Treatment of children with chronic viral hepatitis: what is available and what is in store

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Review article

Background: **At present, therapy of children with chronic hepatitis B and C is still based on few drugs, all burdened by a series of side-effects, unsatisfactory serum conversion rates, and/or drug-resistance. Moreover, selection of subjects to treat with conventional therapies is not univocal, especially during the pediatric age when the disease course is often mild with significant spontaneous seroconversion rate. Our review deals with pros and cons points when a physician decides to design a drug therapy for a child with chronic viral hepatitis, and different possible therapeutic opportunities.**

Methods: **A literature search was performed through PubMed. The newest articles, reviews, systematic reviews, and guidelines were included in this review.**

Results: **The management of children with viral hepatitis is still controversial over whom and when to treat and the use of drug(s). Novel therapeutic strategies have been evaluated only in clinical and preclinical trials involving, for instance, "therapeutic" vaccines. The data on safety and effectiveness of new drugs are also reviewed.**

Conclusion: **The results of reported studies confirmed that at least some of the new drugs, with greater efficacy and/or minor side-effects, will be used clinically.**

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Introduction

Viral hepatitis due to hepatitis B virus (HBV) and C virus (HCV) continue to be a major global health problem, despite the introduction of HBV vaccine. The risk of HBV infection is also increasing in the Western population because of international adoption and immigration flow coming from high prevalence countries.[1]

In this paper, we reviewed the management of chronic HBV and HCV focusing also on available and possible novel pharmacological approaches which still have poor evidence and are controversial in pediatric patients.

A literature search was performed through PubMed using key words such as viral hepatitis treatment/therapy, interferon (IFN), pegylated-IFN (Peg-IFN), ribavirin (RBV), lamivudine, new antiviral drugs, vaccine, viral hepatitis, and children alone or in combination. Original articles, reviews, systematic reviews, and the latest guidelines were selected.

Hepatitis B virus

Chronic hepatitis B (CHB) is a major cause of liver disease worldwide. It is estimated that about 400 million individuals are chronically infected. Up to 40% of the infected individuals will develop complications, including liver failure, decompensated cirrhosis and hepatocellular carcinoma. Their incidence has fallen dramatically in endemic countries where vaccination programs were introduced. However, one needs to remind that approximately 10% of infants born to hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) positive mothers are still infected despite adequate perinatal prophylaxis. Moreover, unrecognized status of celiac disease may be a reason of increased HBV vaccine unresponsiveness, thus, exposing presumptively immune individuals to the risk of hepatitis B infection.[2]

There is a higher risk of developing CHB if HBV infection occurs in perinatal or preschool age, in relation to immaturity of immune defenses. The risk

of developing CHB after exposure to the infection is alarming: up to 90% in infants born from HBeAg-positive mothers, 25%-30% in infants and children infected before 5 years, and <5% in older children and adults. Once infected, the individual can clear the virus or face 4 phases of CHB, which are related to different prognosis and treatment approaches: 1) immune-tolerance phase, characterized by normal or mildly elevated aminotransferase levels, minimal histological activity, increased HBV DNA levels (up to 10^{11}copies/mL), both HBeAg and HBsAg positive; 2) CHB with positive HBeAg, characterized by constantly increased aminotransferase levels, active histology, increased HBV DNA levels (up to 10^{10} copies/mL), both HBeAg and HBsAg positive; 3) CHB with negative HBeAg, increased, often fluctuating aminotransferase levels, active histology with variable grade of fibrosis, moderate and fluctuating HBV DNA levels (10^3-10^8 copies/mL), negative HBeAg and positive HBsAg, and 4) inactive carrier phase, with normal aminotransferases levels, inactive histology with minimal fibrosis, low or undetectable HBV DNA (<10^4 copies/mL), negative HBeAg and positive HBsAg.

Currently, 8 different HBV genotypes (A to H) are identified: genotypes B and C are more common in Asia, A and D more common in Europe and India, A and C predominate in the United States. The genotypes influence the progression of CHB: individuals with genotypes A, B, D or F commonly undergo anti-HBe seroconversion by age of 20 years, while individuals with genotype C seroconvert much later (mean age of 47.8 years).[3]

Who should be treated in pediatric age?

