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Safety and tolerability of obeticholic acid in chronic liver disease: a pooled analysis of 1878 individuals

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Abstract

Background and Aims: Obeticholic acid (OCA) is a farnesoid X receptor agonist used in primary biliary cholangitis (PBC) treatment. Recent studies have expanded OCA use for NASH treatment and results from phase 3 clinical trial have shown beneficial reduction of ≥ 1 stage of fibrosis with no NASH worsening. However, safety concerns still preside, thus we systematically examine the safety profile of OCA in chronic liver disease.

Materials and Methods: A search was conducted in Medline and Embase databases for OCA randomized controlled trials in chronic liver disease. Binary events were pooled with Paule-Mandel random effects model and proportional events were examined in a generalized linear mixed model with Clopper-Pearson intervals.

Results: A total of 8 studies and 1878 patients were analyzed. There was a 75% [risk ratio (RR): 1.75, 95% CI: 1.43–2.15, $p < 0.01$] increased pruritis risk.

Abbreviations: 5-D, 5-Dimensional; 95% CI, 95% confidence interval; AE, Adverse events; CLD, Chronic liver disease; CVD, Cardiovascular disease; ELISA, Enzyme-linked immunosorbent assay; FDA, Food and Drug Administration; FXR, Farnesoid X receptor; HLD, Hyperlipidemia; NAFLD, Non-alcoholic fatty liver diseases; NASH, Non-alcoholic steatohepatitis ; OCA, Obeticholic acid; PBC, Primary biliary cholangitis; PSC, Primary sclerosing cholangitis; RCT, Randomized controlled trial; RoB2, Risk of bias 2; RR, Risk ratio; URTI, Upper respiratory tract infection; UTI, Urinary tract infection.

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OCA increased constipation incidence (RR: 1.88, 95% CI: 1.45–2.43, $p < 0.01$), decreased diarrhea (RR: 0.62, 95% CI: 0.50–0.77, $p < 0.01$), and increased development of hyperlipidemia (RR: 2.69, 95% CI: 1.85–3.92, $p < 0.01$) relative to placebo. Sensitivity analysis in NASH-only studies found a dose-dependent effect with pruritis which increases to RR: 3.07 (95% CI: 1.74–5.41) at 25 mg. However, up to 9.98% (95% CI: 5.01%–18.89%) of NAFLD patients with placebo similarly experience pruritis events. Overall, 16.55% (95% CI: 6.47%–36.24%) of patients with NAFLD on OCA experienced pruritis. There was no significant increase in cardiovascular events.

Conclusions: OCA may represent the first pharmacological treatment approved for NASH. However, pruritis, constipation, diarrhea, and hyperlipidemia were major events with evident dose-dependent effect that affect tolerability in NASH. Future long-term studies for longitudinal safety events are required.

INTRODUCTION

Obeticholic acid (OCA) is a farnesoid X receptor (FXR) agonist that is synthetically derived from endogenous primary bile acid.[1] OCA is a semisynthetic analog of chenodeoxycholic acid that is an endogenous ligand at the FXR[2] and is 100 times more potent. FXR is found in enterocytes and hepatic cells regulating FGF-19 and triglyceride synthesis, hepatic fibrosis, and inflammation, respectively.[3,4] OCA is currently approved by the Food and Drug Administration (FDA) for primary biliary cholangitis (PBC).[5] However, there has since been several clinical trials assessing the efficacy of OCA in primary sclerosing cholangitis (PSC) and NASH. A subset of NAFLD, NASH is characterized as a more progressive and advanced form of the disease, with the presence of inflammation, ballooning, and hepatocellular injury.[6] PBC instead describes the presence of damage of the intrahepatic bile ducts, resulting in fibrosis and potential cirrhosis,[7] while PSC was defined by the presence of chronic bile duct destruction leading to end-stage liver disease.[8] NASH is currently the commonest cause of liver disease globally and a leading cause of liver transplant accounting for 17.38% of transplant in 2014 in the US.[9,10] In PBC and PSC, OCA reduces the progression of disease by inhibiting the exposure of hepatocytes to bile acids while in NASH, OCA suppresses triglyceride synthesis and decreases lipid deposition in the hepatocytes while promoting insulin sensitivity activities that reduces NASH activity.[11,12]

