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REVIEW

Chronic hepatitis C virus infection in children and adolescents: Epidemiology, natural history, and assessment of the safety and efficacy of combination therapy

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Abstract: Hepatitis C virus (HCV) is the most common cause of chronic liver disease of infectious etiology in children. Most of the children infected with HCV are asymptomatic, and only a few of them develop signs and symptoms of end-stage liver disease early in life. It is not possible to predict either in which patients HCV infection will have a bad outcome or the critical time in early adulthood when disease progression will accelerate. The experiences with therapy in children with chronic hepatitis C are based on earlier and continuing data from adult trials. The currently recommended treatment for chronic HCV infection in adults is the combination of peginterferon-α and ribavirin. The choice of this regimen is based on the results of randomized clinical trials that demonstrated the superiority of this combination treatment over standard interferon-α and ribavirin. Recently, results of pivotal, multicenter, interventional open-label studies on combined treatment with peginterferon-α and ribavirin in children have been published, and the US Food and Drug Administration and the European Medicines Agency have approved the combination therapy in those older than 3 years. The aim of this review is to evaluate critically the available data regarding the safety and efficacy of combination treatment with peginterferon-α and ribavirin in children.

Keywords: treatment, peginterferon, ribavirin, adverse events, sustained viral response

Introduction

Hepatitis C virus (HCV), discovered in 1989,[1,2] is a single-stranded ribonucleic acid (RNA) virus and is a member of the genus Hepacivirus in the family Flaviviridae.[3] The most characteristic feature of the HCV genome is the rapid evolution with genetic diversity and variation. Comparison of nucleotide sequences of variants recovered from infected individuals from different geographical regions revealed the existence of at least six major genetic types of HCV among a total of more than 50 genotypes identified worldwide.[3] Each genotype shows more than 20% difference at the nucleotide level and more than 15% difference at the amino acid level compared with any of the other genotypes.[3] Within each genetic group of HCV, a series of more closely related subtypes with 5%–8% diversity in nucleotide sequences and 4%–5% diversity in amino acid sequences were identified. In individual with chronic infection, HCV evolves under the pressure of the immune system and is present in many distinct phylogenetically related variants defined as quasispecies. The average diversity in nucleotide sequences among quasispecies is 0.9%.[3]

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HCV, together with hepatitis B virus, is the predominant cause of chronic viral hepatitis in children and adults.[4] In industrialized countries, since the start of the hepatitis B virus vaccination program, HCV has become the most significant cause of chronic liver disease of infectious etiology in children.[5] The overall worldwide prevalence of HCV varies geographically, but it is estimated at 3% with 150 million people with chronic infection.[5] Data from the Centers for Disease Control and Prevention have shown that the seroprevalence of antibodies to HCV in the United States was 0.2% for children aged 6–11 years and 0.4% for those aged 12–19 years.[6] Similar prevalence was found in western Europe,[7] North America,[8] Mongolia,[9] and Japan,[10] whereas a higher prevalence, up to 10%–15%, was reported in Saudi Arabia and in parts of Africa.[11,12] The seroprevalence of HCV infection in children is generally lower than in adults,[5] and studies assessing the seroprevalence of HCV usually overestimate the prevalence of chronic hepatitis; however, a study undertaken to estimate the direct medical costs of care for chronic HCV-infected children showed that pediatric hepatitis C is an important health care issue, with associated costs in the United States estimated between US $17 and $40 million annually that means US $168–$404 million over a 10-year period.[13]

Before 1992, the mode of acquisition of HCV infection in children was predominantly via transfusion of blood or blood products.[14–16] Childhood cancer survivors, children with hematological disorders necessitating the use of repeated transfusion of blood products, and children with renal failure who were treated with hemodialysis all exhibited a high incidence of HCV infection.[17,18] After the implementation of universal testing of blood products, transmission of virus from the mother to child became the leading source of HCV infection in children.[14–16] Overall, the risk of perinatal transmission of HCV from HCV RNA–positive mothers ranges between 1% and 6% (mean 3%–4%).[19] Many factors were examined in multiple studies in relation to the risk of perinatal transmission of HCV. Different risk factors often coexist in the same mothers.[19] Perinatal transmission is confined almost always to women with detectable HCV RNA in the peripheral blood by the polymerase chain reaction (PCR),[20] but all children born to women with anti-HCV antibodies should be tested for HCV.[21] Some studies reported that a high concentration of serum HCV RNA is associated with a higher risk of transmission,[22–27] whereas others failed to demonstrate this association and found considerable overlapping in concentrations of HCV RNA between transmitting and nontransmitting mothers.[20,28,29] Maternal peripheral blood mononuclear cell infection by HCV,[30,31] membrane rupture of longer than 6 hours before delivery,[29,32,33] and procedures exposing the infant to maternal blood infected with HCV during vaginal delivery are associated with an increased risk of transmission.[29,34] Maternal coinfection with HCV and human immunodeficiency virus[35] and maternal history of intravenous drug use[36] and HCV infection of the sexual partner of the mother[37] predict the risk of perinatal transmission and are dependent on the peripheral blood mononuclear cell infection by HCV.[19] Delivery by Cesarean section is not recommended in pregnant women infected with HCV. Infected mothers can safely breast-feed their infants if the nipples are not damaged.[38–41] A previous delivery of a child infected perinatally with HCV does not increase the risk of transmission in subsequent pregnancies.[42] Immunogenetic factors and HCV genotypes are not related to HCV perinatal transmission.[20,43–45] Despite an increased understanding of the risk factors involved in perinatal transmission of HCV, the ultimate mechanism and the exact timing of mother-to-child transmission of HCV infection are still unknown.[19]

