Hepatitis B virus (HBV) infection remains a major public health problem with an estimated 300 million HBsAg carriers worldwide. In endemic areas like Asia and Africa, where the HBsAg carrier rate is as high as 15%-20%, hepatitis B is primarily a disease of childhood, acquired either perinatally from HBsAg-positive mothers or horizontally from infected mates or family members.\textsuperscript{1,2} In areas of intermediate endemicity (e.g., Italy, Japan, Spain, Greece, Portugal), where 2%-10% of the population is HBsAg carrier, infection occurs in both adults and children. In low endemicity areas (e.g., Northern European countries, USA), infection in infancy and childhood is uncommon and <1% of the population has chronic HBV infection,\textsuperscript{3} which usually, though not exclusively, affects ethnic minorities originating from endemic countries or travelers to endemic areas. These epidemiological data are, however, rapidly changing with the introduction of universal hepatitis B vaccination in some countries, and with an increase in travel facilities and international adoption. While HBV infection in children has dramatically decreased in countries like Taiwan, Italy and the USA that have introduced infant, or infant and adolescent, universal vaccination, the number of infected children is not declining in countries where no universal vaccination policy is in place. Until universal vaccination is introduced worldwide, HBV infection will continue to be a serious problem.

HBV is highly infectious, much more than hepatitis C virus or human immunodeficiency virus, and chronically infected individuals readily infect unvaccinated family members, mates and sexual partners. The probability of becoming a chronic HBV carrier is correlated to the age at infection and the efficiency of the immune system, being highest in children infected within the first year of life, who tend to become immuno-tolerant to the virus. Thus, more than 90% of infected infants, including the 5% who do not respond to HBV vaccination, become chronic carriers as compared to 6%-10% if the infection occurs after the 6th year of life.\textsuperscript{4,5} The majority of chronically infected children are asymptomatic with normal or minimally abnormal liver function tests, but their liver histology often shows progressive inflammatory changes.\textsuperscript{6} Besides posing a serious infection risk to the community, chronically HBV infected children, particularly if male, have a high risk of progressing to cirrhosis and hepatocellular carcinoma.\textsuperscript{6-11} the likelihood of developing these complications being correlated to the length of time to achieve anti-HBe seroconversion.\textsuperscript{12} Spontaneous HBeAg loss in chronically infected children occurs at an annual rate of 10%-16%.\textsuperscript{6,13} while spontaneous loss of HBsAg is as low as 0.6% per year,\textsuperscript{14} the children achieving earlier seroconversion being those with biochemical and/or histological evidence of active disease. Moreover, the annual HBsAg clearance rate is significantly higher in those children who are already anti-HBe positive (= low viral load), than in those with HBeAg (= high viral load) (1.7% vs. 0.4%). A treatment able to speed up anti-HBe serocoversion would therefore have a major impact in avoiding the spread of infection and serious complications.

Treatment with interferon (IFN) does accelerate spontaneous HBeAg clearance.\textsuperscript{15} HBeAg loss has been shown in 30%-40% of Caucasoid children with chronic HBV infection at the end of short courses of IFN-alpha or lymphoblastoid IFN,\textsuperscript{16-21} but in only 8% of Chinese children, who usually acquire the infection at birth.\textsuperscript{22} Baseline features predicting HBeAg clearance during IFN treatment are the same as those associated with a higher rate of spontaneous seroconversion, i.e., histologically active disease, high transaminase activity and low HBV DNA levels. In contrast, children infected vertically, who are more likely to become immuno-tolerant to the virus and have inactive liver histology, low transaminase values and high HBV DNA levels are less likely to clear HBeAg spontaneously and to respond to IFN.\textsuperscript{22} Current European guidelines advise not to treat immuno-tolerant children with normal transaminase levels, high HBV DNA, mild changes on liver biopsy, because the published results in these children do not justify the cost and the particularly demanding nature of IFN treatment, which requires repeated injections.\textsuperscript{23}