Despite the significant prevalence of NASH, there are currently no approved treatments by the FDA for NASH owning to the multitude of factors and complexity in the pathogenesis of the disease.[13–15] There has been several phase III trials conducted in NASH albeit with limited efficacies[13] including PIVENS[16] and REGENERATE.[17] Significantly, OCA is one of the few medications assess for NASH that has mature clinical trial results and one of the top candidates in the drug development pipeline.[18] Phase 2 studies (FLINT) have demonstrated improvements in histology,[19] while recent data from a phase 3 study (REGENERATE) showed OCA achieved a statistically significant improvement in at least 1 stage of fibrosis with no worsening of NASH.[17] In PBC and PSC, several trials including a phase 3 study (POISE) have demonstrated significant improvements in biochemical measurements which can be predictive of improved long-term clinical outcomes.[20] However, despite the significant finding impact of the finding, there remains preexisting safety concerns with the use of OCA. Therefore, we herein conduct a meta-analysis on the safety profile of OCA in chronic liver disease (CLD) based on evidence from randomized control trials (RCTs). A subsequent subgroup analysis of etiologies and placebo groups will subsequently be conducted to assess the rate of events with OCA.

MATERIALS AND METHODS

Search strategy and selection criteria

The current meta-analysis was conducted in conjunct with guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[21] A search was conducted in Medline and Embase electronic database for articles relating to OCA in RCTs and articles were included from inception to July 18, 2022. In addition, to ensure a comprehensive search of literature, the references of included articles from previous meta-analysis were also screened to prevent omission of relevant articles. The full search strategy is detailed in Supplementary Material 1 (http://links.lww.com/HC9/A4). Six independent authors (C.H.N., J.X., A.T., Z.Y.

W., J.N.Y., and R.W.Z.) sieved the identified abstracts, and any discrepancies were resolved by a senior author (M.M.). Only RCTs were included in the analysis, and case reports, case series, and cohort studies were excluded. In our study, CLD encompasses conditions including NAFLD, PBC, and PSC where OCA studies has been performed. Only RCTs with adverse events (AEs) reported were included and duplicated studies from the same clinical trial were excluded. Subsequently, extraction of data from the original articles was performed by 6 authors in independent pairs (C.H.N., J.X., A.T., Z.Y.W., J.N.Y., and R.W.Z.). Data including but not limited to the authors, year, country, doses, baseline demographics, and reported AEs were extracted from individual studies. When mean and SDs were not reported, transformation of values were carried out using preexisting formulae by Wan et al.[22] The study was conducted in accordance with the Declaration of Helsinki. The study was exempt from the institutional review board as no confidential patient information was involved.

Definitions and statistical analysis

The various conditions that CLD encompasses in this analysis were defined by the following: NAFLD was defined as the evidence of hepatic steatosis in either liver biopsy or through noninvasive methods, in the absence of excessive alcohol consumption, viral hepatitis, or autoimmune hepatitis.[23] In the included studies, patients with histological evidence of NASH, NAFLD activity score of at least 4 and NAFLD diagnosed through ultrasonography were recruited. Diagnosis of PBC in the included studies was made through criteria including history of increased ALP levels for at least 6 months; positive anti-mitochondrial antibody titer (> 1:40 titer on immunofluorescence or M2 positive by ELISA) or PBC-specific antinuclear antibodies; or liver biopsy consistent with PBC. Diagnosis of PSC in the included studies was based on cholangiography. Pruritus was assessed through the Pruritus Visual Analog Scale and 5-Dimensional (5-D) Itch Questionnaire. Cardiovascular disease (CVD) encompasses occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary artery disease, angina, congestive heart failure, cardiomyopathy, or arrhythmia. All statistical analysis was performed on rStudio (R, version 4.0.3). Proportional data was analyzed using a generalized linear mixed model with Clopper-Pearson intervals and random effect model was applied for all measures of heterogeneity.[24] A Mantel-Haenszel method with Paule-Mandel estimator was used for the analysis of binary outcomes.[25,26] The Paule-Mandel estimator is the most accurate method for pooled analysis of dichotomous variables.[27] Quality assessment assessing the risk of bias was conducted by the Cochrane Risk of Bias 2 (RoB2) tool.[28] Measures of statistical heterogeneity included the Cochran Q test and I^2 where an I^2 of 25%, 50%, and 75% corresponding with low, moderate, and high degrees of heterogeneity.[29] The measure of heterogeneity is only relevant for a pooled analysis of dichotomous variables and inaccurate in proportional analysis. Publication bias was not assessed as there were insufficient studies ($n < 10$).[30]

