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EXPERT OPINION

Pegylated IFN-α-2a and ribavirin in the treatment of hepatitis C infection in children

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The epidemiology, natural history and efficacy of treatment for chronic hepatitis C in children are presented. An increase in the number of vertical infections of this etiology is suggested. In children, especially in those vertically infected, spontaneous elimination of hepatitis C virus (HCV) is observed more often than it is in adults. The most common HCV genotype detected in children is genotype 1, but Italian researchers have described an increase of infection with genotypes 3 and 4 HCV in children in recent years. In the context of recent opinions suggesting a more rapid progression of HCV 3 genotype infection, treatment of these children should begin immediately. The high efficacy (sustained viral response > 50%), safety (few adverse events with less intensity as compared to adults) and good tolerance of therapy with pegylated IFN α-2a and ribavirin have been revealed in children. The differences in the efficacy and tolerability of HCV treatment between children and adults are described. A recommendation for inclusion and monitoring parameters of children's physical and mental development during HCV treatment is presented. Regarding new anti-HCV therapies with very high efficacy, including IFN-free treatment, the introduction of these therapies to children is recommended.

Keywords: children, HCV infection, treatment of chronic hepatitis C

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HCV infection is a serious public health problem. It is estimated that there are ~ 170 – 200 million people in the world with serum anti-HCV presence. The prevalence of anti-HCV antibodies in children is between 0.2 and 0.4% in the USA and between 12 and 14% in Africa (Egypt, Cameroon).

HCV infection is mainly transmitted by the parenteral route through incorrectly performed simple medical procedures (e.g., injections, blood collection) and non-medical procedures (e.g., manicures, pedicures, tattoos, and piercings). A large number of HCV infections are recorded in drug addicts taking drugs intravenously. A small proportion of HCV infections occur through sexual contact.

Among children infected with HCV in the first years after HCV had been identified the largest group was children with hemophilia and/or thalassemia, who were infected through transfusion of blood products in their early years. In the nineties of the last century the most common HCV infection risk groups turned out to be children with cancer, those who had been hemodialysed or those who had undergone cardiac surgery.

In 2006 a work was published on the transmission of HCV in children undergoing dental and surgical procedures, and in 2008 in the USA a high proportion of HCV infections in teenagers taking drugs intravenously was reported. In many countries, HCV infection is spread by nosocomial infections; thus often hospitalized children are at risk of the infection [1]. In recent years, several authors have focused their attention on the increase in the number of vertical infections of this

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etiology [2,3]. The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition recommends the screening for HCV infection of children born to mothers infected with HCV, children with elevated serum alanine aminotransferase (ALT) and children arriving from countries with a high incidence of HCV infection [4].

The course of HCV infection in children is mostly asymptomatic, biochemical activity of the disease measured by ALT levels remains within normal limits and histopathological changes in the liver are not very advanced [5]. Mild, compared with adults, advancement of morphological changes in the liver does not exclude the serious clinical consequences of the disease. In one study it was demonstrated that in those infected before the age of 20, advanced liver disease occurs after ~ 30 years of infection and clinical consequences such as liver cirrhosis and hepatocellular carcinoma manifest themselves in adulthood [6]. Goodman *et al.* in liver biopsy specimens of 121 treatment-naive HCV-infected children revealed that inflammation, fibrosis, and steatosis were milder than that reported for treatment-naive adults with chronic hepatitis C (CHC), but in the examined group of children there were some with bridging fibrosis or cirrhosis. The positive correlation of inflammation with duration of infection and fibrosis suggests that children with CHC will be at risk for progressive liver disease [7].

