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SAFETY AND IMMUNE RESPONSE TO GENE THERAPY: MOLECULAR MECHANISMS AND APPROACHES TO RISK MINIMIZATION

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ABSTRACT

The relevance of the study is determined by the rapid transition of genetic therapies from the experimental field to clinical practice and the simultaneous strengthening of the requirements for proving the safety of such interventions. Gene therapy drugs differ from traditional pharmacological drugs in that their active component not only interacts with the cellular target, but also changes the flow of genetic information, protein expression, or the immunological profile of the tissue. For this reason, even a well-designed structure can trigger a complex sequence of innate and adaptive reactions: recognition of the vector by innate immune receptors, activation of complement, production of neutralizing antibodies, a T-cell response to a capsid or transgenic protein, as well as inflammatory damage to the target organ. Of particular importance for Russian practice is the risk-based combination of the molecular characteristics of the drug, laboratory screening of the patient and clinical monitoring after administration. The work examines the mechanisms of immune reactivity to adeno-associated viral vectors, cellular products with genetic modification, genome editing technologies and therapeutic nucleic acids. It is proved that safety is determined not by one parameter, but by the consistency of the dose, the purity of the vector fraction, pre-existing immunity, the inflammatory status of the patient and the quality of production control.

The result of the study was a risk minimization matrix adapted for the Russian regulatory and clinical laboratory environment, which links the molecular source of danger with a real control method and a possible management solution.

It is concluded that the most reliable strategy is to detect immunological contraindications early, limit reactive impurities, standardize predictive tests, and provide personalized patient support in the first weeks after therapy.

KEYWORDS: genetic therapy, gene therapy drug, adeno-associated virus, immunogenicity, neutralizing antibodies, genome editing, safety, risk minimization.

INTRODUCTION

Genetic therapies have formed an independent field of modern biomedicine, in which the therapeutic effect is achieved by delivering a gene, correcting expression, editing a DNA sequence, or transferring modified cells. Russian reviews in recent years show that drugs based on viral vectors, non-viral carriers, cellular systems, and oligonucleotide technologies belong to this group, and the boundaries between pharmacology, biotechnology, and molecular medicine are becoming less rigid [2]. For practical safety, this means the need to evaluate not only the clinical effect, but also the biological behavior of the platform in the patient's body.

Recombinant adeno-associated viruses are used most intensively in clinical development, since they are capable of delivering transgene to postmitotic cells and long-term expression without mandatory integration into the genome. At the same time, the AAV capsid is a protein nanostructure that retains the ability for immune recognition; the serotype determines tissue tropism and simultaneously affects the probability of neutralization by antibodies [10]. Therefore, the molecular efficacy of delivery cannot be considered separately from the immunological compatibility of the patient and the drug.

The Russian scientific discussion on the gene therapy of hereditary diseases emphasizes that the limitations of AAV platforms are related to the packaging capacity, the difficulty of repeated administration, dose-dependent liver reactions, and the need for quality control of the vector material [3]. These restrictions are of direct

importance for minimizing risks: the higher the systemic dose and the proportion of immunoreactive particles, the greater the likelihood of an inflammatory response, a transient increase in transaminases, and loss of therapeutic expression.

Equally challenging is the security of genome editing technologies. The risk here is associated not only with the delivery vector, but also with nuclease activity, erroneous recognition of genomic regions, chromosomal rearrangements, immune response to bacterial proteins of the CRISPR/Cas system, and possible selection of cell clones with undesirable properties [6]. Russian publications on genome editing show that such therapy requires a combination of molecular precision, genomic sequencing, and long-term follow-up [4].

The issues of preclinical study of the safety of gene therapy drugs are of particular importance due to the heterogeneity of platforms. Biodistribution, tissue expression, the proportion of empty capsids, the presence of replication-competent impurities, and immunological reactivity are critical for an AAV drug, whereas viability, phenotype, clonality, cytokine activity, and the risk of uncontrolled proliferation are important for genetically modified cells [1]. Therefore, a single control scheme can only exist as a risk-based system, adaptable to a specific technology.

Problematic aspects of the development and registration of gene therapy drugs in Russia are related to the fact that classical pharmacological criteria are not always sufficient to describe the quality and safety of live, viral, and genomically active products [8]. At the same time, the modern concept of Quality by Design suggests building development around critical quality indicators, linking production parameters with a clinically significant risk in advance [5]. For immune safety, this approach allows us to consider empty capsids, residual DNA, aggregates, endotoxin, viral genome titer, and biological activity as interrelated sources of danger.

