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Understanding the Safety Evaluation of New RNA Therapeutics

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DESCRIPTION

Over the past decades, RNA therapeutics has pioneered broad medical applications in rare diseases associated with gene expression and in vaccines to combat the SARS-CoV-2 virus. The exclusive target specificity of RNA therapeutics modulates the translation of disease-causing proteins through downregulation of gene targets or by injecting synthetic mRNAs to translate the encoded target proteins can provide significant advantages over conventional drugs. Most of them were previously thought to be incompatible with other established drugs, including small molecules and antibodies.

RNA therapeutics differs from conventional drugs in terms of their pharmacological mechanism of action and pharmacokinetic properties. Understanding their absorption, distribution, metabolism, and excretion is critical for the development and safety evaluation of new RNA therapeutics. Insight into these properties is important, as most approved RNA therapeutics or candidates have similar modifications in their RNA structure and may exhibit similar ADME processes. RNA therapeutics is oligonucleotides composed of RNA bases (adenine, cytosine, guanine, uracil). Each base is connected to a phosphate backbone that provides structural support to the strand. RNA therapeutics demonstrates their therapeutic efficacy by binding to specific sites in premature RNA *via* Watson-Crick base pairing. Based on their structure, RNA therapeutics can be classified as antisense oligonucleotides and aptamers. FDA approved mRNA vaccines are not covered in this review due to the lack of conventional pharmacokinetic studies. Historically, pegaptanib was the only aptamer-based drug approved by the FDA. Pegaptanib, RNA aptamer, inhibits Vascular Endothelial Growth Factor (VEGF) and has been used to treat age-related macular degeneration. However, with the development of more effective treatment options such as ranibizumab, its use began to decline and eventually its marketing was discontinued.

Defibrotide, a polydisperse mixture of single and double-stranded oligonucleotides of variable length and sequence composition, was the first RNA drug approved in 2016 and is derived from porcine intestinal mucosa. Approved for the treatment of venous-occlusive disease of the liver, it may protect the cells lining blood vessels in the liver and prevent blood from clotting. It has multiple complex mechanisms of action with anti-ischemic and anti-thrombotic properties.

RNA therapeutics interacts with RNA targets in the cytosol or cell nucleus. However, the hydrophobicity of cell membranes limits the ability of RNA therapeutics to diffuse from the blood into peripheral tissues. Therefore, therapeutic uptake of RNA requires different cellular internalization pathways. Effective cellular internalization requires balanced plasma protein binding. Too tightly bound RNA therapeutics to plasma proteins can interfere with tissue distribution from the systemic circulation. In contrast, drugs that are weakly bound to plasma proteins are cleared more rapidly, mainly by blood metabolism or urinary excretion.

Drawbacks of RNA therapeutics have been related to their stability, rapid degradation, and delivery to target cells. As already mentioned modifications to the RNA backbone structure have made it possible to improve stability and prevent rapid degradation. In addition, various delivery systems have been introduced that cross lipid bilayers and protect against degradation using lipid or polymer-based systems. Alternatively, interactions caused by manipulation of gene expression may remain relevant after treatment with RNA therapeutics.

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CONFLICT OF INTEREST

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