RESULTS

Summary of included articles

The initial search from Medline and Embase yielded 876 articles. After removal of 104 duplicates through the title abstract sieve, 772 papers remained for abstract screening. A final 8 studies that analyzed the data collected between 2007 to 2018 were included in the meta-analysis (Figure 1). The effect of OCA in patients with NASH/NAFLD were reported in 4 studies, PBC in 3 studies, and PSC by 1 study. A total of 1878 patients were included in our analysis, with 1222 patients receiving OCA and 656 patients receiving the placebo. All 8 articles were RCTs low risk of bias (Supplementary Material 2, http://links.lww.com/HC9/A5). The summary of included articles can be found in Supplementary Material 3 (http://links.lww.com/HC9/A6).

AEs in CLD

The summary of AE in CLD can be found in Table 1 and the pooled proportional event rates of AEs in CLD can be found in Supplementary Material 4 (http://links.lww.com/HC9/A7). There was an 8% increased risk of any AE in patients on OCA when compared with patients in the placebo arm [risk ratio (RR): 1.08, 95% CI: 1.05–1.11, $p < 0.01$]. There was a 94% increased risk of discontinuation events compared with placebo (RR: 1.94, 95% CI: 1.21–3.09, $p < 0.01$). A subgroup analysis was then conducted to examine the effect of OCA based on systems. In skin and subcutaneous tissue disorders, there was a 75% (RR: 1.75, 95% CI: 1.43–2.15, $p < 0.01$) increased risk of pruritus compared with placebo. In gastrointestinal manifestations, there was generally no increased risk of AEs with OCA expect for an increase incidence of constipation (RR: 1.88, 95% CI: 1.45–2.43, $p < 0.01$) and corresponding decrease in diarrhea (RR: 0.62, 95% CI: 0.50–0.77, $p < 0.01$). In respiratory and infectious disorders, there was no significant increase in the rate of AEs with OCA use. In metabolic-related disorders, there was an increase rate of hyperlipidemia (RR: 2.69, 95% CI: 1.85–3.92, $p < 0.01$) but not CVD (RR: 0.93, 95% CI: 0.32–2.69, $P = 0.40$). In addition,