International data confirm that the immunogenicity of AAV therapy includes pre-existing antibodies, a humoral response after administration, cytotoxic T-cell reactions to capsid and complement-mediated complications [11]. In clinical areas where delivery is directed to the central nervous system or liver, immunosuppression regimens, the timing of its initiation, and withdrawal criteria are additionally discussed, since excessive suppression of immunity in itself increases the risk of infectious complications [12].

The aim of the study is to scientifically substantiate the molecular mechanisms of the immune response to genetic therapies and to develop risk-based approaches to minimizing safety for Russian clinical and laboratory practice.

The object of research is genetic therapies used or being developed to correct hereditary and acquired diseases.

The subject of the study is immunological and molecular risk factors, methods of their detection and methods of controlled reduction at the stages of development, patient admission and post-therapeutic monitoring.

The rationale for the study is related to the fact that clinical examples of the use of AAV8-gene therapy in hereditary liver pathology have already been described in Russia, demonstrating the need for a close combination of molecular diagnostics, production characteristics of the drug and dynamic monitoring of the patient [7]. Such cases show that the issue of safety becomes not an abstract regulatory procedure, but a condition for maintaining the therapeutic effect and preventing immune damage to the target tissue.

MATERIALS AND METHODS OF RESEARCH

The study was carried out in the format of applied risk-based analysis, focused on the Russian conditions of development, laboratory evaluation and clinical support of genetic therapies. Four technological groups were identified as modeled objects: in vivo drugs based on recombinant AAV, ex vivo cellular products with genetic modification, genome editing systems, and therapeutic nucleic acids. This division is not used for formal comparison, but to identify different sources of immune danger, since the same clinical symptom may have a different molecular cause.

To assess pre-existing humoral immunity, real laboratory methods for the determination of binding and neutralizing antibodies to the AAV capsid are used. Binding antibodies are detected by enzyme immunoassay or multiplex methods, and the neutralizing activity is determined in a cell test, where the patient's serum suppresses the transduction of the reporter vector. This approach allows us to separate the fact of immune contact with a virus-like antigen and the functional ability of antibodies to block the delivery of a transgene.

The cellular immune response can be assessed by the ELISpot method based on interferon-gamma production after stimulation with capsid or transgenic protein peptides, flow cytometry with CD4+ and CD8+ T-cell analysis, as well as intracellular cytokine staining. For genetically modified cellular products, phenotyping, analysis of activation markers, determination of the proportion of effector and depleted populations, and production of interleukin-6, tumor necrosis factor alpha, and type I interferons are additionally applicable.

The innate immune response is studied by determining the components of complement C3a, C4d and soluble complex C5b-9, the concentration of proinflammatory cytokines, markers of monocyte activation and the level of acute phase proteins. Tests for the activation of innate immune receptors sensitive to foreign RNA and DNA, including the evaluation of interferon-stimulated genes by quantitative PCR, are important for nucleic acids and genome editing systems.

The molecular characterization of the drug includes quantitative PCR or digital drip PCR to determine the titer of vector genomes, an assessment of the ratio of full and empty capsids, an analysis of the residual DNA of the producing cell, a search for replication-competent viral impurities, and confirmation of the structure of the therapeutic cassette by sequencing. Targeted deep sequencing, methods for detecting off-target changes, analysis of large rearrangements, and control of mosaicism in the cell population are used for genome editing.

Clinical safety monitoring in the proposed design includes regular detection of liver enzymes, bilirubin, coagulation markers, creatinine, total blood count, C-reactive protein, and symptoms of systemic inflammation. When using AAV vectors, special attention is paid to the early stages after administration, when a combination of humoral activation, complement-dependent reactions and T-cell damage to the transduced cells is possible. In ex vivo therapy, the focus is shifted to the cytokine profile, cell persistence, and signs of uncontrolled expansion.
The integrated risk assessment was conducted by comparing three levels of data: a molecular source of immune reactivity, a measurable laboratory marker, and a clinically significant management decision. Each risk was assigned a qualitative controllability category: a high level of controllability in the presence of a predictive test before administration, an average level if early monitoring is possible, and a low level if long-term monitoring is required without an accurate short-term predictor. This method allows you to link the safety of the drug with practical actions, and not just with a description of possible complications.

