Vasculitis and stroke:
Acute and chronic treatments

Pr Mathieu ZUBER

Service de Neurologie et NeuroVasculaire
Groupe Hospitalier Paris Saint-Joseph

Université Paris Descartes
## Disclosures

**Code de santé publique. Article L 4113-13**

<table>
<thead>
<tr>
<th>Stocks</th>
<th>None</th>
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### Studies (Drug trials / Registers) (< 5 years)

<table>
<thead>
<tr>
<th>Company</th>
<th>Study/Project</th>
<th>Role</th>
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<tbody>
<tr>
<td>Sanofi</td>
<td>TAFI</td>
<td>Investigator</td>
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<tr>
<td>Servier</td>
<td>PERFORM</td>
<td>Investigator</td>
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<tr>
<td>Johnson &amp; Johnson</td>
<td>GARFIELD</td>
<td>Investigator</td>
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<tr>
<td>Biogen</td>
<td>CHOLINE</td>
<td>Investigator</td>
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<tr>
<td>Pierre Fabre</td>
<td>LIFE</td>
<td>Investigator</td>
</tr>
<tr>
<td>Boehringer Ingelheiner</td>
<td>RESPECT-ESUS</td>
<td>Investigator</td>
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### Advisory boards & speaker fees (< 3 years)

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<tr>
<td>Bayer</td>
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<td>Euthérapie</td>
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CNS vasculitis – Treatment

Main questions

- When to start?
- Best initial treatment?
- Need for a maintenance therapy?
- Antithrombotic therapies and acute revascularisation in patients with stroke?
- Special treatments for specific conditions?
  - Associated amyloïd deposits
  - Pregnancy
  - Children
**CNS vasculitis – Treatment**

**What is the evidence?**

- **Secondary CNS vasculitis**
  - Specific treatments
  - CNS involvement → pejorative prognosis

- **Primary CNS vasculitis**
  - Early reports: individual cases / limited series
  - Recently: 2 large series

*Vera-Lastra, Delgado, Cruz-Dominguez et al, Clin Rheumatol 2015, 34:729-38*

*Salvarani, Brown, Calamia et al, Ann Neurol 2007, 62:442-51*

*Salvarani, Brown, Christianson et al, Arthritis Rheum 2015, 67:1637-45*

*de Boysson, Zuber, Naggara et al, Arthritis Rheum 2014, 66:1315-26*

*de Boysson, Parienti, Arquizan et al, Rheumatology 2017, 56:439-44*
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Primary CNS vasculitis – Treatment

When to start? - 1

- Individual decision:
  - Highly probable diagnosis?
  - Aggressive evolution?

- Step by step diagnostic strategy:
  - Clinical arguments + MRIc++
  - Angiography+++ 
  - CSF analysis + other procedures

- In all cases, consider:
  - Benefit/risk balance of the brain biopsy (leptomeninges)
  - Usefullness of repeated diagnostic procedures at 4-6 W

## Primary CNS vasculitis – Treatment

### When to start?

#### Characteristics associated with increased mortality during follow-up

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<th>Characteristic</th>
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<th>Univariate P</th>
<th>Multivariate HR (95% CI)</th>
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<td>Age, per 10-year difference</td>
<td>1.39 (1.05–1.85)</td>
<td>0.022</td>
<td>1.52 (1.10–2.09)</td>
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<td>Male vs. female</td>
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<td>Main symptom at presentation</td>
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<td>MRI findings</td>
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* Univariate and multivariate Cox proportional hazards models were used for age-adjusted analysis. HR = hazard ratio; 95% CI = 95% confidence interval; MRI = magnetic resonance imaging; Gd = gadolinium; CSF = cerebrospinal fluid.

† Data were available for 129 patients.

N = 163

Prognostic factors

Contrast enhancement

Relapse = 80% vs 16%, $p=0.0001$

Relapse = 45% vs 15%, $p=0.03$

de Boysson, Zuber, Naggara et al, Arthritis Rheum 2014, 66:315-26
Boulouis, de Boysson, Zuber et al, Stroke 2017, 48:1248-55
### Prognostic factors

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Primary CNS vasculitis – Treatment
Best initial treatment? - 1

Calabrese et al, 1988

N = 46

- 19/20 non treated patients → death or severe sequelae
- 4/13 GC alone
- 10/13 GC + IS → favorable evolution

