Therapy of Hepatitis B Virus Infections – Potential and Limitations

Specific therapy of viral infections has been and still is an underdeveloped field of medicine. While most bacterial infections can be treated with a relatively small set of antibiotics, for most viral infections no drugs are available. There are a few important exceptions, hepatitis B virus (HBV) being one of them. The basis for therapeutic studies on chronic hepatitis B was created by the discovery of the HBV particle by D.S. Dane in 1970 and the HBV DNA polymerase within that particle by W.S. Robinson in 1973 [1]. In a landmark study from T.C. Merigan and W.S. Robinson, chronic hepatitis B was the first infection to be treated with human leukocyte interferon [2] and has remained the only viral infection where interferon has a generally accepted role as pointed out by Brunetto and Bonino in this special issue [pp. 163–170] of *Intervirol*. Merigan and Robinson soon realized that interferon alone was not the solution because only a minority of patients could be cured. They started to combine interferon with the then available nucleoside analogues as additional drugs against HBV, but the toxicity of these early compounds was too high [3]. Further progress was disappointingly slow, partly because the efforts of the medical community and the pharmaceutical industry were small. One reason for this neglect may have been the amazing efficacy of the hepatitis B vaccine which raised the hope that HBV and the disease hepatitis B may disappear by continuous prevention without additional efforts to treat those who were already infected. This attitude, however, is cynical in view of the roughly 600,000 deaths per year due to chronic HBV infection.

New impulses for HBV therapy came from the appearance and explosive spread of HIV in industrialized countries during the early 1980s. Now, the development for an effective antiviral therapy has received highest priority. The USA spent 3.1 billion US dollar in the time up to 2010 for HIV research, and compared to other viral infections, effective HIV drugs came to the market relatively fast. HBV research, the ‘poor cousin’ of HIV research, received only USD 53 million in the same time period [4]. Due to the reverse transcription present in the life cycles of both HBV and HIV (see articles from Glebe and König [this issue, pp. 134–140] and Gürtler [this issue, pp. 212–217]), it could be presumed that inhibitors of the HIV reverse transcriptase would also be active against HBV. Early in the 1990s it was recognized that the reverse transcriptase inhibitor lamivudine was effective in vitro against HBV [5], but the first success in patients was observed only as a kind of positive side effect in HIV-coinfected patients [6]. The pharmaceutical industry finally began to intensify their efforts to test their antiviral candidate substances against HBV, which, for example, led to the development of the licensed drugs adefovir, telbivudine, and entecavir. Currently, however, the most potent HBV drug was again an off-spin from HIV therapy. Although van Bömmel et al. [7] and others noted already in 2002 that the HIV drug tenofovir was very effective against HBV in HIV-coinfected patients, industry preferred to introduce in 2003 the closely related, but much less effective, adefovir for therapy of lamivudine-resistant HBV strains.

Resistance development in chronic hepatitis B patients has been a major obstacle that has led to the withdrawal of many initially promising drugs. Fortunately, the molecular basis of resistance to nucleoside analogues is well understood (see Warner and Locarnini [this issue, pp. 218–224]) and the detection of HBV resistance both at the phenotypic (see Glebe and Geipel [this issue, pp. 225–231]) and genotypic levels (see Neumann-Fraune et al. [this issue, pp. 232–236]) is feasible and implemented at many places. However, due to the resistance problem, there are not many therapy options. Interferon- α , today in its recombinant and pegylated form, is still an option because it seems to reduce – if effective – the intrahepatic viral burden. However, it is limited to a minority of responding patients and is not equally effective against all HBV genotypes (see Kramvis [this issue, pp. 141–150]). Among many experimental therapy concepts (which shall not be discussed in this special issue) the blocking of HBV attachment and/or entry, in particular with the preS1 lipopeptides developed by S. Urban, is very advanced and highly promising. Another approach is to target host factors which either are necessary for the HBV life cycle or interfere with HBV multiplication (see Gehring et al. [this issue, pp. 158–162]). The ultimate goal would be selective degradation of the covalently closed circular HBV DNA. As recently described, this is inducible by interferon- α or lymphotoxin- β via APOBEC3 cytidine deaminases [8]. Immunotherapy with selected combinations of HBV antigens in immunostimulatory settings is also an interesting concept, but not the subject of this special issue.

