FOCAS Trial

Focal Cerebral Arteriopathy Steroid Trial

Pediatric Comparative Effectiveness Trial

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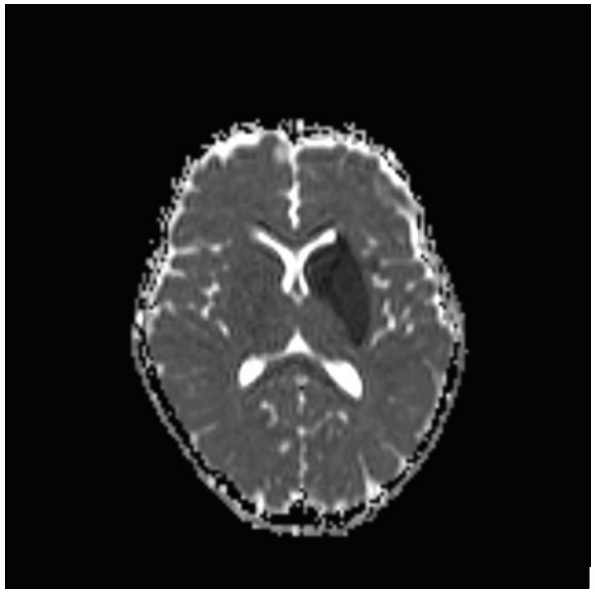
Background

Focal Cerebral Arteriopathy (FCA)

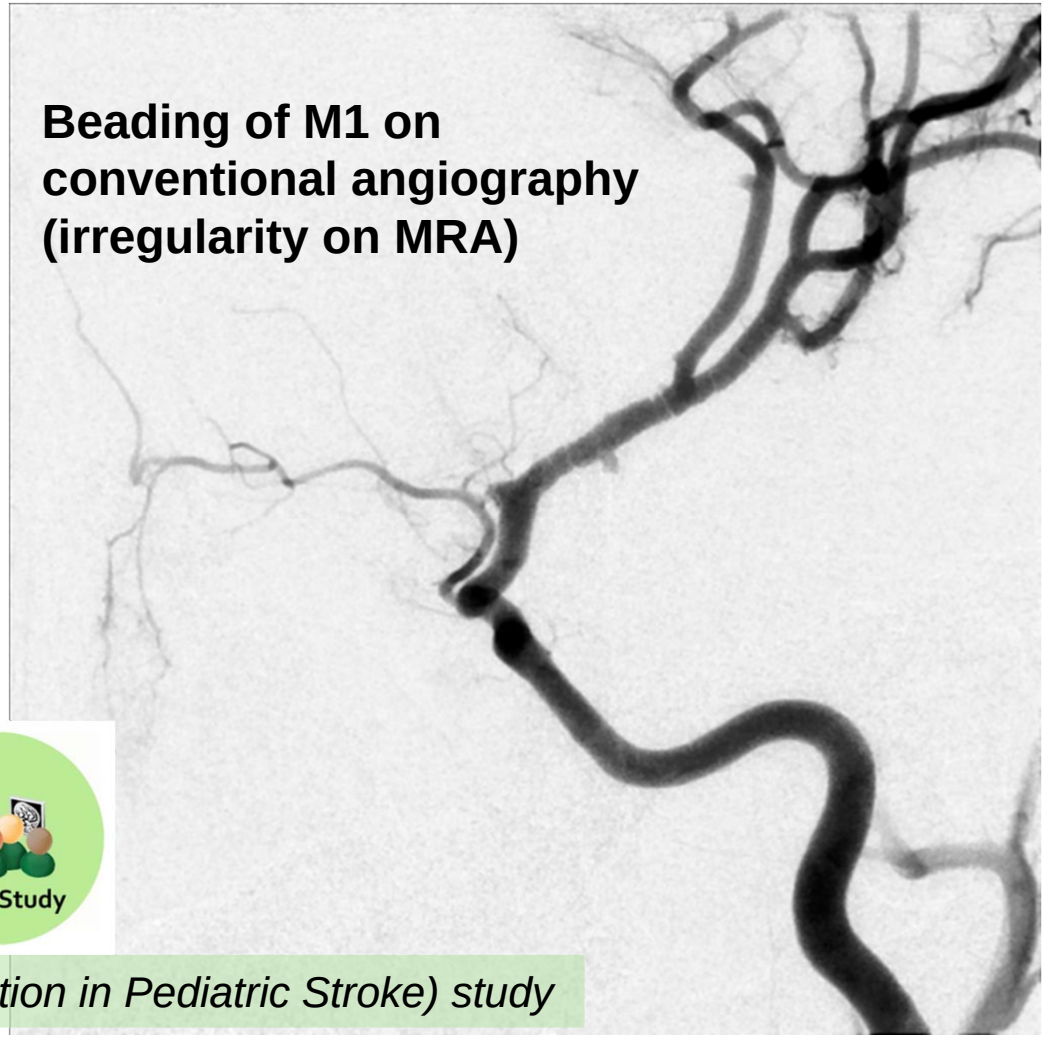
(inflammatory subtype)

