ACR 2013

Updates on vasculitis

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Disclosures

• Consulting and speaker fees
  – Hoffmann-La Roche
  – BMS

• Advisory boards
  – Hoffmann-La Roche
  – GSK

• Educational subventions (CanVasc)
  – Hoffmann-La Roche
  – Abbott Immunology
  – Pfizer-Amgen
  – Janssen-Cilag
  – Euroimmun
Objectives

• Review the main ACR 2013 abstracts on vasculitis

• Discuss whether, why and how these new findings may impact our practice
Large vessel vasculitis
PLENARY - The STAT1 Signaling Pathway In Giant Cell Arteritis
B Hartmann, J Liao, MH Weisman, KJ Warrington, JJ Goronzy, CM Weyand

[Diagram showing IL-17 and IFN-γ pathways, with steroids and antII6 arrows.]
JAK-STAT SIGNALING

Gene expression profiling in arteritic temporal arteries

Nature Reviews Immunology
NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ mice (NSG) mice

engrafted with human medium-sized arteries

reconstituted at D7 with PBMC from patients with biopsy-proven GCA

dexamethasone (15 mg/kg)
or
tofacitinib (4 mg/kg) JAK 1 and 3 inhibitor
or
both
→ for 5 days (D15-20)
or
control
JAK-1 inhibition decreases Th1 cell recruitment
THE JAK KINASE INHIBITOR BLOCKS EGRESS SIGNALS AND SEQUESTERS T CELLS IN LYMPHOID STORAGE SITES
LV-GCA
Treatment Course

• Compared to C-GCA
  • Same disease course\(^1\)
  • More relapses\(^2\)
  • Higher cumulative steroid dose
  • Longer to reach 0 mg

The Relative Risk Of Aortic Aneurysm In Patients With Giant Cell Arteritis Compared With The General Population

J Robson, A Kiran, J Maskell, A Hutchings, NK Arden, B Dasgupta, Wi Hamilton, A Emin, D Culliford, RA Luqmani

GCA and aortic aneurysm
- 18 per 1000 person years (retrospective reviews)
- 22% by 5 years (screening study)
- 17 x more thoracic and 2.4 x more abdominal aortic aneurysms than normal population
- Meta-analysis, 2-8% developed thoracic AA (cohort without systematic screening)
Parallel cohort study / General Practice Research Database (GPRD)

6,999 men and women with GCA matched on a 6:1 ratio on the same GP practice, year of birth (± 3 years) and gender

A competing risk model using aortic aneurysm as the primary outcome and death as the competing, after adjustment for cardiovascular risk factors (BMI, smoking, alcohol, hyperlipidaemia, HTN, diabetes, CVD, stroke, PVD)

- Medical records of a sample of patients attending GP practices in the UK
- Population of over 6.25 million patients from 500 practices
Subhazard ratio for aortic aneurysm = 1.92
(95% CI, 1.52 to 2.41)
In a multivariable model of the GCA cohort:
- male gender $2.10$ (1.38 to 3.19)
- smoking $3.79$ (2.20 to 6.53)
- diabetes $0.19$ (0.05 to 0.77)
Small vessel & ANCA vasculitis
Single center retrospective study of patients of GPA treated with methotrexate for either induction or maintenance between January 1997-December 2012

**74 GPA** (39 c-ANCA/PR3 +, 22 (30%) p-ANCA/MPO +, 13 (17%) ANCA -)
mean age 48.6 +/- 15.3; 26 (35%) male
Bx-proven in 47 patients (77%)
At Dx, BVAS/WG 7.0 +/- 3.9).

56 MTX for induction → effective in 45 (35 newly-diagnosed, 10 relapsing GPA)
18 MTX for maintenance
56 MTX for induction → effective in 45
18 MTX for maintenance

Median follow up 3.5 years (IQR, 1.6–10.3)

19 relapsed (30%)
15 (31%) in the induction group
4 (28%) in the maintenance group

At the time of conclusion of follow-up, 37 (50%) remained on MTX
5 (6.8%) discontinuations due to side effects (LFTs and GI + 1 PCJ)
Patients with a 1st limited flare in the RAVE trial (BVAS/WG 3 and no major BVAS/WG items)

→ Treated per protocol, by increasing PDN to a dose selected by investigator, for 1 month before resumption of a protocol-specified taper with endpoint = 0mg

