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GENE THERAPY OF HEREDITARY MONOGENIC DISEASES: SUCCESSES, LIMITATIONS AND PROSPECTS OF CLINICAL IMPLEMENTATION

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Abstract. The relevance of the topic is determined by the fact that hereditary monogenic diseases remain one of the most complex groups of rare pathologies: the cause of the disease is usually localized in a specific gene, but the clinical course is formed at the level of the whole organism, depends on the age of onset, residual protein function, concomitant organ damage and the availability of early diagnosis. Gene therapy changes the very logic of treating such conditions, since it aims not only at symptomatic slowing of progression, but also at replenishing, suppressing, or correcting a molecular defect.

In Russian clinical practice, this area is developing under conditions of a combination of high scientific expectations and significant organizational constraints: the number of patients is small, drugs are expensive, the production and analytical base require high standardization, and long-term safety cannot be assessed only within the framework of short registration studies.

The purpose of the article is to study the successes, limitations and prospects of clinical implementation of gene therapy for hereditary monogenic diseases, taking into account the Russian system of diagnosis, registration, expert assessment and patient routing.

The object of research is gene therapy and related nucleic technologies used or considered for the treatment of monogenic pathology.

The subject of the study is the clinical, technological, regulatory and organizational conditions for their implementation in the Russian Federation.

Based on the results of the analysis, it was found that the areas where the genetic cause is reliably verified, an early therapeutic window exists, and controlled delivery to the target tissue is available remain the most mature for practical application.

The most significant limitations are related to the immunogenicity of viral vectors, limited AAV capacity, response variability, the need for long-term follow-up, and insufficient uniformity of patient access.

The prospect of clinical implementation in Russia is not related to a simple expansion of the list of drugs, but to the formation of a full cycle: early screening, molecular verification, production and quality control, outcome registers, pharmacovigilance and economically sustainable financing models.

Keywords: gene therapy, monogenic diseases, AAV vectors, CRISPR/Cas9, orphan diseases, clinical implementation, Russian Federation, pharmacovigilance.

INTRODUCTION

The development of gene therapy for hereditary monogenic diseases has become one of the most notable transitions in modern biomedicine from pathogenetic support to etiologically oriented intervention. If, with the traditional approach, the doctor sought to compensate for protein deficiency, reduce inflammation, correct metabolic disorders, or reduce the incidence of complications, then the gene therapy strategy is aimed at the source of the defect: delivering a functional copy of the gene, modifying expression, shutting down the pathological transcript, or editing the sequence. This logic is especially convincing for monogenic diseases, since the causal relationship between the gene variant and the phenotype is more often clearly traced than in multifactorial pathology [10].

However, monogenicity itself does not automatically make the disease a convenient target. Clinical feasibility depends on the size of the gene, the availability of the affected tissue for delivery, the reversibility of the damage that has already occurred, the immunological status of the patient, the age of diagnosis, and the ability to evaluate the result with objective endpoints. Russian reviews in recent years have emphasized that AAV platforms have become a key tool for in vivo delivery, but they remain limited in terms of the capacity of the genetic cassette, immune response, and the complexity of commercially obtaining a stable drug [3].

For the Russian Federation, the problem has its own significance. On the one hand, the country has established research teams, regulatory expertise and separate production sites capable of participating in the development of high-tech medicines. On the other hand, the availability of therapy for rare diseases is determined not only by the fact of registration, but also by the routing of the patient, the timeliness of the molecular diagnosis, the availability of funding, the willingness of the centers to administer the drug and long-term monitoring. According to the Russian accessibility study, in the early 2020s, the domestic market lagged significantly behind the United States and the EU in terms of the number of approved gene therapy drugs, which was explained by the high cost and orphan profile of most indications [5].

The rationale for the study is the need to link the molecular success of gene therapy with issues of real clinical implementation. In monogenic pathology, the result cannot be assessed solely on the basis of the appearance of the drug: it is necessary to understand which nosologies have practical potential for implementation, which barriers restrain scaling, and which criteria should determine the priorities of the national health system.

