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REVIEW ARTICLE

Peginterferon Treatment in Children: A Review of Chronic Hepatitis B and Chronic Hepatitis C Treatment

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***Abstract**: Despite of extensive blood product screening and national immunization programs, chronic hepatitis B and C infections continues to be a global problem with high mortality, morbidity and economic impact. Even though acquisition of these infections mostly occurs in childhood, major problems appear in adulthood. Cirrhosis and HCC are two major expected late events related to chronic hepatitis B and C infections. Rarely, children may also face these complications. To avoid these complications and increase the life expectancy in adults treatment of these two type infections should be started in childhood with appropriate patient selection. In contrast to children, adults are luckier in terms of treatment alternatives. They have the chance to use more potent antivirals with higher genetic barrier and pegylated form of interferons. Recently, the use of pegylated interferon and ribavirin combinations has been approved in children in Chronic HCV infection. However, chronic hepatitis B treatment in children is still dependent on the use of one type antiviral drug and conventional interferon. Treatment in early ages with an antiviral agent that has limited genetic barrier may block the chance of treatment or reduce the response rate in adulthood in chronic hepatitis B infection. This burden indicates the necessity of new therapeutic modalities in children. In this term pegylated interferons may be one of the options. In this article we aimed to review the efficacy and safety of conventional and pegylated interferons, for the treatment of Hepatitis C and B infections in children.*

***Key words**: Peginterferon, Chronic Hepatitis, Children*
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Introduction

Interferons (INF) are naturally produced proteins. Most of the nucleated cells are capable of both secreting and responding to INF which makes the interferon system a powerful defense system against pathogens and an essential component of innate immunity [1]. Alfa, beta and gamma INF's are the three types of identified interferons. Each class has different activities with some overlaps. Alfa interferon's (2a and 2b) are the interferons that are used in hepatitis B and C treatment. They have antiviral and immunomodulatory effects. They also blocks denovo virus production and potentiate the infected cell death [2]. The exact antiviral mechanisms of INF's are not well known; however, some hypothesizes are proposed: Main action of INF is carried out through interferon stimulated gene (ISG) products [3]. There are hundredths of ISG's. A subtype of ISG is virus stress induced gene (VSIG). Same genes can be stimulated by various viral proteins and double stranded RNA [4]. Interferon binds to a common receptor side on the target cell and stimulates the transcription of VSIG through triggering the formation of interferon stimulated gene factor 3 (ISGF3), which in turn stimulates the secretion of different effector proteins like matrix proteins, protein kinase and RNA specific adenosine deaminase [5-8]. Several types of these proteins inhibit not only distinct steps of viral replication but also virion assembly [9]. Immunomodulatory effect of INF's has been studied with different viral infections. They modulate the cytokine response of T helper 1 cells. Interferon increases the INF gamma production, reflecting T helper 1 activity [10]. Sustained serum INF gamma ends up with higher sustained viral response in HCV patients, explaining the activity of INF in HCV infected patients. Pegylated INF-α2a and α2b (pegINF-α2a and pegINF- α2b) are two available pegylated forms that differ from conventional interferons by having a molecule of polyethyleneglycole attached to

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them. Pegylation improves the pharmacokinetics of conventional INF core protein: It enables prolong absorption, limited distribution, longer half life and sustained serum concentration which makes once a week dose regimen possible. The absorption half life of conventional INF is 2.3 hours (both for α2a and α2b) whereas it is 50 hours for pegINF. Desired steady state serum concentration is reached at 12 weeks of therapy [5].

Conventional INF is metabolized in kidneys during reabsorption at proximal tubules. Further break down may occur at the level of cellular receptors [5,11,12]. In contrast, pegINF is metabolized primarily by the liver. However, metabolic byproducts are eliminated in the urine; therefore, in end stage renal disease dose adjustment is necessary for both type of INF's [5]. Furthermore, pegylation prolongs the half life and the effectiveness of INF. Half life of conventional INF is 4-16 hours. This rapid elimination from the serum needs recurrent injection (three times a week s.c) to establish appropriate serum levels. By contrast, the half life of pegINF's ranges between 61-110 hours. Consequently, prolonged absorption, delayed elimination time and higher maximum serum levels enable a more steady state serum concentration requiring only once a week injection compared to three times injection/week of conventional INF and provides higher treatment responses. This also explains the superiority of pegINF over conventional INF in the treatment of viral hepatitis [5, 12]. Both types of peginterferons are licensed and have been used either as monotherapy or combined with antivirals like lamuvudine or ribavirine in the treatment of hepatitis B or C in adults. But pharmacokinetics in children is not thoroughly studied. Schwarz et al. [13] measured the serum concentration of pegINF-α2a in 14 children at 24, 92, 168 hours at week one, and then 4, 8, 12, 24, 40, 48 weeks of treatment. Pegylated interferon dose in this study was adjusted according to body surface area. They observed that steady state was reached at week 12, simulating adult results.

