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Lausanne, 11 January 2018

Vasculitis and stroke :

Acute and chronic treatments

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Disclosures

Code de santé publique. Article L 4113-13

Stocks

None

Studies (Drug trials / Registers) (< 5 years)

Sanofi	TAFI	(Investigator)
Servier	PERFORM	(Investigator)
Johnson & Johnson	GARFIELD	(Investigator)
Biogen	CHOLINE	(Investigator)
Pierre Fabre	LIFE	(Investigator)
Boehringer Ingelheimer	RESPECT-ESUS	(Investigator)

Advisory boards & speaker fees (< 3 years)

Bayer	Pfizer
Sanofi	Esai
BMS	Teva
Boehringer-Ingelheim	
Euthérapie	

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

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

- Primary CNS vasculitis
  - Early reports : individual cases / limited series
  - Recently : 2 large series
    - Mayo Clinic Cohort : N = 101 (2007) → N = 163 (2015)

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

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

    - French Cohort : N = 52 (2014) → N = 109 (2017)

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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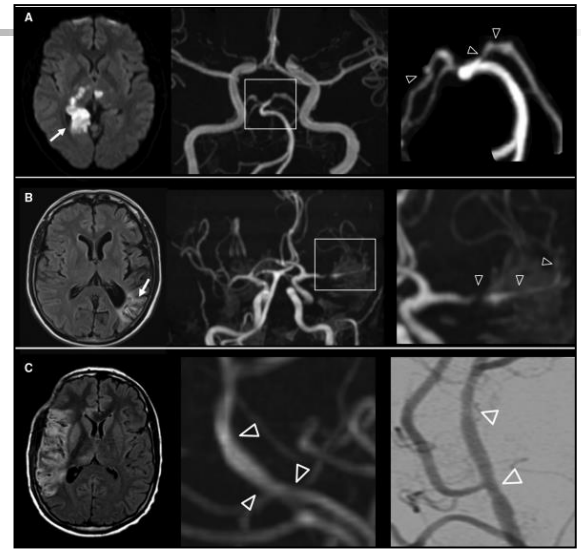
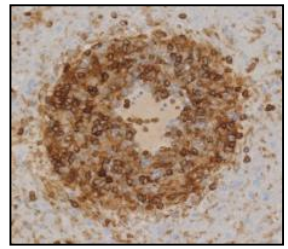
Primary CNS vasculitis – Treatment

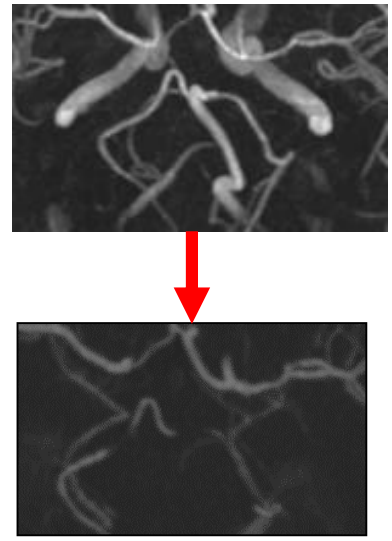
When to start ? - 1



Boulouis et al, Stroke 2017, 48:1248-55

- Individual decision :
  - Highly probable diagnosis ?
  - Agressive 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 ? - 2

