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Research Article

Myopia Control in European Children – Study Protocol and Methodology

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Abstract

Purpose

To report study protocol and methodology of multicentre, randomized, double-blind, placebo-controlled study of the efficacy and safety of low dose atropine eye drops (0.02%, 0.04%) in slowing the progression of short-sightedness (myopia) in children. M.A.R.S. (Myopia and Atropin ReStriction).

Patients and Methods

M.A.R.S. is ongoing, multicentre, randomized, double masked, placebo-controlled phase IIIb trial with three parallel arms. This is a paediatric clinical trial in which 288 children (6-12 years) with myopia (from -0.5 to -4, 75.0 dioptres) will be randomized in period from June 2022 till the end of October 2022. The medicinal product evaluated is highly diluted atropine collyrium (eye drops) in two concentrations (0.02% and 0.04% atropine). In the control arm, a placebo collyrium is administered. The randomization ratio was set as 2:1:1 to the 0.02% atropine, 0.04% atropine, and placebo arms. Randomization takes place electronically in the eCRF REDCap database. Stratification of patients within individual arms is planned according to age intervals (6-7 years, 8-9 years and 10-11 years) and according to 5 centres. Treatment with study medication takes place from the day of randomization for 2 years daily, for the next 1 year, patients will be monitored within the washout period (without treatment) to evaluate the rebound phenomenon. As part of the study, complex of ophthalmological examinations will be performed to evaluate the primary and secondary outcomes of the study. The safety of the treatment will be monitored by recording all adverse events and treatment-related adverse events as well as patient reported outcomes.

Primary outcome is to determine the difference in the axial length of the eye (AXL) during the 12 months application period when applying 0.02% atropine versus placebo.

Secondary outcomes are focused to four atropine treatment aspects: the study treatment's efficacy, mechanism of action, acceptability and safety.

Conclusion

M.A.R.S. clinical trial will enrich the knowledge about myopia and its possible treatment in the early stages in European children. It will be beneficial for paediatric patients, practicing paediatricians and ophthalmologist. In the future it will be helpful not only from a medical point of view, but also in economic aspect of management of progression of myopia in children and all the entire population.

Trial registration numbers

NU21-07-00189; EudraCT No: 2020-002046-16.

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Keywords: Atropine eye drops; Axial length of eye; Low dose atropine; Myopia in children; Progressive myopia

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Introduction

The occurrence of myopia has been progressively increasing for several decades and is now the most common eye disease in the world. The current increase in the incidence of myopia in the young population will be reflected in the growth of the overall prevalence in the future. Mathematical models expect the myopization of half of the global population and estimate the prevalence of high myopia at almost a tenth of the global population in 2050. The WHO considers this trend to be an incipient pandemic [1]. The current prevalence of myopia in the European population of nine-year-old children is 11.4%. As a result of myopization during adolescence, the current population of adult myopes is threefold (37.0%) [1, 2].

Myopia, especially degenerative (> 5.0 D, with prevalence 0.9-3.1%) causes significant risk of serious eye diseases such as macular atrophy, myopic choroidal neovascularization (incidence 5.2 – 11.3 % in high myopia), macular whole (incidence 6 - 8%) or retinal tears with the risk of retinal detachment [2-4]. Highly myopic eyes are also

prone to develop cataracts and glaucoma [5, 6]. In Europe, pathological forms of myopia are the most common cause of vision impairment at productive age [7].

Except genetic factors, myopization is boosted by peripheral retinal defocus. The effect of external factors has also been demonstrated: insufficient time of outdoor stay, excessive visual strain at close range, intensive education. At present, the dominant role of a complex interaction of non-genetic, i.e. retinal, optical and environmental/behavioral influences is assumed [8-12].

Therapeutic concepts are focused on influencing individual etiological modalities [13-16]. the time devoted to staying outside limits the onset and initial development of myopia; however, it does not impact the slowing down of the ongoing myopization. Local growth regulation can also be therapeutically influenced by spectacles and contact lenses. Standard spectacle correction promotes the myopia progression by peripheral hyperopic defocus. Special optical systems reducing peripheral hyperopic defocus have been designed. The orthokeratological concept applying rigid contact lenses at night to achieve corneal flattening is effective predominantly in refractive (corneal) myopia [17,18].

