MAINTENANCE OF REMISSION USING EXTENDED ADMINISTRATION OF PREDNISONE IN SYSTEMIC ANCA-ASSOCIATED VASCULITIS

A PROSPECTIVE, MULTICENTRIC, RANDOMIZED, CONTROLLED, DOUBLE-BLIND TRIAL

Investigator: Pr LEGA Jean Christophe (HCL)
Scientific Investigator: Dr PUECHAL Xavier (AP-HP)
Corticosteroids in ANCA associated vasculitis

- Discrepancies in corticosteroids use between USA and EU
  - **USA**: withdrawal at 6-12 months post-flare
  - **France**: withdrawal at 12-18 months post-flare

Diabetes: 12%
Osteoporosis: 15%
Cataracte: 8%
Corticosteroids in ANCA associated vasculitis

- Discrepancies in corticosteroids use between USA and EU
  - **USA**: withdrawal at 6-12 months post-flare
  - **France**: withdrawal at 12-18 months post-flare

<table>
<thead>
<tr>
<th>Length of corticosteroids administration</th>
<th>Relapse rate (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No withdrawal</td>
<td>14 (10-19)</td>
</tr>
<tr>
<td>Withdrawal after 12 months</td>
<td>29 (16-42)</td>
</tr>
<tr>
<td>Withdrawal before 12 months</td>
<td>48 (39-58)</td>
</tr>
</tbody>
</table>

Walsh et al. Arthritis Care Research 2010
Primary objective:
To compare relapse-free survival of patients continuing low-dose prednisone treatment (5mg) until Week 52 (Month 25 post-flare) versus those who will have prednisone treatment cessation at Week 4 (Month 13 post-flare) on remission maintenance with rituximab therapy, after achievement of remission of GPA or MPA, defined as in patients with GPA or MPA and who will all have received glucocorticoids for 12 months after diagnosis or last flare before inclusion.

Primary assessment criterion:
Survival of patients maintaining a BVAS=0 at Week 120 (Month 42 post-flare), with ITT analysis
MAINEPSAN trial - Inclusion Criteria

- Patients who has been informed about the study and has given his/her written consent prior to participation in the study,

- Patients with newly-diagnosed or relapsing MPA or GPA according to the ACR 1990 criteria and/or revised Chapel Hill Consensus Conference definition, independently of ANCA status,

- Patients aged of 18 years or older,

- Patients in remission (BVAS =0) for MPA or GPA achieved with rituximab or cyclophosphamide or methotrexate,

- Patients who will all have already received glucocorticoids for 12 months after diagnosis or last flare before Day 1.

- Patients having received 500 mg pre-emptive low-dose rituximab maintenance infusions at remission achievement (4 to 6 months after initiation of induction therapy), and 6 months after.

- Patients receiving from 5 to 10 mg/day prednisone dose within 35 days before randomization.
MAINEPSAN trial - Exclusion Criteria (1)

- Patients with **EGPA, or other vasculitides**, defined by the ACR criteria and/or the Chapel Hill Consensus Conference,

- Patients with vasculitis with **active disease defined as a BVAS>0**,

- Patients with **acute infections or chronic active infections** (including HIV, HBV or HCV),

- Patients with **active or recent cancer** (<5 years) or **myelodysplasia**, except basocellular carcinoma and low activity prostatic cancer controlled by hormonal treatment,

- **Pregnant women and lactation**: women of childbearing potential will have to follow an effective method of contraception for the duration of the study,

- Patients with **contraindication to rituximab use**, 

- Patients with **other uncontrolled diseases**, including drug or alcohol abuse, severe psychiatric diseases, that could interfere with participation in the trial according to the protocol,
Patients included in other investigational therapeutic study within the previous 3 months excepted for the PNEUMOVAS trial,

Patients suspected not to be observant to the proposed treatment,

Patients who have white blood cell count ≤ 4000/mm³,

Patients who have platelet count ≤ 100 000/mm³,

Patients who have ALAT or ASAT level greater than 3 times the upper limit of normal,

Patients unable to give written informed consent form prior to study participation,

Patients under legal protection,

Patient not affiliated to a social security scheme or other social protection scheme.
MAINEPSAN trial – Study Design