MATERIALS AND METHODS OF RESEARCH

The work uses a comparative clinical and technological analysis of gene therapy approaches used for monogenic diseases, including the delivery of a functional copy of the gene, oligonucleotide modification of the transcript, ex vivo cell editing and in vivo genome editing. To assess the practical feasibility, a matrix typologization was used according to four criteria: the evidence of a molecular target, the presence of a therapeutic window, controllability of delivery and the possibility of long-term monitoring of outcomes. This approach made it possible to compare the biological prospects of the method with the conditions of real healthcare.

Methods of descriptive statistics, regulatory comparison, and expert grouping of barriers were also used. A method of constructing a process diagram was used to reflect the relationship between molecular diagnostics, drug selection, examination, administration, pharmacovigilance, and registry maintenance.

RESULTS AND DISCUSSION

The clinical success of gene therapy for monogenic diseases is most noticeable in three groups of technologies. The first group is associated with the delivery of a functional copy of the gene using viral vectors, primarily AAV. It is applicable in situations where the disease is caused by loss of function and even partial restoration of expression can change the prognosis. The second group is represented by oligonucleotide approaches, which are not always gene therapy in the narrow sense, but are perceived in the clinic as a genetically targeted treatment, since they change the splicing or expression of a particular gene. The third group is related to genome editing, including CRISPR/Cas9, where therapeutic intervention is transferred to the level of targeted modification of the cell's genetic program [9].

The most convincing example of the transition from an experimental idea to a clinical outcome was the therapy of spinal muscular atrophy. At the same time, not only the drug itself is important, but also the entire system of its application: the earlier the diagnosis is made and the less irreversible damage to motor neurons, the higher the probability of a functional gain. For hereditary retinal dystrophies, the clinical logic is different: the target organ is localized, the injection can be performed in a specialized manner, and the result is evaluated through visual functions. For hemoglobinopathies, the prospect is associated with ex vivo editing or modification of hematopoietic stem cells, where the product can be controlled before being returned to the patient, but a complex transplantation infrastructure is required [11].

To substantiate the Russian implementation model, it is important to separate the registered or close-to-practice technologies from the developments that are still at the preclinical or early clinical stage. Table 1 presents an analytical grouping of clinical scenarios, where each scenario was evaluated from the perspective of not only scientific effectiveness, but also practical feasibility in the context of the Russian system of care for patients with rare diseases.

Table 1 - Clinical scenarios of genetically directed therapy of monogenic diseases in the Russian Federation

Clinical scenario	The molecular purpose	Technological basis	The condition of clinical success	Restriction for the Russian Federation
Spinal muscular atrophy	Restoring SMN function through SMN1 or modification of SMN2	AAV delivery or antisense oligonucleotide	Diagnosis before marked loss of motor neurons	Dependence of the result on early screening and financing
Hereditary retinal dystrophy associated with RPE65	Introduction of a functional copy of the gene into retinal cells	Subretinal AAV delivery	Preservation of viable retinal cells	The need for a specialized ophthalmic surgical team
Hemoglobinopathies	Modification of globin gene expression or editing of regulatory regions	Ex vivo hematopoietic cell editing	High-quality cell laboratory and transplant circuit	High cost and long-term monitoring requirements
Duchenne muscular dystrophy	Delivery of a shortened version of dystrophin or transcript modification	AAV-microdystrophin, oligonucleotide approaches	Early onset before severe muscle loss	Large gene size and immunological risks
Lysosomal storage diseases	Restoration of enzyme activity	AAV delivery, cellular and enzyme combinations	Systemic exposure to irreversible organ damage	The difficulty of choosing endpoints and the duration of the effect

An analysis of table 1 shows that the maturity of the technology does not coincide with the ease of implementation. SMA and retinal dystrophy have a more understandable clinical trajectory, since the target has been identified, and the therapeutic effect can be associated with early intervention. Hemoglobinopathies are promising from the standpoint of ex vivo product manageability, but require infrastructure that is not available in all regions. For Duchenne myodystrophy, the central limitation remains not only the delivery, but also the scale of the affected tissue, and for lysosomal diseases, the systemic nature of the process and the need to prove a stable organ effect.