Characteristics associated with increased mortality during follow-up

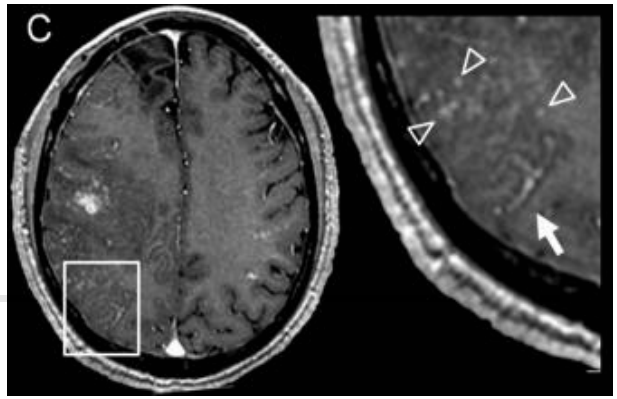
N = 163

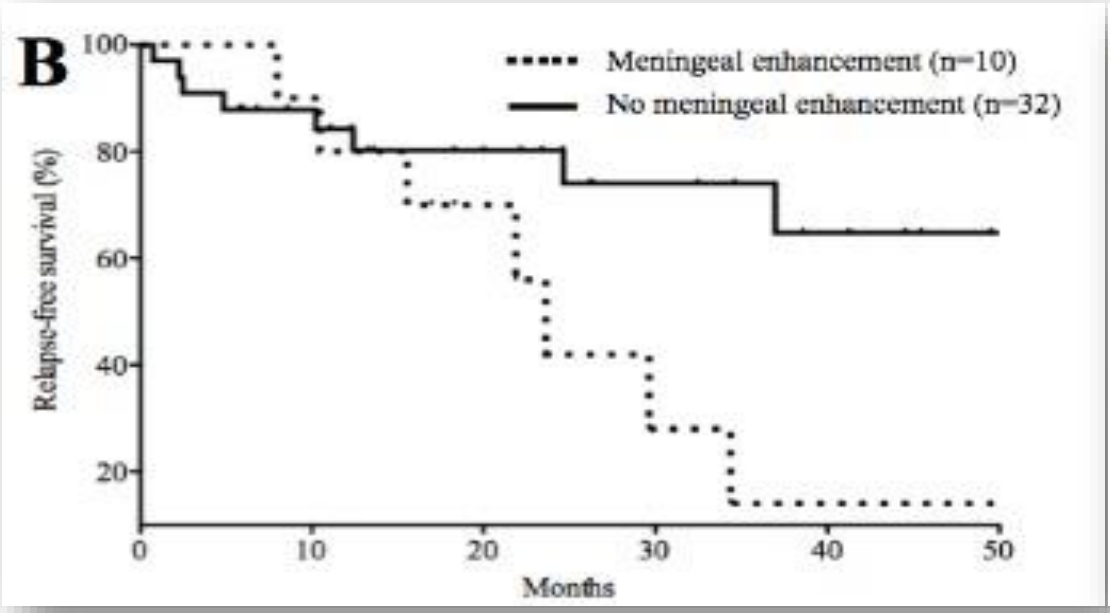
Characteristic	HR (95% CI)	Univariate *P*	Multivariate HR (95% CI)
Age, per 10-year difference	1.39 (1.05–1.85)	0.022	1.52 (1.10–2.09)
Male vs. female	0.80 (0.34–1.88)	0.61	–
Main symptom at presentation			
Headache or constitutional symptom	1.00		
Focal manifestation vs. headache or constitutional symptom	2.42 (0.69–8.52)	0.17	–
Cognitive disorder vs. headache or constitutional symptom	3.40 (0.82–14.0)	0.090	–
Diagnosis by angiography only vs. biopsy	3.28 (1.09–9.82)	0.034	–
MRI findings			–
Infarct vs. no infarct	4.44 (1.61–12.2)	0.004	3.60 (1.31–9.90)
Gd-enhanced lesions or meninges vs. normal or minimal changes	0.20 (0.06–0.67)	0.009	0.24 (0.07–0.83)
Large vessel involvement vs. small vessel involvement†	4.98 (1.47–16.9)	0.01	–
Increased CSF protein level (>70 mg/dl)	1.29 (0.49–3.39)	0.61	–
Cerebral amyloid angiopathy, present vs. absent	0.17 (0.02–1.33)	0.092	–
Prednisone alone vs. cyclophosphamide and prednisone	1.03 (0.46–2.35)	0.94	–
Rapid (<1 month) vs. slow (>1 month) onset	1.27 (0.55–2.94)	0.57	–

* 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.