Children with CHB mostly present in the so-called "immune-tolerance phase" and 7%-16% of them demonstrate spontaneous seroconversion from HBeAg to HBeAb every year. Therefore, when and how to treat these patients are still controversial as treatment guidelines do not clearly refer to pediatric age.[4-7]

Current treatment aims to stop viral replication, thus reducing infectivity and preventing long-term complications. The low replication activity, low viral load, high cytolytic activity of HBV in adults are predictive factors of successful treatment also in children.[8] The goal of treatment is ultimately to clear HBeAg and HBV DNA.[6,7] Uncertainties about the opportunity to start treatment derive from the observation that most of untreated patients with mild disease, and most of those with active hepatic disease undergo spontaneous seroconversion of HBeAg within the first 20 years of life.[3,6,7,9]

Because of the absence of formal guidelines, researchers suggested some criteria for decision-making between pharmacological treatment and clinical/laboratory surveillance. The proposed flow-chart of management shows the following predictors of good response, such as biochemically active CHB, positive hepatitis B surface antigen (HBsAg) for at least 6 months and positive HBeAg and/or HBV DNA >2000 IU/mL, and high grade histological hepatic inflammation (Fig. 1).[1,3,8,10] Patients with HBeAg and increased alanine aminotransferase (ALT) should be monitored for at least 12 months in order to detect the possible spontaneous seroconversion.

Standard therapy

Currently, seven agents for the treatment of CHB have been approved by the Food and Drug Administration (FDA), United States. Only four of these (IFN-α, lamivudine, adefovir, and tenofovir) have hitherto been used in children with CHB (Table 1). In addition, entecavir has been approved for patients older than 16 years.

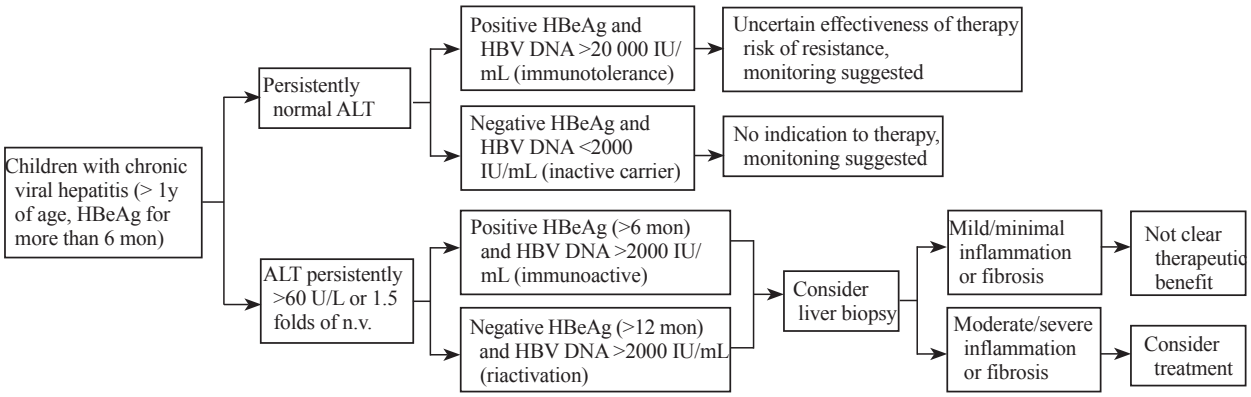

Fig. 1. Proposed flow-chart for the therapeutic management of children affected by chronic hepatitis B with standard of care therapy according to biochemical, virological and histological criteria (modified from Jonas et al[3]). ALT: alanine aminotransferase; HBV: hepatitis B virus; HBeAg: hepatitis B e antigen; n.v.: normal value.

