Review Article

A REVIEW ON CLINICAL OUTCOMES OF BEMPEDOIC ACID AS ADD-ON THERAPY WITH EZETIMIBE FOR THE TREATMENT OF HYPERLIPIDEMIA

Raja Vidhya D ¹, Girija S ², Nila Ganamurali ², Dhivya Dhanasekaran ², Sarvesh Sabarathinam ^{2*}

¹HCL technologies, Elcot sez, Shollinganallur, Chennai, Tamil Nadu, India

²Department of Pharmacy Practice, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, 603 203, Tamil Nadu, India

*Corresponding Author Email: sarveshtvg@gmail.com

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ABSTRACT

Background: Cardiovascular complications are one of the leading causes of global mortality. Statins are intended to produce beneficial effects in reducing the risk of morbidity and mortality in cardiovascular patients. However, it becomes negligible in statin intolerant patients mainly due to muscle related symptoms. **Objective:** The objective of the study is to summarize the results of the studies available on safety and efficacy of bempedoic acid/ezetimibe combination treatment in statin intolerant patients. **Methods:** After comprehensive literature survey, in Cochrane Library, PubMed, Embase and Medline, randomized controlled studies involving statin intolerant hyperlipidemia, patients with low- density lipoprotein ≥ 200 mg/dl and at high risk of cardiovascular disease treated with Bempedoic acid and ezetimibe combination were selected. **Results:** For final quality analysis two clinical trials were selected to assess the safety and efficacy of the combination of Bempedoic acid and Ezetimibe. Data shows Bempedoic acid and Ezetimibe combination significantly lowered the low-density lipoprotein compared to the control groups (placebo vs Bempedoic acid vs ezetimibe). In addition, the data shows significant reduction in highly sensitive C- reactive protein, non-high density lipoprotein cholesterol, total cholesterol and apolipoprotein B. **Conclusion:** Overall, we conclude that the combination of Bempedoic acid and Ezetimibe can be considered as a treatment of choice for the treatment of hyperlipidemia for patients with statin-intolerance or maximally tolerated even to low-dose statins.

Keywords: Bempedoic acid, Cardiovascular complications, Ezetimibe, Hyperlipidemia, Statins, Statin-intolerance

INTRODUCTION

Cardiovascular complications are one of the leading causes of global mortality, which accounts for about 17 million deaths per year (30%) of all global mortality¹.

Elevated cholesterol causes major cardiovascular complications like atherosclerosis and Coronary artery disease. Increased Triglycerides and reduced HDL are some of the potential interpreters of Cardiovascular diseases². In the management of Hyperlipidemia, statins are widely prescribed as the first-line drug of choice³. In the united states, Statin consumer rates were increased from 17.9% (2002-2003) to 27.8% (2012-2013)⁴.

Regardless of the broad utilization of statins in the reduction of triglycerides and cardiovascular entanglements, statin treatment withdrawal, and inability to follow, stays a progressing issue. The primary reason for terminating statin treatment is statin-associated muscle symptoms (SAMSs). Even though the mechanism is unclear, statins are more prone to cause serious adverse events. The major well-documented statin-induced side effects are Muscle disorders and Type 2 diabetes.

It is important to consider all the clinical manifestations of statin toxicity and intolerance, impacting adherence to therapy and later cardiovascular risks. It is very important to understand the wide spectrum of clinical signs of statin's harmfulness and its availability as the only choice of drug, which may impair medication adherence and result in cardiovascular complications. The toxicity of statin is considered when there is inhibition

of HMG-CoA reductase either in subcellular and direct cellular or a fusion of both.

Around 72% of statin reported adverse events are muscle-related, documented as rhabdomyolysis, myositis, and myopathy elevated with serum creatinine kinase⁵.

Role of Bempedoic acid (BA) & Ezetimibe (EZE):

Bempedoic acid is a non-statin, small molecule inhibitor of ATP citrate (MW 344.5g/mol). BA offers a safe and effective oral therapeutic option for lipid-lowering in patients who cannot tolerate statins by lowering LDL-C^{6,7}. Ezetimibe is in a class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol (MW 413.4 g/mol)⁸. Drug profile is given in Table 1.