Hepatitis C in children

Following perinatal transmission, spontaneous HCV RNA clearance, with subsequent transaminases normalization, is a rare event occurring in about 20% of perinatally infected children in the first 5 years of life.[46,47] More than half of the patients who spontaneously clear the infection develop an alanine transaminase peak greater than five times the normal value at the onset of the infection and are infected by HCV genotype 3.[47] In the patients who do not clear the virus, chronic HCV infection tends to persist into adult life.[47,48] Most children with hepatitis C are, thus, expected to contribute to the pool of infected adult patients. The cumulative probability of chronic progression has been estimated in different studies to be around 80%.[46,47] Children with chronic hepatitis C are often asymptomatic.[46,47] Data from a large, multicenter, prospective study of children born to HCV-infected women in Europe showed that hepatomegaly was the only clinical sign reported in 10% of the cohort.[46] The pattern of transaminases during chronic infection in children varies, but almost half of them have sustained cytolysis at follow-up visits.[16,47,49,50] Although HCV-related end-stage liver disease is still the most frequent indication for liver transplantation in adult patients, cirrhosis and hepatocellular carcinoma are rarely seen in young babies or adolescents without underlying disorders. Severe outcomes of chronic hepatitis C have been reported for special groups of patients given multiple blood transfusions, such as children with bleeding disorders or thalassemia.[51] In the largest pediatric observational study

including both babies with perinatal infection and children with parenteral sources of contagion, most of whom remained untreated, persistent viral replication during chronic infection has been demonstrated to lead to end-stage liver disease in a small subgroup characterized by perinatal exposure, maternal drug use, and infection with HCV genotype 1a.[48] Different authors described small case series of cirrhosis in children, which seem to support the evidence that vertically infected children develop cirrhosis more frequently than transfused children with no underlying systemic disease.[52–55] Overall, liver fibrosis seems to increase with the age of the patient and/or with the duration of the disease, and older adolescents and young adults have more severe fibrosis than children.[56,57]

A particular aspect of the host-virus interaction in children with chronic hepatitis C, which affects the progression of HCV-related liver damage, is the production of liver–kidney microsomal antibodies. Liver–kidney microsomal antibodies are rarely seen in adults but are detectable in around 7% of the children with chronic infection.[48] In children with positive liver–kidney microsomal antibodies, liver histology findings are significantly more severe.[58] Similar to adults,[59–61] recent data demonstrate that in children with chronic hepatitis C, the presence of steatosis is associated with more severe fibrosis and a reduced response to interferon-α treatment.[62] Furthermore, with regard to response to the treatment, a marked HCV quasi-species diversification has been described in children during chronic infection that could be important for virus persistence and might impair the response to antiviral therapy during childhood.[63]

In adults with chronic hepatitis C, health-related quality of life is significantly poorer when compared with the normal population.[64,65] The reduction in health-related quality of life is not related to the degree of liver inflammation and improves with therapy, particularly with successful viral eradication.[66] Health-related quality of life is an important health outcome required to inform health-care decision-making for adult patients with chronic HCV infection.[67] A recent study showed for the first time that both the physical and psychosocial health of asymptomatic children with chronic HCV infection are significantly reduced compared with children without HCV. Almost all domains of health were affected, the most significant reductions being in parental assessment of overall health of their child and the impact of the child's health in terms of parental distress and additional time required caring for the child.[68] In a larger analysis, children with HCV were shown to have similar overall health-related quality of life but worse cognitive functioning than their noninfected peers.[69] Moreover, in this study, caregivers were highly distressed about their children's medical circumstances compared with a normative sample.[69]

Treatment for chronic hepatitis C in children

The experiences with therapy in children are based on the earlier and continuing data from adult trials. The currently recommended therapy for chronic HCV infection in adults is the combination of a peginterferon-α and ribavirin.[70] The choice of this regimen was based upon the results of randomized clinical trials that demonstrated the superiority of this combination treatment over standard interferon-α and ribavirin.[70] The addition of polyethylene glycol to interferon-α increases its half-life allowing once-weekly doses, reduces its volume of distribution, and leads to more sustained plasma levels resulting in more viral suppression. Few data are available on monotherapy with interferon-α, on the combined use of interferon-α and ribavirin, and on monotherapy with peginterferon-α in children.[71] Weekly dosing of peginterferon-α is more acceptable than thrice-weekly dosing of nonpegylated interferon-α, especially in children who may be particularly sensitive to the regular need for subcutaneous injections. The use of the combined treatment, peginterferon-α-2b with ribavirin, has been approved by the US Food and Drug Administration (in December 2008) and by the European Medicines Agency (in December 2009) for children older than 3 years and appears as the most effective and safe option among available treatments.

Combined treatment with peginterferon-α and ribavirin

Few studies are available on the combined treatment with subcutaneous peginterferon-α-2a or peginterferon-α-2b and oral ribavirin in children with chronic hepatitis C.[54,72–79] In this review, we examine the results of seven studies on the combined treatment. Only five trials have evaluated the efficacy of this combination therapy, of which four had been fully published[72–75] and one, the PEDS-C trial, is available in abstract form.[76] The PEDS-C trial is the only Phase III, interventional, double-blind, randomized, placebo-controlled, multicenter study designed to compare the efficacy and the safety of peginterferon-α-2a alone with its combination with ribavirin as a treatment of chronic HCV infection in children and adolescents. A formal paper has not been published yet, but the main results of the study have been presented at the 59th Annual Meeting of the American Association for the Study of Liver Diseases.[76] Two further studies described

small cohorts of children with chronic hepatitis C treated with peginterferon-α-2b and ribavirin.[77,78] The first, published by Baker et al, is a retrospective/prospective study reporting observations on 10 adolescents. The second is a retrospective, multicenter, collaborative study by the Japan Society of Pediatric Hepatology on 33 children and young adults.[78] Two more studies on combined treatment have been published, but were excluded from the analysis performed in this review, in one case because it was not possible to extrapolate the children treated with peginterferon-α-2a and those treated with peginterferon-α-2b[79] and the other because the patients enrolled were on treatment at the end of the follow-up.[54]

Inclusion and exclusion criteria

In all the above-mentioned trials, inclusion and exclusion criteria were defined clearly.[72–76] In the PEDS-C abstract[76] and in the article by Wirth et al,[74] the inclusion and exclusion criteria are not fully reported, but the complete lists of the criteria are available to access at ClinicalTrials.gov, the registry of federally and privately supported clinical trials conducted in the United States and around the world, under the identifiers NCT00100659 and NCT00104052, respectively.