IFN-α

IFN has antiviral, anti-proliferative, and immunomodulatory properties. A 24-week treatment with IFN-α 2b can significantly fasten HBeAg seroconversion during the first year in children with CHB compard with controls. But the results after a 5-year follow-up were comparable to those of the controls.[13] HBsAg clearance was significantly higher in treated CHB children than in the controls.[14]

In summary, the present pediatric standard of care (SOC) in the medium to long-term course, does not improve the final rates of HBeAg and HBV DNA seroconversion but accelerates their timing of seroconversion.[13-15] Since steroid priming does not appear to potentiate the effect of IFN-α,[13,16] its role is not defined.

Previous data on the treatment of hepatitis C have shown that therapy with Peg-IFN (which can be administered once weekly), even if supported by little experience in children, appears to be promising in the treatment of pediatric CHB too.[1,3,8] If co-infection with hepatitis D virus occurs, IFN-α-2b represents the first-choice of therapy. It has been reported that treatment of children with chronic hepatitis D has a transient effect, and long-term treatment produces no greater therapeutic effect or biochemical and virological response.[17]

Lamivudine

Lamivudine, a nucleoside analogue, inhibits the HBV reverse transcriptase and can play a role in the treatment of pediatric CHB after continuous oral administration. A multicenter study[18] revealed that lamivudine leads to HBeAg seroconversion in one third and one fourth of 213 CHB patients who were naïve or had previously been treated with the same drug, respectively. This therapy has a significant risk of drug-resistance (mainly related to mutations in the locus YMDD of HBV reverse transcriptase gene). In this study, YMDD mutations occurred in about 50% and 64% of the cases, respectively.

Other nucleoside and nucleotide analogues

Except for adefovir and tenofovir that have already been used in >12 years old children in the United States, different analogues have been approved by the FDA for the treatment of CHB only in adult/adolescent patients. Compared with lamivudine, these drugs appear to be promising because they can be orally administered for a long period with a lower drug resistance.

Adefovir

A pilot study of safety, efficacy and pharmacokinetics showed that adefovir is not superior to placebo in inducing seroconversion in patients aged from 2 to 19 years. HBeAg seroconversion appeared only in 12% of patients after one-year treatment with adefovir. Once achieved, seroconversion is durable in all patients. Patients who have undergone HBeAg seroconversion require life-long treatment.[19] In adults and children, the resistance rate of adefovir was significantly lower than that of lamivudine (0%-29% at 1-5 years of therapy).[19,20]

Entecavir and tenofovir

Entecavir, a nucleotide analogue and HBV polymerase inhibitor, is more effective than lamivudine in inducing HBV DNA suppression, liver histology improvement, and normalization of transaminases. The incidence of resistance is low, with a rate of only 1.2% after 5 years. In the United States, entecavir can be administered from 16 years of age. Recently, the efficacy and safety of entecavir were evaluated in CHB children treated with IFN or lamivudine or adefovir, alone or in combination. After 24 weeks of treatment with entecavir, the HBV-DNA level was significantly reduced to a complete clearance in about 90% of HBeAg negative and 23% of HBeAg positive children. The efficacy and safety of entecavir are currently studied in a phase III trial

Table 1. Available treatments for chronic hepatitis B in children in United States (modified from Murray et al and Ayoub et al[11,12])

Drugs	Age	Advantages	Disadvantages	Side effects	Dose	Success rate (%)
IFN-α	≥2 y	No resistance, short time therapy (16-24 wk)	Parenteral administration, side effects	Flu-like symptoms, bone marrow aplasia, alopecia, hipotiroidism, failure to thrive	5-10 MU/m^2, 3 times/wk for 24 wk	2-58
Lamivudine	≥2 y	Good tolerance, oral administration	Common pharmacological resistance	Need to monitor kidney performance	3 mg/kg/die up to 100 mg/die for ≥52 wk	25-35
Adefovir	≥12 y	Good tolerance, oral administration, effective in HBV lamivudine-resistant pts	Pharmacological resistance less common than lamivudine	Need to monitor kidney performance	10 mg/die for 48 wk	16-23
Tenofovir	≥12 y	Oral administration, effective in HBV lamivudine-resistant pts, no resistance	Pharmacological resistance less common than lamivudine	Need to monitor kidney performance and bone metabolism	300 mg disoproxil fumarate/die for 72 wk	89

