TREATMENT OF ANCA-ASSOCIATED VASCULITIS
AN UPDATE

Loïc Guillevain

Hôpital Cochin, Université Paris Descartes

DU MALADIES SYSTEMIQUES, 7 March 2014
Disclosure of interest regarding this presentation

- Former member of the Scientific Council of the Rituximab Registry for Autoimmune Diseases in France
- Roche has provided, in part, rituximab for the MAINRITSAN 1 and 2 clinical trials
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
HOW TO TREAT VASCULITIDIES

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
Quick effectiveness
Good tolerance
Cure more than obtain a remission
Rapid crescentic glomerulonephritis
Extracapillary proliferation
Capsular rupture
Fibrine
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

Group A: CS + CYC

Group B: CS + CYC + PE

p = NS

MONTHS
PLASMA EXCHANGES IN SEVERE AAV

Plasma exchanges MEPEX

✓ Comparison of pulses MPS to PE in ANCA+ vasculitis with creatininemia > 500 μmol/L

✓ 150 patients

Jayne D et al, JASN 2008
PLASMA EXCHANGES IN SEVERE AAV

Survival

Patient survival

0.0

0.1

0.2

0.3

0.4

0.5

0.6

0.7

0.8

0.9

1.0

0

2

4

6

8

10

12

Months from entry

Group

IV MeP

Pl Ex
PLASMA EXCHANGES IN SEVERE AAV

Months from entry

Renal recovery

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)
Eligibility

- ANCA vasculitis (new or relapsing)
- ANCA positive
- Renal vasculitis GFR < 50ml/min and/or alveolar haemorrhage
FACTORIAL DESIGN

500 Patients: Severe ANCA Vasculitis

Cyclophosphamide (Or Rituximab)

250 pts: Adjunctive Plasma Exchange
250 pts: No Plasma Exchange

125 pts: Standard-Dose Prednisolone
125 pts: Reduced Dose Prednisolone
125 pts: Standard-Dose Prednisolone
125 pts: Reduced Dose Prednisolone
Protocol Overview

- Cyclophosphamide or rituximab
- Azathioprine
- Low Dose GC
- PLEX

- 2 weeks
- 3 - 6 months
- 1 year

2-7 years
Glucocorticoid Dosing

![Graph showing prednisolone mg/day consumption over time with standard and reduced dosing compared.]

(IV MeP 1-3g)
THE NEW ERA: BIOOTHERAPIES ?
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

INFLIXIMAB TO TREAT REFRACTORY AND SEVERE ANCA ASSOCIATED VASCULITIS

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

THE RELANCA STUDY

✓ Adressed to patients who relapsed or did not respond to an optimal CS + IS treatment
✓ Add on therapy (rituximab vs infliximab)
✓ Randomized

De Menthon, Clin Exp Rheumatol 2011, 29: S63
Infliximab

Infliximab 3 mg/kg D1 and D15

Evaluation D45

CR D45

6 infusions

PR D45

14 infusions 5 mg/kg

Failure J45

Infliximab 5 mg/kg

Evaluation D73

Stop

De Menthon, Clin Exp Rheumatol 2011, 29: S63
Rituximab 375 mg/m² 4 weekly infusions

Evaluation at M2

CR or PR
Maintenance M4 M8 and M12

failure
stop

De Menthon, Clin Exp Rheumatol 2011, 29: S63
### Clinical response at M12

<table>
<thead>
<tr>
<th></th>
<th>INFLIXIMAB N=11</th>
<th>RITUXIMAB N=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>PR</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>PR + CR</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Failure</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

De Menthon, Clin Exp Rheumatol 2011, 29: S63
22 patients screened

17 patients included

9 infliximab

2 CR & 2 PR

Long term
1 persistent PR & 2 relapses

2 deaths & 5 failures (4–6 months)

4 switched to rituximab

4 CR

8 rituximab

1 CR & 2 PR

2 CR & 3 PR

1 death on D22

3 failures

2 switched to IVIg, CYC

2 “grumbling”
ANCA + VASCULITIS

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

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

Martinez, 2008

Arthritis Rheum

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%

RITUXVAS: RESULTS

✓ 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 might be considered as an option for first-line therapy for induction of remission of ANCA-associated disease.

