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META-ANALYSIS

Vitamin E for the treatment of children with hepatitis B e antigen-positive chronic hepatitis: A systematic review and meta-analysis

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Abstract

AIM

To assess vitamin E efficacy, defined as its ability to induce hepatitis B e antigen (HBeAg) seroconversion, in children with HBeAg-positive persistent hepatitis.

METHODS

In July 2016, we extracted articles published in MEDLINE and the Cochrane Library using the following search terms: "chronic hepatitis B", "children", "childhood", "therapy", "treatment", "vitamin E", "tocopherols", "tocotrienols". Only randomized controlled trials (RCTs) published in English language were collected.

RESULTS

Three RCTs met inclusion criteria and were considered in the present meta-analysis. Overall, 23/122 children in the treatment group underwent HBeAg seroconversion *vs* 3/74 in the control group (OR = 3.96, 95%CI: 1.18-13.25, P = 0.025).

CONCLUSION

Although our meta-analysis has several limits, including the very small number of available studies and enrolled children with HBeAg positivity-related hepatitis, it suggests that vitamin E use may enhance the probability to

induce HBeAg seroconversion in these patients. Further well designed and adequately sized trials are required to confirm or deny these very preliminary results.

Key words: Hepatitis B; Pediatric hepatology; Viral hepatitis; Immunology

Core tip: Treatment of chronic hepatitis B in children is still an area of uncertainty. Vitamin E, based on immunostimulatory anti-inflammatory activity, has been evaluated in the treatment of pediatric hepatitis B virus infection. These few experiences seem to be encouraging as they suggest a potential role of vitamin E in inducing HBeAg seroconversion, but they need to be confirmed in well-designed and adequately-sized trials.

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection continues to represent a very serious health problem worldwide, both in adults and in children[1], despite several efforts to prevent its spread and to reduce its disease burden, such as vaccination programs[2], the use of safe injection techniques and blood donor screening[3], as well as the introduction, in our therapeutic arsenal, of new and more advanced and effective antiviral treatments[4]. The clinical relevance of this pathogen depends on its ability to insidiously induce, in a large proportion of infected individuals, a necro-inflammatory hepatic disease with different patterns of severity and course, including cirrhosis and hepatocellular carcinoma. Several factors have been demonstrated to influence the prevalence[5], severity and outcome of patients with HBV-related chronic hepatitis. In particular, ethnicity, mode of acquisition and mainly, age at the time of HBV infection represent the major risk factors for the development of a persistent liver disease[6]. Whereas approximately 90%-95% of acutely HBV-infected immunocompetent adults experience a self-limiting hepatitis with the establishment of protective long-lasting immunity, and only the remaining 5%-10% develop chronic hepatitis, neonatal transmission of HBV causes a higher rate of chronic infection[7]. Approximately 90% of infected children in highly endemic countries, where vertical transmission from mother to child is predominant, become persistent carriers[8]. According to the current knowledge, the natural history of long-lasting HBV infection is characterized by three chronological phases, including immune tolerance, immune clearance and low replication status.

Despite a large series of available studies, long-term outcomes of HBV infection acquired in infancy are still unclear. However, the spontaneous or therapy-induced hepatitis B e antigen (HBeAg) seroconversion with HBe antibody development is generally considered a key event in patients with long-lasting HBV-related infection[9], because it is often accompanied by remission of liver disease and confers a favorable course over a long-term follow-up[10]. After HBeAg loss, serum HBsAg persists, but serum aminotransferase levels usually decrease, reaching normal or low values and a significant reduction in HBV replication is observed in a large part of the subjects undergoing HBeAb development[11]. Nevertheless, in some of these patients, the achievement of HBeAg seroconversion is not associated with the improvement of hepatic disease, rather these individuals still present with liver damage with different grades of severity and course and they are at higher risk of developing complications later in life[12]. Persistent HBV-related infection is considered as the result of an impaired immune response against this pathogen, consequently the boosting of antiviral immune response has become an innovative strategy in the attempt to obtain the remission of the infection, which still occurs at very low rate[13,14]. Starting from this assumption,a randomized controlled pilot trial was performed in 2001 in adult patients with HBV-related hepatitis, showing beneficial effects in anti-viral activities in these individuals[15].

Therefore, on the basis of these findings, we aimed to perform a systematic review and meta-analysis to identify and summarize the current evidence on the potential efficacy of vitamin E in the treatment of children with HBeAg-positive persistent hepatitis, defined as its ability to induce HBeAg loss and HBeAb development.

