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REVIEW ARTICLE

Appraisal of Olezarsen for Treatment of Hypertriglyceridemia

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Abstract

Olezarsen is antisense antinucleotide under investigation that inhibits synthesis of apolipoprotein C3 (ApoC3) resulting in reduction of plasma triglycerides levels. In a phase 3 clinical trial of patients having familial chylomicronemia syndrome (FCS) with extreme hypertriglyceridemia at baseline (mean plasma triglycerides 2,630 mg/dl), olezarsen 80 mg administered subcutaneously every 4 weeks decreased triglycerides by 43.5 percentage points (95% CI, 69.1 to 17.9; P<0.001) after 6 months compared with placebo. By 53 weeks, 1 episode of acute pancreatitis occurred in olezarsen group versus 11 episodes in the placebo group, rate ratio (RR) 0.12 (95% CI, 0.02 TO 0.66). Two phase 2 trials evaluated olezarsen in patients with moderately elevated triglycerides (<500 mg/dl) and high cardiovascular (CV) risk recorded similar magnitude of reduction of triglycerides. Olezarsen reduced levels of atherogenic lipoproteins such as ApoC3 by 73%, non-high-density lipoprotein cholesterol (non-HDL-C) by 17-23% and increased high-density lipoprotein cholesterol (HDL-C) levels by 30-40%. Meanwhile, olezarsen increased mean values of low-density lipoprotein (LDL-C) from 22.8 to 37.6 mg/dl in patients with FCS but had no significant effects in patients with high CV risk having higher baseline LDL-C levels. Discontinuation rates due to adverse effects of olezarsen were 9-12% versus 0% with placebo. The most common adverse effects of olezarsen were elevation of liver enzymes, mostly below 3 times the upper limit of normal, and injection-site reactions. Platelet count < 140,000/µl occurred in 18% in patients receiving olezarsen versus 3% with placebo (risk ratio 6.8; 95% CI, 0.91 to 51.3; P=0.03). No patient had severe thrombocytopenia with platelet number < 75,000/µl. Overall, olezarsen is a promising new therapy for hypertriglyceridemia and for prevention of hypertriglyceridemia-induced pancreatitis. Long-term randomized trials are urgently needed to examine the effects of olezarsen on CV events and mortality and establish its long-term safety.

Key Words: *Olezarsen; Hypertriglyceridemia; Apolipoprotein C3; Pancreatitis; Volanesoresen*

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Introduction

APOC3 is a 79 amino acid glycoprotein synthesized in the liver and to a lesser extent by enterocytes, that is transported in the circulation on the surface of plasma lipoproteins, mainly triglyceride-rich lipoproteins [1]. APOC3 increases plasma triglycerides by potent inhibition of lipoprotein lipase (LPL), the enzyme responsible for hydrolysis and clearance of triglycerides from the circulation [1]. In addition, APOC3 increases plasma triglycerides through LPL-independent pathway by reducing hepatic clearance of the remnants of triglyceride-rich lipoproteins [2]. Importantly, APOC3 concentrations may be associated with increased CV risk [3]. Indeed, 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]. Moreover, mutation carriers had 40% reduced risk of coronary artery disease compared to non-carriers [4]. However, subsequent studies have shown that the cardioprotective effects of loss-of-function APOC3 mutations were not present in several ethnic groups such as Asian Indians and that African Americans had low levels of plasma APOC3 and triglycerides irrespective of their genotype [5]. Olezarsen (code ISIS 678354) is an anti-sense oligonucleotide targeting APOC3 messenger ribonucleic acid (mRNA) under investigation [1]. By inhibition of APOC3, olezarsen reverses the hypertriglyceridemia induced by ApoC3. The mean terminal elimination half-life of olezarsen is approximately 3 to 6 weeks independent of dose, making it suitable for subcutaneous administration every 4 weeks [6]. The main purpose of this review is to provide a critical appraisal on olezarsen as a novel therapy for hypertriglyceridemia based on the available studies discussed below.