(since this editorial, rituximab has been approved in the USA (FDA) and in Europe, for induction only, in May 2013)
RITUXIMAB in the long term
Results
A. Time to First Relapse after Complete Remission, According to Treatment

- **CYC-AZA (N=70)**
- **RTX (N=76)**

<table>
<thead>
<tr>
<th>Days from Complete Remission to Relapse</th>
<th>CYC-AZA</th>
<th>RTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>70</td>
<td>76</td>
</tr>
<tr>
<td>10</td>
<td>61</td>
<td>65</td>
</tr>
<tr>
<td>50</td>
<td>51</td>
<td>55</td>
</tr>
<tr>
<td>100</td>
<td>43</td>
<td>45</td>
</tr>
<tr>
<td>150</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

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

![Graph showing time to first relapse after complete remission](image)

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

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>MPO</th>
<th>PR3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>52</td>
<td>94</td>
</tr>
<tr>
<td>10</td>
<td>46</td>
<td>80</td>
</tr>
<tr>
<td>20</td>
<td>44</td>
<td>62</td>
</tr>
<tr>
<td>30</td>
<td>37</td>
<td>52</td>
</tr>
<tr>
<td>40</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

*P < 0.01*
C  Time to First Relapse after Complete Remission, According to Treatment and Baseline Type of ANCA

- Anti-MPO
- Anti-PR3

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)

Probability of Remaining in Complete Remission

Days from Complete Remission to Relapse
D Time to First Relapse after Complete Remission, According to Presence of Three Risk Factors

Overall, $P=0.01$
PR3/GPA/relapsing, $P=0.47$
All others, $P=0.51$

- CYC–AZA, all others ($N=47$)
- CYC–AZA, PR3/GPA/relapsing ($N=23$)
- RTX, all others ($N=47$)
- RTX, PR3/GPA/relapsing ($N=29$)
AZATHIOPRINE, METHOTREXATE FOR MAINTENANCE TREATMENT
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 polyangiiitis: with FFS ≥ 1

IV CYC 0.6 g/m² (d1, d15, d30)

0.7 g/m²/3 wk

Azathioprine 2 mg/kg/d
or
Methotrexate 25 mg/wk

Cotrimoxazole 1600 mg/d
...2 yrs

6-12 mo

12 mo

INDUCTION

MAINTENANCE

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]
Mycophenolate mofetil is not superior to azathioprine to reduce relapses in ANCA-associated vasculitis.
Maintenance treatment

R = 500 mg of rituximab

Azathioprine  2 mg/kg/d then tapered  22 mo

2 wk  5 mo + 2 wk  6 mo  6 mo

Endpoint
28 mo

ANCA workshop 17 april 2013
Results
Results: demographics

✓ 117 patients

✓ 66 men (56.4%) and 51 women (43.6%)

✓ 59 Azathioprine
  ✓ 47 1st flares and 12 relapses

✓ 58 Rituximab
  ✓ 46 1st flares and 12 relapses
Azathioprine group drop outs *

27/59 (45.7%)

- 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
Azathioprine group dropouts

- M0: 8 relapses
- M12: 2 relapses
- M22: 7 relapses
- Stop AZA
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
Rituximab group dropouts

- Stop RTX

- M8
  - 1 relapse

- M18
  - 2 relapses

- M28
Immunoglobulins

<table>
<thead>
<tr>
<th>γ-globulins</th>
<th>D 0</th>
<th>M 28</th>
</tr>
</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>
</tbody>
</table>
### ANCA