When lamivudine, a nucleoside analogue that inhibits HBV replication and is taken orally, was introduced, there appeared to be new hope for children chronically infected by HBV. Unfortunately it was soon shown that in HBV-infected children, as in adults, lamivudine decreases the HBV viral load, but when stopped a rebound of viral replication is observed. In a large multinational study comparing lamivudine with placebo in 286 HBV-positive children with biochemically and histologically active liver disease, a significant reduction in HBV DNA level
was observed at the end of 52 weeks in those treated with lamivudine compared to controls, but the proportion of patients who continued to be HBeAg and HBV DNA negative 6 months after stopping treatment was 17% among children who had been treated with lamivudine and 13% among those who had received placebo, suggesting that lamivudine on its own is not effective in accelerating HBV immune control in chronically infected children with active disease. In addition, 19% of the children treated with lamivudine in this study developed YMDD mutations. A follow up of this study has been recently published, showing that continuing lamivudine treatment for further 12 months in children who did not respond to lamivudine during the first trial is associated with an unacceptable high incidence (64%) of YMDD mutations, which offsets the marginally improved rate of HBeAg loss and HBV DNA negativity.

Combining the anti-viral effect of lamivudine with the immune boosting action of IFN-alpha would appear to offer a rational therapeutic approach. A few studies have used this combination with different timing of lamivudine or IFN-alpha introduction in children with biochemically and histologically active chronic hepatitis B. Disappointingly, virological response, defined in all as anti-HBeAg seroconversion, clearance of HBV DNA and normalization of transaminases, was reported to be improved by the addition of lamivudine in only one study, suggesting that this approach may not be useful in the active phase of the disease. In none of these studies were YMDD mutations investigated.

In the present issue of the Journal, Sokucu et al review retrospectively their experience with IFN-alpha monotherapy (5 MU/m² subcutaneously three times a week for 6 months) versus IFN-alpha-lamivudine combination (IFN 5 MU/m² three times a week for 6 months as above, in association with oral lamivudine 4 mg/Kg/day for one year). The two groups of patients were similar demographically and in terms of disease activity before treatment, all children having biochemically and histologically active disease. Although children treated with the lamivudine-IFN combination had significantly higher HBV DNA loss at 6 months and anti-HBeAg seroconversion at 12 months of treatment compared to those receiving IFN alone, the final response rates at 24 months from the beginning of treatment were similar in the two groups, being 67% and 60% for HBV DNA loss and 73% and 60% for anti-HBeAg seroconversion, respectively. The lack of an untreated control group does not allow us to determine whether either mode of treatment is better than spontaneous HBV DNA loss or anti-HBeAg seroconversion in children of the same ethnic background, geographic location and degree of disease activity. The authors conclude that IFN-lamivudine combination treatment is not indicated for chronic hepatitis B in children.

On the basis of all the above evidence, suggesting that IFN is the only effective treatment for chronic HBV infection in children, acting by accelerating spontaneous anti-HBeAg seroconversion, the question arises as to whether children with chronic hepatitis B should be treated at all. IFN is ‘child unfriendly’, has numerous side effects, including transiently impaired growth, and is very expensive. Though the doubt on whether to treat children with active disease, who are likely to achieve spontaneous seroconversion in childhood or early adulthood, is now legitimate, there remains the problem of what to do with children infected perinatally, in whom HBeAg to anti-HBe seroconversion usually occurs during the third or fourth decade of life. These are the children at high risk of complications, since the duration of infection before anti-HBe seroconversion predisposes to liver disease reactivation and virus replication that in turn are related to the development of cirrhosis and hepatocellular carcinoma. These patients represent the majority of children with chronic HBV infection worldwide, either because of lack of vaccination or because of vaccine failure, observed in 5% of the vaccinated children overall but in 15% of babies of HBeAg-positive mothers.

A treatment strategy efficient in inducing HBV immune control in these immuno-tolerant children is highly desirable. A recently published pilot study shows that, in contrast to the results in children with active disease, the combination of lamivudine and IFN-alpha may be of benefit in children that are immuno-tolerant to HBV. Twenty-three immuno-tolerant children with persistently normal transaminase levels and inactive histology were treated sequentially with combination therapy. Lamivudine was given alone for 8 weeks to decrease the viral load, after which time IFN-alpha was added for 44 weeks to boost virus-specific immune responses. Eighty-two percent of these patients became HBV DNA negative by the end of the 12-month treatment period, though three months later only 5 children (22%) continued to be HBV DNA negative. All these 5 children seroconverted to anti-HBeAg and 4 to anti-HBsAg. After a three-year follow up, the anti-viral response
was sustained. None of the 23 patients developed YMDD mutations. These results represent a considerable improvement on previous reports in immunotolerant children.\(^2\) This therapeutic approach should be tested in large control trials as it challenges the widely held view that children with normal transaminases should not be treated.\(^2\)

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References

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