Lenticulostriate infarct



Wintermark, *AJNR* 2017

Beading of M1 on conventional angiography (irregularity on MRA)

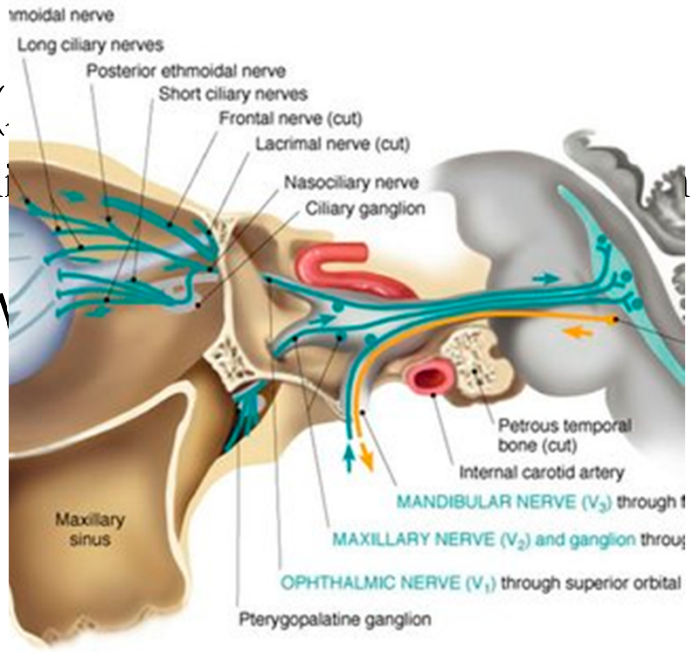


VIPS Study

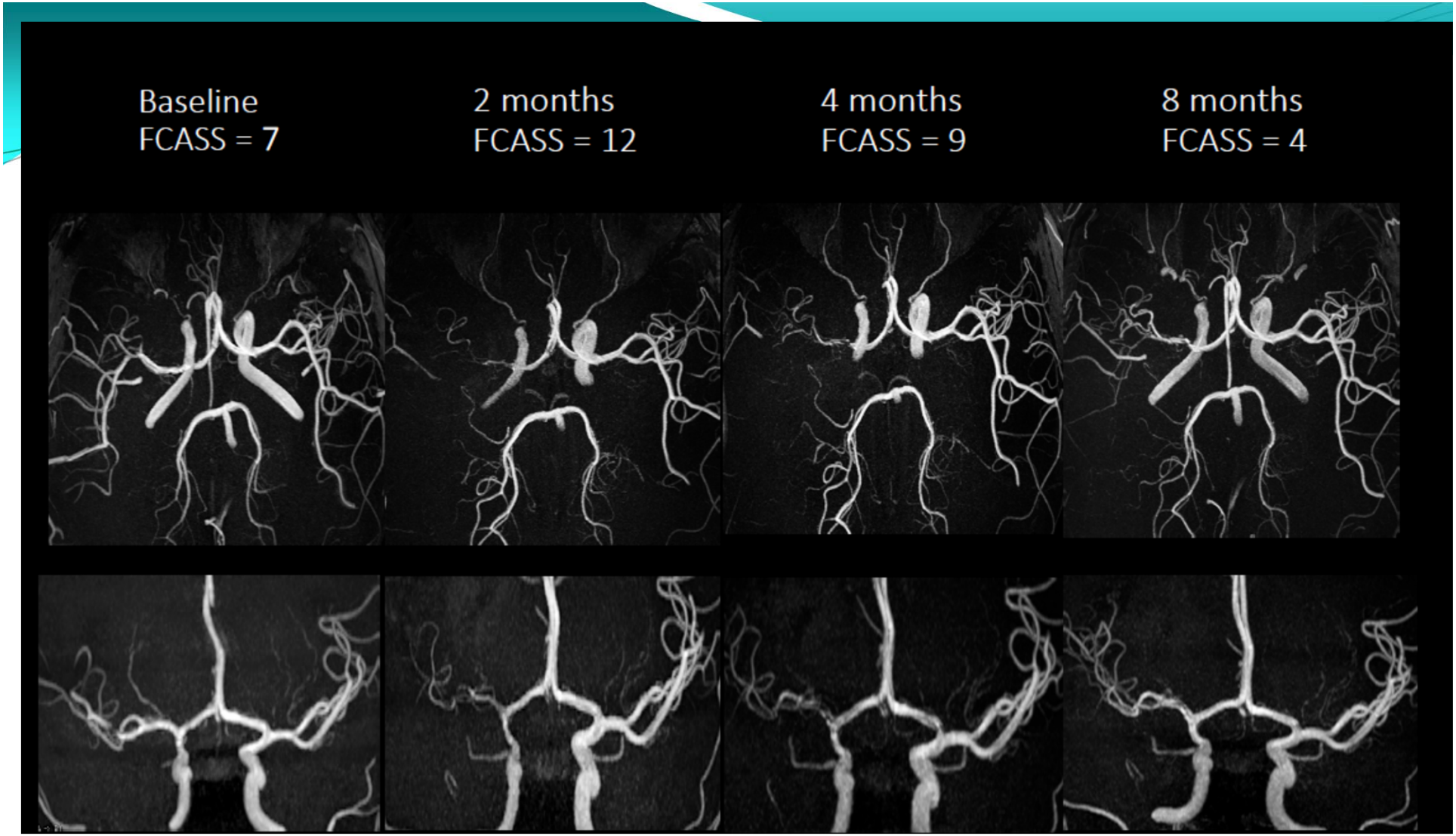
** VIPS (Vascular effects of Infection in Pediatric Stroke) study*

Background: Focal Cerebral Arteriopathy (FCA)

- Leading cause of arterial ischemic stroke (
  - 10% of all childhood AIS cases, ≈1 per 1 milli
    the U.S. per year
- Presumed inflammatory (enhances on VW
- VZV a suspected cause



- Natural history: early progression (days to weeks) followed by stabilization/improvement; does not recur
- **Confers a high risk of recurrent stroke:** 25% (95% CI 12-48%) within 1 year*, most in first 60 days
- Current tx: ASA & supportive care; presumptive steroids