There are several studies available reporting the individual use of Bempedoic acid and ezetimibe that helps in the treatment of hyperlipidemia. But the combination of Bempedoic acid and ezetimibe were found to be more effective for the treatment of hyperlipidemia with or without additional modifying lipid agents in patients who are unable to tolerate even at low dose of statin therapy. This review focuses on the Safety and efficacy of the combination of Bempedoic Acid and Ezetimibe in the management of Hyperlipidemia in patients with statin-intolerance.

MATERIALS AND METHODS

Eligibility criteria

Randomized controlled studies (including phase III clinical trials) that compared the Bempedoic acid and ezetimibe either as add-on therapy or as a combination drug with other treatment groups in patients with elevated cholesterol are included in this review. After the initial search, studies that reported the outcome parameters such as LDL-C, HDL-C, Non-HDL-C, Total cholesterol, Triglycerides, ApoB, and HsCRP and reported adverse events were included in this review.

The Exclusion Criteria were

- Animal studies and case reports.
- Studies that include other combination drug therapies or monotherapies that does not involve Bempedoic acid and ezetimibe either as add-on therapy or as a combination therapy for the treatment of hyperlipidemia.
- Studies without a control group.
- Monotherapy studies of either Bempedoic acid or Ezetimibe.
- Ongoing trials or trials that do not have complete results, unpublished or scientific abstracts.
- Review articles (includes systematic review and meta-analysis).

Study Designs

Study population

There was no limitation imposed on the type of population involved in the clinical trial.

Languages

During the literature search, no limitations were placed on languages. Nevertheless, the trials used have been reported in English only.

Data source

This review was conducted according to preferred reporting items for systematic review and meta-analysis protocols statement 2015. All relevant studies that assessed the clinical outcomes and safety profile of Bempedoic acid and Ezetimibe either as add-on therapy or as a combination used in the management of hyperlipidemia as an alternative for statin therapy were identified. A systematic search was performed independently in Embase, PubMed, ClinicalTrials.gov, and Cochrane Library up to July 31, 2020. A literature search was carried out with the following terms “statin-intolerance, SAMs, Bempedoic acid, Ezetimibe, Non-statin therapy, statin-induced side effects, ETC-1002, Hyperlipidemia, clinical outcomes and safety profile.”

Study selection

The study titles and abstracts were reviewed using the pre-established inclusion criteria. The screening process and reason for the omission of studies were referenced utilizing the preferred reporting system for systematic review and meta-analysis protocols statement flow chart.

Using the predefined criteria, data was extracted from the selected studies such as the first author's name, study site, study design, duration of the study and dose. The findings were eventually compared, based on the parameters such as LDL-C, HDL-C, Non-HDL-C, Total cholesterol, triglycerides, Apo B

and HsCRP, and adverse events. Figure 01 represents the study section flow chart and Figure 02 represents the risk of bias.

RESULTS

Two phase III clinical trials were conducted to assess the safety and efficacy of Bempedoic acid and Ezetimibe as an add-on therapy or as a combination drug. Study-1 included patients with fasting LDL-C ≥ 130 mg/dL for primary prevention or LDL-C ≥ 100 mg/dL for secondary prevention and patients who required lipid modifying therapy as a primary or secondary prevention of cardiovascular diseases. It also included patients who underwent maximally tolerated statin therapy at stable dose for at least 4 weeks prior to screening. Study-2 included patients with the use of stable lipid-modifying therapy for at least 4 weeks prior to screening and fasting LDL-cholesterol was greater than or equal to 100mg/dL at screening are included in the studies¹³. The study included overall 651 participants who were randomized into different treatment groups. The randomization of study participants/sample size for each group is given in Table 2.

The study consisted of an approximate of 1-week screening period, 4-weeks run-in period, and 12-weeks treatment period. In both the trials, the primary outcome was to evaluate the percent change from baseline to week-12 in Low density lipoprotein cholesterol (LDL-C) and the secondary outcome was to assess the percent change from baseline to week-12 in HDL-C, Non-HDL-C, total cholesterol, triglycerides, apoB, and HsCRP and the Treatment-emergent adverse events (TEAEs). Baseline was defined as the mean of the last two non-missing values on or before Day 1.

