pediatric stroke

Study Protocol

High Dose Steroids in Children with Stroke and Unilateral Focal Arteriopathy:

A Multicenter Randomized Controlled Trial

PASTA (Pediatric Arteriopathy Steroid Aspirin) trial

Study Protocol

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Abstract

Rationale

Focal cerebral arteriopathy (FCA), a unilateral, monophasic disease of the intracranial arteries, is one of the most common etiologies of pediatric stroke. Imaging and laboratory evidence suggest an underlying inflammatory mechanism. The arteriopathy can progress over days to weeks, conferring a high risk of additional ischemic brain injury. Given its presumed inflammatory origin, there has been recently an emerging trend to intervene with corticosteroid treatment. However, there is a paucity of evidence on whether steroid treatment improves outcomes.

Aim

The aim of this study is to investigate whether high dose corticosteroids result in greater and faster improvement of focal stenosis in children with stroke and FCA and how this intervention influences neurological and neuropsychological outcomes as well as quality of life.

Sample size estimates

A sample size of 64 patients assigned 1:1 to the two study arms is required to detect a clinically relevant difference of 2.0 in the primary outcome with a power of 80% at a two-sided

alpha-level of 0.05.

Methods and design

This is a Prospective Randomized Open, Blinded Endpoint (PROBE) study involving 27 centers in Europe and Australia. Patients between 6 months and 18 years with a unilateral arteriopathy will be enrolled during a recruitment period of 3 years. A total of 70 participants (accounting for 8% dropouts) will be centrally randomized to standard care (including aspirin) alone or standard care plus high-dose-corticosteroids (experimental arm) in a ratio 1:1.

Study outcomes

The primary outcome measure is change in Magnetic resonance imaging (MRI) based FCA Severity Score (FCASS) from baseline to 1 month, compared between the two study arms. In addition, the study comprises various clinical and imaging-based information as well as analyses of adverse reactions.

Discussion

This will be one of the first prospective treatment trials in the field of pediatric stroke. The preparation for the study has already impacted stroke care of children worldwide through development of international collaborative trial networks and standardized neuroimaging based vascular scoring system.

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Introduction and rationale

Due to the suspected inflammatory cause of focal arteriopathy of the inflammatory type (FCA-i), it is increasingly treated with steroids - so far without firm evidence.[1–4]

In more than half of children with arterial ischemic stroke (AIS), arteriopathy is the underlying cause.[5] This is further subdivided into a small vessel as well as a large vessel bilateral and unilateral arteriopathy depending on the distribution of the affected vessels. The term focal cerebral arteriopathy (FCA) is often used synonymously with the term unilateral arteriopathy in the literature. When the term is used in this sense, no distinction is made as to what is the cause of this arteriopathy.[6]

In addition, the term FCA is used much more specifically for a subtype of unilateral arteriopathy[5,7]: This is a mostly unilateral monophasic disease of the cerebral arteries. Although the exact pathophysiology for the latter remains unknown, there is increasing evidence of a transmural inflammatory process of the vessel wall (see Fig. 1). [8-10] This has led to the additional designation of the term "FCA of the inflammatory type" (FCA-i).[9] Which distinguishes this from other forms of unilateral arteriopathy, such as moyamoya and dissection. The question of the extent to which FCA-i can also be present bilaterally is the subject of current research.

According to a retrospective Australian-Swiss study, steroid treatment in FCA-i is associated with

a significantly better neurologic outcome[1] and an uncontrolled case series, showed that steroid treatment reduced vessel wall enhancement.[10] In contrast, it has also been postulated that infectious mechanisms may play a role in the pathophysiology of FCA-i, and concerns have been raised about possible adverse effects of steroid treatment on these mechanisms.[11,12] The mechanism has best been studied for varicella related FCA-i: After systematic infection varicella virus remains in ganglions ("sleeping"). By reactivation there is a neuronal transport of the virus, followed by inflammatory process in the vessel wall.[13] For other disease-causing microorganisms, the pathophysiology is less clear, but likely similar. Reflective of the resulting uncertainty and equipoise, a Delphi survey of pediatric stroke specialists identified a steroid trial in children with FCA-i as the most important and feasible trial in this research field.[4]