MATERIALS AND METHODS

Search strategy

A systematic computer-based search of published articles, according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis Statement, issued in 2009[16], was conducted through Ovid interface, in order to identify relevant studies on the vitamin E use for the treatment of children with HBeAg-positive chronic hepatitis. The literature review was performed in July 2016. The following electronic databases were used: MEDLINE (1950 to June 30, 2016), the Cochrane Library (until the second quarter of 2016) and EMBASE (1980 to June 30, 2016) for all relevant articles. The search strategy and the search terms were developed with the support of a professional research librarian. The text word sused for the search were identified by means of controlled vocabulary, such as the National Library of Medicine's MESH (Medical Subject Headings) and Keywords. The used MESH terms and keywords were: "chronic hepatitis B", "children", "childhood", "therapy", "treatment", "vitamin E", "tocopherols", "tocotrienols". The PubMed "related articles"

feature as well as the reference lists of retrieved articles was also searched to find additional pertinent studies. If a study was considered potentially eligible by either of the two reviewers, the full-text of this study was further evaluated. Full-text assessment was performed according to eligibility criteria developed to systematically include studies into this review. Selected studies were considered eligible if all the following predefined criteria were met: (1) the research was designed to assess the tolerability and efficacy of vitamin E use for the treatment of children with HBeAg-positive chronic hepatitis; (2) the research studies were designed as randomized studies; (3) the studies were reported in the English language, as peer-reviewed, full-text publications, whereas articles that were not published as full reports, such as conference abstracts, case reports, and editorials were excluded; and (4) sufficient data for the evaluation of HBeAg seroconversion rate were available (Table 1).

Study selection

Data extraction: Two authors (Leandri P and Loggi E), independently and in a parallel manner, performed the literature search, identified and screened relevant articles, based on title or title and abstract. If a study was considered potentially eligible by either of the 2 reviewers, the full article was collected for further assessment. Other two authors (Bacchi-Reggiani ML and Andreone P) independently extracted and tabulated all relevant data from included studies by means of a standardized method, according to the Cochrane handbook section 7.3a checklist of domains. The following information was obtained from each study, by means of a predefined data extraction form, including: First author's name, study design, inclusion and exclusion criteria, year of publication, country of origin, ethnicity, number of cases and controls, diagnostic methods for HBV markers and genome detection. We contacted the authors of the three studies to obtain additional information, including children's seroconversion rate by age groups and by HBV genotype. Unfortunately, access to patients' database was possible only for one study, whereas the above mentioned data, concerning the other two trials, were no longer available for the time period elapsed since their publication. The accuracy of data collection was checked by SF and any disagreements concerning the results were settled by consensus between all authors.

Quality score assessment: Three investigators (Fiorino S, Bacchi-Reggiani ML and Andreone P) independently evaluated the quality of the selected studies, on the basis of the Jadad scale[17] (Table 2). It includes the assessment of the following three items: Randomization (2 points as maximum score), blinding (2 points as maximum score) and an account for all patients (1 point as maximum score).

Any disagreement was resolved by discussion with the other authors. Total score ranges from 0 to 5. Included studies were classified into higher quality ($\geqslant 3$) and lower quality (< 3), on the basis of the total scores.

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were used as the summary statistic. The pooled OR was calculated with both fixed effect (inverse variance weighting) and random effect (Der Simonian and Laird) models. To avoid the exclusion of one among the eligible studies[18], a 0.5 zero-cell correction was used. The variability, expressed in percentage across studies and attributable to heterogeneity beyond chance, was estimated with I^2 statistic. We assessed the extent of small study effects by Egger's test. *P*-values $\leqslant 0.05$ were considered significant for all included studies. Statistical analyses were carried out using STATA/SE version 14.1 (STATA Corp., College Station, TX, United States).

RESULTS

Study selection

We searched in MEDLINE, EMBASE, and Cochrane Library to retrieve works assessing vitamin E use in children with HBeAg-positive chronic hepatitis, our systematic review identified 2471 potential studies, and 2458 of them were excluded after a preliminary review of the titles and/or abstracts. The full texts of the remaining 13 articles were retrieved for a more detailed assessment. Of these, 10 studies did not meet the eligibility criteria, as described, because they were reviews, clinical studies carried out in adults or they were not published in the English language. Therefore, three studies were selected and included in the current meta-analysis. A flow-chart of the study search and selection process is shown in Figure 1.