Interferons show their antiviral effects through two mechanisms: First they inhibit directly viral DNA replication and activate antiviral enzymes [14]. Second they exaggerate immune response against viruses by increasing major histocompatibility antigens type 1, thereby stimulating the activity of T helper and Natural killer cells [14, 15]. In the field of pediatric gastroenterology major clinical indications of INF's are chronic viral hepatitis due to HCV and HBV infections.

Chronic Hepatitis C infection:

Most of the knowledge of INF's came from the treatment of HCV infected patients. HCV is an RNA virus from flaviviridea family and around 170 million people are infected with HCV around the world. Estimated seroprevelance of HCV in the United States is 0.2 % in children younger than 12 years of age, and 0.4% between 12-19 years of age [16]. Moreover, 20-30 % of infected adults suffer from progressive disease, one of the leading indications of liver transplantation. Although screening program has decreased the risk, blood and blood products transfusion are still the main source of infection in adults. In children main acquisition route is mother to infant transmission [17]; 50% of perinatally infected children undergo spontaneous seroclearence, 19%-40.1% being in the first 2 year and 14.9 % after 15 years [16,18]. Although, 20-50% of chronic HCV infected adults progress to liver failure or hepatocellular carcinoma (HCC) clinically significant liver disease is rare in children. Children have less inflammation, fibrosis and steatosis compared to adults, presumably due to shorter duration of infection [17].Yet 5-10% of the vertically infected children develop fibrosis or cirrhosis or even HCC [19-23]. Inflammation is correlated with ALT level, fibrosis and duration of infection rather than the acquisition age. By contrast, fibrosis is correlated neither with age nor duration [17].

Treatment of this global problem is mainly based on INF's and ribavirin which is a guanosin analog with antiviral effect. Studies on adult population have shown that pegINF with or without ribavirin are more effective than conventional INF with or without ribavirin combination [24-26]. Food and drug administration (FDA) approved pegINF-α 2a for the treatment of chronic hepatitis C infection in adults in October 2002. Before and after this approval both peginterferon monotherapy or peginterferon– ribavirin combination have been studied extensively. Treatment end points include sustained biochemical response, histological response, biochemical and virological response at the end of the treatment (48 week). These responses can be described as follow [27]:

1. *Sustained viral response (SVR):*
   Defined as undetectable serum HCV RNA (below 50 IU/ml) at 24 week after treatment cessation [28, 29],
2. *End of treatment response (ETR):*
   Clearance of HCV RNA at the end of treatment,
3. *Biochemical response (BR):*
   Normalization of ALT or decrease ALT levels below the upper limit,
4. *Histological response (HR):*
   2 points decrease of inflammation score compared to pre-treatment scores.

Since the histological response accompanies with virologic response, the ultimate goal of treatment is to achieve SVR.

Considerable better biochemical responses (38-45%), ETR (60-69%), SVR (30-39%) and histological responses (88%) have been observed with pegINF-α2a in adults compared to conventional INF-α2a where biochemical responses are reported to be 9-25%, ETR 12-28 %, SVR 3-39%. Adverse effects are also shown to be similar to INF- α 2a group [30]. However, the compliance is better in pegINF group. Studies showed that peginterferon increased the odds of sustained response also in genotype 1 patients: Sustained virologic response (SVR) was 13-31% with peginterferon alfa- 2a compared to 0-15% in conventional INF in genotype 1 [24,25,30]. Even patients without response or with relapse may experience histological improvement at a rate of 36%. In adults 180 µg /kg dosing regimens is associated with best outcome.

In an attempt to increase the response both conventional INF and pegINF were combined with ribavirin (INF: 3-6 MIU /three times a week s.c., pegINF-α 2a 180 µg, pegINF- α 2b 1,5 µg /kg/once a week s.c, Ribavirin: 800-1200mg/day p.o divided in two dose). Addition of ribavirin to INF enabled a ETR rate of 52% and SVR rate of 44%. Whereas combining pegINF with ribavirin increased SVR to 51-71% (depending on genotype, viral load and drug dose). Overall SVR was 51% in genotype 1 patients with a dose of 180 µg /week pegINF-α 2a and 1000-1200 mg/day ribavirin. By contrast, in non genotype 1 HCV SVR was achieved in 77% of patient. Furthermore, analysis of the effect of viral load demonstrated that SVR was 46% in high viral load, 61% in low viral load in genotype1 patients, SVR was as high as 49-52% in compensated cirrhotic patients [10,25,31-35]. Therefore, currently recommended therapy for Chronic HCV infection in adults consists of pegINF and ribavirin combination [27, 29].

