“CLEAR ADVANTAGE” FROM TARGETING INFLAMMATION RISK OVER LDL RISK

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Abstract

ABSTRACT Statins and bempedoic acid (BA) additively and independently lower CRP. Recent secondary analyses of the CLEAR trials found CRP lowering more effective than LDL lowering at reducing MACE (major adverse cardiovascular events) thereby suggesting an advantage from targeting CRP over LDL. Statins lower CRP by via targeting eNOS, whereas BA lowers CRP via targeting ATP citrate lyase. The rationale for combining atorvastatin 80 with BA 180 is to simultaneously target two independent mechanisms for lowering CRP in patients with high risk of MACE from vascular inflammation.

HIGHLIGHTS

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ABSTRACT
Statins and bempedoic acid (BA) additively and independently lower CRP.
Recent secondary analyses of the CLEAR trials found CRP lowering more effective than LDL lowering at reducing MACE (major adverse cardiovascular events) thereby suggesting an advantage from targeting CRP over LDL. Statins lower CRP by via targeting eNOS, whereas BA lowers CRP via targeting ATP citrate lyase. The rationale for combining atorvastatin 80 with BA 180 is to simultaneously target two independent mechanisms for lowering CRP in patients with high risk of MACE from vascular inflammation.

Key words: atorvastatin; bempedoic acid; inflammation risk; LDL risk; MACE; CLEAR Wisdom study; endothelial dysfunction; eNOS; NLRP3 inflammasome; ATP citrate lyase

BACKGROUND AND RATIONALE: the background and rationale for a single combination of atorvastatin and bempedoic acid (ATOR 80:BA180) is based on the five following points:
1] the results of the CLEAR Wisdom study of BA added to maximally tolerated background statin therapy of hyperlipidemia, in addition to showing tolerability and safety, demonstrated BA lowered CRP by 17%. This occurred both additively and independently of LDL and CRP lowering by background statins (1), a finding also seen in a secondary analysis of the earlier CLEAR Harmony trial (2).

2] results of a recent meta-analysis of three large outcomes study demonstrated CRP risk is both independent of and more predictive of MACE than LDL risk regardless of the presence or absence of background statins (3,4). As discussed in reference 5, and illustrated in the attached figure, inflammation from oxidative stress drives LDL risk thereby explaining why CRP risk better predicts MACE along with the rationale for prioritizing the targeting inflammation risk over LDL risk.

3] statins lower CRP risk by a mechanisms that differs from lowering of CRP by BA.
CRP risk is related to activation of the NLRP3 inflammasome which is prevented by improving endothelial function, i.e. eNOS activation (6,7). And statins, as initially shown almost 25 years ago, activate of eNOS independently of lowering LDL (8).

BA, on the other hand, is an inhibitor of ATP citrate lyase (ACLY). The gene for ACLY is
located on chromosome 17q21.2. (9). ACLY is subject to inhibition by small molecule inhibitors and siRNA (10). To date, studies with CRISPR-cas9 have only involved in-vitro systems. ACLY has two independent actions. One is activation of the NLRP3 inflammasome with inflammation of atherosclerotic plaques mediated by macrophages (10, 11). This may contribute to endothelial cell dysfunction (12) that further explains the benefit of eNOS upregulation by statins (8). The other function of ACLY is increasing LDL synthesis (10). Therefore, BA lowers CRP risk by a mechanisms separate from that of statins as a result of inhibiting ACLY. And when combined with a statin, CRP risk is lowered by two separate and independent mechanisms.

4) potential advantage in the treatment of high-risk patients as a result of using a single compliance enhancing drug instead of a statin plus low dose colchicine that was used to target inflammation risk in the LODOCO study (13).

5) Both atorvastatin and bempedoic acid are already approved and currently marketed drugs. Atorvastatin has multiple trials showing outcome benefits. And 80 mg was well tolerated in the TNT and PROVE-IT trials. Aside from infrequent non-life-threatening minor side effects that resolved with drug discontinuation, BA has been shown to be safe and well tolerated administered on top of statin backgrounds. This was shown in CLEAR Harmony (14) as well as in CLEAR Wisdom (1). Furthermore, adding BA to a high dose atorvastatin background has been free of drug-drug interactions. Point estimates of bempedoic acid effects on steady-state atorvastatin and ortho-hydroxy atorvastatin area under the curve were <30% and not clinically meaningful. Bempedoic acid 180 mg added to stable high-dose atorvastatin therapy effectively lowers LDL-C in patients with hypercholesterolemia without causing clinically important increases in atorvastatin exposure (15). This suggests that ATOR 80: BA 180 would have an advantage over colchicine by not requiring discontinuation during periods of clarithromycin, anti-fungal and anti-rejection drug use (16). ATOR 80 : BA 180 would also have an advantage over rosuvastatin 20 : BA 180, another potential combination, as atorvastatin is felt to be less likely to cause statin induced diabetes.

Similarly to atorvastatin, when used as a single agent without a statin background, as in CLEAR Outcomes, the incidence of a primary end-point event was significantly lower with bempedoic acid than with placebo as were the incidences of a composite of death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction, fatal or nonfatal myocardial infarction and coronary revascularization (17). Furthermore, inflammation assessed by hs CRP predicted risk for future cardiovascular events and death better than hyperlipidemia assessed by LDLc. BA lowered both CRP and LDL by similar amounts but reduction of events
by BA was related to CRP lowering since risk related to LDL did not change from quartile 1 to quartile 4 (4).

As for obtaining regulatory approval for this combination, a study looking at the effect of on ATOR 80:BA 180 on inflammation risk could begin in patients with heterozygous familial hyperlipidemia (HeFH) and CRP=/>2.0. Patients would be randomized to ATOR 80:BA 180 vs ATOR 80 plus BA placebo and LDL would be reduced to 50 or less, to control for risk reduction from lowering LDL, by adding open label ezetimibe and PCSK9 s as needed to both groups, with outcomes evaluated by monitoring MACE.

SUMMARY
1] Statins and BA additively and independently lower both CRP.
2] Lowering CRP has been found more effective than LDL lowering for reducing MACE in both statin tolerant and intolerant patients.
3] Statins lower CRP by activating eNOS, whereas BA lowers CRP by inhibiting ATP citrate lyase.
4] whereas previous attempts to target both CRP risk have involved the use of a statin plus a separate agent for CRP lowering, ATOR 80: BA 180 may do the same with the “advantage” of being one compliance enhancing agent.
5] regulatory approval for ATOR 80: BA 180 should begin with a study looking at MACE in HeFH patients randomized to receive ATOR 80:BA 180 vs ATOR 80:BA placebo.

REFERENCES


The MACE Inflammation "Iceberg"

- Ox LDL
- Foam Cell Macrophages
- Atheromatous Plaques
- Plaque Rupture
- Thrombosis

Superoxide (ROS) $\rightarrow$ NLRP3 $\rightarrow$ Caspase -1

Figure 2: Vesuvius inflammation and MACE

References: Diets, inflammation, MACE, major adverse cardiac events, LDL, NLRP3, Ox LDL, plaque rupture, plaque instability, inflammation, MACE.