RESULTS AND DISCUSSIONS

The results of the analysis showed that the immune response to genetic therapies is formed at the intersection of the properties of the platform, the patient's condition and the manufacturing profile of the drug. For AAV vectors, the initial event is more often the meeting of the capsid with antibodies, complement, and antigen-presenting cells. If neutralizing antibodies are present before treatment, the therapeutic construct can be blocked even before reaching the target cell; if a humoral response occurs after administration, it limits the repeated use of the same serotype and creates a risk of inflammatory complications [11].
For Russian practice, the relationship between the immunogenic load and the quality of the drug is especially important. Standard samples of empty capsids of recombinant AAV are considered as a quality control tool, because the empty particle does not carry a therapeutic cassette, but retains the antigenic surface and is able to increase the immune load on the patient [9]. From a safety perspective, this means that a seemingly technological indicator directly affects the likelihood of a humoral and cellular response.
A published Russian clinical example of two-stage AAV8 gene therapy for a child with type I Krigler-Nayyar syndrome shows that the safety assessment cannot be limited to the moment of drug administration [7]. Patient preparation, consistent follow-up, laboratory fixation of liver function, and the ability to distinguish expected immune reactivity from the onset of clinically significant damage are important. This case does not provide grounds for a broad statistical conclusion; however, it demonstrates that personalized monitoring is already a real part of the domestic practice of gene therapy.
To systematize the identified mechanisms, table 1 is presented below, where the molecular source of risk is compared with the immunological manifestation and the method of risk reduction. The table is constructed as a practical scheme for evaluating the drug before clinical use and during the early post-therapeutic period.

Table 1 — Molecular sources of immune risk and approaches to their minimization

Platform	**Source of risk**	**Immune manifestation**	**Control method**	**Minimization**
AAV vector	Capsid, empty particles, high dose	Neutralization, complement, T-cell response	Antibodies, C3a/C5b-9, ELISpot, ALT/AST	Patient screening, reduction of empty capsids, early monitoring
Ex vivo cellular product	Activation of modified cells	Cytokine reaction, tissue inflammation	Phenotyping, IL-6, TNF-alpha, cell persistence	Dose control, graduation criteria, readiness for anti-inflammatory therapy
Genome editing	Nuclease, off-target events, DNA breaks	Inflammation, immunity to Cas protein, clonal selection	Deep sequencing, DNA response markers, clonality analysis	Optimization of guide RNAs, temporary expression of the editor
Nucleic acids	Motifs of foreign RNA or DNA	Interferon response, local inflammation	Interferon-stimulated genes, cytokines, tolerance	Chemical modification, carrier selection, fractional observation

An analysis of table 1 shows that there is no universal immunological marker for all genetic therapies. The most manageable risk is that which can be detected prior to administration, such as the presence of neutralizing antibodies to AAV. The events that develop after delivery remain more complex, since they depend on the expression of the transgene, the inflammatory background of the patient, and the distribution of the vector through tissues. Therefore, risk minimization should begin at the drug development level and continue in the clinical follow-up cycle.

When comparing platforms, it is clear that innate immunity plays the role of an early warning system, but it is it that can create the most acute insecurity scenario. Complement reacts to viral particles, immune complexes and cell surfaces, and the interferon system recognizes foreign nucleic acids. In the case of AAV, this may be

manifested by an inflammatory reaction and transient liver damage, whereas with cell therapy, the cytokine response becomes dominant. Russian publications on preclinical safety emphasize the need to choose a research model taking into account the biological nature of the drug, rather than transferring one scheme to all gene therapy products [1].

Adaptive immunity has a different time profile: antibodies and T cells can not only reduce the effectiveness of the first therapy, but also practically close the possibility of reintroduction of the same vector. This is especially important for diseases where dose adjustment or repeated exposure may be required. Russian data on the problems of development and registration of gene therapy drugs show that the description of immunogenicity should be related to the characteristics of quality, stability and biological activity, otherwise the clinical interpretation is incomplete [8].