Study characteristics

Three randomized controlled studies, assessing the use of tocopherols in children with HBV-related chronic infection and rate of HBeAg seroconversion, met inclusion criteria and were considered in the present meta-analysis[18-20].

Overall, the three trials involved 122 children, randomized to receive treatment according to an intention-to-treat protocol with different doses of vitamin E, and 74 controls. One study was performed in Turkey, one in Germany and one in Italy. The baseline characteristics of these included studies and their participants are summarized in Table 1. All considered studies described serological assays, which were employed to detect viral infection markers. Serum samples were tested for the presence of both viral antigens and host antiviral antibodies, using both enzyme-linked immunosorbent assayor radioimmunoassay, as well as of HBV-DNA, by means of liquid hybridization[18] or real time PCR[19,20].

Overall, according to the Jadad scale, two trials were classified into higher quality[19,20] and one into lower quality[18] studies (Table 1).

The end-point of this meta-analysis was to estimate the potential antiviral efficacy of vitamin E, defined as its

Table 1 Characteristic of included studies evaluating the use of vitamin E in children with hepatitis B e antigen-positive chronic hepatitis

First author/ year	Study design/ country of origin	Sample size	Treat and VE dose	Treat period/ follow-up	End-points	Main results	Quality score[3]	Tolerability
Dickici B, 2007	PRT (1:1) Turkey	58 enrolled children in the immune-tolerant phase (1) 30 treated patients M/F: 21/9 (2) Age (yr): (9.0 ± 3.8) No data concerning age 28 untreated patients M/F: 23/5 Age (yr): (8.5 ± 4.5) No data available for children's seroconversion rates by age groups and by HBV genotype	100 mg/d *vs* no treatment	3 mo/6 mo	HBV-DNA clearance HBeAg seroconversion	No antiviral-effects induced by vitamin E treatment	1	No side effects
Gerner P, 2008	PRT (3.1) Germany	92 enrolled children # (1) 69 in treatment group (2) 23 in placebo group 76 children completed the study (1) 56 in treatment group M/F: 34/22 Age (yr): 10.4 (2) 20 in placebo group M/F: 12/8 Age (yr): 11.8 No data available for children's seroconversion rates by age groups and by HBV genotype	From 200 to 600 IU/d depending on body weight *vs* placebo	6 mo/12 mo	HBV-DNA clearance HBeAg loss HBeAg seroconversion	VE may induce HBeAg seroconversion, but further studies are required	5	Well-tolerated Self-limited gastroenteritis cases
Fiorino S, 2016	PRT (1:1) Italy	46 enrolled patients (1) 23 in treatment group (18 in immune-tolerant phase and 5 in immune-reactive group) (2) 23 in placebo group (17 in immune-tolerant phase and 6 in immune-reactive group) 40 children completed the study (1) 20 in treatment group M/F: 15/5 Age (yr): (11.9 ± 3.8) (2) 20 in placebo group M/F: 16/4 Age (yr): (10.2 ± 3.5) HBeAg seroconversion in vitamin E Age (yr)/number pts/ genotype 2/0 3/0 4/1 (D[1]) 5/0 6/2 (1A, 1D)	15 mg/kg per day *vs* no treatment	12 mo/ 12 mo	(1) safety and tolerability (2) HBeAg loss/anti-HBe seroconversion (3) efficacy of VE in inducing: (1) $\geqslant 2 \log_{10}$ sustained decrease in serum HBV-DNA *vs* baseline	VE may induce HBeAg seroconversion, but further studies are required	3	Generally good safety profile Self-limited gastroenteritis (nausea, vomiting, upper abdominal pain, diarrhoea), headache, fatigue Adverse events: ALT flare

7/0																			
8/3 (1C, 2D)																			
9/0																			
10/2 (1C, 1D)																			
11/0																			
12/1 (1D)																			
13/6 (1A, 1C, 4D[2])																			
14/3 (1A[1], 1D, 1NA[1])																			
15/0																			
16/2 (1D, 1F)																			
17/3 (3D[2])																			
HBeAg seroconversion in the control group																			
Age (yr)/number pts/ genotype																			
2/1 (B)																			
3/0																			
4/1 (D)																			
5/1 (A)																			
6/1 (D)																			
7/0																			
8/3 (1C, 2F[1])																			
9/1 (D)																			
10/1 (C)																			
11/5 (1A, 2C, 2D)																			
12/2 (1A, 1E)																			
13/2 (1B, 1D)																			
14/4 (2A, 2NA)																			
15/1 (D)																			
16/0																			
17/0																			