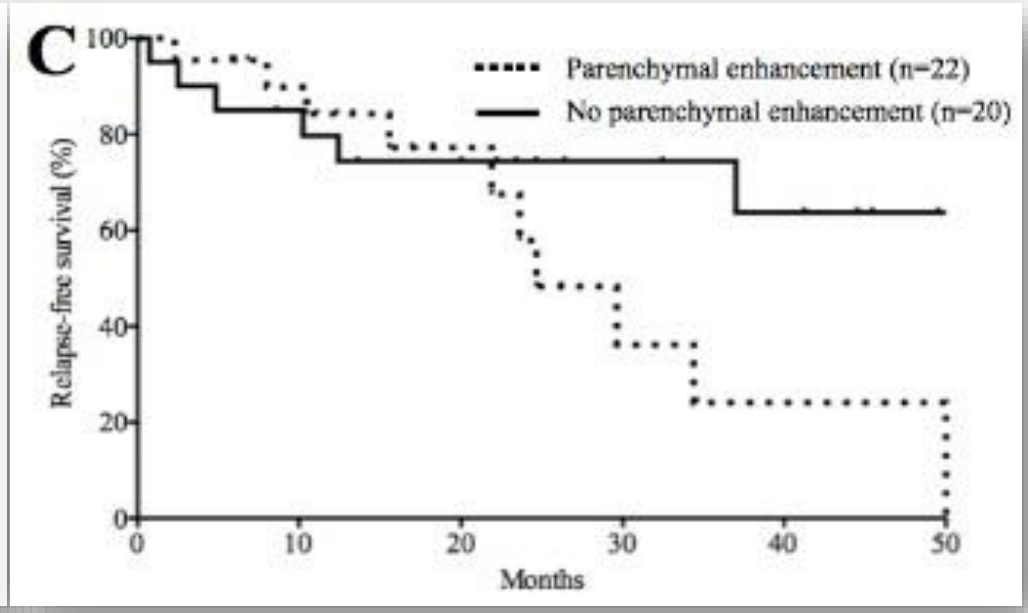
Salvarani et al, Arthritis Rheum 2015,67:1637-45 ; de Boysson et al, Rheumatology 2017, 56:439-44

Prognostic factors
Contrast enhancement





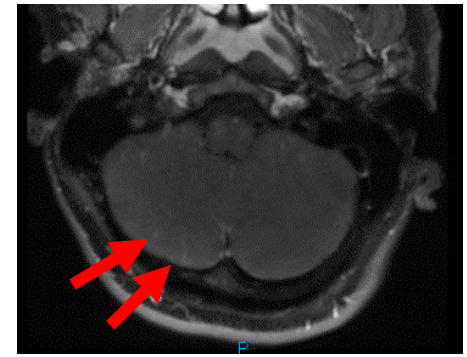
Relapse = 80% vs 16%, *p=0.0001*



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
Contrast enhancement



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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

