Vasculitis Updates

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Disclosures

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

• Advisory and study boards
  – Hoffmann-La Roche
  – GSK
  – Sanofi

• Educational subventions (CanVasc)
  – Hoffmann-La Roche
  – Abbott Immunology
  – Pfizer-Amgen
  – Janssen-Cilag
  – Euroimmun
  – Terumo-BCT
  – BMS
The vasculitis train
CanVasc founded in November 2010

CanVasc Objectives

The CanVasc group was officially created the 1st November 2010, in Toronto.

The proposed CanVasc objectives are to:

1. **organize a dedicated health and research network** with identification of referral (multidisciplinary) centers across Canada for patients with vasculitis. Establishment and regular updates of **Recommendations for the diagnostic and therapeutic management** of patients is part of this objective.

2. **initiate, conduct, and promote studies** (from CanVasc, VCRC or other vasculitis research groups) on vasculitides across Canada (epidemiological, observational, fundamental and, ultimately, therapeutic studies), using an efficient, established and rapidly mobilisable network.

3. **develop educational and awareness programs for health care providers** (training sessions, fellowship, annual meeting...).

4. **stand as the Canadian referral group to identify needs in vasculitis** and consider new drug approvals for vasculitis in Canada (advisory group).
Explore CanVasc and its affiliated centers across Canada

CanVasc is the Canadian network for research on vasculitides. It was created in November 2010 by Drs. Pagnoux, Cirelli and Khalidi. The main goal was to identify referral medical centers and physicians across Canada with expertise in vasculitis and who were willing to be part of this new research group (core members). Among its several other aims, important ones are to help conduct studies on vasculitis, provide support and educational material on vasculitides for physicians and other health care professionals and, eventually, optimize the therapeutic management of patients with these rare diseases.

CLICK HERE for more information on CanVasc.
CLICK HERE for more information on national CanVasc meetings.
CanVasc FORUM (and link to CanVasc DropBox) can be ACCESSED FROM HERE (for CanVasc registered physicians only).

CanVasc recommendations for the management on ANCA-associated vasculitides are now available and published

One of the objectives of CanVasc is to harmonize and optimize the treatment of patients with vasculitides and, eventually, improve their outcomes, wherever they live in Canada. The development of recommendations will help achieve this goal. For the past 3 years, CanVasc core members had been working hard to develop these recommendations for the management of ANCA-associated vasculitides. They are now (November 1st, 2015) published in the Journal of Rheumatology (link HERE), with an executive summary in the Canadian Journal of Kidney Health and Disease (link HERE).

Recommendations for the other vasculitides are under development.

Review studies on vasculitis actively recruiting in Canada

Several prospective studies on vasculitis are ongoing across the world, including in several Canadian centers. Have a brief overview of these latter ones, including ABROGATE, CLASSIC, PEXIVAS, DOCVAS, BrainWorks, RITAZAREM and TAPIR on the study webpage and determine whether any of your patients could participate to any of them.

PATIENTS can also ENROLL THEMSELVES directly into the VCRC contact registry or the V-PPRN research network! Several studies are ongoing and rolling already with the active participation of patients leaving in North America, including some studies led by CanVasc researchers! See the links to these registry and network and get more information on this very innovative way to conduct patient-oriented research on the Link page.

Update your knowledge on vasculitis with CanVasc online materials

- READ the latest CanVasc reviews of recent articles: commended summaries of selected and important articles on vasculitis, for physicians to keep up the pace with scientific publications on vasculitis on the Vasculitis page!
- How the classification of vasculitides can help and impact their therapeutic management. June 2015
- Recommendations from the EGPA Task Force group. May 2015
General Information on Vasculitides & Article reviews

Vasculitides are a group of diseases, being all potentially life-threatening and/or affecting vital organs, like heart, lungs or brain, with frequent irreversible damage. With prompt and adapted treatment, the survival at 1 year exceeds 90%, thus the importance to recognize these diseases and refer patients to experienced centers for their management.

Vasculitides are characterized by inflammation of vessel walls, mainly arteries, but sometimes also veins, with or without thrombus, necrosis and granulomas. They can be secondary (to several infections, but also other systemic diseases or cancers, or occur as a reaction to medications or toxic exposures, like leva-misole, or cocaine). According to the 1994 Chapel Hill nomenclature, primary vasculitides were classified based on the size of the predominantly affected vessels.