[1]Identifies 1 patients undergoing HBeAb seroconversion in a subgroup of patients; [2]Identifies 2 patients, who underwent HBeAg seroconversion; [3]According to the Jadad scale. PRT: Prospective randomized trial; IT: Immune-tolerant; IR: immune-reactive; VE: Vitamin E; CVR: Complete virological response, defined as sustained HBeAg loss/anti-HBe seroconversion together with serum HBV-DNA reduction < 2000 IU/mL; ALT: Alanine-aminotransferase; NA: Not available; HBeAg: Hepatitis B e antigen; M: Male; F: Female.

ability to induce HBeAg loss and HBeAb development. A pooled estimate was performed on the basis of the considered studies. Overall, we observed that vitamin E use induced HBeAg seroconversion in 18.8% patients (23 seroconversion among 122 patients in the treated children *vs* 3 among 74 controls, OR = 3.96, 95%CI: 1.18-13.25, P = 0.025, I^2 = 0.0%) (Figure 2). Children's seroconversion rates by age groups and by HBV genotype were available only for one of the three trials (Table 1).

Sensitivity analysis and publication bias risk

To evaluate the effect of each individual study on the overall meta-analysis estimate, one study at a time was excluded, but the exclusion of any single research did not cause a significant alteration of the final decision and did not suggest the possibility of publication bias, but the number of considered studies is very small and this factor suggests caution in data interpretation.

DISCUSSION

The natural history of HBV-related persistent infection in childhood as well as the indications for the appropriate use of the antiviral therapy still represent an area of considerable uncertainty in this subset of patients, although an expert panel consensus[21] and some meta-analyses[22,23] have been proposed to guide physicians in the treatment decision-making process. As no definitive guidelines exist, according to available recommendations, the criteria for the management of these subjects in the real-life clinical setting have to be carefully evaluated before initiating any type of antiviral therapy. In particular, treatment is considered appropriate in HBeAg-positive children with persistently elevated (about 1.5-2.0 times the laboratory upper limit of normal), or exceeding 60 IU/L serum alanine aminotransferase and moderate/severe inflammation/fibrosis on liver biopsy[8]. Some drugs, such as interferon-α (IFN-α)[24], lamivudine[25], entecavir[26], adefovir[27] and tenofovir[28] have been approved for these patients. However, their use is limited by important side effects, risk of resistance development, high costs and, mainly, age of the treated subjects[29]. Most of these antiviral compounds have been licensed for children over 12 years old and only IFN-α as well as entecavir have been approved for a pediatric population aged between 2 and 18 years[24,26]. In addition, to date, no therapy is considered appropriate in HBeAg-positive children in the immune tolerance phase. A risk of resistance development to antiviral drugs exists in this group of patients[21]. To date, on the basis of these results, a long-term follow-up is the only approach currently applied to these children and further therapeutic approaches or treatment schedules are required[30].

Therefore, according to preliminary observations on the beneficial role of vitamin E as therapy in patients with chronic hepatitis B in a randomized controlled pilot

Table 2 Jadad scale is a procedure for assessing the methodological quality or risk of bias in randomized controlled trials, adapted from Jadad *et al*[17]

Item	Maximum points	Description
Randomization	2	1 point if randomization is mentioned 1 additional point if the method of randomization is appropriate 1 point has to be deducted if the method of randomization is inappropriate (minimum 0)
Blinding	2	1 point if blinding is mentioned 1 additional point if the method of blinding is appropriate 1 point has to be deducted if the method of blinding is inappropriate (minimum 0)
An account of all patients	1	The fate of all patients in the trial is known, if no data are reported the reason is stated

trial several years ago[15], we had the aim to understand whether this compound could exert useful and safe therapeutic effects against HBV in childhood. We performed a systematic review and meta-analysis to search studies available in the literature assessing vitamin E ability to induce HBeAb seroconversion in children with HBeAg-positive persistent hepatitis. We found only three trials[18-20] meeting inclusion criteria for our meta-analysis, but, surprisingly, two of them reported high rates of HBeAg loss and HBeAb development[19,20].