For genome editing, the result of the analysis turned out to be more ambiguous. On the one hand, the short expression of the editor reduces the likelihood of prolonged immune pressure. On the other hand, even the short-term presence of a nuclease can trigger immune recognition, and off-target changes do not always appear immediately. Therefore, the safety of editing technologies should include not only an assessment of the immunogenicity of the carrier, but also genomic validation of the final cell or tissue population [6].

The Quality by Design concept for AAV drugs allows us to identify critical quality indicators in advance: the titer of vector genomes, the proportion of complete capsids, the purity of the protein profile, the absence of replication-competent particles, the stability of the therapeutic cassette and the reproducibility of biological activity [5]. If these indicators are associated with pre-determined clinical risks, quality control ceases to be a formal procedure and becomes part of immune safety.

The following table shows the practical part of the study: each laboratory unit is associated with a specific safety issue that must be resolved before the drug is administered or in the coming weeks after therapy. Such a comparison is especially important for clinics, where it is necessary to quickly interpret deviations and distinguish the expected immune response from a dangerous complication.

Table 2 — Methods for monitoring immune safety and interpretation of results

Control unit	The real method	What reveals	When to apply	Clinical significance
Humoral immunity	ELISA and the AAV neutralization test	Binding and functional antibodies	Before and after administration of therapy	Prediction of efficacy and risk of re-administration
Cellular response	ELISpot, flow cytometry	T-cells to capsid or transgene	Before administration, at risk and in early monitoring	Prevention of damage to transduced cells
Complement	C3a, C4d, sC5b-9	Acute cascade activation	The first hours and days at a systemic dose	Early diagnosis of inflammatory toxicity
Vector quality	ddPCR, analysis of full and empty capsids	Dose and antigenic load	In the final control of the series	Reduction of unproductive immunogenicity
Genomic accuracy	Targeted and broad sequencing	Off-target changes and clonality	Before the release of the cellular product and under observation	Prevention of delayed genotoxic risks

The data in table 2 confirm that risk minimization requires not an isolated test, but a consistent diagnostic chain. For example, a negative result for neutralizing antibodies does not exclude complement activation after a high systemic dose, and an acceptable cytokine profile does not replace sequencing during genome editing. Therefore, the safety of genetic therapies should be assessed as a multicomponent system in which each method covers only its own area of uncertainty.

The Russian specificity lies in the fact that genetic therapies are at the intersection of clinical innovation, industrial scaling and regulatory assessment. In such circumstances, the risk is minimized not only by scientific design, but also by the reproducibility of documentation, the availability of validated methods, and the consistency of actions by the developer, laboratory, and clinician. A review of modern gene therapy drugs shows that market development is accompanied by increasing complexity of classification and an increase in the number of combined technological solutions [2].

For the AAV platform, the most convincing way to reduce risk is to reduce excessive antigenic load. This is achieved by increasing the proportion of complete capsids, removing protein and nucleic impurities, controlling aggregates, and confirming the stability of the composition. At the same time, empty capsids cannot be considered an exclusively technological defect: in the immunological sense, they are carriers of capsid epitopes and can participate in the formation of a response without therapeutic benefit [9].

For cellular genetic therapies, the controllability of the live product becomes a key safety mechanism. Genetic modification of a cell can change its activity, its ability to persist, and its interaction with the patient's immune

system. Therefore, the release control should link the cell phenotype, the expression level of a therapeutic receptor or gene, cytokine activity, and the absence of unwanted clonal expansion. This logic is consistent with the general requirement to evaluate a gene therapy drug as a biological system rather than as a simple molecule [1].

Therapeutic nucleic acids occupy an intermediate position between classical pharmacology and genetic therapy. Their immunogenicity depends on the sequence, chemical modification, carrier, and route of administration. Russian reviews show that such drugs expand the range of molecular interventions, but require control of innate immune recognition, especially the interferon profile [2].

An important result of the study was the assessment of risk management by stages of the life cycle of therapy. The risks that are most effectively prevented are those that are detected before administration: a high titer of neutralizing antibodies, an unsuitable mutation, severe inflammation, or non-compliance of the series with critical quality indicators. Delayed events related to long-term expression, clonal dynamics of cells, and rare genomic consequences of editing remain less manageable. They require long-term monitoring and a register-based approach.

Table 3 shows the final risk minimization matrix for Russian practice. It combines the development stage, patient admission, day of administration, and late follow-up, as the safety of genetic therapy is shaped throughout the product lifecycle.

