New drugs in chronic hepatitis B

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Chronic hepatitis B (CHB) is affecting more than 300 millions people in the world (1). Its incidence varies among different parts of the world. In endemic areas such as South-East Asia, hepatitis B virus (HBV) infection occurs early in life and leads to chronicity in the vast majority of the cases (2). In nonendemic areas such as Western Europe, acquisition of HBV occurs later and CHB only occurs in 5 to 10% of the cases. CHB leads to cirrhosis in around 20% of the cases and cirrhosis exposes to the risk of hepatocarcinoma with an annual incidence of 3 to 4% (3). Before such an evolution, the importance of prevention by vaccination should be promoted.

At the stage of CHB, and until now, interferon-alpha (INF) is the only recomended drug in Europe. This drug may induce an inhibition of HBV replication with an e seroconversion in around 40% of CHB patients infected by the wild type virus (4). These data must be put in comparison to a 5 to 10% annual rate of spontaneous seroconversion. In contrast, results obtained with IFN in CHB patients infected by a precore mutant virus are disappointing and limited to 5 to 10% (5). In all CHB patients, IFN may induce numerous side effects (6).

Taking into account the limited efficacy of IFN and its side effects as well as the incidence of CHB, the emergence of new therapies is not surprising. This review will be limited to drugs which are now studied in clinical practice : nucleoside analogues, thymosin alpha, polyadenur, cytokines and vaccinotherapy.

Nucleoside analogues

Numerous nucleoside analogues are now under development. One of them is present on the market and another one will be available in the following months.

Ganciclovir

Ganciclovir is an acyclic nucleoside analogue of guanine. Its spectrum is cytemagalovirus, Herpes simplex virus, Epstein-Barr virus and varicella-zona virus. It has also been shown in vitro and in vivo that ganciclovir exerts some effects on HBV. Its efficacy remains however limited (7). Moreover, the absence of an oral form is another limitation to its use in clinical practice.

Lamivudine

Lamivudine is a deoxycytidine analogue which inhibits viral DNA synthesis, mainly through its incorporation into new synthetized HBV DNA. It exerts also a competitive inhibiting effect against the DNA polymerase which codes for HBV. Numerous studies have been conducted with lamivudine in CHB patients. Phase 2 studies have demonstrated that a dose of 100 mg daily inhibits HBV replication in the vast majority of patients (8). Phase 2 and 3 studies have put in advance the safety of lamivudine administration, the occurrence of a very low incidence of side effects as well as the virological and histological efficacy of the drug (9-10).

In CHB patients infected by the wild type virus, e seroconversion rate after one and two year(s) treatment is around 20% and 35%, respectively (11). In CHB patients infected by the precore mutant virus, preliminary results suggest that lamivudine therapy is more efficaceous than IFN (12). These very positive results are counterbalanced by the risk of emergence of lamivudine-resistant virus which incidence is directly related to the duration of treatment and the immune status of the patient (13,14). The clinical importance of these lamivudine-resistant viruses seems to be limited even if long term consequences remain unknown. It must also be outlined that cessation of lamivudine therapy is associated with reemergence of HBV. Such a phenomenon may induce liver decompensation in cirrhotic patients. The use of lamivudine in patients with CHB late-stage liver disease appears however very positive by inducing stabilisation and even an improvement in numerous patients. This improvement may even lead to remove the patient from liver transplant waiting list.

Famciclovir

Famciclovir is a guanine nucleoside analogue which spectrum is herpes virus but also HBV. In comparison to lamivudine, it seems to be less efficaceous and results of phase 3 study has conducted the company to interrupt its development in CHB patients (15).

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Other analogues

Numerous other analogues are under development. Among them, adefovir is currently the most promising since its potency seems to be superior to lamivudine and it is also efficaceous against lamivudine resistant viruses (16). Phase 3 studies have been recently started. Long-term safety must however still be demonstrated in view of the recent drawback observed with another nucleoside analogue, lobucavir.

Thymosin alpha

Thymosin alpha is a synthetic polypeptide able to modulate humoral and cellular immunity. Its efficacy is similar to that of IFN but it seems to induce less side effects (17).

Polyadenur

Polyadenur (polyA-polyU) is a synthetic immunomodulator which is formed by a double RNA branch. It has been used in combination with IFN and this combination appears to be superior to IFN alone (18).

Cytokines

Among cytokines, interleukin 12 (IL-12) and IL-2 have been given in CHB patients. These two cytokines have shown a certain degree of efficacy but they induce numerous side effects which will limit their clinical use (19,20).

Vaccinotherapy

Several pharmaceutical companies are conducting studies in which different kind of prophylactic or therapeutic vaccines are given to CHB patients. The aim of this approach is to obtain an induction of immune response by presenting HBV enveloppe epitopes and/or by inducing post-translational modification in viral proteins. A deficit in immune response has been demonstrated in CHB patients with Th1/Th2 (21).

Until now, results are relatively disappointing even if some encouraging data have also been reported. For example, administration of a preS2/S vaccine has induced a suppression or an inhibition of HBV replication in around 40% of the patients in an open study (22). However, using the same vaccine, a prospective controlled study did not confirm these results (23).

Conclusion

More studies must be performed using all these new drugs. However, the therapeutic field for CHB patients will be profoundly modified in the following years. It seems highly likely that drug combination will be the next step. Recent data obtained in 11 patients with the combination of thymosin alpha, lamivudine and famciclovir are very impressive showing lost HBeAg in 7 patients. However, such results deserve confirmation (24).

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