MAINRITSEG

MAINtenance of remission with **RIT**uximab versus azathioprine for patients with newly-diagnosed or relapsing **E**osinophilic **G**ranulomatosis with polyangiitis.

A prospective, randomized, controlled, double-blind study.

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Benjamin Terrier

PHRC 2015

MAINRITSEG: Background 1/2

CHUSPAN trials long-term follow-up of EGPA (BP and MP):

- **These therapeutic strategy in EGPA has led to good remission and survival rates.**
- The probability of uncontrolled disease, **without maintenance therapy,** was **similar in patients whatever the FFS score at inclusion** and remains to be improved.
  - **In EGPA BP FFS=0** (only GC without maintenance):
    - M28: vasculitis flares: 28.4%
    - M28: asthma/rhinosinus leading to ↑GC or other IS: 30.2%

giving a total of 58% patients with uncontrolled disease at M28.

- **In EGPA MP FFS ≥ 1** (GC and 6 or 12 IV CYC without maintenance),
  - M28: vasculitis flares: 29.7%
  - M28: asthma/rhinosinus leading to ↑GC or other IS: 30.5%

giving a total of 60% patients with uncontrolled disease at M28.

Cohen P, Arthritis Rheum 2007; Ribi C, Arthritis Rheum 2008; Samson M, J Autoimmun 2013

MAINRITSEG: Background 2/2

CHUSPAN trials long-term follow-up of EGPA (BP and MP):

=> Without maintenance therapy, relapses remain a matter of concern and uncontrolled disease is observed in almost half of the patients at M28, leading to high cumulative morbidity and damage.

- **(h): As with other AAV, EGPA patients would also benefit from maintenance to avoid relapses and allow GC tapering.**
- **Only one trial has yet evaluated medication (MEPO) for EGPA maintenance therapy.**

=> Thus, it remains unmet needs to improve the long-term outcome and to evaluate maintenance regimen in controlled studies of EGPA patients.

Cohen P, Arthritis Rheum 2007; Ribi C, Arthritis Rheum 2008; Samson M, J Autoimmun 2013

MAINRITSEG: Objective

Main Objective

To compare RTX versus AZA maintenance therapy :

- **on duration of remission**, defined as accrued duration in weeks where BVAS=0 and prednisone dose ≤7.5 mg/day,
- in patients with relapsing or newly-diagnosed EPGA
- receiving standard of care therapy including GC therapy reduction/withdrawal.

MAINRITSEG: Objective

Secondary Objectives

To investigate RTX versus AZA maintenance therapy on:

- proportion of patients remaining in remission with a BVAS=0 and prednisone dose ≤7.5 mg/day at month 28
- number and severity of vasculitis relapses and asthma/rhino-sinusal exacerbations
- time to vasculitis relapses
- time to significant asthma/rhino-sinusal exacerbations
- corticosteroid sparing effect
- safety,
- survival,
- damage,
- and quality of life.

MAINRITSEG: Primary endpoint

The primary endpoint is the total duration of remission over the 28 month study period, i.e.

- the accrued number of weeks where a patient remains in remission **with BVAS=0 and prednisone dose ≤7.5 mg/day.**

MAINRITSEG: Secondary endpoints 1/2

The secondary endpoints are:

- % of patients remaining in remission with a BVAS=0 and prednisone dose ≤7.5 mg/day over the 28 month study period
- % of patients remaining in remission with a BVAS=0 over the 28 month study period
- % of patients with at least one vasculitis relapse (major, minor, either) over the 28 month study period
- % of patients with ≥ one significant asthma/rhino-sinusal exacerbation defined as “a worsening of asthma/rhinosinus disease leading to ≥ the doubling of the existing maintenance dose of GC for ≥ 3 days or hospital admission or an emergency department” visit over the 28 month study period
- time to first vasculitis relapse
- time to first significant asthma/rhinosinus exacerbation