In the adults treatment durations, cost effectivity, factors affecting the outcome and the difference among two types of pegylated form have been recently studied and some statements have been achieved: Genotype 1, high viral HCV load, high ALT caution (pretreatment ALT average divide by upper normal limit (UNL) are poor prognostic factors for both INF and pegINF treatment. 180µg/kg PEG IFN alfa 2a and 1-1,5µg/kg once a week dosing regimens are reported to be associated with best outcome [30, 29,36]. According to results of IDEAL clinical trail which has been recently published, 1µg regimen was as effective as 1,5 µg. This issue is may be important in terms of adverse events [36]. But appropriate dosing regimen has to be studied in details in children.

Treatment duration for genotype 1 and non genotype 1 (mainly 2 and 3) are handled separately: 48 weeks treatment duration seems mandatory for genotype 1 patients providing some situations: those genotype 1 patients who attain an early virologic response (EVR; at least 2 log decrease in HCV RNA compared to pretreatment levels) should be treated for 48 weeks. Failure to decrease HCV RNA at least 2 log at 12 weeks of treatment is strongly associated with non response [26, 27, 37]. Therapy should be discontinued earlier for these patients. On the other hand, EVR doesn't have any clinical utility in genotype 2 or 3 patients. Most of these patients respond to treatment before 12 weeks. And a standard 24 weeks treatment is advised in these patients. In an attempt to further decrease the treatment duration earlier time points such as rapid virologic response (RVR) has also been studied. Rapid virologic response is defined as undetectable HCV RNA with PCR at treatment week 4. In genotype 1 patients who achieve RVR, 24 week treatment seems enough in some studies [38]. But still the statement: Genotype 2 or 3 patients achieving RVR can be treated for 12-16 week is not sufficiently supported yet. Furthermore, although 12-16 week duration seems comparable with standard 24 week schedule in RVR attained patients, it is associated with high relapse rate [29, 39-42].

Cost effectivity of pegINF- ribavirin combination has been studied in adults by extrapolating the long term outcome of treatment with Markov model [29] and it has been found to be cost effective compared to conventional INF and ribavirin combination [43,44]. PegINF-ribavirin therapy showed a 0.9 year increase in life expectancy and cost saving of $3761 in life time medical cost with a further increase when a genotype analysis is performed and treatment is defined according to this [5].

Two types of pegylated interferons have been compared in a few trials. While increasing the pharmacokinetic properties of the interferon core protein, pegylation leads to a decrease in its biological activity in invitro studies. For example, biologic activity of pegINF-α 2b is just 28% of the original interferon alfa 2b core protein. This is further decreased in pegINF-α2a (7%). The importance of this invitro difference has been studied invivo: After a dose of 180 µg maximum serum concentration was reached at 48-168 hours with pegINF-α2a and remained stable by time, whereas 78% of the pegINF-α2b treated patients (1 µg /kg) had undetectable drug concentration at 168 hours [45]. Silva et al. [46] report that there is a 16 fold higher drug serum exposure with pegINF-α2a compared to pegINF-α 2b. But despite this higher drug exposure with pegINF-α2a, interferon induced gene response and virologic response at week 8 were significantly better with pegINF-α2b. [46]. The impact of these findings on SVR has been recently studied in a large scale, multicenter randomized control trials.

Authors compared 180 µg pegINF-α2a with two different dosing regimen of pegINF-α 2b (1 µg /kg or 1, 5 µg /kg): Both types of pegINF were found to be equally effective in terms of SVR. Moreover, patients who received 1 µg/kg pegINF- α2b achieved comparable SVR with those who received 1, 5 µg /kg, which may be important in terms of adverse events [36].

Due to the hope of spontaneous sereoclereance and presence of milder liver disease, treatment of HCV in children has been an issue of argument. Yet severe fibrosis or cirrhosis and HCC has been reported also in children and since treatment increases the life expectation in adults chronic HCV infection is also treated in children above 2 years of age [11, 43]. But clinical trials do not include hundreds or thousands of patients as in adults. So unfortunately most of the statements are projected from adults to children and are not as strong as adults.

