

Bempedoic Acid: The Latest in Lipid-lowering

SANJAY KALRA*, NAVNEET AGRAWAL†

ABSTRACT

Bempedoic acid is a novel nonstatin drug that has recently been approved for the management of hypercholesterolemia, in patients with established atherosclerotic cardiovascular disease (ASCVD) or with heterozygous familial hypercholesterolemia (HeFH). This editorial describes the basic and clinical pharmacology of bempedoic acid, and suggests a pragmatic approach to its use in clinical practice.

Keywords: Bempedoic acid, cholesterol, dyslipidemia, familial hypercholesterolemia, CV risk reduction, residual risk, statin, statin intolerance

Dyslipidemia is an important contributor to the burden of atherosclerotic cardiovascular disease (ASCVD). Ensuring optimal lipid levels is an effective way of reducing ASCVD. Conventionally, statins have been used to manage dyslipidemia.¹ However, there still remains a residual risk of cardiovascular disease (CVD) which cannot be mitigated by statins. Some individuals are not able to tolerate the drug, while others do not respond even to maximal doses. Alternatives to statins, such as fibrates, ezetimibe and PCSK9i (proprotein convertase subtilisin/kexin type 9 serine protease inhibitors) are limited by lack of tolerability, efficacy and affordability, respectively.² This is unfortunate, because lipid-lowering is considered low-hanging fruit, for CVD risk reduction, as compared to glucose and weight management. There is a lack of suitable therapies that can serve as complements or alternatives to statins. Keeping this in context, the approval and availability of bempedoic acid in India is a welcome development.

BASIC PHARMACOLOGY

Bempedoic acid is an orally administered pro-drug with the IUPAC name 8-hydroxy-2,2,14,14-tetramethyl-

pentadecanedioic acid. It inhibits the hepatic enzyme adenosine triphosphate-citrate lyase (ATP-citrate lyase), after being activated to its thioester with coenzyme A, by the enzyme SLC27A2. ATP-citrate lyase acts on hepatic biosynthesis of cholesterol, upstream of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase.³ Thus, its mechanism of action is distinct from, and complementary to, that of statins.

The absorption of bempedoic acid is not affected by food or timing of administration. It reaches peak concentration in 3.5 hours, and has a half-life of 21 ± 11 hours. Excretion is through the renal (70%) and fecal (30%) route.

CLINICAL PHARMACOLOGY

Bempedoic acid has been approved by the United States Food and Drug Administration (USFDA) and the European Medicine Association (EMA). Bempedoic acid has been shown to reduce LDL-C (low-density lipoprotein cholesterol), total cholesterol, non-HDL-C (non-high-density lipoprotein cholesterol) and apolipoprotein B (apo B) levels significantly. In a trial of 2,230 patients with a mean baseline LDL-C of 103.2 ± 29.4 mg/dL, bempedoic acid reduced the mean LDL-C level by 19.2 mg/dL at 12 weeks (-16.5% from baseline).⁴ In the CLEAR (Cholesterol-Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) Serenity study, statin intolerant patients, with a mean baseline LDL-C of 157.6 mg/dL, bempedoic acid significantly reduced LDL-C (placebo-corrected difference, -21.4%), non-HDL-C (-17.9%), total cholesterol (-14.8%), apo B (-15.0%) and high-sensitivity C-reactive protein (CRP, -24.3%; $p < 0.001$ for all comparisons).⁵

It can be used as a standalone drug and as part of fixed-dose combination with ezetimibe. It can also be used

*Dept. of Endocrinology
Bharti Hospital, Karnal, Haryana, India

†Dept. of Diabetology
Diabetes Obesity and Thyroid Centre, Gwalior, Madhya Pradesh, India

Address for correspondence

Dr Sanjay Kalra

Dept. of Endocrinology, Bharti Hospital, Karnal, Haryana, India

University Center for Research & Development, Chandigarh University
Mohali, Punjab, India

E-mail: brideknl@gmail.com

with statins. It must be noted that concomitant use with bempedoic acid increases blood levels of statins, especially simvastatin and pravastatin. The reason is not known, as bempedoic acid does not interact with the cytochrome P450 enzyme.