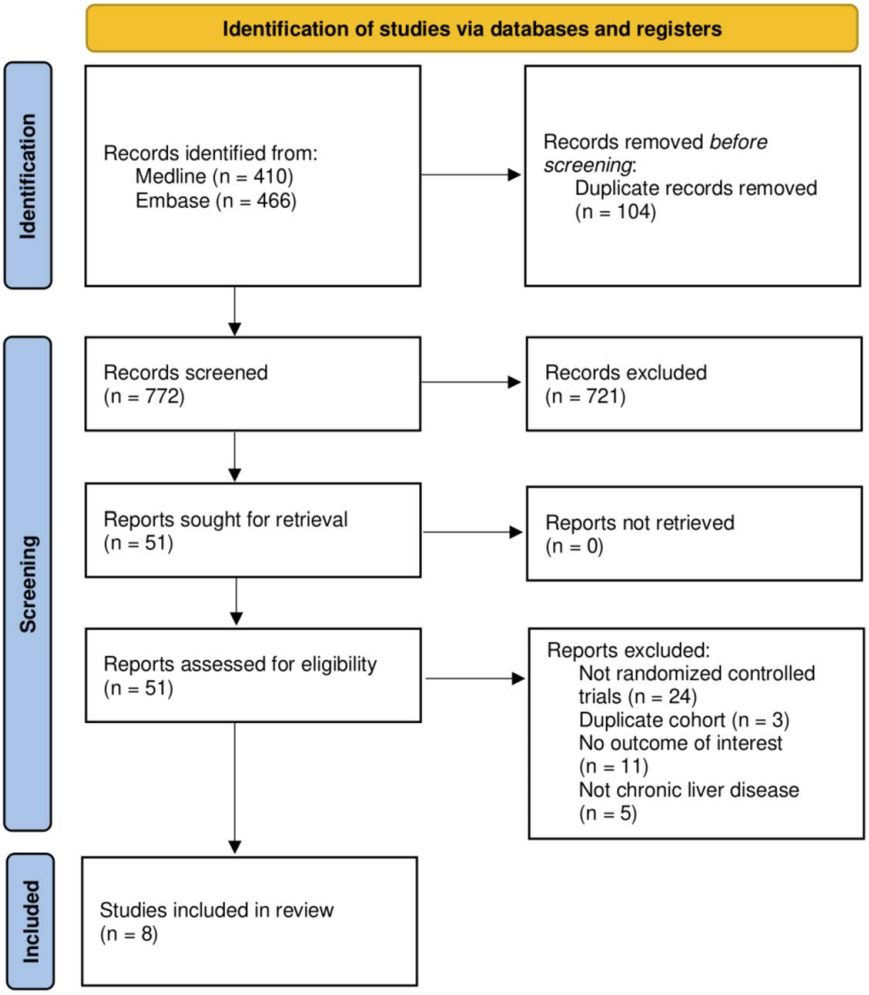

FIGURE 1 PRISMA flowchart of systematic review.

there was no increase rate of other AEs with OCA. In 1581 patients with chronic liver diseases receiving OCA, mortality events were reported in 2 individuals. Similarly, there were 2 mortality events reported in 768 patients of the placebo group. Nevens et al.[20] reported liver decompensation events including hepatic encephalopathy and esophageal varices in patients with PBC. Of 143 patients receiving OCA, there were 2 events of hepatic encephalopathy, while none were observed in the placebo group with 73 individuals. However, 2 events of esophageal varices were reported in 73 patients within the placebo group, while none were observed in the 143 patients receiving OCA.

AEs in NAFLD

A sensitivity analysis of PBC only trials can be found in Supplementary Table 5 (http://links.lww.com/HC9/A8) and similar findings were found compared with the overall population. In a sensitivity analysis including only NAFLD studies (Table 1), there was similarly an increased risk of total AEs compared with placebo with OCA (RR: 1.08, 1.05–1.11, $p < 0.01$). Pruritic events were similarly higher in patients with OCA relative to placebo (RR: 2.20, 1.38–3.53, $p < 0.01$). Similarly, constipation events (RR: 1.98, 95% CI: 1.51–2.59, $p < 0.01$) were higher in OCA with lower rate of diarrhea. In NAFLD patients, there was a dose-dependent effect for events of pruritus and constipation at dose of 5, 10, and 25 mg (Figure 2). A single-arm proportional meta-analysis was then conducted to examine the reported AE in patients on the placebo arm (Table 2). Up to 6.24% (95% CI: 4.63%–8.37%) and 11.42% (95% CI: 9.20%–14.08%) had events leading to discontinuation and serious AEs, respectively. Up to 9.98% (95% CI: 5.01%–18.89%) of patients had pruritis events with placebo and 4.24% (95% CI: 2.04%–8.63%) CVD events.

