Exploring volanesorsen: a promising approach to preventing acute pancreatitis in severe hypertriglyceridemia

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Introduction

Alexander *et al.* recently discussed a novel treatment approach for preventing acute pancreatitis (AP) in patients with severe hypertriglyceridemia (sHTG) (1). sHTG is established with a triglyceride (TG) quantity of ≥500 mg/dL according to American literature (2,3). Research indicates it is reasonable to target fasting serum TG below 500 mg/dL to prevent hyper triglyceridemic pancreatitis (4). It is a significant risk factor for AP and contributes to approximately 10% of pancreatitis cases. The risk of AP is proportional to the plasma levels of TG-rich lipoproteins and chylomicrons (5).

The classical reason for increased TG is multifactorial chylomicronemia (MCM). This state is induced by gene modifications and by nourishment containing too much adipose tissue and simple carbohydrates. Other states induce MCM too are overweight, drinking ethanol, and uncontrolled diabetes (6).

Although the Food and Drug Administration (FDA) has granted approval for fibrates, n-3 fatty acids, and niacin to treat sHTG, the evidence substantiating their effectiveness in reducing the occurrence of AP remains inadequate. Furthermore, there is a notable absence of evidence indicating a decreased incidence of AP among patients undergoing pharmacologic interventions to lower TG levels (1).

Investigating the role of apolipoprotein C-III (apo-CIII) in contemporary studies

Apo-CIII is a little glycoprotein made up of 79 amino acids, conceal by the *APOC3* gene. It raises TG by lowering lipoprotein lipase (LPL) activity, impede TG elimination from the plasma, boost liver very-low-density lipoprotein (VLDL) production going into the plasma, and promoting foster sub-endothelial storage of low-density lipoprotein (LDL) (7). Research has indicated that mutations causing loss of function in the *APOC3* gene are associated with low TG levels and a reduced risk of ischemic cardiovascular disease (8,9). Consequently, seeking a treatment targeting

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APOC3 to reduce apo-CIII concentrations and TG levels was a logical step in sHTG treatment development. Volanesorsen, the first antisense oligonucleotide planned to aim APOC3, handle by impeding APOC3 mRNA, leading in a cutting of apo-CIII production by liver cells (10).

To the best of our knowledge, there are three major clinical trials on volanesorsen in the literature. The APPROACH study, the initial phase 3 patient study on volanesorsen, was a multi-center, double-blind, randomized, placebo-controlled carried out on 66 patients during a 52-week interval. Its objective was to determine whether the use of volanesorsen was related with a reduction in TG amounts compared to placebo in patients with MCM. At 90 days, patients receiving volanesorsen 300 mg once a week showed a 77% decrease in TG amounts, compared to an 18% rise in the placebo group. The treatment effects of volanesorsen were sustained for 6 months, at which time TG levels were lower by a mean of 53% in the volanesorsen group, compared to a 25% mean increase in the placebo arm. At 12 months, TG amounts were lowered by 40% in the volanesorsen arm, whereas amounts in the placebo arm raised increased by 9%. The placebo arm did undergo AP episodes, with five episodes in three patients, while the treatment arm group did not undergo any such episodes (11).

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The COMPASS trial, another pivotal study, was a multi-center, randomized, double-blind, placebo-controlled study realized in 114 patients with fasting plasma TG >500 mg/dL over a period of 52 weeks. The aim was to examine if treatment with volanesorsen, compared to placebo, was correlated with lower plasma TG in patients with MCM. After three months, they observed a 71.2% reduction in mean plasma TG from baseline in patients receiving volanesorsen 300 mg once a week, correlated with a 0.9% rise in the placebo arm (P<0.0001). These data were in agreement with the findings of the APPROACH study. Additionally, a significant diminution in the volanesorsen arm was seen regarding other lipid measurements such as chylomicron TGs, apo-B48, VLDL-cholesterol (VLDL-C), and non-high-density lipoprotein cholesterol (non-HDL-C) (12). These data were also in agreement with those of the APPROACH study (11,12).

The OLE-APPROACH study, an open label extension of the APPROACH study, was a phase 3 trial designed to evaluate the efficacy and safety of long-term volanesorsen treatment in three patient groups with familial chylomicronemia syndrome (FCS) (13). Key endpoints included changes in fasting TG and other lipid parameters, as well as safety, over 52 weeks. The first group consisted of patients from the APPROACH (n=44) trial, where volanesorsen bring down TG amounts from index study baseline by 48%, 55%, 50%, and 50% at months 3, 6, 12 and 24, respectively. The second group included COMPASS study participants (n=5), with diminutions of 65%, 43%, 42%, and 66% at months 3, 6, 12 and 24, respectively. The third group consisted of treatment-naive population with patients who had not be part in either study where diminutions of 60%, 51%, 47%, and 46% were seen at the same intervals (13). These diminutions were under the primary efficacy time point of related trials (77.0% in APPROACH and 71.2% in COMPASS), and volanesorsen's effectiveness seemed to diminish over time in the treatment-naive population. Dose reductions or treatment pauses due to thrombocytopenia during the trial might explain this phenomenon, with 65% having once week doses bring down every 2 weeks and 75% undergo a dose cessation (10-13).

