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ACTIVE CLINICAL TRIALS TESTING NEW THERAPIES FOR STARGARDT DISEASE

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SUMMARY

Purpose: To provide information on currently ongoing clinical trials for Stargardt disease.
Methods: We have searched the clinical trial register (www.clinicaltrials.gov) for the keyword „Stargardt" and list active ongoing studies.
Results: There are currently eight registered clinical trials enrolling patients with Stargardt disease; all in phase I or II aiming at four mechanisms of action: inhibition of the production of vitamin A toxic dimers, gene therapy restoring wild type transcription of the *ABCA4* gene, neuroprotection preventing retinal cells from oxidative damage, and replacement of the damaged retinal pigment epithelium using stem cell therapy. The basic prerequisite for enrolment in the vast majority of clinical trials is confirmation of the clinical diagnosis by mutational analysis.
Conclusion: The wide variety of therapies that are registered as clinical trials for Stargardt disease significantly raises the possibility that effective treatments will be available in the near future for this currently incurable condition and that molecular genetic testing should be increasingly considered.

Key words: Stargardt disease, clinical trial, *ABCA4,* mutation

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INTRODUCTION

Stargardt disease and its variant fundus flavimaculatus are hereditary pathologies of the retina which afflict the pigment epithelium and photoreceptors, with an approximate incidence of 1 case per 10 000 of the population. The pathology is manifested in a reduction of central visual acuity, which typically originates in childhood or early adolescence, although manifestation may also occur at a later age (25). A characteristic clinical finding is the presence of yellowish stains in the macula and diffusely around the entire fundus together with thinning of the layers of the retina in the macula (13, 16). The macula takes on the appearance of wrought metal and a scar gradually forms with yellow stains of a character of lipofuscin deposits around the edges. The most reliable clinical method enabling the identification of Stargardt disease is considered to be examination of autofluorescence of the ocular fundus, which manifests a malfunction of distribution. In the areas of accumulation of lipofuscin deposits, autofluorescence is accentuated, whereas by contrast it is lacking in areas of atrophy of the RPE, around which there are irregular grainy areas (12). Optical coherence tomography, fluorescence angiography, examination of the visual field and electroretinograhpy are also used in diagnosis, and may provide further useful information.

Stargardt disease manifests a recessive type of heredity. It is conditioned by mutations in the gene ABCA4, which codes the protein sharing in the transport of used parts of photoreceptors. Mutations in this lipase, which is specific for photoreceptors, influence the processing of vitamin A, which leads to an accumulation of the toxic bisretinoid A2E, known as vitamin A dimer. This state results in necrosis of the retinal pigment epithelium and photoreceptors (22). Mutations in the genes ELOVL4 and PROM1 are very rare and are linked with pathologies similar to Stargart disease (19, 23).

To date no effective treatment is available for Stargardt disease. It is recommended that patients protect their eyes using sunglasses against intensive blue light and ultraviolet radiation, which can cause an increased accumulation of toxic compounds in the retina. Increased consumption of foods rich in vitamin A and vitamin A supplements are unsuitable (14).

New therapeutic methods are being developed intensively. Some have already advanced to the stage of clinical testing, which as a rule is in several phases. In phase I safety is monitored and the maximum tolerated dose is stipulated. It is mostly conducted on one non-randomised group of volunteers. In phase II the effective dose of the drug is determined, again mostly within the framework of a non-randomised trial, used on patients. Phase III compares the efficacy of the new drug with the standard therapy, and testing is conducted on two groups of patients. One group is treated using standard therapeutic procedures, the second group is administered the new treatment and classification and evaluation is generally double-blind. On the basis of the results of this phase the drug may be registered. In the final phase IV, adverse effects of the drug are monitored following registration and upon long-term use (https://clinicaltrials.gov/ct2/about-studies/learn) (10).