Primary and Secondary Outcomes:

The primary outcome was to assess the percent change from baseline to week-12 in LDL-C. The mean (standard deviation) baseline LDL-C for the fixed-dose combination (FDC) group was found to be 153.80 (40.526) mg/dL in study-1 and for the Bempedoic acid + Ezetimibe (BA+EZE) group was found to be 129.77 (30.871) mg/dL in study-2. The percent change from baseline to week-12 in LDL-C for different treatment groups is given in Table 3.

In both the studies, the results show that the LDL-C levels were significantly lowered in the FDC and BA+EZE groups but increased in patients who received a placebo. In Study-1, the difference of Least-Squares (LS) means for the FDC group with Bempedoic acid group, ezetimibe group, and placebo group was found to be -19.0 (CI -95% [-26.1 to -11.9], $P < 0.001$), 13.1 (CI -95% [-19.7 to -6.5], $P < 0.001$) and -38.0 (CI-95% [-46.5 to -29.6], $P < 0.001$) with the Standard error of the mean 3.60, 3.37 and 43.2 respectively. The difference of LS means in Study-2 was -28.45 (CI-95% [-34.376 to -22.531], $P < 0.001$) with the Standard error of the mean 3.022.

In Study-1, a significant reduction was observed in the levels of Non-HDL-C, Total cholesterol, and apoB in the FDC group when compared with other treatment groups (Bempedoic acid group and Ezetimibe group) from baseline to week-12 (Table 3).

The studies also show that the levels of Non-HDL-C, Total cholesterol, and ApoB were increased with the placebo treatment group. The difference in LS mean for FDC/BA+EZE group vs placebo was reported as -33.7 (CI-99% [-43.9 to -23.4], $P < 0.001$), -27.1 (CI-99% [-35.1 to -19.1], $P < 0.001$) and -30.1 (CI-99% [-39.9 to -20.3], $P < 0.001$) in Study-1 and -23.6 (CI-95% [-

29.005 to -18.121], $P < 0.001$), -17.99 (CI-95% [-21.940 to -14.030], $P < 0.001$) and -19.32 (CI-95% [-23.908 to -14.732], $P < 0.001$) in Study-2 respectively. Triglycerides levels were increased in both BA+EZE and placebo groups in Study-2 whereas the level was decreased in the FDC group and increased in the placebo group and Bempedoic acid group in Study-1 (Table 3).

Although there were no significant differences between the treatment groups, the HDL-C levels were slightly decreased from baseline to week-12 in all the treatment groups, especially with the FDC and BA+EZE groups. Studies also show that there was a decrease in the HsCRP level with patients who received FDC/BA+EZE, whereas the level was increased in the placebo treatment group.

Adverse Events

The mortality rate was found to be none in both the studies. Serious TEAEs occurred in 7.48%, 6.36%, 9.17%, and 1.82% in the FDC, Bempedoic acid, Ezetimibe, and Placebo groups in Study-1 and 3.45% and 2.76% in BA/EZE and Placebo groups in Study-2 respectively. In Study-1, cardiac disorders such as Acute myocardial infarction, Angina pectoris, Atrial fibrillation, Coronary Artery Disease, and Myocardial ischemia occurred in one patient (0.93%) each in the FDC group. Acute myocardial infarction occurred in two patients (1.82%) in the Bempedoic acid group and three patients (2.75%) in the Ezetimibe group. One patient in the Bempedoic acid group (0.91%) and placebo group (1.82%) encountered Myocardial infarction. One patient (0.91%) was diagnosed with Supraventricular tachycardia in the Bempedoic acid group, one patient (0.92%) with Congestive cardiac failure in the Ezetimibe group and one patient (1.82%) with Coronary artery disease in the Placebo group. Other serious TEAEs such as Non-cardiac chest pain, Rhinovirus infection, Hemiparesis occurred in one patient (0.91%) each in the Bempedoic acid group. One patient (0.91%) each with Diverticulitis, Pneumonia, Confessional state (psychiatric disorder) and COPD was observed in patients who received Bempedoic acid and adverse events such as Pneumonia, Coronary vascular graft stenosis, Limb Injury, Renal artery occlusion Respiratory failure, Chronic respiratory failure and Deep vein thrombosis was observed in Ezetimibe group (one patient [0.92%] in each of the AE's). In Study-2, the following adverse events have occurred in one patient each (BA+EZE group [0.55% each]: Intestinal obstruction, Bronchitis, Osteoarthritis, Hepatic cancer, Syncope and Dysuria and Placebo group [1.15% each]: Bacterial pneumonia, Deliberate poisoning, Subdural hematoma, Subdural hemorrhage, and Breast cancer).