In particular, in Fiorino's trial a very high percentage of children (7/23, 30.4%), receiving vitamin E supplementation for 12 mo with a follow-up period of further 12 mo, obtained HBeAg clearance *vs* 1/23 (4.3%), in the control arm at the end of the follow-up period (24 mo)[20]. However, it has to be considered that a substantial percentage of HBeAg loss (23.2%) was also observed in the group of vitamin E-treated children for 6 mo with an additional follow-up period of 12 mo in comparison to the placebo arm (8.7%) in Gerner's research[19]. HBeAg seroconversion rates obtained in the above mentioned studies are higher in comparison to those observed in trials enrolling patients who were treated with nucleotide/nucleoside analogues. A recent research performed by Chan *et al*[31], using TDF (tenofovir disoproxil fumarate) or TDF + FTC (emtricitabine) in adult immune-tolerant patients, showed low percentage of HBeAg loss and HBeAb development (5% and 0% respectively) over 192 wk. The reasons explaining these high seroconversion rates in children supplemented with vitamin E in comparison to subjects treated with TDF analogs, mainly in Fiorino's study, are not completely understood and deserve further investigations. Nevertheless, some very interesting issues have to be considered: (1) different mechanisms of vitamin E and nucleotidic/nucleosidic analogue action; (2) duration of the treatment period; and (3) vitamin E dosage used.

Nucleos(t)ide analogues exert antiviral activities by means of well-known direct as well as indirect mechanisms: (1) suppression of HBV replication mainly through the inhibition of reverse transcription process in the viral lifecycle[32]; (2) partial restoration of the impaired

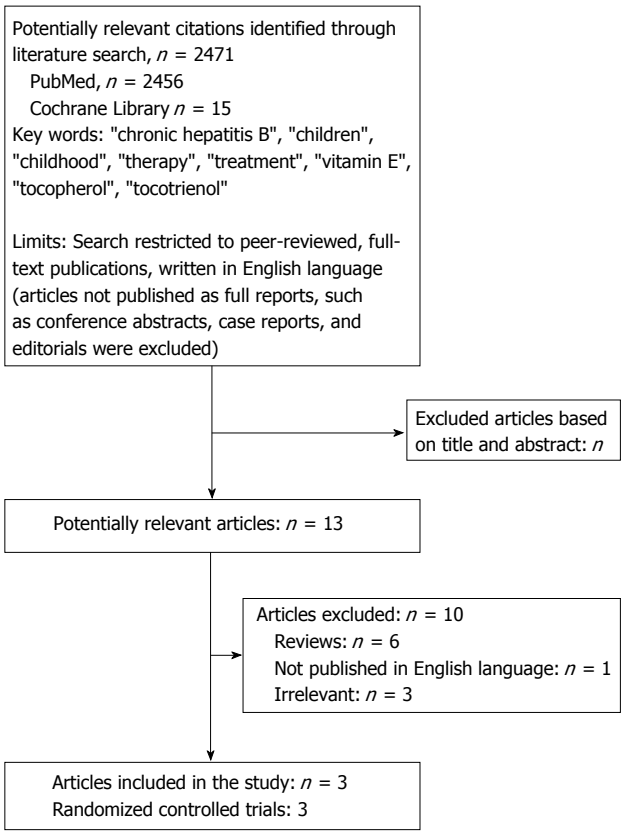

Figure 1 Study flow diagram concerning vitamin E use in children with hepatitis B e antigen positive chronic hepatitis.

immune response, as shown by significant reductions in the percentages of $CD4^+CD25^{high}$ T regulatory cells, programmed death-ligand 1 (PD-L1) receptor expression on $CD4^+$ T cells and pro-inflammatory cytokine production[33,34]. Therefore, antigen-viral burden reduction is associated with the improvement of anti-HBV activity of immune cells. According to our current knowledge, vitamin E exerts its beneficial effects by means of similar mechanisms. It is well known that vitamin E plays critical roles for normal cellular functions[35]. This essential lipid-soluble compound, acting as a free radical "scavenger", exerts potent antioxidant effects[35] in all cellular membranes[36] and contributes to their protection from oxidative injury[37,38]. In addition, *in vitro* and *in vivo* studies have suggested that vitamin E is also able to improve immune-system functions[39], mainly by increasing cell-mediated-immunity[40,41]. Mechanisms involved in these complex processes remain poorly understood, but, a recent systematic review has summarized its possible intracellular targets and suggested its potential direct antiviral or immunostimulating activities against HBV[42]. Vitamin E is able to influence the transcriptional function of some cellular genes by directly interacting with their promoter sequences[42-44] and it may modulate the post-transcriptional regulation of protein synthesis[45-47]. In particular, very preliminary studies have demonstrated that vitamin E is able to regulate the expression profiles of some microRNAs, but it is conceivable that it interacts with a larger number of these molecules[41,43,44]. In par-

