Year in Review: Vasculitis

פרופ' יאיר מולד
יחידה לארמיתולוגיה
מרכז רפואיות רבין – ב''ח ביבליוסון
Giant-cell arteritis
FDA News Release

FDA approves first drug to specifically treat giant cell arteritis

May 22, 2017

The U.S. Food and Drug Administration today expanded the approved use of subcutaneous Actemra (tocilizumab) to treat adults with giant cell arteritis. This new indication provides the first FDA-approved therapy, specific to this type of vasculitis.
Giant-cell arteritis (GCA)

• GCA is the most common vasculitis after 50 years.

• GCA can be categorized into cranial GCA and extra cranial GCA.

• Cranial GCA involves branches of the external carotid artery, especially the superficial temporal artery which causes temporal arteritis.

• Large vessel GCA affects the aorta, subclavian, vertebral, carotid, axillary, iliac, and femoral arteries.

• These two GCA entities can occur in isolation.

• GCA has a strong association with PMR (30–40%).
LVV in GCA and PMR

• At the time of diagnosis, up to 80% of GCA patients as well as 30% of patients with PMR have subclinical LV inflammation demonstrated on US or 18F-FDG PET.

• Patients with treatment refractory PMR commonly have cranial and/or extra-cranial arteritis on imaging.

• The fact that between ∼20 and ∼50% of patients with PMR have an inadequate response to initial GC therapy and/or relapse within the first year may reflect the possibility that at least some of them may suffer from subclinical GCA or LVV.

Revised GCA diagnosis criteria used in the Tocilizumab in GCA Trial.

## Definition

1. Age $\geq 50$ years
2. History of ESR $\geq 50$ mm/hour
3. And at least one of the following:
   - Unequivocal **cranial symptoms of GCA** (new onset localized headache, scalp or temporal artery tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication)
   - Unequivocal **symptoms of polymyalgia rheumatica** (PMR), defined as shoulder and/or hip girdle pain associated with inflammatory stiffness
4. And at least one of the following:
   - Temporal artery biopsy revealing features of GCA
   - Evidence of **large-vessel vasculitis** by angiography or cross-sectional imaging study such as magnetic resonance angiography (MRA), computed tomography angiography (CTA), or positron emission tomography-computed tomography (PET-CT)
ARTICLE

The immunoinhibitory PD-1/PD-L1 pathway in inflammatory blood vessel disease

Cornelia M. Weyand¹  |  Gerald J. Berry²  |  Jörg J. Goronzy¹

Breakdown of Tissue Tolerance in GCA

- The healthy vessel wall has 3 layers: the *vasa vasorum* containing adventitia, the **elastic medium**, and a **thin intima** composed of 1–2 layers of endothelial cells.
- In GCA, disease-inducing T cells and Mφs enter the vessel wall through the intima, infiltrate into the medium, and form granulomatous arrangements.
- Wall remodeling includes neoangiogenesis of microvessels and mobilization of myofibroblasts that create a hyperplastic and lumen-occlusive intima.
GCA: Pathophysiology

• Genetic background:
  • HLA –DRB1*04, particularly the HLA –DRB1*0401, DRB1*0404, or DRB1*0408 haplotypes have been reported to be expressed by 60% of patients affected by PMR or GCA.

• Innate and adaptive immune activation in GCA:
  • Activation of adventitial dendritic cells (DC), via TLR, allows the production of certain cytokines and chemokines that are responsible for recruitment of CD4+ T cells (main cells implicated in pathogenesis of GCA).
  • CD4+ T cells infiltrate the adventitia, via vasa vasorum where endothelial cells express adhesion molecules like ICAM-1 and vascular cell adhesion molecule -1 (VCAM-1).
  • Once Th1/TH17 cells have infiltrated the arterial wall, they produce large amounts of IFN gamma and IL-17.
  • IFN gamma via chemokines (CCL2, CXCL9, CXCL10, and CXCL11), produced by stimulated vascular smooth muscular cells (VSMC), leads to recruitment of monocytes that then merged into multinucleated giant cells.