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<tr>
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<th>Mayo Clinic Cohort (N = 163)</th>
<th>French Cohort (N = 97)</th>
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<tr>
<td><strong>Prednisone</strong></td>
<td>94%</td>
<td>98%</td>
</tr>
<tr>
<td>Initial pulse treatment</td>
<td>42%</td>
<td>72%</td>
</tr>
<tr>
<td><strong>Immunosuppressor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cyclophosphamide</td>
<td>49%</td>
<td>84%</td>
</tr>
<tr>
<td>• Others (MMF - Ritux)</td>
<td>45%</td>
<td>82%</td>
</tr>
<tr>
<td></td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Medial Follow-up</td>
<td>12 (0-13.7)</td>
<td>55 (5-198)</td>
</tr>
<tr>
<td>Relapses</td>
<td>36%</td>
<td>27%</td>
</tr>
<tr>
<td>Mortality</td>
<td>15%</td>
<td>6%</td>
</tr>
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Calabrese and Mallek, Medicine 1988, 67:20-39

**Primary CNS vasculitis – Treatment**

**Best initial treatment? - 2**

**Diagnosis of Primary CNS Vasculitis**

**Favorable prognosis anticipated**
- Distal vessel disease
- Meningeal enhancements
- No/few ischemic lesions

- **Methylprednisone pulse therapy** (1000 mg 3 to 5 days) then **Oral prednisone 1 mg/kg**

  **Response**
  - Progressive tapering
  - **Addition of IV CYC 0.7 mg/m² each 3-4 w (or oral CYC 2mg/kg)**

  **No response or insufficient**

**Unfavorable prognosis anticipated**
- Proximal vessel disease
- Cerebral infarcts
- Rapidly progressive disease course

- **4-6 months**
- **Association of Methylprednisone pulse therapy with IV CYC**

  **No response or insufficient**

  **Consider switching to Rituximab (RTX) / Mycophenolate mofetil (MMF)**

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De Boysson, Zuber, Naggara et al, Arthritis Rheum 2014, 66 : 1315-26
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Primary CNS vasculitis – Treatment

Need for a maintenance therapy?
The French Cohort experience

- N = 97, median follow-up 55 months [5-198]
- Maintenance therapy
  - N = 48 (49%)
  - AZA >> MMF, MTX
  - Mean starting delay of 4 months after CYC induction
  - Mean duration: 24 months [6-72]

![Graph showing modified Rankin Scale](image)

22% of relapses
45% of relapses

Log-rank test: p=0.02

No. at risk
- Maintenance: 48 40 33 29 24 16
- No Maintenance: 49 38 31 23 19 17

Time of Evaluation

de Boysson et al, Rheumatology 2017, 56:439-44
Primary CNS vasculitis – Treatment

When can we stop?

- **Remember factors of relapse**
  - MRI: leptomeningeal enhancements

- **Consider targets of the treatment** (depending of initial status)
  - Clinical: no headache / evolutive neurological status
  - Biological: no inflammatory CSF
  - Radiological:
    - MRI: no gadolinium-enhancements
    - Angiography: no new vascular stenoses

CNS vasculitis – Treatment

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Cerebral Amyloid Angiopathy – related inflammation

Inflammatory - CAA

Amyloid-β-related angiitis

- Glucocorticoids: 74% vs 78%
- Combination IS + GC: 12% vs 33%

Chung et al, J Neurol Neurosurg Psychiatry 2011, 82: 253-7
Salvarani et al., Neurology 2013, 81: 596-603
Chu et al, J Alzheimer Dis, 2016, 51: 525-32
Primary CNS vasculitis – Treatment

Pregnancy & Child

- Pregnancy:
  - GC and AZA: possible
  - CYC: cytotoxic and teratogenic (T1)
  - RTX: precautionary principle
  - MMF: strictly contraindicated

- Children:
  - 2 types:
    - Medium-large vessel disease (MLVD) → multiple strokes
    - Small vessel disease (SVD) → microvascular inflammation (lymphocytic vasculitis)

- More standardised treatments:
  - MLVD: GC + CYC → ↓ GC + MMF
  - SVD: GC + MMF → ↓ GC + MMF

Primary CNS vasculitis – Treatment

Take home messages

- Delay and intensity of treatment are individual decisions based on multiple criteria
- Importance of pronostic factors: vessel size involvement, leptomeningeal enhancement
- Induction: GC + IS (CYC) for 4-6 months
- Maintenance therapy: tapering dose GC + MMF (AZA, MTX) up to 2 years
- Future:
  - New drugs for dysimmune diseases: complement inhibition therapies, new recombinant humanized monoclonal antibodies, etc...
  - Controlled trials?