27è Curs de Formació Continuada

Quin paper ha de tenir el Rituximab en el tractament de les vasculitis?

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25/11/2015
• AAV
• Renal phenotype
• Pathogenic role of ANCA/Ab mediated damage
• Current disease course and concerns SOC
• Rituximab
  – Induction, maintenance
  – Hypogammaglobulinemia
  – Conclusions/ Take home message
Main cause
RPGN.
4% ESRD

20% AAV

ESRD

2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides
Renal phenotype

• Pauci-immune necrotizing GN
  Usually Associated with systemic vasculitis

• Non Renal involvement at RB
  – Multiple Mononeuritis
  – Purpura
  – Respiratory disease: 94% destructive lesions of the upper airways have PR3+

• Renal limited disease:
  – > 90 % ANCA +
  – 81 MPO +

Kitching AR, NDT 2004;19:365
Patient stratification in renal vasculitis is key issue for therapeutic, epidemiological and basic research
Refining phenotypes in ANCA-associated vasculitis.

GWAS found both MHC and non-MHC associations. GPA and MPA were genetically distinct.

The strongest genetic associations were with the ANCA serotype, not with the clinical syndrome.

PR3 ANCA-and MPO ANCA-associated vasculitis are distinct autoimmune syndromes.
ANCA and Renal outcome

Original Article

MPO-ANCA patients had a worse renal prognosis due to more severe glomerular injury

ANCA serotype and histopathological classification for the prediction of renal outcome in ANCA-associated glomerulonephritis

Luis F. Quintana, Nuria S. Peréz, Erika De Sousa, Lida M. Rodas, Meryl H. Griffiths, Manel Sóle and David Jayne

Division of Nephrology, Department of Medicine, University of Cambridge, Vasculitis and Lupus Clinic, Addenbrooke’s Hospital, Cambridge, UK, Servicio de Nefrología y Trasplante Renal, Hospital Clínic, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universidad de Barcelona, Barcelona, Spain, Department of Histopathology, Addenbrooke’s Hospital, Cambridge, UK and Department of Pathology, Hospital Clinic, Barcelona, Spain

Pathogenic role of ANCA

**ANTI-MPO ANTIBODIES**
- Rag2 (-/-)
- Wild type

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**SERUM ANTI-MPO ANTIBODIES**
- Necrotising and crescentic glomerulonephritis without immune deposits
- Necrotising and crescentic glomerulonephritis without immune deposits
- AAV-like pulmonary capillaritis
- AAV-like cutaneous vasculitis

**ANTI-BSA ANTIBODIES**
- Rag2 (-/-)
- Wild type

**ANTI-BSA ANTIBODIES**
- Rag2 (-/-)
- Wild type

No evidence of glomerular abnormalities or systemic vasculitis

No evidence of glomerular abnormalities or systemic vasculitis

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Day Cj  Clinical and experimental Rheumatology 2003;21: S35-S48
Falk RJ  J Nephrol 2004;17:S3-S9
Xiao H  J Clin Invest 2002
Central role of B cells in AAV organ damage

1. Auto-antigen St
2. T Cell Cytokines
3. B Cell Cytokines
4. B Cell clonal proliferation
5. Neutrophil activation
6. B cell differentiation to plasma cells

Walsh, KI 2007
ANCA vasculitis survival

1 year: 84%
5 years: 73%

• MORTALITY
80% without treatment during the first year

All patients

Induction therapy

Maintenance therapy

Long-term follow-up
The natural history of AAV has evolved from one of high mortality, ESRD and high ODR

chronic relapsing disease > 50%

where a fine balance exists between the benefits and the risks of therapy.
Relapse Risk

- Switch in ANCA status
- PR3+ (RELANCA)
- + FC GPA than MPA
- ENT involvement
- Better renal function <200umol/L
- Steroid minimization ??

Rasmussen et al, Clin Exp Rheumatol 2013
Rheumatology 2006;45:724-9
BSR guidelines for ANCA vasculitis: Ntatsaki et al, Rheumatology 2014
Toxicity Risk

**Infection**
- Mortality 11.1% in Y 1
  - 59%: drug- SAE
  - 14%: disease activity

**Neoplasia**
- SIR of cancer 2.1, 95% CI 1.5–2.7
- CYC cumulative dose > 36 g
- Haematological, bladder and NM skin cancer
- After a long latency period

*J Rheumatol, 35 (2008), pp. 100–105*
Rituximab

- Chimeric (mouse/human) IgG1/anti-CD20 monoclonal Ab
- Rituximab depletes circulating and resident B cells
  - ADCC, CDC, apoptosis
  - FcR dependent
- Licensed in 1997 for non-Hodgkin’s lymphoma
- 2005- AAV

B cell specific
CD20 -/- “normal”
Not down modulated
Rituximab as induction therapy

Table 2
Efficacy of RTX as induction therapy of AVV: randomized trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (no. RTX group)</th>
<th>Randomization</th>
<th>Follow-up</th>
<th>Remission induction RTX/control %</th>
<th>Adverse events RTX/controls %</th>
<th>Mortality RTX/control %</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVE (2010) [44]</td>
<td>197 (63)</td>
<td>RTX vs. Oral CYC</td>
<td>6 months</td>
<td>64/53 relapsing disease 67/42</td>
<td>22 vs. 33 solid tumors 1/1</td>
<td>1 vs. 2 deaths</td>
</tr>
<tr>
<td>RITUXVAS (2010) [45]</td>
<td>44 (33)</td>
<td>RTX + 2 CYC doses IV vs. IV CYC 3–6 m</td>
<td>12 months</td>
<td>76/82</td>
<td>42 vs. 36</td>
<td>18 vs. 18</td>
</tr>
</tbody>
</table>


