is well documented, it is evident that the overall response rate of 20% is far from satisfactory. Early findings which showed that corticosteroid withdrawal therapy might increase the response to INFα treatment gathered great optimism (18). However, a large US multicentre trial showed that prednisone followed by INFα was effective but not better than INFα alone (19) and a meta analysis also did not demonstrate a significant increase in efficacy of INFα when prednisone pre-treatment was added (20). In contrast, a major European multicentre trial included 200 patients, showed that prednisolone

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pre-treatment significant enhanced the effect of lymfoblastoid Interferon in terms of hepatitis Be antigen clearance and seroconversion to anti hepatitis Be (21). This treatment was particulary successful in patients with active disease. There was no evidence that Prednisolone withdrawal was less safe than Interferon alone. Therefore the debate about whether or not to use prednisolone withdrawal therapy is not yet closed.

The optimal treatment duration of INFα in chronic hepatitis B is still after many years poorly defined. This was further investigated by a EUROHEP trial which evaluated the efficacy and acceptability of prolonged INFα treatment in patients with chronic hepatitis B (22). Prolonged treatment was well tolerated in the large majority of the patients and a therapy up to 32 weeks was superior to the standard course of 16 weeks. More important was the finding that a serum hepatitis B-DNA value under 10 pg/ml after 16 weeks of treatment was predictive of a good response associated with prolonged treatment. In fact, only patients who reached this cut-off level experienced a sustained response after extension of the treatment. In contrast to the concept of a fixed treatment course, more evidence became available that the duration of INFα treatment is best modified by online measurement of the quantity of the viral marker (23). Usually hepatitis B-DNA is monitored for this purpose by standard hybridization assay, however recent studies pointed out that the fall in hepatitis Be antigen level between weeks 0 and 4 of therapy is probably the most important independent predictor of response (24).

Until recently no control trials had been published evaluating the benefits of retreatment with INFα and most physians are reluctant to reexpose their patients to a second course of INFα. In a recently published EUROHEP trial a sustained clearance of hepatitis B-DNA and hepatitis Be antigen was observed in 30% of the patients who received retreatment with INFα as compared with 10% who spontaneously cleared these markers in the untreated control group. No baseline features could be selected which predict response. Thus, retreatment with INFα should be considered as a therapeutic option in patients who failed during a previous treatment.

Although currently, for the treatment of chronic hepatitis B, nucleoside analogues are dominating the literature, one should not forget that the only well proved and validated treatment for chronic hepatitis B is still INFα. Based on our current knowledge INFα should therefore always be taken in consideration as the first therapy in the majority of our patients with chronic hepatitis B.