IFN: interferon; HBV: hepatitis B virus; pts: patients.

involving children aged 2-17 years.[21] In CHB children who have developed lamivudine resistance during the treatment, add-on adefovir treatment and entecavir monotherapy exhibited more effective virological responses compared with adefovir monotherapy.[22]

Tenofovir is another nucleotide analogue structurally related to adefovir. In adult patients with adefovir-resistant CHB, tenofovir produced better therapeutic results[23] and also good tolerance.[24] Adverse effects of tenofovir on bone mineralization have been debated.[25,26] Since the duration of tenofovir treatment could be several years, its role in children with CHB infection might need careful supportive evidence. A most recent trial in adolescents (age >12 years) showed high success in HBV DNA decrease (<400 copies/mL by week 72 in 89% of tenofovir treated patients) but was unable to show improved HBV serology compared with placebo. Still, treatment obtained a statistically significant higher composite endpoint of HBV DNA decline <400 copies/mL, ALT normalization and HBeAg loss or seroconversion (21.0% *vs.* 0%, $P<0.05$).[11]

Telbivudine

Telbivudine is the last nucleotide analogue approved by the FDA, United States, for the treatment of CHB especially in both compensated and decompensated cirrothic adults.[27]

Vertical transmission

A large proportion of pediatric CHB patients have acquired their infection vertically (mother-to-child transmission, MTCT). In most (>90%) of patients with vertically-acquired infection, the infection is due to induction of an immune-tolerant state.[28] Hence, management of CHB during pregnancy and strategies to prevent MTCT are extremely important. Despite appropriate immunoprophylaxis and prompt administration of immunoglobulin against HBV together with the first dose of vaccine at birth, up to 10% of infants born to mothers with highly viremic HBV (HBV DNA ≥7 log IU/mL) mothers become chronically infected.[29] There has been poor consensus on whether antiviral therapy before delivery would lower the viral load adequately to prevent transmission.[30,31] More recently, the efficacy of treatment with lamivudine,[32] telbivudine[33] or tenofovir[29] in third-trimester pregnant women showed that newborns of the mothers who received antiviral treatment had a significantly lower incidence of intrauterine exposure.

Future research

Vaccine "therapy"

The rationale of a therapeutic vaccine, which can be administrated alone or in combination with conventional anti-HBV drugs, is to increase immune responses in chronically infected subjects. Compared with SOC therapy, the administration of vectors containing the highly immunogenic PreS region of gene sequence in patients older than 15 years has shown good tolerability but poor seroconversion rate.[34] One of the problems seems to be related to the depletion of T-mediated response in chronically infected subjects, who consequently have decreased ability to respond to the immunological stimulus of a therapeutic vaccine. Recently, the attempt to increase the immunogenicity of therapeutic vaccines has led to the intranasal administration of recombinant HBsAg and HBeAg (vaccine known as NASVAC). This strategy is actually under phase III experimentation in adults.[35]

Hepatitis C virus

HCV infection involves approximately 180 million people. This infection can develop into acute and chronic hepatitis with possible evolution to liver cirrhosis and liver cancer. As to the HCV, there are 6 major genotypes and more than 80 subtypes with different prevalence. Genotypes 1 and 1b are the most common in Europe and in the United States, and together with genotype 2, they represent the majority of genotypes worldwide. Genotypes 2 and 3 appear more easily treated and have a higher rate of spontaneous clearance.[36] The most common infection in children is characterized by vertical transmission that accounts for up to 60% of children with hepatitis C.[37] Factors associated with high-risk vertical transmission are represented by a large number of maternal copies of HCV RNA ($>10^6$ copies/mm^3), HIV co-infection, drug abuse per se, and prolonged delivery.[38-40] Polymorphisms of rs1297986 locus, close to the interleukin *IL28B* gene (recently studied in relation to the post therapy viral clearance in adults) are not involved in the vertical transmission of HCV. Polymorphism, however, is independently associated with the spontaneous clearance both in children with genotype 1 infection[38] and in those with genotype 2 and 3 infection.[41]

