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COMMENTARY

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In vivo PCSK9 base editing: From the concept of lifelong lipid lowering to early clinical exploration of one-time therapy

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Management of low-density lipoprotein cholesterol (LDL-C) is one of the most evidence-based fields in the prevention and treatment of cardiovascular disease. Over the past several decades, lipid-lowering therapy has continued to advance, from statins and ezetimibe to monoclonal antibodies targeting proprotein convertase subtilisin–kexin type 9 (PCSK9) including small interfering RNA drugs such as Inclisiran, which profoundly changed the landscape for cardiovascular disease (CVD) prevention.[1-2] However, in the real world, long-term oral medication or repeated injection therapy still faces problems such as poor adherence, financial burden, and treatment discontinuation. For patients with heterozygous familial hypercholesterolemia or premature coronary heart disease, lipid-lowering therapy is often not a short-term intervention, but rather a long-term management that may last for decades. Thus, it remains a great challenge to achieve a safe, potent, and durable LDL-C control in the field of CVD prevention.

Table 1. Comparison of major LDL-C-lowering therapeutic modalities

Therapeutic modality	Potential candidates	Major clinical benefits	Key limitations
Statins with or without ezetimibe	First-line therapy for most patients requiring LDL-C reduction; primary and secondary prevention; FH as background therapy	Oral administration; low cost; extensive randomized outcome evidence; broadly accessible	Long-term adherence required; statin intolerance in some patients; LDL-C may remain above target in very-high-risk patients
PCSK9 monoclonal antibodies	Patients with ASCVD or FH whose LDL-C remains above target despite maximally tolerated therapy	Potent LDL-C lowering; cardiovascular outcome benefit demonstrated in large randomized trials; reversible pharmacological effect	Repeated subcutaneous injections; cost and access barriers; adherence burden over years
siRNA-based PCSK9 inhibition	Patients requiring durable PCSK9 suppression with less frequent dosing; ASCVD or FH with insufficient LDL-C control	Approximately 50% LDL-C reduction with twice-yearly dosing after initial administration; less frequent dosing may improve adherence; no permanent DNA editing	Requires repeated administration; long-term cardiovascular outcome evidence is still evolving; injection-site reactions; effect wanes if treatment is discontinued
In vivo PCSK9 base editing	Potential future option for selected high-risk patients with heterozygous FH, premature coronary artery disease, very-high-risk CVD, persistently elevated LDL-C despite standard therapy, or poor long-term adherence	Single-infusion strategy; potentially durable or permanent PCSK9 suppression; early evidence of substantial LDL-C reduction	Early-phase evidence only; irreversible or long-lasting genomic intervention; off-target and long-term safety unknown; no outcome data yet

The recently published phase 1 Heart-2 study provided a novel approach to this troublesome dilemma. This study evaluated the safety and efficacy of VERVE-102 in adult patients with heterozygous familial hypercholesterolemia or premature coronary artery disease. VERVE-102 was an *in vivo* base-editing therapy with a purpose not to transiently inhibit PCSK9 protein or mRNA expression, but rather to durably inactivate PCSK9 at the DNA level in hepatocytes through a single intravenous infusion, thereby achieving long-term LDL-C reduction.[3]

The theoretical basis for targeting PCSK9 is exceptionally solid. Human genetic studies first found that loss-of-function variants in PCSK9 was associated with lifelong lower LDL-C levels and a substantially reduced risk of coronary heart disease.[4] These early findings suggested that partial lifelong inactivation of PCSK9 can lower serum LDL-C level and reduce CVD risk without noticeable adverse effects. Subsequently, in the FOURIER trial, treatment with Evolocumab reduced serum level of LDL-C to a very low level and significantly reduced cardiovascular events in patients with CVD.[2] By comparison, the key innovative point of VERVE-102 was not choosing PCSK9 as a therapeutic target but converting an already well-validated pharmacological intervention into a one-time somatic genome-editing therapy, thereby transforming a long-term and repeated dosing model into a durable target modulation after a single treatment.

The interim analysis of the Heart-2 study included 35 participants, who received a single intravenous infusion of VERVE-102 at six dose levels ranging from 0.3 to 1.0 mg/kg.[3] The enrolled population had a high cardiovascular risk: most patients had heterozygous familial hypercholesterolemia, the mean baseline LDL-C level was 129 mg/dl, and the majority of patients received statin therapy, with a considerable proportion receiving high-intensity statin therapy.[3] The results of Heart-2 study demonstrated that after VERVE-102 treatment for four weeks, serum PCSK9 levels were decreased in all dose groups with the most significant reduction in the high-dose group. Serum levels of PCSK9 and LDL-C were decreased by an average of 88% and 62%, respectively and the absolute reduction in serum levels of LDL-C was 78 mg/dl.[3] This finding indirectly suggests effective suppression of hepatic PCSK9 expression. Importantly, the magnitude of LDL-C reduction after VERVE-102 treatment was similar to that after a long-term treatment with PCSK9 inhibitors and PCSK9 monoclonal antibody. However, VERVE-102 treatment achieved this goal through a single infusion rather than repeated drug administration or injection.[2-3]