<table>
<thead>
<tr>
<th>%</th>
<th>DIAGNOSIS</th>
<th>REMISSION (obtained with CYC)</th>
<th>M 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZATHIOPRINE</td>
<td>93.2</td>
<td>69.6</td>
<td>60.8</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>94.7</td>
<td>53.7</td>
<td>24.4</td>
</tr>
</tbody>
</table>

The same proportion of anti-PR3 and anti-MPO was observed at M28.
## CD19 on Rituximab

<table>
<thead>
<tr>
<th></th>
<th>B cell at M28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapses</td>
<td>CD19 = 0, in 3/3 patients ANCA anti PR3, + 2/3</td>
</tr>
<tr>
<td>Remission</td>
<td>54.5 % achieved B cell reconstitution*</td>
</tr>
</tbody>
</table>

° 2 missing data
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)
<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>
# Severe adverse events

<table>
<thead>
<tr>
<th>Drug intolerance &amp; miscellaneous</th>
<th>Azathioprine</th>
<th>Rituximab</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis</td>
<td>3</td>
<td>0</td>
<td>recovery</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>1</td>
<td>1</td>
<td>recovery</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2</td>
<td>0</td>
<td>recovery</td>
</tr>
<tr>
<td>Anemia</td>
<td>2</td>
<td>0</td>
<td>recovery</td>
</tr>
<tr>
<td>Chills fever</td>
<td>0</td>
<td>2</td>
<td>recovery</td>
</tr>
</tbody>
</table>
# Severe adverse events

<table>
<thead>
<tr>
<th>Cancers</th>
<th>Azathioprine</th>
<th>Rituximab</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin cancer (basocellular)</td>
<td>2</td>
<td>0</td>
<td>surgery</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>0</td>
<td>1</td>
<td>medical treatment</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>1</td>
<td>0</td>
<td>death</td>
</tr>
</tbody>
</table>
### Severe adverse events

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Azathioprine</th>
<th>Rituximab</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
<td>0</td>
<td>treatment</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>2</td>
<td>2</td>
<td>recovery</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>1</td>
<td>0</td>
<td>recovery</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1</td>
<td>0</td>
<td>recovery</td>
</tr>
</tbody>
</table>
## Severe adverse events

<table>
<thead>
<tr>
<th>Metabolic and others</th>
<th>Azathioprine</th>
<th>Rituximab</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>4</td>
<td>5</td>
<td>treatment</td>
</tr>
<tr>
<td>Hip osteonecrosis</td>
<td>1</td>
<td>1</td>
<td>surgery</td>
</tr>
<tr>
<td>Cataract</td>
<td>4</td>
<td>2</td>
<td>surgery</td>
</tr>
</tbody>
</table>
Deaths during follow-up (28 months)

2/117 (1.7%)

- Azathioprine: 2 (3.3%)
  - Septicemia 5 months after inclusion, at the time of relapse and treatment intensification
  - Death 24 months after inclusion, of pancreatic cancer
- Rituximab: 0 (0%)
Event free survival

P = 0.002
Overall survival

\[ P = 0.162 \]
Conclusion

✓ Rituximab is superior to azathiothriprine to maintain remission in ANCA-associated vasculitides

✓ A 500-mg dose every 6 months is sufficient to maintain remission. Relapses are rare.

✓ Treatment tolerance was good, with a limited number of side effects, mainly transient.
Conclusion

✓ Gammaglobulins level decreased moderately during follow up and did not impact significantly the occurrence of infectious side effects

✓ ANCA disappeared in most patients treated with rituximab and in a minority of patients who received azathioprine
Comments and questions
✓ Do we need treatment monitoring?
   ✓ ANCA
   ✓ CD19
   ✓ Immunoglobulins

✓ Is rituximab effective on all clinical manifestations?

