TREATMENT OF ANCA-ASSOCIATED VASCUITIS

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Cours DU, 11 mars 2016
Disclosure of interest regarding this presentation

Roche has provided, in part, rituximab for the MAINRITSAN 1 and 2 clinical trials
CLINICIAN’S AND PATIENT’S NEEDS

- Quick effectiveness
- Good tolerance
- Cure more than obtain a remission
CONVENTIONAL TREATMENT FOR VASCULITIS

- Cyclophosphamide + steroids in systemic disease
- Methotrexate for non-renal GPA
- CS alone in some patients without poor-prognosis factors (FFS 0) (EGPA, MPA)
- Azathioprine or methotrexate for maintenance treatment
Pulse cyclophosphamide treatment

- 0.6 to 0.7gr/sq.m (or 15 mg/kg) D0, D15, D30
  - then every 3 weeks until remission
  - 0.5 gr/sq.m in case of renal insufficiency or in patients > 65 yr.old
Rapid crescentic glomerulonephritis
QUICK EFFECTIVENESS:
PLASMA EXCHANGES
Severe PAN without HBV, CSS and MPA

Indication of plasma exchanges

CS+IV CYC vs CS + IV CYC + PE

Guillevin, Arthritis Rheum 1995; 38: 1683
Guillevin, Arthritis Rheum 1995; 38: 1683
Comparison of pulses MPS to PE in ANCA+ vasculitis with creatininemia > 500 µmol/L

150 patients
PLASMA EXCHANGES IN SEVERE AAV

Survival

Months from entry

Patient survival

Group

IV MeP

Pl Ex
PLASMA EXCHANGES IN SEVERE AAV

Renal recovery

Months from entry

Group

IVMep

P Ex

Jayne, JASN 2007, 18: 2180-7
PEXIVAS
Randomised trial of plasma exchange and glucocorticoids in ANCA associated vasculitis
Hypothesis

1. PLEX increases the time to develop ESRD or death in severe AAV

2. Reduced GC will not increase ESRD or death and will reduce adverse events (esp. infections)
THE NEW ERA: BIOOTHERAPIES?
THE WGET STUDY
Etanercept for maintenance treatment in AAV

- Objective: to maintain remission
- Obtained in 72.4% patients, 49% relapses
- No significant difference
- High rate of malignancies in the etanercept group

INFLIXIMAB TO TREAT REFRACTORY AND SEVERE ANCA ASSOCIATED VASCULITIS

✓ 10 patients (7 GW, 2 RA vasculitis, 1 cryo)
✓ 10 responded, 5 CR, 5 PR
✓ 1 pt stopped the treatment (allergy)

INFLIXIMAB TO TREAT REFRACTORY AND SEVERE ANCA ASSOCIATED VASCULITIS

✓ Long term response
✓ 70% responders relapsed
✓ conclusion: suspensive treatment only

ANCA + VASCULITIS

Treatment of relapses of ANCA+ vasculitis with IgIV (IGANCA)

IV IMMUNOGLOBULINS TO TREAT REFRACTORY AND SEVERE ANCA ASSOCIATED VASCULITIS

✓ RESULTS

✓ 21 patients have been included

✓ 20/21 initial responses

✓ at 9 months
  ✓ 13 CR, 1 PR, 7 relapses
  ✓ at 24 months: 7 complete remissions

IV IMMUNOGLOBULINS TO TREAT REFRACTORY AND SEVERE ANCA ASSOCIATED VASCULITIS
RITUXIMAB
Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis


Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

RAVE

1 to 3 pulses MPS

CS+CYC oral, 3 to 6 months

RTX 375 X 4 + CS + placebo CYC

AZA 12-15 months

Placebo AZA

CROSS OVER IF NEEDED

RAVE: RESULTS

✓ Primary endpoint (BVAS=0, stop CS at 6 months) reached by:

✓ 63 of the 99 patients in the rituximab group 64%

✓ 52 of 98 in the control group 53%

✓ The treatment difference of 11% between the groups met the criterion for non inferiority (P<0.001)

RAVE: RESULTS

✓ Secondary endpoint (BVAS 0, < 10 mg CS, at 6 months) reached by:

✓ 70 patients treated with rituximab 71%

✓ 61 patients in the control group 62%

RAVE: RESULTS

✓ **Adverse events:**

✓ No significant differences between the treatment groups

✓ **Events leading to discontinuation of treatment:**

✓ 14 patients in the rituximab group 14%

✓ 17 in the control group 17%

RITUXVAS: RESULTS

✓ Severe adverse events occurred

✓ 14 of the 33 patients in the rituximab group

42%

✓ 4 of the 11 patients in the control group

36%

Infections occurred in

- 12 of the 33 patients in the rituximab group, 36% (total of 19 infections)
- 3 of the 11 patients in the control group, 27% (total of 7 infections)

RITUXIMAB in the long term
Results
A Time to First Relapse after Complete Remission, According to Treatment