To assess the severity of stenosis and the course of FCA-i in a standardized manner, the Focal Cerebral Arteriopathy Severity Score (FCASS) was developed in 2018. It is calculated based on the degree of arterial stenosis in MR, CT or conventional angiography in five cerebral arterial segments. Consistent with the natural history of FCA-i, FCASS increases in the first months of the disease and then decreases thereafter. The score was shown to be reliable and to correlate with long-term outcome as well as stroke volume. [12,14]

The objectives of this study are to evaluate if early anti-inflammatory treatment may influence

the course of arteriopathy, improve clinical outcomes, and prevent stroke recurrence in children with FCA-i.

The primary hypothesis is, that children with FCA-i treated with a course of high dose methylprednisolone/prednisolone will show greater improvement of focal stenosis and arteriopathy as measured by FCASS.

Methods

Design

This is a PROBE-study, comparing a high-dose course of intravenous methylprednisolone/oral prednisolone plus standard care versus standard care alone in children with FCA-i. The study will be conducted in 27 centers in Australia, Austria, France, Germany, Switzerland, and the United Kingdom.

Recruitment of participants is planned to occur over a period of 36 months. The data collection is shown in Fig. 2.

At the time of this publication the study protocol was approved by all corresponding regulatory authorities and the local ethic committees in Switzerland (BASEC-ID: 2021-00453), Austria (EK Nr: 2136/2021), France (N° de dossier: 21.04056.000061–22014), Germany (Aktenzeichen:

2022-066-f-A) as well as UK (IRAS ID: 305395) and Australia (RCH HREC Reference Number: 78937). The study is registered at ClinicalTrials.gov (NCT04873583).

Patient population

All patients older than 6 months and younger than 18 years with unilateral FCA-i will be screened on admission. The complete eligibility criteria are provided in table 1.

Inclusion criteria	Exclusion criteria
1. Written informed consent (legal representative) 2. Age 6 months to under 18 years 3. Randomization possible within 48 hours of diagnosis and maximum 96 hours after symptom onset 4. Symptomatic unilateral cerebral arteriopathy (newly acquired neurological deficits of proven ischemia and unilateral stenosis/vessel irregularity on neuroimaging) 5. Female participants age ≥ 13: Negative pregnancy test	1. Previous stroke 2. Genetic vasculopathies include ACTA2, neurofibromatosis type 1, trisomy 21 3. Moyamoya or sickle cell disease 4. Craniocervical arterial dissection 5. Primary (small vessel) and secondary angiitis of the CNS 6. Bilateral arteriopathy 7. Underlying systemic disorders e.g., rheumatological 8. On steroid treatment at disease onset 9. Contraindication to corticosteroid treatment 10. Inability to follow study-procedures 11. Participation in another interventional study

Table 1: Eligibility criteria

The diagnosis of unilateral cerebral arteriopathy (inclusion criterion 4) will be made on site by the respective study team. If the diagnosis is not clear, the sponsor will be contacted to review the MRI images together with the neuroradiologists at the sponsor's site. Subsequently, the sponsor and study site will seek a joint agreement as to whether or not the patient fulfills the eligibility criteria.

Randomization and blinding

Allocation will be done in a 1:1 ratio of standard care alone (including aspirin) or standard care plus corticosteroids (See Fig. 3) using web-based randomization with secuTrial.

Probabilistic minimization will be used, accounting for the following stratification factors: age (6 months through 5 years, 6 years through 11 years, 12 years to under 18 years) and pediatric National Institute of Health Stroke Scale (Ped-NIHSS; < 7, 7 to 12, >12).