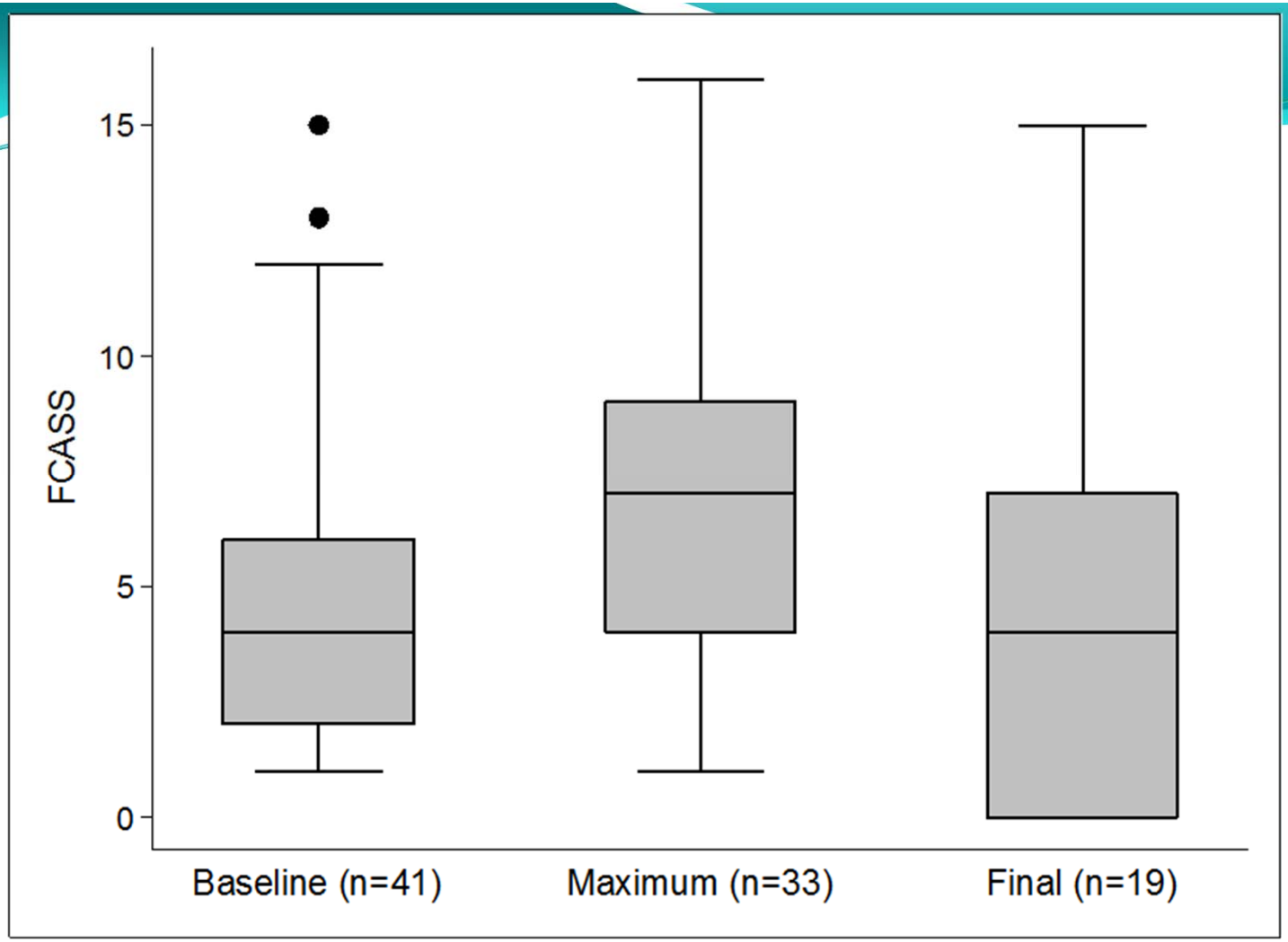


Natural history: worsens over days to weeks
then improves over months

FCASS=FCA Severity Score

Fullerton, Wintermark, *Stroke* 2018

VIPS Study



Maximum FCASS: median of 8 days (IQR 5, 35.5) post-stroke
(probably peaks earlier; analysis limited by timing of clinical imaging)

FCASS=FCA Severity Score

Fullerton, *Stroke* 2018

VIPS Study

Background: Steroid Trials for FCA

- 2017: Australian/European **Delphi consensus** of child neurologists with stroke interest; identified steroid trial for FCA as **#1 priority** for the field (Steinlin, *Dvlpt Med Child Neurol* 2017)
- Led to: **PASTA** (Paediatric Arteriopathy Steroid Aspirin) phase 3 RCT proposal to determine if steroids **reduce time to recovery**
  - Partially funded (France), begins enrolling Jan 2020
- 2017 survey of **24 VIPS sites**
  - 15 (63%) had given steroids for FCA
    - 10/15 perceived it was helpful
    - 9/15 reported side effects: irritability, weight gain, hypertension, "worsening infxn" x 1
  - 11 (46%) had concerns about steroid tx: 11 lack of data, 5 side effects
  - 23 (96%) felt a trial was needed
  - 22 (92%) were willing to randomize in a trial