Probability of Remaining in Complete Remission

Days from Complete Remission to Relapse

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>CYC–AZA (N=70)</th>
<th>RTX (N=76)</th>
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<tbody>
<tr>
<td></td>
<td>70</td>
<td>76</td>
</tr>
<tr>
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<td>70</td>
<td>76</td>
</tr>
<tr>
<td>10</td>
<td>61</td>
<td>65</td>
</tr>
<tr>
<td>20</td>
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<td>55</td>
</tr>
<tr>
<td>30</td>
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<td>45</td>
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<tr>
<td>40</td>
<td>3</td>
<td>5</td>
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</tbody>
</table>

P=0.76
B  Time to First Relapse after Complete Remission, According to Baseline Type of ANCA

- MPO (N=52)
- PR3 (N=94)

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>MPO</th>
<th>PR3</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>5</td>
<td>3</td>
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</tr>
</tbody>
</table>
Time to First Relapse after Complete Remission, According to Treatment and Baseline Type of ANCA

Overall, $P<0.01$
- MPO, $P=0.34$
- PR3, $P=0.71$

- CYC–AZA, MPO (N=26)
- CYC–AZA, PR3 (N=44)
- RTX, MPO (N=26)
- RTX, PR3 (N=50)
MAINTENANCE TREATMENT IN VASCULITIS
Comparison of 3 to 6 mo. oral CYC + CS then azathioprine or oral CYC for 12 mo.+ 10 mg/d CS. After 12 mo all the patients were treated with azathioprine

150 patients followed for 18 mo.

Randomized trial of cyclophosphamide versus azathioprine as remission maintenance therapy for ANCA-associated vasculitis

**Systemic Wegener’s granulomatosis:**
- ≥ 2 organs involved
- or kidney involvement
- or 1 organ involved + general symptoms (fever, weight loss...)

**Microscopic polyangiitis:**
- with FFS ≥ 1

**IV CYC** 0.6 g/m² (d1, d15, d30)

0.7 g/m²/3 wk

**Azathioprine** 2 mg/kg/d

**Methotrexate** 25 mg/wk

**Cotrimoxazole** 1600 mg/d

**INDUCTION**

6-12 mo

**MAINTENANCE**

12 mo

...2 yrs

Relapse-free survival curves

Relapse-free survival at 18 mo: AZA 77.9% [66.9–89.0]; MTX 82.4% [72.4–92.3]

Relapse-free survival at 24 mo: AZA 67.5% [53.9–81.0]; MTX 72.6% [60.0–85.2]

p = 0.36

AZA n = 55

MTX n = 59

WEGENT

Mycophenolate mofetil is not superior to azathioprine to reduce relapses in ANCA-associated vasculitis
Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

Maintenance treatment

$R = 500 \text{ mg of rituximab}$

- 2 wk
- 5 mo + 2 wk
- 6 mo
- 6 mo

Azathioprine 2 mg/kg/d then tapered 22 mo

Endpoint 28 mo

Guillevin, NEJM 2014; 37: 1771-80
Results
Results: demographics

✓ 115 patients
✓ 65 men (56.5%) and 50 women (43.4%)
✓ 58 Azathioprine
  ✓ 47 1st flares and 11 relapses
✓ 57 Rituximab
  ✓ 45 1st flares and 12 relapses

Guillevin, NEJM 2014; 37: 1771-80
Azathioprine group drop outs *

27/58 (46.5%)  

✓ 17 major relapses (28.8%)  
✓ 5 for severe adverse events (8.5%)  
✓ 5 stopped treatment for other reasons, mainly personal (8.5%)  

* Several causes for the same patient  

Guillevin, NEJM 2014; 37: 1771-80
Rituximab group drop outs *

6/58 (10.3%)

✓ 3 major relapses (5.2%)

✓ 3 stopped treatment for other reasons, personal for 1

* Several causes for the same patient

Guillevin, NEJM 2014; 37: 1771-80
Immunoglobulins

<table>
<thead>
<tr>
<th>γglobulins</th>
<th>D 0</th>
<th>M 28</th>
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</thead>
<tbody>
<tr>
<td>AZA</td>
<td>6.1</td>
<td>8.1</td>
</tr>
<tr>
<td>RTX</td>
<td>6.8</td>
<td>7.4</td>
</tr>
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</table>

Guillevin, NEJM 2014; 37: 1771-80
The same proportion of anti-PR3 and anti-MPO was observed at M28.

Guillevin, NEJM 2014; 37: 1771-80
Severe adverse events (treatment-related or not) *

✓ Azathioprine: 44 in 25 patients (46.3%)

✓ Rituximab: 45 in 25 patients (43.8%)

* Events not related to AAV are not considered in this presentation (ex: surgery for hernia, present before the disease occurred)

Guillevin, NEJM 2014; 37: 1771-80
<table>
<thead>
<tr>
<th>Infections</th>
<th>Azathioprine</th>
<th>Rituximab</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung infections</td>
<td>2</td>
<td>1</td>
<td>recovery</td>
</tr>
<tr>
<td>GI infections</td>
<td>1</td>
<td>2</td>
<td>recovery</td>
</tr>
<tr>
<td>Herpes zooster</td>
<td>1</td>
<td>1</td>
<td>recovery</td>
</tr>
<tr>
<td>Septicemia</td>
<td>1</td>
<td></td>
<td>death</td>
</tr>
<tr>
<td>Tuberculosis, mycobacteria</td>
<td>1</td>
<td>1</td>
<td>recovery</td>
</tr>
<tr>
<td>Pneumocystis</td>
<td>0</td>
<td>1</td>
<td>recovery</td>
</tr>
</tbody>
</table>
Deaths during follow-up (28 months)