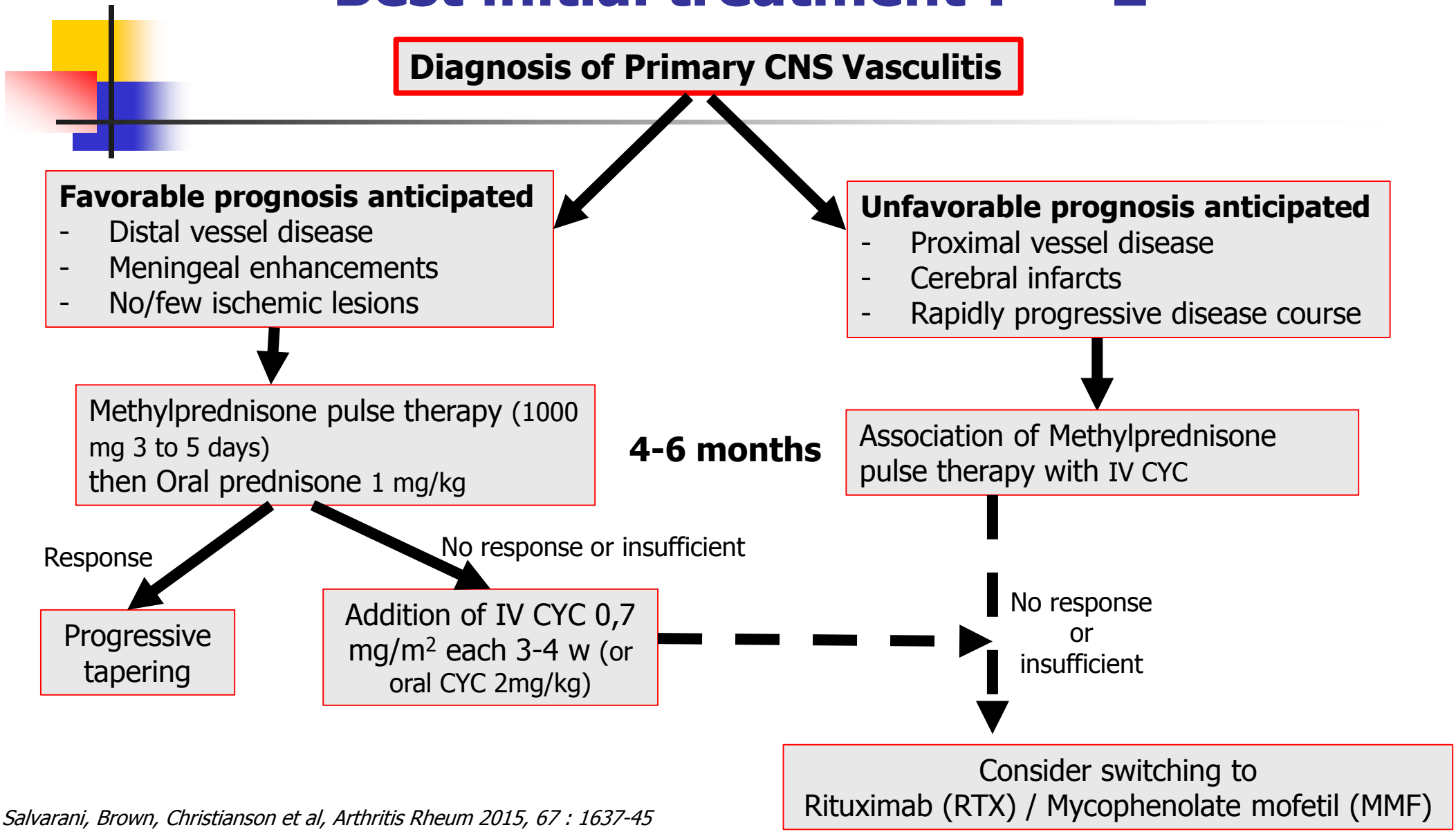
	Mayo Clinic Cohort (N = 163)	**French Cohort (N = 97)**	
Prednisone Initial pulse treatment	94% 42%	98% 72%	
Immunosuppressor • Cyclophosphamide • Others (MMF - Ritux)	49% 45% 4%	84% 82% 2%	*< 0,0001*
Median Follow-up	12 (0-13,7)	55 (5-198)	
Relapses	36%	27%	*0,20*
Mortality	15%	6%	*0,015*

Calabrese and Mallek, Medicine 1988,67:20-39

Salvarani, Brown, Christianson et al, Arthritis Rheum 2015, 67 : 1637-45
De Boysson, Zuber, Naggara et al, Arthritis Rheum 2014, 66 : 1315-26