In terms of safety, the early results of VERVE-102 study were generally assuring but require cautious interpretation. No dose-limiting toxicity or death occurred in the study, and all participants completed infusion per protocol.[3] Infusion-related reactions occurred in 20% of participants, with a mild to moderate severity.[3] Nonetheless, the study population was small and it is still premature to be optimistic about the safety of this delivery platform in

patients with CVD. Furthermore, the long-term safety after VERVE-102 therapy remained elusive. As VERVE-102 acts at the DNA level, it may produce long-term or even permanent effects. Unlike traditional lipid-lowering therapies that can be discontinued in case of adverse effects, unintended editing may result in unexpected consequences that may persist for a long time. Therefore, long-term hepatic safety, immune responses, sustained low-PCSK9 exposure, and off-target risks require systematic evaluation. Although preclinical off-target screening in primary human hepatocytes, tissue-distribution assessment in nonhuman primates, and germline-transmission risk assessment in mice were conducted in this study, these safety evidence cannot replace long-term follow-up in a large patient population.

Durability of VERVE-102 efficacy is another important issue. The authors reported that reduction in serum levels of PCSK9 and LDL-C was relatively stable during follow-up; some participants were followed for at least 1 year, and the longest follow-up reached 18 months.[3] However, this study adopted a dose-escalation design, in which the lower-dose groups were enrolled earlier and had longer follow-up, whereas the highest-dose group, although showing the strongest lipid-lowering effect, had a relatively shorter follow-up duration. Therefore, at present, the therapeutic efficacy of VERVE-102 appeared durable within a short period of time, and it remained unknown whether its efficacy can be maintained for several years or even decades.

This study has several limitations. First, this study was a non-prespecified interim analysis, with a sample size of only 35 participants, and therefore may not detect low-frequency serious adverse events. Second, the study population was predominantly Caucasians, and nonclinical off-target screening was mainly based on cells from White donors, which limited extrapolation of safety assertion to populations with different genetic backgrounds. Finally, this study did not design hard clinical endpoints such as cardiovascular death, non-fetal myocardial infarction, and stroke.

The therapeutic role of VERVE-102 in clinical practice deserves further consideration. If future studies confirm its long-term safety and stability of efficacy, VERVE-102 might become the treatment of choice in patients with heterozygous familial hypercholesterolemia, premature coronary heart disease, very-high-risk CVD, hypercholesterolemia unresponsive to conventional lipid-lowering therapy, or poor adherence to drug administration. However, for most patients with hypercholesterolemia but without aforementioned conditions, existing lipid-lowering therapies remain the treatment of choice, as they were supported by a large amount of randomized clinical trials.[1,2] Population-level estimates suggest that heterozygous familial hypercholesterolemia affects approximately 1 in 300 individuals, with substantially higher enrichment among patients with ischemic heart disease or premature ischemic heart disease.[5] However, the proportion ultimately suitable for VERVE-102 cannot yet be defined. VERVE-102 is not intended to correct a specific inherited PCSK9 mutation; rather, it somatically inactivates hepatic PCSK9 by editing a defined splice-site sequence. Thus, suitability will likely depend on clinical risk, residual LDL-C burden, adherence barriers, and the absence of sequence variation interfering with guide-RNA binding, rather than on a particular PCSK9 mutation. Compared with inclisiran, which reduces LDL-C by approximately 50% with twice-yearly dosing and avoids permanent DNA modification, VERVE-102 offers the possibility of a single-course intervention with durable PCSK9 suppression. This advantage must be weighed against irreversibility, off-target risk, long-term safety, and the lack of outcome data (Table 1). Thus, PCSK9 base editing should be viewed as a potential future option for selected high-risk patients rather than a simple replacement for siRNA-based therapy.

Despite these limitations and considerations, the scientific significance of VERVE-102 study should not be underestimated. It represents an important exploration of a new model of lipid-lowering therapy. From the perspective of translational medicine, VERVE-102 study also demonstrated a novel pathway in developing cardiovascular therapeutics: identifying protective targets through human genetic discoveries, validating their clinical applicability through pharmacologic studies, and then mimicking naturally protective variants through *in vivo* base editing. PCSK9 is an ideal testing ground for this strategy, because its genetic evidence, mechanistic basis, and pharmacological validation are all highly robust. In contrast, many cardiometabolic targets may not possess a clear biological basis and a wide safety window. Thus, the successful experience of PCSK9 editing should not be generalized to other targets with lower levels of validation.

In summary, the phase 1 study of VERVE-102 provided early clinical evidence for lowering serum level of LDL-C through single-dose *in vivo* PCSK9 base editing. This study showed that a single infusion of VERVE-102 can produce dose-dependent, substantial, and sustained reduction in serum levels of PCSK9 and LDL-C with preliminarily acceptable safety profile during a short-term follow-up. Larger, randomized, longer-term studies in diverse populations are needed to define safety, durability, off-target risk, and cardiovascular outcomes. Only after these questions are adequately answered may *in vivo* PCSK9 base editing truly enter clinical practice in CVD prevention.

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DECLARATION OF INTERESTS

The authors declare no competing interests.