47 patients (24%) experienced limited flares (25RTX, 22 CYC)
38 patients (81%) were PR3-ANCA+ and 29 (62%) were previous relapsers

→ first limited flare on average 7.6 months (range 1.8–17.2) after entry
  - 28 patients (60%) were off PDN at the time of the flare
  - mean CS dose at flare 7.1 mg (2.5–20.0) for those on PDN
  - 9% of the CYC/AZA patients were still on CYC, 86% were on AZA
Efficacy Of Glucocorticoids To Treat Limited Flares In ANCA-associated Vasculitis

E Miloslavsky1, U Specks, PA Merkel, P Seo, RF Spiera, CA Langford, GS Hoffman, CGM Kallenberg, EW St. Clair, N Tchao, L Ding, DIkle, B Jepson, P Brunetta, JH Stone

→ average follow-up of 7.0 months (0.7–16.3)

PDN dose used to treat limited flares 19.5 mg OD (2.5–80)

36 patients (77%; 18 RTX, 18 CYC) achieved remission again, an average of 2.5 months after the increase in PDN

BUT 22 patients (47%) had recurrent flares
  13 limited (8 RTX, 5 CYC), 9 severe (5 RTX, 4 CYC)

→ Only 11 patients (23%) who experienced limited flares were able to achieve remission, discontinue PDN, and maintain remission through month 18

→ Alternative approaches including continuing CS indefinitely or increasing or changing concomitant IS must be considered
Safety Of Remission Induction With Rituximab Versus Cyclophosphamide In Patients 65 and Older With Severe ANCA-Associated Vasculitis

E Miloslavsky, U Specks, PA Merkel, PSeo, RF Spiera, CA Langford, GS Hoffman, CGM Kallenberg, EW St. Clair, N Tchao, L Ding, D Ikle, B Jepson, P Brunetta, JH Stone

55 RAVE patients ≥ 65 years old (36 RTX, 19 CYC/AZA) vs. 142 patients < 65 years old (63 RTX, 79 CYC/AZA)

Treatment regimens achieved similar efficacy in both age groups

Patients ≥ 65 had more SAEs (Grade 3) - cytopenias
All 4 deaths during the study period occurred in patients ≥ 65 (2 RTX, 2 CYC)

<table>
<thead>
<tr>
<th></th>
<th>Under 65 (95% CI)</th>
<th>65 and Older (95% CI)</th>
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<tbody>
<tr>
<td>Mean baseline BVAS/WG</td>
<td>7.84</td>
<td>8.51</td>
</tr>
<tr>
<td>Mean baseline creatinine</td>
<td>1.33</td>
<td>1.74</td>
</tr>
<tr>
<td>PR3-ANCA</td>
<td>74.6%</td>
<td>45.5%</td>
</tr>
<tr>
<td>MPO-ANCA</td>
<td>25.4%</td>
<td>54.5%</td>
</tr>
<tr>
<td>Achieved complete remission at 6 mos</td>
<td>61.3%</td>
<td>50.9%</td>
</tr>
<tr>
<td>Remained in complete remission at 18 mos</td>
<td>37.3%</td>
<td>32.7%</td>
</tr>
<tr>
<td>Mean total prednisone dose (g)</td>
<td>7.07</td>
<td>5.73</td>
</tr>
<tr>
<td>Total adverse events/patient year</td>
<td>10.51 (10.07–10.97)</td>
<td>11.50 (10.73–12.3)</td>
</tr>
<tr>
<td>Severe adverse events (Grade ≥3)/patient year</td>
<td>0.52 (0.42–0.63)</td>
<td>1.06 (0.83–1.32)</td>
</tr>
<tr>
<td>Severe infections/patient year</td>
<td>0.10 (0.06–0.16)</td>
<td>0.21 (0.12–0.34)</td>
</tr>
<tr>
<td>Severe cytopenias/patient year</td>
<td>0.03 (0.01–0.06)</td>
<td>0.23 (0.14–0.37)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>
No differences comparing the 2 treatment arms

OK for rituximab in patients ≥ 65 years old

... but WHY rituximab???
Retreatment With Rituximab In The Rituximab In ANCA-Associated Vasculitis (RAVE) Trial
E Miloslavsky, U Specks, PA Merkel, P Seo, RF Spiera, CA.Langford, GS Hoffman, CGM Kallenberg, EW St Clair, N Tchao, L Ding, D Ikle, B Jepson, P Brunetta, JH Stone

