GENE THERAPY FOR INHERITED RETINAL AND OPTIC NERVE DISORDERS: CURRENT KNOWLEDGE

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SUMMARY

The aim of this review is to provide a comprehensive summary of current gene therapy clinical trials for monogenic and optic nerve disorders.

The number of genes for which gene-based therapies are being developed is growing. At the time of writing this review gene-based clinical trials have been registered for Leber congenital amaurosis 2 (LCA2), retinitis pigmentosa 38, Usher syndrome 1B, Stargardt disease, choroideremia, achromatopsia, Leber hereditary optic neuropathy (LHON) and X-linked retinoschisis. Apart from *RPE65* gene therapy for LCA2 and *MT-ND4* for LHON which has reached phase III, all other trials are in investigation phase I and II, i.e. testing the efficacy and safety.

Because of the relatively easy accessibility of the retina and its ease of visualization which allows monitoring of efficacy, gene-based therapies for inherited retinal disorders represent a very promising treatment option. With the development of novel therapeutic approaches, the importance of establishing not only clinical but also molecular genetic diagnosis is obvious.

Key words: gene therapy, monogenic retinal diseases, optic nerve atrophy, mitochondrial disease

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INTRODUCTION

Although inherited disorders of the retina are one of the most common causes of severe loss of sight in childhood age and early adulthood (49), therapeutic options in clinical practice are limited to the treatment of certain accompanying symptoms, but without the possibility of influencing the degenerative processes in the photoreceptors themselves. In the treatment of this group of disorders gene therapies represent an entirely new approach. They are focused on the transmission of a fully functional copy of a gene, with the aim of replacing the diminished or zero function of the protein that is coded by the mutated gene, and/or on the regeneration or stabilisation of the impaired retinal structure (40). With regard to its easy accessibility, small dimensions, immunological privilege, compartmentalisation and possibility of contralateral control, the eye is an ideal target organ for gene therapy (37).

OBJECTIVE

The objective of our study was to present a summary overview of the ongoing clinical trials testing gene therapy of hereditary disorders of the retina and optic nerve.

METHODS

The literary research focused on principles, recommended procedures, application and results of gene therapy for monogenic hereditary disorders of the retina and optic nerve in the stage of clinical trials. The source of information on the ongoing clinical trials was the international register of clinical trials https://clinicaltrials.gov.

RESULTS

Fundamental prerequisites for application of gene therapy

Gene therapy is a therapeutic procedure in which genetic material is introduced into the genome of cells, replacing or influencing the expression of protein participating in the pathogenesis of a specific disorder. Although this treatment has been used successfully in the past, e.g. in the case of severe immune deficits (42), it remains only an experimental therapy, which may bring with it a range of adverse effects.

For the development and application of gene therapy it is necessary to know the cause of a genetically conditioned disease on a molecular level, and therefore to determine the gene responsible for the origin of the disorder. Accumulated observations on the genetic causes of monogenic disorders are entered into the OMIM (Online Mendelian Inheritance in Man) database, which is accessible at the address http://www.omim.org and at present contains over 5 000 records. A further step is to determine the specific mutation causing the pathological process in the given patient. Within the framework of development, an evaluation is conducted as to whether manifestations of the di-

sorder are eradicated or alleviated following the application of gene therapy. At the same time, therapy must not have negative impacts on vitally important functions of the organism.

The strategy of gene therapy is stipulated with regard to the above-stated requirements. If the cause of the disorder is a deficiency of a product of the mutated gene, it is sufficient to incorporate a normal ("wild type") sequence of the gene into the genome of the relevant cells (fig. 1A) or alleviate the manifestations of the disorder by the introduction of a therapeutic gene (fig. 1B). However, if the modified product of a mutated gene of the character of an aberrant protein has a pathological effect, it is necessary either to block the mutated gene (fig. 1C) or to correct it (fig. 1D) (56).

Gene therapy can be performed in vivo, in which the target cells are a component of the organism throughout the entire period of treatment, or in vitro, in which the target cells are removed from the body of the organism and returned to their original location after the implementation of treatment (25).