The first inclusion criteria for all the studies was the presence of chronic hepatitis C with detectable serum HCV RNA[72–78] independent of HCV genotype and the mode of infection.[72–78] In the study by Wirth et al[74] published in 2010, in the PEDS-C trial,[76] and in the study by Baker et al[77] patients were enrolled only if HCV RNA was detected for more than 6 months before treatment. In the study by Jara et al[73] strict chronic infection inclusion criteria were defined, and HCV RNA was required to be detectable for a minimum of 3 years to exclude spontaneous resolution of HCV infection that rarely occurs in children longer than 3 years after exposure to HCV. For the same reason, in the same study, all the patients had continuous or intermittently elevated transaminases for a minimum of 3 years.[73] In the study by Wirth et al[74] published in 2010, patients were excluded if the serum alanine transaminase level was more than 10 times the upper limit of normal within the 6 months before the beginning of the treatment. In the remaining studies, the enrollment was independent of the levels of serum transaminases.[72,76–78]

The pretreatment liver biopsy was not mandatory in the three trials.[72,73,75] In the study by Wirth et al[74] published in 2010, a pretreatment liver biopsy with evidence of fibrosis, inflammatory activity, or both was an inclusion criteria for all the patients with the exception of children aged 3–11 years with elevated alanine transaminase within 1 year before enrollment. In the PEDS-C trial, a liver biopsy, obtained within 24 months from the start of the treatment and showing chronic liver disease as indicated by inflammation and/or fibrosis not consistent with other known liver diseases and not normal, was required.[76] The liver biopsies were available from all the 10 patients enrolled in the study by Baker et al.[77]

Exclusion criteria across different studies included neutropenia,[72–74,76–78] thrombocytopenia,[72–74,76–78] anemia,[72–78] human immunodeficiency virus coinfection,[72–78] hepatitis B virus coinfection,[72–78] decompensated liver disease and cirrhosis,[72–78] psychiatric and neurologic diseases,[72–78] renal insufficiency,[72–76] alcohol or drug dependence,[74–76] retinopathy,[74–76] and other coexisting medical conditions.[72–78] In the study by Baker et al[77] three patients had hemophilia, one had von Willebrand disease, and one had Hirschsprung disease. Three studies excluded patients previously treated for HCV infection.[74–76] In the study by Wirth et al[72] published in 2005, they enrolled patients irrespective of previous treatment, but only five of the patients enrolled had received interferon-α monotherapy. In the study by Jara et al[73] nonresponders to interferon-α monotherapy were eligible for enrollment but could not account for more than 25% of the patients' population. A negative pregnancy test was required in most studies for females with reproductive potential before the start of medication.[72–74,76,78] With regard to the presence of nonorgan-specific autoantibodies and autoimmune liver disease, in the study by Wirth et al[72] published in 2005 and in the retrospective analysis by the Japan Society of Pediatric Hepatology,[78] patients were excluded if positive before treatment for liver–kidney microsomal antibodies or for antinuclear and anti-smooth muscle antibodies, respectively. In the PEDS-C trial, patients were excluded if antinuclear antibodies were ≥1:160, antismooth muscle antibodies ≥1:180, and anti-liver–kidney microsomal antibodies ≥60 U.[76] In the study by Jara et al[73] patients testing positive for antinuclear antibodies, smooth muscle antibodies, and liver–kidney microsomal antibodies were enrolled if other features did not suggest autoimmune hepatitis. In the study by Wirth et al[74] published in 2010, patients were excluded if antinuclear antibodies were >1:160. In two studies,[72,78] all the patients were defined "thyroid normal" before treatment. Jara et al[73] reported two patients with small elevations either in thyroid-stimulating hormone (TSH) level or in thyroxin level at baseline. In the study published by Wirth et al[74] in 2010 and in the PEDS-C trial,[76] patients were enrolled if they had normal TSH, absence of antithyroid antibodies, and no history of poorly controlled thyroid disease. In the same study, no patients should have received any systemic antiviral therapy in the 6 weeks before the first dose of study drug, with the exception of those who had taken or

were expected to require acyclovir for herpetic lesions.[76] Also, in the study by Baker et al[77] patients were excluded from the treatment if they had received any antiviral treatment other than interferon.

Type of treatment and doses

As shown in Table 1, combination therapy with peginterferon-α-2a and ribavirin was used in two of the seven studies.[75,76] All the other studies evaluated combination therapy with peginterferon-α-2b and ribavirin.[72–74,77,78] The dose of subcutaneous peginterferon-α-2b administered to patients in the trials and in the retrospective studies was 1.5 μg/kg once weekly, whereas for peginterferon-α-2a was 100 μg/m^2. Only in the study by Jara et al[73] the dose of peginterferon-α-2b was 1 μg/kg once weekly. Ribavirin was administered orally at the dosage of 15 mg/kg/d in two divided doses.

