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# New Approaches for Treatment of Hypertriglyceridemia

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## Abstract

**Background:** Apolipoprotein C3 (APOC3) is a glycoprotein and angiopoietin-like protein 3 (ANGPTL3) is a protein, both synthesized in the liver and under normal conditions lead to elevation of circulating triglycerides. A novel strategy to lower triglycerides is using drugs that inhibit formation of APOC3 or ANGPTL3.

**Main objective:** To provide an appraisal of inhibitors of APOC3 and ANGPTL3.

**Methods:** Pubmed search was conducted until July 18, 2024. Search terms were volanesorsen, olezarsen, ploziran, zodasiran, apolipoprotein C3, triglycerides, pancreatitis, safety. Randomized clinical trials, reviews, expert opinions, and pertinent animal studies were reviewed.

**Results:** Volanesorsen and olezarsen are anti-sense oligonucleotide targeting APOC3 messenger ribonucleic acid (mRNA). Plozasiran is a small interfering RNA (siRNA) that blocks synthesis of APOC3, whereas zodasiran is a siRNA that blocks synthesis of ANGPTL3. Maximum mean reductions of plasma triglycerides versus baseline were 77% with volanesorsen and versus placebo reduction was 53% with olezarsen, 62% with plozasiran and 63% with zodasiran. In addition, volanesorsen, olezarsen and ploziran decreased incidence of acute pancreatitis in patients with severe hypertriglyceridemia. However, volanesorsen and olezarsen may increase levels of low-density lipoprotein cholesterol (LDL-C), and zodasiran may decrease levels of high-density lipoprotein cholesterol (HDL-C). Thrombocytopenia is the most concerning safety issue associated with use of volanesorsen, and to a lesser extent olezarsen. Injection site adverse events were most common with volanesorsen, whereas mild increase in hepatic transaminases was most common with olezarsen. Worsening glycemic control is another concern observed with the 2 siRNA ploziran and zodasiran.

**Conclusions:** Agents inhibiting APOC3 and ANGPTL3 are effective in lowering triglycerides levels and prevention of acute pancreatitis induced by severe hypertriglyceridemia. Long-term randomized trials are needed to establish their long-term safety and impact on cardiovascular (CV) events and mortality.

**Keywords:** volanesorsen; olezarsen; plozasiran; zodasiran; triglycerides; apolipoprotein c3; angiopoietin-like protein 3

## Introduction

APOC3 and ANGPTL3 normally increase levels of circulating triglycerides by inhibition of lipoprotein lipase (LPL), the enzyme responsible for hydrolysis and clearance of triglycerides from the circulation [1]. APOC3 is a 79 amino acid glycoprotein synthesized in the liver and to a lesser extent by enterocytes [1]. In addition to inhibition of LPL, APOC3 raises plasma triglycerides through LPL-independent pathway by reducing hepatic clearance of the remnants of triglyceride-rich lipoproteins [2]. Moreover, APOC3 concentrations may be associated with increased CV risk [3]. In fact, Mendelian randomization studies in European population have shown that heterozygous carriers of loss-of-function mutation in the APCO3 gene had lower circulating levels of triglycerides and APOC3, by 39% and 46% respectively, compared with noncarriers [4]. Furthermore, mutation carriers had 40% reduced risk of coronary artery disease compared to non-carriers [4]. ANGPTL3 is synthesized in the liver and normally increases serum triglycerides not only by inhibition of LPL but also by inhibition of endothelial lipase and increasing hepatic secretion of triglycerides [1]. Dewey et al [5] have found that heterozygous loss-of- function variants in the ANGPTL3 gene are associated with lower circulating levels of triglycerides, LDL-C an HDL-C and 39% lower odds of coronary artery disease.

In the recent decade, may drugs emerged aiming at lowering circulating levels of triglycerides by inhibition of synthesis of APOC3 and ANGPTL3 [6-15]. Olezarsen is another antisense antinucletide that inhibits APOC3 [10-12]. Olezarsen has the same nucleotide sequence and backbone chemical structure of volanesorsen [10-12]. Yet, oleszarsen is conjugated to a carbohydrate ligand, triantennary N-acetylgalactosamine ($GalNAc_3$), for asialoglycoprotein receptors that are abundant on the surface of

 

hepatocytes. Thus, $GalNAc_3$ facilitates the entry of olezarsen to the nuclei of hepatocytes [16]. The enhanced hepatic uptake of olezarsen by $GalNAc_3$ results in using lower dosing and injection volume and longer duration of action, and therefore less frequency of administration, when compared with volanersen [13]. Moreover, the liver-specific uptake of olezarsen virtually decreases the chance of adverse or off-target effects [16]. Plozasiran is si RNA inhibiting APOC3 [13,14]. Zodasiran is a si RNA inhibitor of ANGPTL3 [15]. Table 1 summarizes the main features and differences between the preceding 4 drugs. The main purpose of this review is to provide a critical appraisal of these 4 agents representing a novel approach for treatment of hypertriglyceridemia based on the available studies discussed below.