Most of the adverse events are mild or moderate. There was no significant difference in the frequency of TEAEs occurred between the different treatment groups (Table 4).

In Study 1, 8 patients (7.48%) suffered from Urinary Tract Infection, four patients (3.74%) each with Nasopharyngitis and constipation, three patients (2.80%) with Hypertension, two patients (1.87%) with Headache, and one patient (0.93%) reported Anemia in FDC group.

In Study-2, five patients (2.76%) in each experienced Nausea, Sinusitis, and Urinary tract infection in the BA+EZE group. Fourteen patients (7.73%) had an increase in blood uric acid and seven patients (3.87%) had an increase in Liver function tests. Eight patients (4.42%) experienced Headache, 2 (1.10%) with Diabetes mellitus

and four patients (2.21%) each with Nasopharyngitis and decreased Glomerular filtration rate in the BA+EZE group.

Muscle-related TEAEs were seen in all the treatment groups. In Study-2, patients experienced Myalgia (1.66% in the BA+EZE group and 2.30% in the placebo group) and Muscle spasms (3.31% in the BA+EZE group and 3.45% in the placebo group). Two patients (1.87%) in the FDC group, five patients (4.55%) in the Bempedoic acid group, two patients (1.83%) in the Ezetimibe group, and one patient (1.82%) in the Placebo group experienced Myalgia (Study-1). Muscle spasms were reported by two patients (1.87%) in the FDC group, one patient (0.91%) in the Bempedoic acid group, and four patients (3.67%) in the Ezetimibe group in Study-1. Other muscle-related TEAEs such as Arthralgia (1 patient in FDC group, 4 patients in Bempedoic acid group, 4 patients in Ezetimibe group and 2 patients in Placebo group) and Back pain (3 patients each in FDC group and Bempedoic acid group, 4 patients in Ezetimibe group and 2 patients in Placebo group) was also reported in Study-1.

DISCUSSION

Bempedoic acid is a newly approved drug by the U.S. FDA for the treatment of Hyperlipidemia. It acts as an Adenosine triphosphate-citrate lyase (ACL) inhibitor, which is involved in cholesterol biosynthesis in the liver. Ezetimibe is also a lipid-lowering compound that inhibits the absorption of intestinal cholesterol. Several studies reported the individual use of Bempedoic acid and ezetimibe that help in the treatment of hyperlipidemia. But the combination of Bempedoic acid and ezetimibe were found to be more effective for the treatment of hyperlipidemia with or without additional modifying lipid agents in patients who are unable to tolerate even at low dose of statin therapy.

Overall, we found four completed clinical trials for the combination use of Bempedoic acid and ezetimibe. Two trials were rejected as they have not met the inclusion criteria (In one trial, Bempedoic acid and ezetimibe was used as a triple therapy along with atorvastatin, and the second trial was conducted to evaluate the safety and efficacy of the combination drugs in patients with diabetes). Out of 2 clinical trials, one trial (Study-2) was conducted to evaluate the safety and efficacy of Bempedoic acid (180mg) as an add-on therapy for Ezetimibe (10 mg) in patients with elevated LDL-C, which was also published as a research article by Ballantyne et al. (2018). Another trial (Study-1) was to evaluate the safety and efficacy of Bempedoic acid (180mg) plus ezetimibe (10 mg) as a fixed-dose combination compared to Bempedoic acid, Ezetimibe and Placebo in patients with maximally tolerated statin therapy which was also published by Ballantyne et al. (2020). The reason for selecting these two trials was that, both the trials evaluated the effect of these drugs with the patients who had elevated cholesterol and used the same dose of Bempedoic acid and ezetimibe either as a combination or as an add-on therapy.