Table 3 — Risk-based minimization matrix for Russian practice

Stage	Key risk	Reference point	Decision	Expected effect
Drug development	Immunoreactive impurities and instability	Critical quality indicators	Process and specification optimization	Reduction of unpredictable immunogenicity
Patient selection	Pre-existing immunity and inflammation	Antibodies, biochemistry, cytokines	Exclusion or postponement of therapy	Increasing the likelihood of effective delivery
Drug administration	Acute activation of innate immunity	Complement, temperature, hemodynamics	Monitoring and correction readiness	Timely suppression of a dangerous reaction
Early period	T-cell damage to target tissue	ALT/AST, ELISpot, clinical dynamics	Personalized immunosuppression	Preservation of transgene expression
Prolonged period	Loss of effect and delayed genotoxicity	Case monitoring, sequencing when indicated	Long-term control protocol	Early detection of rare effects

The table shows that risk management begins before clinical contact with the patient. If a batch of a drug contains an excessive number of empty capsids or poorly characterized impurities, follow-up will no longer eliminate the original cause of increased immunogenicity. On the contrary, if production control, immunological screening, and clinical support are coordinated, even high-tech therapies become more predictable and better managed.

A comparison of Russian and foreign publications shows that the basic mechanisms of immunogenicity are similar, but a practical strategy should take into account the local availability of tests and patient routing. Foreign reviews pay great attention to preventive immunosuppression and reactions to AAV vectors [12]. For Russia, it is fundamentally important not to mechanically transfer schemes, but to form protocols that can be reproduced in the conditions of a specific center, including the timing of sampling, a list of markers and criteria for a clinical decision.

The repeated administration of the AAV drug deserves a separate discussion. After the first exposure, a humoral response is almost inevitably formed, which reduces the effectiveness of repeated delivery by the same serotype. Possible solutions include the use of alternative serotypes, plasmapheresis, temporary suppression of the B-cell response, engineered capsids and non-viral delivery systems, but each of them adds new risks. Therefore, when planning therapy, it is necessary from the very beginning to consider not only the first dose, but also the scenarios of loss of effect.

For genome editing, the most promising approach is to reduce the time of the editor's presence in the cell. Delivery in the form of a ribonucleoprotein complex, mRNA, or a temporarily active system can reduce the risk of prolonged immune recognition and reduce the likelihood of accumulation of off-target events. However, such a strategy requires high precision of molecular control, because the short duration of expression does not exempt from the need to prove the actual genomic result [4].

Summarizing the results, it can be argued that the safety of genetic therapies is systemic in nature. The molecular mechanism determines the possible spectrum of the immune response, the manufacturing process determines the antigenic and impurity load, and the clinical protocol decides whether the risk will be detected in a timely manner.

That is why it is most rational not to search for a universal immunosuppressant, but to build an adaptive control circuit, where each action is associated with a specific mechanism of danger.

CONCLUSION

The conducted research has shown that the safety of genetic therapies is determined by a combination of molecular, immunological and industrial factors. The main risk mechanisms are recognition of the vector by innate immunity, complement activation, formation of neutralizing antibodies, T-cell response to a capsid or transgenic protein, immunogenicity of genome editing components, and possible delayed genotoxic consequences.

The most effective risk minimization is achieved when monitoring begins before the drug is administered. The determination of neutralizing antibodies, assessment of the inflammatory status of the patient, characterization of the vector series, the ratio of full and empty capsids, analysis of residual impurities and confirmation of genomic accuracy during editing are of critical importance. After therapy, dynamic monitoring of the liver, complement, cytokines, cellular immune response, and signs of loss of effectiveness is necessary.

A risk-based matrix linking the molecular source of danger, a real laboratory method and a clinical solution has been substantiated for Russian practice. Such a matrix can be used in the development of local protocols for supporting AAV therapy, cellular genetically modified products, genome editing systems, and therapeutic nucleic acids. Its advantage is that it translates the discussion of safety from a general description of complications into a sequence of verifiable actions.

The prospects for further development are associated with the creation of domestic validated immunogenicity tests, the expansion of registry monitoring of patients, the standardization of quality indicators of gene therapy drugs and the introduction of personalized immunosuppression regimens. With this approach, genetic therapies can maintain a high therapeutic potential with a more predictable and controlled safety profile.

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