Duration of treatment

The duration of the treatment is relatively variable among the different studies. Table 1 summarizes the protocols used. In most studies, patients infected with HCV genotypes 1 and 4 were planned to receive treatment for 48 weeks and were withdrawn from treatment if qualitative HCV PCR was positive at treatment week 24. Wirth et al[74] in 2010 discontinued the treatment also in patients with <2 $\log_{10}$ drop in HCV RNA at treatment week 12. In the study by Jara et al[73] patients with genotypes 1 or 4 who tolerated well the treatment were not advised to stop it if HCV RNA was positive after 24 weeks of treatment. In the retrospective study by Tajiri et al[78] some patients with genotype 1 were treated for 72 weeks. Children with HCV genotypes 2 and 3 were treated usually for 24 weeks, but in some studies, the treatment was prolonged up to 48 weeks.[72,74,76,78]

Response to treatment: definitions

Multiple definitions of the response to treatment are possible according to the detection or nondetection of plasma HCV RNA as measured by quantitative real-time PCR at different time intervals from the beginning or from the end of the treatment. To make possible the comparison among the different results, certain definitions need to be clarified. Table 2 summarizes the most commonly accepted definitions of the responses to treatment. Some authors instead of the detection have used the variations in the HCV RNA levels to characterize the response to treatment. Wirth et al[74] in 2010, eg, used a <2 $\log_{10}$ drop in HCV RNA at treatment week 12

Table 1 Type of treatment, doses, duration, and schedules of clinical evaluations and laboratory tests for the assessment of safety and efficacy in the different studies

Study	Type of treatment and doses	Duration	Clinical evaluations and laboratory tests for the assessment of safety and efficacy
Wirth et al[72]	PEG-IFN-α-2b 1.5 μg/kg/wk Ribavirin 15 mg/kg/d	G1: 48 wk G2, G3: 8 patients for 48 wk, 5 patients for 24 wk	Treatment weeks: 2, 4, 8, and then every 12 wk until the EOT. FU: wk 12 and 24 after the EOT
Jara et al[73]	PEG-IFN-α-2b 1 μg/kg/wk Ribavirin 15 mg/kg/d	G1: 48 wk G2, G3: 24 wk	Treatment weeks: 1, 2, 3, 4, 8, 16, 20, 24, and then 4-wk to 12-wk intervals until the EOT FU: wk 12 and 24 after the EOT
Wirth et al[74]	PEG-IFN-α-2b 60 μg/m^2/wk (1.5 μg/kg/wk) Ribavirin 15 mg/kg/d (max 1,200 mg = 90 kg)	G1, G4: 48 wk G3 with load $>$ 600,000 IU/mL:[a] 48 wk G3 with load $>$ 600,000IU/mL: 24 wk G2: 24 wk	Treatment weeks: 2, 4, 12, 24, 30, 48 FU: wk 4, 12, and 24 after the EOT
Sokal et al[75]	PEG-IFN-α-2a 100 μg/m^2/wk Ribavirin 15 mg/kg/d (max 1,200 mg)	G1, G4, G5, G6: 48 wk G2, G3: 24 wk	Treatment weeks: 2, 6, 12, 24, 36, 48 FU: wk 12 and 24 after the EOT
Schwarz et al[76]	PEG-IFN-α-2a 180 μg/1.73 m^2/wk Ribavirin 15 mg/kg/d (max 1,200 mg)	All genotypes: 48 wk	–
Baker et al[77]	PEG-IFN α-2b 1.5 μg/kg/wk Ribavirin 800 mg/d	G1: 48 wk G3: 24 wk	Treatment weeks: 2, 4, 24, 48 FU: weeks 24 after the EOT
Tajiri et al[78]	PEG-IFN-α-2b 1.5 μg/kg/wk Ribavirin 15 mg/kg/d $<$ 40 kg; 600 mg/d 40–60 kg; 800 mg/d 60–80 kg; 1 g/d $>$ 80 kg	G1: 48 wk, 72 wk for 4 patients G2: 24 or 48 wk (no. not provided)	Treatment weeks: 2, 4, 6, 8, and then every 4 wk until the EOT FU: wk 12 and 24 after the EOT

Note: [a]Eight of nine patients infected with G3 with load $>$ 600,000 IU/mL were treated for 24 wk instead of the protocol-defined 48 wk.
Abbreviations: PEG-IFN, peginterferon; EOT, end of treatment; FU, follow-up; G, genotype; wk, week.

Table 2 Definitions of the response to treatment according to HCV RNA detection as measured by quantitative real-time polymerase chain reaction and to the time interval from the beginning or from the end of the treatment

Rapid virological response: undetectable plasma HCV RNA at treatment week 4
Early virological response: undetectable plasma HCV RNA at treatment week 12
Sustained virological response: undetectable plasma HCV RNA 24 wk after the end of treatment
End of treatment response: undetectable plasma HCV RNA at the end of treatment
Relapse: undetectable plasma HCV RNA at last treatment visit, detectable HCV RNA at the last follow-up visit
Nonresponder: detectable HCV RNA at treatment week 24
Breakthrough: reappearance of HCV RNA in serum while still on treatment

Abbreviation: HCV, hepatitis C virus.

as an additional criteria to define a nonresponder patient. In the study by Sokal et al[75] early virological response (EVR) was defined as an at least a 2 $\log_{10}$ drop in HCV RNA levels at week 12 compared with baseline. As a consequence, different definitions are available in different studies. Unless otherwise specified, in this review, the response to treatment is described according to the definitions of Table 2.