Rituximab dose 375 mg per square meter per week for 4 weeks
Primary end point: Remission without steroids
CR: BVAS=0

The results of both studies demonstrate that RTX is not inferior to CYC for induction of remission. RTX may be more efficacious than CYC in patients with relapsing disease.
Rituximab Versus Cyclophosphamide for ANCA-Associated Vasculitis with Renal Involvement


- Follow up study at 18m
- RTX vs CYC and Aza
- 102 ptes had renal involvement
- Mean GFR was lower in RTX group
- No differences in CR, GFR, SAE, deaths
- Steroids accounted for many AE
Renal outcomes from RAVE

The importance of steroids as the only fast-acting drug available needs to be taking into account.

The majority of relapses in RTX group occurred after B cell recovery.

Patients with Cr>4mg/dl were not enrolled.

No differences in CRR but the RTX group did not receive maintenance after B cell reconstitution or discontinuation of steroids at 5.5 m.
Rates of the composite outcome of death, ESRD and relapse did not differ between RTX vs CYC+Aza.

In the Rituximab group, B cell return was associated with relapse.

Steroids use for 12 months
24% ptés received PE
Rituximab for maintenance treatment: MAINRITSAN

115 ptes, > GPA, 58 Aza vs 57 Rituximab.

500 mg of rituximab on days 0 and 14 and at months 6, 12, 18 or daily aza until month 22.

At 28th month 17 ptes relapsed with AZA and 3 ptes with Rituximab.

Similar collateral effects
Rituximab Vasculitis Maintenance Study (RITAZAREM)

Induction
- MP pulses D1-3
- 0.5 or 1 mg/kg
- CS 10 mg/d
- ± Plasmapheresis
- RTX 375 mg/m² x 4

Maintenance
- Rituximab 1000 mg
- Azathioprine 2 mg/kg/d (MTX or MMF)

Relapsers (1M or 3m) ANCA+

P 90% alpha 5%:
- superiority HR = 0.42
- time to M or M relapse

ENDPOINT
36 → 48
- Closure: last patient reaches M36

N=190 → 160 RDM
- 40 in North America across 12 centers (2 CA)
What is the interval of RTX administration?

1 g every 6 months for 24 months.

Risk factors for further relapse:
- PR3-associated disease
- switch from ANCA - to +
- return of B cells within 12 months.

B cell depletion: CD19+ <0.01 x 10^9/l

Original article

Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis

Federico Alberici¹ ² ³, Rona M. Smith¹ ², Rachel B. Jones¹ ², Darren M. Roberts¹ ², Lisa C. Willcocks¹ ², Afzal Chaudhry¹ ², Kenneth G. C. Smith¹ ² ⁴ and David R. W. Jayne¹ ²

This study supports the efficacy and safety of a fixed-interval RTX maintenance regimen in 67 relapsing/refractory AAV ptes.
The questions are still open.....

- Should be based on biomarkers?
  The French Group has started a second study with RTX for maintenance
  1) ANCA - B cells
  2) fixed arm
- MAINRITSAN II (NCT 01731561).
- Post- RTX, patients reconstitute B cell by 18 m
- Which dose?
Rituximab adverse events

• IMMUNODEFICIENCY INDUCED BY B-CELL DEPLETION
  – Hypogammaglobulinemia: lymphoma and rheumatoid arthritis but data are scarce for other autoimmune indications.

The severity of hypogammaglobulinemia was categorized by the nadir serum IgG concentration measured during clinical care.
Hypogammaglobulinaemia: IgG level <6 g/l for at least 3 months

- moderate 3-5.9g/l
- severe <3 g/l

243 ptes
median follow up :42 m
26% before rituximab
56% during follow-up

IgG replacement was initiated because of recurrent infection in 12 (4.2%).

Rituximab is associated with an increased risk of hypogammaglobulinemia but recovery of IgG level can occur.

RAVE: levels of IgG, IgA and IgM, did not differ significantly between SOC and RTX.

Low IgG levels were not associated with severe infections.
RTX transient immunodeficiency

- The ability to mount specific antibody responses remained impaired for at least 6 months following RTX.

- The effect of recurrent long-term administration of RTX on the immune system has to be awaited.

- BLYS/APRIL ???

Blood 2013; 122:1946–1953
Conclusions

Alberici, NDT 2014
Conclusions

• **Rituximab:**
  - Some newly diagnosed patients with AAV
    • women with child-bearing potential
    • patients with active vasculitis and severe infection
    • it may be too early to use it as a first-line treatment in all new AAV patients.
  - Maintenance: may be more effective in anti-PR3 AAV
  - severe disease relapse
  - No effective in some granulomatous manifestations ??

  - No information in patients with advanced renal presentations or lung haemorrhage.
Conclusions

CYC/AZA:

- Patients newly diagnosed MPO-ANCA+positive with no fertility, compliance or malignancy concerns
Moltes gràcies!!

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