- **Large vessel vasculitides** affect the aorta and its major branches and include two main conditions: Giant Cell Arteritis which is seen almost exclusively in individuals older than 50 years and which can cause irreversible blindness in up to 15-20 percent of the cases, and Takayasu’s arteritis, which affects mostly women younger than 40 years-old and can cause arterial limb claudication and/or strokes.

- **Medium vessel vasculitides** include Polymyalgia Nodosa which can affect individuals of all ages and cause infarctions of multiple organs, including the gut, kidneys, heart, muscle and nerves. Before the development of anti-hepatitis B virus vaccine, and the subsequent massive worldwide vaccination campaigns, more than half the cases of polyarteritis nodosa were due to HBV infection. In contrast, Kawasaki Disease is seen mostly in children younger than 4 years-old and has a predilection for the coronary arteries.

- **Small vessel vasculitides** include several entities. The most “famous” ones are associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCA) in the serum of affected patients (at least some of them). These ANCA-related vasculitides include Granulomatosis with Polyangiitis (Wegener’s), Microscopic Polyangiitis and Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). These diseases can cause pulmonary-renal syndrome which is characterized by lung hemorrhage and rapidly progressive renal failure. Non-ANCA small vessel vasculitides include many different entities, like Henoch-Schönlein purpura, which is usually a self-limited disease mostly seen in children, and cryoglobulinemic vasculitis (most commonly associated with chronic hepatitis C virus infection). Anti-GBM (glomerular basement membrane) antibody disease (sometimes named Goodpasture disease when it affects lungs and kidney) has been recently included officially in the list of these vasculitides mainly affecting small sized vessel and causing renal disease (with linear deposition of anti-GBM antibodies in the glomeruli) and/or avascular hemorrhage.

- **Other vasculitides**: Behcet’s disease is a particular vasculitis that can affect vessels of all sizes, including the veins. Isolated CNS vasculitis is an extremely challenging condition as it affects the vessels of the brain diffusely and can cause various clinical manifestations. Buerger’s disease (obliterative thromboangiitis) causes digital ischemia and gangrenous lesions, due to medium- and small-sized artery vasculitis and thrombosis, but also superficial vein thromboses and concerns almost exclusively smokers (classified as a medium-sized vessel vasculitis in Japan).
The CanVasc website

Summary table of ongoing studies

<table>
<thead>
<tr>
<th>Condition</th>
<th>Study Name</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe GPA/MPA with lung or kidney</td>
<td>PEXIVAS (&lt;2 weeks)</td>
<td><a href="#">website</a></td>
</tr>
<tr>
<td>Not too severe GPA/MPA</td>
<td>CLASSIC</td>
<td></td>
</tr>
<tr>
<td>GPA/MPA entering remission</td>
<td>BREVAS (&lt;2 wks remission)</td>
<td></td>
</tr>
<tr>
<td>GPA on prednisone for maintenance</td>
<td>TAPIR [website]</td>
<td></td>
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<tr>
<td>Relapsing non-severe GPA</td>
<td>ABROGATE</td>
<td></td>
</tr>
<tr>
<td>Relapsing severe GPA/MPA</td>
<td>RITAZAREM (at relapse) [website]</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>VCRC cohort (any time)</td>
<td><a href="#">website</a></td>
</tr>
<tr>
<td></td>
<td>VCRC contact <a href="#">registry</a> (any time)</td>
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<tr>
<td>PACNS</td>
<td>DCVAS (&lt;2 years)</td>
<td></td>
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<tr>
<td></td>
<td>INTERSpace</td>
<td></td>
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<tr>
<td></td>
<td>BrainWorks (for children, adults soon)</td>
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To read more information on each study, click on the name on the study when a link is available and/or read below.

NOTE (14 April 2015). Inclusions in the GIACTA study (bociluzumab for GCA) are closed in Canada.

NOTE (5 February 2015). Inclusions in the MIRRA study (mepolizumab in refractory EGPA) are closed in Canada. The study is still enrolling in US and Europe but should also reach its enrollment targets there soon.

If you still need more detail on these studies or if you think that one of your patients could be eligible for any of this study, do not hesitate to contact us as well (admin@canvasc.ca).

PEXIVAS

PEXIVAS trial is a multicentre, international, phase III, open label randomised controlled therapeutic trial to investigate plasma exchange and glucocorticoid dosing in the treatment of ANCA-associated vasculitis. It is conducted under the aegis of the VCRC, ELVAS and NHR. Several centers in Canada are participating, including centers involved in CanVasc, like Hamilton, where Dr. M. Walsh (associate member of CanVasc), who originally worked on the trial design and is the main investigator for Canada, is established.