Methods

• Patients with severe flare were eligible to receive open-label RTX (OLR) between 6 and 18 mos
  – Severe flare - BVAS/WG > 3 or one major item
  – 375mg/m² weekly x 4

• Outcomes
  – Complete remission – BVAS/WG = 0 and prednisone = 0
  – Complete response – BVAS/WG = 0 and prednisone < 10mg
  – Remission – BVAS/WG = 0
  – Limited flare – BVAS/WG ≤ 3
  – Severe flare – BVAS/WG > 3 or one major item
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=17</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Originally assigned to RTX</td>
<td>16</td>
<td>(94%)</td>
</tr>
<tr>
<td>PR3-ANCA positive</td>
<td>14</td>
<td>(82%)</td>
</tr>
<tr>
<td>GPA</td>
<td>15</td>
<td>(88%)</td>
</tr>
<tr>
<td>Relapsing disease at entry</td>
<td>11</td>
<td>(65%)</td>
</tr>
<tr>
<td>Received CYC prior to study entry</td>
<td>9</td>
<td>(53%)</td>
</tr>
<tr>
<td>Mean time to OLR* (range in days)</td>
<td>367</td>
<td>(225-556)</td>
</tr>
<tr>
<td>Mean prednisone dose at OLR (n=5)</td>
<td>8.5</td>
<td>(2.5-15mg)</td>
</tr>
<tr>
<td>BVAS/WG at OLR (range)</td>
<td>5.3</td>
<td>(3-11)*</td>
</tr>
<tr>
<td>Renal flare</td>
<td>5</td>
<td>(29%)</td>
</tr>
<tr>
<td>Diffuse alveolar hemorrhage</td>
<td>1</td>
<td>(6%)</td>
</tr>
<tr>
<td>Detectable B-cells at flare</td>
<td>15</td>
<td>(94%)</td>
</tr>
<tr>
<td>Rising ANCA at flare</td>
<td>14</td>
<td>(82%)</td>
</tr>
</tbody>
</table>

OLR – Open label rituximab
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>15 (88%)</td>
</tr>
<tr>
<td>Time to remission (days)</td>
<td>57 (27-181)</td>
</tr>
<tr>
<td>Complete response (pred &lt; 10mg)</td>
<td>12 (71%)</td>
</tr>
<tr>
<td>Time to complete response (days)</td>
<td>142 (95-256)</td>
</tr>
<tr>
<td>Complete remission</td>
<td>8 (47%)</td>
</tr>
<tr>
<td>Time to complete remission (days)</td>
<td>182 (121-256)</td>
</tr>
<tr>
<td>Flares within 1 year after OLR</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>BVAS/WG at flare</td>
<td>2.5 (2-3)</td>
</tr>
<tr>
<td>Time to flare from OLR (days)</td>
<td>244 (78-428)</td>
</tr>
</tbody>
</table>
Rituximab Versus Azathioprine For Maintenance In Antineutrophil Cytoplasmic Antibodies-Associated Vasculitis: Follow Up At 39 Months
**Induction**

- MP pulses d1–3
- CS
- ± PE
- 6–9 pulses (CYC)

**Maintenance**

- Azathioprine 2 mg/kg/d
- Rituximab 500 mg
  - d1,14, 6, 12, 18 mo

**Endpoints**

- 18-75 y.o.
- GPA, MPA, KLD
- ANCA+ and/or Bx

**Note:**

- newly diagnosed (2/3)
- relapsing (1/3)

**Additional information:**

- GPA, MPA, KLD
- ANCA+ and/or Bx
Median duration of follow-up = 43.6 months (IQR, 38.0-49.5)

**MAJOR RELAPSE**

- $28/54 = 51.9\%$ in the AZA arm
- $10/55 = 18.2\%$ in the RTX arm

HR 0.27 (0.15-0.53), $P=0.0001$
Behcet’s disease
Multi-systemic disorder with a remitting-relapsing nature

→ Retrospective study on 258 patients (ISG criteria)
  F/M: 130/128, mean age: 41.1 +/- 11.5 years
  125 (48.4%) with mucocutaneous type
  133 patients (51.6%) with major organ involvement

≥1 of any disease manifestations = active

Mean follow-up duration was 45.8 +/- 36.5 months (2–165)
→ 1757 visits
Mean follow-up duration was 45.8 +/-36.5 months (2–165) → 1757 visits