Several studies on Asian population showed effect of local atropine eye-drops on reduction of myopia progression (ATOM I and II, LAMP) [19,20] The effect was dose dependent, however stronger rebound phenomen in wash-out period was observed in stronger concentrations (0.5%). There are two main clinical trials verifying the benefits and risks of two-year administration of 0.01% atropine in European children. The Irish MOSAIC [21] and British multicenter CHAMP-UK [12] studies.

The purpose of M.A.R.S. clinical trial is to extend clinical knowledge about the effect of highly diluted atropine topical application on the axial length growth of myopic eyes in the population of European children. While previous studies primarily monitored the development of a spherical equivalent, recent attention is focused on AXL as a more explicit parameter directly affected by atropine and highly correlated to myopic complications. The trial is designed as a multicenter, randomized, double-blind, placebo-controlled phase IIIb study with three parallel arms. The evaluated medicinal product is highly diluted atropine collyrium (eye drops) in two concentrations (0.02% and 0.04% of atropine).

Design of Study

Summary of design

Clinical trial M.A.R.S. is a multicentre, randomized, double-blind, placebo-controlled phase IIIb trial with three parallel arms. This is a pediatric clinical trial in which 288 patients will be randomized. The medicinal product evaluated is highly diluted atropine collyrium (eye drops) in two concentrations (0.02% and 0.04% atropine). In the control arm, a placebo collyrium will be administered. Treatment with study medication will take place from the day of randomization for 2 years daily, for the next 1 year, patients will be monitored within the washout period (without treatment) to evaluate the rebound phenomenon. As part of the study, ophthalmological examinations will be performed to evaluate the primary and secondary objectives of the study. The safety of the treatment will be monitored by recording all adverse events and treatment-related adverse events (TRAEs) as well as Patient Reported Outcomes (PROs).

Randomization

Randomisation period is from June 2022 till end of October 2022. The aim is to randomize 288 subjects. The randomization ratio was set as 2:1:1 to the 0.02% atropine, 0.04% atropine, and placebo arms. Randomization will take place electronically in the eCRF REDCap database. Stratification of patients within individual arms is planned according to age intervals (6-7 years, 8-9 years and 10-11 years) and according to centers.

Blinding and unblinding

Study participants, their parents/legal guardians as well as examining physicians and study nurses will be blinded to the administered medicinal product. All preparations will be administered in an identical pharmaceutical form (eye drops).

If the study participant shows a significant deterioration in his health and it is necessary to obtain information about the administered study medication in order to decide on the appropriate treatment, the examining physician may exceptionally unblind the subject. This activity can be performed directly in the REDCap electronic database. Information about assigned treatment must not be disclosed to the patient or his/her parent/guardian. It is necessary to consult whether unblinding is necessary with the principal investigator at the given center, and inform the contracting authority.

Participants

Inclusion criteria

The patient must meet all of the following criteria to be included in the study:

1. Age 6-12 years (up to and including the 12th birthday on the day of randomization)
2. Diagnosis of myopia – spherical component of refraction -0.5 Dsf to -4.75 Dsf and astigmatism 0 to -2.5 Dcyl in at least one eye1
3. BCDVA of the worse eye better or equal to 0.2 logMAR (according to the ETDRS test, 85 cd/m2)
4. Index of corneal topography (front surface of the cornea): KI > 1.07; ISV < 37 in at least one eye
5. Normal eye findings and medical history in both eyes (with the exception of spectacle correction and banal eye diseases, e.g. acute conjunctivitis in the medical history, irrigation of tear ducts in early childhood)
6. Normal binocular function of both eyes (in the sensory and motor component) with the exception of exophoria equal to or greater than 8 DP incl. in an alternating masking test with prisms
7. Normal intraocular pressure (≤ 22 torr, non-contact applanation) in both eyes
8. Fulfilment of the indication criterion "AXL growth in 6-8 months" in the 9-month follow-up period before inclusion in the study according to the data in the patient's medical records in at least one eye: (Table 1)
9. Willingness of the patient and his/her parents/guardian to undergo a two-year period of daily application of eye drops, a three-year period of clinical examinations every six months and weekly diary entries during this period.