✓ What to do in the long term?
   ✓ Efficacy
   ✓ Tolerance
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

2 wk

R  R  R  R

On demand

Monitoring

Endpoint 28 mo
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

Months
MAINRITSAN extension – Results

Relapse-free survival according to ANCA specificity
MAINRITSAN
Long term follow up

Relapse-free survival according to ANCA specificity
Relapse-free survival according to ANCA specificity
Mainritsan
Long term follow up

Relapse-free survival according to ANCA specificity
MAINRITSAN
Long term follow up

Relapse-free survival according to type of flare
Relapse-free survival according to type of flare
MAINRITSAN
Long term follow up

Relapse-free survival according to type of flare
MAINRITSAN extension – Results

Relapse-free survival according to type of flare

![Graph showing relapse-free survival over months for different types of flare.]
MAINRITSAN
Long term follow up

✓ Median duration of follow-up: 42.7 months (IQR, 36.5-48.1 months)

✓ Major relapses
  ✓ 10/55 (18.2%) in the RTX arm
  ✓ 28/51 (54.9%) in the AZA arm

✓ Deaths
  ✓ 0/55 (0%) in the RTX arm
  ✓ 3/51 (5.9%) in the AZA arm
MAINRITSAN
Long term follow up

3 deaths:
- 1 from infection
- 1 from cancer
- 1 from M. ischemia

P = 0.07
MAINRITSAN extension – Results

Event-free survival (%) vs Months

HR 0.36 (0.19-0.66), P=0.0009

RTX
AZA
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 Mouton¹, Thomas Papo¹⁴, Xavier Puéchal¹, Gregory Pugnet¹⁵, Maxime Samson⁴, Jean Sibilia¹⁶, Benjamin Terrier¹, Frederick Vanderghynst¹⁷, Loïc Guillemin¹, 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
Recommendations

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.
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
Recommendations

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
8. The FVSG recommends prescribing rituximab as maintenance treatment, according to the results of the MAINRITSAN 1 trial

9. Rituximab reintroduction is not recommended for patients who developed severe side effects (cytopenia, pneumonia)

10. Monitoring of gammaglobulin levels and CD19 is recommended but their impact on treatment decision warrants further study
How to orientate treatments

- Adapt treatment to markers of activity
- Adapt treatment to markers of relapse
- Adapt treatment to comorbidities
- Adapt treatment to genetic markers able to:
  - Precise diagnosis
  - Identify patients: “relapsers” and “non relapsers”
  - Identify patients who could experience infections or other side effects
British cohort
1184 pts and 5844 controls
European replication cohort
1454 pts and 1666 controls

Genetically Distinct Subsets within ANCA-Associated Vasculitis

Paul A. Lyons, Ph.D., Tim F. Rayner, Ph.D., Sapna Trivedi, M.R.C.P., M.Phil.,
Bo Baslund, M.D., Ph.D., Paul Brenchley, Ph.D., Annette Bruchfeld, M.D., Ph.D.,
Afzal N. Chaudhry, Ph.D., F.R.C.P., Jan Willem Cohen Tervaert, M.D., Ph.D.,
Panos Deloukas, Ph.D., Conleth Feighery, M.D., Wolfgang L. Gross, M.D., Ph.D.,
Loic Guillemin, M.D., Iva Gunnarsson, M.D., Ph.D., Lorraine Harper M.R.C.P., Ph.D.,
Zdenka Hrušková, M.D., Mark A. Little, M.R.C.P.I., Ph.D., Davide Martorana, Ph.D.,
Thomas Neumann, M.D., Sophie Ohlsson, M.D., Ph.D., Sandosh Padmanabhan, M.D., Ph.D.,
Charles D. Pusey, D.Sc., F.Med.Sci., Alan D. Salama, F.R.C.P., Ph.D.,
Jan-Stephan F. Sanders, M.D., Ph.D., Caroline O. Savage, F.Med.Sci., Ph.D.,
Mårten Segelmark, M.D., Ph.D., Coen A. Stegeman, M.D., Ph.D., Vladimir Tesař, M.D., Ph.D.,
Augusto Vaglio, M.D., Ph.D., Stefan Wieczorek, M.D., Benjamin Wilde, M.D.,
Jochen Zwerina, M.D., Andrew J. Rees, M.B., F.Med.Sci., David G. Clayton, M.A.,

Lyons et al, NEJM 2012.
Relationships between Clinical Subtype and ANCA Specificity in ANCA-Associated Vasculitis and Associations of the MHC Locus with Proteinase 3 ANCA and Myeloperoxidase ANCA.