DISCUSSION

The forthcoming wave of NAFLD is a major global concern currently affecting 25%–33% of the global population.[31] Yet, despite the significant prevalence, morbidity, and mortality, there remains a lack of effective pharmacological treatments for NASH.[18]

TABLE 1 Summary of adverse events in chronic liver disease

	Combined Population					NAFLD Only				
	Risk Ratio	95% CI	I^2 (%)	Cochran *Q*	*p*	Risk ratio	95% CI	I^2 (%)	Cochran *Q*	*p*
General adverse events										
Total adverse events	1.08	1.05–1.11	2.00	0.43	< **0.01**	1.08	1.05–1.11	0.00	0.51	< **0.01**
Leading to treatment discontinuation	1.94	1.21–3.09	44.20	0.07	< **0.01**	1.40	0.67–2.92	85.60	< 0.01	0.36
Serious adverse events	1.30	0.91–1.85	34.20	0.17	0.15	1.10	0.86–1.40	26.70	0.24	0.44
Skin and subcutaneous tissue disorders										
Pruritus	1.75	1.43–2.15	66.60	< 0.01	< **0.01**	2.20	1.38–3.53	75.30	< 0.01	< **0.01**
Gastrointestinal disorder										
Nausea	1.01	0.83–1.22	0.00	0.52	0.92	1.00	0.81–1.24	0.00	0.57	0.98
Vomiting	1.04	0.63–1.72	34.60	0.19	0.88	1.18	0.86–1.63	0.00	0.44	0.30
Constipation	1.88	1.45–2.43	0.00	0.69	< **0.01**	1.98	1.51–2.59	0.00	0.62	< **0.01**
Abdominal pain	1.04	0.83–1.29	0.00	0.91	0.74	1.06	0.84–1.32	0.00	0.82	0.63
Diarrhea	0.62	0.50–0.77	0.00	0.86	< **0.01**	0.57	0.45–0.73	0.00	0.83	< **0.01**
Abdominal pain upper	1.16	0.78–1.72	24.50	0.26	0.46	1.30	0.96–1.76	0.00	0.92	0.09
Dyspepsia	0.98	0.40–2.43	20.60	0.26	0.97	1.24	0.33–4.57	0.00	0.55	0.75
Respiratory and infectious disorder										
UTI	0.91	0.65–1.28	17.30	0.28	0.60	1.15	0.90–1.48	0.00	0.75	0.26
URTI	1.03	0.80–1.32	0.00	0.57	0.83	1.12	0.86–1.47	0.00	0.86	0.40
Sinusitis	0.91	0.67–1.24	0.00	0.78	0.55	0.91	0.66–1.25	0.00	0.76	0.55
Cough	1.15	0.83–1.59	0.00	0.80	0.41	1.23	0.88–1.74	0.00	0.83	0.23
Metabolism and nutrition factors										
CVD	0.93	0.32–2.69	21.90	0.28	0.90	1.77	0.74–4.26	0.00	0.42	0.20
HLD	2.69	1.85–3.92	0.00	0.49	< **0.01**	2.69	1.85–3.92	0.00	0.49	< **0.01**
Others										
Fatigue	0.93	0.77–1.11	0.00	0.70	0.40	0.87	0.71–1.06	0.00	0.61	0.17
Headache	0.79	0.63–0.99	0.00	0.87	**0.04**	0.77	0.59–1.01	0.00	0.67	0.06
Dizziness	1.00	0.71–1.43	0.00	0.73	0.98	1.00	0.71–1.43	0.00	0.73	0.98

Abbreviations: CVD indicates cardiovascular disease; HLD, hyperlipidemia; URTI, upper respiratory tract infection; UTI, urinary tract infection.
Bolded $p \leq 0.05$ denotes statistical significance.

Bariatric surgery proposed for use in NASH while effective is invasive and a less preferred option.[32] OCA may instead represent the first of many agents that may potentially be approved for the treatment of NASH to combat the global burden of the disease.[33] While OCA is approved by the FDA for use in PBC, concerns over safety and tolerability still preside. Here, we pooled safety data of OCA from clinical trials in NAFLD, PBC, and PSC. The disease pathophysiology between autoimmune cholestatic liver diseases and NASH are quite different. Therefore, a post hoc sensitivity analysis within NAFLD was subsequently conducted and the main AEs included pruritis, constipation, and hyperlipidemia with an evident dose-dependent effect.