FoCAS

- Goal: to obtain clinically useful evidence to guide the management of focal cerebral arteriopathy (FCA)
- Initial Study Question: are corticosteroids efficacious in treating FCA?
- Initial 2017 Design: Phase II RCT of corticosteroid therapy versus control; imaging endpoint, Δ FCA Severity Score

Table 1		Investigational Therapy		
Study Arm	**Aspirin***	**IV steroids**	**PO steroids**	**PO acyclovir**
Intervention	x	x	1 month (3 months if relapse monitoring rule is triggered)	x
Control	x			
*Standard therapy for arteriopathic stroke				

- **Emergent concern in 2018: changing equipoise**
  - 2017 publication: Swiss/Australian cohort study suggesting benefit of steroids in FCA (Steinlin, *Stroke* 2017)
  - US investigators increasingly using steroids
  - Questioning the ethics of randomizing a child to the control arm
  - Potential impact: decreased enrollment & high cross-over from control to intervention arm

Trial Design to Match Current Practice

- 2018 survey of VIPS sites (Oct 2018)
  - 2/20 always treat with corticosteroids (2/20)
  - 13/20 treat those with disease progression (13/ 20)
  - 5/20 never treat
- Current clinical question: *Is it best to wait and just treat those with disease progression (and high certainty of FCA diagnosis), or should we treat immediately, as soon as we suspect FCA, to prevent disease progression?*
- Solution: comparative effectiveness (CE) approach to leverage current differences in approach to steroid therapy for FCA

FOCAS Primary Aim

- *To compare the effectiveness of two current strategies for treating FCA with corticosteroids: (A) early treatment of all suspected FCA patients, versus (B) treatment of only FCA patients that demonstrate disease progression.*
- **Hypothesis:** Early corticosteroid treatment to prevent disease progression (Strategy A) leads to overall better outcomes than delayed treatment in the subset that progress (Strategy B).
- Study design allows for real world uncertainty around FCA dx at presentation
- **Primary endpoint (Imaging Outcome):** Change in FCASS on MRA from baseline to 1 month.
  - FCA Severity Score: Sums scores (0 for no involvement; to 4 for complete occlusion) applied to 5 arterial segments affected in FCA
  - *Higher maximum FCASS correlates with larger infarct size and poorer outcomes* (Fullerton, Stroke 2018)
- **Secondary endpoints (Imaging & Clinical Outcomes):** Infarct volume at 1 month; Pediatric Stroke Outcome Measure

Table. Baseline and maximum FCASS stratified by 1-year neurological outcomes (PSOM).

	Baseline		Maximum*		Delta†
1-year PSOM	n	Median (Range)	n	Median (Range)	Median (Range)
0-1 (no/mild deficits)	25	4 (1, 15)	21	6 (2, 15)	1 (0, 7)
1.5-3 (moderate)	12	5 (1, 13)	9	9 (3, 16)	4 (0, 9)
3.5-6 (severe)	2	7 (2, 12)	2	12 (8, 16)	5 (4, 6)
6.5-10 (profound)	0	- (-)	0	- (-)	- (-)
>1 (moderate/severe)	14	5 (1, 13)	11	9 (3, 16)	4 (0, 9)

*Time from index stroke to imaging with maximum FCASS: median 5 days (range 0, 189 days; IQR 2, 15); includes all of those with both follow-up (with or without progression) and PSOM score at one-year (n=32),

†Maximum minus baseline FCASS

P=0.037

FoCAS Inclusion/Exclusion (condensed)

Inclusion Criteria

1. Age **1 through 18 years** at stroke/TIA ictus (ineligible as of 40th birthday)
2. Acute AIS or TIA in prior **4 days**
3. High clinical suspicion for FCA
4. Imaging c/w FCA: unilateral focal irregularity, banding, or stenosis (>50%) of the distal internal carotid artery (ICA) or its proximal branches without evidence of atherosclerosis or dissection
5. Consent (and assent when appropriate) to study procedures
6. Minimum neuroimaging (brain MRI/A) performed on a clinical basis and available for central review
7. Ability to return for research MRA (or CTA) scans at 1 month post-stroke