Primary CNS vasculitis – Treatment

Best initial treatment ? - 2



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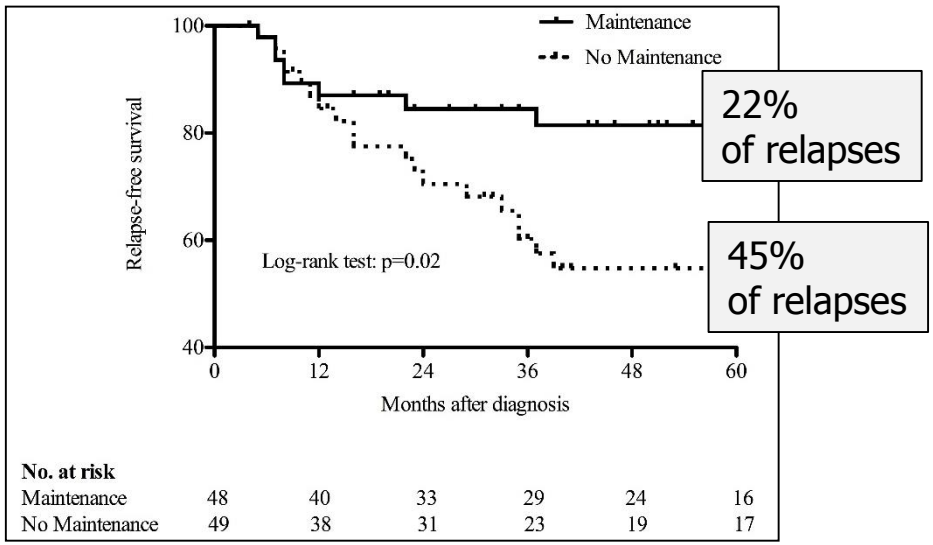
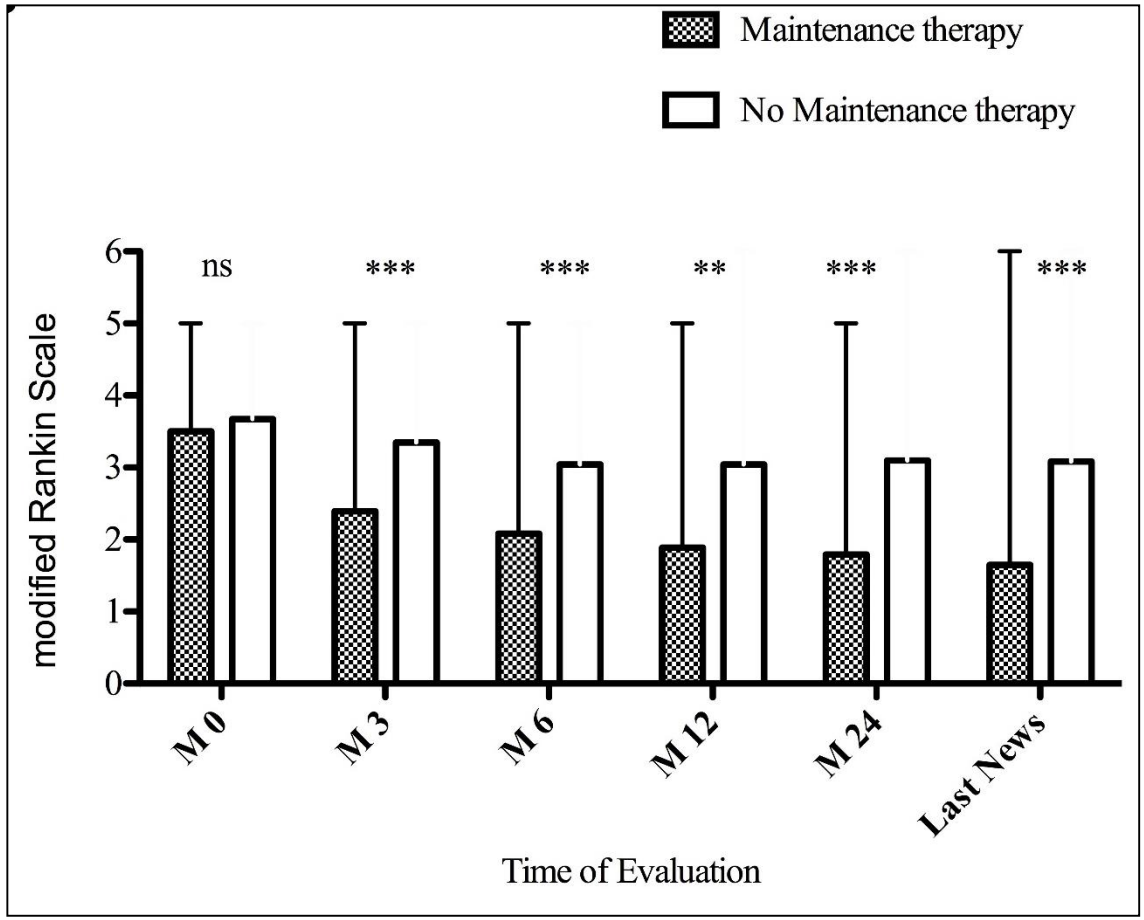
Need for a maintenance therapy ?