Regarding the BROADEN study, this was a randomized, placebo-controlled, phase 2/3, 1 year trial with open-label prolongation and post follow-up periods. Patients obtain once a week subcutaneous volanesorsen 300 mg versus placebo. The primary goal was the percentage difference from baseline in fasting TG after one trimester. Additional goals were looking at the relative percentage modification in liver fat fraction, visceral adiposity, and glycosylated hemoglobin amounts. In the BROADEN study, the least squares mean (LSM) percentage modifications in fasting TG amounts from baseline to 3 months demonstrated a diminution of 88% in the volanesorsen arm versus a decrease of 22% in the placebo arm, with a net difference of 67% in favor of volanesorsen treatment. Similar results were seen at 6 and 12 months, with an 81% decrease in the volanesorsen group versus a 6% increase in the placebo group after one semester, and a 59% diminution in the volanesorsen arm versus a 7% rise in the placebo arm at 1 year (14). In the BROADEN study, volanesorsen significantly reduced serum TG amounts and liver steatosis in patients with familial partial lipodystrophy.

In all these studies, the primary endpoint was a diminution in TG amounts, and they all concluded a significant diminution among patients treated with

volanesorsen. Meanwhile, AP incidence was a secondary or exploratory endpoint in these studies.

Meta-analysis of volanesorsen in preventing AP in hypertriglyceridemia

Alexander *et al.* conducted a fixed-effects meta-analysis, utilizing individual patient data from APPROACH, COMPASS and BROADEN studies. The primary objective was a comprehensive evaluation of volanesorsen's impact on AP incidence in individuals with sHTG (1). All three studies were randomized controlled trials, involving patients with TG levels exceeding 500 mg/dL (11-13). AP evaluation followed the revised Atlanta criteria by an independent committee (15).

In this meta-analysis, demographic characteristics and baseline lipid profiles exhibited uniformity across trial groups. Notably, 40% in the volanesorsen group and 51% in the placebo group had a history of pancreatitis before randomization, correlating with mean (± standard deviation) fasting TG levels of 1,543±1,060 and 1,714±1,273 mg/dL, respectively (1). During randomized treatment, AP manifested in 2% of volanesorsen patients compared to 10% in the placebo group, accounting for 11 of 207 patients [odds ratio, 0.18; 95% confidence interval (CI): 0.04 to 0.82]. Importantly, AP had occurred before randomization in 10 of the 11 patients exhibiting AP during the treatment period (1). The authors concluded that volanesorsen significantly reduced AP incidence among patients with sHTG.

Side effects of volanesorsen

Looking at the BROADEN trial which was an open label randomised controlled study. The study was carried out for a year. Follow up were realized after the treatment period. According to the protocol, one group receive volanesorsen 300 mg by a subcutaneous approach done every week. The control arm receives once a week placebo. The principal outcome looked at the modification in percentage from the start 3 months ago regarding the TG reduction. Additional outcomes were looking at modification in percentage of the liver fat proportion and abdominal organ fraction of fat and glycosylated haemoglobin.

This new drug does carry some unwanted effects. Thrombopenia seems to be the most frequent ones. Other unwanted effects are less in frequency but still equal or above 10%. The gastrointestinal tract has many unwanted effects ranging from belly pain (27%), feeling sick (18%), dysentery (15%), being sick (15%). From the neurological system, we do have sore head (21%), muscular rheumatism (15%). Other unwanted effects are tiredness (21%), nosebleed (15%), upper respiratory tract infection (15%), blood spots (12%), stiffness in a joint (12%), too high blood sugar (12%). Nevertheless, in the control group belly pain (21%), tiredness (9%), sore head (15%), feeling sick (6%), muscular rheumatism (3%), dysentery (6%), being sick (9%) and upper respiratory tract infection (21%) were also present in the control arm (14). In the cohort of treated patients, nine had to stop the medication related to unwanted effects. Five linked to thrombopenia and other due to associated unwanted effects like inflammation on the injection place, tiredness, shivering, sudation and massive swealing (14).

Applying volanesorsen results to bedside care

Despite restricted approval in the US for patients with FCS, volanesorsen proves effective for sHTG. However, off-target side effects, including injection site reactions and drug-induced thrombocytopenia, hinder its widespread use. This adverse effect can be severe, with an unclear underlying mechanism (10). Following the APPROACH trial outcomes, volanesorsen gained approval for genetically confirmed FCS patients in the European Union and the United Kingdom, driven by concerns about its risk-benefit ratio (10,16). Meanwhile, more potent drugs like olezarsen, a third-generation antisense oligonucleotide targeting apo-CIII, might offer a better safety profile than volanesorsen, with no drug-induced thrombocytopenia observed in clinical trials (17,18).

Conclusions

Alexander *et al.*'s exploration of volanesorsen, as a treatment for sHTG shows promise, particularly in preventing AP. The clinical trials highlight its efficacy, though challenges like diminishing effectiveness in treatment-naïve populations and dose adjustments due to thrombocytopenia need attention. The meta-analysis reinforces volanesorsen's role in reducing AP incidence. Despite restricted US approval, its effectiveness for sHTG, coupled with concerns about side effects—like drug-induced thrombocytopenia—underscores the need for ongoing research. Newer

alternatives, like olezarsen may offer improved safety, therefore, the likelihood of volanesorsen becoming a widespread option for preventing AP at the clinical bedside appears to be relatively low. Continued investigation is crucial for optimizing outcomes in affected individuals.

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Footnote

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