Results of clinical trials and metaanalysises revealed 48-50% biochemical response and 36-47% SVR with INF for 6 months duration in children [47-51]. Jacobson et al. [52] rewieved the literature concerning HCV infected children treated with conventional INF monotherapy between 1990 and 2000. They reached to 12 clinical trial and 7 abstracts, only four having control group and reviewed the results of 366 treated and 105 untreated children. Although some variations were observed in terms of treatment duration (6-1 year) and INF dose (3-1.75 MUI/m), they observed that SVR did not differ among interferon types (INF-α2a, INF-α2b or Lymphoblastoid form), duration of treatment and dosage. When the studies were pooled; ETR was 54% (0-91%) and SVR was 36% (0-73%). Although ETR was better in children, SVR responses were consistent with adults' rates (9-25%, 3-39% respectively) [30]. In this study 71 out of 91 children were infected with genotype 1. Among none- genotype 1 patients 70% showed sustained response, 15% relapsed and 15% did not respond. In contrast 27% of the genotype 1 patient achieved sustained virologic response, 25% had relapsed and 48% did not respond. In another study SVR was attained in 80% of genotype 2 patients and in 30.4% of genotype 1 patients, confirming that viral genotype is a predictor of response and genotype 1 is a poor response factor for INF treatment also in children [47]. On the other hand, Matsuko et al. [53] observed only a 26 % SVR with conventional INF even though the patients were genotype 3 and 4. In several other studies regarding INF-α 2a in which predominant patient genotype was genotype 1 biochemical response rate was 50-65%, ETR was 53-65% and SVR was 20-53% [11,48,54]. In these studies with limited patient (12-20) most of the responders were genotype 1. So genotype one may not be a poor prognostic indication for INF treatment in children in contrast to adults.

Thirthyfour HCV infected child were treated with conventional INF-α for 6 months and evaluated for SVR at least 6 months after treatment cessation [47]. Sixteen patients (47%) had SVR with accompanying histologic response. Fifteen out of these 16 responders (93.8%) achieved RVR and remain in complete response state at the end of fallow up. So loss of viremia at 1 months of treatment seems as a strong predictor for long term response also in children. But this needs further studies including genotype analyses.

As in adults INF (3-5MIU/m) was combined with ribavirin (15 mg/kg) and SVR was increased to 49-64 % [32, 55-58].

Observing the superiority of pegINF over conventional INF without any additional adverse effect of pegINF in adults encouraged the pediatricians to use pegINF in the management of HCV. Approval for children came much later at December 12, 2008 for pegINF-α 2b and ribavirin combination. Schwarz et al. [13] studied the efficacy of PegINF monotherapy in children between 2-8 years of age. 180 µg /1.73 m^2 pegINF-α 2a (dose adjusted according to body surface area) was given to 14 child with chronic HCV infection for 48 week period. And patients were evaluated for SVR at 72nd week. Forty six percent of the patients were genotype 1 and most of the patient had mild liver disease without marked inflammation and fibrosis. Six out of 14 (43%) patients attained SVR at week 72. This was better than the adult results (30-39%). HCV RNA was undetectable in 57% of patient at week 24 and in 50% at week 48 (ETR). The superiority of 6 months pegINF monotherapy on conventional INF plus ribavirin treatment with same duration was supported in other child studies and at the end of 6 months of fallow up after 6 months treatment SVR was 50-61% among all of the patients and %53 in genotype 1 (18/34) [59, 60]. So considering the side effects of ribavirin authors advised pegINF monotherapy [13].

On the other hand recently pegINF-α2b plus ribavirin combination was approved by FDA in the treatment of HCV infection in children [61]. In an open label pilot study Jara et al [28] evaluated the efficacy of pegINF-α2b (1 µg /kg/week s.c once a week) and ribavirin (15 mg/kg/day) combination. Three out of 30 patients had genotype three and the remaining 27 had genotype 1 or 4. Overall 15 patients (50%); all of the three genotype 3 patients and the rest being genotype 1or 4 achieved SVR. Twelve out of 15 patients who were HCV RNA negative at 24 week completed the 48 week treatment and 11 attained SVR. None of the 10 patients who were still HCV RNA positive at 24 week of treatment achieved SVR. 26 patient were genotype one with 20 being naive. And 11 of these naive patients (55%)

attained SVR. In this study EVR was a predictor of SVR. All SVR attained patients had EVR at week 12. While the established profile in adults is that; EVR suggest ETR but it does not strongly suggest SVR. Only 65-75% of patient with EVR achieves ultimately SVR in adults.