Inclusion of patients in clinical trials is always conditioned by a range of criteria. With regard to the very nature of genetically conditioned disorders, the standard procedure and at the same time the first step is generally to determine the cause of the disorder on a molecular genetic level. The different genetic background, together with the possible presence of pre-existing antibodies against viral vectors, are the cause of variability of the initial clinical parameters for the application of gene therapy in individual patients. A high level of specific neutralising antibodies is one of the exclusion criteria for the studies (30). Current disadvantages of gene therapy of retinal disorders include the high financial and technological demands, as well as the necessity to apply treatment in a "therapeutic window", before irreversible damage to the tissue has occurred (5).

Vectors used for gene therapy

Genetic information is transmitted into the target cells with the help of carriers referred to as vectors. The cell into which the gene is introduced, and within which the gene's functional expression (expression of genetic information) simultaneously takes place, is referred to as the transduced cell. An ideal vector should penetrate into a large number of target cells, and the expression of the introduced gene in the transduced cell should take place after a sufficiently long time in order to attain the required therapeutic effect. Furthermore, the vector must not be toxic for the target cells or generate adverse effects in the recipient such as viral infections or autoimmune reactions (36). We divide vectors into viral and non-viral. Due to a range of disadvantages of physical and chemical vectors, viral vectors, in particular adenoviral and retroviral vectors, are currently being

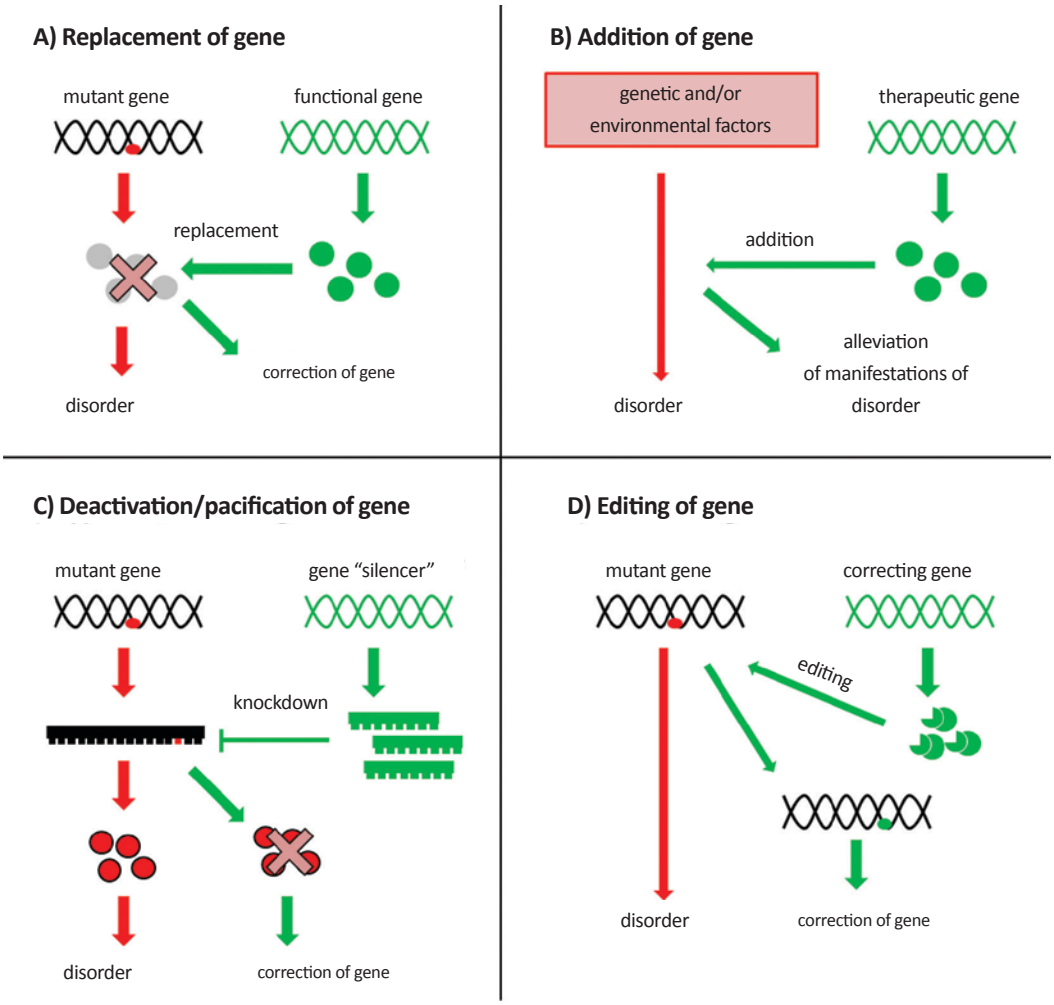

Fig. 1 Strategies used in gene therapy (56)