Trial participants and local data collectors will not be blinded, as steroid treatment causes obvious clinical signs and symptoms. Imaging outcomes will be centrally assessed by blinded neuroradiologists.

The telephone-interview-based assessments of RRQ (Recurrence and Recovery Questionnaire), mRS (modified Rankin Scale) and VABS (Vineland Adaptive Behavior Scales) will be performed

blinded centrally for all study participants.

Intervention

Participants in both study arms will be treated based on standard care, including antithrombotic treatment with daily oral aspirin (3-5mg/kg/day, maximum 150mg/day). The hyperacute treatment (including intravenous thrombolysis and endovascular thrombectomy) may be performed according to local protocol. Start with any type of anticoagulation is possible and should be done as by local protocol. Switch or start of aspirin is mandatory at latest at inclusion. Suggestions (see supplementary) for standard care are given to the sites but noncompliance is not a deviation to the protocol. These suggestions have been discussed and approved by the international steering committee of the PASTA trial (see Appendix 1).

In addition, participants in the treatment arm will receive 3 days of intravenous methylprednisolone 30mg/kg/day (max. 1000mg/dose) in one daily dose. This is followed by therapy with oral prednisolone 1 mg/kg/day (max. 40mg/day) for 2 weeks and 0.5mg/kg/day (max. 20mg/day) for another 2 weeks.

Outcomes

The Primary Outcome is the change in FCASS from baseline examination to 1 month. In

addition, various imaging data, clinical and safety outcomes will be assessed (see table 2).

Primary Outcome
• Change in FCASS from baseline to 1 month
Secondary Outcomes
Imaging
• Change in FCASS from baseline to 6 months
• Volume of stroke (in FLAIR and DWI-sequences) at baseline, 1, 3 and 6 months by modified pediatric ASPECTS
• Residual arteriopathy at 6 months by FCASS
Clinical
• Functional impairment outcome by PSOM at 1, 3, 6 and 12 months
• Recovery by RRQ at 1, 3, 6, and 12 months
• Degree of disability or dependence by mRS at 1, 3, 6, and 12 months
• Adaptive function by VABS at 6 and 12 months
• For children aged >2 years, quality of life at 12 months, by PSQLM
• Neurocognitive outcome at 12 months
Mixed clinical/imaging
• Stroke recurrence assessed at 1, 6 and 12 months defined as: - New focal neurological deficit(s) or - Worsening of the neurological deficits by > 4 pedNIHSS points lasting for more than 24 hours with new or increased diffusion restriction in the corresponding vascular territory, or - New areas of clinically silent infarction, remote from the initial infarct
Safety Outcomes
• Late diagnosis of progressive large to medium vessel childhood primary angiitis of the CNS
• Adverse events (abnormal blood pressure, abnormal blood glucose, behavioral problems, infections, gastrointestinal irritation, electrolyte abnormalities requiring

intervention or weight gain) ● Infectious episodes requiring hospitalization ● Serious adverse events related to the study intervention requiring medical intervention

Table 2: Outcome Measures. FCASS: Focal cerebral arteriopathy severity score; ASPECTS: Alberta stroke program early CT score, PSOM: Pediatric Stroke Outcome Measure; RRQ: Recurrence and Recovery Questionnaire; mRS: modified Rankin Scale; VABS: Vineland Adaptive Behavior Scale; PSQLM: Pediatric Stroke Quality of Life Measure; ped NIHSS: pediatric National Institute of Health Stroke Scale.

Imaging Outcomes

Magnetic resonance imaging and angiography (MRI/MRA) will be performed at baseline, 1 and 6 months and, if clinically indicated at 3 months. The imaging protocol will comprise at least DWI/ADC, FLAIR, T2-weighted, time of flight (ToF) MR angiography and SWI sequences. At baseline neck vessel and vessel wall imaging should be considered. MRIs should be performed at 3 Tesla and without sedation or anesthesia if possible. All images will be assessed centrally by two independent neuroradiologists.