Age-range	Growth of AXL in 6M	Growth of AXL in 7M	Growth of AXL in 8M
6−7 let	0,10 mm	0,11 mm	0,12 mm
8−9 let	0,11 mm	0,12 mm	0,13 mm
10−11 let	0,12 mm	0,13 mm	0,14 mm

Table 1: Growth of AXL in children before inclusion to the study. (Inclusion criteria).

Exclusion criteria

A patient who meets at least one of the following criteria may not be included in the study:

1. General disease predisposing to myopia (Marfan's, Stickler's syndrome) or affecting visual functions (diabetes mellitus, chromosomal anomalies)
2. Previous pharmacological, surgical and/or orthokeratological therapy for myopia 3) Previous long-term treatment with atropine (i.e., more than 14 days)
3. Presence and/or history of allergic reaction to ophthalmic (atropine; cycloplegic – cyclopentolate, tropicamide; local anaesthetics – e.g. oxybuprocaine, etc.)
4. Presence of strabismus, amblyopia, glaucoma, corneal damage and/or scarring, and current and/or previous ocular conservative, contactology, and/or surgical therapy
5. Presence and/or history of general illness (including allergies, myasthenia gravis, cardiac, respiratory and/or renal-urological disease and/or dysfunction)
6. Presence or planned initiation of long-term (i.e. longer than 14 days) general and/or local drug therapy and/or planned surgical therapy for the period of participation in the study
7. Concomitant use of monoamine oxidase inhibitors (MAOIs)
8. Pregnancy, possibly breast feeding
9. Presence of rhinitis sicca

Evaluated Medicines

Atropine collyrium, concentration 0.02% and 0.04%

The evaluated medicinal product is prepared as an IPLP according to the technological prescription in the General Hospital Pharmacy.

Active substance: Atropine in salt form Atropini sulfas monohydricus

Excipients: Sodium chloride Carbethopendecinii bromidum (antimicrobial additive).

Outcomes of Study

Primary outcomes and monitored parameters

The primary outcome of the clinical evaluation is to determine the difference in the axial length of the eye (AXL) during the 12M application period when applying 0.02% atropine versus placebo.

We hypothesize that 0.02% atropine will be more effective than placebo, i.e., that the change in AXL will be greater in the placebo arm than in the active treatment arm.

Secondary outcomes and monitored parameters

Secondary outcomes related to effectiveness:

- AXL difference over a 12M application period when applying 0.04% atropine versus placebo
- AXL difference over a 12M application period when applying 0.02% atropine versus a concentration of 0.04%
- AXL difference over the 24M application period when applying 0.02% and 0.04% atropine versus placebo and each other
- Rebound phenomenon in both active arms (0.02% and 0.04%) in the period 24M−36M against placebo and each other
- Difference of spherical equivalent of cycloplegic refraction (SER) over the 12M application period (0.02% and 0.04% versus placebo and each other)
- SER difference over the 24M application period (0.02% and 0.04% against placebo and each other) • AXL/CR index difference over the 12M application period (0.02% and 0.04% against placebo and each other)
- Difference of the AXL/CR index for the 24M application period (0.02% and 0.04% against placebo and each other)
- Visual functional characteristics (BCDVA – best corrected distance visual acuity; BCNVA – best corrected near visual acuity; contrast sensitivity; colour sensitivity)

Secondary outcomes related to the mechanism of the origin and development of the disease

- Other growth characteristics of the eye (anterior segment biometry: corneal topography and keratometry, anterior chamber, lens thickness, anterior chamber horizontal dimension (WTW); choroidal thickness)
- Functional characteristics of the eye (NPA - test of near point of accommodation; NPC - test of near point of convergence; accommodation facility)
- SE peripheral defocus
- Influence of genetic disposition (refractive defect of parents, body height and BMI)
- Influence of lifestyle (staying outdoors, working close to home, including technology)

Secondary outcomes related to safety and tolerability of treatment

- Intensity, severity and frequency of any side effects
- Systemic (heart rate and other reported adverse events)
- Ophthalmological TRAEs
- Visual comfort of subjects
- Change in retinal vascularization, RNFL – retinal layers of nerve fibres, intraocular pressure, iris colour
- Static photoreaction (photopic and [scotopic] mesopic pupil diameter) ▪ NPA, NPC and accommodative facility