According to the preclinical assessment, the publications emphasize that gene therapy drugs have specific risks that are not limited to the usual toxicity.: These are long-term persistence, inappropriate expression, risk of insertion events, immune reactions, and potential environmental impact [1]. Therefore, clinical implementation should be built as a managed system, where each stage is associated with a risk assessment.

In the Russian context, AAV vectors are particularly important, since they are considered for a number of hereditary diseases and allow the delivery of genetic material in vivo. However, the advantages of AAV - relative non-pathogenicity, tissue tropism, and the possibility of prolonged expression - simultaneously create requirements for strict control of the capsid, the ratio of full and empty particles, residual impurities, and immunogenicity. The Quality by Design approach described for AAV drugs demonstrates that quality should be established not at the final batch check, but at the product and process design stage [4].

The following table summarizes the limitations that most often determine whether a gene therapy technology can move from the research or registration plane to sustainable clinical practice. Such a grouping is necessary for interpreting Russian perspectives, since the same molecular technology can be implemented in the federal center and practically inaccessible in routine regional routing.

Table 2 - Limitations of the clinical implementation of gene therapy for monogenic diseases

Restriction Group	Manifestation in gene therapy	Practical consequence	Possible direction of the solution
Biological	Immune response to capsid or transgene, presence of neutralizing antibodies, irreversible tissue damage	Not every patient with a confirmed mutation is a candidate for treatment.	Early diagnosis, immunological screening, personalized timing of intervention
Technological	Limited AAV capacity, difficulty of purification, variability of infection titer	Cost growth and strict quality control requirements for the series	Transition to QbD, standardization of analytical techniques, development of producer cell lines
Clinical	Small samples, heterogeneity of the phenotype, lack of long-term observations	The difficulty of assessing the effectiveness and risk of delayed complications	National registries, single endpoints, post-registration studies
Regulatory issues	The need for an expert assessment of the unique mechanism of action and special safety studies	Increased development time and cost	Harmonization of EAEU requirements, adaptive expertise, scientific consultations for developers
Organizational and economic	High price of single-dose drugs, concentration of experience in federal centers	Uneven access and dependence on budget solutions	Centralization of routing, stock mechanisms, evaluation of the result in real practice

An analysis of table 2 shows that the main obstacle is not one isolated risk, but a combination of them. Even with the proven effectiveness of the drug, the patient may lose the therapeutic window due to late diagnosis. Even with a registered technology, the center may not be ready for implementation and subsequent monitoring. Therefore, the prospects for clinical implementation in Russia should be assessed not only by the number of registered drugs, but also by the completeness of the support system, including genetic diagnosis, interdisciplinary expertise, pharmacovigilance and financing [5].

For a real study in the Russian Federation, a matrix of clinical implementation readiness was built based on five criteria: diagnostic detectability, availability of a technological platform, clinical evidence, manageability of safety and organizational accessibility. The assessment is qualitative in nature, but reflects the practical situation: priority is given not to the most effective technology, but to the one that can be replicated in the care system for a particular patient [8].

Table 3 shows the results of the matrix evaluation. The "high" level means that the scenario has proven clinical applicability and can be implemented if a specialized center is available. The "medium" level means the need to expand infrastructure, evidence base, or funding. The "low" level reflects a situation where the technology is promising, but its mass clinical implementation in Russia is still limited.

Table 3 - Matrix of readiness for the clinical implementation of gene therapy for monogenic diseases in the Russian Federation

Direction	Diagnostic readiness	Technological readiness	Security and monitoring	Organizational accessibility	Final interpretation
SMA	High with the development of neonatal screening	High for registered approaches	Long-term monitoring is required	Average due to cost	The most mature scenario for early detection
RPE65-retinopathy	Average, depends on the genetic ophthalmology	High in specialized centers	Local administration makes it easier to control	Average due to narrow routing	Feasible with preserved target tissue
Hemoglobinopathies	Medium, requires clarification of the molecular variant	Medium, ex vivo contour is complex	Product control is possible before administration	Low cost outside major centers	The prospect is related to the transplantation infrastructure
Duchenne muscular dystrophy	High with molecular confirmation of DMD	Average, AAV, and oligonucleotide	Immune and muscle risks are significant	Medium-low	Requires early selection and quality control of AAV

		approaches are limited			
Lysosomal storage diseases	Average, depends on enzyme and genetic diagnosis	Medium-low for gene therapy	Long-term organ monitoring is needed	Low	It is still more promising as a combined direction

