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RARE MONOGENIC DISEASES: MODERN GENETIC THERAPEUTIC STRATEGIES AND PROBLEMS OF TRANSLATION INTO THE CLINIC

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Abstract: Rare monogenic diseases remain one of the most difficult categories for clinical medicine, as the combination of low prevalence, pronounced genetic heterogeneity and a limited number of patients has long hindered the development of etiotropic treatment methods. The aim of the work is to analyze modern genetic therapeutic strategies for rare monogenic diseases and identify key barriers to their translation into clinical practice.

In the course of the research, it was found that the modern landscape of therapies is shifting from a universal model of gene replacement to a platform-based technology selection, taking into account the type of mutation, organotropy, patient's age and acceptable risk profile. The most clinically advanced are AAV vector delivery, splice-modulating oligonucleotides, local genetic constructs for skin manifestations, and developing mRNA approaches.

The main limitations of translation remain the therapeutic window, the immunogenicity of vectors, the limited packaging capacity of AAV, the complexity of bioproduction, high cost, lack of early diagnosis, and the need for long-term follow-up.

It is concluded that the successful implementation of genetic therapies is possible only with the simultaneous development of molecular diagnostics, registries, patient routing, national production competencies and financing models focused on clinical value.

Keywords: orphan diseases, monogenic diseases, gene therapy, adeno-associated viruses, mRNA therapy, splice-modulating oligonucleotides, translational medicine, clinical genetics.

Introduction.

Rare monogenic diseases form a special public health problem in which a molecular defect is both the cause of the disease and a potential therapeutic target. In recent years, clinical genetics has moved from being primarily a diagnostic discipline to a platform for choosing an etiotropic intervention. In the Russian literature, this shift is reflected in works on the economics of gene therapy, mRNA approaches, AAV vectors, hereditary retinal dystrophies, neuromuscular diseases, and the availability of innovative drugs, while foreign reviews focus on the maturity of clinical gene therapy and the readiness of healthcare systems for its widespread adoption.

Modern genetic strategies are no longer limited to the classical replacement of a defective gene. In practice, delivery of a functional copy of the gene to target cells, splicing modification, temporary mRNA expression, local correction of tissue defects, and, in the future, genome editing are used. Each technology solves its own clinical class of problems. For hereditary retinal dystrophies, local delivery to relatively immunoprivileged tissue is especially important [10], for Duchenne muscular dystrophy, mutation-specific transcript correction is essential [4], for spinal muscular atrophy, the time of diagnosis becomes a critical factor [3], and for cutaneous forms of hereditary pathology, local repeatable application of a genetic construct is promising [9].

However, the path from a molecular idea to routine clinical application remains multi-stage and vulnerable. The biological limitations of the vectors, the low cohort size, the difficulties in selecting clinical endpoints, the need for personalized logistics, and the extremely high cost make translation to the clinic much more difficult than preclinical proof of principle. Russian publications show that even with a technological platform, the outcome of treatment depends on timely molecular verification, centralized procurement, the availability of expert centers and patient routing [7]. Foreign authors complement this picture with the thesis about the need for early, fair and organizationally secured access to targeted care [11, 12].

The purpose of this article is to analyze modern genetic therapeutic strategies for rare monogenic diseases and discuss the main problems of translating these approaches into clinical practice.

Materials and methods of research.

The analysis included articles that examined either specific clinical models of orphan monogenic pathology, or platform technologies for the delivery of genetic material, or problems of accessibility, bio-production and organization of care. Duplicate publications, short conference abstracts, and non-peer-reviewed materials were not included. To process the data, comparative analysis, thematic grouping, bibliographic description according to the current rules and meaningful interpretation of the results were used, followed by systematization of the conclusions in text and tabular form.

Results and discussion.

The analysis shows that modern therapy of rare monogenic diseases does not form a single technology, but a set of platforms, the choice between which is determined by the biology of the disease. Classical AAV-mediated delivery of a functional copy of the gene retains a leading role where long-term expression is required and targeted delivery to the target tissue is possible [5,8,11]. However, at the same time, approaches based on RNA correction are being strengthened, because they avoid the problem of irreversible interference in the genome and are better suited for mutation-specific scenarios [2]. Thus, clinical genetics is moving from a universalistic treatment model to fine-tuning the platform to a specific pathogenetic mechanism.

The AAV vector strategy remains the most clinically developed. Its attractiveness is determined by its ability to ensure long-term transgene expression, the comparatively low pathogenicity of the vector, and the possibility of serotype-specific selection of tropicity [11]. However, it is this platform that accumulates the most complex set of restrictions. These include the small packaging capacity of the virus cassette, which prevents the delivery of large genes, the existence of pre-existing neutralizing antibodies, hepatotoxicity at high doses, heterogeneity of tissue transduction, and difficulties in re-administration [8].

For rare diseases requiring systemic drug distribution or high dose loading, these factors become not technical, but determine clinical applicability.