Table 1 Viral vectors used for gene therapies and their properties (53)

	Retrovirus	Lentivirus	Adenovirus	Adeno-associated virus
Genetic material	RNA	RN	dsDNA	ssDNA
Size of genome	7-11 kb	8 kb	36 kb	4.7 kb
Cloning capacity	8 kb	8 kb	7-35 kb	< 5 kb
Form of integration	Stable	Stable	Episomal*	Stable/episomal
Target cells	Only dividing	Dividing and non-dividing	Dividing and non-dividing	Dividing and non-dividing, unsuitable for haematopoietic
Expression of viral proteins	No	Yes/No	Ano/Ne (dle typu vektoru)	Ne
(according to type of vector)	Yes/No	Pomalá, konstitutivní	Rychlá, přechodná	Průměrná, konstitutivní, přechodná
(according to type of vector)	*No*	*Ex vivo*	*Ex/in vivo*	*Ex/in vivo*
Expression of transgene	Slow, constitutive	Slow, constitutive	Rapid, transitory	Average, constitutive, transitory
Method of transformation	Ex vivo	Ex vivo	Ex/in vivo	Ex/in vivo
Pre-existing antibodies against vectors	Improbable	Probable	Ano	Yes
Immunogenicity	Low	Low	High	Average

*episomial – reversible integration into genome DNA of host

used in clinical trials testing therapies for retinal disorders in humans (table 1) (36).

Genes linked with pathogenicity and the reproduction of viral particles are removed from viral particles. These are then replaced with an expression cassette (fig. 2). DNA is prepared, recoded into mRNA by a process of transcription, in which non-coding sequences (introns) are cut out, and this is transcribed back into cDNA, which contains only the coding sequences of the gene (exons). cDNA is bordered at the 5'-end by a promoter which triggers the expression of the gene, and at the 3'-end by a transcription terminator and a polyadenylation signal, which terminates the expression (26).

The risk of use of viral vectors consists in the fact that genetic information is inserted into the genome of the recipient more or less at random. This may lead to a disturbance of the sequence of another gene with functional consequences, e.g. change in the proto oncogene or in the tumour-suppressor gene may trigger malignant transformation of cells. Another problem is the unstable expression of the gene, caused by potential immunogenicity of viral vectors, causing inflammatory reactions (40). A further application of the viral vector may not necessarily be sufficiently effective, since antibodies are generated against the vector (7). Repeated application of therapeutics into the subretinal region also carries the risk of damage or detachment of the retina (fig. 3, table 2) (8). Also problematic is the stipulation of a therapeutic dose and the quantity of applied viral particles. In the initial stages of gene therapy, high doses of viral vectors in the treatment of ornithine transcarbamylase deficiency caused a massive inflammatory reaction and death of the patient (48). Subsequently the conditions were made more stringent for the application of gene therapies, and this serious adverse situation has not since been repeated.

Methods of application of vectors

In the treatment of retinal disorders, intravitreal and subretinal injections are used most frequently for the application of vectors (fig. 3, table 2). Although application into the vitreous body is less invasive for the retina, transduction takes place especially in the inner layers of the retina, thus in the Müller and ganglion cells. A barrier to the penetration of vectors and pharmaceuticals into a greater depth of the retina is formed by the membrana limitans interna and other retinal layers. For the application of viral vectors into the layer of photoreceptors and the layer of cells of the retinal pigment epithelium (RPE) subretinal application is more suitable, in which the vector is injected into a vesicle between the aforementioned layers, and is thus in close contact with them. Within 14 hours the cells of the RPE containing subretinal fluid completely absorb the viral vector. The effectiveness is 5-10x higher than upon application into the vitreous body. However, a disadvantage is the greater risk of potential complications in connection with the surgical procedure (table 2) (35).