The first Canadian patient has been enrolled in late March 2011 in Hamilton, which was the first open center in Canada. All other Canadian centers (London, Edmonton, Vancouver, SMH-Toronto, MSH-Toronto, Calgary, UHN-TGH-UWHTH-Toronto, Montreal, Ottawa) are now also opened and have enrolled patients. At present and after almost 4 years of recruitment, more than 500 patients (around 200 in Canada, just offer the UK for the countries with the greatest numbers of patients recruited) have already been
CanVasc recommendations

- for the management of ANCA-associated vasculitides (01/11/2015)

Prognostic scores

- FFS 1996
- Revisited 2009 FFS

Activity scores

- BVAS version 2003 (active form sheet)
  - link to online BVAS calculator (only for new active manifestations)
  - BVAS v3 (active form sheet + scoring scale)
  - BVAS v3 (active and persistent form sheet + scoring scale)
- BVAS/GPA (WG)
  - Formula for scoring BVAS/GPA (WG)
- BVAS version 1996 (original)
- PVAS (Pediatric score)
- IgG4-RD responder index
- ITAS 2010 (Takayasu arteritis)
- ITAS 2010 glossary
Therapeutic studies

• VCRC studies
• Pharma-sponsored studies
• Descriptive studies
• Canadian-VCRC-CanVasc studies
  – PEXIVAS
  – ARAMIS (skin vasculitis)
CanVasc recommendations

• Establishment and regular updates of recommendations for the diagnostic and therapeutic management of patients with vasculitis

→ Publication on AAV
→ NAQs for GCA and TAK
CanVasc Recommendations for the Management of Antineutrophil Cytoplasm Antibody-associated Vasculitides


ABSTRACT. Objective. The Canadian Vasculitis research network (CanVasc) is composed of physicians from different medical specialties and researchers with expertise in vasculitis. One of its aims is to develop recommendations for the diagnosis and management of antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) in Canada.

Methods. Diagnostic and therapeutic questions were developed based on the results of a national needs assessment survey. A systematic review of existing non-Canadian recommendations and guidelines for the diagnosis and management of AAV and studies of AAV published after the 2009 European League Against Rheumatism/European Vasculitis Society recommendations (publication date: January 2009) until November 2014 was performed in the Medline database, Cochrane library, and main vasculitis conference proceedings. Quality of supporting evidence for each therapeutic recommendation was graded. The full working group as well as additional reviewers, including patients, reviewed the developed therapeutic recommendations and nontherapeutic statements using a modified 2-step Delphi technique and through discussion to reach consensus.

Results. Nineteen recommendations and 17 statements addressing general AAV diagnosis and management were developed, as well as appendices for practical use, for rheumatologists, nephrologists, respirologists, general internists, and all other healthcare professionals more occasionally involved in the management of patients with AAV in community and academic practice settings.

Conclusion. These recommendations were developed based on a synthesis of existing international guidelines, other published supporting evidence, and expert consensus considering the Canadian healthcare context, with the intention of promoting best practices and improving healthcare delivery for patients with AAV. (J Rheumatol First Release November 1 2015; doi:10.3899/jrheum.150376)

Key Indexing Terms: ANCA-ASSOCIATED VASCULITIS DRUG THERAPY QUALITY OF HEALTHCARE PRACTICE GUIDELINES CONSENSUS DEVELOPMENT CONFERENCE VASCULITIS
CanVasc recommendations for the management of antineutrophil cytoplasm antibody (ANCA)-associated vasculitides – Executive summary

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Abstract

The Canadian Vasculitis research network (CanVasc) is composed of physicians from different medical specialties, including rheumatology and nephrology and researchers with expertise in vasculitis. One of its aims was to develop recommendations for the diagnosis and management of antineutrophil cytoplasm antibody (ANCA)-associated vasculitides in Canada. This executive summary features the 19 recommendations and 17 statements addressing general AAV diagnosis and management, developed by CanVasc group based on a synthesis of existing international guidelines, other published supporting evidence and expert consensus considering the Canadian healthcare context.
Diagnosis of ANCA-associated vasculitis (AAV)
- **Statement 1:** The role of ANCA testing
- **Statement 2:** The role of tissue biopsy