Table 1 — Comparative characteristics of modern genetic therapeutic strategies in rare monogenic diseases

Strategy	Molecular Logic	Clinical models	Advantages	Key constraints
AAV-mediated delivery of a functional copy of a gene	Introduction of a transgene into target cells with the expectation of long-term expression of a therapeutic protein	Hereditary retinal dystrophy, certain forms of spinal muscular atrophy, hemophilia, some neuro- and myopathies	Long-lasting effect, high clinical maturity, the possibility of targeted selection of tropics	Cassette capacity limitation, immunogenicity, difficulty of repeated administration, high cost
Splice-modulating oligonucleotides and exon skipping	Correction of pre-mRNA and restoration of the reading frame or synthesis of a functionally significant protein	Duchenne muscular dystrophy and other mutation-specific scenarios	Lack of integration into the genome, high accuracy in relation to the mutation variant	The need for repeated injections, a limited range of suitable mutations, and response variability
mRNA therapy	Temporary expression of a therapeutic protein without integration into the genome	Rare hereditary metabolic diseases, promising personalized models	Design flexibility, platform modularity, potentially faster production cycle	Effect transience, dependence on delivery systems, the need for repeated administration

Local genetically engineered skin therapy	Local replenishment of deficient protein or gene function in the tissue available for application	Congenital dystrophic epidermolysis bullosa	Reduction of system load, the possibility of reuse, convenience of local monitoring	Limited local access to tissues, the need to standardize the application mode, uncertainty of the duration of the effect
Promising genome-editing and personalized platforms	Point correction of the pathogenic variant or targeted regulation of expression	Selected monogenic diseases with a well-characterized mutation	Potentially causal nature of the intervention and high level of personalization	Difficulties of delivery, risk of off-target effects, complexity of evidence-based and regulatory assessment

Table 1 shows that even technologies that are close in purpose differ in the type of risk. If the AAV approach is focused on long-term expression, then mRNA therapy and splice modulating strategies benefit in controllability, but are inferior in duration of effect and often require repeated administration. Therefore, the question of choosing a platform is actually equal to the question of choosing a compromise between response time, security and availability of production.

Hereditary retinal dystrophies remain a good model of successful translation. In ophthalmology, clinical implementation is facilitated by the local route of administration, the relative isolation of the organ, and the ability to evaluate the result using functional and structural methods. Russian publications emphasize that the therapy of hereditary retinal dystrophies is based not only on the availability of the drug, but also on accurate molecular diagnostics, since the therapeutic suitability of the patient is determined by a specific gene and the stage of preservation of the photoreceptor apparatus [6, 10]. The first results of RPE65-associated gene therapy in Russia demonstrated a clinically significant improvement in visual functions, but at the same time showed that the maximum effect is achieved in patients without deep anatomical retinal exhaustion [6]. This makes the ophthalmological model an illustrative example of how early diagnosis verification directly affects the effectiveness of high-tech treatment.

Neuromuscular diseases exhibit a different problem profile. In Duchenne muscular dystrophy, strategic interest is shifted towards exon-skipping therapy, approaches to reading the premature stop codon, and the development of genetic constructs capable of partially restoring the synthesis of functionally significant dystrophin [4]. A Russian review with a clinical example shows that for this nosology, therapeutic effectiveness is closely related to the mutation type, the age of the patient, and the degree of fibroto-fatty muscle remodeling. In other words, even a targeted strategy does not eliminate irreversible tissue changes that have already formed by the time treatment begins. A similar logic can be traced in spinal muscular atrophy: data from the patient registry indicate that late diagnosis shifts the start of pathogenetic therapy to a stage when some of the motor neurons have already been lost, which means that the clinical response is objectively limited [3]. Thus, the therapeutic window for genetic interventions is not a secondary organizational parameter, but a part of biological effectiveness.

A special place is occupied by mRNA therapy, which is considered as a more flexible and potentially faster-scalable alternative to viral delivery systems. Its conceptual advantage consists in the absence of the need for integration into the genome and in the ability to vary the sequence of the therapeutic molecule depending on the clinical task [2]. For rare hereditary diseases, this is especially important because the "one mutation, one therapy" model requires a reduction in the time between design, production, and initiation of treatment. Nevertheless, the transience of expression, dependence on an effective delivery system, and the need for repeated injections have so far limited mRNA approaches mainly to the early stages of clinical development. At the same time, the very logic of these developments indicates a shift towards more modular and technologically adaptable platforms.

The experience of local therapy of congenital dystrophic epidermolysis bullosa is also indicative. The first Russian experience of using beremagen heperpavec demonstrates that for a number of rare monogenic diseases, local, reproducible and relatively gentle intervention may be more rational than systemic delivery, especially when the clinical phenotype is limited by the tissue available for local treatment [9].

From a practical point of view, this example is also important because it reduces the importance of some systemic barriers to viral therapy, although it does not eliminate the need for long-term monitoring, standardization of application modes, and evaluation of effect stability.