Costimulatory and coinhibitory signals in T cell regulation.


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Immunoinhibitory checkpoint deficiency in medium and large vessel vasculitis

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Edited by Tasuku Honjo, Graduate School of Medicine, Kyoto University, Kyoto, Japan, and approved December 19, 2016 (received for review October 10, 2016)

\textit{PROC NATL ACAD SCI U S A.} 2017;114(6):E970-E979.
PD-L1 low Immunostimulatory DC’s and MØ’s in GCA

• A critical protection mechanism toward avoiding immune cell infiltrates into the vessel wall comes from wall-embedded DCs.
• Spontaneously, these wall-residing DCs are positive for PD-L1, providing a negative signal to all those T cells that express PD-1.
• Temporal-artery biopsies of lesions from patients with active GCA are densely filled with DCs, yet they lack PD-L1.
• Ex vivo differentiated DCs from blood precursor cells of GCA patients and age-matched controls demonstrated significantly lower PD-L1 surface density, whereas costimulatory ligands were present at similar amounts.
• Functionally, such PD-L1 low DCs fail to attenuate T cell responses, creating unopposed T cell stimulation.
• Interestingly, PD-L1 expression on patient-derived DCs correlated inversely with systemic inflammatory markers, compatible with a role of PD-L1 low DCs in overall immune regulation.
Selective Defect of PD-L1 Expression in GCA DCs

• PD-L1 expression on resting and activated T cells, as well as on B cells, was indistinguishable between GCA patients and age-matched controls.

• In contrast, GCA CD14+ monocytes are PD-L1low and this phenotype was maintained after differentiation into DCs.

• In resting and LPS-activated GCA DCs, PD-L1 transcripts were markedly reduced (Fig. 2A).
  – Flow cytometry confirmed PD-L1 protein reduction on resting and stimulated DCs (Fig. 2 B and C) to about 50% of expression levels in healthy counterparts.

• In GCA DCs, responses to LPS and IFN-γ stimuli were dampened, particularly IFN-γ-dependent induction (Fig. 2 D and E).
Low Expression of the Inhibitory Ligand PD-L1 in GCA

- Vessel-wall invasive T cells in GCA are almost exclusively CD4+ memory cells that intermingle with highly activated macrophages and giant cells.
- **PD-L1 transcripts were abundant in healthy arteries, but expressed at low levels in GCA-affected arteries** (Fig. 1A).
- Conversely, **PD-1 transcripts were essentially absent in healthy vessels, but present at high concentrations in arteries with GCA** (Fig. 1B).
- **These data reflect the absence of T cells in normal arteries and dense T-cell infiltrates in the vasculitic lesions of GCA.**
- **Highly activated DCs participating in the vasculitic infiltrates are consistently stained negative for PD-L1** (Fig. 1C).
- **The majority of T cells in granulomatous lesions expressed the surface receptor PD-1** (Fig. 1 D and E), suggesting selective recruitment/retention of PD-1+ T cells.

Hui Zhang et al. PNAS 2017;114:E970-E979
Tissue-invading T cells in GCA are unopposed because of the failure of PD-L1 expression on endothelial cells and on DCs.

Most lesional T cells are PD-1^{pos}.

Functional consequences of unrestricted T cell activation are multifold: 1) hyperactivation of T cells, 2) durable T cell expansion and survival, 3) hyperstimulation of Mφs, 4) unopposed access to privileged tissue zones, 5) support for myofibroblast growth, and 6) enhanced angiogenesis of microvascular networks.
Trial of Tocilizumab in Giant-Cell Arteritis


NEJM 2017; 317 – 328.
GiACTA trial design

- A multicenter, randomized, double-blind, and placebo-controlled study designed to test the ability of tocilizumab to maintain disease remission in patients with GCA.
- The trial consists of a 52-week blinded treatment phase followed by 104 weeks of open-label extension.
- Patients were randomized into one of four groups:
  - Group A (TCZ 162 mg weekly plus a 6-month prednisone-taper);
  - Group B (TCZ 162 mg every other week plus a 6-month prednisone-taper);
  - Group C (placebo plus a 6-month prednisone-taper);
  - Group D (placebo plus a 12-month prednisone taper).
GiACTA Study: Results