Classification of **Disease Severity**
- **Statement 3:** Severe disease in AAV

The Role of Referral Centers for Vasculitis
- **Statement 4:** Management of AAV patients with Referral Centers for Vasculitis
Remission Induction of Newly Diagnosed AAV

Severe, Newly-Diagnosed AAV

Limited GPA and non-severe EGPA/MPA, Newly-Diagnosed

Remission Maintenance

Relapsing Disease

Refractory Disease and Specific Disease manifestations

Additional and Experimental Therapies

Follow-up and Monitoring
Special patient groups

**Statement 13:** Planning and managing *pregnancy*

**Statement 14:** Management of *pediatric patients*

**Statement 15:** Classification of pediatric patients with AAV

**Statement 16:** Management of pediatric patients with newly diagnosed AAV

**Recommendation 20:** Management of pediatric patients with relapsing or refractory AAV
Recommendation 2

We recommend using high dose glucocorticoids with rituximab as 1st line remission induction therapy in patients with severe GPA or MPA in whom cyclophosphamide is contraindicated or in whom cyclophosphamide presents an unacceptable risk of infertility.

Two RCTs have shown RTX (375mg/m² x 4 weekly infusions) to be non-inferior to cyclophosphamide at inducing remission in adults with organ or life-threatening disease. In RITUXVAS (n= 44) remission at 6 months was achieved in 91% and 82% of patients treated with cyclophosphamide and rituximab respectively (a non-significant difference). In the Rituximab for ANCA-associated Vasculitis (RAVE) study (n= 197), 64% of the rituximab group patients were in remission off glucocorticoids at 6 months compared to 54% of the cyclophosphamide group (a non-significant difference). In both RCTs, there was no evidence that rituximab is a safer alternative to cyclophosphamide (comparable rate of adverse events in both treatment groups, including infections). For patients in whom cyclophosphamide is not tolerated or there is a valid contraindication to cyclophosphamide, we recommend presenting a case for the funding of rituximab, which is more expensive. We believe that preservation of fertility, when there are no clearly effective methods of doing so, is a valid justification for the use of rituximab in certain individuals, especially patients of child-bearing age. The approved regimen for rituximab in Canada is that used in the RAVE and RITUXVAS trials: 4x weekly infusions of 375mg/m². An alternate regime of 2 x 1g rituximab infusions administered 14 days apart (as used in the treatment of rheumatoid arthritis) may be of comparable efficacy, based on retrospective studies only. We therefore recommend using the former regimen when feasible. See Appendix 4 for rituximab prescribing protocols.

Evidence 1B, Strength of recommendation A

Barriers to implementation. In August 2012, The Canadian Drug Expert Committee (CDEC) approved rituximab for the induction of remission in adult patients with severely active GPA or MPA who have a history of severe reaction to cyclophosphamide, in whom cyclophosphamide is contraindicated or who have failed an adequate trial of cyclophosphamide. Rituximab is currently approved according to these criteria in Ontario, British Columbia, Alberta, Saskatchewan, Nova Scotia and Newfoundland (see Appendix 7). The drug approval process is underway in the other provinces.

Previous Guidance

2014 BSR
All patients with newly diagnosed AAV should be considered as having a potentially severe life- or organ threatening disease and therefore should be assessed for treatment with glucocorticoids (GCs) and pulsed i.v. CYC or RTX.

RTX is as effective as CYC for remission induction of previously untreated patients and is preferable when CYC avoidance is desirable (infertility, infection).

Both commonly used RTX protocols (375 mg/m²/week for 4 weeks; 1000mg repeated after 2 weeks) appear equally effective for induction of remission. The licensed and recommended RTX dosing protocol for the treatment of AAV is 375 mg/m²/week for 4 weeks.

2011 FVSG
For first-line treatment, rituximab may be prescribed for the same indications as cyclophosphamide to induce remission of certain GPA and MPA forms. It should preferentially be prescribed to women of childbearing age, especially when they are over 30 years old.

Because rituximab was not superior to cyclophosphamide in 2 randomized-controlled clinical trials, the therapeutic choice for a first disease flare is left to the discretion of the treating physician. That decision should be based on the patient's medical history, morbidity factors preexisting AAV, the vasculitis symptoms to be treated and the patient's opinion.

The dose of 375mg/m²/week x 4 weeks, established to treat lymphoma, was evaluated in the randomized RAVE trial on AAV. Therefore, we recommend that dose with an evidence level of 1.