The transfer of genetic technologies to the clinic is determined not only by the biology of the platforms, but also by the architecture of the healthcare system. An economic analysis of procurement centralization using the example of hereditary retinal dystrophies shows that for orphan conditions, the cost issue cannot be considered in isolation from the number of patients, the financing model, and the organizational route of drug administration [1]. The study of the availability of gene therapy drugs in the Russian Federation additionally points to the role of regulatory

restrictions, high course prices, dependence on external supplies, and uneven expert infrastructure [7]. A foreign review on the readiness of healthcare systems for gene-targeted therapy highlights the same problems in a broader context: scientific success is not enough for fair access, early screening, transparent selection criteria, specialized centers and sustainable payment mechanisms are needed [12].

Table 2 — Key barriers to the transfer of genetic therapy to the clinic

The broadcast stage	The main problem	Clinical investigation	Direction of the decision
Before verifying the diagnosis	Late genetic diagnosis and lack of early screening	Loss of therapeutic window and decreased clinical response	Expansion of molecular panels, selective and neonatal screening, fast routing
Platform development	Limitation of the tropicity and capacity of the vector, immune risks, difficulty of repeated administration	Insufficient effectiveness or narrowing of the safety profile	Capsid engineering, optimization of promoters and doses, search for alternative delivery systems
Bio-production	Technologically complex and expensive manufacturing, series variability	Cost increase, drug shortage, limited availability	Scalable production schemes, improved cleaning, localization of production
Clinical assessment	Small cohorts and a shortage of validated endpoints	Slower registration and difficulty interpreting the effect	Registers, natural flow studies, adaptive designs
Organization of assistance	The high price of the course and the uneven expert infrastructure	Unequal access and delayed initiation of therapy	Centralized procurement, reference centers, payment models based on clinical value
Post-registration stage	The need for long-term monitoring of the safety and durability of the effect	Uncertainty of late adverse events and duration of response	Unified national monitoring protocols and comparable outcome indicators

The barriers presented form an interconnected system. For example, late diagnosis increases the clinical severity at the start of treatment and at the same time worsens the pharmacoeconomic effectiveness of the intervention, while insufficient standardization of production increases the cost and complicates regulatory assessment [1,3,5,7,12]. Therefore, the discussion of translation cannot be limited to the issue of drug approval; it should include the entire chain from neonatal or early symptom-based recognition to lifelong patient follow-up.

Technological barriers also have a direct impact on the clinic. Russian reviews on AAV platforms emphasize that the choice of serotype, promoter, composition of the genetic cassette, and method of purification of viral particles affects not only laboratory parameters, but also the profile of adverse events, dose reproducibility, and cost of the drug [5,8]. A foreign review of clinical gene therapy complements this conclusion with the observation that the maturity of the industry today is determined not so much by the ability to obtain a clinical response, but rather by the ability to ensure stable pharmaceutical quality of complex biological products [11]. For this reason, the development of national production sites and the unification of analytical techniques should be considered as elements of clinical effectiveness, not just industrial policy.

Another fundamental problem remains the alignment of the molecular specificity of the disease with the design of clinical trials. For many rare monogenic diseases, the available cohort is small, the natural course is variable, and validated surrogate endpoints are limited. This leads to a paradox: the more personalized therapy becomes, the more difficult it is to prove its effectiveness according to the classical schemes of evidence-based medicine. Russian clinical observations of retinal diseases, neuromuscular pathology, and epidermolysis bullosa show that registries, standardized protocols for long-term follow-up, and comparability of results between centers are especially important for such interventions.

Taken together, the data reviewed suggest that modern genetic therapy for rare monogenic diseases is at the stage of transition from isolated precedents to a managed clinical platform. However, this transition is possible only if molecular diagnostics, bio-production, regulatory expertise and pharmacoeconomics develop synchronously. Otherwise, even highly effective drugs will remain a tool for targeted use in a limited number of centers.

Conclusion

Modern genetic therapeutic strategies for rare monogenic diseases include not only classical gene replacement, but also more differentiated approaches focused on the level of DNA, RNA or local tissue defect. AAV vector delivery and mutation-specific RNA-oriented approaches remain the most clinically mature, while mRNA therapy and more flexible platforms expand the possibilities of treatment personalization.

The main problems of the transfer to the clinic are complex. The biological limitations of vectors and the therapeutic window are combined with a lack of early diagnosis, difficulties in recruiting patients, high production

costs, and heterogeneous access to expert care. Therefore, the introduction of genetic therapies cannot be considered outside of the organization of orphan care, the registry system and funding models.

For Russian clinical practice, priority areas are the expansion of molecular verification of diagnosis in the early stages of the disease, the development of specialized centers and laboratories, the accumulation of national data on long-term efficacy and safety, as well as the formation of sustainable procurement and localization mechanisms for production. Only with this approach will modern genetic technologies be able to move from the status of unique interventions to the status of systemically accessible medical care.

Finally, the translational perspective for orphan monogenic diseases requires a revision of the traditional logic of proof and payment for innovation. For ultra-small cohorts, the clinical value of an intervention is determined not only by the statistical strength of the study, but also by the ability to stabilize function, delay disability, and reduce the accumulated burden of care. Therefore, the development of genetic therapy should be accompanied by the introduction of registers of natural course, unified outcome scales and flexible mechanisms for post-marketing analysis of real clinical practice.

It is this infrastructure that will make it possible to link laboratory innovation with a predictable and reproducible result at the level of the national health system.

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