- TCZ combined with a 26-week prednisone taper was superior to either a 26-week or 52-week prednisone taper plus placebo with regard to the sustained remission of GCA.
- TCZ treatment was associated with a reduction in the cumulative prednisone dose over the 52-week trial period.
A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of Giant Cell Arteritis

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Curry L. Koening,10 Antoine G. Sreih,11 Robert Spiera,12 Carol A. McAlear,11
Kenneth J. Warrington,3 Christian Pagnoux,6 Kathleen McKinnon,8 Lindsy J. Forbess,9
Gary S. Hoffman,1 Renée Borchin,2 Jeffrey P. Krischer,2 and Peter A. Merkel,11
for the Vasculitis Clinical Research Consortium
Study design

- All eligible patients were treated with abatacept 10 mg/kg (500 mg for < 60 kg, 750 mg for 60–100 kg, and 1000 mg for > 100 kg) by IV infusion on days 1, 15, 29, and week 8 together with prednisone 40–60 mg/day followed by a standardized tapering schedule.
- At week 12, if they were in remission, patients underwent a double-blinded randomization to switch to placebo or to continue abatacept given every 4 weeks thereafter (Figure 1).
- At the time of randomization, all patients were on prednisone 20 mg/day with tapering continuing after randomization such that both treatment arms discontinued prednisone at week 28.
- The need to increase the prednisone dose or to restart prednisone after discontinuation for the treatment of GCA was considered a relapse criterion.
Relapse-free survival of GCA patients receiving IV Abatacept vs. placebo

• In the intent-to-treat analysis of the 41 randomized patients, the relapse-free survival rate at 12 months was 48% for those receiving abatacept and 31% for those receiving placebo ($P = 0.049$).

• A longer median duration of remission was seen in patients treated with abatacept (median duration 9.9 months) compared to those receiving placebo (median duration 3.9 months; $P = 0.023$).

Ustekinumab for refractory giant cell arteritis: A prospective 52-week trial

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Ustekinumab for refractory GCA: Results.

At week 52, median (IQR) mean daily prednisolone dose decreased from 20mg to 5mg (p < 0.001).

Six patients (24%) stopped prednisolone completely.

No patient experienced a relapse of GCA while receiving ustekinumab.

Median (IQR) CRP decreased significantly from 12.9 (5.3, 42) to 6 (2.6, 12.5) mg/L (p = 0.006).

CT angiography demonstrated improvement of LVV in all patients studied.

No unexpected adverse events were observed with ustekinumab.
EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice

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Marco A Cimmino,10 Eric Clark,11 Bhaskar Dasgupta,12,13 Andreas P Diamantopoulos,14
Haner Direskeneli,15 Annamaria Iagnocco,16 Thorsten Klink,7 Lorna Neill,17
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Wolfgang A Schmidt24

EULAR recommendations for the use of imaging in LVV in clinical practice

1. In patients with suspected GCA, an early imaging test is recommended to complement the clinical criteria for diagnosing GCA. Imaging should not delay initiation of treatment.
   - Imaging should be performed before or as early as possible after initiation of therapy, best within 1 week, because treatment with glucocorticoids rapidly reduces the sensitivity of imaging.
   - Treatment, however, should never be delayed in patients with a strong suspicion of GCA due to outstanding imaging or other diagnostic tests, because ischemic complications such as blindness occur almost exclusively before initiation of therapy.

2. In patients in whom there is a high clinical suspicion of GCA and a positive imaging test, the diagnosis of GCA may be made without an additional test (biopsy or further imaging). In patients with a low clinical probability and a negative imaging result, the diagnosis of GCA can be considered unlikely.
   In all other situations, additional efforts towards a diagnosis are necessary.