MAINRITSEG: Secondary endpoints 2/2

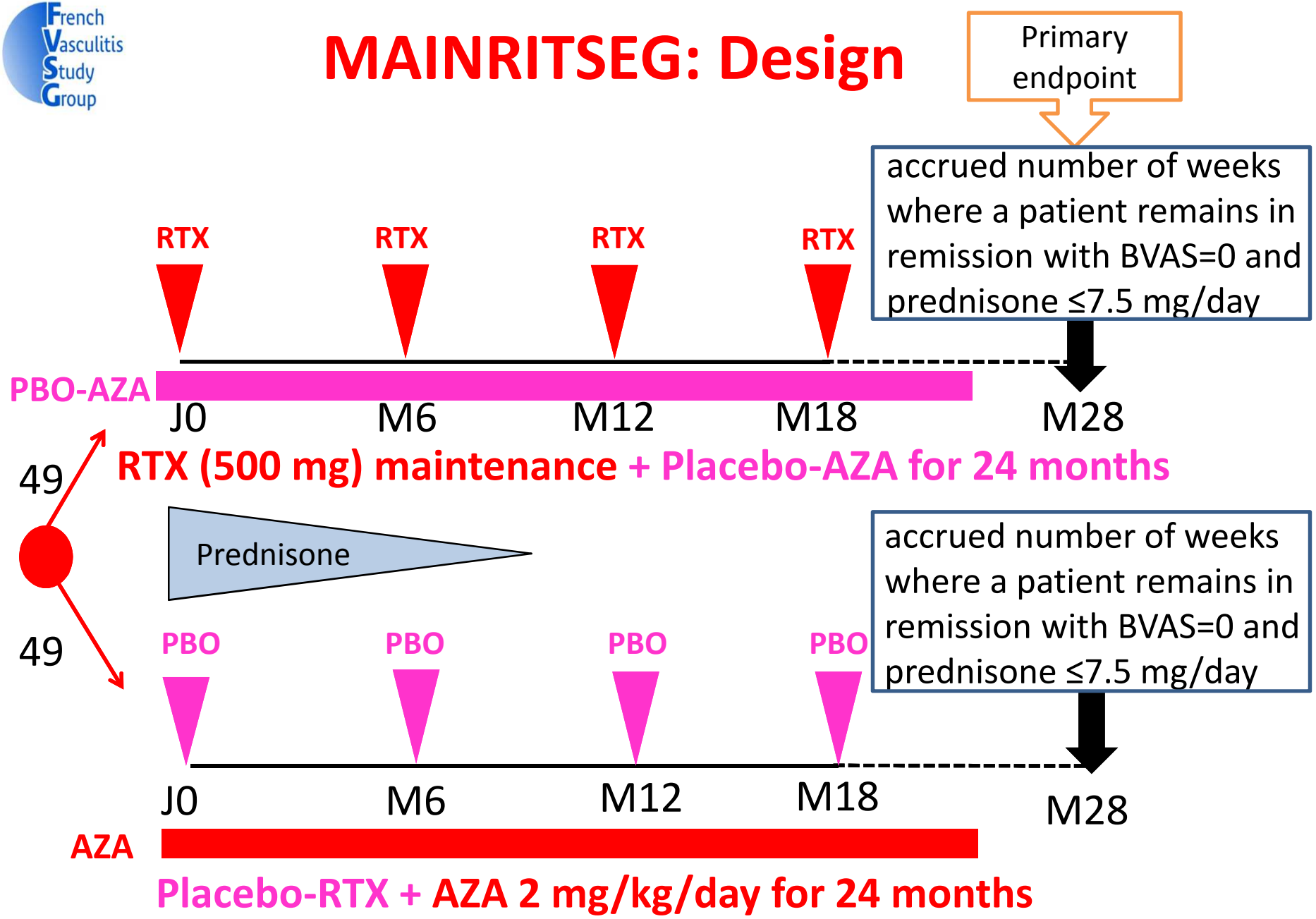
The secondary endpoints are:

- prednisone dose at months 6, 12, 18, 24 and 28, and area under the curve over the 28 month study period
- mean blood eosinophilia, CRP and fibrinogen
- % of patients with AEs, SAEs, AE leading to drug stop or termination from study, and selected severe AEs including grade ≥ 3 AE (CTCAE), deaths, cancers, necessitating H, or infusion reactions contraindicating further infusions.
- infusion reactions (within 24 hours of infusion) that result in the cessation of further infusions
- number and causes of deaths
- the vasculitis activity (BVAS), damage (VDI), disability (HAQ) and quality of life (SF36) scores
- the number of days of H over the 28 month study period.

MAINRITSEG: Inclusion criteria

- Patients with a diagnosis of **EGPA** (ACR and/or revised Chapel Hill)
- 18 years of age or more,
- with **newly-diagnosed disease or presenting with a vasculitis flare** within the past year,
- **within 30-360 days following vasculitis remission (BVAS=0) achieved with an induction regimen similar to the one used in the REOVAS trial : CS seuls ou avec RTX ou CYC IV (5-10g),**
- **with stable GC dose for 30 days or no more** (≠ < 7.5mg/day),
- independently of ANCA status,
- after oral IS cessation if started at remission.

MAINRITSEG: Design



MAINRITSEG Other procedures

Patients receiving RTX or placebo-RTX infusion will receive premedication including 100 mg of MP, paracetamol and dexchlorphéniramine (Polaramine©).

In accordance with standard of care, in the absence of clinical manifestations, to obtain total GC therapy duration after disease onset/flare of ~ 12 months, **both groups will receive the same predefined GC tapering regimen of 1 mg/day/month, until discontinuation.**

MAINRITSEG: Stratification

The patients will be stratified with a covariate adaptative randomization according to:

- Newly diagnosed vs. relapsing EGPA
- Vasculitis severity (FFS=0 vs. FFS ≥1)
- ELISA ANCA status (positive vs. negative)
- Induction therapy with GC vs. cyclophosphamide vs. rituximab.

Statistical analyses: Department of Epidemiology, Clinical Research Unit Paris Descartes, INSERM U 738, **supervised by Pr Philippe Ravaud.**

MAINRITSEG: Number of scheduled patients

Total number of scheduled patients to be recruited: 98

- **The proportion of patients experiencing vasculitis relapse or asthma-rhino-sinusal exacerbation is expected to be 35% at 28 months** in the AZA control group,
- *i.e.* a total of 35% of patients are expected to have an uncontrolled disease at M28 in the AZA control group.
- The primary (h) of the MAINRITSEG trial is a ↘of at least 66% of the rate of uncontrolled disease at 28 months (35% =>12%)
- Based on this hypothesis, using a bilateral test, we calculated that 98 patients will be required for the study to have **80% power to detect a 66% reduction in the relative risk with a two-sided alpha level of 5%, 49 patients in each arm**.

MAINRITSEG: 1ère inclusion après sept 2017

- Les patients doivent être informés le plus tôt possible de cette étude évaluant le maintien de la rémission
- Les patients peuvent être inclus en dehors de REOVAS
- Les patients peuvent être inclus et randomisés dans MAINRITSEG à la visite de M12 de REOVAS :
  - A la visite précédente = J270 de REOVAS, information
  - à M12, visite finale de REOVAS, si le patient est en rémission avec corticoïdes stable depuis 1 mois
  - après information et recueil consentement
  - soit randomisation et traitement par IV immédiat
  - soit nouveau RdV dans les 30 jours pour perfusion

MAINRITSEG

Bonnes inclusions !

French Vasculitis Study Group

www.vascularites.org

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