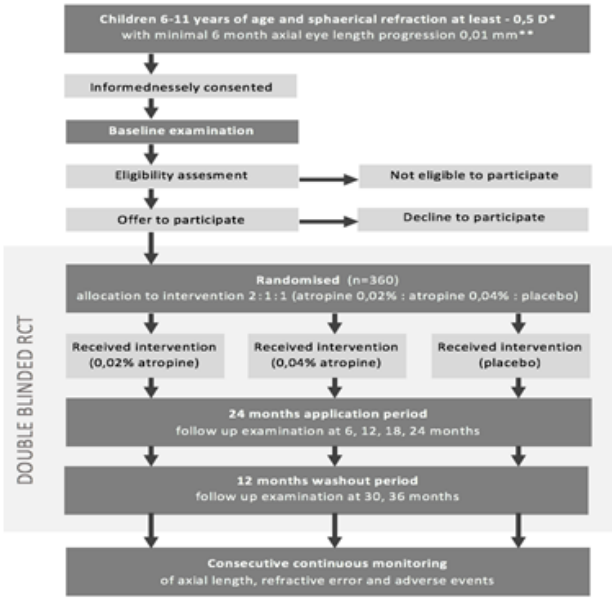

Figure 1: M.A.R.S. study flow chart with outcome timeline.

			Application period						Washout period	
			Visit 1 Baseline	Visit 2 0,5 months	Visit 3 6 months	Visit 4 12 months	Visit 5 18 months	Visit 6 24 months	Visit 7 30 months	Vidsit 8 36 months
Standard clinical practice		Medical History: record/update	✓	✓	✓	✓	✓	✓	✓	✓
		Eye Morphology: anterior/posterior segment	✓	✓	✓	✓	✓	✓	✓	✓
		Binocularity: motoric and sensoric functions	✓		✓	✓	✓	✓	✓	✓
Study Intervention		Dispensing of Study Medication: 0,02%, 0,04% atropine and placebo	✓	✓	✓	✓	✓	✓		
		Compliance		✓	✓	✓	✓	✓		
Primary outcome		Ocular Axial Length (AXL)	✓		✓	✓	✓	✓	✓	✓
Secondary outcomes	Efficacy	Best-corrected Distance / Near VA	✓	✓	✓	✓	✓	✓	✓	✓
		Subjective Refractive Error **	✓	✓	✓	✓	✓	✓	✓	✓
		Contrast Sensitivity	✓			✓		✓		✓
		Colour Vision	✓			✓		✓		✓
		Cycloplaegic Refractive Error	✓			✓		✓		✓
	Mechanism	Lifestyle (anamnestic)		✓	✓	✓	✓	✓	✓	✓
		Parental Refractive Error (anamestic)	✓							
		Height	✓		✓	✓	✓	✓	✓	✓
		Weight (BMI)	✓							
		Anterior Segment Biometry (K1, K2, CCT, ACD, LT, WTW)	✓		✓	✓	✓	✓	✓	✓
		Subfoveal Chorioideal Thickness *	✓		✓	✓	✓	✓	✓	✓
		Periferal Retinal Defocus *	✓			✓		✓		✓
	Acceptability	Side Effects Monitoring: iatrogenic presbyopia & photophobia		✓	✓	✓	✓	✓	✓	✓
		Quality of Life and Discomfort related to Treatment: younger participant perspective***			✓	✓	✓	✓		
		Quality of Life Atropine Treatment Impact: older participant perspective ***			✓	✓	✓	✓		
		Quality of Life Atropine Treatment Impact: parental perspective ***			✓	✓	✓	✓		
		Pupillar Diameter: photopic, scotopic (mesopic)	✓		✓	✓	✓	✓	✓	✓
		Pupillar Dynamics *	✓		✓	✓	✓	✓	✓	✓
		Accommodation and Vergence: NPA, NPC, AF	✓		✓	✓	✓	✓	✓	✓
		Accomodation Dynamics *	✓			✓		✓		✓
	Safety	Side Effects and Adverse Events Monitoring		✓	✓	✓	✓	✓	✓	✓
		Heart Rate	✓	✓	✓	✓	✓	✓	✓	✓
		Corneal Surface Irritation	✓		✓	✓	✓	✓	✓	✓
		Retinal Nerve Fiber Layer (RNFL)	✓		✓	✓	✓	✓	✓	✓
		Macular Microcirculation *	✓		✓	✓	✓	✓	✓	✓
		Intraocular Pressure	✓			✓		✓		✓
		Bulbar Redness *	✓			✓		✓		✓
		Iris Colour	✓			✓		✓		✓
		Metamorfopsia	✓			✓		✓		✓
		Pregnancy Test	✓							