Tab. 1 Registrované klinické zkoušky testující nové terapie pro Stargardtovu makulární degeneraci (STGD)

Identifikační číslo	Překlad názvu studie	Testovaný přípravek	Stav	Fáze	Způsob podávání	Státy, kde zkoušky probíhají	Design	Potvrzené příčinné mutace v genu *ABCA4* jako kritérium zařazení	Publikace
Typ: Terapie modifikovaným vitaminem A									
NCT02402660	Tolerabilita a vliv ALK-001 na STGD	ALK-001 (C20-D3-retinyl acetát)	Nabírá pacienty	II	Per os	USA	Randomizovaná, dvojitě slepá, placebem kontrolovaná studie	Ano	(6)
Typ: Genová terapie									
NCT01367444	Bezpečnostní studie zvyšujících se dávek subretinálně injikované SAR422459 pacientům se STGD	StarGen™	Nabírá pacienty	I, II	Subretinální injekce	USA, Francie	Nerandomizovaná	Ano	(4)
NCT01736592	Studie stanovující dlouhodobou bezpečnost, toleranci a biologickou aktivitu SAR422459 u pacientů se STGD	StarGen™	Zařazení pouze na pozvání	I, II	Subretinální injekce	USA, Francie	Nerandomizovaná	Ano	(4)
Typ: Terapie neuroprotektivními látkami									
NCT01278277	Suplementace šafránem u pacientů se STGD (STARSAF02)	Šafrán získaný z pestíků *Crocus Sativus*	Aktivní, ale nenabírá	I, II	Per os	Itálie	Randomizovaná, dvojitě slepá	Ano	(7)
Typ: Buněčná terapie									
NCT01345006	Subretinální transplantace hESC diferencovaných do buněk RPE (MA09-hRPE) u pacientů se STGD	Buňky MA09-hRPE	Aktivní, ale v současné době nenabírá	I, II	Subretinální transplantace	USA	Nerandomizovaná	Ano nebo ochota podstoupit genetické testování	(17, 18)
NCT02445612	Dlouhodobé sledování pacientů po subretinální transplantaci hESC diferencovaných do buněk RPE u pacientů se STGD	Buňky MA09-hRPE	Zařazení pouze na pozvání	I/II	Subretinální transplantace	USA	Nerandomizovaná	Ano nebo ochota podstoupit genetické testování	(17, 18)
NCT01469832	Bezpečnost a tolerance subretinální transplantace hESC diferencovaných do buněk RPE u pacientů se STGD	Buňky MA09-hRPE	Aktivní, ale v současné době nenabírá	I/II	Subretinální transplantace	Velká Británie	Nerandomizovaná	Ano nebo ochota podstoupit genetické testování	(17, 18)
NCT01920867	Léčba kmenovými buňkami v oftalmologii	Autologní kmenové buňky získané z kostní dřeně	Nabírá	Neuvedena	Retrobulbární, subtenonská, intravitreální, intraokulární a intravenózní injekce	USA	Nerandomizovaná	Ne	(20, 21)

hESC = lidské embryonální kmenové buňky, RPE = retinální pigmentový epitel

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OBJECTIVE

The objective of the study is to present an overview of the newly developed methods of treating Stargardt disease, in which clinical testing on patients has already been commenced.

METHODS

We searched the international clinical trial register (www.clinicaltrials.gov) for the keyword "Stargardt".

RESULTS

As of 9 September 2015 we had found 20 records of clinical trials testing new drugs and methods for Stargardt disease, a summary of active studies is presented in Table 1.

The clinically tested therapeutic procedures are focused on a number of different biological mechanisms. The first sets as its objective to prevent the generation of toxic dimers of vitamin A in the eye, without at the same time influencing the physiological process of conversion of vitamin A, which is essential for the correct function of the retina. Patients are administered the substance C20-D3-retinyl acetate (ALK-001). This concerns chemically modified vitamin A, substituting natural vitamin A.

The second procedure is gene therapy, which sets as its objective compensation for the reduced or zero function of the mutated gene ABCA4 by the introduction of a fully functional copy with the help of vectors.

Substances acting neuroprotectively, i.e. protecting the retinal cells against damage by photo-oxidation such as saffron, are also being tested. The ongoing clinical trial is determining the influence of short-term supplementation by saffron on the retinal functions in patients with Stargardt disease or fundus flavimaculatus. These three above-mentioned procedures relate to patients with relatively well preserved retinal functions, with the aim of slowing or halting the progression of the disease.

The last approach is stem cell therapies, which are being developed for patients with an advanced finding, i.e. necrosis of a large proportion of cells of the retinal pigment epithelium and photoreceptors, the objective being to replace already expired cells.

