INBORN ERRORS OF METABOLISM - II

RECENT ADVANCES IN INBORN ERRORS OF METABOLISM - GENE THERAPY AND EMERGING THERAPEUTICS

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Abstract: *Inborn errors of metabolism comprise a heterogeneous group of genetic disorders associated with significant morbidity and mortality. Therapeutic strategies for disorders with inborn errors of metabolism, have been substantially evolved - from conventional modalities like dietary modification and enzyme replacement towards targeted molecular interventions and precision therapies. Emerging therapeutic modalities in inborn errors of metabolisms include viral vector gene therapy, in vivo and ex vivo genome editing, epigenome editing, ribonucleic acid-based therapeutics, small-molecule chaperones and next-generation protein and cell therapies that offer transformative and potentially curative outcomes. This review summarises recent advances across these platforms, highlighting disease-specific progress in multivarious inborn errors of metabolism-disorders.*

Keywords: *Inborn errors of metabolism, Emerging therapies, Gene therapy, Genome editing, RNA therapeutics*

Points to Remember

- ***Therapeutic strategies for inborn errors of metabolism are expanding from conventional management strategies such as dietary intervention, cofactor supplementation and enzyme replacement to newer personalised gene-based therapies.***
- ***These advancements in therapies include novel chaperones / other small molecules, enzyme replacement therapy strategies, therapies related to metabolic bypass and repurposed drugs.***
- ***High-end viral and non-viral gene delivery platforms, genome editing and RNA therapeutics and their efficacy, safety, are being studied widely and in various stages of development for a variety of IEMs.***
- ***In vivo gene therapy involves vector delivery directly to the patient, predominantly using adeno-associated virus vectors. Ex vivo hematopoietic stem cell - lentiviral gene therapy enables central nervous system cross-correction, providing durable benefit in leukodystrophies.***
- ***Lipid nanoparticle-mRNA and extracellular vesicle-based systems are emerging as repeatable, low immunogenicity alternatives, with growing promise for hepatic and CNS-targeted IEMs.***
- ***CRISPR, base editors and prime editors enable single-base correction with low genotoxic risk, provide an effective therapeutic alternative. Preclinical and murine studies seem promising but need further evaluation to establish clinical translation of benefits.***
- ***Availability and affordability of these therapeutic advances still remain a great challenge. Therefore, scaling up production of these newer therapies to meet the demand and lowering costs to ensure equitable access to these life-saving treatments is a much needed action.***

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