Pediatric Issues in New Therapies for Hepatitis B and C

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Two antiviral treatments have been approved for hepatitis B virus (HBV) infection by the US Food and Drug Administration (FDA) for use in children: interferon (IFN)-α, 6 MU/m^2 three times a week subcutaneously for 6 months, and lamivudine, 3 mg/kg/d orally for 12 months. Twenty-six percent to 58% of children treated with IFN become HBV DNA negative, and up to 38% become negative to hepatitis B e antigen (HBeAg). Lamivudine, a nucleoside analogue that blocks viral replication by inhibition of the HBV polymerase, has been associated with comparable rates of seroconversion of HBeAg to anti-HBe. Loss of surface antigen occurs in less than 5% of patients treated with lamivudine, compared with 3% to 33% in those treated with IFN-α. Fifty percent to 65% of children treated with lamivudine clear HBV DNA after 12 months of therapy, but relapse rates have not been clarified. Patients treated with lamivudine develop drug-resistant (YMDD) mutants in the HBV polymerase at the rate of 16% to 32% per year. No treatments for children with hepatitis C virus (HCV) have been approved by the FDA. However, published reports describe treatment with IFN monotherapy and combination therapy with IFN and ribavirin. Trials of PEG-IFN alone or in combination with ribavirin are in progress. Given the lack of data regarding treatment of HCV in children, it is generally agreed among pediatric hepatologists that the optimal treatment is within the context of randomized, controlled trials.

Introduction

Hepatitis B virus (HBV) infects at least 350 million people worldwide, 25% to 30% of whom have acquired HBV via perinatal transmission or in early adulthood. These people are at high (up to 40%) risk for fatal complications of HBV, including liver failure, chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). The US Food and Drug Administration (FDA) has approved two antiviral treatments: interferon (IFN)-α and lamivudine, an HBV polymerase inhibitor. In this paper, safety and efficacy profiles for each agent and for combination therapy are reviewed. Special considerations such as HBV nephropathy and liver transplantation in children with HBV are discussed. In general, therapy is most effective when given to children with hepatitis B e antigen (HbeAg) positivity, detectable serum HBV DNA, and abnormal serum aminotransferases.

No article concerning hepatitis in children would be complete without mentioning that infection with HBV is preventable by vaccine. After routine infant HBV immunization, the prevalence of hepatitis B surface antigen (HBsAg) among children decreased from 10.5% to 1.7% in Taiwan, from 7.5% to 0% in American Samoa, and from 10.3% to 0.6% in The Gambia [1–3]. In Taiwan, the incidence of HCC among children aged 6 to 14 years decreased by 50% after introduction of routine HBV immunization [4]. In the United States, according to unpublished data from the Centers for Disease Control, from 1990 to 1998, the incidence of acute hepatitis B among children aged less than 15 years decreased from 0.66 to 0.16 in 100,000. Among adolescents aged 15 to 18 years, the incidence decreased to 0.96 from 1.94 in 100,000 [5]. These data provide a strong argument for the view that the most effective way to eradicate HBV is through universal infant vaccination. Armstrong *et al.* [6] estimated that, before universal vaccination was initiated in the United States in 1991, HBV infected at least 8700 non-Asian children and at least 7300 Asian-American children aged less than 10 years annually, excluding perinatal infection. The total estimate, not including perinatal infection, ranged from 12,000 (95% CI, 5500–27,700) to 24,900 (95% CI, 16,700–42,3000), depending on the approach used to estimate infection prevalence. Therefore, despite major success in reducing chronic HBV infection in children, there are many thousands of children worldwide who do not receive the benefit of the HBV vaccine and who may benefit from some type of antiviral therapy.

Although worldwide prevalence rates of chronic hepatitis C virus (HCV) infection in the pediatric age group are not known, at least 150,000 children in the United States are estimated to have chronic hepatitis C. In the past, the major route of transmission of HCV in children was via blood and blood products, so that groups at particular risk included children with thalassemia, hemophilia, and leukemia, or those who had undergone organ transplantation, had experienced renal failure requiring dialysis, or

were born prematurely. Screening of blood donors has drastically reduced the risk of HCV infection through blood transfusion, making maternal-fetal transmission the main source of infection in children. The natural history, diagnosis, and treatment for children with HCV are described in this review.