Gene therapy of retinal disorders in the stage of clinical trials

Clinical testing has a number of phases. In phase I the maximum tolerated dose is determined in one non-randomised

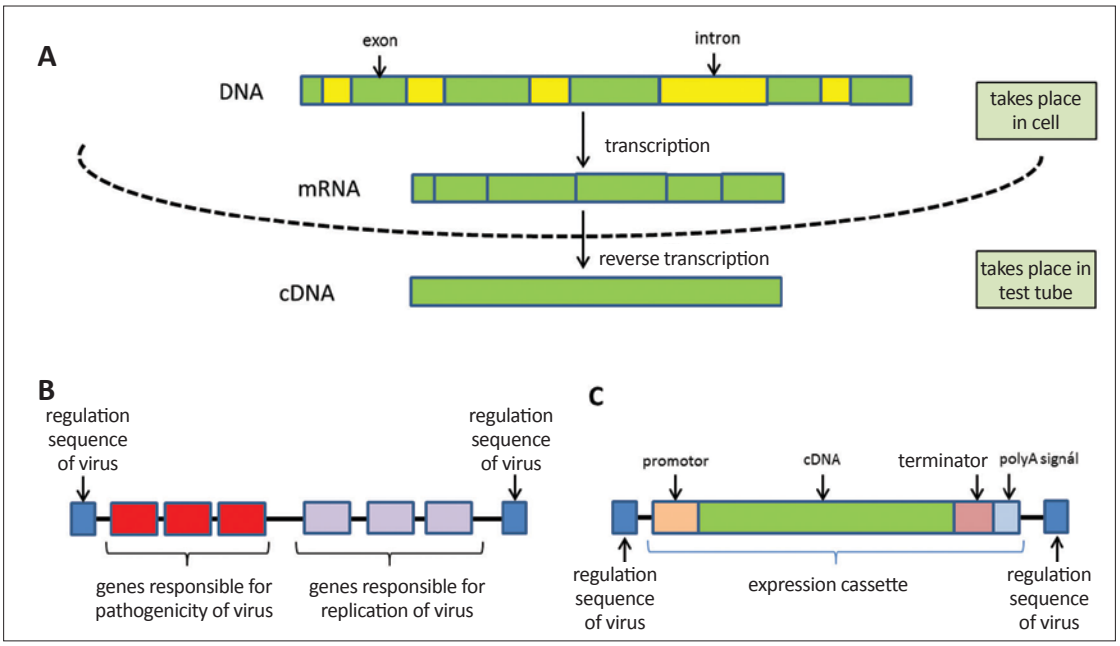

Fig. 2 Schema of preparation of cDNA (A), structure of original (B) and adjusted (C) viral vector

group of volunteers, and its safety is monitored. In phase II the effective dose of the medicament is determined on patients, again mostly within the framework of a non-randomised trial. In phase III one group is treated with ordinary procedures, and the new treatment is applied to the second group. The efficacy of the new medicament is therefore compared against the standard therapy. The classification and evaluation are generally double-blind. On the basis of the results of phase III the medicament may be registered. In the final phase IV the adverse effects of the medicament are monitored following registration and in long-term use (https://clinicaltrials.gov/ct2/about-studies/learn) (24).

Leber's congenital amaurosis 2

Leber's congenital amaurosis (LCA) is a genetically heterogeneous group of disorders conditioned by mutations in at least 22 genes (23). LCA2 (OMIM #204100) is an autosomally recessive disease originating on a background of mutati-