Figure 2: M.A.R.S. assessments schedule at baseline examination, application and washout periods.

Legends : ACD anterior chamber depth, AF accommodation facility, ATI Amblyopia treatment index, AXL Axial length, BMI Body mass index, CCT Central corneal Thickness, LT Lens Thickness, NPA Near point of Accommodation NPC Near point of convergence, VA Visual acuity,

if instrumentation available, ## if VA worsened.

- Corneal and conjunctival irritation (Oxford fluorescein test) • Compliance reported by the patient (or parents, legal representative)
- Quality of life and discomfort associated with therapy: self-report by younger patients • Impact of atropine therapy on quality of life (Paediatric Eye Disease Investigator Group [PEDIG] ATI questionnaire) assessed by patient and parent/guardian

Timeline of Study Protocol

M.A.R.S. is a placebo-controlled, double-masked, multicentre, randomised clinical trial (RCT) designed to assess the efficacy, mechanism, acceptability and safety of long time locally administered highly diluted (0,02% and 0,04 %) atropine in the deceleration of myopia progression. The trial protocol comply with Standard Protocol Items Recommendations for Interventional Trials (SPIRIT guidelines). The progress of subjects through the M.A.R.S. trial periods declare study flow chart partially conforming the CONSORT group recommendations [16]. The crucial step of RCT design is ramification into three entirely parallel branches. Eligible participants are allocated to 0, 02% atropine (50 % of subjects), 0, 04 % atropine (25 % of subjects) and placebo (25 % of subjects) eye drops administration every evening for 24-months application period. No local pharmacological intervention is administered during consecutive 12-months washout period. Beside scheduled outcome measurements, participants' myopia is managed according to standard clinical practice. (Figure 1).

Study visits

At the baseline visit (visit 1), objective eligibility of each subject to participate in the trial is assessed by judging of adherence to inclusion criteria. The subjective intention-to-treat potential of parents/guardians and participants is confirmed during entrance interview. If necessary, the tray out of parental ability to instil and children ability to tolerate instillation of eye drops is allowed with artificial tears. After the baseline visit, all participants will attend a trial centre every six months (± 2 weeks) across application and washout periods for scheduled output measurements. Entire set of measurements and examinations completed at baseline visit is conducted during study visits, excluding visit 2 assigned to early adverse events' detection scheduled two weeks after start of medication. Slightly reduced set of measurements is administered at odd visits. (Figure. 2).

Following completion of the wash out period by visit 8 (in 36. month of RCT), the standard clinical care will be offered continuously to all participants. Their refractive error development and possible adverse events will be evaluated.

M.A.R.S. assessments schedule at baseline examination, application and washout periods

Legends : ACD anterior chamber depth, AF accommodation facility, ATI Amblyopia treatment index, AXL Axial length, BMI Body mass index, CCT Central corneal Thickness, LT Lens Thickness, NPA Near point of Accommodation NPC Near point of convergence, VA Visual acuity, # If instrumentation available, ## if VA worsened.