Lyons et al, NEJM 2012.
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 of anti-TNF is very limited.
Conclusions

✓ 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.vascularrites.org

Referral Center for
Rare Systemic and Autoimmune Diseases
Rituximab in France
A retrospective study on 80 patients
The FVSG and the French Society of Internal Medicine cohort

Charles P et al, Rheumatology 2013,
Before the results of prospective trials (RAVE, RITUXVAS) rituximab was mainly prescribed for relapses of AAV.

Rituximab is not yet approved for treatment of AAV and prescription can be prescribed only by or after opinion of referral centers.
### MAIN DISEASES

<table>
<thead>
<tr>
<th>Disease</th>
<th>n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, years, mean (SD)</td>
<td></td>
<td>48 (17)</td>
</tr>
<tr>
<td>GPA</td>
<td>70 (87)</td>
<td></td>
</tr>
<tr>
<td>MPA</td>
<td>7 (9)</td>
<td></td>
</tr>
<tr>
<td>EGPA</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Isolated RPGN</td>
<td>2 (2)</td>
<td></td>
</tr>
</tbody>
</table>

Charles P et al, Rheumatology 2013, in press
## DEMOGRAPHICS

<table>
<thead>
<tr>
<th>ANCA status</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cANCA</td>
<td>64 (80)</td>
</tr>
<tr>
<td>pANCA</td>
<td>13 (16)</td>
</tr>
<tr>
<td>PR3</td>
<td>65 (81)</td>
</tr>
<tr>
<td>MPO</td>
<td>11 (14)</td>
</tr>
<tr>
<td>ANCA-negative</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

Charles P et al, Rheumatology 2013, in press
## DEMOGRAPHICS

<table>
<thead>
<tr>
<th>Organ involvement</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENT and upper airway</td>
<td>60 (75)</td>
</tr>
<tr>
<td>Eye</td>
<td>32 (40)</td>
</tr>
<tr>
<td>Kidney</td>
<td>44 (55)</td>
</tr>
<tr>
<td>Lung and lower airway</td>
<td>57 (71)</td>
</tr>
</tbody>
</table>

Charles P et al, Rheumatology 2013, in press
Patients’ characteristics at the time of the 1\textsuperscript{st} infusion

Charles P et al, Rheumatology 2013, in press
Characteristics at the time of the 1\textsuperscript{st} infusion

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at 1\textsuperscript{st} rituximab cycle (years)</td>
<td>53 (17)</td>
</tr>
<tr>
<td>Disease duration before 1\textsuperscript{st} rituximab cycle (months)</td>
<td>54 (19–91)</td>
</tr>
<tr>
<td>Number of relapses before 1\textsuperscript{st} rituximab cycle</td>
<td>1 (1–2)</td>
</tr>
</tbody>
</table>

Charles P et al, Rheumatology 2013, in press
### Justification for rituximab treatment

<table>
<thead>
<tr>
<th>Indication</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction of remission</td>
<td>73 (91)</td>
</tr>
<tr>
<td>Frequent relapses</td>
<td>19 (24)</td>
</tr>
<tr>
<td>Persistent disease activity despite therapy</td>
<td>44 (55)</td>
</tr>
<tr>
<td>- Fertility concern</td>
<td>3 (4)</td>
</tr>
<tr>
<td>- High cumulative CYC dose</td>
<td>33 (41)</td>
</tr>
<tr>
<td>- Malignancy</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Maintenance treatment</td>
<td>7 (9)</td>
</tr>
</tbody>
</table>

Charles P et al, Rheumatology 2013, in press
## Immunosuppressants before the 1st RTX infusion