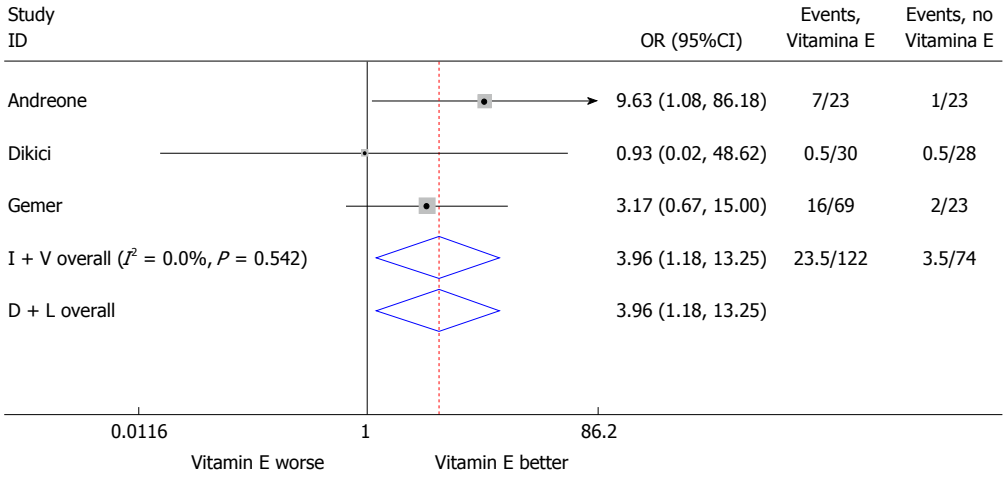

Figure 2 The relationship between vitamin E use and hepatitis B e antigen seroconversion in published studies. The area of each black square is proportional to the statistical size and the centre of the square is placed at the point of estimate. Error bars indicate 95%CIs for the estimate for each study. I + V: Inverse variance method; D + L: DerSimonian and Laird method.

ticular, it has been reported that vitamin E increases the expression of 8 oxidative stress-associated miRs, including miR-16, miR-21, miR-122, miR-125b, miR-146a, miR-155, miR-181a, miR-223[44]. The tight modulation of the synthesis of these miRs, due to their pleiotropic effects, might increase the protective immune response against the virus. Some microRNAs, which are modulated by vitamin E, possess a double function. They are required not only to preserve the normal function of the immune system[48], mainly of the cell-mediated arm[49], and to prevent the development of a redundant and abnormal inflammatory response[50,51], but they also exert a direct anti-HBV activity[52]. These premises may help us to explain the positive preliminary results of our meta-analysis. It is conceivable to think that vitamin E supplementation may contribute to the improvement of the anti-HBV activity of the immune system by means of a direct anti-viral action both by decreasing its replication abilities and by boosting the host's immune cell responses. The slow but progressive decline of HBV replication associated with HBeAg loss/HBeAb seroconversion, as described in 2 of the 3 studies included in our meta-analysis, corroborates the hypothesis that vitamin E acts as an immunomodulator resulting in a global antiviral activity. Interestingly, a delayed response has already been reported, with the use of immunomodulatory drugs for the treatment of adults with CHB[53]. In Fiorino's study, HBeAg seroconversion was also observed in additional 7 of 11 previously non-responder patients in the vitamin E supplemented group, with an extended follow-up for an additional period of 12 mo[20]. This observation underlines the importance of the duration of the treatment period and might contribute to explaining, at least in part, the absence of children responding to vitamin E therapy in Dickici's study[18]. In this trial, the period of supplementation with this compound was only three months long, in addition the dosage used was equal to 100 mg/d for three months, probably not enough to induce an improvement of anti-viral immune responses. Therefore, both dosage and duration of vitamin E supplementation represent very important factors that must be considered when its anti-viral efficacy is evaluated. Taking into considerable account all the described factors, our study seems to suggest that vitamin E use may effectively enhance the probability to induce HBeAg seroconversion in these patients, even in children in the immune-tolerant phase. However, it has to be considered that our meta-analysis has several limits. First, the very small number of available studies enrolling children with HBeAg positivity-related hepatitis, as well as the small size of these trials may increase publication and selection biases; second, one research study has been carried out in Asia[18] and 2 studies in Europe[19,20], it is not known whether differences in response rates, following vitamin E use, may exist among children belonging to different ethnicities or depending on the different prevalence of HBV genotypes; third, the study design did not include the use of placebo in control groups in two studies[18,20]; fourth, it has to be taken into account that HBeAg seroconversion rate in children in the immunetolerant phase is < 2% among children younger than 3 years and 4%-5% among older children[54] and that data concerning HBV genotypes as well as children's seroconversion rates by age groups were available only for one of the studies considered for the meta-analysis. Therefore, this limit precludes further proper assessments of the potential vitamin E benefits in children under 14 years as well as of its potential efficacious dose. However, in the study by Fiorino *et al*[20], patients who responded to vitamin E treatment were respectively 4 (1 child), 13 (2 children), 14 (2 children), and 17 (2 children) years old at the enrollment (Table 1).