Chronic Hepatitis B infection:

Approximately 5% of world population is infected with HBV virus. Route of transmission can be vertical (transplasental or perinatal) or horizontal. Perinatal transmission accounts for nearly half of the chronic infections [4]. Transplasental transmission accounts for %2.4-15 percent of infants born to infected mother [62]. Although transplasental transmission can not be interrupted by vaccine, implantation of routine hepatitis B vaccination into national immunization programmes has led to decline in the prevalence of Hepatitis B infection worldwide [63,64]. According to center of disease control and prevention (CDC) incidence rate of acute HBV infection declined from 3/100000 population to 0.34 /100000 and chronic infection rate decreased from 10 to 1% in some eastern countries [65-68]. There is also a chance of spontaneous seroconversion being 2% /year of children less than 3 years of age and 5% /year of children above 3 years of age [69,71]. Yet HBV infection is a global problem and 25% of HBV carriers who are infected in infancy die from HCC or liver cirrhosis [62, 63]. In adults annual incidence of HCC in asymptomatic HBV carriers is 0.1% but it reaches to 3-6% in HBV related cirrhosis. Eight-17 % of HBeAg positive chronic hepatitis B patient and 13%-33% of Hbe Ag negative develop cirrhosis in five years [70]. Although acquisition starts in childhood, infection is mainly asymptomatic in children and complications become apparent in adulthood. But it is also a childhood problem because 95 % of vertically infected neonates, 25-50% of children aged between 1-5 years and 6-10 % of acutely infected children unfortunately progress to chronic hepatitis B [19, 71]. Probability of developing chronic hepatitis is inversely proportional with age at time of acquisition. Hepatocellular carcinoma and cirrhosis develops more frequently in patients who acquire the infection in early childhood than who acquire later in life. Furthermore complications may appear also in childhood [11, 12]. In an Italian study development of cirrhosis was observed in 3.4 % of HBs Ag carrier children during a mean fallow up of 4 years duration [65]. Although it is rare, HCC may also develop even in childhood [72]. In one study 2% of Caucasian children developed HCC at their long term fallow up [73].

Presence of HBsAg in serum for at least 6 months is defined as chronic hepatitis B infection. In its natural course three phases of chronic hepatitis B has been identified: Immunotolerant phase, immunoclearence (seroconversion) phase and post seroconversion phase (replicative or nonreplicative)

The immunotolarent phase is characterized with positive HBsAg, HBeAg and high HBV DNA and normal aminotransferases. It is the phase where immune system does not react against virus. Most of the perinatally infected children are in this phase and may stay for a long period until adulthood. But some may progress to immunoclearence phase where they have elevated aminotransferases with positive HBsAg, HBeAg, high HBV DNA and negative anti HBs and anti HBe. Prominent liver damage occurs in the seroconversion phase and it may be permanent and severe enough to progress to cirrhosis. Moreover in spite of HBe seroconversion HBV DNA integration may occur and HCC develop insidiously [62, 72]. Some of the patient in immunoclerence phase sequentially normalize aminotransferases, undergo a spontaneous HbeAg clearance, HBeAg seroconversion and anti Hbe formation with decreased HBV DNA and become inactive carriers. Some of the inactive carriers may lose also HBsAg in the future. But a fraction of them regain active replication with hepatic inflammation progression, elevated aminotransferases and high DNA levels though HBeAg is negative and antiHBe is positive. This situation is known as HbeAg negative hepatitis B infection and it is much more strongly associated with HCC [74]. The inactive carrier state is relatively stable and reactivation of HBV after anti HBeAg seroconversion is rare in children [74, 73]. But still progression of fibrosis has been observed. Treatment response is based of biochemical, virologic and histological response. Response to treatment occurs in three steps: First achieving undetectable DNA with PCR, second loss of HBeAg and seroconversion of anti Hbe and last step loss of HBsAg. The later occurs very rarely. There is still a risk of reactivation at the first two phases.

Progression of liver damage and HCC has been associated with persistent viral replication and clinical and histological improvement accompanies suppression of viral replication. Viral replication is measured with serum HBV DNA and HbeAg. Loss of HBeAg, appearance of anti HBe and disappearance of HBV DNA is the main virologic event modifying the course of liver disease. Clearance of HBeAg, achieved either with treatment or not decreases the complications and increases survival [76]. The optimal goal of antiviral treatment is to clear HBsAg permanently. But even in adults the current treatment alternatives are not sufficient to achieve this l. So current treatment goal is to prolong survival and improve long term outcomes in adults by preventing

progression of liver injury through reducing viral replication, in childhood.