Assessment of safety and efficacy

Clinical evaluations and laboratory tests for the assessment of safety and efficacy were performed in the different studies following different schedules (Table 1). According to the previous definitions (Table 2), for the complete assessment of efficacy, important HCV RNA determinations are those planned at treatment week 4 (rapid virological response [RVR]), 12 (EVR), 24 (end of treatment response [ETR] for some patients), 36, 48 (ETR for some patients), and every 12 weeks for another 24 weeks after the end of the treatment (sustained virological response [SVR]). Clinical and laboratory evaluations were usually more frequent in the first months of the treatment in order to detect adverse events. A reasonable approach suggests clinical and laboratory evaluations every 2 weeks in the first phase of therapy, monthly up to 6 months, every 3 months for the remaining period of treatment, and for another 6 months after the end of the treatment.[80]

Different approaches have been used in different studies with regard to pregnancy test and adequate contraception. These points are important in sexually active females of child-bearing potential. Pregnancy tests before the start of medication were performed only in some studies.[72–74,76,78] During antiviral therapy and for 6 months after the end of treatment, adolescents were instructed to use birth control[73,78] or adequate contraception was compulsory.[75,76] Exclusion of pregnancy during treatment was done by routine pregnancy testing,[73,77] by parent's and patient's report at each visit,[72] or when a possibility of pregnancy was present.[78]

In the PEDS-C trial, ophthalmologic examinations including slit lamp at enrollment and after 24 and 48 weeks of treatment were performed.[76]

End points of the studies

The primary end point in all the studies was the SVR rate.[72–78] Biochemical response (defined as the normalization of serum alanine transaminase levels) was an end point only in some studies.[72–74]

Sustained virological response

SVR rates in the seven studies are summarized in Table 3 and range from 33% to 81%.[72–78] When only the results of the trials were analyzed, the range is, irrespective of the genotype, 50%–68%.[72–76] It is important to note that the overall SVR is not a representative result of a trial and does not allow the comparison of the results of different trials because distribution of genotypes and of the other determinants of SVR are different across the trials.

Significant predictors of SVR

The roles of different factors as predictors of SVR are reported in Table 4. The viral genotype,[72,74,75] the viremia levels among patients with genotype 1 infection,[74] and the HCV RNA status at treatment week 4 (RVR)[74,78] and 12th (EVR)[73,74] have been demonstrated to be predictive of SVR in children who received combined treatment. As expected, based on adult's studies, the rates of virological response were significantly higher in patients infected with HCV genotypes 2 or 3 than in patients infected with other genotypes.[72,74,75] In the PEDS-C study, SVRs for genotype 1 and genotype non-1 were 47% and 80%, respectively.[76] In a recent study enrolling 12 adolescents infected with HCV genotype 4 treated with peginterferon-α-2b and ribavirin, the SVR was observed in 75% of the patients treated.[81] With regard to the mode of acquisition of HCV infection, in the study by Jara et al[73] treatment was particularly effective in patients with parenterally acquired infection. However, statistical significance was not reached, probably due to the small number of enrolled patients.[73] A similar tendency was demonstrated by Wirth et al[72] and by Tajiri et al.[78]

In the study by Wirth et al,[74] among patients with HCV genotype 1 infection, SVR was significantly higher in those with baseline viral loads <600,000 IU/mL than in those

Table 3 Virological response to treatment in the different studies

Study	Patients	Age, years mean (range)	RVR	EVR	Treatment week 24	Treatment week 48	SVR	Details of treatment
Wirth et al[72]	62	10.6 (2–17)	NP	38 (62.3%)	43 (70%)	39 (63.9%)	36 (59%)	Treatment stopped for adverse event: 1 Treatment stopped for lack of response: 18 Treatment stopped for breakthrough: 6 Relapse: 3 (G1)
Jara et al[73]	30	10 (3.5–16)	1 (3.3%)	15 (52%)	18 (64%)	NP	15 (50%)	Treatment stopped for adverse event: 3 Treatment stopped for lack of response: 4[a] Treatment stopped for breakthrough: 2 Relapse: 1 (G1)
Wirth et al[74]	107	10 (3–17)	NP	G1 45 (62.5%)	NP	NP	70 (65%)	Treatment stopped for adverse event: 1 Treatment stopped for lack of response: NP Treatment stopped for breakthrough: NP Relapse: 12% of the G1
Sokal et al[75]	65	NP (6–17)	NP	42 (68%)[b]	NP	44 (69.8%)[c]	43 (68.2%)	Treatment stopped for adverse event: 2 Treatment stopped for lack of response: 8 Treatment stopped for breakthrough: 0 Relapse: 0 2 patients lost during the FU
Schwarz et al[76]	55	10.8 (NP)	NP	NP	NP	NP	29 (53%)	Treatment stopped for adverse event: 2 Treatment stopped for lack of response: NP Treatment stopped for breakthrough: NP Relapse: NP
Baker et al[77]	10	15.8 (11.7–18.6)	NP	NP	NP	7 (70%)	3 (33.3%)	Treatment stopped for adverse event: 1 Treatment stopped for lack of response: 0 Treatment stopped for breakthrough: 0 Relapse: 4 (G1)
Tajiri et al[78]	33	17 (7–30)	22 (66.7%)	10 (30.3%)	NP	NP	27 (81.8%)	Treatment stopped for adverse event: 1 Treatment stopped for lack of response: 3 Treatment stopped for breakthrough: NP Relapse: 1 (genotype NP) 1 patient stopped treatment for expensiveness

Notes: [a]In this study, patients with HCV G1/4 who tolerated well the treatment were not advised to stop it if HCV RNA was positive at 24 wk; [b]EVR is defined as at least a 2 $\log_{10}$ drop in HCV RNA at treatment week 12 compared to baseline; [c]Data are "end of treatment response" that means 24 wk for genotype 2 and genotype 3 (no relapse was reported) and 48 wk for other genotypes.

Abbreviations: RVR, rapid virological response; EVR, early virological response; SVR, sustained virological response; NP, not provided; G1, genotype 1; FU, follow-up; wk, week.