The main purpose of current HBV therapy is the permanent suppression of HBV replication in patients with chronic hepatitis B, which leads to suppression of HBV-induced inflammation and prevents development of cirrhosis and hepatocellular carcinoma (see van Bömmel [this issue, pp. 171–180]). This suppression is in some ways unexpected because nucleos(t)ide analogues do not eliminate the intranuclear HBV covalently closed circular DNA which exists as a kind of minichromosome. The analogues also do not suppress HBV gene expression and antigen production. It is well established that HBV pathogenicity is mainly caused by the cellular immune response

to HBV antigens [9], but obviously HBV DNA replication is a second necessary factor. An intrinsic disadvantage of this therapy is that its duration is indefinite unless additional effects reduce and finally control HBV expression.

The currently licensed drugs are approved for treatment of active chronic hepatitis B, but there are many other potential applications which are described in this special issue. Severe or fulminant courses of acute hepatitis B may justify an antiviral therapy (see Tillmann and Patel [this issue, pp. 181–188]). Reactivation of occult HBV infections is a dangerous side effect of certain forms of immunosuppression which can be prevented by early antiviral therapy (see Raimondo et al. [this issue, pp. 189–195]). If antiviral therapy is initiated too late, liver transplantation is the last option to save the patient. But for a sustained cure, reinfection of the transplant must be prevented, and besides hepatitis B immunoglobulin, preemptive antiviral therapy has become increasingly important (see Roche and Samuel [this issue, pp. 196–201]). In many HBV-infected persons immunopathogenesis is so low that, according to current guidelines [10], there is no need for therapy. Nevertheless, it may be advisable in some situations to treat these persons as well if they are highly infectious and come into close contact with people. This recommendation applies in particular to HBV-infected healthcare providers who perform exposure-prone procedures and for pregnant women with very high viremia levels (see Gerlich [this issue, pp. 202–211]). Specific problems occur in patients with HIV coinfection (see Gürtler [this issue, pp. 212–217]).

Many publications on these aspects exist, but they are spread over the literature. It was the goal of the editors to assemble these topics in one timely issue of *Intervirology*, mainly from the view point of medical virology and clinical hepatology. We hope that this special issue stimulates the optimization and optimal use of HBV therapy. We thank all authors for their valuable contributions as well as S. Karger AG and the Editor-in-Chief Jean-Claude Manuguerra for giving us the opportunity to realize this publication.

Wolfram H. Gerlich, Giessen
Dieter Glebe, Giessen
Lutz G. Gürtler, Munich
Rolf Kaiser, Cologne

References

- 1 Gerlich WH: Medical virology of hepatitis B: how it began and where we are now. *Virol J* 2013;10:239.
- 2 Greenberg HB, Pollard RB, Lutwick LI, Gregory PB, Robinson WS, Merigan TC: Effect of human leukocyte interferon on hepatitis B virus infection in patients with chronic active hepatitis. *N Engl J Med* 1976;295:517–522.
- 3 Sacks SL, Scullard GH, Pollard RB, Gregory PB, Robinson WS, Merigan TC: Antiviral treatment of chronic hepatitis B virus infection: pharmacokinetics and side effects of interferon and adenine arabinoside alone and in combination. *Antimicrob Agents Chemother* 1982;21:93–100.
- 4 Hatzakis AI, Wait S, Bruix J, et al: The state of hepatitis B and C in Europe: report from the hepatitis B and C summit conference. *J Viral Hepat* 2011;18(suppl 1):1–16.
- 5 Doong SL, Tsai CH, Schinazi RF, Liotta DC, Cheng YC: Inhibition of the replication of hepatitis B virus in vitro by 2',3'-dideoxy-3'-thiacytidine and related analogues. *Proc Natl Acad Sci USA* 1991;88:8495–8499.
- 6 Benhamou Y, Dohin E, Lunel-Fabiani F, Poynard T, Huraux JM, Katlama C, Opolon P, Gentilini M: Efficacy of lamivudine on replication of hepatitis B virus in HIV-infected patients. *Lancet* 1995;345:396–397.
- 7 van Bömmel F, Wünsche T, Schürmann D, Berg T: Tenofovir treatment in patients with lamivudine-resistant hepatitis B mutants strongly affects viral replication. *Hepatology* 2002;36:507–508.
- 8 Lucifora J, Xia Y, Reisinger F, et al: Specific and nonhepatotoxic degradation of nuclear hepatitis B virus cccDNA. *Science* 2014;343:1221.
- 9 Guidotti LG, Chisari FV: Immunobiology and pathogenesis of viral hepatitis. *Annu Rev Pathol* 2006;1:23–61.
- 10 European Association for the Study of the Liver: EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol* 2012;57:167–185.