In addition, it has to be considered that some meta-analyses[55,56] have reported that long-term administration of vitamin E, at dosages exceeding 150 UI once a day, is associated with serious negative outcomes, such as an increase in all-cause mortality. However, although the conclusions of these studies are rather questionable[57-60]

because of the meta-analytic approaches used and no severe side effects have been described in the three included trials, with the exception of some adverse events, represented by flares of transaminases, these results suggest caution in the generalization of vitamin E administration in the pediatric population before confirmation of the effectiveness and safety of this compound. Certainly, vitamin E, which was administered at high dosage to the children in the reported trials, has to be considered as a drug, with possible benefits as well as with potential risks. Therefore, to date these limiting factors prevent the formulation of definitive recommendations on the role of this type of treatment in children with HBeAg-positive hepatitis. However, to our knowledge this is the first attempt to quantitatively assess the therapeutic effects and efficacy of vitamin E in the treatment of these subjects. These patients suffer from a viral-related liver disease, a condition associated with a deficiency in immune system responses. Therefore, the use of vitamin E in patients with HBV chronic infection might represent an approach combining the direct antiviral effect of nucleoside/nucleotide analogues on HBV replication together with the immune-enhancing role of this fat-soluble compound. Therefore, further well-designed and adequately-sized trials are required to confirm or deny these preliminary, but apparently very interesting and promising, results with the aim to establish the potentially useful dose of vitamin E to induce HBeAg seroconversion.

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COMMENTS

Background

Hepatitis B virus (HBV) chronic infection in childhood continues to represent a very important clinical problem in several countries worldwide and the treatment indications for this subset of patients are still an area of considerable uncertainty. Clear-cut guidelines are lacking, therefore, to date, therapeutic decisions are only based on the consensus of expert panels.

Research frontiers

A defective immune response is considered a crucial factorin maintaining a persistent infection in subjects with HBV. Drugs able to restore anadequate immune activity could contribute to promote an effective control of this infection.

Innovations and breakthroughs

In the real-life clinical setting, a wide proportion of children with persistent HBV infection remain untreated and a conservative approach is generally applied in these subjects. Therefore, the introduction of additional therapies and different strategies in clinical practiceis required. Since several years ago, vitamin E has emerged as a compound with a large spectrum of immune-stimulatory activities and its use could improve the defective immune activity detectable in several diseases, including chronic viral infections. This research field could be very interesting, but this kind of application requires caution. Some reports, although rather questionable, report possible harmful effects, when this compound is used at high dose.

Applications

Vitamin E administration could represent one among the options for the treatment of children with HBV-chronic infection, either as mono-therapy in the developing countries with limited economic resource or, for the future, in combination with standard antiviral drugs. The decrease in viral replication and antigen burden as well as the restoration of an adequate immune function might represent an effective approach for the management of patients with HBV persistent infection.

Peer-review

The authors underwent a meta-analysis to evaluate the role of vitamin E administration to children with immune tolerant HBV infection. Results showed a nearly four-fold likelihood of achieving HBeAg seroconversion in those children receiving vitamin E. Sensitivity analysis showed that exclusion of any of the three studies did not change results.

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