Table 4 Predictors of sustained virological response

Study	Genotype	Route of infection	Transaminases	Age (y)	Sex	Viral load (IU × 10^3/mL)	Previous treatment
Wirth et al[72]	G1: 22 (47.8%) G2, G3: 13 (100%) G4: 1 (50%) $P = 0.0003$	Parenteral: 19 (70.4%) Vertical: 12 (48%) Unknown: 5 (55.5%) Parenteral vs vertical P 0.08	Normal: 24 (66.6%) Elevated: 12 (48%)	<11: 17 (54.8%) >12: 19 (63.3%)	–	–	Naive: 34 (60.7%) NR: 2 (40%)
Jara et al[73]	G1: 12 (44%) G3: 3 (100%) G4: 0 of 1	Parenteral: 7 (78%) Vertical: 8 (38%) P 0.1	–	<12: 9 (45%) >12: 6 (60%)	Male: 9 (53%) Female: 6 (46%)	–	Naive: 11 (55%) NR: 1 (17%)
Wirth et al[74]	G1: 53% G2: 93% G3: 93%[a] G4: 80% P 0.0005	Parenteral: 11 (91.7%) Vertical: 47 (62.7%) Others: 12 (60%)	Normal: 42 (66.7%) Elevated: 28 (63.6%)	3–11: 41 (61.2%) 12–17: 29 (72.5%)	Male: 33 (64.7%) Female: 37 (66.1%)	<600: 46 (79.3%) >600: 22 (48.9%) $P < 10^{-3}$ for G1	Previously untreated
Sokal et al[75]	G1, G4–6: 27 (59%) G2, G3: 16 (94%) $P < 0.01$	–	Normal: 24 (80%) Elevated: 19 (58%) $P < 0.001$ for G1, G4–G6	–	–	<500: 17 (23%) >500: 22 (55%)	Previously untreated
Baker et al[77]	G1: 2 (22.2%) G3: 1 (100%)	Parenteral: 2 (40%) Vertical: 1 (33.3%)	Normal: 1 (25%) Elevated: 2 (33.3%)	>12: 3 (33.3%)	Male: 1 (20%) Female: 2 (40%)	<600: 2 (40%) >600: 1 (20%)	Naive: 1 (33.3%) NR: 2 (66.6%)
Tajiri et al[78]	G1: 16 (80%) (4 treated for 72 wk) G2: 11 (84.6%)	Parenteral: 18 (90%) Vertical: 8 (66.7%) Sporadic/others: 1 (100%) Parenteral vs vertical P 0.1	Normal: 6 (75%) >30 U/L: 21 (84%)	–	Male: 15 (88.2%) Female: 12 (75%)	>850: 15 (75%) <850: 12 (92.3%)	Naive: 15 (88.2%) NR: 12 (75%)

Abbreviations: G, genotype; NR, nonresponder.

with baseline viral loads >600,000 IU/mL (72% vs 29%, $P = 0.0006$). In the study by Jara et al[73] EVR defined as HCV RNA–negative status at week 12th and >2 $\log_{10}$ decrease in viral load at week 12th was predictive of a SVR. In the study by Wirth et al[74] published in 2010, RVR and EVR were strong predictors of SVR. Overall, 89% of patients infected with HCV genotype 1 and with RVR and 84% of those with EVR attained SVR.[74] In the study by Tajiri et al[78] RVR was significantly associated with SVR (odds ratio = 19.85; 95% confidence interval, 1.43–275.2; $P = 0.02$). Among adult patients, the younger age has been associated with better response rates, whereas in the pediatric studies, age does not seem to influence response.[72–78] In the studies by Wirth et al[72,74] and in the study by Jara et al,[73] adolescents seemed to have better response, but the results did not reach statistical significance. No significant relationship was found between transaminases' levels, sex, previous treatment, and the outcome of combined treatment.[72–78] Few data are available on the effect of continuing treatment on nonresponders. In the study by Jara et al[73] 6 children with genotypes 1 and 4 continued therapy for 48 weeks even if HCV RNA was positive at treatment week 24; at the end of the treatment, all children remained HCV RNA positive. The only study reporting the influence of histological examination of the liver on the response to treatment was the Spanish study from Jara et al[73] that did not show any relationship between the Knodell index and the SVR. Overall, in the different studies, inflammatory activity and fibrosis on histological examination were homogeneously low; therefore, the correlation between histological appearance and response to treatment cannot be expected.

Virological surveillance while on therapy is important to determine the predictors of response and predictors of nonresponse. It would be important to identify early nonresponders to apply stopping rules. In the study by Jara et al[73] no cases with <2 $\log_{10}$ reduction at week 12 (ie, without EVR) achieved SVR. In the study by Wirth et al[74] published in 2010, of the 20 patients who did not have an EVR, 14 did not achieve SVR while 6 did.

Children with HCV genotypes 2 and 3 were treated usually for 24 weeks, but in different studies, the treatment was prolonged up to 48 weeks.[72,74,76,78] In the study by Wirth et al,[72] eight patients infected with HCV genotypes 2 and 3 were treated for 48 weeks. All of them showed EVR, so it was not possible to obtain any information on the efficacy of prolonging the treatment for 48 weeks in terms of SVR. In the study by Wirth et al,[74] patients with genotype 3 infection and baseline viral loads ≥600,000 IU/mL were planned to be treated for 48 weeks, but all attained SVR including 8 of 9 who were treated for 24 weeks. No information is available on the only patient who was treated for 48 weeks, particularly if he or she had or had not achieved EVR. No data are available on the issue of the efficacy of treatment of patients with HCV genotype 2 infection for 48 weeks instead of 24 weeks from the two remaining studies who adopted the same protocol.[76,78]

The reappearance of HCV RNA in serum while still on treatment (ie, breakthrough) was a common event (Table 3). Interestingly, among the different studies, all the patients who relapsed were infected by HCV genotype 1.