EULAR recommendations for the use of imaging in LVV in clinical practice

3. **Ultrasound of temporal-axillary arteries** is recommended as the first imaging modality in patients with suspected predominantly cranial GCA. A non-compressible ‘halo’ sign is the ultrasound finding most suggestive of GCA.
   - The ‘halo’ sign at temporal arteries revealed a pooled sensitivity of 77% and a pooled specificity of 96% as compared with the clinical diagnosis of GCA.
   - The detection of temporal artery stenosis or occlusion did not increase the diagnostic yield over the halo sign alone.
   - False-positive halos might occasionally be detected in other forms of vasculitis (eg, in ANCA-associated vasculitis), in infectious diseases or in patients with (severe) arteriosclerosis.

4. High resolution MRI of cranial arteries to investigate mural inflammation may be used as an alternative for GCA diagnosis if ultrasound is not available or inconclusive.

5. CT and PET are not recommended for the assessment of inflammation of cranial arteries.
EULAR recommendations for the use of imaging in LVV in clinical practice

6. Ultrasound, PET, MRI and/or CT may be used for detection of mural inflammation and/or luminal changes in extracranial arteries to support the diagnosis of LV-GCA. Ultrasound is of limited value for assessment of aortitis.

7. In patients with suspected Takayasu arteritis (TAK), MRI to investigate mural inflammation and/or luminal changes should be used as the first imaging test to make a diagnosis of TAK, assuming high expertise and prompt availability of the technique.
EULAR recommendations for the use of imaging in LVV in clinical practice

8. PET, CT and/or ultrasound may be used as alternative imaging modalities in patients with suspected TAK. Ultrasound is of limited value for assessment of the thoracic aorta.

9. Conventional angiography is not recommended for the diagnosis of GCA or TAK as it has been superseded by the previously mentioned imaging modalities.

10. In patients with LVV (GCA or TAK) in whom a flare is suspected, imaging might be helpful to confirm or exclude it. Imaging is not routinely recommended for patients in clinical and biochemical remission.
EULAR recommendations for the use of imaging in LVV in clinical practice

11. In patients with LVV (GCA or TAK), MRA, CTA and/or ultrasound may be used for long-term monitoring of structural damage, particularly to detect stenosis, occlusion, dilatation and/or aneurysms.
   – The frequency of screening as well as the imaging method applied should be decided on an individual basis.

12. Imaging examination should be done by a trained specialist using appropriate equipment, operational procedures and settings.
Eosinophilic Granulomatosis with Polyangiitis
FDA News Release

FDA approves first drug for Eosinophilic Granulomatosis with Polyangiitis, a rare disease formerly known as the Churg-Strauss Syndrome

December 12, 2017

The U.S. Food and Drug Administration today expanded the approved use of Nucala (mepolizumab) to treat adult patients with eosinophilic granulomatosis with polyangiitis (EGPA), a rare autoimmune disease that causes vasculitis, an inflammation in the wall of blood vessels of the body. This new indication provides the first FDA-approved therapy specifically to treat EGPA.
Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis


The inflammatory effects of the eosinophil
• **IL-5** plays a fundamental role in the proliferation, maturation in the bone marrow, recruitment and activation at sites of allergic inflammation of eosinophils.

• The engagement of **IL-5R** results in differentiation and maturation of eosinophils in the bone marrow, enhanced cell migration, release of granule proteins, and respiratory burst of eosinophils. (left side).

• **Anti-IL-5 monoclonal antibodies** (*mepolizumab* and *reslizumab*) bind to different epitopes of IL-5 blocking its ligation to interleukin-5Rα highly expressed on the human eosinophil membrane. the anti-interleukin-5Rα antibody on eosinophil (right side).

- A multicenter, double-blind, parallel-group, phase 3 trial.
- Patients with relapsing or refractory EGPA who had received treatment for at least 4 weeks and were taking a stable prednisolone or prednisone dose to receive **300 mg of mepolizumab SC or placebo**, administered every 4 weeks, plus standard care, for 52 weeks.
- The glucocorticoid dose had to remain stable between baseline and week 4 and could thereafter be reduced at the investigator's discretion.
- Participants who were receiving immunosuppressive therapy were required to continue a stable dose for the duration of the trial.
Efficacy End Points in the Intention-to-Treat Population.