Natural History of Hepatitis B Virus

The age at which HBV is acquired is strongly correlated with outcome. The risk of developing chronic hepatitis B in children acquiring HBV infection before the age of 1 year, between 2 and 3 years, between 4 and 6 years, and later than 7 years is 70% to 90%, 40% to 70%, 10% to 40%, and 6% to 10%, respectively [7]. However, cirrhosis and HCC are rarely seen in children, suggesting that treatment before the development of complications of chronic liver disease should be a priority. This is especially important because the relative lifetime risk of HCC in chronic HBV carriers is at least 100 to one, compared with the risk for uninfected subjects [8•].

Diagnostic Approach to Hepatitis B Virus

Children who are positive for HBsAg should have liver function assessed by serum aminotransferases, total and direct bilirubin, albumin, international normalized ratio (INR), and complete blood count, for evidence of hypersplenism. HBeAg and serum HBV DNA should be assessed because they indicate actively replicating HBV. Serum α-fetoprotein, a relatively insensitive marker of HCC, should be assessed annually. Because both HIV and HCV are bloodborne pathogens, evidence for these pathogens should be sought before antiviral therapy is contemplated. Liver biopsy should be performed in children before initiation of any antiviral therapy. Baseline liver ultrasound for cirrhosis and HCC should be performed. The frequency with which follow-up imaging studies should be done has not been determined.

Treatment for Hepatitis B Virus

The long-term goals of therapy include reduction of hepatic inflammation and the evolution of chronic hepatitis, cirrhosis, and HCC; reduction of HBV transmission; and elimination of the social stigma attached to the diagnosis of chronic HBV. Short-term goals include normalization of serum aminotransferases, loss of HBeAg and HBV DNA, seroconversion to anti-HBe and, ultimately, loss of HBsAg and development of anti-HBs. Because children with HBV usually have mild histologic changes, most studies have not assessed histologic endpoints. The two most widely tested therapeutic agents have been the immune modulator IFN-α and the antiviral agent lamivudine, a nucleoside analogue that inhibits HBV replication via blockage of HBV polymerase.

IFN exerts antiviral effects on the HBV virus through multiple mechanisms, including enhanced CD8 T-cell, virus-specific killing, upregulation of natural killer cells, upregulation of class I major histocompatibility complex antigen presentation, and activation of cellular endonucleases. In the largest randomized, controlled trial of IFN for children with HBV, 26% of the 70 children treated with 6 MU/m^2 three times a week for 6 months cleared HBV DNA and lost HbeAg, compared with 11% of the 74 control subjects [9]. Results of a number of pediatric trials of various doses of IFN-α are summarized in Table 1. The major effect of IFN-α in children with chronic HBV may simply be to accelerate the spontaneous course of HBV infection. Bortolotti *et al.* [10] found that conversion to anti-HBe in children with chronic HBV occurred in at least 60% 5 years after IFN therapy, whether or not they responded to the drug initially, a seroconversion rate identical to that observed in untreated children in a similar age group. However, IFN treatment was associated with loss of HBsAg in at least 25% of respondents, compared with 0% of nonresponders and untreated children. Children who are the most likely to respond to IFN are those with high serum aminotransferases and low levels of HBV DNA [11].

The FDA has approved IFN-α at a dosage of 6 MU/m^2, subcutaneously three times a week for 6 months in children aged 1 to 18 years. In children aged less than 1 year, IFN treatment for cavernous hemangioma has resulted in a 10% to 20% rate of spastic diplegia, probably caused by IFN-induced cytokines crossing the blood-brain barrier [12]. Other contraindications include moderate cytopenias, severe renal or cardiac disorders, autoimmune diseases, and neurologic disorders. Adverse effects include flulike symptoms, anxiety, depression, anorexia, weight loss, hair loss, bone marrow suppression, thyroid disorders, and autoantibody induction. Children undergoing IFN treatment should be monitored regularly for hemoglobin, hematocrit, leukocyte count, absolute neutrophil count, platelet count, serum aminotransferases, renal function, and thyroid function.