**Table 1:** Comparison of new agents targeting APOC3 and ANGPTL3 for treatment of hypertriglyceridemia

| Agent | Volanesorsen [6-9] | Olezarsen [10-12] | Plozasiran [13-14] | Zodasiran [15] |
|---|---|---|---|---|
| Type of agent | Antisense oligonucleotide that inhibits synthesis of APOC3 | Antisense oligonucleotide that inhibits synthesis of APOC3 | Small interfering RNA that inhibits synthesis of APOC3 | Small interfering RNA that inhibits synthesis of ANGPTL3 |
| Types of patients studied | FCS, multifactorial chylomicronemia, partial lipodystrophy | FCS, moderate hypertriglyceridemia at high CV risk | Severe hypertriglyceridemia, mixed hyperlipidemia | Mixed hyperlipidemia (triglycerides 150-499 mg/dl and either LDL-C ≥70 mg/dl or non-HDL-C ≥100 mg/dl |
| Frequency of subcutaneous administration | Once weekly | Once q4 weeks | Q12 weeks | Q12 weeks |
| Effects on triglycerides | -77% vs baseline | -53% | -62% | -63% |
| Effects on APOC3 | -84% vs baseline | -74% vs placebo | -78% | ND |
| ANGPTL3 | ND | ND | ND | -74% |
| Effects on non-HDL-C | -46% | -18% to -23% | -24% | -36% |
| Effects on HDL-C | 61% | 40% | 46% | -25% |
| Effects on LDL-C | 135% vs baseline | 69% | -14% | -20% |
| Effects on APOB | 20% | 18% to -18% | -19% | -22% |
| Occurrence of acute pancreatitis | 2% with volanesorsen vs 10% with placebo, OR 0.18 (95% CI, 0.04 to 0.82) | one episode with olezarsen vs 11 episodes with placebo (Rate Ratio 0.12 (95% CI, 0.02 to 0.66) | 0.6% with plozasiran vs 3.3 with placebo (Odds ratio 0.18 (95% CI, 0.02 to 2.02) | ND |
| Percentage of patients with platelets <100,000/µL | 48% with volanesorsen vs 0% with placebo {Wiz], and 12% with volanesorsen vs 3% with placebo | 5% with olezarsen vs 3% with placebo | ND | ND |
| Percentage of patient with worsening glycemic control (rise of glycated hemoglobin by 0.3% to 0.5% + need for additional therapy | ND | ND | 20% with plozasiran (50 mg) vs 10% with placebo | Worsening glycated hemoglobin and need for additional diabetes therapy with the highest dose 200 mg |

Values are maximum mean percentage change compared with placebo unless stated otherwise.
Abbreviations: APOC3: Apolipoprotein C3, RNA: ribonucleic acid, ANGPTL3: angiopoietin-like protein 3, ND: not determined

## Overview of the trials of inhibitors of APOC3 and ANGPTL3

Inhibitors of APOC3 and ANGPTL3 were evaluated for treatment of different types of hypertriglyceridemia in several diseases (table 1). Thus, volanesorsen and olezarsen were evaluated in patients with familial chylomicronemia syndrome (FCS), a rare genetic disease characterized by extreme elevation of triglycerides and propensity for acute pancreatitis [6,10]. In addition, volanesorsen was evaluated in subjects with multifactorial chylomicronemia and partial lipodystrophy, and

 

olezarsen was assessed in patients with moderate hypertriglyceridemia at high CV risk [7,8,11]. Plozasiran was evaluated in patients with severe hypertriglyceridemia and mixed hyperlipidemia [13,14]. Finally, zodasiran was evaluated in one trial of patients with mixed hyperlipidemia [15].

## Effects of inhibitors of APOC3 and ANGPTL3 on fasting triglycerides and other lipoproteins

While no head-to-head trials exist between different agents targeting APOC3 and ANGPTL3, comparison of their effects on lipoproteins using the maximum effective dose of each drug may give an idea about their relative efficacy. The latter also varies according to baseline lipid levels and type of underlying disease (table1). In terms of triglycerides reduction, volanesorsen seems to be the most effective drug leading to a maximum mean decrease of 77% in fasting triglycerides relative to baseline [6,7].