<table>
<thead>
<tr>
<th>Immunosuppressant</th>
<th>N (%), grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>78 (97), 13</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>55 (69), 18</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>24 (30), 7</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>19 (24), 1</td>
</tr>
</tbody>
</table>

Charles P et al, Rheumatology 2013, in press
<table>
<thead>
<tr>
<th>Biotherapy</th>
<th>N (%), months</th>
</tr>
</thead>
<tbody>
<tr>
<td>— Infliximab</td>
<td>7 (9), 6</td>
</tr>
<tr>
<td>— Other biotherapies</td>
<td>4</td>
</tr>
<tr>
<td>— Intravenous immunoglobulins</td>
<td>19 (24), 6 (3–9)</td>
</tr>
<tr>
<td>— Plasma exchange</td>
<td>10 (7PE)</td>
</tr>
</tbody>
</table>

Charles P et al, Rheumatology 2013, in press
Rituximab infusion schedule

Charles P et al, Rheumatology 2013, in press
**Rituximab infusion schedule**

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 infusions of 375 mg/m²/week</td>
<td>55 (69)</td>
</tr>
<tr>
<td>2 1-g infusions at 2-week interval</td>
<td>17 (21)</td>
</tr>
<tr>
<td>4 infusions of 500 mg/week</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Charles P et al, Rheumatology 2013, in press
Combined treatments

Concomitant immunosuppressive therapy

- CYC
- Azathioprine
- Mycophenolate mofetil
- Methotrexate

Charles P et al, Rheumatology 2013, in press
Response to rituximab

Charles P et al, Rheumatology 2013, in press
<table>
<thead>
<tr>
<th></th>
<th>Before rituximab therapy N=80</th>
<th>6 months after 1st rituximab infusion N=77</th>
<th>12 months after 1st rituximab infusion N=77</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active disease, n (%)</td>
<td>73 (91)</td>
<td>7 (9)</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Complete remission, n (%)</td>
<td>7 (9)</td>
<td>51 (66)</td>
<td>55 (71)</td>
</tr>
<tr>
<td>Partial remission, n (%)</td>
<td>0</td>
<td>19 (25)</td>
<td>11 (14)</td>
</tr>
<tr>
<td>DEI median (IQR)</td>
<td>2 (2–4)</td>
<td>0 (0–0)</td>
<td>0</td>
</tr>
<tr>
<td>BVAS</td>
<td>7 (5–12)</td>
<td>0 (0–1)</td>
<td>0</td>
</tr>
<tr>
<td>VDI median</td>
<td>0 (0–1)</td>
<td>1 (0–1)</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td>Prednisone, mg</td>
<td>20 (9.5–44)</td>
<td>10 (5–12)</td>
<td>5 (5–10)</td>
</tr>
</tbody>
</table>

Charles P et al, Rheumatology 2013, in press
Adverse events

Charles P et al, Rheumatology 2013, in press
<table>
<thead>
<tr>
<th>Infections</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary infections</strong></td>
<td></td>
</tr>
<tr>
<td>– <em>Pseudomonas aeruginosa</em></td>
<td>2</td>
</tr>
<tr>
<td>– <em>Aspergillus</em></td>
<td>2</td>
</tr>
<tr>
<td>– Pneumonia (no microbiologic data)</td>
<td>2</td>
</tr>
<tr>
<td>– <em>Pseudomonas</em> + <em>Aspergillus</em></td>
<td>1</td>
</tr>
<tr>
<td>– <em>Pseudomonas</em> + <em>Aspergillus</em> + <em>Pneumocystis</em> + <em>M. avium</em> (→ death)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Septic shock</strong> <em>(E. coli)</em></td>
<td>1</td>
</tr>
<tr>
<td><strong>Pyelonephritis</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Erysipelas</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Pneumococcal meningitis</strong> (→ death)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Febrile neutropenia</strong></td>
<td>1</td>
</tr>
</tbody>
</table>
Charles P et al, Rheumatology 2013, in press