In children, especially those vertically infected, spontaneous elimination of HCV is observed more often than it is in adults. Spontaneous recovery involved 21 – 28% of the children in two studies [8,9]. The factors predisposing to its occurrence were younger age, female gender, normal ALT levels, HCV infection with genotype 3 and genotype CC IL-28B [8,9]. Italian researchers have focused their attention on the significant increase in infection with genotypes 3 and 4 HCV in children in recent years. In the context of spontaneous elimination of HCV and the effectiveness of treatment of HCV genotype 3 infection, this phenomenon, in their opinion, may contribute to the modification of the clinical course of HCV infection in this group of patients [10]. On the other hand, recently there have appeared studies showing that genotype 3 HCV infections progresses more rapidly [11,12]. El Serag and Kanwal showed a slightly greater risk of developing hepatocellular carcinoma (HCC) in patients with HCV genotype 1b, and possibly genotype 3, than in patients infected with other HCV genotypes [12]. Kanwal *et al.* revealed that HCV genotype 3 infection is associated with a significantly increased risk of developing cirrhosis and HCC compared to HCV genotype 1 infection and that this association is independent of patients' age, diabetes, body mass index, or antiviral treatment [13]. Therefore, early treatment of young children is important, especially for those infected with genotype 3 HCV.

Our own findings indicate an increase in the number of infections with HCV genotype 4 in children who are identified as patients difficult to treat [14]. Psychological studies carried out on 114 children in average 11 years chronically infected with HCV and their parents showed that although HCV infection in the early stages does not impair intellectual ability or cause emotional or behavioral problems in children, it causes great stress for parents. From assessments of their health-related quality of life it is seen that in children infected with HCV in the first year of life there is a reduced sense of good health, but they are much less focused on concerns about their health in the future than their parents are [15,16].

In assessing quality of life (QOL) on the basis of behavioral/emotional functioning and cognitive status, children undergoing treatment for hepatitis C during the Peds-C study, after 24 weeks of treatment, exhibited mean physical QOL scores that had declined significantly from their baseline, although the scores remained in the average range. As opposed to adults, the majority of children experienced no clinically significant change in their physical QOL, behavioral adjustment, level of depression, or cognitive functioning during or after the pegylated IFN (PegIFN) α-2a+ ribavirin (RBV)/placebo treatment [17].

Antiviral therapy of HCV infection in children is based on prevention of disease progression and of serious clinical sequela in the form of liver cirrhosis and/or HCC. The main reason for treating children infected with HCV is the difficulty in predicting the early deterioration of the disease in the light of its serious consequences. Another argument 'for treatment' is its high efficacy and good tolerance. Compared to adults, in children with hepatitis C treated with PegIFN + RBV there are observed high response rate (sustained viral response [SVR] > 50% in genotype 1 infected children compared to 40% in adults) and an SVR, which means that the disease is cured. In children there are present favorable factors for response, for example, low viral load, short duration of HCV infection, better compliance connected with parents overseeing their children's and less fibrosis [18]. Long-term monitoring of children who achieved an SVR to treatment has confirmed the high efficacy of the therapy in this group of patients [19]. Kelly *et al.* have indicated that SVR after IFN/RBV treatment predicts the long-term elimination of HCV in pediatric patients [19].

Two large prospective multicenter studies showed a high frequency of durable virological response in children with CHC treated with PegIFN and RBV. In children infected with genotype 1 HCV treated with PegIFN α-2b + RBV it amounted to 53%, in patients treated with PegIFN α-2a + RBV it was 47%. On the basis of this the two therapeutic regimens have been approved by the FDA [20].

In the current recommendations of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition further assessment of maturation according to the Tanner score has also been recommended, as well as evaluation of the parameters of the metabolic syndrome, bone age BMI and HOMA, both before and during treatment [21].

Interferon treatment for CHC has been associated with the development of retinopathy in 19 – 29% of adults. Ophthalmologic complications are infrequent in children (2 – 3%). However, because of the potential severity of ischemic

retinopathy and uveitis, prospective ocular assessment should remain part of the monitoring strategy for children who are treated with interferon for HCV [22].

Meta-analysis of eight studies evaluating the efficacy and safety of therapy with PegIFN α-2a or α-2b and RBV in 438 children with CHC showed that the treatment was safe and effective, both in children and teenagers. Early viral response (EVR) was achieved by 70% of the respondents and SVR by 58%. Both the EVR and SVR was more often achieved by children infected with genotypes 2 and 3 as compared to those infected with genotype 1 or 4 of HCV. In 4% of children their therapy was discontinued due to adverse effects and in 15% because of a lack of virologic response. Relapses occurred with 7% of respondents. The most common adverse events were: leukopenia, neutropenia, and local reactions; in some of the studies there was a slight inhibition of growth during therapy [23]. According to Kelly *et al.* the linear growth rate was impaired during treatment with a rapid increase in the 6 months immediately after treatment. Growth normalized in the majority of children during the long-term follow-up [19].