Lamivudine is a nucleoside analogue that blocks viral replication by termination of the proviral DNA chain during elongation and inhibition of the HBV polymerase. Preliminary pharmacokinetic studies have shown that a dosage of 3 mg/kg/d orally is appropriate for children aged 2 to 12 years [13]. In the largest pediatric study to date, 191 children with chronic HBV were randomly assigned to receive lamivudine (3 mg/kg, maximum of 100 mg) once daily for 52 weeks, and 91 received placebo. Twenty-three percent exhibited a virologic response (absence of HBeAg and HBV DNA in serum) at 52 weeks, compared with 13% of placebo-treated patients (P=0.04) [14••]. Treatment efficacy assessed in a variety of ways is shown in Table 2. The median time for normalization of alanine aminotransferase (ALT) values was 24 weeks. The higher the baseline ALT value, the higher the virologic response. Other baseline characteristics associated with increased virologic

Table 1. Response rates for interferon alfa in children with chronic hepatitis B

Study	Treatment (duration)	Subjects, *n*	Response (%)	Controls, *n*	Response (%)
Ruiz Moreno *et al.* [40]	10 MU/m^2 three times a week (3 mo)	12	HBV DNA negative (33) HBeAg negative (33)	12	HBV DNA negative (25)
Ruiz Moreno *et al.* [41]	10 MU/m^2 three times a week (6 mo)	12	HBV DNA negative (58)	12	HBV DNA negative (17)
	5 MU/m^2 three times a week (6 mo)	12	HBV DNA negative (42)		
Utili *et al.* [42]	3 MU/m^2 three times a week (12 mo)	10	HBV DNA negative (30) HBeAg negative (20)	10	HBV DNA negative (10) HBeAg negative (10)
Sokal *et al.* [43]	9 MU/m^2 three times a week (16 wk)	29	HBV DNA negative (48) HBeAg negative (38)	25	HBeAg negative (8)
Barbera *et al.* [44]	7.5 MU/m^2 three times a week (6 mo)	21	HBeAg negative (30)	37	HBeAg negative (13.5)
	3 MU/m^2 three times a week (6 mo)	19	HBeAg negative (21)		
Sokal *et al.* [9]	6 MU/m^2 three times a week (6 mo)	70	HBV DNA negative (26) HBeAg negative (26)	74	HBV DNA negative (11) HBeAg negative (11)

HBeAg—hepatitis B e antigen; HBV—hepatitis B virus; mo—months; wk—weeks.
Data from Chongrisawat and Poovorawan [8•].

response included a histologic activity index score higher than 4 and a baseline HBV DNA less than 800 mEq/mL. Nineteen percent (31 of 166) of the lamivudine-treated patients developed drug-resistant mutations in the YMDD motif of the HBV polymerase gene. Only one of the children with the YMDD mutation lost HbeAg, but median HBV DNA and ALT levels were substantially lower at week 52 compared with baseline in this group despite development of the mutation.

A few authors have reported on the combination of IFN and lamivudine for treatment of children with chronic HBV. Dikici *et al.* [15] found that 12 months of combination therapy was associated with higher rates of ALT normalization and clearance of HBV DNA, compared with IFN alone; however, the complete response rate (HBeAg/anti-HBe seroconversion plus clearance of HBV DNA plus normalization of ALT) 6 months after cessation of therapy did not differ between groups.

A few reports have discussed HBV management after liver transplantation in children, but little information is available about the treatment of HBV-associated nephropathy. Shapira *et al.* [16] reported that lamivudine, 3 mg/kg/d for 14 to 36 months, was associated with clearance of HBV DNA and normalization of ALT in three pediatric liver recipients; one child developed lamivudine resistance after 22 months, and one developed progression of liver fibrosis. All three remained positive for HBeAg and HBsAg, and all tolerated the drug well. In the child who developed lamivudine resistance, addition of famciclovir, 750 mg orally each day, was associated with seroconversion and the disappearance of serum HBV DNA [17]. Bhimma *et al.* [18] reported that treatment of HBV nephropathy with IFN for 16 weeks was associated with higher clearance of HbeAg and remission of proteinuria in about half of the patients treated with IFN, compared with no remission of proteinuria in the untreated control subjects.