Exclusion Criteria

1. Prior arterial ischemic stroke or silent infarction on brain MRI
2. Risk factors for intracranial dissection: connective tissue disorder (e.g., Ehlers-Danlos type IV, Marfan syndrome, osteogenesis imperfect); severe head trauma in the week preceding AIS/TIA
3. Risk factor… …yndrome that predis… neurofibro… …le cell anemia, M… …cranial radiation t…
4. Risk factors for secondary vasculitis or vasospasm: acute meningitis, systemic lupus erythematosus or other autoimmune disorder that can cause vasculitis, recent cocaine/amphetamine use (prior week), recent subarachnoid hemorrhage (prior week)
5. Risk factors for cardioembolism: complex congenital heart disease; recent cardiac surgery or catheterization (prior week); endocarditis or other cardiac valve disease with vegetations; deep vein thrombosis (DVT) with right-to-left cardiac shunting lesion
6. Imaging consistent with embolism: abrupt occlusion of intracranial artery(ies); bilateral/multifocal infarctions
7. Contraindication to corticosteroid therapy (e.g., baseline immunosuppression, significant infection, etc.) as determined by the treating physicians.

Exclude patients likely to have an alternate diagnosis

Treatment Strategies

- Two-arm 1:1 randomization:
  1. Strategy A: Treat all children with suspected FCA with corticosteroids as soon as the diagnosis is made.
  2. Strategy B: Treat just the subset of children that develop evidence of FCA disease progression.

- Third observational arm (not randomized):

  Strategy C ("control"): Treat no children with FCA with corticosteroids.

Strategy	Standard Therapy	Corticosteroids: **Who**	Corticosteroids: **When**
A	ASA and supportive care	All	After FCA diagnosis
B	ASA and supportive care	Subset with FCA disease progression	After FCA progression
C	ASA and supportive care	None	N/A

Corticosteroid Intervention

- Standard steroid "pulse" followed by oral taper
  - Methylprednisolone IV : 30 mg/kg/day (maximum of 1 g/day) x 3 consecutive days
  - Prednisolone po x 4 weeks
- Arm B (treat if/when disease progression)
  - Research MRI/A on Day 5 post-stroke (all arms)
  - **Disease progression**: worsening neurological deficits (increase in pediatric NIHSS ≥1), recurrent TIAs or strokes, worsening FCA severity (increase in FCASS ≥2 from baseline) or increasing infarct size by >10%, or new infarcts, on imaging
  - Determined by FOCAS Central Review Team, reviewing clinical & imaging data in real time and discussing with treating physicians

FOCAS 2ary Aims

- *Aim 2: To describe the natural history of FCA and identify clinical and imaging predictors of FCA disease progression.*
  - Imaging predictors: baseline FCASS & infarct volume; VWI when available
  - Clinical predictors: clinical e/o infection including VZV
  - Laboratory predictors: herpesvirus serologies, NGS pathogen detection

- *Aim 3: To determine the safety and tolerability of corticosteroid therapy for FCA.*

Schedule of Evaluations

Evaluation	Entry	24 hours	5-days (+/- 2 days)	1 mo	3 mo	12 mo
Informed Consent	X					
Documentation of FCA	X					
Documentation of Medical Treatment	X	X	X	X		
In Person Clinical Assessment	X	X	X	X	O	O
Telephone Clinical Assessment						X
Clinical Brain MRI/MRA	X				O	X
Research Brain MRI/MRA			X	X		
Herpes serologies	X			X		
X=required; O=optional						

Sample Size & Enrolling Sites

- Goal N=55 randomized 1:1 to Arm A or B
  - 25 per group→96% power to detect a clinically significant difference in delta FCASS
- Anticipated enrollment
  - In VIPS: sites enrolled 0-5 FCA cases/site/year
  - FOCAS:
    - 0.75 cases/site/year
    - 3 cases/site over a 4-year enrollment period

Biggest Challenges

- Rare disease, infrequent enrollments
- Large effort for few cases
- Need for annual retraining
- Children's hospitals lack experience in stroke trials

- Uncertainty (potential misclassification) around initial FCA diagnosis, and around defining "disease progression" to trigger treatment in Arm B
  - But a comparative effectiveness design allows for these "real-world" ambiguities, comparing the effectiveness of two current treatment approaches (not proving efficacy)

We need data to guide FCA management…

Thank you…

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