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Management of hepatitis C virus infection in childhood

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ABSTRACT

Infection with hepatitis C virus (HCV) is a worldwide health problem with more than 170 million infected individuals. In children, since 1992 almost all infections occurred through vertical transmission from an infected mother to her newborn infant. Natural history of HCV infection in children is not yet well defined, most children are asymptomatic and may remain so for decades. Most infected individuals (60-80%), regardless of their age at infection, become chronically infected with HCV. Spontaneous resolution in children appears to be infrequent. Positive HCV antibody implicate that patient has been exposed to the virus (EIA test). To discriminate between active or resolved HCV viral infection it is necessary to perform HCV RNA (PCR). Liver biopsy assess degree of liver injury and exclude concurrent diseases. HCV chronic infection is slow progressive in childhood. Progression of fibrosis seems to be a function of infection duration. Treatment objective is clearance of HCVRNA. IFNα is recognized as the drug approved for hepatitis C treatment in pediatric population. Combination therapy with IFNα or pegylated IFNα plus ribavirin is recently approved by US FDA and EMEA and clinical trials are in progress.

Key words. Children. Chronic hepatitis C. Hepatitis C virus. IFN. Pegylated IFN. Ribavirin.

INTRODUCTION

Infection with hepatitis C virus (HCV) is a worldwide health problem with more than 170 million infected individuals.[1,2] There is geographic variation in the incidence and prevalence of this infection.

HCV antibodies in children are between 0.2% and 0.4%, with an age-dependent increase in seroprevalence (0.2% for children aged 6-11 years and 0.4% for children aged 12-19 years).[3] Since 1992 almost all infections occurred through vertical transmission from an infected mother to her newborn infant.[4]

A recent report of Italy showed 40% reduction in the number of infected children seen from 2000 to 2004 by comparison with the previous 5 years. The low prevalence of HCV infection in children can be explained by the disappearance of post transfusion hepatitis in developed countries and the low efficacy of mother-to-child transmission, which has become the principal source of infection in the pediatric setting.[5-7]

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Natural history of HCV infection in children is not yet well defined; most children are asymptomatic and may remain so for decades. Diagnosis is generally made screening risk factor patients, elevated aminotransferases in routine tests and household HCV infected adults.[8]

Treatment strategies in adults have had a significant impact on the management of children with HCV chronic infection. All efforts now are towards to early diagnosis, safety and efficacy treatment.

EPIDEMIOLOGY AND RISK OF TRANSMISSION

After blood donor screening began in the 1990's, the risk of contracting HCV from blood and derivatives became extremely low in developed countries, intravenous drug abuse and high-risk sexual behavior are maintaining the reservoir of infection in adults and groups of adolescents. Transmission through infected blood products, however, remains a risk in countries where strict recommendations for screening blood products are not reliably adhered to. Horizontal transmission for family members is uncommon.[4]

In children vertical transmission is responsible for most "new infections", however, has an efficiency of only about 5%.[6-8]

Risk of maternal-infant transmission is increased (up to 22%) by level of maternal HCV viral load such as HIV co infection.[8-9]

Vertical transmission is almost always confined to women who have detectable HCV RNA. There is an extremely low risk of transmission with undetectable or intermittent viremia, even though the risk of infection in this clinical situation is as low as 0.3%.[9-10]

Presumably, both intrauterine and intrapartum infections occur. The mode of delivery does not affect risk of HCV transmission. Membrane ruptures longer than six hours and internal fetal monitoring were associated with an increased risk of transmission. Current recommendations are that women with HCV without HIV co-infection can be advised to breast feed.[8,9,11,12]

Recent studies showed that girls were twice as likely to be infected as boys. This finding, may reflects differences between males and females in hormonal or genetic susceptibility or immunological response to infections.[9-13]

Diagnoses of HCV infection in exposed infants is hampered by passive transfer of maternal antibodies during pregnancy persisting up to 13 to 18 months of life.[14] HCVRNA polymerase chain reaction (PCR) testing is highly specific, but its sensitivity is low at birth and in the first days of life (22%) while it increases at one month of age and thereafter (> 75%).[9-15]

A child born to a seropositive mother is considerer to be infected if serum HCVRNA is detectable in at least two separate determinations between 2- 6 months and whit persistence of anti-HCV antibodies after the first year of life. Chronic infection is defined as the persistence of HCV RNA for at least six months and resolution is determined by the persistent disappearance of HCVRNA.