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]





de Boysson et al, Rheumatology 2017, 56:439-44

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 gadolinum-enhancements
    - Angiography : no new vascular stenoses

Zuber M. Primary angiitis of the CNS. In : Uncommon causes of strokes. J. Biller & L Caplan eds, Cambridge University Press, 2018, in press

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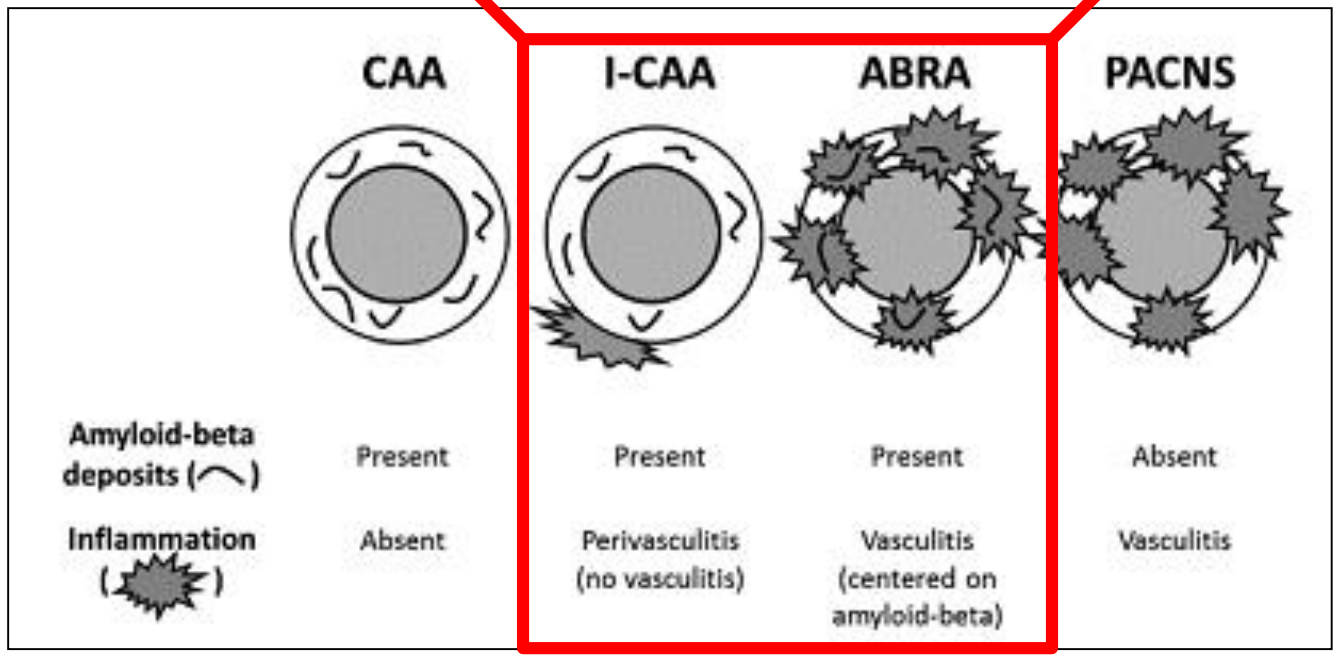
Cerebral Amyloid Angiopathy
– related inflammation

Inflammatory - CAA | **Amyloid-β-related angiitis**



Glucocorticoïds :	74%	*vs*	78%
Combination IS + GC :	12%	*vs*	33%

Chung et al, J Neurol Neurosurg Psychatry 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

Hutchinson et al, Lancet Neurol 2010,9:1078-80 ; Sen et al, Rheumatology 2010,49:806-11 ; Rosati et al, Joint Bone Spine 2017,84:353-6

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 $\pm$ 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 ?