Adverse events

Table 5 summarizes the most common adverse events reported in the studies on combination therapy with peginterferon-α-2a and ribavirin, and Table 6 reports the causes of dose reduction and treatment discontinuation.[72–78] Almost all the children enrolled experienced at least one mild adverse event.[72–74,78] Flu-like symptoms including fever, decreased appetite, asthenia, and fatigue were observed usually during the first weeks of treatment, and in most patients resolved or became milder during the second 6 months.[72–75,77,78] Only one patient reported by Wirth et al[72] in 2005 developed diabetes mellitus that persisted even after the end of the treatment. In this patient, therapy was continued without changing dosage and SVR was achieved.[72] The development of nonautoimmune thyroid disease is possible in untreated children with chronic HCV infection.[82] Among the available series on combined treatment, only one study reported the results of thyroid assessment before the beginning of the treatment,[73] whereas others enclosed thyroid function abnormality among the exclusion criteria.[72,74,76,78] During treatment, in the different studies, the emergence of antithyroid antibodies, of elevation of TSH, and of hypothyroidism requiring substitutive therapy was significant (Table 5).[72–75,78] The highest incidence of thyroid dysfunction was reported by Wirth et al[74] in 2010. In this study, 23% of the patients had at least 1 abnormal TSH value during the treatment or follow-up phases and 3% had clinical hypothyroidism.[74] Five girls received levothyroxine, three for clinical hypothyroidism and two for elevated TSH. Three of these five patients were still receiving the medication at the end of the 24-week follow-up period.[74] Across the different studies, thyroid function abnormalities, TSH abnormalities, and antithyroid antibodies disappeared in most of the patients after the end of treatment, and levothyroxine was discontinued.[72,78] Jara et al[73] reported two patients who developed antithyroid antibodies during the treatment, and the

Table 5 Major adverse events reported in the studies

		Wirth et al[72] 2005	Jara et al[73] 2008	Wirth et al[74] 2010	Sokal et al[75] 2010	Baker et al[77] 2007	Tajiri et al[78] 2009
Patients reporting adverse events n (%)		62 (100)	30 (100)	107 (100)	Not specified	Not specified	33 (100)
Endocrine	Increased TSH	6 (10)	6 (20)	25 (23)	7 (11)	0	–
	Hyperthyroidism	0	2 (7)	0	1 (2)	0	–
	Clinical hypothyroidism	–	0	3 (3)	–	0	2 (5)
	Antithyroid antibodies	7 (11)	4 (13)	–	–	0	6 (16)
	Levothyroxine treatment	5 (8)	0	5 (5)	–	0	2 (5)
Blood and lymphatic system	Anemia (hemoglobin <10 g/dL)	3 (5)	–	12 (11)[a]	3 (5)	1 (10)[a]	6 (16)
	Leukopenia (<5,000/μL)	51 (82)	–	11 (10)[a]	–	9 (90)[a]	6 (16)[a]
	Neutropenia	34 (55) <2,000/μL	9 (30) <1,000/μL	35 (33) <1,500/μL	11 (17)[a]	–	–
	Thrombocytopenia (<100,000/μL)	1 (1)	–	–	1 (2)[a]	8 (80)[a]	4 (11)
Gastrointestinal	Nausea	–	8 (24)[b]	19 (18)	15 (23)[b]	–	–
	Vomiting	–	–	29 (27)	–	–	8 (22)
	Abdominal pain	–	13 (43)	22 (21)	25 (38)	–	2 (5)
	Diarrhea	–	–	1 (1)	9 (14)	–	–
Skin and subcutaneous	Alopecia	9 (14)	3 (10)	18 (17)	6 (9)	–	9 (24)
	Sore mouth/throat	–	13 (43)	–	10 (15)	–	3 (8)
	Injection site erythema	8 (13)	10 (33)	31 (29)	9 (14)	–	3 (8)
	Dermatitis	–	–	–	19 (29)	–	–
	Pruritus	–	–	1 (1)	4 (6)	–	–
Psychiatric or behavioral	Mood swing/irritability	9 (14)	12 (40)	25 (24)	22 (34)	–	2 (5)
Musculoskeletal	Arthralgia	–	–	18 (17)	2 (3)	–	–
and connective	Myalgia	–	10 (33)	18 (17)	6 (9)	–	–
General	Headache	–	20 (66)	66 (62)	29 (45)	–	10 (27)
	Weight decrease	12 (19) >5%–<10%	27 (90)	20 (19)	–	7 (70)	–
	Flu-like	50 (82)	30 (100)	–	–	–	–
	Pyrexia	31 (51)	30 (100)	86 (80)	35 (54)	–	35 (94)
	Decrease appetite	–	23 (77)	24 (22)	14 (21.5)	–	–
	Asthenia	1 (1)	–	16 (15)	22 (34)	–	20 (54)
	Fatigue	–	22 (73)	32 (33)	–	–	–
	Anorexia	13 (21)	–	31 (29)	–	–	7 (19)

Notes: [a]Threshold not provided; [b]Data are nausea and vomiting.
Abbreviation: TSH, thyroid-stimulating hormone.

Table 6 Causes of dose reduction and treatment discontinuation

	Dose reduction	Treatment discontinued for adverse events
Wirth et al[72]	4 (6%) 3 for neutropenia (<1,700/μL) 1 for weakness	1 local reaction at injection site (week 10)
Jara et al[73]	7 (23%) for neutropenia (<1,000/μL)	1 high-grade fever, hallucinations (week 1), 2 hyperthyroidism (weeks 16 and 36)
Wirth et al[74]	27 (25%) 13 for neutropenia (<750/μL) 11 for weight loss 7 for anemia (<10 g/dL) 1 for pruritus, 1 for vomiting, 1 for diarrhea	1 thrombocytopenia (week 42)
Sokal et al[75]	18 (28%) 11 for neutropenia (threshold not provided) 3 for anemia (<10 g/dL) 1 for thrombocytopenia, 1 for weakness, 1 for laboratory abnormalities	1 acute hepatitis 1 laboratory abnormality/thyrotoxicosis
Baker et al[77]	5 (50%) 4 for weight loss 1 for anemia (<10 g/dL)	1 not specified
Tajiri et al[78]	21 (63%) 6 for neutropenia (1,400–1,800/μL) 11 for anemia (undefined) 4 for weakness	1 severe degree anemia, leucopenia, and lethargy

condition persisted off-therapy. Furthermore, hyperthyroidism[73] and thyrotoxicosis[75] have been reported as reasons for discontinuing the treatment in three patients (Table 6).