OCA is a FXR antagonist that results in the accumulation of bile acids that manifest as pruritis.[34] In our meta-analysis, OCA resulted in a 75% (RR: 1.75, 95% CI: 1.43–2.15, $p < 0.01$) increase rate of pruritis. A sensitivity analysis conducted within the NAFLD population however found a higher rate of pruritis (RR: 2.20, 95% CI: 1.38–3.53, $p < 0.01$). The difference in findings can be attributed to the disease pathogenesis where pruritis is comparatively more common in the natural history of PBC and PSC relative to NAFLD.[35] Within the population of NAFLD, there was an evident dose-dependent effect (Figure 2) where there was three times increased risk of pruritis at 25 mg (RR: 3.07, 95% CI: 1.74–5.41, $p < 0.01$). However, a pooled analysis of the placebo found that a 10th of NAFLD similarly

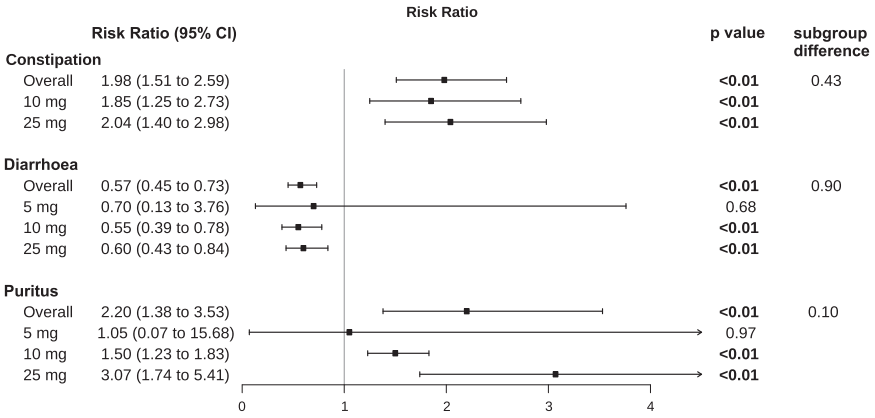

FIGURE 2 Summary forest plot of adverse events in patients with NAFLD.

TABLE 2 Pooled proportional event rates of obeticholic acid and placebo in NAFLD

	NAFLD Treatment Group				NAFLD Placebo Group			
	Effect size (%)	95% CI	I^2 (%)	Cochran *Q*	Effect Size (%)	95% CI	I^2 (%)	Cochran *Q*
General adverse events								
Total adverse events	82.56	70.32–90.44	85.60	< 0.01	78.89	66.25–87.68	72.00	0.03
Leading to treatment discontinuation	8.80	5.17–14.60	94.00	< 0.01	6.24	4.63–8.37	—	—
Serious adverse events	12.56	10.55–14.88	65.00	0.09	11.42	9.20–14.08	—	—
Skin and subcutaneous tissue disorders								
Pruritus	16.55	6.47–36.24	93.00	< 0.01	9.98	5.01–18.89	80.00	< 0.01
Gastrointestinal disorder								
Nausea	11.75	10.11–13.60	0.00	0.42	11.72	9.48–14.41	—	—
Vomiting	5.95	4.79–7.37	22.00	0.26	5.02	3.59–6.98	—	—
Constipation	8.32	5.22–12.99	33.00	0.16	1.52	0.23–9.25	30.00	0.23
Abdominal pain	9.64	8.23–11.27	47.00	0.15	8.89	7.10–11.07	27.00	0.24
Diarrhea	6.71	5.52–8.14	0.00	1.00	11.98	9.78–14.60	0.00	0.84
Abdominal pain upper	6.94	5.69–8.45	0.00	0.88	5.33	3.85–7.33	—	—
Dyspepsia	2.45	1.02–5.75	0.00	0.43	1.23	0.31–4.77	46.00	0.17
Respiratory and infectious disorders								
UTI	5.78	2.86–11.33	45.00	0.11	5.37	2.69–10.45	60.00	0.08
URTI	7.42	6.17–8.91	0.00	0.98	6.70	5.07–8.81	0.00	0.87
Sinusitis	4.95	3.92–6.23	0.00	0.96	5.46	3.98–7.44	0.00	0.41
Cough	5.09	4.05–6.39	0.00	0.72	4.13	2.87–5.92	0.00	0.88
Metabolism and nutrition factors								
CVD	7.14	4.19–11.91	0.00	0.94	4.24	2.04–8.63	0.00	1.00
HLD	7.40	6.10–8.95	43.00	0.18	2.74	1.73–4.31	—	—
Others								
Fatigue	11.35	9.78–13.14	0.00	0.83	13.13	10.79–15.88	17.00	0.27
Headache	5.51	4.24–7.14	33.00	0.16	6.33	3.31–11.76	14.00	0.32
Dizziness	4.13	3.22–5.29	20.00	0.29	4.01	2.85–5.61	0.00	0.43