References

1. WONG K.H., CHEUNG A.M., O'ROURKE K. *et al.* Effect of alpha-Interferon treatment in patients with hepatitis Be antigen-positive chronic hepatitis B. *Ann. Intern. Med.*, 1993, **119** : 312-323.
2. KROGSGAARD K., CHRISTENSEN E., BINDSLEV N. *et al.* Relation between treatment efficacy and cumulative dose of alpha interferon in chronic hepatitis B. European concerted action on viral hepatitis (Eurohep). *J. Hepatol.*, 1996, **25** : 795-802.
3. JANSSEN H.L.A., BROUWER J.T., NEVENS F. *et al.* Fatal hepatic decompensation associated with interferon alfa. *BMJ*, 1993, **306** : 107-108
4. FATTOVICH G., GUISTINA G., REALDI G. *et al.* Long-term outcome of hepatitis Be antigenpositive patients with compensated cirrhosis treated with interferon alfa. *Hepatology*, 1997, **26** : 1338-1342.
5. KORENMAN J., BAKER B., WAGGONER J. *et al.* Long-term remission of chronic hepatitis B after alpha-interferon therapy. *Ann. Intern. Med.*, 1991, **114** : 629-634.
6. CARRENO V., CASTILLO I., MOLINA J. *et al.* Long-term follow-up of hepatitis B chronic carriers who responded to interferon therapy. *J. Hepatol.*, 1992, **15** : 102-106.
7. KROGSGAARD K. Long-term follow-up investogator group, EUROHEP *et al.* The long-term effect of treatment with interferon-α_{2a} in chronic hepatitis B. *J. Viral Hepatitis*, 1998, **5** : 389-397.
8. LAU D.T., EVERHART J., KLEINER D.E. *et al.* Long-term follow-up of patients with chronic hepatitis B treated with interferon alfa. *Gastroenteology*, 1997, **113** : 1660- 1667.
9. NIEDERAU C., HEINTGES T., LANGE S. *et al.* Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *New Eng. J. Med.*, 1996, **334** : 1422-1427.
10. DI MARCO V., LO IACONO O., CAMMA G. *et al.* The long- term course of chronic hepatitis B. *Hepatology*, 1999, **30** : 257-264.
11. LIN S.M., SHEEN I.S., CHIEN R.N. Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection. *Hepatology*, 1999, **29** : 971-974.
12. TABOR E. Tumor suppressor genes, growth factor genes, and oncogenes in hepatitis B virus-associated hepatocellular carcinoma. *J. Med. Virol.*, 1994, **42** : 357- 365.
13. OON C.G. Long-term survival following treatment of hepatocellular carcinoma in Singapore : evaluation of Wellferon in the prophylactics of high-risk pre-cancerous conditions. *Cancer Chemother. Pharmacol.*, 1992, **31** : 137S-142S.
14. IKEDA K., SAITOH S., SUZUKI Y. *et al.* Interferon decreases hepatocellular carcinogenesis in patients with cirrhosis caused by the hepatitis B virus. A pilot study. *Cancer*, 1998, **82** : 827-835.
15. International Interferon-a hepatocellular carcinoma study group. Effect of Interferon-a on progression of cirrhosis to hepatocellular carcinoma : a retrospective cohort study. *The Lancet*, 1998, **351** : 1535-1539.
16. HUO T.I., WU J.C., LEE P.C. *et al.* Sero-clearance of hepatitis B surface antigen in chronic carriers does not necessarily imply a good prognosis. *Hepatology*, 1998, **28** : 231-236.
17. LORIOT M.A., MARCELLIN P., WALKER F. *et al.* Persistence of hepatitis B virus DNA in serum and liver from patients with chronic hepatitis B after loss of HBsAg. *J. Hepatology*, 1997, **27** : 251-258.
18. FEVERY J., ELEWAUT A., MICHIELSEN P. *et al.* Efficacy of interferon alfa-2b with or without prednisone withdrawal in the treatment of chronic viral hepatitis B. A prospective double-blind Belgian-Dutch study. *J. Hepatology*, 1990, **11** : S108-S112.
19. PERRILLO R.P., SCHIFF E.R., DAVIS G.L. *et al.* A randomized, controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chonic hepatitis B. *New Eng. J. Med.*, 1990, **323** : 295-300.
20. COHARD M., POYNARD T., MATHURIN P. *et al.* Prednisone- interferon combination in the treatment of chronic hepatitis B : direct and indirect mete analysis. *Hepatology*, 1994, **20** : 1390-1398.
21. KROGSGAARD K., MARCELLIN P., TREPO C. *et al.* Prednisolone withdrawal therapy enhances the effect of human lymphoblastoid interferon in chronic hepatitis B. *J. Hepatology*, 1996, **25** : 803-813.
22. JANSSEN H.L.A., GERKEN G., CARRENO V. *et al.* Interferon alfa for chronic hepatitis B infection : increased efficacy of prolonged treatment. *Hepatology*, 1999, **30** : 238-242.
23. NAGATA I., COLUCCI G., GREGORIO G.V. *et al.* The role of HBV DNA quantitative PCR in monitoring the response to interferon treatment in chronic hepatitis B virus infection J. *Hepatology*, 1999, **30** : 965-969.
24. HEIJTINK R.A., KRUINING J., HONKOOP P. *et al.* Serum HbeAg quantitation during antiviral therapy for chronic hepatitis B. *B. J. Med. Virol.*, 1997, **53** : 282-287.
25. CARRENO V., MARCELLIN P., HADZIYANNIS S. *et al.* Retreatment of chronic hepatitis Be antigenpositive patients with recombinant interferon alfa-2a. *Hepatology*, 1999, **30** : 277-282.