Guerry et al., 2011
Rituximab is as effective as CYC for remission induction of previously untreated patients. Rituximab may be preferred, especially when CYC avoidance is desirable.

KDIGO
We recommend that rituximab and corticosteroids be used as an alternative initial treatment (of pauci-immune focal and segmental necrotizing GN) in patients without severe disease or in whom cyclophosphamide is contraindicated.
Appendices

• Appendix 1: Level of evidence and grading of therapeutic recommendations
• Appendix 2: Suggested tests and investigations in AAV
• Appendix 3: Classifying disease severity in AAV
  EULAR/EUVAS
  Wegener’s Granulomatosis Etanercept Trial (WGET)
  Five Factor Score (FFS, 1996)
  Revised FFS (2011)
• Appendix 4: EULAR/EUVAS definitions of disease states

• Appendix 5: Drug prescribing in AAV
  Cyclophosphamide, Glucocorticoids, Rituximab, Methotrexate, Azathioprine, Leflunomide, Mycophenolate mofetil, Intravenous immunoglobulins
• Appendix 6: Vaccinations in AAV
• Appendix 7: Canadian prescribing regulations for rituximab
• Appendix 8: Existing provincial criteria for rituximab coverage
• Appendix 9: Useful websites and links
• Appendix 10: Complete list of CanVasc centers and members
Drs. Lucy McGeoch (adult rheumatology), Marinka Twilt (pediatric rheumatology)

**CanVasc core members/Co-authors/Principal reviewers of all drafts:**

**CanVasc associated members/Co-authors/Principal reviewers of all drafts:**
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**Additional reviewers for Draft 2:**
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**VF Canada:** John Stewart, Katherine Smith, Barbara Tuntoglu (board)

Sandra Messier, admin. support
Quoi de neuf dans les vascularites (à ANCA)?
Levamisole stimulates NETs through muscarinic receptors
Neutrophil-Related Gene Expression and Low-Density Granulocytes Associated With Disease Activity and Response to Treatment in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Peter C. Grayson,1 Carmelo Carmona-Rivera,1 Lijing Xu,2 Noha Lim,2 Zhong Gao,2 Adam L. Asare,2 Ulrich Specks,3 John H. Stone,4 Philip Seo,5 Robert F. Spiera,6 Carol A. Langford,7 Gary S. Hoffman,7 Cees G. M. Kallenberg,8 E. William St.Clair,9 Nadia K. Tchao,2 Steven R. Ytterberg,3 Deborah J. Phippard,2 Peter A. Merkel,10 Mariana J. Kaplan,1 and Paul A. Monach,11 for the Rituximab in ANCA-Associated Vasculitis–Immune Tolerance Network Research Group

Objective. To discover biomarkers involved in the pathophysiology of antineutrophil cytoplasmic antibody–associated vasculitis (AAV) and to determine whether low-density granulocytes (LDGs) contribute to gene expression signatures in AAV.

Methods. The source of clinical data and linked biologic specimens was a randomized controlled treatment trial in AAV. RNA sequencing of whole blood from patients with AAV was performed during active disease at the baseline visit and during remission 6 months later. Gene expression was compared between patients who met versus those who did not meet the primary trial outcome of clinical remission at 6 months (responders versus nonresponders). Measurement of neutrophil-related gene expression was confirmed in peripheral blood mononuclear cells (PBMCs) to validate the findings in whole blood. A negative-selection strategy isolated LDGs from PBMC fractions.

The Rituximab in ANCA-Associated Vasculitis (RAVE) trial

1-5 Division of Rheumatology, Institute of Clinical Evaluative Sciences (ICES), Toronto, Ontario, Canada; 6 Division of Rheumatology, Northwestern University, Evanston, Illinois; 7 Department of Medicine, Division of Rheumatology, University of Michigan, Ann Arbor, Michigan; 8 Department of Internal Medicine, Division of Rheumatology, University of Cincinnati, Cincinnati, Ohio; 9 Department of Medicine, Division of Rheumatology, Vanderbilt University Medical Center, Nashville, Tennessee; 10 Division of Rheumatology, Institute of Clinical Evaluative Sciences (ICES), Toronto, Ontario, Canada; and 11 Division of Rheumatology, Institute of Clinical Evaluative Sciences (ICES), Toronto, Ontario, Canada.
NORAM

– MTX vs oral CYC for induction for 12 months
– Non-inferiority trial (d=15%) for remission at 6 mo
– 100 p. with “early systemic” WG for 12 mo.