American Association for the Study of Liver Disease (AASLD) and European Association for the study of liver (EASL) published treatment guidelines for adults and recommended that patient should be monitored at least for 6 months for HBsAg positivity: Those who are in replicative state of immunoclerence phase (ALT level at least 2 times upper limit of normal, HBV DNA above 20.000 IU/ml should be treated [29,76,77]. However consensus guidelines for the treatment of Hepatitis B infection in children have not been established yet. But reviewers recommends treatment for children over 2 years of age with documented chronic Hepatitis B infection (presence of HbsAg for 3-6 months) evidence of replication (positive HbeAg and HBV DNA above 20.000 or 10^5) and ALT consistently elevated at least 1,5-2 times of upper normal level [71,78]. Since it is uncommon in children there is no data on treatment of HbeAg negative children [71]. Since patients in immuntolerant phase have low probability of seroconversion and poor response to treatment, even compared to patients in immunoclerence phase with low HBV DNA, there is no need to treat these patients [70].

Currently seven drugs are approved in adults for the treatment of Hepatitis B infection: INF, PegINF, lamuvidine (LAM), telbuvidine, entacavir, tenofovir and adefovir. But treatment alternatives are not as rich as adults in children. Only lamuvudine and conventional INF has been licensed in children.

Lamuvidine is a good antiviral agent but is not as potent as the other antiviral drugs. Moreover, LAM is associated with a high viral resistance compared to some other antiviral agents. Telbuvidine is also a potent antiviral drug but it is associated with high viral resistance (%10 in 1 year), slightly better than LAM. Entacavir and tenofovir are potent antiviral drugs with a higher genetic barrier (lower viral resistance) and are preferred antivirals. But neither entecavir nor tenofovir is approved by FDA for children [70, 79]. Therefore, currently only LAM can be used as antiviral agent in children.

Response to treatment is evaluated differently in INF and nucleoside analog treatments:

Virologic response is defined as decline in HBV DNA levels bellow 2000 IU/ml at 24 weeks of therapy on interferon therapy whereas it was defined as undetectable HBV DNA with real time PCR assay within 48 weeks of antiviral therapy [80].

Serologic response is defined as HBeAg seroconversion and appearance of anti HBe on both types of therapy.

Primary none response; is defined as less than 1 log IU/ml decrease in HBV DNA level from baseline at 3 months of treatment for both type of treatment modalities. Ideal end point of treatment is sustained HBsAg loss with or without seroconversion of anti HBs. The other end points include:

1. Durable HbeAg seroconversion in HbeAg positive patients.
2. In case of not achieved HbeAg seroconversion, sustained undetectable HBV DNA either under nucleoside analog treatment or after interferon treatment.

Durable complete virologic response rate was observed in 23-65% of children and response with LAM was prominent in preschool children [51,81,82]. Lamuvudin is easier to administer, cheap, has no serious side effect but it has 2 drawbacks: one induction of YMDD mutation, second uncertainty about the duration of treatment. Hartman et al. [83] reported that LAM is effective in decreasing HBV DNA levels in previously none responders to INF. 44% (8 of 18) of their patient remained HBV DNA cleared at 1 year of treatment. But LAM resistance was as high as 65% at the end of one year which was unacceptable. Furthermore, same authors reported the long term results of these groups of patient after 4 year of fallow up under LAM treatment: Additional 4 patients (18%) achieved seroconversion and a gradual decline in the participant's number has been observed duo to low compliance. So in long term, LAM did not improve the seroconversion and needs long period so compliance is weak [84].

Adult studies have shown that LAM treatment over one year not only increase the rate of seroconversion but also LAM resistance: Prolonging the LAM treatment 24 months after 52 weeks of treatment brings an additional 23% HBV DNA clearance. But Longer LAM treatment was associated with a higher YMDD mutations as high as 15-17% at first year, 27-38% at 2^{nd} year, 40-49% at 3^{th} year and 47-65% at 4^{th} year [85-90].

Another disadvantage of LAM is cross resistance with many new agents such as entecavir and telbuvudin. Entacavir response is lower and viral resistance is higher in LAM resistant patients compared to nucleoside naive wild type HBV infected patients. 6% of LAM resistant patients are also resistant to entecavir [91]. So emergence of mutant strains under LAM, which is the only approved antiviral in children, restricts the long term use of LAM and further blocks the chance of treatment with other more potent antiviral drugs in adulthood.

In an attempt to overcome above mentioned problems and increase treatment outcomes, INF's were introduced. A significant benefit of INF therapy has

been observed in chronic HBV infected patient especially in those with high ALT levels (> 2 times and lower DNA levels similar to adults). Recommended dose of conventional INF' is 5-10 MIU/m^2 3 times a week for 4-6 months. They have been used as monotherapy or combined with LAM, sequentially or simultaneously. In all of these studies early responses seem superior but in long term, results are nearly similar to untreated groups. Durable complete response with INF in children differs between 37-56% [51, 71, 76, 81, 92].