Methods and Statistical Analysis

PubMed search was conducted until June 26, 2024. Search terms were olezarsen, volanesorsen, apolipoprotein C3, triglycerides, pancreatitis, safety. Randomized clinical trials, reviews, expert opinions, and pertinent animal studies were reviewed. No original statistical analysis was performed in this review as all data were presented unchanged from corresponding studies.

Effects of olezarsen on incidence of acute pancreatitis in familial chylomicronemia syndrome

FCS is a rare genetic disease characterized by extreme hypertriglyceridemia (> 880 mg/dl) due to loss of LPL activity due to biallelic loss-of-function (LOF) mutations in the gene encoding LPL or related genes essential for LPL function [7]. In a double-blind, phase 3 trial, Stroes et al [8] randomized 66 patients with the FCS to 3 groups. Group 1 (n=22) was assigned to olezarsen 80-mg q4weeks, group 2 (n=21) was assigned to 50-mg q4weeks (n=21) and group 3 (n=23) to matching placebo for 49 weeks [8]. Mean age of patients was approximately 45 years, 57% women, and 85% were Whites. At baseline, their mean plasma levels of fasting triglycerides were 2,630 mg/dl [8]. After 6 months, the difference between the 80-mg olezarsen group and placebo group in the percent change in fasting triglycerides, the first primary endpoint, was 43.5 percentage points (95% CI, -69.1 to –17.9; $P < 0.001$) [8]. The corresponding difference with the 50-mg dose of olezarsen (the second primary outcome) was not statistically significant being -22.4%

(95% CI, -47.2 to 2.5; P=0.08) [8]. At 6 months, placebo-corrected difference in fasting levels of APOC3, a secondary endpoint, were -73.7 percentage points (95% CI, -94.6 to -52.8) and -65.5 percentage points (95% CI, -82.6 to -48.3) with the 80-mg and 50-mg doses, respectively [8]. The previous reductions in circulating triglycerides and APOC3 concentrations were maintained at 12 months [8]. Patients with FCS are prone to develop acute pancreatitis [7]. The latter was one of the study secondary outcomes. In fact, 71% of patients included in the study had history of acute pancreatitis within the previous 10 years. By 53 weeks, 11 episodes of acute pancreatitis occurred in the placebo group (in 7 patients) compared with 2 episodes in the olezarsen groups (1 episode with 80-mg and 1 episode with 50-mg); RR 0.12 (95% CI, 0.02 to 0.66) [8].

Olezarsen for hypertriglyceridemia in patients with high cardiovascular risk

Two phase 2 randomized trials evaluated olezarsen in patients with moderate hypertriglyceridemia (defined as fasting triglycerides 150-499 mg/dl) who had documented CV disease or increased CV risk (defined as presence of type 2 diabetes, or at least 2 CV risk factors such as men ≥ 55 years of age or women ≥ 65 years, current tobacco use, family history of CV disease, LDL-C ≥ 160 mg/dl) [9,10]. Table 1 depicts an overview of the design and main results of the phase 3 trial and the 2 phase 2 trials of olezarsen. In the study of Bergmark et al [9], the 50-mg and 80-mg doses of olezarsen decreased triglycerides levels at 6 months by 49.3 percentage points and 53.1 percentage points, respectively, as compared with placebo (P < 0.001). Most of the effect of olezarsen on reducing circulating triglycerides occurred after 1 month i.e. after a single dose of the drug and persisted through 12 months of follow-up [9]. Moreover, the degree of triglyceride lowering was consistent in subgroups of patients classified by age, sex, body mass index, diabetes status, and fibrate therapy [9]. In the second phase 2 trial by Tardif et al [10], multiple dose regimens of olezarsen were used

Table 1. At 6 months, the 50 mg-dose q4 weeks reduced triglycerides by 60 percentage points compared with an increase of 6 percentage points with placebo (P < 0.0001) [9]. Taken together, the 3 trials suggest that olezarsen lowers triglycerides by approximately 43 to 60 percentage points [8-10].