Remission at 6 mo
MTX 89.8%
CYC 93.5% (P=0.041)

Relapse at 18
MTX 69.5%
CYC 46.5% (P = 0.023)

CYC Leukopenia
MTX liver enzymes

# Abatacept

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n (%)</th>
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<tr>
<td>Disease improvement</td>
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</tr>
<tr>
<td>Remission (BVAS/WG=0)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Relapse</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Reached common closing</td>
<td>14 (70)</td>
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<table>
<thead>
<tr>
<th>Parameter</th>
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<tr>
<td>Time from entry to remission (months)</td>
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<td>1–19</td>
</tr>
<tr>
<td>Time from remission to relapse (months)</td>
<td>6.7</td>
<td>5–9</td>
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<tr>
<td>Time on study before common closing/early termination</td>
<td>12.3</td>
<td>2–35</td>
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<tr>
<td>Remission duration before common closing (months)</td>
<td>14.4</td>
<td>4–20</td>
</tr>
<tr>
<td>VDI at common closing/early termination</td>
<td>3.0</td>
<td>0–7</td>
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BVAS/WG, Birmingham Vasculitis Activity Score for Wegener’s Granulomatosis; VDI, Vasculitis Damage Index.

Relapsing non-severe GPA within <28 days (modified ACR criteria):

a. No disease manifestations that would be scored as a major element in the BVAS/WG

b. Absence of any disease feature that poses an immediate threat to either a critical individual organ or the patient’s life

treatment failure rate through 12 months

150 patients
Treatment of severe GPA/MPA

**CYCLOPHOSPHAMIDE**

- 15 mg/kg (d1,14,28 then q3wk)
- 2 mg/kg/d

**INDUCTION**

- AZATHIOPRINE 2 mg/kg/d
- METHOTREXATE 0.3 mg/kg/wk
- LEFLUNOMIDE 20 mg/d
- MYCOPHENOLATE MOFETIL 2 g/d

+ Corticosteroids

3 - 6 months

**MAINTENANCE**

> 18 months
Severe AAV

Induction immunosuppressive therapy

Adjunctive Plasma Exchange

Standard-Dose GC

Reduced Dose GC

No Plasma Exchange

Standard-Dose GC

Reduced Dose GC

Follow-Up

ESRD

Death

700 patients
Up to 7 years f/u
Treatment of severe GPA/MPA

**CYCLOPHOSPHAMIDE**
- 15 mg/kg (d1,14,28 then q3wk)
- 2 mg/kg/d

**RITUXIMAB**
- 375 mg/m²/week

**AZATHIOPRINE** 2 mg/kg/d

**METHOTREXATE** 0.3 mg/kg/wk

**LEFLUNOMIDE** 20 mg/d

**MYCOPHENOLATE MOFETIL** 2 g/d

+ adjuvant/prophylactic measures: cotrimoxazole, osteoporosis treatment, etc

+Corticosteroids

**INDUCTION**
- 3 - 6 months

**MAINTENANCE**
- > 18 months
RAVE

1 to 3 MP pulse(s)

CS + oral CYC * 3 to 6 mo
+ placebo RTX

Rituximab** + CS
+ placebo CYC

AZA → M18

Placebo AZA

<350 µM no severe AH ANCA+

* oral CYC 2 mg/kg/d

** RTX 375 mg/m² x 4
A Time to First Relapse after Complete Remission, According to Treatment

- CYC–AZA (N=70)
- RTX (N=76)

P=0.76

No. at Risk

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<th>CYC–AZA</th>
<th>RTX</th>
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<td>76</td>
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<td>300</td>
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<td>45</td>
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<td>400</td>
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Better response in relapsers
(vs newly-diagnosed)

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<tr>
<th></th>
<th>Rituximab</th>
<th>Cyclophosphamide</th>
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<tr>
<td>New Dx (N=96)</td>
<td>60.4%</td>
<td>64.6%</td>
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<tr>
<td>Relapsers (N=101)</td>
<td>66.7%</td>
<td>42.0%</td>
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P = 0.013

ANCA-type and Treatment Response
Achievement of Complete Remission by 6 Months in RAVE

- Rituximab
  - MPO-ANCA: 60.6% (n=66)
  - PR3-ANCA: 65.2% (n=131)