NATURAL HISTORY AND DIAGNOSIS

Most infected individuals (60-80%), regardless of their age at infection, become chronically infected with HCV.[16]

Spontaneous resolution in children appears to be infrequent: in three large series, including vertical and horizontal acquisition, HCV clearance occurred in 5.6-10%,[5,9,17] children infected with genotype 3 (81% of whom were vertically infected) had the highest rate of viral clearance (22%) compared to other genotypes.[5,9]

In 266 vertically HCV infected children, 17% showed viral clearance by 2, 24% by 3, and 25% by 5 years of age (median age 14. 9 m).[17]

Transfusion acquired infection have a higher chance of spontaneous clearance than vertical acquisition. HCV genotype, viral load and immunotolerance in young infants, were proposed to influence viral resolution.[9-18]

Once chronicity is established, such as in older children, serological and histological features seem to be independent of the source and time of infection.[19] Illness is generally asymptomatic and characterized by a bening course during the first two decades of life. Advanced liver disease is rare during childhood and there are no reports of acute liver failure in HCV pediatric infected patient.[18] Clinical symptoms are mild and nonspecific in only 20% of cases during early childhood. Hepatomegaly is present in 10% of infected children.

HCV- associated cryoglobulinemia, vasculitis and porphyria cutanea tarda are not reported in children.[20]

Aminotransferases remains usually normal or mildly abnormal levels but it is not a reliable indicator of abscense of hepatic injury.[8,16,17,21]

Positive HCV antibody implicate that patient has been exposed to the virus (EIA test). Anti-HCV antibodies may be undetectable during first few weeks after HCV exposure or in immunocompromised patients.[18]

To discriminate between active or resolved HCV viral infection it is necessary to perform HCV RNA (PCR). HCV RNA PCR may be intermittently negative.

HCV genotype and HCV-RNA viral load provide useful information for predicting response to therapy. HCV genotype is also used to determine the length of therapy.[8-18]

Liver biopsy assess degree of liver injury and exclude concurrent diseases specially in children with normal transaminases who are being considered for treatment.[8-18] Histological picture is similar to those of adults. Necrotic inflammation and fibrosis are usually milder, though liver damage is greater in older patients and progression to cirrhosis has been noted.[7,9,18,19,20,22]

TREATMENT

HCV chronic infection is slow progressive in childhood therefore, there is no uniform consensus about timing for treatment. Progression of fibrosis seems to be a function of infection duration, when no other risk factors for liver damage are present. HCV cirrhosis and its complications in adulthood and universal recurrence in post transplant reci-

Table 1. Selected Treatment trials in children with chronic HCV infection.[18 modif]

Study	N° Studied*	Treatment regimen	Sustained response** (%) All Types	HCV type 1	HCV type 2/3
González-Peralta, *et al.*	11	IFN-ribavirin	64	40	100
Strickland, *et al.*	12	IFN-ribavirin	50	50	N/A ***
Bruix and Sherman	41	IFN-ribavirin	61	53	100
Peters and Terrault	118	IFN-ribavirin	46	36	84
Sasaki, *et al.*	14	PEGIFN	38	38	N/A
Ni, *et al.*	59	PEGIFN-ribavirin	59	50	100
Iorio, *et al.*	30	PEGIFN-ribavirin	50	4	100
Fried, *et al.*	107	PEGIFN-ribavirin	65 ***	53 ****	93 ****
Di Bisceglie, *et al.*	55	PEGIFN-ribavirin	53	47 ****	80 ****
	59	PEGIFN-alone	21	18****	36 ****
Jara, *et al.*[30]	30	PEGIFN-ribavirin	50	44	100
Wirth, *et al.*[31]	107	PEGIFN-ribavirin	65	53	93