Thus, pediatric HBV management has received increased attention in the past few years, thanks in part to changes in FDA policies in favor of treatment trials in children. Other nucleoside analogues under consideration include famciclovir and adefovir dipivoxil. Pegylated interferon (PEG-IFN), currently being studied for its effects on adults with HBV, should also be considered for experimental antiviral trials in children with HBV. Because there is still much to be learned in this area, testing of potential antiviral agents in randomized, controlled trials is strongly recommended. This careful approach would maximize the opportunity to learn the best way to treat this potentially serious liver disease of childhood.

Hepatitis C Virus

Screening of blood donors for HCV has drastically reduced the risk of acquisition via blood transfusion, but there is no means of preventing maternal-fetal transmission of HCV infection. Maternal transmission occurs in 0% to 15% of pregnancies in anti-HCV–positive women, with higher rates in HIV-infected mothers (5%–36%) and in those with high viral loads. Maternal transmission is the major source of the infection in the pediatric age group [19–21]. Chronic hepatitis C develops in 55% to 80% of infected children [22,23].

Natural history

Chronic HCV infection is usually insidious in children. It will be missed unless it is investigated in such high-risk children as recipients of blood transfusion before 1990, injection drug users, and children born to HCV-viremic women. Occasionally the infection progresses more rap-

Table 2. Efficacy of lamivudine in children with chronic hepatitis B

Response at week 52	Placebo, *n* (%)	Lamivudine, *n* (%)	Odds ratio (95% CI)	*P*-value*
Total, *n*	95	191		
Virologic response†	12 (13)	44 (23)	2.1 (1.0–4.1)	0.04
Sustained normalization of ALT‡	11 (12)	100 (55)	8.4 (4.2–16.9)	<0.001
Virologic response and acquisition of anti-HBe	12 (13)	42 (22)	1.9 (1.0–3.9)	0.06
Loss of HBeAg	14 (15)	50 (26)	2.1 (1.1–3.9)	0.03
HBV DNA undetectable§	15 (16)	117 (61)	8.4 (4.5–15.7)	<0.001
Loss of HBeAg	0	3 (2)	—	—

*Values were calculated with the use of the chi-square test.
†A virologic response was defined by the absence of HBeAg and HBV DNA in serum.
‡Only patients with baseline ALT levels that exceeded the upper limit of the normal range were included in the analysis (88 in the placebo group and 183 in the lamivudine group).
§Levels were undetectable on branched-chain DNA assay with a lower limit of detection of 0.7 mEq/mL.
ALT—alanine aminotransferase; HBeAg—hepatitis B e antigen.
Data from Jonas *et al.* [14••].

idly to chronic liver disease, as reported in a child who acquired HCV via blood transfusion and progressed to cirrhosis by 28 months of age [24]. Given that an estimated 5% to 10% of chronically infected people may succumb to either cirrhosis or liver cancer, serious consideration should be given to the development of treatment protocols for infected children [25].

Diagnostic approach

Children at risk for HCV because they received blood or blood products before 1990 should be screened, as should recipients of organs before 1990, injection drug users, and children born to anti-HCV–positive women. Screening should be with third-generation, enzyme-linked immunosorbent assays, which shorten the duration of the preserologic window to 4 to 6 weeks after exposure [26•]. If the antibody is present, viral RNA should be tested with the qualitative polymerase chain reaction (PCR) assay. The quantitative assay should be done if therapy is contemplated because changes in the viral load may predict response to therapy. Viral genotype should be assessed because genotypes 1 and 4 are predictive of relatively poor response to IFN. In infants aged less than 18 months, antibody-based testing is confounded by passively transferred maternal IgG, and HCV RNA is the only reliable way to demonstrate active infection.

Liver function should be assessed by serum aminotransferases, total and direct bilirubin, alkaline phosphatase, INR, and complete blood count. Serum α-fetoprotein for HCC should be done at baseline; the optimal subsequent interval between tests has not been determined. Liver ultrasound should be done for changes of cirrhosis or HCC. Because serum aminotransferases are a poor index of hepatic histology, liver biopsy should be performed at baseline. In addition, because HBV and HIV are also bloodborne pathogens and individuals are sometimes coinfected, evidence for these pathogens should be sought before therapy is contemplated.