Compared with placebo, mean reductions of fasting triglycerides of 62% were achieved by plozasiran, 63% with zodasiran and 53% with olezarsen [10-15] (table 1). As expected from their mechanisms of actions, the APOC3 inhibitors: volanesorsen, olezarsen and plozasiran, lowered levels of APOC3 by 74 to 84%, whereas the ANGPTL3 inhibitor zodasiran decreased ANGPTL3 levels by 74% with its highest dose. [10-15] (table 1). In addition, the 4 drugs had generally beneficial effects on other lipoproteins. Thus, they lowered non-HDL-C levels by 18% to 46% (table 1). However, the above agents exert several undesirable effects on lipid profile. These effects are discussed below under "Safety of APOC3 and ANGPTL3 inhibitors".

## Effects of APOC3 inhibitors on incidence of acute pancreatitis

One clinical benefit demonstrated by APOC3 inhibitors was the prevention of acute pancreatitis induced by severe hypertriglyceridemia (i.e., fasting triglycerides > 500 mg/dl). In an analysis of 3 trials of patients with serum triglycerides > 500 mg/dl, acute pancreatitis occurred in 2% (n=2) and 10% (n=9) of patients randomized to volansorsen and placebo, respectively; odds ratio, 0.18; 95% CI, 0.04 to 0.82) [9]. Regarding olezarsen, 2 episodes of acute pancreatitis occurred in 2 patients randomized to olezarsen compared with 11 episodes in 7 patients receiving placebo; rate ratio 0.12 (95% CI, 0.02 to 0.66) [10]. In another randomized trial including patients with severe hypertriglyceridemia (mean baseline fasting triglycerides levels 897 mg/dl), plozasiran use was associated with tendency towards low frequency of acute pancreatitis, 1 of 165 patients in the plozasiran group versus 2 of 61 in the placebo group; odds ratio 0.18; 95% CI, 0.02 to 2.02) [14]. Taken together, available data suggest that APOC3 inhibitors are effective in decreasing incidence of acute pancreatitis as result of lowering circulating triglyceride concentrations.

## Safety of APOC3 and ANGPTL3 inhibitors

### Injection site-related adverse events

All APOC3 and ANGLPT3 inhibitors are given subcutaneously at different time intervals (table 1). Local injection site-related adverse effects were mild and did not lead to drug discontinuation except with volanesorsen. Thus, these reactions occurred in up to 18% of volanesorsen-treated patients (versus 0% with placebo) and were the cause of drug discontinuation in 12% of subjects [7]. Mild injection site reactions were more common with olezarsen compared with placebo; 14% and 9%, respectively [11]. In case of zodasiran, injection-site reactions occurred in 4-6% of patients versus 2% with placebo [15]. Injection-site reactions were not reported in association of use of plozasiran [13,14].

### Thrombocytopenia

Thrombocytopenia (normal platelet count in most laboratories is 160,000-360,000/µl) was the main concerning adverse effect related to use of volanesorsen. Thus, in one trial of patients with FCS, platelet number dropped to below 100,000/µl in 15 of 33 (48%) of patients receiving volanesorsen but in no patients receiving placebo [6]. In addition, 2 patients had severe thrombocytopenia with platelets number dropping below 25,000/µl [6]. Thrombocytopenia was the main cause of rejection of volanesorsen approval by the Federal Drug Administration (FDA) [16]. However, volanesorsen was approved since 2019 by the European Union and UK under the trade name Waylivra, for treatment of FCS [17]. Thrombocytopenia is milder and less common with olezarsen with platelet count < 140,000/µl occurring in 18% of patients taking olezarsen versus 3% with placebo, risk ratio 6.8 (95% CI, 0.91 to 51.1; P=0.03) [11]. No patient taking olezarsen had platelet count < 75,000/µl [11]. Both olezarsen and volanesorsen have the same nucleotide sequence and backbone chemical structure [10,16]. Yet, oleszarsen is conjugated to a carbohydrate ligand, triantennary N-acetylgalactosamine ($GalNAc_3$), for asialoglycoprotein receptors that are abundant on the

 

surface of hepatocytes. Thus, $GalNAc_3$ facilitates the entry of olezarsen to the nuclei of hepatocytes [10,16]. The enhanced hepatic uptake of olezarsen by $GalNAc_3$ results in using lower dosing and injection volume and longer duration of action, and therefore less frequency of administration, when compared with volanesorsen (table 1). Thus, the liver-specific uptake of olezarsen virtually decreases the chance of adverse effects such as thrombocytopenia compared with volanesorsen [16]. Thrombocytopenia was not reported with plozasiran and zodasiran [13-15].

### Worsening glycemic control

Deterioration of glycemic status was observed with the use of the 2 siRNA plozasiran and zodasiran despite different targets, APOC3 and ANGPTL3, respectively (table 1) [13-15]. The mechanism of worsening glycemic control is unclear. Insulin resistance, as measured by the Homeostatic Model Assessment for Insulin Resistance (HOMA-R), was not significantly changed with plozasiran [13,14] or zodasiran [15]. Rosenson et al [15] speculated that increased hepatic gluconeogenesis due to increased substrate delivery to the liver could be one underlying cause of worsening glycemic control but this mechanism requires further studies.