Both the study results showed that the combination of Bempedoic acid (180mg) and Ezetimibe (10 mg) had a positive impact on reducing LDL-C. A study reported by Thompson et al. (2016) conducted a phase IIb trial in which they compared the effect of two doses of Bempedoic acid (120 mg and 180 mg) as a monotherapy or combined with Ezetimibe (10 mg) and Ezetimibe alone for the treatment of LDL-C14. The study concluded that the combination of Bempedoic acid and Ezetimibe (180 mg of BA and 10 mg of EZE) was more effective than the monotherapy of Bempedoic acid and Ezetimibe for reducing LDL-C level. They also stated that the reduction of LDL-C was similar in both statin-tolerant and statin-intolerant patients. Studies

showed a decrease in the levels of Non-HDL-C, Total cholesterol, and ApoB. A slight reduction in the HDL-C level was also observed in both the FDC group and BA+EZE groups, and the study by Ballantyne et al. (2018) mentioned that the significance of the changes in HDL-C was unknown¹⁵. Although Study-1 showed a slight decrease in Triglycerides, the combination of Bempedoic acid and ezetimibe had minimal effect on Triglycerides. HsCRP is an inflammatory biomarker that is

associated with cardiovascular risks. An increase in HsCRP level associates with increased cardiovascular risks such as Coronary heart disease, Atherosclerotic cardiovascular disease¹⁵. Both the studies showed decreased HsCRP level when compared to other treatment groups which can be considered as a positive effect on the combination of drug therapy by minimizing cardiovascular risks.

Table 1: Drug profile of Bempedoic acid & Ezetimibe^{9,10}

DESCRIPTION	BEMPEDOIC ACID	EZETIMIBE
Dose and Route	180 mg orally	10mg orally
Half-life	21 ± 11 hours	22 hours
Absorption	Primarily absorbed in the small intestine	Initially conjugated to a pharmacologically active phenolic glucuronide (Ezetimibe-glucuronide)
T _{max}	3.5 hours	4 to 12 hours
Distribution	The Apparent volume of distribution (V/F) is 18 L	The Relative Volume of distribution (V/F) is 107.5L.
Metabolism	Initially by acyl glucuronide	Primarily via glucuronide conjugation
Excretion	70% in urine, 30% in feces	78% in feces and 11% in urine

Table 2: Demographics of selected studies.

References	Treatment groups	Study site	Duration	Masking	Participants /Sample size	Age (years) [Mean (standard deviation)]	Gender (No. of participants)	
							Male	Female
Clinical Trial-1 (NCT03337308)/ Ballantyne et al., (2020)¹¹	FDC (Bempedoic acid + Ezetimibe)	4 sites in US (Iowa, New Hampshire, North Carolina, Tennessee)	23-Oct-2017 to 18-Jul-2018	Quadruple (participant, care provider, investigator, outcome assessor)	108	63.0 (9.97)	50 (46.3%)	58 (53.7%)
	Bempedoic Acid				110	65.2 (9.54)	45 (40.9%)	65 (59.1%)
	Ezetimibe				109	64.4 (8.91)	52 (47.7%)	57 (52.3%)
	Placebo				55	65.6 (10.74)	33 (60.0%)	22 (40.0%)
Clinical Trial-2 (NCT03001076)/ Ballantyne et al., (2018)¹²	Bempedoic acid + Ezetimibe (BA + EZE)	US (Texas)	29-Nov-2016 to 12-Feb-2018	Triple (participant, investigator, outcome assessor)	88	63.8 (10.77)	72 (39.8%)	109 (60.2%)
	Placebo (Placebo + Ezetimibe)				181	63.7 (11.32)	32 (36.4%)	56 (63.6%)

In Study-1, three sites were found not to have followed Good Clinical Practice; therefore, study was completed with all data from those sites are removed