Treatment

No treatments for children with HCV have been approved by the FDA. However, published reports describe treatment with IFN monotherapy and combination therapy with IFN and ribavirin. Trials of PEG-IFN alone or in combination with ribavirin are in progress. Given the lack of data regarding treatment of HCV in children, it is generally agreed among pediatric hepatologists that the optimal treatment is within the context of randomized, controlled trials. Children to be considered for treatment include those with viremia who are aged more than 2 years (because viral clearance may occur before this and IFN treatment in young infants may result in spastic diplegia) who have inflammation on liver biopsy [12]. Children with normal ALT values should not be excluded from therapeutic trials because it is not yet clear that ALT is a good predictor of response to therapy. The usual exclusion criteria for IFN-based treatment trials in adults apply in children.

Jacobson *et al.* [27•] provided a useful analysis of the results of IFN monotherapy in the English-language literature. They surveyed 366 treated children and 105 untreated control subjects in a total of 19 trials in five countries. Sustained viral response (SVR), defined as absence of HCV RNA by PCR 6 months after cessation of therapy, was 36% for the entire group; the SVR for genotype 1 was 27%, and the SVR for non-genotype 1 was 70% (Fig. 1). These results contrast with the 8% SVR reported for adults [28]. One major conclusion to be drawn from this survey is that children appear to respond better to IFN compared with adults. Although publication bias may have affected the results, they are biologically plausible because children have a shorter duration of infection, precirrhotic liver disease, and lower viral loads, all of which predict a favorable response to IFN monotherapy in adults [29]. Another conclusion is that children infected with genotype 1 exhibit a less favorable response to IFN monotherapy, similar to results in adults. The emergence of combination therapy and PEG-IFN–based therapies, which are more effective

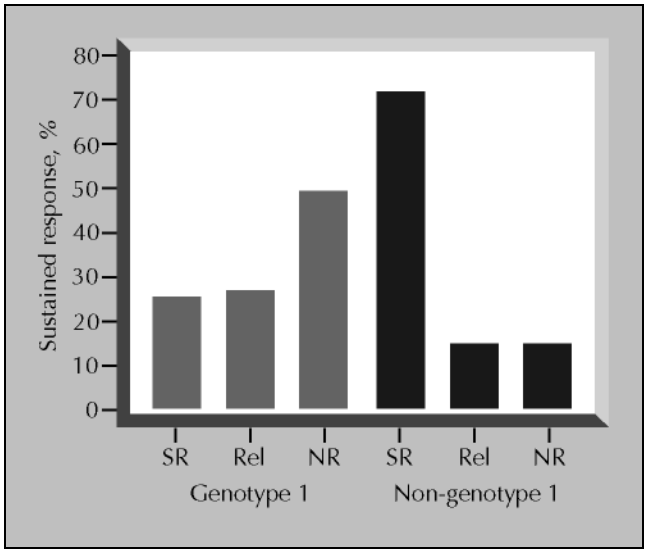

Figure 1. Sustained-response rate (SR), relapse (Rel), and nonresponse (NR) rates to interferon-α are shown for 75 children with chronic hepatitis C virus in whom genotype was characterized. (*From* Jacobson *et al.* [27•]; with permission.)

than IFN monotherapy in adults, suggests that IFN monotherapy should no longer be considered in children with HCV. However, the results with monotherapy will be useful for comparison when newer therapies for children with HCV become available.

Several reports have been published concerning the efficacy and safety of ribavirin in combination with IFN for children with HCV (Table 3) [30–34]. Ribavirin dosage ranged from 8 to 15 mg/kg/d and IFN dosage from 3 to 6 MU/m^2 three times a week subcutaneously for 1 year. Results were superior to those observed for IFN alone, with HCV RNA clearance rates from 47% to 70% 6 months or more after therapy. Wirth *et al.* [34] recently reported an overall SVR of 61% in 41 children; gender, ALT level, route of transmission, and IFN pretreatment had no influence on SVR. Ribavirin-induced hemolysis resulted in significantly lower hemoglobin levels at 6 and 12 months of treatment with return to baseline values 6 months after cessation of therapy.