Effects of olezarsen on apolipoprotein C3 and other lipoproteins

As result of inhibition of APOC3 mRNA expression by olezarsen, ApoC3 levels were significantly decreased by olezarsen by approximately 73 percentage points vs placebo at 6 months [8-10]. In addition, compared with placebo, there were significant reductions in several atherogenic lipoproteins with olezarsen such as very-low density lipoproteins (VLDL), non-HDL-C and apolipoprotein B (APOB) by 49%, 23%, and 18.5%, respectively [9]. Moreover, olezarsen increased HDL-C levels at 6 months by 30-40% with either 50 mg or 80 mg olezarsen (P<0.0001) Table 1 [9,10]. However, in patients with FCM having low baseline LDL-C, olezarsen (80 mg) significantly increased LDL-C levels from 22.8 mg/dl to 37.6 mg/dl at 6 months and increased the APOB from 58.4mg/dl to 69.0 mg/dl [8]. Meanwhile, it was reassuring that olezarsen had neutral effects on LDL-C concentrations in patients with high CV risk having mean baseline LDL-C levels in the range of 69-88 mg/dl [9,10].

TABLE 1

Overview of the 3 randomized trials of olezarsen

Doses of olezarsen 50 mg or 80 mg were given once q4 weeks subcutaneously. P values are versus placebo.

Reference	Stroes et al [8]	Bergmark et al [9]	Tardif et al [10]
Design	Phase 3, randomized, double-blind, placebo-controlled (n=66), multi center in 11 countries	Phase 2b, randomized, double-blind, placebo-controlled (n=154), multicenter in the US and Canada	Phase 2, randomized, double-blind, placebo-controlled, dose-ranging (n=114), multicenter in the US and Canada
Duration of intervention	49 weeks	12 months + 13-week follow-up	12 months + 13-week follow-up
Age, sex	Mean 44 years, 60% women	Median 62 years, 42% women	Median 65 years, 40% women
Disease types	Familial chylomicronemia syndrome	90% with high CV risk and 10% with triglycerides > 500 mg/dl, 67% with type 2 diabetes	80% with established ASCVD, 20% at high risk for ASCVD
Baseline median triglycerides (IQR), mg/dl	2,086 (683-6898) in the 80 mg-group	241 (179-357)	262 (222-314)
Placebo-corrected change in triglycerides after 6 months using maximum effective dose	-43.5% (95% CI, -69.1 to -17.9; P< 0.001) with 80 mg, and -22.4% (95% CI, -47.2 to 2.5; P=0.08) with 50 mg (non-significant)	-53.1% (95% CI, 43.4 to 62.9: P<0.001) with 80 mg (n=57), and -49.3% (95% CI, 39.5 to 59.0; P<0.001) with 50 mg (n=58)	-66% with 50 mg (n=22) (P<0.0001)
Placebo-corrected change in apolipoprotein C3 after 6 months	-73.7% (95% CI, 52.8 to 94.6; P<0.001) with 80 mg and 65.5% with 50 mg (95% CI, 48.3 to 82.6; P<0.001)	-73.2% (95% CI, 62.5 to 83.9; P<0.001) with 80 mg and 64.2% with 50 mg (95% CI, 53.6 to 74.7; P<0.001))	-74% (95% CI-80 to -66; P<0.0001) with 50 mg
Placebo-corrected change in non-HDL-C after 6 months	-17.7% (95% -34.6 to -8.0) with 50 mg	-23.1% (95% CI, -34.0 to -12.1; P< 0.0001) with 80 mg, -25% (95% CI, -36.3 to -14.5; P<0.0001) with 50 mg	-20% with 50 mg (n=22) (P=0.0009)
Placebo-corrected change in HDL-C after 6 months	Not reported	39.6% (95% CI, 26.6 to 52.6; P<0.0001) with 80 mg, 39.6% (95% CI, 26.7 to 52.6; P<0.0001) with 50 mg	30% with 50 mg (P<0.0001)
Placebo-corrected change in LDL-C after 6 months	LDL-C increased from 22.8 mg/dl to 37.6 mg/dl with 80 mg, and from 16.7 mg/dl to 18.1 mg/dl. Statistical significance not reported	-7.7% (95% CI, -24.2 to 8.7, P=0.36) with 80 mg and -9.9% (-26.3 to 6.6; P=0.24) with 50 mg, both non-significant	10% (P=0.28), non-significant
Comments	Reduction in incidence of acute pancreatitis, 2 episodes with olezarsen vs 11 episodes with placebo	Reduction of triglycerides was consistent in subgroups classified by age, sex, severity of hypertriglyceridemia, diabetes, and fibrate therapy.	Different dose regimens were used: 10 mg qweek, 15 mg q2 weeks, 10 mg or 50 mg q4 weeks.