Bortolotti et al. [73] evaluated long term outcomes of a total of 107 children with chronic hepatitis B infection who were treated with INF-α 2a. Hbe Ag clearance was reported to be 32%, 12 months after the end of treatment. All responders were HbeAg negative at the end of 5 years. Moreover 50% of the non responders cleared HBeAg at 69 months after treatment cessation. But during a mean of 69 months fallow up 60% of the INF treated group and 65% of untreated patients had HBeAg clearance and seroconversion. This study demonstrated that INF treatment accelerates the natural course of hepatitis B rather than adding an additional treatment success. However 25% of treated patient cleared also HBsAg which couldn't be observed in any of the untreated patient.

Vo Thi Diem [92] compared the long term results of 37 INF-α 2a treated and untreated patients. During a mean fallow up of 5 years HbeAg and HBsAg clearance rates did not differ between treated and untreated group (54.1% and 8.1% versus 35.1% and 2.7%, respectively) After 7 year follow up, cumulative HBeAg clearance were 53.5% compared with 33.5% in untreated patient being statistically insignificant. In terms of HbeAg seroconversion children with elevated baseline ALT responded better than ALT normal groups in treatment group; whereas it didn't differ in untreated children. Moreover, 7 year cumulative HBsAg clearance was 8.9% in treated group and 4.0% in untreated group.

Iorio et al. [51] evaluated the long term outcome of hepatitis B infection in INF treated (41) and untreated (67) children for a median period of 12 years (5-24 years). Patients received INF-α 2b or lymphoblastoid INF for 6-12 months. Complete response (HBeAg clearance and undetectable HBV DNA) was observed in 80% of the treated patients; whereas it was observed in 69.3% of the untreated group. After 6 years rate of response in treated and untreated patients overlapped (63.4% vs. 62.7 %). So HbeAg clearance did not changed at long term. Although 6 untreated (9.7%) and 4 (9.8%) treated child achieved HBsAg clearance, difference was insignificant.

No considerable difference was observed even between sequentially administered LAM - INF α combination and simultaneously administered INF α – LAM combination (29,6% vs. 42,8%) [93].

Childhood infections, since they are mostly in immunotolerant phase, are the predictors of non response to INF. Other poor responsive factors are Asian ethnicity, male sex, immunosupression duo to disease (HIV) or treatment, coexistence of HDV infection, HbeAg negative chronic hepatitis B, low serum ALT, high level of serum HBV DNA, mild liver necroinflamation [94,95]. Advantages of INF are low probability of resistance and fix treatment duration. Disadvantages are the need to multiple injections, cost and side effects.

Reproduction of the pegINF improved the virological, biochemical and histological outcome in HBV hepatitis in adults. PegIFN's have been studied extensively and were found to be superior to conventional IFN's in terms of ALT normalization, HbeAg clearance and HBV DNA response in adults [96]. Monotherapies with pegINF was superior to LAM plus pegINF combination or LAM monotherapy in terms of HBeAg seroconversion (32%, 27%, and 19% respectively) [95,96]. At short term, at the end of 52 week treatment HbeAg loss was observed in 63% in pegINF and LAM combination in contrast to 28% of LAM monotherapy. In long term (3 years) sustained virologic response (HBeAg clearance) was 29% in combination and 9% in LAM monotherapy [86]. Studies show that pegINF-LAM combination is superior to LAM monotherapy but it does not provide any additional benefit on pegINF monotherapy (35% vs. 36% respectively) [97].

Furthermore comparing conventional INF-α2a and pegINF-α2a revealed pegINF superiority over INF in terms of combined outcome of HbeAg seroconversion, ALT normalization and HBV DNA response (24%,12% respectively). But Liver histology improvement is not different between pegINF monotherapy groups and LAM groups [97]. Dose discontinuation was more prevalent in pegINF group compared to LAM group [96]. Quality of life scores decreased during treatment but returned to normal in PEG group compared to LAM group.

PegINF's were extensively studied in adults. In children there is only one preliminary report evaluating the rapid viral response of pegINF treatment in children (98). They reported a favorable outcome at 4 weeks of the treatment (100µg /m^2/week) in terms of HBV DNA suppression and antiHBe seroconversion. They observed HBV DNA disappearance in 6 out of 13 children without any side effect. But long term effect and end of treatment effects needs to be evaluated and compared to conventional INF [98]. Nevertheless

pegINF is not approved in Chronic HBV infection in children.