- Remission rate was significantly greater in the Mepolizumab treatment arm (28% vs. 3% of the participants had ≥24 weeks of accrued remission; odds ratio, 5.91; 95% confidence interval [CI], 2.68 to 13.03; P<0.001).

- A total of 44% of the participants in the mepolizumab group, as compared with 7% of those in the placebo group, had an average daily dose of prednisolone or prednisone of 4.0 mg or less per day during weeks 48 through 52 (odds ratio, 0.20; 95% CI, 0.09 to 0.41; P<0.001).

- The safety profile of mepolizumab was similar to that observed in previous studies.

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Table 2. Efficacy End Points in the Intention-to-Treat Population.²

<table>
<thead>
<tr>
<th>End Point</th>
<th>Mepolizumab (N=68)</th>
<th>Placebo (N=68)</th>
<th>Odds Ratio or Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accrued weeks of remission over 52-wk period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 wk</td>
<td>32 (47)</td>
<td>55 (81)</td>
<td>5.91 (2.68–13.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;0 to ≤12 wk</td>
<td>8 (12)</td>
<td>8 (12)</td>
<td></td>
<td></td>
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<tr>
<td>12 to ≤24 wk</td>
<td>9 (13)</td>
<td>3 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 to ≤36 wk</td>
<td>10 (15)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;36 wk</td>
<td>9 (13)</td>
<td>2 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission at wk 36 and wk 48</td>
<td>22 (32)</td>
<td>2 (3)</td>
<td>16.74 (3.61–77.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Remission within the first 24 wk that was sustained until wk 52</td>
<td>13 (19)</td>
<td>1 (1)</td>
<td>19.65 (2.30–167.03)</td>
<td>0.007</td>
</tr>
<tr>
<td>First EGPA relapse</td>
<td>38 (56)</td>
<td>56 (82)</td>
<td>0.32 (0.21–0.50)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

² Odds ratios are shown for the analyses of the two primary end points and for the secondary analysis of remission within the first 24 weeks that was sustained until week 52. For the analysis of accrued weeks in remission, the odds ratio is for 24 or more weeks of accrued remission. Remission was defined as a BVAS of 0 (on a scale from 0 to 63, with higher scores indicating greater disease activity) and a prednisolone or prednisone dose of 4.0 mg or less per day. For the time-to-event analysis of the first relapse of EGPA, the hazard ratio is shown. Participants with a first EGPA relapse were those who had a relapse before the completion of the planned trial period or who withdrew prematurely from the trial.

Remission and First Relapse of EGPA in the Intention-to-Treat Population.

- The annualized relapse rate was 1.14 in the mepolizumab group, as compared with 2.27 in the placebo group (rate ratio, 0.50; 95% CI, 0.36 to 0.70; P<0.001).
- A higher percentage of participants in remission at both week 36 and week 48 (32% vs. 3%; odds ratio, 16.74; 95% CI, 3.61 to 77.56; P<0.001).
- Remission did not occur in 47% of the participants in the mepolizumab group versus 81% of those in the placebo group.

GPA and MPA maintenance therapy.

The French Vasculitis Study Group studies
Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides

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MAINRITSAN trial patients’ 60 month follow-up: Methods

• The 28-month Maintenance of Remission using Rituximab in Systemic ANCA-associated Vasculitis trial compared rituximab with azathioprine to maintain remission in patients with newly diagnosed or relapsing GPA, MPA or renal-limited ANCA-associated vasculitis.

• Thereafter, prospective patient follow-up lasted until month 60.

• The primary endpoint was the major-relapse rate at month 60.

• Relapse and serious adverse event-free survival were also assessed.
Kaplan-Meier curves for the probability of remaining relapse free according to treatment group.

- Post-randomisation probabilities of remaining major relapse free (A): HR for azathioprine-group patients vs rituximab recipients was 2.51; p=0.003; remaining major or minor relapse free (B) (HR 2.11; p=0.012);
- Survival rate (C): At 60 months, overall survival rates were 100% for the rituximab group and 93.0% for the azathioprine group (95% CI 86.7% to 99.9%) (p=0.045)
- Severe adverse event free-survival (D) rates were comparable between the two treatment arms (HR 1.02 (95% CI 0.63 to 1.62; p=0.951).