Abbreviations: CVD indicates cardiovascular disease; HLD, hyperlipidemia; URTI, upper respiratory tract infection; UTI, urinary tract infection.
Bolded $p \leq 0.05$ denotes statistical significance.

experience pruritis with placebo. This could be attributed to the presence of hepatic and systemic inflammation, accompanied by impaired bile acid metabolism in NAFLD.[36,37] In addition, subjective AE events are by nature challenging to document in clinical trials. The Self-Assessment Method for Statin Side-effects or Nocebo (SAMSON) trial found that patients inform to be receiving stain despite receiving placebo, in reality, reported similar event rates to the treatment group.[38] Pruritus was the most reported AE in a retrospective cohort study of 64 PBC patients with 41% of patients experiencing pruritus[39] while moderate or severe pruritus was also reported in one fifth of 123 NAFLD patients in a recent prospective cohort study.[40] In a recent real-world prospective cohort of 125 PBC patients with OCA, 35% of individuals experience an AE that was mainly attributed to pruritus (32%).[41] However, only 9 (7.2%) patients had a *de novo* pruritis and 10 (8.3%) patients had a discontinued event from itch. The reported rates are significantly smaller compared with reported rates in clinical trials with up to 56% of patients reported pruritis at 5–10 mg with OCA in the POISE trial.[20] While the results are encouraging, it is important to note that in the real-world prospective cohort, the doses of OCA were low with majority of patients on a 5 mg regime. The potential treatment for CLD using OCA can contribute to increased pruritus severity and precipitate pruritus in some, this can cause decreased quality of life and compliance to treatment regime.[42,43] There have been recommendations published which described multi-faceted management strategies including nonpharmacological treatment, pharmacological treatment, and titration of OCA dose given that the dose-dependent effect illustrated to manage pruritus.[43]

OCA acts as an FXR agonist which regulates the *de novo* synthesis of primary bile acids. Primary bile acids are synthesized from cholesterol and FXR-dependent inhibition of de novo bile acid synthesis can lead to the accumulation of cholesterol. The resultant disruption in lipid metabolism is clinically significant in NAFLD. Unlike other CLDs, NASH patients are significantly predisposed to having CVD events with up to 44.6% having coronary heart disease.[44,45] In contrast, cholestatic liver disease is predominantly characterized by the formation of lipoprotein X, which is nonatherogenic and does not increase the risk of CVDs.[46,47] Hence, with regards to cholestatic liver disease patients with no additional cardiovascular risk factors, lipid-lowering medications are not indicated unless individual risk and benefit assessment prove otherwise.[47] While there were no associated increase in CVD events from OCA use in this meta-analysis, the follow-up duration of these trials may not have been sufficient for longitudinal events of CVD to mature as a result from perturbations to the lipid profile.[48] There was, however, a notable increase in hyperlipidemia in NAFLD patients with OCA (RR: 2.69, 95% CI: 1.85–3.92, $p < 0.01$). In the REGENATE study, 41% of patients OCA 25 mg were prescribed with statins at baseline and 17% of patients had increase in LDL compared with 7% in placebo. To circumnavigate the elevation in LDL with OCA, a recent phase 2 clinical trial (CONTROL) showed that atorvastatin used in combination with OCA can reduce LDL without increasing AE.[49]