Risks

Possibility of adverse effects

The parasympatholytic effect of the application of even highly diluted atropine (0.02% and 0.04%) brings about mydriasis and a reduction of the accommodation reaction (iatrogenic presbyopia). Any subjective problems (ranging from a feeling of mild glare to photophobia) caused by dilated pupils and/or their reduced photoreaction (restriction of reflex narrowing when adjusting exposure to incident light) will be compensated in the study by using photochromic eyeglass frames. Reduction of the accommodation reaction subjectively felt as a limitation for close school work (reading, writing, working with mobile digital devices, etc.) will be compensated within the study with the help of bifocal (possibly progressive) glasses. From the point of view of frequency, the conducted studies rank between very common and frequent, but they are not serious. Classical anticholinergic side effects may also occur (mental changes, tachycardia, dry mouth, reduced sweat production glands, reddening of the skin, micturition disorders or increased intraocular pressure - they are not serious and their frequency is very low) and symptoms associated with a different reaction of the immune system to the drug (allergic conjunctivitis, dermatoconjunctivitis, allergic edema and/or eczema of the eyelids, urticaria, possibly anaphylactic shock. Another risk is the possibility of assigning the patient to the placebo arm, in which the active study medication will not be administered and therefore no beneficial effect on the progression of myopia is expected.

Adverse effects and serious adverse effects. AE & SAE Serious adverse events related to the participants' participation in the trial are reported in accordance with the guidance from the European Clinical Trials Directive 2001/20/EC (https://ec.europa.eu/health/human-use/clinical-trials/directive_en).

Statistics

Determining the sample size: A total of 288 patients will be randomized to the study, of which 72 to the placebo arm, 72 to the arm with collyrium with a concentration of 0.04% atropine and 144 patients to the arm with collyrium with a concentration of 0.02% atropine (i.e. in a randomization ratio of 1: 1 : 2). The number of patients was determined based on the primary hypothesis of the study, which is a comparison of the change in AXL over 12 months of treatment in the placebo arm vs. in the arm with an atropine concentration of 0.02%. The determined sample size will allow detecting a difference in AXL change over 12 months of 0.1 mm at a significance level of α=0.05 and a test power of β=0.8, which is sufficient for this type of study. The expected drop-out rate (i.e. the proportion of patients who will be randomized but do not complete the study in terms of evaluation of the primary efficacy parameter after 12 months of treatment) is 10%. Multiplicity of testing was not taken into account in the sample size calculation, as additional efficacy analysis will be assessed as secondary (change in AXL placebo vs concentration 0.04%; concentration 0.02% vs 0.04% at 12 and 24 months; placebo vs concentration 0.02% over 24 months).

Efficiency analysis: The primary efficacy parameter will be the change in AXL values after 12 months of treatment compared to baseline values. Comparison of changes in AXL values between study arms will be performed by unpaired t-test (if the prerequisites for the use of this test are met) or the non-parametric alternative Mann-Whitney U test. ANOVA will be used to compare efficacy between study arms when adjusting for baseline values and other covariates.

Comparisons of efficacy parameters expressed as binary or categorical data (e.g. proportions of patients) will be performed by Fisher's exact test and Chi-square test.

Safety analysis: The safety analysis will be based primarily on the evaluation of all recorded AEs, including SAEs assessed according to severity, intensity and relationship to the study medication, and on the evaluation of the results of ophthalmological instrumental examinations. Safety data will be evaluated primarily descriptively.

Level of importance: For confirmatory statistical testing, the significance level will be used: $\alpha = 0.05$. Deviations from the statistical plan: All deviations from the original statistical plan will be recorded and justified in the final clinical trial report.

Data Control and Protection, Quality Assurance

Centres conducting clinical trials will be regularly monitored to ensure the safety of trial subjects and the quality and integrity of research data obtained. The chief medical examiner is responsible for the correctness and completeness of the data entered into the eCRF. Each investigator undertakes to cooperate with the monitor, to make available to him the internal medical records of the patients and to enable him to control the conduct of the clinical evaluation in accordance with the applicable legislation and the requirements of good clinical practice. Monitoring will take place according to the Monitoring Manual. A report will be drawn up from each monitoring visit on the progress, findings and resolution of any irregularities. Examinees undertake to familiarize themselves with the monitor's report and to ensure that all possible discrepancies are rectified.

The Ministry of Health CZ, SÚKL and the ethics committee have the right to conduct an audit/inspection of the clinical evaluation carried out in the centres. Therefore, examinees also undertake to cooperate fully with auditors and inspectors.

Patients will be marked with identification codes in the clinical trial. The key to this pseudonymization will be stored by the examining physician at the centre conducting the clinical trial.