Indications for treatment

There is no unanimous consensus on the treatment of children with chronic hepatitis C (CHC). But the treatment may prevent the progression of the disease, avoid serious sequelae, and reduce the risk of infection.[42] However, the absence of clinical and laboratory symptoms in most patients, expensive drugs, potential side-effects, slow progression, and ineffective treatment especially in

those patients with genotype 1, puzzle physicians to design an antiviral therapy.[43] Since 5% of pediatric patients will develop a severe liver disease, antiviral treatment is required, at least for those infected with more responsive genotypes[44] The guidelines for the management of HCV, formulated by the North American Society of Gastroenterology Hepatology and Nutrition, suggest that children with hepatitis C who demonstrate persistently elevated serum aminotransferases or those with progressive disease (i.e. fibrosis on liver histology) should be considered for treatment.[45] A recent review analyzing thirteen non-randomized studies and one trial dealing with treatment with Peg-IFN plus RBV in children with chronic HCV infection showed a sustained viral response rate ranging from 28.6% to 81.8%. However there are different opinions about the indications and modes of treatment.[46]

Standard therapy: a combination of interferon and RBV

Peg-IFN α, in association with RBV, is currently used for the first-line therapy (SOC) of CHC.[38,45] Peg-IFN α enhances the immune response against HCV by triggering the phagocytic activity of macrophages and stimulating the cytotoxic activity of lymphocytes against target cells infected by the virus. Two different Peg-IFN α products are available, Peg-IFN α-2a and Peg-IFN α-2b.

RBV is a guanosine analogue preventing the HCV RNA synthesis by inhibiting the HCV RNA polymerase. In the adult population, it is used to determine the rate of sustained virological response (SVR) in 50% of patients with genotype 1 and 80% of patients with genotypes 2 and 3.[44] In a large pediatric study, the therapy with Peg-IFN α plus RBV resulted in a SVR (defined by the disappearance of HCV RNA at 24 weeks after discontinuation of the therapy) in more than half of the patients with genotypes 1, 4, 5 and 6, and in more than 90% of patients with genotypes 2 and 3.[47] The main features of the two drugs are summarized in Table 2.

Tailored therapy

A recent approach to CHC treatment in adults is characterized by "individualization" (tailored therapy) and/or predictive parameters of SVR.[48]

Host-related predictive parameters

In genotype 1 adult patients, response to the treatment was found to be associated with a single nucleotide polymorphism (SNP) next to the *interleukin 28-B* gene on chromosome 19, encoding IFN-λ-3. The locus of interest is rs 12979860, in which a SNP determines allelic heterogeneity (C or T allele). The response to standard therapy in patients with HCV genotype 1 is higher for CC polymorphism compared with CT and TT polymorphisms.[49] Pediatric data have become available very recently and they confirm the role of this polymorphism also in this age.[39]

HCV-related factors

HCV genotype, pretreatment viral load and initial virological response are important predictors of SVR. As mentioned above, patients with genotypes 2 and 3 respond to therapy better than those with genotypes 1 and 4. Moreover, a lower starting viral load predicts therapeutic success, such as fast seroconversion of HCV RNA.

Response-related therapy

The correlation between the rapid disappearance of HCV RNA and the achievement of SVR allowed to introduce the model of response-related therapy.

"Early viral response" (EVR) is defined by the decrease of HCV RNA >2 log10 compared with pre-treatment (partial EVR) and disappearance (complete EVR) at week 12 of therapy. Based on these considerations (validated in adults), patients with genotypes 1 and 4 with complete EVR can reduce the duration of treatment to 24 weeks in contrast to conventional 48 weeks. Conversely, in people who do not reach EVR, treatment should be considered for an extension up to 72 weeks.

Patients with a favorable genotype (2 or 3) are subjected to a 24-week treatment. This modular approach constitutes an interesting perspective for pediatric patients even though no preliminary evidences are available.[50]

Therapeutic perspectives

Studies have focused on the role of a series of new drugs which interfere with HCV replication in adults are currently tested in clinical trials.