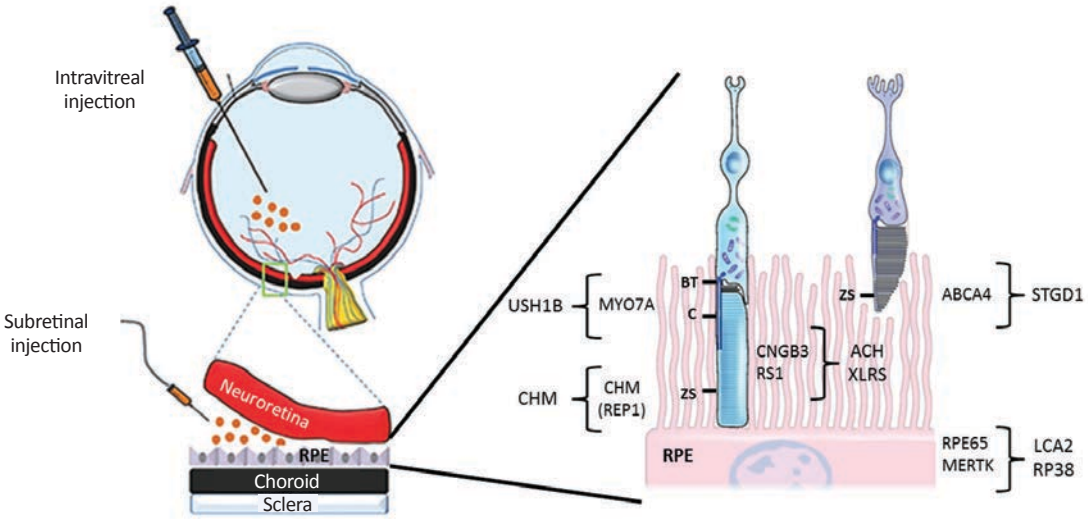

Fig. 3 Methods of application of viral vectors and localisation of proteins coded by genes whose mutations cause retinal disorders, and for which clinical trials with gene therapy are being conducted (taken from http://www.retinalphysician.com and 53). ABCA4 – ATP-binding cassette, subfamily A, member 4; ACH – achrompatopsia; BT – basal body; C – cilium; CNGB3 – Cyclic Nucleuotide Gated Channel Beta 3; CHM – choroideremia; CHM (REP1) – Rab Escort Protein 1; LCA2 – Leber's congenital amaurosis type 2; MERTK – Mer receptor tyrosine kinase; MYO7A – myosin VIIA; RPE – retinal pigment epithelium; RPE65 – retinal pigment epithelium-specific 65 kDa protein; RP38 – retinitis pigmentosa 38; RS1 – retinoschin; STGD1 – Stargardt's disease type 1; USH1B – Usher's syndrome type 1B; XLRS – X-linked retinoschisis; ZS – outer segment

Table 2 Various methods of application of viral vectors in retinal disorders (57)

Method of application	Target cells	Advantages	Disadvantages
Intravenous	Inner layers of retina	No ocular adverse effects in connection with surgical procedure	Opsonisation and phagocytosis of particles, transfection of other tissues
Periocular	Photoreceptors, RPE	Non-invasive for retina	Low transfection of retina and RPE
Intravitreal	Inner layers of retina	Rare ocular adverse effects	Risk of endophthalmitis and retinal detachment
Subretinal	Photoreceptors, RPE	Greatest effect of transfection	Invasive, retinal detachment may lead to cell death
Suprachorioidal	Photoreceptors, RPE	No elevation of neuroretina	Greater speed of elimination

RPE – retinal pigment epithelium

ons in the gene RPE65 (retinal pigment epithelium-specific 65 kDa protein) (18). This gene is virtually exclusively exprimated in the RPE, where it shares in the recycling of opsin and rhodopsin by converting all-trans-retinoids into 11-cis retinal. Insufficient function or absence of RPE65 leads to an accumulation of trans-retinyl esters with a subsequent degeneration of photoreceptors (10).

Despite the fact that the incidence of the disorder is relatively rare (less than 1 afflicted per 1 000 000 born children), LCA2 has been proposed for gene therapy, mainly due to the early manifestation of the disorder, the relatively long-preserved structure of the retina and the availability of animal models (8). The first results of therapy from a dog model published in 2001 demonstrated a significant long-term persisting improvement of visual functions following the subretinal application of a recombinant adeno-associated virus (AAV2) containing RPE65 cDNA (1). In 2007 the first phase I (NCT00481546, NCT00516477; clinicaltrials.gov) and phase II clinical trials were registered (NCT00643747; clinicaltrials.gov), with a plan to include a total of 39 patients with LCA2 by May 2015 (clinicaltrials.gov). At present a phase III trial is under way with subretinal application of modified AAV2 (NCT00999609; clinicaltrials.gov).

