Treatment of ANCA-associated vasculitides

Certainties and controversies

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Conflict of interest

- **Advisory board**: Roche, Chugai, Vifor, LFB, Grifols, AstraZeneca

- **Consulting fees**: Roche, Chugai, LFB, Grifols, GSK, AstraZeneca

- **Travel expenses**: Roche, LFB, Grifols, Octapharma, GSK, Janssen
Chapel Hill 2012 Consensus conference

- Immune Complex Small Vessel Vasculitis
  - Cryoglobulinemic Vasculitis
  - IgA Vasculitis (Henoch-Schönlein)
  - Hypocomplementemtic Urticarial Vasculitis (Anti-C1q Vasculitis)

- Medium Vessel Vasculitis
  - Polyarteritis Nodosa
  - Kawasaki Disease

- Anti-GBM Disease

- ANCA-Associated Small Vessel Vasculitis
  - Microscopic Polyangiitis
  - Granulomatosis with Polyangiitis (Wegener’s)
  - Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

Jennette, Arthritis Rheum, 2013
ANCA-associated vasculitis

Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries)

Associated with ANCA targeting myeloperoxidase or proteinase 3

Systemic disease with pulmonary, ENT and renal involvement
GPA/MPA vs. EGPA: Distinct phenotypes

- Lung involvement
- Renal involvement
- Heart involvement
- ANCA
- Biology
GPA/MPA vs. EGPA : Distinct trials

- Lung involvement
- Renal involvement
- Heart involvement
- ANCA
- Biology

RAVE, MAINRITSAN, RITAZAREM, ...

GPA

MPA

EGPA

MIRRA, REOVAS, ...
Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis

Double-blind RCT
197 patients

99 patients
Prednisone + oral CYC 3-6 mo. + placebo-RTX

98 patients
Prednisone + RTX 375 mg/m²/wk x 4 + placebo-CYC

AZA 12-15 mo.

Nothing

INDUCTION

ENTRETIEN

RTX = CYC

<table>
<thead>
<tr>
<th></th>
<th>RTX (n=99)</th>
<th>CYC (n=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPA (%)</td>
<td>75</td>
<td>76</td>
</tr>
<tr>
<td>MPA (%)</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>1st flare (%)</td>
<td>48</td>
<td>49</td>
</tr>
<tr>
<td>ENT (%)</td>
<td>61</td>
<td>56</td>
</tr>
<tr>
<td>Pulmonary (%)</td>
<td>52</td>
<td>54</td>
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<tr>
<td>AH</td>
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<td>24</td>
</tr>
<tr>
<td>Renal (%)</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>54</td>
<td>69</td>
</tr>
</tbody>
</table>


Primary outcome: BVAS = 0 at 6 months and no steroids

RTX arm 63/99 (64%)
CYC arm 52/99 (53%)

P<0.001 for non-inferiority
P=0.09 for superiority

Relapsing patients subgroup
RTX arm 67% vs. CYC arm 42%
P=0.01 for superiority

Excluded patients:
- Alveolar hemorrhage requiring mechanical ventilation
- Rapidly progressive enal failure with serum creatinin >350 μmol/L

CONCLUSIONS
Rituximab therapy was not inferior to daily cyclophosphamide treatment for induction of remission in severe ANCA-associated vasculitis and may be superior in relapsing disease. (Funded by the National Institutes of Allergy and Infectious Diseases, Genentech, and Biogen; ClinicalTrials.gov number, NCT00104299.)
Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis


**Hypothesis**
RTX/CYC > CYC

**Phase 2, open-label**
44 patients

- 11 patients
  - Prednisone + CYC IV 3-6 mo.

- 33 patients
  - Prednisone + RTX 375 mg/m²/wk x 4 + CYC IV day 1/15

**INDUCTION**

- AZA

**ENTRETIEN**

- Nothing

<table>
<thead>
<tr>
<th></th>
<th>RTX /CYC (n=33)</th>
<th>CYC (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>GPA (%)</td>
<td>55</td>
<td>36</td>
</tr>
<tr>
<td>MPA (%)</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Renal-limited</td>
<td>9</td>
<td>27</td>
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<tr>
<td>Renal (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Dialysis (%)</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>PLEX (%)</td>
<td>24</td>
<td>27</td>
</tr>
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</table>
Primary endpoints

Sustained remission rates at 12 months:

- Sustained remission rates in the rituximab group:
  25/33 (76%)
  (P=0.68)

- Sustained remission rates in the control group:
  9/11 (82%)

Severe adverse events:

- Severe adverse events in the rituximab group:
  14/33 (42%)
  (P=0.42)

- Severe adverse events in the control group:
  4/11 (36%)
  (P=0.77)

Death:

- 6/33 (18%) in the RTX/CYC group vs. 1/11 (9%) in the control group

CONCLUSIONS

A rituximab-based regimen was not superior to standard intravenous cyclophosphamide for severe ANCA-associated vasculitis. Sustained-remission rates were high in both groups, and the rituximab-based regimen was not associated with reductions in early severe adverse events. (Funded by Cambridge University Hospitals National Health Service Foundation Trust and F. Hoffmann-La Roche; Current Controlled Trials number, ISRCTN28528813.)
Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis


Induction phase

- 1 g x 3 i.v. methylprednisolone
- Prednisone (1 mg/kg/j) puis 20 mg à 3 mois puis 10 mg à 6 mois
- CYC i.v. (0.6 g/m² x 3 puis 0.7 g/m² x 3)

Maintenance phase

- R = 500 mg RTX-fixed dose
- Evaluation at 28 months

Hypothesis
RTX > AZA

2 sem. 5 mois 6 mois 6 mois

AZA 2 mg/kg/j puis diminution 22 mois
Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis


<table>
<thead>
<tr>
<th></th>
<th>AZA (n=58)</th>
<th>RTX (n=57)</th>
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<tbody>
<tr>
<td>GPA (%)</td>
<td>69</td>
<td>82</td>
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<tr>
<td>MPA (%)</td>
<td>31</td>
<td>18</td>
</tr>
<tr>
<td>1st flare (%)</td>
<td>81</td>
<td>79</td>
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<tr>
<td>ENT (%)</td>
<td>71</td>
<td>84</td>
</tr>
<tr>
<td>Pulmonary (%)</td>
<td>66</td>
<td>58</td>
</tr>
<tr>
<td>Renal (%)</td>
<td>71</td>
<td>70</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>58</td>
<td>68</td>
</tr>
<tr>
<td>Nervous system</td>
<td>33</td>
<td>40</td>
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</table>

CONCLUSIONS

More patients with ANCA-associated vasculitides had sustained remission at month 28 with rituximab than with azathioprine. (Funded by the French Ministry of Health; MAINRITSAN ClinicalTrials.gov number, NCT00748644; EudraCT number, 2008-002846-51.)
Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides

Terrier B et al, Ann Rheum Dis, 2018

HR AZA vs RTX:
2.51 [1.35 ; 4.69]  
P=0.003

HR AZA vs RTX:
2.11 [1.19 ; 3.73]  
P=0.012
Antiproteinase-3-ANCA positivity and azathioprine arm were independently associated with higher risk of relapse. HRs of positive ANCA to predict relapse increased over time.

**Conclusion** The rate of sustained remission for ANCA-associated vasculitis patients, following rituximab-based or azathioprine-based maintenance regimens, remained superior over 60 months with rituximab, with better overall survival.
Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2)

Charles P, Terrier B et al, Ann Rheum Dis, 2018

Open-label, multicenter, randomized controlled trial

Patients in complete remission after induction therapy with glucocorticoids plus RTX or CYC

Individually tailored RTX regimen based on ANCA and CD19

Randomization

Fixed-schedule RTX regimen

Primary endpoint
Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2)

Charles P, Terrier B et al, Ann Rheum Dis, 2018

Number of relapses at month 28

14 relapses (17.3%) in 13 tailored-infusion recipients vs. 8 (9.9%) in 8 fixed-schedule patients (P=0.22)

Rituximab infusions

3 (IQR 2–4) infusions in the tailored-arm

5 (IQR 5–5) infusion in the fixed-arm

Safety

85% in the tailored-arm vs. 91% in the fixed-arm with at least one AE (P=0.33)

Conclusion AAV relapse rates did not differ significantly between individually tailored and fixed-schedule rituximab regimens. Individually tailored-arm patients received fewer rituximab infusions.
Should rituximab be used in very severe vasculitis forms (alveolar hemorrhage, renal failure)?

Recommendations of the French Vasculitis Study Group on the use of rituximab in AAV
Should rituximab be used in very severe vasculitis forms (alveolar hemorrhage, renal failure)?
What is the optimal dose and duration in maintenance phase?

Charles, Ann Rheum Dis, 2018
PR3 vs. MPO-ANCA: Distinct prognosis at the rituximab era

Rituximab as induction therapy

Rituximab as maintenance therapy

What is the optimal dose and duration of rituximab in maintenance phase?

Terrier, Ann Rheum Dis, 2018
What is the optimal duration in maintenance phase?

- Comparison of 18 months vs. 46 months
- Primary endpoint: relapse free survival
- Results probably presented at ACR 2019
- Will statistical power be enough for subgroup analyses?

MAINRITSAN 3
Extension of MAINRITSAN 2
Patients still in remission
97 patients

RTX 500 mg at day 0, M6, M12 and M18

Placebo at day 0, M6, M12 and M18

10 months 10 months

FVSG FRENCH MACRODIPSIS STUDY GROUP
What is the optimal dose in maintenance phase?