Safety and Adverse Events:

All adverse events with pegINF are reported to be reversible and similar to conventional IFN based protocols (table 1). Most frequently observed adverse event is flue like syndrome which is characterized by fever, fatigue, myalgia, abdominal pain, nausea, vomiting, and headache [28, 47, 82]. Fever was more prominent in pegINF-2a. Whereas neutropenia was observed more frequently in peg INF-α2b [54]. Side effects of INF unique to pediatric population are weight loss and decrease in linear growth [16, 46, 53]. Weight loss is shown to be observed in %4.8-20 of children at 24 week but it returned to normal at 48 week of the treatment [28]. Although growth was disturbed in 22 of 26 children by 1.6 cm compared to the growth velocity to the 50 percentile of their matched age and sex growth catch up was attained 6 months after treatment [28]. Mild behavioral problems are observed nearly in all children and continued through the treatment protocol. Most of the adverse events are observed to be transient. Dose modifications are required most commonly for anemia due to the use of ribavirin in HCV treatment, neutropenia, weight loss and hyperthyroidism [28]. Therapy may be discontinued prematurely in case of signs of depression and uncontrolled hyperthyroidism [28].

Table 1: Adverse effects of pegINF treatment [26,28,30,47,82]

Adverse event	%
Flue like syndrome	**83**
General malaise	**79**
Headache	**42**
Leucopenia	**17**
Alopecia	**17**
Decreased appetite	**76**
Constipation	**10**
Erythema at injection side	**33**
Weight loss	**66.6**
Weight loss >5% of baseline	**23.3**
Irritability	**33.3**
Dizziness	**23.3**
Anxiety	**6.6**
Infection	**80**
Thrombocytopenia	**4-6 (Adult)**
Depression	**16-30 (Adult)**
Antithyroid antibodies	**13.3**
Hyperthyroidism	**6.6**

The association of HCV with none organ specific autoantibody (NOSA) and autoimmune disease are well known. HCV patients have more NOSA than HBV patients. Most found autoantibodies are SMA that fallowed by ANA, LKM. Moreover, 34% of HCV infected patients are found to have NOSA and NOSA positive patients respond to treatment poorly than NOSA negative patients (18% vs. 55%, respectively) [99]. Presence of LKM is associated with ALT flares during INF treatment [100]. Moreover, INF treatment either pegylated or not induces further NOSA production (18%) [100]. One of the prominent adverse effects of pegINF or conventional INF treatment is throid dysfunction. In addition, clinicians should be aware of the fact that HCV infection itself may increase the tendency toward thyroid dysfunction. Non-immune, subclinic hypothyroidism are seen in untreated HCV infected children more than controls (11.1% vs. 2.7%) [101]. The risk of developing autoimmune thyroid disease and the impact of both conventional and pegINF in chronic HCV infected children have been studied in recent study [100]. In this study, 15.5% of 123 interferon treated children (of these, 21 received INF monotherapy, 40 received INF combined with ribavirin, and 62 treated with pegINF-α2b) developed thyroid dysfunction. Overall, 14 patient and 7 out of 62 pegINF-α2b/ ribavirin treated children developed thyroid peroxides antibody during the treatment. Moreover, none of the other two group but 3 out of the pegINF group continued to posses this antibody 12 months after the treatment. Although none of the children demonstrated clinically significant hypo or hyperthyroidism signs, 6 children needed L-Thyroxin and 2 needed this treatment even after 12 months after the cessation of the treatment.

PED-C Trial is an ongoing multicenter study, evaluating the efficacy and safety of pegINF in children with 11 participating center. Recently, participating centers published histopathological features of liver biopsies from 121 children but safety and efficacy results for this study are not published yet [17, 102].

PegINF treatment also seems promising in the treatment of HCV in children. Concerning ETR and SVR either combined with ribavirin or not, response rates are comparable and may be better than adults. Since combination of pegINF with ribavirin increases response rates, currently recommended treatment consists of pegINF and ribavirin combination. However, clinical utility of EVR, RVR and the effect of genotype or viral load are not as accurate as adults and needs to be evaluated in further large scale clinical trials. Other than the deviation from linear growth and weight loss, no additional adverse events have been observed in children. The other adverse events are comparable with adults. FDA approved the use of

pegINF- α2b; however, further studies are needed to evaluate the difference of the two pegylated forms.

Hepatitis B infection is still a global problem. Most of the children are in immunotolerant phase and need no treatment for years. In order to improove quality of life and reduce the cost for the treatment of late complications associated with the infection, the treatment of children with hepatitis B infection in immunoclerence phase is critical. In contrast to adults, treatment of chronic hepatitis B is very effete in children. Lamuvidine, the only antiviral agent that is licensed in children, cannot provide sufficient response due to mutation reasons. Even INF treatment is not different from untreated follow ups in long term. So, clinical trials offering new treatment alternatives are warranted. PegINF's have been proven safe in hepatitis c infected children and it can be one of the options also in chronic hepatitis B as documented in one preliminary report [98].

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