### Elevation of hepatic transaminases

The most common adverse effects of olezarsen were elevation of liver transaminases occurring in 47%, 37%, and 3% with olezarsen 50-mg, 80-mg, and placebo, respectively ($P<0.001$) [10,11]. Yet, elevation of transaminases more than 3-fold was uncommon (2-7% with olezarsen versus 0% with placebo [11].

### Undesirable effects on lipid profile

While significant reductions in levels of fasting triglycerides and atherogenic lipids such as non-HDL-C occur with use of volanesorsen, olezarsen, ploziran and zodasiran, some undesirable effects on lipid profile should be emphasized. First, both volanesorsen and olezarsen significantly increase levels of LDL-C (table 1) [6,7,10]. The elevation in LDL-C values was more evident with volanesorsen reaching up to 136% increase versus baseline in patients with FCS who were characterized by low plasma concentrations of LDL-C levels (approximately 30 mg/dl) [6]. Second, volanersorsen increases levels of the atherogenic ApoB in patients with FCS by 20% [6]. The effects of olezarsen on ApoB levels were variable; an increase of 18% in patients with FCS and a decrease of 18% in patients with hypertriglyceridemia and increased CV risk [10,11]. Third, zodasiran lowers HDL-C levels by approximately 25% (table 1) [15].

## Advantages and limitations of APOC3 and ANGPTL3 inhibitors

### Advantages

The 4 above-mentioned APOC3 and ANGPTL3 inhibitors have the following advantages. First, their high efficacy in lowering mean triglycerides levels by 53% to 66% versus placebo and by 77% versus baseline (table 1). Second, this reduction in serum triglycerides occurred on top of other medications given to lower triglycerides such as N-3 fatty acids, fibrates and statins without evidence of attenuation of their efficacy or drug interaction [7,11-15]. Third, volanesorsen, olezarsen and plozasiran proved effective in lowering the incidence of hypertriglyceridemia-induced acute pancreatitis (table 1) [9,10]. Fourth, their relatively infrequent subcutaneous administration once every 4 weeks (olezarsen) or every 12 weeks (ploziran and zodasiran) should facilitate patient's adherence with therapy.

### Limitations

APOC3 and ANGPTL3 inhibitors suffer from the following limitations. First, their effects on CV events are not studied. Second, their safety beyond 1 year is unknown, particularly with respect to their effects on liver function, platelet number and incidence of diabetes. Third, they were not evaluated in different ethnic groups such as African Americans and Asians who might have different responses. Fourth, subcutaneous administration and its attendant skin reactions may not be acceptable for some patients. Fifth, their high costs will be an obstacle to many patients. Advantages and limitations of the APOC3 and ANGPTL3 inhibitors are summarized in table 2.

 

**Table 2:** Advantages and limitations of agents targeting APOC3 and ANGPTL3 for treatment of hypertriglyceridemia

| | Advantages | Limitations |
|---|---|---|
| Volanesorsen | Highly effective in lowering triglycerides and prevention of acute pancreatitis | Can cause severe thrombocytopenia and frequent injection site reactions, increase LDL-C. injected once weekly during the first 3 months then once q2 weeks [17]. |
| Olezarsen | Effective in lowering triglycerides, injected once every 4 weeks, effective in preventing pancreatitis | Increases hepatic transaminases, may cause mild thrombocytopenia |
| Plozasiran | Injected q12 weeks, effective in preventing pancreatitis | Worsening glycemic control |
| Zodasiran | Injected q12 weeks | Decreases HDL-C, worsening of glycemic control |

*Abbreviations: LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol*

## Conclusions and current needs

No doubt, the inhibitors of APCO3 and ANGPTL3 represent a step forward for treatment of severe forms of hypertriglyceridemia in which no effective therapy is currently available. The 4 agents discussed above are characterized by high efficacy in lowering triglycerides of various causes by more than 50%. Moreover, volanesorsen, olezarsen and plozasiran may prevent hypertriglyceridemia-induced acute pancreatitis. In general, short-term safety of these agents is reassuring, except for volanesorsen which causes severe thrombocytopenia. Long-term randomized clinical trials are urgently needed to study the effects of this novel treatment of hypertriglyceridemia on CV events and mortality. These trials should represent various ethnic groups and include patients with co-morbidities such as diabetes, obesity, chronic kidney and liver diseases. In addition, pertinent safety concerns should be closely monitored in these trials as pre-specified adverse effects such as thrombocytopenia and hepatotoxicity with olezarsen and incidence of diabetes and exacerbation of glycemic control with ploziran and zodasiran.

### Conflict of interest

The authors do not have any conflicts of interest to declare

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