In all patients there was an improvement of visual acuity in the treated eye, nevertheless to a considerably variable degree (6, 22, 35). Orientation of the patients in weak light also improved. Sensitivity of the retina measured with the help of a psycho-physiological test with blue and red stimuli on a white and coloured background following adaptation to darkness (47) increased within the course of 1 to 2 months after application of the vector. A further improvement was observed after a period of 6 to 12 months. Subsequently sensitivity of the retina again began to decrease, however, in certain patients after 3 years it remained higher than before the application of gene therapy. The parts of the visual field corresponding to the location of the subretinal injection of the vector were also improved, in which eccentric fixation was generated in these areas in 40% of patients (8). A more fundamental improvement in the function of the retina was observed in older patients. However, by contrast with dog models, changes were not detectable in humans upon electroretinographic examination. The last published study determined that degenerative processes of retinal photoreceptor cells were not halted and continued further following gene therapy. It is assumed that the effect of this treatment is highly dependent on the applied quantity of the vector, and that the applied doses were low (5).

Retinitis pigmentosa 38

Non-syndromic retinitis pigmentosa (RP) is a genetically heterogeneous group of progressive retinal disorders, conditioned by mutations in at least 50 genes (https://sph.uth.edu/retnet/). RP38 (OMIM #613862) is a very rare autosomally recessive form of RP associated with mutations in the gene MERTK (Mer proto-oncogene, tyrosine kinase), causing 1% of non-syndromic RP (44). MERTK is an enzyme necessary for the phagocytosis of separated outer segments of RPE photoreceptors. Loss of the enzyme is a condition of a defect in the phagocytosis of the photoreceptors, with an accumulation of non-degraded rhodopsin metabolites among them, leading to their apoptosis and degeneration of the retina (12). A characteristic symptom of the early phase of RP38 is spotty autofluorescent retinal deposits. Night blindness originates in the first decade of life, and is followed by affliction of the function of the cone cells, frequently with atrophy of the macula (11).

Rat models with mutations in the MERTK gene have been studied for a long period. In these a very rapid accumulation of metabolites takes place among the photoreceptors, as well as a loss of photoreceptors from the 20th day after birth and their complete absence from the 60th day. As a result these models are suitable also for an evaluation of the processes and efficacy of gene therapy in humans.

In a pre-clinical trial, copies of the MERTK gene were introduced into the retina of a rat model with the help of lentiviral vectors, which led to a preservation, and in certain animals also a partial renewal of retinal functions 7 months after application (52). A recent study on a rat model demonstrated that amino-acid substitution of tyrosine with phenylalanine in position 733 in the capsid of the AAV vector enabled preservation of the structure and function of the retina at least 1 year after application (13).

In a phase I clinical trial registered in 2011 (NCT01482195; clinicaltrials.gov) an AAV2 vector was applied to three patients subretinally, renewing the function of the MERTK gene without serious side effects (8).

Usher's syndrome 1B

Usher's syndrome (USH) is a genetically heterogeneous disorder, in which 11 causal genes have been located and mapped to date. Autosomally recessive type 1 is caused by mutations in five known genes (39). All are exprimated in hair cells of the inner ear and photoreceptors of the retina. The form USH1B (OMIM #276900) is caused by mutations in MYO7A (myosin VIIA), the product of which plays an im-

portant role in the transport of opsin in the cells of the photoreceptors and RPE, and is essential for the normal course of the Wald visual cycle (33). In contrast with the hair cells of the ear, the development of photoreceptors is not afflicted, and their necrosis does not take place until during the course of life, as a consequence of an accumulation of metabolites and subsequent dysfunction of synapses (8). USH1B is the most severe form of the syndrome with congenital loss of auditory functions, with affliction of visual functions during the first decade of life and vestibular areflexia. Its prevalence in the European population is estimated at 4.2 cases per 100 000 of the population (16).

Due to the considerable size of the MY07A gene, lentiviral vectors were chosen for its transmission, since they have a greater capacity for the transmitted gene, although they have a lower effectiveness of trasnduction in the photoreceptors than AAV vectors. On a mouse model the renewal of opsin transport was demonstrated (21), which in 2012 led to the commencement of a phase Ia/II clinical trial with the drug UshStat (NCT01505062; clinicaltrials.gov). The preliminary results of these studies have not yet been published. Since damage to the photoreceptors takes place in USH1B immediately from the beginning of the disorder, the next step is attempts to package MYO7A into a more effective AAV vector, which is capable of expression also in this type of cell (8).

