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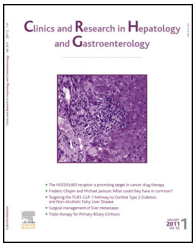

ORIGINAL ARTICLE

Fenofibrate is effective adjunctive therapy in the treatment of primary biliary cirrhosis: A meta-analysis

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Summary
Background and aim: Fenofibrate is a potential novel therapy for primary biliary cirrhosis (PBC). We performed a systematic review and a meta-analysis of studies of fenofibrate in PBC.
Methods: Electronic database search was performed for relevant studies. A search of abstracts presented in the main scientific meetings in the field and articles in press was also performed. Random effect model was used to pool the effect size across studies for changes in alkaline phosphatase, GGT, bilirubin and IgM levels before and after treatment and the overall rate of complete response to fenofibrate therapy.
Results: Six studies with 102 patients met the inclusion criteria. All studies were case series and in all, patients who had no or incomplete response to UDCA had fenofibrate added at a dose of 100—200 mg daily. Treatment duration ranged from 8—100 weeks. Treatment with fenofibrate was associated with a significant decrease in alkaline phosphatase (—114 IU/L, 95% CI: —152 to —76, $P < 0.0001$); a significant decrease in GGT level (—92 IU/L, 95% CI: —149 to —43; $P = 0.0004$); significant decrease in total bilirubin (—0.11 mg/dL, 95% CI: —0.18 to —0.08; $P = 0.0008$); and a significant decrease in IgM level (—88 mg/dL, 95% CI: —119 to —58; $P < 0.0001$). The complete response rate was 69% (95% CI: 53—82%) with an odds ratio of 82.8 (95% CI: 21.6—317.2; $P = 0.024$) while on fenofibrate.

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Conclusions: Fenofibrate at doses of 100—200 mg daily appears to be effective adjunctive therapy in PBC patients who had no or incomplete response to UDCA. There is a critical need for larger scale randomized trials to determine its effect on liver-related morbidity and mortality (or progression towards end-stage disease).
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Introduction

Primary biliary cirrhosis (PBC) is a chronic immune-mediated liver disease, characterized by progressive destruction of inter-lobular biliary ducts and chronic cholestasis, eventually leading to liver fibrosis and biliary cirrhosis.

For over 20 years, ursodeoxycholic acid (UDCA) has been the only treatment for PBC approved by US and European drug administrations. Long-term use of UDCA (13—15 mg/kg/day) in patients with PBC improves serum liver biochemistries and survival free of liver transplantation, approximating overall survival to that of a matched control population [1]. However, about 30—50% of patients do not respond to UDCA optimally as assessed by known criteria for biochemical response [2]. Those patients represent the group in need for additional therapies, having increased risk of disease progression and decreased survival free of liver transplantation [1].

Fibrate derivatives have long been used for the management of dyslipidemia. Fibrates are peroxisome proliferator-activated receptor alpha agonists, and both in vivo and in vitro studies have suggested that these drugs have anti-inflammatory [3], anti-fibrotic [4,5] and anticholestatic [6,7] effects.

The anti-inflammatory activity and potential protective effect of the biliary epithelium by stimulation of biliary phosphatidylcholine secretion through transactivation of *MDR3* gene transcription [8] and possibly non-MDR3-dependent mechanisms [6,7] combined with their noticeable lowering effect on alkaline phosphatase levels have led to a growing interest in the use of fibrates in treatment of PBC [9,10].

Recently Cochrane database reviewers in their meta-analysis, which included six randomized clinical trials on bezafibrate from Japan, concluded that it has an effect on decreasing the activity of serum alkaline phosphatase in patients with PBC as compared to no intervention or when used with ursodeoxycholic acid (UDCA) [11].

While bezafibrate is not universally available, fenofibrate is commonly used in the US for the treatment of dyslipidemia and prevention of hard cardiovascular endpoints [12]. Although no randomized trials have been conducted to assess its efficacy in PBC, multiple uncontrolled studies have reported considerable improvement in biochemical markers of PBC disease activity by adding fenofibrate to treatment regimen of patients with incomplete or no response to bile salt therapy. In the present study, we aimed to perform a systematic review and a meta-analysis of the efficacy of fenofibrate in inducing complete response as well as assess its effects on biochemical markers in patients with PBC.

Methods

Literature search

A comprehensive and systematic literature search was performed to identify all reports (including articles in press in relevant journals and bibliographic search) examining the use of fenofibrate in patients with PBC. The electronic databases searched included MEDLINE (PubMed), Scopus, and ScienceDirect (as of September 30, 2014). In addition, a search of abstracts presented in the main scientific meetings in the field (AASLD and EASL) and articles in press was undertaken. The key words and terms searched included: fibrate OR fenofibrate in combination with (AND) PBC OR ''biliary cirrhosis'' OR ''liver disease'' OR cirrhosis. The search was performed within the title, abstract, and key words.

Study selection and inclusion criteria

Two authors (AG and HM) independently searched the literature and identified studies for the review. The abstracts of studies selected by either author were then scanned by both authors to determine their eligibility for the meta-analysis. Disagreements were resolved by consensus between the two authors and after discussion with a senior author (CL) when necessary. Studies published in English language with sufficient data on the outcomes were included in the analysis. Individual data from the study by one of the authors (RP) were obtained from the author directly since the published report did not include needed information [9,24]. Duplicate and non-English language reports were excluded from the analysis.

Data extraction and quality assessment

Data extracted included the following pre-defined characteristics and variables: first author last name, date of publication, study design, patient characteristics, treatment dose and duration, concomitant therapies and outcomes of interest. Since all studies identified were case series, the quality of each study was assessed using the checklist developed by Moga et al. (Institute of Health Economics, Alberta, Canada) to assess the quality of case series [13]. The tool is composed of 18 items and studies with 14 or more ''yes'' responses is considered of acceptable quality.

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