The results obtained allow us to conclude that the Russian implementation model should be nosologically differentiated. For SMA, early detection is a critical link; for RPE65-retinopathy - specialized ophthalmogenetic routing; for hemoglobinopathies - readiness for cell therapy; for Duchenne myodystrophy - control of production and immune safety of the AAV vector. The universal scheme of "registering a drug and referring a patient" is insufficient, since gene therapy requires an individual match of the molecular cause, stage of the disease, target tissue and technological resource [8].

Of particular importance is the distinction between clinical success and sustained clinical implementation. Success in the study can be achieved on a small group of carefully selected patients, whereas implementation requires a repeatable result in people with different ages, concomitant conditions, and regional access conditions. Russian work on modern gene therapy drugs shows that the range of platforms is expanding in the world: siRNA, mRNA, antisense nucleotides, viral and plasmid constructs [2]. However, for monogenic diseases, the key question remains which of these platforms can provide not a temporary laboratory improvement, but a clinically significant and measurable change in the course of the disease.

The introduction of gene therapy also changes the role of the geneticist. He becomes not only a specialist in diagnosis, but also a participant in the selection of a patient for high-tech treatment. The need to correctly interpret the gene variant, predict the functional effect, compare the diagnosis with the therapeutic window, and explain the long-term risks to the family makes genetic counseling a central element of clinical routing. Educational publications on genome editing emphasize that doctors' awareness is a prerequisite for the future application of molecular developments in the treatment of hereditary pathology [9].

THE PROSPECTS FOR THE COMING YEARS ARE LINKED TO THREE AREAS

The first direction is to improve delivery. New AAV serotypes, capsid modification, tissue-specific promoters, and reduction of off-target expression should increase the benefit-risk ratio.

The second area is the development of genome editing, including ex vivo editing of hematopoietic cells and potential in vivo solutions. Foreign clinical studies of CRISPR/Cas9 in hemoglobinopathies and transthyretin amyloidosis have shown that editing has already gone beyond the laboratory concept, but requires strict safety control and long-term monitoring [11].

The third direction is organizational. The gene therapy of monogenic diseases will be effective only when integrated with neonatal screening, advanced molecular diagnostics programs, registry infrastructure, and orphan care financing mechanisms. The presence of specialized federal centers in Russia is an advantage, but it does not eliminate the problem of early detection in the regions. If a patient is admitted to an expert center after irreversible organ damage, even the most modern drug will not be able to realize its potential.

The limitations of the present study are related to the fact that the readiness assessment was performed as a clinical and organizational model, rather than as a prospective patient observation. Nevertheless, the chosen approach makes it possible to show the systemic conditions without which individual clinical successes cannot be transformed into accessible practice. For further research, Russian registries with unified endpoints are needed, comparing the age of initiation of therapy, genotype, phenotype, adverse events, and economic parameters. Only such a base will allow us to move from expert expectations to an evidence-based assessment of the national effectiveness of gene therapy.

CONCLUSION

The gene therapy of hereditary monogenic diseases is one of the most promising areas of modern clinical medicine, as it allows to influence the causal molecular defect. The most significant successes have been achieved where the disease has a clear genetic target, accessible target tissue, an early therapeutic window, and objective endpoints. For Russia, the most mature scenarios are SMA and certain hereditary retinal diseases, while hemoglobinopathies, Duchenne myodystrophy, and lysosomal storage diseases require more sophisticated infrastructure and long-term monitoring.

The main limitations of clinical implementation are related to the immunogenicity of vectors, production complexity, high cost, lack of long-term safety data, and uneven availability of molecular diagnostics.

The prospect of implementation is determined not only by the number of registered drugs, but also by the ability of the healthcare system to provide a complete patient route: early detection, genetic verification, expert selection, safe administration, registry monitoring and assessment of real outcomes. In the coming years, the development of AAV

platforms, CRISPR/Cas9, Quality by Design approaches, and national registries may become the basis for broader and controlled clinical implementation of gene therapy for monogenic diseases in the Russian Federation.

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