Table 2. Main features of drugs adopted for treatment of hepatitis C in children (modified from Wirth et al[43])

Drugs	SVR	Genotype 1	Genotypes 2-3	Doses
IFN-α	0-76%	-	-	-
IFN-α+ribavirin	27-64%	36-53%	>80%	IFN, 3 millions U, 3 times/wk; RBV, 15 mg/kg/d
Peg-IFN-α-2b/a+ribavirin	-	44-59%	>90%	Peg-IFN, 60 mg/mq, 1 time/wk; RBV, 15 mg/kg/d

IFN: interferon; SVR: sustained virological response; RBV: ribavirin.

Albinterferon and Peg-IFN lambda

Albinterferon is a protein consisting of IFN α-2b genetically fused to human albumin. A trial in adults showed that albinterferon is effective as Peg-IFN α in inducing SVR in patients with HCV infection. Being administered every 2 weeks, albinterferon can hopefully be taken as an alternative for the treatment of hepatitis C,[51] particularly in children. The EMPOWER and SELECT-2 trials showed that controlled release IFN α-2b (CR2b) not only produces comparable results, but also reduces flu symptoms by 50%.[52,53] Peg-IFN lambda 1 (IL-29) is a new class of IFN that binds to a receptor different from that of Peg-IFN α. The receptor for IFN lambda is more hepatocyte-specific and thus has the potential for the improvement of side-effects. The results from the recent Phase 2b EMERGE clinical trial showed that Peg-interferon lambda has a higher rate of RVR in genotypes 1 to 4. In addition, there is an improvement of anemia and flu-like symptoms.[54]

Protease NS3/4 inhibitors

HCV NS3 serine protease and its cofactor NS4A promote the cleavage of viral polyprotein into 4 non-structural proteins. The inhibition of this system not only inhibits viral replication, but also promotes innate immunity by preventing cleavage of the Toll-IL1-receptor domain and IFN β promoter simulator (IPS-1). Two of these inhibitors (telaprevir and boceprevir) have been approved for marketing in May 2011 in the USA for the treatment of adults with HCV infection and since then they have become available also in other countries. Telaprevir, administered in addition to SOC therapy, increases the SVR by about 20% in untreated patients (SVR 75%-80%) and 30% in SOC non-responders with genotype 1. Boceprevir increases the SVR in treated patients with genotype 1 only after prolonged administration.[55] Both drugs help to reduce the time of treatment. However, there are specific side-effects such as rash, anemia (sometimes needing the use of erythropoietin and/or dose reduction), itch, nausea and diarrhea after the administration of telaprevir, and anemia and dysgeusia after use of boceprevir. Their use is currently still not warranted in pediatric age.[44,48] A large series of protease inhibitors of 2nd and 3rd generations are presently under experimentation.

Other new antivirals against HCV

A number of novel drugs, orally administered in (triple) combination with standard therapy IFN combinated with RBV are at present tested in various stages of clinical trials in adults, significantly increasing the rates of HCV RNA seroconversion in genotype 1, and leading to the recovery of patients with genotypes 2 and 3. Their possible application in children is therefore highly desirable. Table 3 shows their possible sites of action.

Vaccine is used to stimulate the immune response against HCV. To date, the main problems are related to the hypervariable regions of the viral genome encoding for pericapsidic viral envelope components which promote the continuous escape of virus from the host immune response. Two major categories are now being studied: 1) Preventive vaccines for non-infected subjects. The vaccines are able to inhibit the entry of HCV into the cell or to eliminate HCV after the first contact;[56] 2) "Therapeutic" vaccines for infected individuals alone or in combination with antiviral therapy stimulate an immune response to accelerate seroconversion.