By signing the informed consent, the parents/legal representative of the child express their consent to the fact that the examining physician can present the child's non-anonymized internal health documentation to authorized persons (i.e. monitor, auditor, or inspector). All clinical trial documentation, both paper and electronic, is confidential and must not be made available to anyone outside of the designated clinical trial team. All personal data about the subjects of the evaluation will be protected according to the applicable legislation. Medical records related to the study will be kept at the canter for 15 years.

Ethical Aspects

The clinical evaluation will be conducted in accordance with the applicable legislation and the requirements of good clinical practice according to the ICH-GCP Guidelines, in order to ensure the rights and safety of the subjects of the clinical evaluation and the integrity of the obtained research data. All relevant documents and their possible significant changes will be assessed by the ethics committee. Patients falling into the category of so-called vulnerable subjects, namely children aged 6–12, will be included in the clinical evaluation.

Parents or the child's legal representative will receive written information and an informed consent form for the parent/legal representative, while the examining physician will be informed in an understandable manner about the nature, purpose and significance of the clinical evaluation before the child's inclusion in the study. The parents/legal representative will also be informed about the measures that will be taken for the protection of personal data and also about the fact that in the event of damage to health as a result of the clinical evaluation, liability insurance has been arranged for the investigator and the sponsor, in accordance with the applicable legislation, whose possible compensation of the assessment subjects is also ensured.

Paediatric patients will receive information from the investigator about the clinical trial tailored to their level of knowledge and reasoning, including information about the benefits and risks of participating in the clinical trial. The explicit wish of informed paediatric patients to refuse participation or to withdraw from the clinical evaluation at any time will be respected. Written information and an informed consent form will be prepared for patients who will reach the age of 12 at the time of enrolment in the study.

Paediatric patients and their parents/guardians will be given sufficient time to thoroughly review the written information and informed consent form and will be allowed to ask additional questions that must be answered satisfactorily by the examining physician.

Clinical evaluation funding and insurance

This is an academic clinical evaluation without the participation of pharmaceutical companies. It is supported from institutional and grant sources.

Compulsory insurance of subjects of clinical evaluation will be ensured in accordance with legal requirements and rules of good clinical practice.

Discussion

Myopia control therapeutic concepts are focused on influencing individual etiological modalities. Standard practices are inspired by environmental/behavioural factors of myopization. The time spent in the outdoor environment limits the onset and subsequent initial development of myopia, but surprisingly, it has no effect on the slowing down of already ongoing myopization [13]. The influence of the external environment is not related to physical activity but to the action of natural visual stimuli [12, 14], and/or the influence of the natural spectral composition of light on the release of dopamine, or other neurotransmitters slowing the growth of the axial length of the bulb. The effect of ultraviolet radiation on the properties of scleral collagen is also a potential benefit [15]. Although the proportion of long-term accommodative load when looking down is conclusive [16] the effect of the use of modern technologies (mobile communication devices) is still controversial [17]. Local growth regulation can also be influenced therapeutically through glasses and contact lenses. Standard spectacle correction, however symptomatically necessary, promotes the progression of myopia [10] by increasing the area of the peripheral retina exposed to hyperopic defocus. Optical systems reducing peripheral hyperopic defocus related to the asphericity of the myopic elongated eye were newly designed for the correction of myopia. Bifocal correction glasses, or contact lenses have a peripheral zone with a lower minus power than their central part, which projects the fixed object into the centre of the retina. In the case of contact lenses, peripheral hyperopic defocus is reduced by several segments, the so-called plus segments [22]. Progressive (so-called multifocal) systems differ only in the adjustment of the transition zone between segments. They were clinically tested, for example, within the COMET study [23]. Lenses with an extended depth of field base their effectiveness on the universal (i.e. bidirectional) ability to reduce defocus [1]. Their effectiveness supports the theory of myopic defocus. The

orthokeratological concept of applying hard, oxygen-permeable contact lenses at night with the aim of limiting the progressive arching of the cornea and/or achieving its flattening is effective especially in refractive (curvature) myopias [24].