The degree of arterial stenosis at different time points is measured using FCASS in MRA.

Stroke Volume is measured by modified pediatric ASPECTS, a semi quantitative imaging score in childhood stroke where each abnormal area is assigned one point. Higher scores represent greater volumes, with a maximum possible score of 30 (15 per hemisphere).[15,16]

Clinical Outcomes

The pedNIHSS, an adaptation of the adult NIHSS to the pediatric population, is used to assess the severity of stroke.[17] The Pediatric Stroke Outcome Measure (PSOM), which is used to determine neurologic outcome, was developed, and validated specifically for pediatric stroke. It addresses pediatric specific domains such as development, behavior and cognition in addition to sensory-motor and language function.[18,19] To improve quality of data for pedNIHSS and PSOM, explanatory videos were created for all investigators. These are available at (https://www.pasta-trial.ch).

By telephone, the modified Rankin Scale (mRS) is collected to determine disability or dependence and the Recurrence and Recovery Questionnaire (RRQ) to determine recovery and recurrence. In addition, the Vineland adaptive behavior scale (VABS) is collected to monitor behavior and cognitive abilities. The VABS and mRS are widely used tests, which are well validated.[20,21] The RRQ was specifically developed and validated for pediatric stroke patients and addresses pediatric- specific problems of manifestation of stroke and also difficulties in reliable clinical examination.[22]

At the end of follow-up, Quality of life is assessed using the Pediatric Stroke Quality of Life Measure (PSQLM)[23] and standardized neurocognitive testing (using either WISC-V or WPPSI-IV, depending on age) is performed. Within the framework of this examination, children over the

age of 8 are additionally assessed for executive functions using subtests of the Delis-Kaplan Executive Function System (D-KEFS) and attention using Continuous performance task (CPT-III).

Data monitoring body

On site monitoring will be conducted at the first 5 sites that enroll a participant as soon as their first participant has reached the 30-day follow-up visit. Subsequent on-site and remote monitoring visits will be done randomly and by risk-based assessment.

Central data monitoring and validation will be performed according to a separate monitoring plan continuously for each site. This will include regular verification of the completeness, accuracy, and plausibility of the entered data and to query the site and follow up anything requiring clarification. No interim analyses are planned and no safety stopping points are defined.

Sample size estimates

For 13 patients of a retrospective study the standard deviation of the change in FCASS from baseline to maximum severity of arteriopathy was 2.8.[14] Based on this standard deviation and a two-sample means test, 64 patients (32 in each group) are required to detect a difference of 2.0 with a power of 80% at a two-sided alpha-level of 0.05.

To account for dropouts (8%), we will enlarge the sample size to 70 patients (35 in each group).

Statistical Analyses

The primary analysis will follow the intention-to-treat (ITT) principle. The primary outcome and secondary continuous variable outcomes that are measured multiple times during follow-up will be assessed in a repeated-measure, mixed-effects linear model.

Neurocognitive outcomes measured at 1 year will be analyzed using a mixed-effects linear model, binary outcomes (recovery, residual arteriopathy) will be assessed using generalized linear mixed-effects models, Time-to-event outcomes (stroke recurrence, infection requiring hospitalization, progressive arteriopathy) will be analyzed using Cox-regression, accounting for the stratification factors used at randomization (country and baseline FCASS).

We will perform a subgroup analysis according to baseline FCASS (<8 vs ≥8), accompanied by an appropriate test of interaction. Moreover, we will test whether the baseline FCASS (used continuously) has an influence on the association between steroid treatment and modified ASPECT score, i.e. whether there is effect modification (interaction).

Scores measured repeatedly over time (FCASS, mRS, PSOM, VABS, modified pediatric ASPECT) might be considered as categories. Patients may shift from category to category several times

over the duration of follow-up. We will additionally use mixed effects ordered logistic regression analysis on this data (shift analysis). Moreover, we will perform subgroup analysis according to country and baseline FCASS (<8 vs ≥8).