Among these vaccines, globe immune GI-5005 and IC41 appear the most promising. Vaccines based on epitopes of NS3, restricted HLA-A2, and modified NS3 are used to stimulate a specific T mediated response. Finally, the use of vaccines consisting of the NS gene 3/4a, whose expression is under the control of a CMV promoter, in combination with IFN and RBV is promising in inducing HCV seroconversion.[56,57]

Conclusions

Choice of which children with CHB or CHC need treatment is still matter of debate.[3,6,38,43,45,49] Also, the most recent guidelines for management of CHB in childhood issued by the European Society of Gastroenterology Hepatology and Nutrition are

Table 3. Possible sites of action of the new antiviral drugs in replicative phases of hepatitis C virus (HCV)

Class and target	Sites and mode of action
Neutralizing antibodies	Inhibit cell entry
NS3/NS4a proteases inhibitors	Inhibit tanslation and processing of poliproteins
RNA inside ribosome inhibitors	Inhibit trascription
Helicase inhibitors	Inhibit trascription
NS5A inhibitors	Avoid viral assembly and envelope glycosylation
NS4B inhibitors, ciclophillin inhibitors, HMGCoA inhibitors	Avoid formation of vesicles from the cell infected membrane that are essential to constitute the complex of viral assembly
Toll-like receptors agonists	Enhance immune response against HCV

NS: nuclear scaffold; HMGCoA: hydroxy-methyl-glutaryl-Coenzyme A.

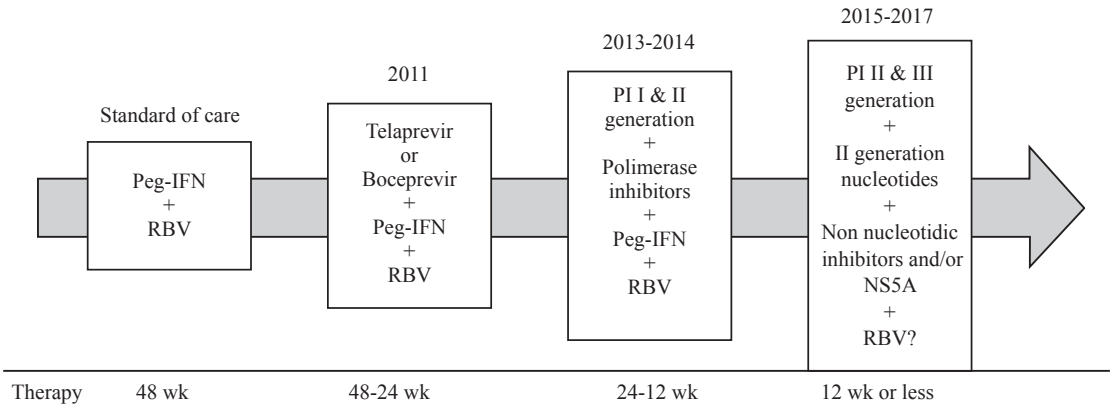

Fig. 2. Present and future therapeutic options for chronic hepatitis C aiming to a progressive increase of effectiveness, reduction of side effects and time of treatment, and possibly oral route administration. Peg-IFN: Peg-interferon; RBV: ribavirin ; PI: protease inhibitors; NS: non-structural.

inconclusive on this matter.[58]

Further studies of Peg-IFN are necessary for the treatment of HBV in children. New antiviral drugs, nucleoside and nucleotide analogues, are characterized by a lower drug resistance rate *vs.* lamivudine.

For children with hepatitis C, SOC therapy is based on the combination of Peg-IFN and RBV. New therapeutic perspectives are necessary especially for the unfavorable genotypes 1 and 4. The use of algorithms guided by the *IL28B* polymorphisms probably will be increasingly helpful to modulate the doses and duration of SOC therapy also in children with unfavorable prognostic predictors.

Other novel therapeutic strategies, often used in combination with SOC therapy in adults, consist of active drugs against the entry of HCV cell and the different stages of the viral replicative cycle. The results of preliminary studies show that at least some of these (with greater efficacy and/or minor side effects) will soon be used clinically. Cocktails of these drugs (which can be administered alone or in combination with IFN and/or RBV), with greater effectiveness, oral route administration, fewer side-effects, shorter duration of treatment, minor drug resistance, fewer times of daily administrations, are expected in the near future (Fig. 2). For both virus B and C, therapeutic vaccines continue to be tested as a possible treatment at all ages but still show unsatisfactory results.

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