Anemia, leukopenia, and neutropenia were common side effects and common causes of treatment discontinuation or dose reduction (Tables 5 and 6).[72–75,77,78] It is difficult to compare the prevalence of these side effects in the different studies. The lower values under which dose reduction or discontinuation were required were always defined, but the criteria for diagnosing and reporting anemia, leukopenia, and neutropenia as side effects were often not provided.[72–75,77,78] It can be speculated that even if it has not been specified, the lower value of the normal range for age and sex was used. Generally, the mean hemoglobin levels were described to decrease during the first 6 weeks of treatment. Subsequently, hemoglobin levels stabilized but remained below the normal range during the treatment and rose to former values at the end of the follow-up. Only the study by Baker et al[77] stated that bone marrow stimulants were not used in any of the patients to prevent or treat anemia. The patients enrolled in the study by Jara et al[73] received oral vitamin E supplements during treatment to alleviate ribavirin-induced hemolytic anemia. Across the different studies, leukocytes and neutrophils' counts tended to decrease during the first 2 weeks of treatment and in the majority of patients were below the normal value at week 6th of treatment. Subsequently, the counts stabilized but remained below the normal range for the remainder of the treatment period, increasing rapidly to baseline values after the completion of treatment. The median platelet count decreased progressively below the normal values during the first 12 weeks of treatment. After the treatment was completed, the median platelet counts returned to normal values at 12 weeks of follow-up.

Nausea, vomiting, and abdominal pain are the most common gastrointestinal symptoms reported. Transient behavioral changes have been described in 5%–40% of the patients enrolled in the available series;[72–75,77,78] Sokal et al[75] reported an 18% prevalence of insomnia.

With regard to the development of nonorgan-specific autoantibodies, only the study by Jara et al[73] provided detailed information. Seven patients became antinuclear antibodies positive during treatment;[73] high antinuclear antibodies' titer (1:640) was detected in one patient. Antinuclear antibodies positivity persisted at low titers in the five patients who had this marker at baseline. No patient developed liver–kidney microsomal antibodies during the study. Patients with detectable liver–kidney microsomal antibodies at baseline showed either stable or varying titers. No specific liver function events occurred in antinuclear antibodies-positive or liver–kidney microsomal antibodies-positive patients during or after therapy.

One of the major issues of the treatment with interferon in children is the growth. Many patients had significant weight loss during the treatment. In the study by Wirth et al,[72] no patient lost more than 10% of his or her weight before therapy. The mean decrease in body weight was 4.8% by

week 24 in the study by Jara et al[73] but returned to baseline values by week 48. Compensatory weight gain after the discontinuation of the treatment was described in most patients by Wirth et al.[74] On one side, a nonsignificant weight decrease was observed at the end of treatment by Sokal et al.[75] On the other side, weight gain was described in 5% of the patients enrolled in the study by Wirth et al[72] and in two patients reported by Baker et al.[77] With regard to height, in the study by Jara et al[73] growth during the 48-week treatment period was reduced in 22 of 26 cases by 1.6 cm compared with the growth velocity 50th percentile for age and sex. Growth velocity was entirely normal in the 6-month period after the end of treatment; however, the modest decrease in height percentile observed during therapy was not recovered.[73] Wirth et al[74] described a clearly inhibited growth (ie, growth velocity below the 3rd percentile) in 70% of the patients during the treatment phase. During the follow-up period, most patients demonstrated faster than normal growth or improved growth velocity, which was approximately two-fold greater during the follow-up period than during the treatment period.[74] Decrease in mean height percentile during treatment seemed to be related to the duration of the treatment in patients whose treatment duration was longer than in those whose treatment duration was shorter.[74] No significant effect on height growth was observed in the study by Sokal et al[75] where the follow-up height values were comparable to the pretreatment height values. The long-term effects of treatment on children's growth are currently under investigation in some of the patients treated in the study published by Wirth et al[74] who are currently enrolled in a 5-year follow-up study.

A recent study has been published on ophthalmologic complications as a satellite of the PEDS-C trial describing ischemic retinopathy, uveitis, and transient monocular blindness in 3 of 114 patients (2.6%).[83]

Conclusion

HCV is the most common cause of chronic liver disease of infectious etiology in children. Most of the children infected with HCV are asymptomatic, and only a few of them develop signs and symptoms of end-stage liver disease early in life. It is not possible to predict in which patient HCV infection will have a bad outcome or the critical time in early adulthood when the disease progression will accelerate.

Peginterferon-α plus ribavirin treatment has been established as standard therapy in adults with chronic HCV infection. Data on the efficacy of combined treatment with peginterferon-α and ribavirin in children are encouraging and support the wider use of the treatment in children with chronic infection. The combination therapy is highly effective in children infected with HCV genotypes 2 and 3 (SVR > 90%). Around 50% of the children infected with HCV genotype 1 will achieve SVR with this treatment. The combined treatment generally is tolerated well, but the safety is still a concern. The limited data, so far available, on the use of peginterferon-α and ribavirin in children demonstrate that adverse events are common but only a few patients experienced severe adverse events during the treatment.

It is important that in the future, children with chronic HCV infection be treated in the contest of clinical trials in specialized centers with close monitoring of side effects. Further studies with larger number of patients will be helpful in elucidating predictors of response and possible modifications of the current treatment schedule that could improve the efficacy.

Disclosure

The authors report no conflicts of interest in this work.

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