The effect on the progression of the axial length of the bulbs was verified by the ROMIO and TO-SEE clinical studies [18]. For in clinical practice, a comparison of the resulting effectiveness of individual therapeutic concepts is relevant present meta-analytic studies. The most extensive was presented by the American Ophthalmological Society association [25]. This is a meta-analysis of 16 procedures performed on a total of 5422 eyes. Her the results confirmed a statistically significant effect only with long-term application of highly diluted (0.01%) of atropine (see below) and are in good agreement with other clinical and meta-analytic studies [26].

The mechanism by which highly diluted atropine slows the development of myopia, i.e. acts against growth the axial length of the bulb and the increase in refractive error has not yet been fully investigated [27]. Original the assumption of a connection with the influence of accommodation was ruled out by experiments on chicken's models [22]. Current nonaccommodative hypotheses about the effect of topically applied atropine on scleral remodelling is assumed by several possible mechanisms.

The first is the non-selective action of atropine on muscarinic M1 and M4 amacrine receptors cells with a subsequent cascade of neurochemical events in the retina [28]. Another option is non-muscarinic mechanism inhibiting the synthesis of glucosaminoglycans in scleral fibroblasts [29]. Another idea about the possible effect of atropine on the emmetropization process is based on the increased effect of ultraviolet radiation on scleral collagen with a wider pupil [15]. A marginal direction of research is the study of the effect of atropine on chronic inflammatory processes of the eye causing an acceleration in the growth of its axial length [30].

Several studies on Asian population showed effect of local atropine eye-drops on reduction of myopia progression (ATOM I and II, LAMP) [19, 20]. There are two main clinical trials verifying the benefits and risks of two-year administration of 0.01% atropine in European children, the Irish MOSAIC and British multicentre CHAMP-UK. Our M.A.R.S. study bring extension of clinical knowledge about the effect of topical application of highly diluted atropine on the growth of the axial length of myopic eyes of European children. The Oxford Centre for Evidence-Based Medicine (OCEBM) rates the level of this knowledge related to the Asian population at the first level, while the evidence of effectiveness within the non-Asian, i.e. European, population is only at the fourth level [30]. The aim is to supplement the experimental knowledge of efficacy and safety obtained in the rigorous conditions of randomized blinded placebo-controlled clinical trials. The primary intention is to supplement the expected results of the Irish RCT MOSAIC (EudraCT no. 2016-003340-37) and the British RCT CHAMP-UK (EudraCT no. 2017-004108-23) [31]. Which verify the effectiveness of 0.01% atropine in European children. The M.A.R.S. study has a design very similar to these studies and plans to apply atropine concentrations of 0.02% and 0.04% in the active branches and allow a mutual comparison of the dose-dependent effectiveness in a multiple range of assessed concentrations. The secondary aim is to supplement knowledge about the dynamics of bulbar growth after withdrawal of stronger concentrations of atropine, which are more susceptible to the rebound phenomenon than 0.01% (31). Higher atropine concentrations similar to those planned in the M.A.R.S. were administered in the LAMP RCT (NCT02130167) [32]. A limitation of this study was the impossibility of a placebo-controlled assessment of the rebound phenomenon. In contrast, the study of M.A.R.S. has a placebo arm design suitable to supplement missing observations of the rebound phenomenon within the European population.

Conclusion

The benefits for the study participants mainly represent the possibility of slowing down the onset of growth dynamics of the eyeball. Children randomized to both active arms are likely to have less disharmony of the axial length of the eyeball and the optical power of the anterior segment of the eye. They will not be burdened by the usual progression of dioptric values of corrective aids, but above all there will be a lower level of risk of health complications that are associated with the length of the eyeball. Indeed, slowing myopia by one dioptre represents a 40% reduction in the risk of myopic maculopathy [33]. Beneficial psychosocial effects can be found not only in connection with participation in the active arms of the study, but also in children randomized to the placebo arm, e.g. in advanced medical supervision, in a personal contribution to the development of modern, clinical evidence-based medicine, and in helping to improve health services for others generation.

M.A.R.S. clinical trial will enrich the knowledge about myopia and its possible treatment in the early stages of myopization (up to – 5 dioptres in European children. It will be beneficial for paediatric patients, practicing paediatricians and ophthalmologist. In the future it will be helpful not only from a medical point of view, but also in economic aspect of management of progression of myopia in children and all the entire population.

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