Discussion

Treatment of pediatric stroke is limited to secondary prevention in the vast majority of cases.[24–26] In contrast, treatment of FCA-i with steroids would be a therapy that directly intervenes in the acute course of the disease. There is much experience with the steroid dosing regimen, which is consistent with standard practice for other immunotherapy treatment protocols in children. [27,28] But there is no evidence for this treatment in FCA-i. Despite this lack of evidence, a recent review (meta-analysis) on immunotherapy in pediatric stroke has shown that 80% of children with FCA-i were treated with corticosteroids.[2] For this reason, and because of the fact that FCA-i is at high risk for stroke recurrence, the project that we present here has been identified as the most important pediatric trial for the treatment of AIS.[4,29] Aside from the trials of stroke prevention in sickle-cell disease[30], this is one of the first randomized, controlled treatment trials in pediatric AIS. In addition, the PASTA study is generating one of the largest prospective cohorts of patients with FCA-i. This will make it possible to systematically study FCA-i in an unprecedented way and to obtain a better insight into the pathophysiology of FCA-i.

Nevertheless, the study has some limitations. The diagnosis of FCA-i remains challenging in the acute setting for the following reasons: According to the traditional definition, the disease is monophasic - this cannot be detected in the acute situation. Imaging findings often overlap with intracranial dissection, so that differentiation is often difficult. Moyamoya is differentiated from FCA-i by the presence of collateral vessels. However, these may be absent in early stage moyamoya.[31] Biomarkers such as varicella serology in CSF are only effective in certain cases.[32] In recent years, vessel wall imaging has been increasingly used as a diagnostic biomarker.[33] However, vascular wall imaging with contrast enhancement cannot be performed within a study setting for ethical reasons. Overall, the diagnosis is therefore still often based on expert opinion by experienced stroke specialists. Accordingly, the inclusion criteria for this study were defined more broadly - so that the presence of unilateral arteriopathy after exclusion of any differential diagnoses is sufficient. As a support the centers will be guided in diagnosis by the sponsor team and their neuroradiologists experienced in this diagnosis.

As FCA-i is a rare disease, the number of cases in each center included in the study is very low. This means that the experience of the investigators of the individual centers in handling the study will be low and stratification by center is not possible. This and the lack of complete blinding of the investigators increases the risk of observer bias. Since the imaging outcomes and

thus the primary outcome are collected centrally, they are not affected by this risk. To reduce risk in recording clinical outcomes, investigators were provided with videos for learning the ped-NIHSS and PSOM in a standardized manner. In addition, the collection of various clinical outcomes is done centrally via telephone interview by a blinded investigator. As a further limitation, it should be mentioned that a surrogate marker was chosen as the primary outcome here. However, it could be shown that this correlates with the clinical outcome and that this has a high reliability.[12,14] In addition, to validate the results of the primary outcome, various clinical outcomes will also be assessed in the PASTA study.

Summary and conclusion

This prospective, parallel group, two-arm, randomized controlled, open-label clinical trial with blinded assessment of outcome will show if high-dose steroid treatment in addition to standard care is better than standard care alone in patients with FCA-i.

Trial status

This is protocol version 5, dated August 22, 2022, Site initiation started on November 2021. To date 7 participants have been randomized.

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Authors' Contributions/Conflicts of Interest Statement

MS, HF, MM, FO and SB designed the study, MS, AD, EP, JF and SB obtained funding. MS, PM, LS, and MB wrote the study protocol. DB wrote this publication. MS, LS, MSa, RM, GO, DB are involved in the set-up of the study, data collection, analysis, and interpretation of the data. EP is the expert in charge of the organization of the MRI. All Steering Committee members mentioned as authors and all Principal investigators have read the protocol, given input and accepted it with a signature. All authors read, edited, and approved the final manuscript. The Authors declare that there is no conflict of interest

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