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The HRs for relapse for patients with PR3-ANCA specificity and azathioprine arm were 2.04 (95% CI 1.06 to 3.91) (p=0.032) and 2.72 (95% CI 1.55 to 4.76) (p<0.001) in multivariate analysis, respectively.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Univariate and multivariate analysis of factors predictive of vasculitis relapse in treated patients</th>
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</thead>
<tbody>
<tr>
<td><strong>Variables</strong></td>
<td><strong>HR (95% CI)</strong></td>
</tr>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.00 (0.98 to 1.02)</td>
</tr>
<tr>
<td>Male (vs female)</td>
<td>1.00 (0.59 to 1.68)</td>
</tr>
<tr>
<td>GPA (vs MPA or renal-limited vasculitis)</td>
<td>2.08 (1.07 to 4.03)</td>
</tr>
<tr>
<td>PR3-ANCA (vs MPO-ANCA or no ANCA)</td>
<td>2.18 (1.18 to 4.00)</td>
</tr>
<tr>
<td>Serum creatinine &gt;2.27 mg/dL</td>
<td>0.58 (0.30 to 1.10)</td>
</tr>
<tr>
<td>Ear, nose and throat involvement</td>
<td>1.59 (0.83 to 3.02)</td>
</tr>
<tr>
<td>Pulmonary involvement</td>
<td>1.04 (0.61 to 1.76)</td>
</tr>
<tr>
<td>Cardiovascular involvement</td>
<td>1.10 (0.60 to 2.00)</td>
</tr>
<tr>
<td>Induction to remission ANCA evolution (persistence vs disappearance)</td>
<td>1.09 (0.65 to 1.82)</td>
</tr>
<tr>
<td><strong>Multivariate analysis</strong></td>
<td></td>
</tr>
<tr>
<td>PR3-ANCA (vs MPO-ANCA or no ANCA)</td>
<td>2.04 (1.06 to 3.91)</td>
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<tr>
<td>Serum creatinine &gt;2.27 mg/dL</td>
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<tr>
<td>Ear, nose and throat involvement</td>
<td>1.18 (0.59 to 2.35)</td>
</tr>
<tr>
<td>Arm (AZA vs RTX)</td>
<td>2.72 (1.55 to 4.76)</td>
</tr>
</tbody>
</table>

ANCA, antineutrophil cytoplasmic antibodies; AZA, azathioprine; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, antiproteinase 3; RTX, rituximab.
MAINRITSAN trial: Conclusion

• In conclusion, the long-term follow-up of MAINRITSAN trial patients showed that the lower risk of major relapses of ANCA-associated vasculitides observed at 28 months with 500 mg rituximab infusions administered on days 1 and 15 then every 6 months until month 18, compared with azathioprine, was sustained over 60 months, especially for patients with granulomatosi with polyangiitis and PR3-ANCA.

• PR3-ANCA specificity and positive ANCA over time were able to identify patients who might require longer and repeated maintenance treatment.

EXTENDED REPORT

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)

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Study aim and Methods

• **MAINRITSAN trial** was undertaken to evaluate ANCA and circulating CD19+ B cells as indicators to reinfuse rituximab to maintain remission.

• To do so, an individually tailored rituximab regimen, adapted to ANCA-positivity or ANCA-titer change and/or circulating CD19+ B cell repopulation, was compared with fixed-schedule rituximab infusions, in patients (GPA, MPA) who were in complete remission at the time of inclusion.

• Patients were randomized at a 1:1 ratio to receive maintenance therapy with either an ‘individually tailored’ (according to laboratory findings every 3 months) or ‘fixed-schedule’ (control) RTX regimen within 1 month after completing induction treatment, if they had received cyclophosphamide or MTX, or 4–6 months after the last RTX infusion, if it had been used to obtain remission.

