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Mini Review

RNA-based Therapeutics in Cardiology: Dawn of a New Era?

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Introduction

The COVID-19 pandemic had the inadvertent effect of bringing RNA-based therapeutics on to center stage, as both the Pfizer-BioNTech and Moderna COVID vaccines (BNT162b2 and mRNA-1273, respectively) were made of mRNA species that were chemically modified and encapsulated in lipid-nanoparticles to elicit a robust protective immune response against SARS-Co-V-2 virus. With this newfound spotlight, RNA-based drugs may finally get a much-needed breath of new life, as the previously touted therapeutic class with much potential has struggled for years to materialize into practical treatment options in clinical medicine.

It may surprise many who are not in the field of advanced lipidomics that the first commercial oligonucleotide lipid-lowering drug, mipomersen (Ionis Pharmaceutical), received FDA approval almost a decade ago in 2013 for treatment of homozygous familial hypercholesterolemia. It targeted mRNA of ApoB-100 for RNase-H mediated degradation to achieve LDL cholesterol lowering [1]. Mipomersen has failed to gain widespread clinical traction and recognition; this is in part due to concerns over its hepatotoxicity, but more importantly due to the success of monoclonal antibody-based PCSK9 inhibitors, alirocumab and evolocumab. However, the tide may be turning favorably for oligonucleotide drugs thanks to the wide adoption of mRNA-based COVID vaccines. Conceptually, oligonucleotide-based therapeutics have the advantage of being a class of "designer" drugs capable of theoretically targeting any protein by simple sequence permutations on a shared parental carrier backbone. Chemical stability and biocompatibility, which have been their Achilles' heels for decades, are now transforming into an unexpected advantage by conferring a therapeutic durability that is unmatched by any oral agents or antibody-based drug classes. This is exemplified by the drug inclisiran (Alnylam Pharmaceuticals/Novartis), a synthetic siRNA molecule that targets PCSK9 mRNA for degradation and in clinical trials demonstrated steep and sustained LDL suppression with injection every six months [2]. Compared to monoclonal-antibody based PCSK9 inhibitors which required monthly subcutaneous injection, inclisiran can suppress PCSK9 expression for six months or longer and provide the intriguing treatment option of twice yearly, vaccine-like administration to ease of therapeutic access and improve compliance. Another oligonucleotide-based agent that targets lipoprotein (a) or Lp(a) and regulates lipid metabolism is at advanced stages of drug development [3] and may soon become a new therapeutic option in lipid management and cardiovascular risk reduction.

Beyond lipid lowering, oligonucleotide-based drugs are displaying their clinical applicability in an area that has historically been more friendly: genetic diseases. In most cardiovascular diseases, genetic links are frustratingly complex if not outright elusive; ATTR cardiac amyloidosis is a rare exception, having a well-defined causative, heritable and targetable genetic mutation. Moreover, mutated transthyretin, the protein implicated in ATTR amyloidosis that misfolds into fibrils and deposits in places such as neurons and heart muscles, happens to be made in the liver, which is the organ of first-pass uptake and thus the ideal target location for most oligonucleotide-based therapeutic agents. A pair of oligonucleotide drugs, patisiran (Alnylam Pharmaceutical) and inotersen (Ionis Pharmaceutical/Akcea Therapeutics), received

FDA approval in 2018 for treatment of polyneuropathy caused by ATTR mutation. While the primary endpoints in the supporting clinical trials were that of neurological and functional status scores, selected secondary cardiac endpoints showed promise in their use for cardiac ATTR amyloidosis [4,5], a relentlessly progressive infiltrative cardiomyopathy that had until recently been a bleak diagnosis without treatment options.

Over the past decade, oligonucleotide-based therapeutic agents have offered much in promise but have been modest in terms of market success, with only two drugs having received FDA approval for cardiovascular applications (four if including ATTR targeting agents with off-label use). To those who have believed in these drugs' unique elegance and potential, the progress may be painstakingly slow. To the clinical providers and the general public, though, their development represents a concrete transition from mere concepts on paper to bona fide drugs with remarkable efficacy and safety profile. Boosted by the timely public adoption and recognition of Pfizer and Moderna's mRNA based COVID vaccines, we may look forward to an era of emerging oligonucleotide-based medications in the global fight against cardiovascular diseases..

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