Stargardt's disease

Stargardt's disease is a genetically heterogeneous disorder caused by mutations in three genes. The most common autosomally recessive type of Stargardt's disease (STGD1, OMIM #248200) is conditioned by mutations in the gene ABCA4 (ATP-binding cassette subfamily A member 4), which codes the protein contributing to the transport of used parts of photoreceptors into the RPE (2). Mutations in this lipase influence the processing of vitamin A, which leads to an accumulation of toxic bis retinoid A2E, a so-called vitamin A dimer. The result is the necrosis of RPE and photoreceptor cells (57).

A characteristic clinical finding of Stargardt's disease, which affects 1 out of 10 000 of the population, is the presence of yellowish stains in the macula, or diffused around the entire fundus, together with a thinning of the layers of the retina in the macula. A scar progressively forms in the macula, with yellow stains of the character of lipofuscin deposits at the edges or around the entire ocular fundus (32, 46).

Because the size of the cDNA gene ABCA4 substantially exceeds the capacity of regular AAVs, lentiviral vectors were used in the development of gene therapy. On the basis of positive results on a mouse model (29), in 2011 a phase I/II clinical trial was registered with the pharmaceutical StarGen (NCT01367444; clinicaltrials.gov). Its results have not yet been published. In a further trial from 2012, nanoparticles were used for the transmission of a functional copy of ABCA4 on a mouse model for this disease. Following application persistent expression of ABCA4 was recorded, as well as an improvement of adaptation to darkness and a reduction of the accumulation of lipofuscin. However, this procedure has not yet been registered for clinical trials (20).

Choroideremia

Choroideremia (OMIM #303100) is a retinal disorder with heredity bound to the X chromosome, afflicting 1 out of 50 000 men. The disease is caused by mutations in the gene CHM (Rab Escort Protein 1), whose product regulates the transport of vesicles in processes of endocytosis and exocytosis (34) by means of post translational modification (prenylation) of proteins. Patients with choroideremia have a reduced or zero quantity of this enzyme, which leads to defects of opsin transport to the outer segments of the photoreceptors, malfunctions of migration of melanosomes in the RPE cells and reduced phagocytosis of the outer segments of the photoreceptors of the RPE cells (3). The result is degeneration of the choriocapillaris, RPE and photoreceptors. However, it is not clear as to which part of the retina is primarily afflicted upon choroideremia. It is known that a deficiency of CHM leads to functional affliction of the retina before necrosis of the RPE, but it has not been clarified as to whether this concerns a consequence of the deficit or a non-specific influence of the stress on the RPE cells (14). With regard to the fact that damage to the choroid and retina, including the RPE, occurs in the case of choroideremia, it is necessary to ensure the effective transduction of vectors in multiple layers of the cells.

The first step in the development of gene therapy was the preparation of an AAV vector, which implanted the entire CHM gene into the lymphocytes and fibroblasts obtained from patients with choroideremia (4). In the next phase a lentiviral vector was prepared, the application of which on a mouse model led to a partial renewal of enzymatic activity in the RPE cells (51). In 2011 a clinical trial was registered (NCT01461213; clinicaltrials.gov), within the framework of which a functional copy of CHM was applied into the subretinal region of 6 patients, with the help of an AAV vector. An increase in retinal sensitivity was observed in all patients upon microperimetry 6 months after treatment. Average visual acuity improved by 3.8 letters on ETDRS (Early Treatment Diabetic Retinopathy Study) optotypes. In 2015 a further 3 gene therapies were registered using the same principle (NCT02341807, NCT02553135, NCT02407678; clinicaltrials.gov).

Leber's hereditary optic neuropathy

Leber's hereditary optic neuropathy (LHON; OMIM #535000) is the most common mitochondrial disorder manifested in bilateral acute or subacute loss of sight (31, 43). Specific mutations in mitochondrial genes in the case of LHON cause degeneration of the retinal ganglion cells and atrophy of the optic nerve. In more than 90% of cases one of three mutations is determined in the genes MT-ND1 (mitochondrially encoded NADH: ubiquinone oxidoreductase core subunit 1), MT-ND4 and MT-ND6 (43).