Table 3: Primary and Secondary outcome parameters

References	Treatment groups	LDL-C (percent change)	HDL-C (percent change)	Non-HDL-C (percent change)	Total cholesterol (percent change)	Triglycerides (percent change)	Apo B (percent change)	HsCRP (percent change)
Clinical Trial-1 (NCT03337308) / Ballantyne (2020)¹¹	FDC (Bempedoic acid + Ezetimibe)	-36.2 (2.56)	-5.59 (12.269)	-31.9 (2.23)	-26.4 (1.90)	-7.90 (25.633)	-24.6 (2.38)	-35.1 (-56.5 to -2.3)
	Bempedoic acid	-17.2 (2.52)	-5.40 (14.688)	-14.1 (2.17)	-12.1 (1.83)	7.94 (42.312)	-11.8 (2.18)	-31.9 (-62.6 to 7.7)
	Ezetimibe	-23.2 (2.18)	-2.11 (11.590)	-19.9 (2.05)	-16.0 (1.59)	-2.46 (33.402)	-15.3 (1.97)	-8.2 (-34.4 to 32.0)
	Placebo	1.8 (3.49)	-0.54 (12.799)	1.8 (3.28)	0.7 (2.46)	5.47 (31.992)	5.5 (2.97)	21.6 (-18.5 to 68.5)
Clinical Trial-2 (NCT03001076) / Ballantyne et al. (2018)¹²	Bempedoic acid + Ezetimibe (BA + EZE)	-23.46 (1.945)	-7.27 (1.214)	-18.38 (1.668)	-15.11 (1.282)	4.70 (3.068)	-14.58 (1.497)	-32.521 (-55.556 to 10.714)
	Placebo (Placebo + Ezetimibe)	4.99 (2.299)	-1.38 (1.389)	5.19 (2.202)	2.88 (1.553)	9.23 (4.218)	4.74 (1.786)	2.088 (-32.143 to 49.224)

*The values were given in least-squares mean (Standard error).

Percent change from baseline to week-12 was calculated as [(outcome parameter value at week-12 minus baseline value) divided by (baseline value)] multiplied by 100. Outcome parameters - LDL-C, Non-HDL-C, HDL-C, total cholesterol, triglycerides, apoB and HsCRP.

The Percent change from Baseline was analyzed using an analysis of covariance (ANCOVA) model with percent change from Baseline as the dependent variable, treatment as a fixed effect and baseline as a covariate. In the ANCOVA model, missing data at Week 12 were imputed using multiple imputation method considering adherence to treatment

Table 4: Adverse Events in Treatment groups^{11,12}

Adverse Events	Study – 1				Study - 2	
	FDC Group n (%) (n=107)	Bempedoic Acid Group n (%) (n=110)	Ezetimibe Group n (%) (n=109)	Placebo group n (%) (n=55)	FDC Group n (%) (n=181)	Placebo Group n (%) (n=87)
Serious Adverse Events	8 (7.48)	7 (6.36)	10 (9.17)	1 (1.82)	5 (2.76)	3 (3.45)
Other Adverse Events	26 (24.30)	27 (24.55)	26 (23.85)	12 (21.82)	46 (25.41)	18 (20.69)
Most Common TEAEs*						
Acute Myocardial Infarction	1 (0.93)	2 (1.82)	3 (2.75)	0 (0.00)	NR	NR
Vertigo	NR	NR	NR	NR	0	2 (2.30)
Vulvovaginal mycotic infection	NR	NR	NR	NR	0	2 (2.30)
Intestinal Obstruction/Constipation	4 (3.74)	0	2 (1.83)	0	1 (0.55)	0
Nausea	NR	NR	NR	NR	5 (2.76)	0
Hypertension	3 (2.80)	5 (4.55)	2 (1.83)	0	NR	NR
Headache	2 (1.87)	4 (3.64)	2 (1.83)	1 (1.82)	8 (4.42)	3 (3.45)
Urinary tract infection	8 (7.48)	3 (2.73)	3 (2.75)	2 (3.64)	5 (2.76)	(5.75)
Nasopharyngitis	4 (3.74)	6 (5.45)	4 (3.67)	1 (1.82)	4 (2.21)	1 (1.15)
Dyspnoea	0	0	1 (0.92)	2 (3.64)	NR	NR
Anaemia	1 (0.93)	2 (1.82)	1 (0.92)	2 (3.64)	NR	NR
Sinusitis	NR	NR	NR	NR	5 (2.76)	0
Increased Blood uric acid	NR	NR	NR	NR	14 (7.73)	2 (2.30)
Increased Liver function test	NR	NR	NR	NR	7 (3.87)	0
Decreased Glomerular filtration rate	NR	NR	NR	NR	4 (2.21)	0
Diabetes mellitus	NR	NR	NR	NR	2 (1.10)	2 (2.30)
Musculoskeletal and connective tissue disorders						
Arthralgia	1 (0.93)	4 (3.64)	4 (3.67)	2 (3.64)	NR	NR
Back Pain	3 (2.80)	3 (2.73)	4 (3.67)	2 (3.64)	NR	NR
Muscle spasms	2 (1.87)	1 (0.91)	4 (3.67)	0	3 (1.66)	2 (2.30)
Myalgia	2 (1.87)	5 (4.55)	2 (1.83)	1 (1.82)	6 (3.31)	3 (3.45)
Osteoarthritis	0	0	0	0	1 (0.55)	0