19.8–43.9% of the patients were on IS
35.3–59.3% under colchicine or NSAIDs
6.4–45% were noncompliant patients (without any treatment)

Patients clinically active in 67.2% (n=1182) of the total visits

Major cause of activity = aphthous ulcers (39.4–63.2%)
  genital ulcer: 3.5–27.1%
  erythema nodosum: 8.2–22.5%
  papulopustular lesions: 18.2–33.7%
  arthritis: 21.3–33.5%
  uveitis: 0.5–8.5%
  vascular involvement: 2.5–10.8%

No difference IS vs non-IS therapies…
PLENARY - Apremilast For The Treatment Of Behcet’s Syndrome: A Phase II Randomized, Placebo-Controlled, Double-Blind Study
G Hatemi, M Melikoglu, R Tunc, C Korkmaz, BT Ozturk, C Mat, PA Merkel, K Calamia, Z Liu, L Pineda, RM Stevens, H Yazici, Y Yazici
**Inclusion criteria**

>18 years old
Behcet’s based on ISG criteria
Active ulcer (oral or genital) in the past 28 d
≥2 oral ulcers at the time of randomisation

**Exclusion criteria**

No active uveitis
No active major organ disease in past 12 mo
No concomitant IS, topical CS

*No colchicine in any arm*
• 3 Turkish + 1 US sites
• Endpoint = n of oral ulcers at week 12
<table>
<thead>
<tr>
<th></th>
<th>Placebo n=56</th>
<th>Apremilast n=55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>32%</td>
<td>29%</td>
</tr>
<tr>
<td>White</td>
<td>98%</td>
<td>96%</td>
</tr>
<tr>
<td>Duration of disease, yr</td>
<td>5.7</td>
<td>4.9</td>
</tr>
</tbody>
</table>
Primary End Point: Mean Number of Oral Ulcers at Week 12

Intent-to-Treat Population, LOCF (N=111)

- Placebo crossover to apremilast
- Apremilast discontinuation

*P<0.0001 vs. placebo.

- Reduced oral ulcer burden over 12 weeks was corroborated on an individual patient basis
  - Mean oral ulcer AUC for apremilast was 1/3 of the mean oral ulcer AUC for placebo (P<0.0001)
• Significant improvement in oral ulcer pain

• Significant clearance of genital ulcers (100% vs 50%)

• Similar and low SAE rate (3.6% vs 5.4%), mainly headache, nausea, diarrhea
IgG4 related disease
PLENARY - Rituximab For The Treatment Of IgG4-Related Disease: A Prospective Clinical Trial


63% achieve remission with CS
Open label study
RTX 1g x 2

EI = disease response (decline of IgG4 score ≥2) and off PDN at month 6

30 patients (16 MGH, 14 Mayo)
Mean age 63 (42-82)
87% M
10/30 had high IgG4 serum level at Dx

RTX alone when possible → alone in 26/30
92% achieve the EI

3 required additional CS (→ 2 CR, 1 CS-depdt)
5 relapses (only 1 before 6 months)

7 SAE but none attributed to RTX
All IgG4-RD subjects exhibit an increase in circulating CD19^hi^CD20^+^CD38^+^CD27^+^ plasmablasts.

**CD19^+^CD38^+^CD27^+^ Absolute numbers**

- Healthy Control
- IgG4-RD Patient

**Cell number/mL**

- 10^5
- 10^4
- 10^3
- 10^2
- 10^1
- 10^0

Healthy Control  IgG4-RD Patient
Conclusions, 1/3

Role of TH1 pathway in GCA $\rightarrow$ IFN-gamma $\rightarrow$ STAT1 ; NOTCH $\rightarrow$ triple hit model

![Diagram showing vascular wall, IL-6-IL-17 dependent immunity, IL-12-IFNγ dependent immunity, signal sending, signal receiving, easily controlled, steroid resistant, dispensable for vasculitis, indispensable for vasculitis, host protection.](image)
Conclusions, 2/3

Rituximab, again…
– for patients >65 years old
– to re-treat if relapses
– for maintenance

BUT… *for how long?*
Conclusions, 3/3

• Two “outsiders” did pretty well
  – Behcet’s disease and apremilast
  – IgG4-related syndrome and rituximab

GOOD JOB!