Although these results represent an advance in the management of children with chronic HCV, several considerations warrant caution. The first is the proven teratogenicity of ribavirin, the second is that none of the trials were controlled, and the third is that PEG-IFN, which has been associated with improved virologic response rates in adults, may be as efficacious in children as the combination of IFN and ribavirin. Given that children respond better to IFN monotherapy than do adults and that large numbers of adolescent HCV-infected young women of child-bearing age would be exposed to possible teratogenicity of ribavirin if that agent were used for treatment, PEG-IFN alone or in combination with ribavirin should be studied in large-scale multicenter trials before firm conclusions can be drawn regarding the optimal therapy for children and adolescents with chronic HCV.

Challenges with HCV infection exist in a number of pediatric populations. Ribavirin induces a dose-dependent hemolysis and should thus be used with caution in children with hemolytic anemia. However, Li *et al.* [35] treated 18 children and young adults with thalassemia with combination therapy for 48 weeks and achieved a 72% SVR. This excellent result was all the more remarkable because 14 of the children were genotype 1 and four were genotype 6. However, because transfusion requirements increased considerably during the study, hemoglobin should be monitored frequently if this approach is contemplated.

Strader [36] recently reviewed treatment issues in understudied populations with HCV, of which children headed the list. Although this review did not specifically focus on children, some extrapolations can be made. The data suggest that therapy for patients with hemophilia should be done with the optimal therapy used for nonhemophiliac populations. Patients with renal transplants do not tolerate IFN well because IFN induces both acute and chronic graft rejection [37,38]. The common management challenges of IFN induction of autoantibodies, preexisting cytopenias, psychiatric conditions, neurologic illness, and treatment of problematic populations such as the homeless were raised. Another pediatric subpopulation that has received almost no attention is that of children coinfected with HIV and HCV. Resti *et al.* [39••] commented that, as with adults, stable HIV disease should be evident for children before treatment can be considered, and compliance to the combination of highly active antiretroviral therapy and anti-HCV treatment is likely to be a challenge. Likewise, data regarding the management of acute HCV in children who have undergone liver transplantation are lacking. All of these issues should be investigated in the pediatric age group before firm recommendations can be made.

Conclusions

Treatment of children with chronic HBV has shown that both IFN and lamivudine are associated with some antiviral effects in at least 25% of children. IFN may be somewhat more effective than lamivudine, and the latter drug is better tolerated clinically. However, emergence of the YMDD mutant in a substantial proportion of children suggests that more effective agents for management of HBV are urgently needed.

The most effective treatment for children with HCV to date is IFN in combination with ribavirin. However, the teratogenicity of ribavirin and the lack of controlled trials limit enthusiasm for this approach. Large-scale trials comparing PEG-IFN with and without ribavirin are needed, along with trials of non-IFN–based agents as they emerge. Perhaps the most dramatic improvement in the treatment of HBV and HCV in children is the widespread recognition that effective treatment for this previously understudied age group would be both humanitarian and highly cost-effective.

Table 3. Preliminary results with interferon alfa plus ribavirin in children with chronic hepatitis C

Study	Patients, *n*	Treatment schedule	HCV RNA clearance, %*
Bunn *et al.* [30]	61		At 6 mo
		IFN-α, 3 MU/m^2 for 48 wk +	
		Ribavirin, 8 mg/kg/d	52
		Ribavirin, 12 mg/kg/d	47
		Ribavirin, 15 mg/kg/d	58
Woynarowski *et al.* [31]	24		At 18 mo
		IFN-α, 3 MU/m^2 × 12 mo	18
		IFN-α, 3 MU/m^2 +	70
		Ribavirin, 15 mg/kg/d x 12 mo	
Lackner *et al.* [32]	12		At 24 mo
		IFN-α, 6 MU/m^2 +	50
		Ribavirin, 15 mg/kg/d × 12 mo	
Christensson *et al.* [33]	11	IFN-α, 5 MU/m^2 +	64
		Ribavirin, 15 mg/kg/d × 12 mo	

*Clearance rate is the percentage of patients who are HCV RNA negative.
HCV—hepatitis C virus; IFN—interferon; mo—months.
Data from Resti *et al.* [39••].

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