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ORIGINAL ARTICLE

Extended duration versus standard duration of peginterferon alfa-2a in treatment of chronic hepatitis B: A systematic review and meta-analysis

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Summary In the last decade, PEG-IFNa-2a has been widely used in the treatment of chronic hepatitis B (CHB). The current standard duration is 48 weeks; however, several studies based on small sample sizes have indicated that treatment extended beyond 48 weeks improved clinical outcomes than standard 48 weeks of therapy. Therefore, we performed a meta-analysis to compare the efficacy and safety of extended duration versus standard duration treatment with PEG-IFNa-2a monotherapy for patients with CHB. Four studies comprising of 350 patients were included in our study. Our analysis showed that extended treatment resulted in a higher HBsAg clearance rate compared with the standard treatment at the end of treatment, 24 and 48 weeks post-treatment [odds ratio (OR) = 2.45, 95% confidence intervals (CI) (1.17—5.11), $P = 0.02$; OR = 3.17, 95% CI (1.62—6.21), $P < 0.01$; OR = 5.02, 95% CI (1.63—15.45), $P < 0.01$, respectively]. Higher HBeAg seroconversion rates were also obtained in the extended treatment group than the standard treatment group at the end of treatment and 48 weeks post-treatment [OR = 2.09, 95% CI (1.10—3.98), $P = 0.02$, and OR = 2.67, 95% CI (1.39—5.13), $P < 0.01$, respectively]. In addition, extended treatment was superior to standard treatment in HBV-DNA inhibition rate at 48 weeks post-treatment [OR = 3.15, 95% CI (1.51—6.57), $P < 0.01$]. Therefore, extended treatment with PEG-IFNa-2a beyond 48 weeks may be a promising strategy to achieve higher rates of sustained HBV-DNA inhibition, HBeAg seroconversion and HBsAg clearance off-therapy for patients with CHB.

Abbreviations: CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; IFN, interferon; HBV, hepatitis B virus; PEG-IFNa-2a, peginterferon alfa-2a; OR, odds ratio; CI, confidence intervals; RCT, randomized controlled trials.

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Introduction

Chronic hepatitis B (CHB) is a serious and widely epidemic disease, with approximately 400 million people being infected worldwide [1]. Patients infected with hepatitis B virus (HBV) are predisposed to developing liver cirrhosis, liver failure and also have a relatively high risk of developing hepatocellular carcinoma (HCC). Early treatment against CHB infection is therefore crucial for reducing morbidity and mortality [2].

Antiviral therapy has been recognized as the first choice for CHB treatment, which is approved to be an efficient method to ameliorating hepatic inflammation and fibrosis, further preventing liver cirrhosis and hepatocellular carcinoma [3—6]. Currently, there are two kinds of antiviral agents licensed for the treatment of CHB patients: interferon (conventional or pegylated interferon) and nucleos(t)ide analogues. Although nucleotide analogues have gained popularity by convenience of usage and by causing permanent inhibition of HBV replication, they require life-long administration while additionally increasing incidence of drug-resistance [7—9]. As a result, a limited course of interferon (IFN) is still a more attractive therapeutic option for enhancing the host cell-mediated immune response in clearing the HBV and providing a more sustained response in the post-therapy period than nucleotide analogs [10]. Weekly administration of PEG-IFNa-2a improves patients' compliance rate and obtains much better pharmacokinetics, and several practice guidelines for the management of CHB have considered it as a first-line therapy for patients with CHB [11,12].

The current recommended standard duration of PEG-IFNa-2a therapy is 48 weeks. Although the standard therapy of PEG-IFNa-2a can improve the HBeAg seroconversion rate to some extent, achieving HBsAg seroclearance/seroconversion and a sustained virological response after treatment remains a clinical challenge. Interestingly, in recent years, several studies have demonstrated that treatment extended beyond 48 weeks with PEG-IFNa-2a resulted in better clinical benefits, significantly increasing rates of viral suppression, ALT normalization, and HBsAg clearance. However, the number of patients in these clinical trials is too small to draw a clear conclusion. Therefore, we performed a meta-analysis including a larger number of patients by collecting data from multiple databases to compare the efficacy and safety of extended and standard durations of PEG-IFNa-2a monotherapy for patients with CHB.

Methods

Search strategy

We performed a systematic literature retrieval using electronic databases including PubMed, EMBASE, Cochrane Library databases, CNKI (China National Knowledge Infrastructure, Beijing, China), Wanfang Database (Wanfangdata Co., Ltd, Beijing, China) and CBM (China Biomedical Database, Beijing, China). The retrieval was finished in October 2014. The search strategy was based on MeSH terms combined with free text words. The search terms used were: 'hepatitis B' or 'HBV' and 'peginterferon' or 'pegylated interferon'. Titles and abstracts were assessed for eligibility and full-text copies of all articles deemed to be potentially relevant were retrieved for further extraction of the study details. A standardized eligibility assessment was performed independently by two reviewers (Zhengyan Wang and Ling Sun).

Criteria for inclusion and exclusion

Inclusion criteria:

- study design: both randomized controlled trials (RCT) and non-randomized controlled studies were considered;
- study population: patients who were more than 18 years old, without gender restrictions, diagnosed with CHB;
- intervention: compared extended durations (>48 weeks) to standard durations (=48 weeks) of PEG-IFNa-2a monotherapy for treatment of patients with CHB;
- follow-up time: at least for 24 weeks after treatment;
- outcomes: at least reported one of the following outcomes: HBsAg clearance rate, HBV-DNA inhibition rate, HBeAg seroconversion rate;
- language of publication: English or Chinese.

Exclusion criteria:

- study population: non-adult population, women with pregnancy or lactation, patients who received liver transplantation, patients co-infected with hepatitis A virus, hepatitis C virus, hepatitis D virus or human immunodeficiency virus, patients with a history of alcohol or drug abuse, hepatocellular carcinoma, decompensated liver disease, autoimmune liver disease, serious medical or psychiatric illness;
- intervention: concurrently or sequentially using nucleotide analogues, corticosteroid, immunosuppressive agents; previous treatment with interferon-based therapy, antineoplastic therapy within the 12 months preceding enrolment;
- outcomes: not reporting any of the outcomes efficacy;
- republished studies or the full-text were not available.

Data collection and assessment of quality

Studies were screened according to the inclusion and exclusion criteria and data was extracted by using a predesigned data extraction form by two authors independently. The extracted data included: country(ies) of study, treatment patient characteristics, sample size, duration of PEG-IFNa-2a, dose of PEG-IFNa-2a, HBsAg clearance rate, HBV-DNA inhibition rate, HBeAg seroconversion rate, adverse effects, withdrawal rate and reason for withdrawal. For duplicated publications, only the most recent or the most complete report was included.

All included studies were assessed for methodological quality by two independent authors, as recommended by the Cochrane Handbook for RCTs [13] and the Newcastle-Ottawa Scale (NOS) for observational studies [14]. Disagreements