Abbreviations: ASCVD: atherosclerotic cardiovascular disease, IQR: interquartile range, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol.

Effects on lipoprotein particle size

The Olezarsen Trial Investigators analyzed the effects of olezarsen on lipoprotein particle size by nuclear magnetic imaging (NMR) in patients enrolled in the phase 2 trial of Bermark et al mentioned above [9,11]. Although olezarsen (50 mg q4 weeks) had no significant effects on LDL-C concentrations, the drug increased LDL particle size by 2.7% vs 0.5% with placebo after 6 months (P=0.003) [11]. This effect could potentially be of clinical benefit since the smaller LDL-C particles are more atherogenic than larger ones [12,13]. In the same analysis, compared with placebo, olezarsen led to a reduction in concentrations of large-sized and medium-sized triglyceride rich remnants and to an increase in concentrations of small HDL-C particles [11]. The association between HDL particle size and CVD is still a matter of debate but a large study using NMR showed that small HDL particles were associated with decreased mortality [14]. The shift to larger LDL particles and increase in smaller HDL particles by olezansern might potentially decrease atherogenicity of the lipid profile. However, this concept must be confirmed by demonstration of reduction in CV events by olezarsen in future trials.

Effects of Olezarsen on Glycemic Control and Inflammatory Markers

Olezarsen had no significant effects on glycemic control or inflammation as reflected by levels of glycated hemoglobin and C-reactive protein, respectively [9,10].

Safety of olezarsen

Discontinuation rates due to adverse effects of olezarsen were higher than placebo and for unclear reasons were not dose-related. Thus, discontinuation rates were 12%, 5% and 0% with the 50-mg dose, 80-mg dose, and placebo respectively, (P=0.04; 50-mg dose versus placebo) [9]. In the trial of FCS, corresponding rates were 9%, 5%, and 0% (P value not reported) [8]. 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) [9]. Yet, elevation of transaminases more than 3-fold was uncommon (2-7% with olezarsen versus 0% with placebo [9]. Thrombocytopenia was an adverse effect of special interest since it was reported with the related drug volanesorsen (see below). Decrease in platelet count < 140,000/µl (normal range in most laboratories 160,000-360,000/µl) was recorded in 18% of patients taking olezarsen versus 3% with placebo, risk ratio 6.8 (95% CI, 0.91 to 51.1; P=0.03) [9]. Platelet count < 100,000/µl occurred in 5% of patients receiving 80-mg olezarsen, 3% of patients receiving placebo and in none of subjects receiving 50 mg olezarsen [9]. No patient taking olezarsen had platelet count < 75,000/µl. Mild injection site reactions were more common with olezarsen compared with placebo 14% and 9%, respectively [8].

Volanesorsen versus olezarsen

Volanesornen is another antisense oligonucleotide targeting APOC3 mRNA and is considered the parent drug of olezarsen [1]. Table 2 depicts the main differences between olezarsen and volanesorsen. Both olezarsen and volanesorsen have the same nucleotide sequence and backbone chemical structure [8]. 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 [1,8]. Interestingly, 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 [1,15-17]. Moreover, the liver-specific uptake of olezarsen virtually decreases the chance of adverse or off-target effects [1]. Despite the absence of head-to-head comparison of these 2 antisense antinucleotides, volanesorsen seems more effective than olezarsen in lowering fasting triglycerides Table 2. Volanesorsen was approved by the European Union and the UK for the treatment of familial chylomicronemia syndrome. However, the Federal Drug Administration (FDA) in the US rejected volanesornen approval because of increased rates and severity of thrombocytopenia. 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 [16]. In addition, 2 patients had severe thrombocytopenia with platelets number below 25,000/µl [16]. Injection-side adverse effects seemed to be more common and more severe with volanesorsen than olezarsen, Thus, 12% (9 of 75) of patients discontinued volanesorsen due to injection site adverse effects versus none with placebo [17]. With the use of olezarsen, no discontinuation due to injection site reactions were reported.