Jonas *et al.* prospectively determined changes in weight, height, body mass index and body composition during and after treatment of 107 children with hepatitis C treated with PegIFN α-2a +/- RBV in the PEDS-C trial. Decrements of up to 0.50 z score were observed for weight, height and BMI during therapy compared to baseline ($p \leq 0.01$). These effects were generally reversible with the cessation of therapy, although height-for-age z scores had not returned to baseline after 2 years of observation [24].

Schwarz *et al.* evaluated the safety and efficacy in children with CHC, 55 treated with PegIFN α-2a and RBV combined therapy compared with 59 children treated with PegIFN α-2a monotherapy. SVR was achieved by 53% of children treated with Peg-INF α-2a + RBV compared to 21% treated with PegIFN α-2a monotherapy. The sustained virological response was maintained for a minimum of 2 years. The most common side effect was neutropenia, leading to dose modification of PegIFN in 40% of patients [25].

In our own study performed in 170 children with HCV infection who completed treatment with IFN α-2b + RBV or PegIFN α-2b + RBV (group I, n = 119 and group II, n = 51 respectively) SVR achieved 62 (51%) out of 119 children from group I and 24 (47%) out of 51 from group II. In the responders in group I, the mean levels of serum hemoglobin after 24 weeks of treatment and at the end of therapy were significantly lower than the mean levels at baseline. In the group treated with PegIFN α-2b and RBV, the mean serum hemoglobin levels at week 12 were lower in the responders than in the non-responders ($p < 0.05$). In both the responders and non-responders from both groups, leukocyte counts decreased during treatment and after 12 weeks, they were more significantly lower than the baseline value. The decrease was more marked in children treated with PegIFN α-2b + RBV ($p < 0.05$). After 12 weeks of treatment, the platelet count was low in children from group II who had achieved SVR. We concluded that the mild decrease in hemoglobin levels and leukocyte and platelet counts during treatment with IFN and RBV in children with CHC may be factors responsible for SVR induction [26].

In an international multicenter study evaluating the safety and efficacy of PegIFN α-2a and RBV treatment of naive children with CHC it has been shown that the use of this therapy helped to achieve an SVR in 27/47 (57%) of children infected with genotype 1, 4, 5 or 6 and in 16/18 (89%) of children infected with genotype 2 or 3 HCV [18].

A meta-analysis of five prospective studies evaluating the efficacy of therapy with PegIFN α-2a or α-2b and RBV in 318 children with CHC showed that 193 (60.7%) of those treated received SVR, including 93% of those infected with genotype 2/3 HCV, 55% of those infected with genotype 4 and 51% of those with genotype 1 HCV. Treatment was found to be safe and well tolerated [27].

In a multicenter Polish study, which included 44 children with CHC treated with PegIFN α-2a and RBV, sustained virologic response was observed in 77.5% of patients. Factors influencing a favorable response to treatment such as low baseline viral load and low severity of fibrosis in the liver were determined [28].

Domagalski *et al*. demonstrated that higher SVR rates were observed in children with the CC allele marker of rs 12979860 and the TT allele of rs 8099917 marker IL-28B as compared to the children with the alleles respectively for CT and TT rs 12979860 and TG and GG rs 8099917 [29]. Shaker *et al.* suggest determination of rs 12979860 polymorphism of the IL-28B and rs 3021097 for IL-10 as the selection criteria for the treatment of children infected with HCV genotype 4 with PegIFN + RBV [30].

In a study evaluating the use of PegIFN α-2a with RBV both as a full course of treatment and as the continuation of treatment after recombinant interferon with RBV, it was demonstrated that it was effective, safe and well tolerated. The sustained virologic response was observed in 61% of treated children. A positive factor in response treatment was the short period of the HCV infection. Among the adverse events leucopenia dominated, but it did not require discontinuation of therapy [31].

Approval of pegylated interferons for the treatment of CHC in children has contributed to an increase in the effectiveness of therapy, as well as to an improvement of patient's QOL.