- RTX 1 g every 4 months (total 5 g) vs. 500 mg every 6 months (total 2.5 g)

- Primary endpoint: relapse free survival

- Concerns about using such dose of RTX on the risk of severe infections
Do all patients require a maintenance treatment?

- Morbidity and mortality of immunosuppressive agents
- Significant predictors of mortality: advancing age, eGFR <15 mL/min
- Patients with higher creatinine levels have a lower risk of relapse (sHR 0.39 [95% CI 0.22-0.69] for a creatinine level >200 μmol/L)
- Could patients with ESRD benefit from the absence of maintenance treatment?

**MASTER—ANCA**

Patients with ESRD in remission

- Discontinuation or non-initiation of IS therapy
- Continuation or initiation of IS therapy

24 months of follow-up

*Flossman, Ann Rheum Dis, 2011*  
*Walsh, Arthritis Rheum, 2012*
What place for plasma exchanges before 2018?

<table>
<thead>
<tr>
<th>Indications of plasma exchanges in combination with glucocorticoids and cyclophosphamide/rituximab</th>
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<tbody>
<tr>
<td>Rapidly progressive glomerulonephritis with serum creatinin &gt;500 µmol/L</td>
</tr>
<tr>
<td>Rapidly progressive glomerulonephritis with serum creatinin between 150 and 500 µmol/L <strong>BUT</strong> rapid progression of renal failure</td>
</tr>
<tr>
<td>Severe alveolar hemorrhage (massive hemoptysis, acute respiratory distress syndrome)</td>
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<tr>
<td><em>Rapidly extensive mononeuritis multiplex</em></td>
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<tr>
<td><em>Refractory vasculitis despite optimal treatment</em></td>
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</table>
Treatment of severe renal vasculitis with serum creatinin >500 µmol/L

Comparison between pulses of MP vs. PLEX, in combination with oral CYC

Primary endpoint: dialysis independence at 3 months (49% with MP vs. 69% with PLEX, P=0.02)

Secondary endpoints: renal survival at 12 months (57% with MP vs. 81% with PLEX, P=0.008)
Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear

*Walsh M et al, Kidney Int, 2013;84:397-402*

- HR for death/ESRD for PLEX vs. MP: 0.81 (IC 95% 0.53-1.23)
- HR for death for PLEX vs. MP: 1.08 (IC 95% 0.67-1.73)
- HR for ESRD for PLEX vs. MP: 0.64 (IC 0.40-1.05, P=0.08)
- No long-term benefit of PLEX
704 patients with severe ANCA-associated vasculitis:
- Renal failure with eGFR <50 mL/min
- Alveolar hemorrhage
- Composite primary endpoint: time to death/ESRD (= dialysis for >12 weeks)

PLEX Arm: 7 PLEX over 14 days

Walsh, Trials, 2013
Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial

Primary outcome occurred in 28% of patients allocated to PLEX compared to 31% in the no PLEX group (HR 0.86, 95% CI 0.65 to 1.13; P=0.27)
Analysis of patients with AH suggesting a signal in favor of PLEX, with a relative risk of achieving the composite primary endpoint of 0.95 in the absence of AH, 0.65 in the presence of moderate AH and 0.67 in the presence of a severe AH (P=NS)

Possible benefit at 1 year and in severe alveolar hemorrhage?
Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial

- Primary outcome occurred in 28% in the reduced GCs group and 26% in the standard GCs group (absolute risk difference 2.3%, 90% CI -3.4% to 8.0%; non-inferiority hypothesis met)

- Serious infections in the first year occurred less often in the reduced GCs group compared to the standard group (incidence rate ratio 0.70, 95% CI 0.52 to 0.94; P=0.02)

*Walsh, ERA EDTA Congress, 2018*
What place for plasma exchanges after 2018?

Recommendations of the French Vasculitis Study Group on the use of PLEX in AAV
What place for plasma exchanges after 2018?

Recommendations of the French Vasculitis Study Group on the use of PLEX in AAV

Although the use of PLEX must be reduced, we cannot exclude their interest in some patients, in particular:

- Patients with severe alveolar hemorrhage
- Patients with persistent worsening of renal failure despite conventional GCs combined with cyclophosphamide or rituximab
- Patients presenting with a RPGN and/or AH without certainty in the diagnosis, at least until the results of anti-GBM antibodies and/or the certainty of the diagnosis.
Take home messages

- Rituximab has been a major therapeutic advance in the management of AAV.
- The use of rituximab is well defined in many situations in GPA and MPA.
- Uncertainties still remain in some forms of AAV and on the optimal (dose, duration) in maintenance.
- Optimal regimen in maintenance phase is currently under evaluation.
- The use of PLEX has still probably have a role but has to be clarified.
Acknowledgements

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www.vascularites.org