Strengths and limitations

The current study synthesized the safety and tolerability profile of OCA in CLD and sensitivity analysis for NAFLD patients. There are, however, several limitations to the analysis. We are limited by the reporting of AEs by clinical trials and reporting definitions may differ between studies. In addition, longitudinal events of mortality and decompensation remains limited in clinical trials due to the short duration of follow-up. The small number of patients on high-dose OCA and the dose-dependent effect of OCA could also result in the underrepresentation of AEs that might emerge on high-dose OCA. Last, there remains residual heterogeneity between trials that may influence the event rates.

CONCLUSIONS

The current meta-analysis summarizes the AEs related with OCA used in CLD with an in-depth detailed analysis for NAFLD patients and pruritis, constipation and hyperlipidemia are the main AEs reported with a dose-dependent effect. With these events are an unfortunate byproduct of the mechanism of action, these events can be easily controlled or reduce with appropriate measures. NASH remains the leading cause of liver transplant and the safety profile while imperfect may provide the first of many drugs to be approved for NASH by the FDA.

AUTHOR CONTRIBUTIONS

All authors approve the final version of the manuscript, including the authorship list and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Conceptualization and methodology: C.H.N., M.M. Data curation: C.H.N., J.X., A.T., Z.Y.W., J.N.Y., R.W.Z., C.T., G.H.Z.W., M.T., D.C., D.J.H.T., N.W.S.C., K.E.C. Formal analysis and investigation: C.H.N., J.X., A.T., Z.Y.W., J.N.Y., R.W.Z. Writing—original draft: C.H.N., A.S.P.T., J.X., Z.Y.W., J.N.Y., C.E.F., R.W.Z., C.T., G.H.Z.W., M.T., D.C., D.J.H.T., N.W.S.C., K.E.C., D.Q.H., B.N., M.S.S., A.J.S., M.N., M.M. Writing—review and editing: D.Q.H., M.N., M.S.S., A.J.S., M.M.

CONFLICT OF INTEREST

A.J.S. is the President of Sanyal Biotechnology and has stock options in Genfit, Akarna, Tiziana, Indalo, Durect, and Galmed. He has served as a consultant to Astra Zeneca, Nitto Denko, Enyo, Ardelyx, Conatus, Nimbus, Amarin, Salix, Tobira, Takeda, Jannsen, Gilead, Terns, Birdrock, Merck, Valeant, Boehringer-Ingelheim, Lilly, Hemoshear, Zafgen, Novartis, Novo Nordisk, Pfizer, Exhalenz, and Genfit. He has been an unpaid consultant to Intercept, Echosens, Immuron, Galectin, Fractyl, Syntlogic, Affimune, Chemomab, Zydus, Nordic Bioscience, Albireo, Prosciento, Surrozen, and Bristol Myers Squibb. His institution has received grant support from Gilead, Salix, Tobira, Bristol Myers, Shire, Intercept, Merck, Astra Zeneca, Malinckrodt, Cumberland, and Norvatis. He receives royalties from Elsevier and UptoDate. M. Noureddin has been on the advisory board for 89BIO, Gilead, Intercept, Pfizer, Novo Nordisk, Blade, EchoSens, Fractyl, Terns, Siemens, and Roche Diagnostics. He has received research support from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Madrigal, Novartis, Pfizer, Shire, Viking, and Zydus. He is a minor shareholder or has stocks in Anaetos, Rivus Pharma, and Viking. All other authors have no conflicts of interests.

DATA AVAILABILITY STATEMENT

All articles in this manuscript are available from Medline and Embase.

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