The use of the first-generation protease HCV-inhibitors telaprevir and boceprevir has been sanctioned by the FDA and EMA since 2011 for adults. In adults, genotype 1 non-responders have also demonstrated SVR rates ranging between 59 and 66%, depending on the duration of boceprevir treatment, compared to 20% with previous standards of care [32]. A pediatric trial with boceprevir for naives and non-responders was induced in 2012 in the USA and Poland and stopped in 2013 according to the sponsor of this trial decision.

In 2013 and 2014 new anti-HCV direct-acting antiviral agents (DAA) sofosbuvir (the first polymerase HCV inhibitor, effective with all HCV genotypes) and simeprevir (NS3-4A protease HCV inhibitor effective in genotype 1 and 4 HCV infection) were approved by the FDA and EMA as a triple (with PegIFN + RBV) combined therapy or as an IFN-free treatment and their high treatment efficacy > 80% with few adverse events has been noted [33]. Given that efficacy data should be extrapolated from adults to children and approved therapy regimens should be included in future pediatric trials, especially for children with contraindication for IFN, IFN intolerance and non-responders to PegIFN and RBV.

1. Conclusion

Current treatment of HCV infections in children and adolescents with PegIFN and RBV is highly efficient, safe and well tolerated. The efficacy of PegIFN + RBV treatment in children is comparable to triple (PegIFN + RBV + boceprevir/telaprevir) HCV therapy in adults. Now we are entering the era of pangenotype IFN-free HCV therapies for adults, included as special patients populations as HIV-HCV co-infected, post-transplant, and so on. It seems to be important to introduce these possibilities to children, especially to children with contraindication for IFN (e.g., autoimmune disorders), IFN intolerance/IFN unwilling and non-responders to PegIFN and RBV. However, delaying current treatment until approval is finalized for these new therapies is not desirable because of potential serious clinical consequences. Independent of the schedule of therapy in pediatric patients monitoring the parameters of physical and mental development during therapy is recommended.

2. Expert opinion

The key findings of this article are the legitimacy of treatment of HCV infections in children, high treatment efficacy and safety. Antiviral therapy of HCV infection in children is based on prevention of disease progression and of serious clinical sequela in the form of liver cirrhosis and/or HCC. Mild advancement of morphological changes in the liver does not exclude the serious clinical consequences of the disease. It was recently revealed that HCV genotype 3 infection is associated with a significantly increased risk of developing cirrhosis and HCC independently of patients' age; therefore, early treatment of young children is important. The main reason for treating children infected with HCV is the difficulty in predicting the early deterioration of the disease in the light of its serious consequences. Another argument 'for treatment' is its high efficacy and good tolerance. In children with CHC treated with PegIFN + RBV a high response rate (SVR > 50% in genotype 1 infected children compared to 40% in adults) is observed. SVR after IFN/RBV treatment predicts the long-term elimination of HCV.

The most common adverse events were: leukopenia, neutropenia, local reactions and, in some studies, slight inhibition of growth during therapy with a rapid increase in the 6 months immediately after treatment. It was revealed that the mild decrease in hemoglobin levels and leukocyte and platelet counts during treatment with IFN and RBV in children with CHC may be factors responsible for SVR induction.

The majority of children experienced no clinically significant change in their physical QOL, behavioral adjustment, level of depression or cognitive functioning during or after the PegIFN α-2a + RBV.

The weaknesses of the treatment of HCV in children are new HCV therapies included IFN-free regimens that are inaccessible for children. For adults, the use of the first-generation protease HCV-inhibitors telaprevir and boceprevir has been sanctioned by the FDA and EMA since 2011. In 2013 and 2014 new anti-HCV DAA sofosbuvir (the first polymerase HCV inhibitor) and simeprevir (NS3-4A protease HCV inhibitor) were approved as a triple (with PegIFN + RBV) combined therapy or as an IFN-free treatment and their high treatment efficacy; > 80% with few adverse events has been noted. Given that efficacy data should be extrapolated from adults to children and approved therapy regimens should be included in future pediatric trials, especially for children with contraindication for IFN, IFN intolerance and non-responders to PegIFN and RBV. However, delaying current treatment until approval is finalized for these new therapies is not desirable because of potential serious clinical consequences. Independent of the schedule of therapy in pediatric patients monitoring the parameters of physical and mental development during therapy is recommended.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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