TABLE 2

Volanesornen versus olezarsen

	Olezarsen [8-10]	**Volanesorsen [16,17]**
Drug profile	Anti-sense antinucleotide conjugated to ($GalNAc_3$) to enhance hepatic cell uptake	Similar anti-sense antinucletide sequence but unconjugated
Magnitude of reduction of triglycerides	43%-66% vs placebo at 6 months	73%-77% at 3 months vs baseline
Frequency of subcutaneous administration	Once every 4 weeks	Once weekly
Percentage of patients with platelet count <100,000/µl in FCS	Not reported	45% volanesorsen vs 0% with placebo
Percentage of patients with platelet count <100,000/µl in patients with multifactorial CS	Not reported	12% volanesorsen vs 3% with placebo (in patients with multifactorial chylomicronemia syndrome)
Percentage of patients with platelet count <100,000/µl in patients at high CV risk	5% of patients with 80-mg olezarsen (80 mg) vs 3% with placebo	Not studied
Frequency of injection site skin reactions	14% vs 9% with placebo	12% vs 0% with placebo (CompASS)
Approval status	Was granted fast-track designation by FDA	By European Union, in the UK and Brazil

Abbreviations: $GalNAc_3$: triantennary N-acetylgalactosamine, FCS: familial chylomicronemia syndrome, CS: chylomicronemia syndrome, CV: cardiovascular, FDA: Federal drug administration

Advantages of olezarsen

Olezarsen has several advantages. First, its high efficacy in lowering triglycerides by approximately 43% to 66%

Table 1. Second, the drug proved effective in lowering the incidence of hypertriglyceridemia-induced acute pancreatitis in patient with FCS [8]. Third, its relatively infrequent subcutaneous administration once every 4 weeks should facilitate adherence.

Disadvantages of olezarsen

Olezarsen suffers from the following drawbacks. First, effects of olezarsen on CV events are not studied. Second, its safety beyond 1 year is unknown, particularly with respect to its effects on liver function and platelet number. Third, it was not evaluated in different ethnic groups such as African Americans, Asians who may have different responses.

Limitations of this Review

The limitations of this review reflect those of the available studies mentioned above. Thus, overall data is restricted to 3 clinical trials that evaluated limited number of patients, mainly of White ethnicity Table 1. Long-term safety and efficacy of olezarsen beyond 1 year are not known. In addition, no data is available regarding the cost effectiveness of olezarsen compared to other available drugs that lower triglycerides such as fibrates and fish oil.

Clinical Implications and Current Needs

While olezarsen has not been approved yet by the FDA, available data suggest that this drug may be indicated in cases of hypertriglyceridemia of severe (triglycerides > 500-880 mg/dl), and extreme degree (triglycerides > 880 mg/dl) not responding to lifestyle changes and traditional medications such as fibrates, fish oil, and niacin. In addition, another important indication would be the prevention of triglyceride-induced acute pancreatitis [8]. Long-term and adequately powered clinical trials are required to examine the impact of olezarsen on CV morbidity and mortality in patients with hypertriglyceridemia. Such trials should be sufficiently large to investigate the effects of olezarsen in different subgroups of patients including those with diabetes, CV, hepatic and kidney disease. In terms of safety, special attention should be directed in future studies towards the effects of olezarsen on platelet number and liver function tests.

Conclusion

No doubt, olezarsen is a promising agent for treatment of hypertriglyceridemia and prevention of associated pancreatitis. Overall, the drug is effective on short-term. Further studies are required to determine the best candidate patients who may get the most benefits from it and to clarify its long-term safety and efficacy.

Conflict of Interest

The author does not any conflict to declare.

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