• **Tailored-infusion-arm** patients always received 500 mg of rituximab at randomization;

• **Then ANCA and CD19+ B lymphocytes were assessed every 3 months.**

• Another 500 mg were infused when ANCA status differed from the previous control (ie, reappearance after being negative, indirect immunofluorescence-determined ≥2-dilution–titre increase and/or at least doubled ELISA PR3 or myeloperoxidase (MPO) arbitrary units) or CD19+ B cell counts exceeded 0/mm3.

• **The control group** received the MAINRITSAN trial regimen: 500 mg rituximab infusion on days 0 and 14 post-randomization and at months 6, 12, 18 after the first infusion.
Relapse rates were comparable to that of rituximab-treated patients in the MAINRITSAN trial

- Comparing tailored versus fixed-schedule rituximab infusions, respectively: relapse-free survival rates were 83.8% (95% CI 76.1% to 92.3%) vs 86.4% (95% CI 79.2 to 94.2) (p=0.58) (figure) and major relapses occurred in 6 (7.4%) vs 3 (3.7%) patients (p=0.23).
- VDIs (mean ±SD) for the tailored and fixed-schedule rituximab-infusion arms, respectively, were 1.64±1.41 and 1.86±1.70 at inclusion and 1.99±1.57 and 2.09±1.97 at 28 months.
- Glucocorticoid doses and durations since inclusion did not differ significantly between the two arms.
- No significant difference between-group gammaglobulin-level differences or decreases were observed throughout the trial.
- Rate of SAE’s was comparable between the groups.
ANCA-cell and B-cell-repopulation-related AAV relapses

- Five ANCA-evolution profiles were identified (table 2); none was associated with relapses.
- At month 28, 46/76 (60.5%) tailored-infusion recipients were ANCA-positive vs 26/71 (36.6%) fixed-schedule patients (p=0.06).
- In addition, circulating B cells were not detected in 10 (45.4%) patients who relapsed and 4 (18.2%) were ANCA-cell-negative and B-cell-negative.
- All relapses, including the two censured, were analyzed.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>ANCA evolution and B-cell detection patterns throughout follow-up for patients with ≥1 relapses or none</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter profile</td>
<td>Patients with</td>
</tr>
<tr>
<td></td>
<td>≥1 relapse(s)</td>
</tr>
<tr>
<td></td>
<td>(n=22)*</td>
</tr>
<tr>
<td>ANCA evolution (%)</td>
<td></td>
</tr>
<tr>
<td>Always negative</td>
<td>7 (31.8)</td>
</tr>
<tr>
<td>Negative at inclusion and became positive</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Positive at inclusion and became negative</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Positive at inclusion and titre rose</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Positive at inclusion and remained stable</td>
<td>9 (40.9)</td>
</tr>
<tr>
<td>Circulating CD19+ B cell evolution (%)</td>
<td></td>
</tr>
<tr>
<td>Always negative</td>
<td>11 (50)</td>
</tr>
<tr>
<td>Detected at least once</td>
<td>11 (50)</td>
</tr>
<tr>
<td>ANCA and circulating CD19+ B cell evolutions (%)</td>
<td></td>
</tr>
<tr>
<td>ANCA-negative and no circulating B cells detected</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>Other</td>
<td>18 (81.8)</td>
</tr>
</tbody>
</table>

Values are expressed as n (%).
*At the last visit, 23 patients had suffered 24 relapses; 2 relapses that occurred after month 28 were censored in the principal analysis. Thus, with 1 missing value and 1 patient who relapsed twice, we have 22 patients with ≥1 relapses.
MAINRITSAN2 trial: Conclusion

• Relapse rates were comparable to that of rituximab-treated patients in the MAINRITSAN trial (3/57 (5.2%) with a major relapse.

• This trial’s findings also demonstrated that it is indeed possible to maintain remission with fewer infusions, even though a non-significant trend towards more relapses was observed for patients receiving the individually tailored regimen.

• More patients remained ANCA-positive in the individually tailored regimen ($p=0.06$)

• Relapses could also occur in the absence of circulating B cells, perhaps because B-cell repopulation could be only at sites of active disease or because the CD19+ B lymphocyte count is not strictly associated with CD27 +memory B-cell reemergence.

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