2/115 (1.7%)

- Azathioprine: 2 (3.5%)
  - Septicemia 5 months after inclusion, at the time of relapse and treatment intensification
  - Death 24 months after inclusion, of pancreatic cancer
- Rituximab: 0 (0%)
P = 0.002
Ongoing study:
MAINRITSAN 2
✔ Objectives

✔ To determine whether treatment adapted to ANCA status and CD19 is as effective as a fixed administration schedule

✔ Safety in each arm
✔ Inclusions 162 within 11 months (completed)
Maintenance treatment

R = 500 mg of rituximab

2 wk  5 mo +  6 mo  6 mo

R  R  R  R  R

Endpoint
28 mo

On demand

Monitoring

On demand
Effectiveness on all clinical manifestations
RTX IN REFRACTORY GPA) RTX is more Efficient in Vasculitic than in Granulomatous Manifestations

- significant reduction in BVAS and activity of all organ systems (p<0.05)
- higher rate of unchanged/refractory activity in granuloma compared to vasculitis e.g. in orbital granuloma vs. alveolar hemorrhage (p<0.05)
Long term follow up of MAINRITSAN 1
MAINRITSAN
Long term follow up

✓ Median duration of follow-up: 43.6 months (IQR, 38.0-49.5 months)

✓ Major relapses
  ✓ 10/55 (18.2%) in the RTX arm
  ✓ 28/51 (54.9%) in the AZA arm
MAINRITSAN
Long term follow up

Study period  Extended FU

Relapse-free survival (%)

HR 0.27 (0.15-0.53), P=0.0001
MAINRITSAN
Long term follow up

Relapse-free survival according to ANCA specificity

[Graph showing relapse-free survival over time for different treatments]
Relapse-free survival according to ANCA specificity
Rituximab: Recommendations of the French Vasculitis Study Group (FVSG) for induction and maintenance treatments of adult, antineutrophil cytoplasm antibody-associated necrotizing vasculitides

Pierre Charles¹,², Boris Bienvenu³, Bernard Bonnotte⁴, Pierre Gobert⁵, Pascal Godmer⁶, Éric Hachulla⁷, Mohamed Hamidou⁸, Jean-Robert Harlé⁹, Alexandre Karras¹⁰, Jean-Christophe Lega¹¹, Alain Le Quellec¹², Alfred D. Mahr¹³, Luc Mouthon¹, Thomas Papo¹⁴, Xavier Puéchal¹, Gregory Pugnet¹⁵, Maxime Samson⁴, Jean Sibilia¹⁶, Benjamin Terrier¹, Frederick Vanderheynst¹⁷, Loïc Guillevin¹, for the FVSG¹
1. Cyclophosphamide and rituximab both effectively induce AAV remission but the FVSG recommends rituximab in the following situations (expert consensus):

- Patients who have already relapsed
- After IV CYC failure
- Young patients with fertility concerns
- Patients who have already received >10 grams of CYC
2. Rituximab can be prescribed to AAV (MPA, GPA) patients, even in the absence of ANCA

3. Rituximab cannot yet be recommended for EGPA patients (no prospective study) or minor forms of GPA that do not require cytotoxic drugs
Recommendations

4. Rituximab cannot be prescribed only to achieve steroid-sparing

5. Age is not a limitation for rituximab use but its safety profile is not sufficient to propose rituximab as first-line therapy to induce remission in elderly patients

6. Combining rituximab and cytotoxic drugs at “full dose” is not recommended but combinations of several drugs warrant being evaluated at lower dose
7. Prophylaxis against infections is recommended

- Cotrimoxazole for PJP
- Anti-TB drugs if needed
- Vaccination is highly recommended (pneumonia, influenza) as soon as possible before treatment
- IVIg SHOULD NOT be prescribed systematically for infection prophylaxis
- For hypogammaglobulinemic patients, IVIg prescription should follow the recommendations established for secondary immune-deficiency management
Conclusions

✓ Treatment of AAV is rapidly improving

✓ Rituximab is the competitor of cyclophosphamide for remission induction

✓ Other biotherapies have a more limited place and punctual place in the treatment of AAV, especially IgIV. The place for anti-TNF is very limited.

✓ New drugs are evaluated: mepolizumab (EGPA), abatacept, chemokines (ANCA-vasculitides)
To maintain remission, a treatment is needed

Rituximab is taking the first place to maintain remission.

However, the optimal treatment duration is not yet established.

Relapse occur also when rituximab is prescribed for maintenance, but with a delay which needs to be more precisely evaluated.
www.vascularites.org

Referral Center for Rare Systemic and Autoimmune Diseases

Hôpital Cochin Paris