**LEGEND:**
- Green: Prednisone Treatment
- Purple: Placebo Treatment
- Orange: Prednisone & Placebo Combination Treatment

**Inclusion**
- Prednisone 5-10 mg/day
- Placebo

**Randomization**
- Prednisone 5mg/day Experimental Arm
- Placebo 5mg/day Control Arm

**Run-In Period**
- Prednisone Tapering 1mg/wk

**Treatment Period**
- Day 35
- Day 1
- W4
- W12
- W24
- W36
- W48
- W52
- W60
- W72
- W84
- W96
- W108
- W120

**Follow-Up Visits**

**Primary Endpoint**

**Induction**
- RITUXIMAB 500 mg M0
- RITUXIMAB 500 mg M6
- RITUXIMAB 500mg M12
- RITUXIMAB 500 mg M18

**Maintenance**

18 Months after last RITUXIMAB infusion

= M4 to M6 Post Remission of GPA-MPA
<table>
<thead>
<tr>
<th>Semaine</th>
<th>M0</th>
<th>M0</th>
<th>M0</th>
<th>M0</th>
<th>M1 à M12</th>
<th>M12</th>
<th>M12</th>
<th>M12</th>
<th>M12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>32 gélules actif 5 mg</td>
<td>7 gélules Placebo 4 mg</td>
<td>7 gélules Placebo 3 mg</td>
<td>7 gélules Placebo 2 mg</td>
<td>7 gélules Placebo 1 mg</td>
<td>7 gélules Actif 4 mg</td>
<td>7 gélules Actif 3 mg</td>
<td>7 gélules Actif 2 mg</td>
<td>7 gélules Actif 1 mg</td>
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</tbody>
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<thead>
<tr>
<th>Experimental Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg actif</td>
</tr>
<tr>
<td>placebo 4 mg</td>
</tr>
</tbody>
</table>

**Note:**

1 Kit «décroissance» de 4 piluliers

X 11 piluliers de 32 gélules Actif 5 mg
<table>
<thead>
<tr>
<th>Control Arm</th>
<th>M0 Semaine 1</th>
<th>M0 Semaine 2</th>
<th>M0 Semaine 3</th>
<th>M0 Semaine 4</th>
<th>M1 à M12</th>
<th>M12 Semaine 1</th>
<th>M12 Semaine 2</th>
<th>M12 Semaine 3</th>
<th>M12 Semaine 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo 5 mg</td>
<td>Placebo 5 mg</td>
<td>Placebo 5 mg</td>
<td>Placebo 5 mg</td>
<td>Placebo 5 mg</td>
<td>Placebo 5 mg</td>
<td>Placebo 4 mg</td>
<td>Placebo 3 mg</td>
<td>Placebo 2 mg</td>
<td>Placebo 1 mg</td>
</tr>
<tr>
<td>4 mg actif</td>
<td>3 mg actif</td>
<td>2 mg actif</td>
<td>1 mg actif</td>
<td></td>
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</table>

32 gélules placebo 5 mg

1 Kit « décroissance » de 4 piluliers

X 11 piluliers de 32 gélules placebo 5 mg
MAINEPSAN trial – Study Design

**STRATIFICATION**
- Newly diagnosed vs. relapsing vasculitis
- Anti-PR3 status (positive vs. negative) at diagnosis for newly-diagnosed vasculitis or at last relapse
- ELISA ANCA status (positive vs. negative) at inclusion (M12 after initiation of treatment)
- Methotrexate versus Rituximab or Cyclophosphamide at the diagnosis or relapse of vasculitis
146 patients

In regards of the MAINEPSAN results, the primary hypothesis of the trial is a relative decrease of 60% of the relapse rate at 24 months post-flare, i.e. 14% vs 34%

Based on this hypothesis, using a bilateral test, we calculated that 140 patients would be required for the study to have 80% power to detect an absolute 20% reduction with a two-sided alpha level
Etude MAINEPSAN

Répartition géographique des 38 centres
MainePSan
Acknowledgments

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HCL
Mr Yoann Lherm
Mr Laurent Villeneuve
Pr François Gueyffier

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THANKS FOR YOUR ATTENTION

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