*In Most common TEAEs, adverse events occurred in more than 2% of patients in either of the treatment groups was mentioned

*NR-Not Reported

Figure 1: Study selection flow chart

Figure 2: Risk of bias

Most of the adverse events were mild or moderate. Overall, nine participants from Study-1 (2-FDC group, 3-Bempedoic acid group, 3-Ezetimibe group, and 1-placebo group) and six participants from Study-2 (3-BA+EZE group and 3-placebo group) discontinued the trial due to adverse events. The frequency of TEAEs was almost similar in all the treatment groups. In Study-2, a high incidence of increased blood uric acid was observed. However, a study reported by Ballantyne et al. (2018) stated that within the first 4 weeks, the mean uric acid level was stabilized (Study-2) and also a review article published by Dai et al., explained that the elevated levels of uric acid could be due to Bempedoic acid which competes for the renal transporters of the uric acid excretion^{15,16}. The frequency of adverse events especially muscle-related TEAEs, was similar between the combination drug treatment groups and the other treatment groups. Hence, irrespective of these adverse events Bempedoic acid either as add-on therapy or as a combination therapy can be used for the treatment of hyperlipidemia because of its positive clinical outcomes with no additional or serious side effects compared to its monotherapy. The combination therapy can also have a positive effect on minimizing cardiovascular risks by decreasing the HsCRP levels.

CONCLUSION

Overall, we conclude that Bempedoic acid either as add-on therapy or as a combination drug with Ezetimibe can have a positive clinical outcome for the treatment of hyperlipidemia especially for patients with statin-intolerance or maximally tolerated even to low-dose statins than prescribing both the drugs as a monotherapy. More research needs to be conducted to investigate the long-term safety and efficacy of the combination of Bempedoic acid and Ezetimibe.

LIMITATIONS

There are some limitations that should be acknowledged. First, we selected only two of these trials for our review since Bempedoic acid is a newly approved drug and no further research articles have been published yet for the combination of Bempedoic acid and ezetimibe. There were a lot of studies that explained the safety and efficacy of Bempedoic acid and ezetimibe separately as a monotherapy, but no research studies were found for the safety and efficacy of the combination of Bempedoic acid and Ezetimibe other than these two clinical trials. By this short narrative review, we provide a current overview on the clinical outcomes through which many researchers or healthcare professionals can get some idea about this drug therapy and come up with a lot of studies that can be conducted with the use of this combination therapy by which we can further identify the safety and efficacy of this combination therapy. Second, the time duration of the studies was limited. Further studies need to be carried out to evaluate the long-term effects of the combination drug therapy. Third, both studies were conducted only in the US. Studies in different countries can help in evaluating the effect of the combination of drugs in different population groups.

ABBREVIATION

ApoB- Apolipoprotein B
BA- Bempedoic acid
CVD- Cardiovascular disease
EZE- Ezetimibe
FDA-Food and Drug Administration
FDC-Fixed-dose combination
HDL-C- High-Density Lipoprotein-Cholesterol
HsCRP- High sensitivity C-reactive protein

LDL-C-Low density lipoprotein-Cholesterol
Non-HDL-C- Non-High-Density Lipoprotein-Cholesterol
SAMSs- Statin-associated muscle symptoms

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