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SEVERE HYPERTRIGLYCERIDEMIA AFTER USE OF BEMPEDOIC ACID

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ABSTRACT

Bempedoic is a new drug for the management of hypercholesterolemia, approved since 2020 by the EMA for use in Europe. In this case report, we describe a 65-year-old woman with sudden worsening of hypertriglyceridemia after the introduction of bempedoic acid. Triglyceride levels normalized quickly on withdrawal of the drug. With this case report, we want to reveal a possible association between bempedoic acid and the paradoxical occurrence of hypertriglyceridemia. Furthermore, we want to emphasize the limited evidence regarding the use of bempedoic acid in patients with pre-existing hypertriglyceridemia.

KEYWORDS

Bempedoic acid, hypertriglyceridemia, adverse events

LEARNING POINTS

- Bempedoic acid is a new drug with a proven positive effect on LDL reduction and cardiovascular outcomes.
- Metabolic adverse events, especially hyperuricemia and gout, following the use of bempedoic acid are well documented.
- The current literature provides very limited evidence regarding the use of bempedoic acid in patients with pre-existing hypertriglyceridemia, so caution is advised regarding use of this drug this population.

CASE DESCRIPTION

A 65-year-old woman, with known chronic kidney disease (KDIGO stage III-B), presented at the nephrology outpatient clinic for routine follow-up. She is known to have dyslipidemia, treated with ezetimibe (EZETROL®) and fenofibrate (LIPANTHYLNANO®). As the patient developed myalgia under simvastatin, further use of a statin was contraindicated. With ezetimibe and fenofibrate, LDL was 111 mg/dl and triglycerides were 480 mg/dl. Because of comorbidities (diabetes mellitus type 2, arterial hypertension and chronic kidney disease), the patient was considered very high risk for cardiovascular events. LDL <55 mg/dl was our target according to the ESC guidelines[1]. Since this was not achieved, we decided to add bempedoic acid (NILEMDO®) 180 mg to the therapeutic regimen.

Three months after starting bempedoic acid, the patient presented again to our department for a lipid profile and to check for side-effects. We noticed a sudden increase in triglyceridemia (2537 mg/dl). Because of this unexpected finding, the sample was checked manually. It was highly

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lipemic, which confirmed true hypertriglyceridemia *(Fig. 1)*. Since the LDL level is calculated indirectly from triglycerides, LDL could not be determined. We performed a dechallenge test by stopping bempedoic acid and monitoring lipid evolution with consecutive blood samples. The lipid profile improved gradually. After 1 week, triglycerides had dropped to 2087 mg/dl. After 2 more weeks, they had dropped further to 699 mg/dl. *Figure 2* and *Table 1* show the evolution of these values from 2 years before to 1 month after the use of bempedoic acid. It is notable that the pre-exiting modest hypertriglyceridemia had remained stable under ezetimibe + fenofibrate with a value that never exceeded 500 mg/dl. A re-challenge test was proposed but refused by the patient because of the possible risk of pancreatitis.

The chronic hypertriglyceridemia of this patient was related to her metabolic syndrome, characterized by overweight (BMI 28 kg/m^2) and type II diabetes mellitus. She was not known to have any hepatic or pancreatic dysfunction. Alcohol consumption was limited to 2–3 units a week. No other new drugs had been introduced over the previous months.

DISCUSSION

Bempedoic acid is a new drug for the management of hypercholesterolemia, indicated when LDL goals are not reached under the maximum tolerated dose of a statin or in the case of statin intolerance. It works through inhibition of the ATP citrate lyase, an enzyme involved in hepatic cholesterol synthesis. Trials show an average LDL reduction of 16%–23% following 3 months of therapy[2–4]. Furthermore, the CLEAR Outcomes trial recently showed that use of bempedoic acid resulted in a statistically significant reduction in the risk of major cardiovascular events[5]. Bempedoic acid was approved in 2020 by the EMA for use in Europe. Even though it is not mentioned by the manufacturer, hypertriglyceridemia might be an uncommon side effect as shown by our case.

To our knowledge, this is the first reported case of a possible association between bempedoic acid and hypertriglyceridemia. As demonstrated above, the use of this drug in patients with metabolic syndrome (and subsequent predisposition to hypertriglyceridemia) might be a risk factor for severe evolutive hypertriglyceridemia. To date, most of the large-scale randomized controlled trials (RCT) have included few patients with pre-existing hypertriglyceridemia. The median triglyceridemia of patients included in the CLEAR Harmony Trial was 126 mg/dl[2]. In the trial of Laufs *et al.*, median triglyceridemia was 156.5 mg/

Figure 1. The blood sample of our patient. After centrifugation, the serum was highly lipemic because of severe hypertriglyceridemia (2537 mg/dl)

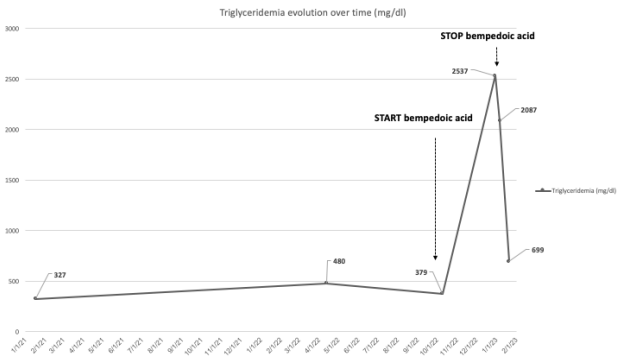

Figure 2. Evolution of the lipid profile from 2 years before until 2 months after the use of bempedoic acid

	fenofibrate + ezetimibe			fenofibrate + ezetimibe + bempedoic acid	fenofibrate + ezetimibe	
	17/01/21	12/04/22	09/10/22	30/12/22	06/01/23	20/01/23
LDL (mg/dl)	48.6	N/A	94.2	N/A	N/A	N/A
HDL (mg/dl)	31.0	24.0	25.0	7.0	9.0	17.0
Triglycerides (mg/dl)	**327**	**480**	**379**	**2537**	**2087**	**699**

Table 1. Evolution of the lipid profile in our patient from 2 years before until 2 months after the use of bempedoic acid

dl and patients with a baseline triglyceride level >500 mg/dl were excluded[3]. Finally, Banach *et al.* reported a median baseline triglyceridemia of 126–153 mg/dl, depending on the subgroup[4].

Furthermore, it has already been documented that bempedoic acid is associated with the development of metabolic dysregulation, especially hyperuricemia and gout[6]. The manufacturer reports an incidence of 3.8%. This adverse event is especially seen in patients with pre-existing hyperuricemia[7]. This group includes patients with metabolic syndrome, just like our patient. We believe that bempedoic acid may exacerbate hypertriglyceridemia in selected patients with pre-existing high triglyceride levels, just as it may trigger gout in patients with pre-existing hyperuricemia. The temporal sequence of this reaction leads us to suspect that bempedoic acid may be the trigger. Although causality is difficult to prove with a case report, the calculated Naranjo score (adverse drug reaction probability scale) points in the same direction. This score of 6/12 indicates 'probable causality' between the medication and the reaction[8].

These data suggest a lack of evidence regarding the use of bempedoic acid in pre-existing hypertriglyceridemia. Additional large-scale RCTs would therefore be appropriate to test our hypothesis and confirm causality. Given the limited experience with this drug, pharmacovigilance is important.

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