Studies are ongoing to determine the effect of bempedoic acid on cardiovascular morbidity and mortality. A systematic review and meta-analysis of 11 trials has shown bempedoic acid to be associated with a reduction in composite cardiovascular outcomes (relative risk [RR] 0.75), along with reduction in LDL-C (21.4%) and CRP (24.3%) levels. In contrast to statins, it is also associated with a reduction in rates of new-onset or worsening of diabetes (RR 0.65).⁶ It is apt to point that bempedoic acid is an AMPK (adenosine monophosphate kinase) activator. Though its clinical significance in the context of lipid-lowering is unknown, AMPK activation is a feature of modern glucose-lowering drugs.

Bempedoic acid inhibits the transporter proteins SLC01B1, SLC01B3 and SLC22A7. Inhibition of SLC22A7, and inhibition of renal tubular OAT2, may lead to a rise in uric acid and precipitate gout. Increase in uric acid usually occurs within the first month of treatment, and persists. The average increase in uric acid at 12 weeks of therapy is 0.8 mg%. The placebo-subtracted risk of gout is 1.1%, and is higher in persons with previous history of gout.⁷ Tendon rupture has been seen in 0.5% patients, and is more common in persons aged >60, those on corticosteroids or fluoroquinolones, those with renal failure or previous history of tendon disorders.

Apart from gout, adverse events include muscle spasms, back or limb pain, gout and tendon rupture of the rotator cuff of the shoulder, biceps tendon or Achilles tendon. These adverse effects are rare, however.

PRAGMATIC USAGE

Bempedoic acid can be used in all patients with dyslipidemia, as an adjunct to diet and statins/other lipid-lowering therapy, if existing therapy is unable to achieve the goal. It is also indicated in persons with statin intolerance.³ Bempedoic acid may also be used in heterozygous familial hypercholesterolemia (HeHF), and in persons with ASCVD to lower LDL-C, if it is felt that statin monotherapy will not be able to achieve target LDL-C goal alone.

Table 1 is a list of the clinical indications, concerns, caveats, checkpoints and contraindications associated with bempedoic acid use. The dose is 180 mg orally, once a day, with or without food.

Table 1. Bempedoic Acid: Pragmatic Prescription

Clinical indication: dyslipidemia

Initiation of therapy

- Heterozygous familial hypercholesterolemia
- Established ASCVD
- Multiple risk factors for ASCVD

Where it is unlikely that maximal statin therapy will be able to achieve target LDL-C

Intensification of therapy

- When maximally tolerated statin dose is unable to achieve target LDL-C

Interchange of therapy

- When statin therapy is contraindicated or not tolerated

Contraindications

- Avoid concomitant use with simvastatin >20 mg, pravastatin >40 mg
- Pregnancy/lactation
- Severe renal impairment (eGFR <30)
- Severe hepatic impairment (Child-Pugh C)

Concerns

- Risk of gout (OR 3.29)
- Risk of muscular disorders (OR 2.60)
- Worsening of renal function (OR 4.24)

Check points

- Monitor serum uric acid periodically; treat as appropriate

Caveats

- Be careful in persons with previous history of gout, renal failure, concomitant corticosteroid use, fluoroquinolone use

ASCVD = Atherosclerotic cardiovascular disease; LDL-C = Low-density lipoprotein cholesterol; eGFR = Estimated glomerular filtration rate; OR = Odds ratio.

It can be used safely in elderly persons; in those with diabetes irrespective of their glucose-lowering therapy; and with mild-moderate renal or hepatic impairment. It does not have any effect on the QT interval. It can be prescribed with all doses of atorvastatin, rosuvastatin and ezetimibe.

SUMMARY

Bempedoic acid represents a significant breakthrough in lipid management. Current prescribing information and data

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