These mutations lead to a faulty alignment of complex I of the respiratory chain in mitochondria, which influences the formation of ATP and the generation of an undesirable quantity of reactive acid radicals. As yet it is not clear as to why the effect of these mutations primarily afflicts the optic nerve and not the nervous system as a whole (9).

Transfection of mitochondrial DNA is very difficult. For the development of gene therapy it was necessary to prepare a

vector transfecting nuclear DNA with a sequence that directs the protein generated in the cytoplasma into the mitochondria. This procedure was tested on a mouse and rat model (15, 19). Intravitreal application led to a longer preservation of retinal ganglion cells and an improvement of sight in model animals.

The continuous results of a phase III study (NCT01267422; clinicaltrials.gov) with intravitreal application of an AAV vector with the gene MT-ND4 on 9 patients demonstrated an improvement of visual acuity and sensitivity of the visual field. However, the thickness of the retinal nerve fibre layer was not increased (55).

Achromatopsia

Achromatopsia (OMIM #262300) is characterised by a malfunction of the cone cells and occurs with a prevalence of 1 per 30 000 of the population (50). Of the five genes described to date responsible for the origin of the disorder, mutations in the gene CNGB3 (cyclic nucleotide gated channel beta 3) are the cause of approximately 50% of cases (27). Impairment of the formation of CNG channels (cyclic nucleotide gated ion channel) causes an influx of cations into cells, which leads as far as their apoptosis. By contrast with cone cells, these channels do not appear on rod cells, and as a result scotopic vision remains preserved (38).

Subretinal application of an AAV vector carrying the gene CNGB3 tested on dog models demonstrated the possibility of renewing the function of the cone cells and photopic vision independently of the position of the mutation. However, the therapeutic efficacy and stability of expression of the introduced gene was influenced by the age of the tested animal at the time of application, and the type of the used promoter (28).

In November 2015 two phase I and II clinical trials were commenced with subretinal application of AAV vectors (NCT02610582, NCT02599922; clinicaltrials.gov).

X-linked retinoschisis

X-linked retinoschisis (XLRS, OMIM #312700) is a monogenically conditioned ocular pathology with manifestation in the first decade of life, with a prevalence of 1 person afflicted per 5-25 000 of the population (17). The disease is caused by mutations in the gene RS1 (retinoschisin 1), which in male patients lead to fissure more frequently of the inner layers of the retina, usually in the macular area, accompanied by a decrease of visual acuity (45). The product of the gene is exprimated in the photoreceptors and bipolar cells of the retina. Its function has not been completely clarified, but it is assumed that it contributes to the adhesion of the aforementioned cells (41).

Various serotypes of AAV vectors were tested on a mouse model. Their efficacy depends on the used promoter, and also on the age of the tested animal. Injection of an AAV vector into the retina of a mouse model at the age of 7 months improved the structure of the retina, but not the electroretinographic parameters. In younger animals a partial improvement of the structure and function of the retina takes place following application. These studies indicated that before the implementation of gene therapy for XLRS it is necessary to consider carefully the method of supply, the selection of the vector and the type of used promoter (8).

In 2015 two phase I and II clinical trials (NCT02317887) and NCT02416622; clinicaltrials.gov) with intravitreal application of AAV serotypes 2 and 8 were registered.

Gene therapy within the context of the Czech Republic

None of the several dozen clinical trials testing gene therapy for ocular pathologies currently ongoing are being implemented at centres in the Czech Republic. This unfavourable situation is due to a number of reasons. Of fundamental significance is the lack of legislation stipulating the regulations for clinical trials applying gene therapy, which prevents Czech clinical centres from taking part in international multicentric trials. A role is also played by the insufficient number of experts who could monitor new preparations, and the low level of informedness on the part of the lay and frequently also the professional public concerning rare pathologies, of which hereditary disorders of the eye are no exception.

CONCLUSION

Gene therapies represent a promising approach in the treatment of ocular disorders, in particular for retinal diseases, for which no functioning pharmaceuticals or therapeutic methods are currently available. However, it shall take several years yet before the results of the clinical trials currently in progress are evaluated, and their potential long-term favourable effect is demonstrated.

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