DISCUSSION

The newly developed therapies of Stargardt disease are aimed at a range of various different approaches, from preventing the formation of toxic metabolites (6) through substituting the function of a defective gene (2), neuroprotection of the retina (5) up to the replacement of dead cells, which have been reprogrammed into a phenotype of the retinal pigment epithelium (24).

By exchanging three hydrogen atoms for deuterium in vitamin A, a deuterated vitamin A termed ALK-001 has been developed, which prevents the generation of toxic vitamin A dimers, leading to a reduction of the formation of lipofuscin without influencing the retinal function (6). The mechanism of formation of lipofuscin in the retina as a waste cytotoxic product of the metabolism of the outer segments of the photoreceptors has not yet been fully clarified. It is thought that it is generated in the outer segments of the rods as a by-product of a reaction which takes in the retinal chromophore rhodopsin. Lipofuscin is a compound of partially digested proteins and lipids, and accumulates in the endosomal compartment of the RPE. Its sole known component is bisretinoids, condensation products of two retinal molecules (1).

Stargardt disease occurs on a background of the presence of mutations in a single gene, and thus concerns a monogenic pathology, which is appropriate for gene therapy. However, a drawback of ABCA4, mutations of which cause Stargardt disease in the great majority of patients, lies in the fact that this is a large gene which is not suitable for transmission via adeno-associated viral (AAV) vectors, which have hitherto been viewed as the most successful in gene therapy of monogenic ocular pathologies (2). As a result, new AAV vectors, lentiviral vectors and non-viral compact DNA nanoparticles are being developed (9). The last two in particular have a large capacity and their use has led to a positive influence on the course of the pathology in Abca4 (-/-) in a model on mice (8, 11).

With regard to the fact that Stargardt disease originates on a background of oxidative damage to the retinal cells, the third therapeutic approach ensues from trials which have indicated that saffron has a neuroprotective effect (5, 15). Specifically it has been determined that sown saffron stigmas contain high concentration of a number of chemical compounds, including crocin and crocetin, the multiple C=C bonds have antioxidant potential. In addition, it is known that these compounds do not have side effects and their application is safe (7).

A considerable amount of hope has been invested in therapy using stem cells, which have the capacity to convert into any cell type, in a range of other disciplines as well as ophthalmology. Clinical trials applying human embryonic stem cells terminally differentiated into retinal pigment epithelial cells have been registered for Stargardt disease. Various doses of cells are transplanted in patients subretinally, within the range of tense of thousands, and their healing, visual functions of the patient and complications of therapy are observed (17, 18). Another trial is testing the use of stem cells derived from bone marrow in ophthalmology. Candidates are patients with a whole range of pathologies, in addition to Stargardt disease there are also various hereditary or acquired retinopathies and optical neuropathies (20, 21). In the case of Stargardt disease, retrobulbar, subtenon and intravitreal application of cells is being tested. Local eye therapy is followed by the intravenous application of cells (S. Levy, Margate, USA, personal communication).

It is necessary to note that the process of using stem cells has a range of drawbacks, which amongst other factors include the immune response, which may represent a significant problem influencing the results of therapy. As a result, research utilising induced pluripotent stem cells is also taking place, residing in the fact that the patient's own stem cells are taken, e.g. fibrocytes from

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the skin, which are reprogrammed in tissue cultures via an intermediate degree of stem cells into cells of the retinal pigment epithelium or photoreceptors. The launch of clinical trials using induced pluripotent stem cells is expected in the very near future (24).

With the development of new targeted therapies, there is increasing significance of diagnosis on a molecular genetic level. Due to the risk of failure of treatment or potential damage, especially in the case of invasive gene therapies, the determination of causal mutation confirming clinical diagnosis is with only one exception a condition for inclusion in active clinical trials (Table 1).

For all newly tested therapies it applies that even the best results on animal models preceding clinical trials testing a given drug or therapeutic method do not guarantee success in humans. For example, only recently it was demonstrated that gene therapy of the mutated gene RPE65, in contrast with the model on dogs, has no long-term effect on humans. The examiners are of the view that the applied dose was most probably too low for humans (3).

CONCLUSION

Even despite the shortcomings in connection with new therapeutic procedures, the developments to date are bringing hope that effective treatment of pathologies conditioned by mutations in the gene ABCA4 can be expected in the near future.

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