*HCV = hepatitis C virus; IFN = interferon; PEGIFN = pegylated interferon. * Number of HCV-infected patients treated in the studies cited. ** Undetectable serum HCV RNA 6 months after stopping treatment. *** Sustained response was noted in 4 of 5 (80%) of enrolled children with HCV genotype 4. **** Only percentages presented in preliminary report (abstract).*

pients justify medical decision in favor of treatment. Therefore, children are ideal candidates for treatment. The shorter the duration of infection with mild histological disease, the better the response to treatment.[8,9,18,20,21]

A review of published trials with Interferon (IFN) monotherapy in 105 children showed average an end- of- treatment response (ETR) of 54% and sustained virological response (SVR) of 36%. The SVR in genotype 1 was 27% versus 70% for non genotype 1 (p: 0.001). The SVR rates were higher than those reported in adults.[23]

Different trials with combination therapy were done and others are in progress (Table 1).

PRIMARY GOAL OF TREATMENT

Clearance viral infection (HCV RNA non detectable in serum), regression or delay in liver fibrosis, prevention of chronic liver disease and development of HCC and improve quality of life.

Benefits of treatment are not restricted to biochemical, histologic or virologic response: quality of life, risk of hepatocellular carcinoma, and mortality risk may be favorably affected by treatment, even in the absence of sustained viral response.[4,18,24,25]

CONSIDERING TREATMENT

IFN alfa is recognized as the drug approved for hepatitis C treatment in pediatric population. As in adults, combination therapy with IFNα or pegylated IFNα and ribavirin in children under clinical trials, support its efficacy in sustained virological response (SVR) compared with IFNα alone. Recently, the US FDA and EMEA have approved combined pegylated-IFNα2b plus ribavirin treatment for children.[20] Principal advantage of PEG-IFNα is the extended serum half-life conferred by pegylation of the IFN molecule, which confers a once-weekly administration and improved efficacy and a safety profile similar to that of IFNα.[18]

Treatment should be considered in children between 3 to 18 years old, anti HCV (+), HCVRNA (+) for at least 6 months and normal or abnormal ALT.

Patients are excluded if they have comorbid medical conditions that could compromise the safety, efficacy and tolerability of drugs.[4,20]

Liver biopsy remains the gold standard for assessing the severity of inflammation and fibrosis, and rule out concurrent diseases particularly in children whit normal liver tests. Inflammation and fibrosis are less common than in adults but significant fibrosis and cirrhosis may develop during childhood. In a series of 112 pediatric patients with chronic hepatitis C the degree of fibrosis correlated with age and duration of infection.[27,28]

There are different opinions about performing liver biopsy in genotypes 2 and 3 whose sustained virological response rates exceed 80%.[7,18,26]

HCV genotype should be identify to establish treatment duration and probability of response. For genotypes 1 and 4, therapy is recommended for at least 48 weeks, overall SVR is 50% .Genotypes 2 and 3 should be treated only for 24 weeks; overall SVR is 83-100%.[18-20]

Viral load is necessary to evaluate virological response during treatment.

Treatment objective is clearance of HCVRNA below the detection limit of PCR technique employed (30-50IU/mL). Then, therapy should continue in order to eradicate infection in the liver.

TREATMENT SCHEDULE AND MONITORING

The dose of IFNα monotherapy is 3 MIU/m^2 subcutaneously 3 times a week.[8,23]

PEG-IFNα-2b (60 μg/m^2/week or 1-1.5 μg/kg/wk) or α2a (100 μg/m^2/week) subcutaneously plus Ribavirina (15 mg/kg/day) twice orally is used in combination therapy.[18,20,23,26,29]

Adverse events are common during treatment, particularly transient "flu- like syndrome", leukopenia and neutropenia related to IFN. Although rare, depression and suicidal ideation attempt occurs in treated children. Antithyroid antibodies are common and clinical thyroid disease occurs but rarely becomes permanent.[4,18,20,26,29]

The most common adverse effect of ribavirin is a reversible hemolytic anemia. Ribavirin is also known to be teratogenic.[4,18,20,26,29]

Liver, hematology, thyroid and other routine tests should be periodically done in order to detect adverse events for evaluate eventually reduction or interruption medication. HCV RNA titers are measured at 4, 12, 24, 36 and 48 weeks, and every 12 weeks for another 6 months after the end of treatment.

Diagnosis and treatment strategies in children should be prescribe and supervise by pediatric hepatologist.[8]

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