- Cyclophosphamide
  - MPO-ANCA: 63.6%
  - PR3-ANCA: 47.7%

P-value:
- MPO-ANCA: P=0.80
- PR3-ANCA: P=0.04

Treatment of severe GPA/MPA

**INDUCTION**
- **CYCLOPHOSPHAMIDE**
  - 15 mg/kg (d1, 14, 28 then q3wk)
  - 2 mg/kg/d
- **AZATHIOPRINE** 2 mg/kg/d
- **METHOTREXATE** 0.3 mg/kg/wk
- **LEFLUNOMIDE** 20 mg/d
- **MYCOPHENOLATE MOFETIL** 2 g/d
- + adjuvant/prophylactic measures: cotrimoxazole, osteoporosis treatment, etc
- + Corticosteroids

**MAINTENANCE**
- > 18 months

**RITUXIMAB**
- 375 mg/m2/week

The diagram illustrates the treatment protocols for severe GPA/MPA, with different medications and dosages used during induction and maintenance phases.
The Assessment of Prednisone In Remission Trial (TAPIR)

Key eligibility criteria include:

- Diagnosis of granulomatosis with polyangiitis (GPA)
- Required ≥ 20 mg/day of prednisone at some point in the last 12 months
- GPA currently in remission
- Currently taking between 6 mg and 20 mg of prednisone per day
- Age 18 or older
- Randomized to reduce prednisone dose to either 5 mg or 0 mg a day using standardized taper
- Subjects followed for 6 months
60 patients
Primary hypothesis is a difference of ≥30% in the relapse rate.
157 patients with a median follow-up of 3.1 years

IS for >18 months, a 29% reduction (HR, 0.71; 95% CI, 0.42–1.19; p = 0.19)

IS for >36 months, a 66% reduction (HR, 0.34; 95% CI, 0.15–0.76; p = 0.008)

*Springer et al. Medicine 2014;93: 82–90*
REMAIN

Trial Overview

Before Entry
Diagnosis of ANCA associated vasculitis

Induction treatment with cyclophosphamide for at least 3 months followed by maintenance treatment with azathioprine

Entry to REMAIN and Randomisation
(4-24 months after diagnosis)

Follow-up
(3 monthly evaluations)

Start of REMAIN trial regimens
(18-24 months from diagnosis)

prednisolone and azathioprine withdrawal of therapy

Follow-up
(3 monthly evaluations)

Study end
(30 months after start of trial regimens and 48-54 months from diagnosis)
REMAIN: Immunosuppressive regimen

- **CYC**
  - 18 to 24 months

- **AZA**
  - 0.75 mg/kg/d
  - 5 mg/d
  - 7.5 mg/d

- **STER**
  - 5 mg/d
  - 1 mg/kg/d

- **Withdrawal**
  - 18 to 24 months

- **Continue**
  - 48 to 54 months
Results: primary end-point

Survival without relapse

Subjects at risk

<p>| | | | | | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>C (n=53)</td>
<td>50</td>
<td>43</td>
<td>38</td>
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<tr>
<td>W (n=45)</td>
<td>39</td>
<td>30</td>
<td>21</td>
<td>16</td>
<td>5</td>
</tr>
</tbody>
</table>

P<0.0001
76 in the rituximab group had a CR
24 (32%) relapsed before M18

70 in the CYC had a CR
20 (29%) relapsed before M18

(P=0.16)
Treatment of severe GPA/MPA

**CYCLOPHOSPHAMIDE**
- 15 mg/kg (d1,14,28 then q3wk)
- 2 mg/kg/d

**AZATHIOPRINE** 2 mg/kg/d

**METHOTREXATE** 0.3 mg/kg/wk

**LEFLUNOMIDE** 20 mg/d

**MYCOPHENOLATE MOFETIL** 2 g/d

**RITUXIMAB**
- 375 mg/m2/week

**INDUCTION**
- 3 - 6 months
- + Corticosteroids

**MAINTENANCE**
- > 18 months
- + Corticosteroids

+ adjuvant/prophylactic measures: cotrimoxazole, osteoporosis treatment, etc.
Retreatment With Rituximab In The Rituximab In ANCA-Associated Vasculitis (RAVE) Trial

E Miloslavsky et al. RAVE study group

26 patients experienced severe flares (15 in the RTX arm) within 18 months

→ RTX again

**Effective (CR) in 23 of them (88%)**
13 of the 15 RTX (87%)

(1 died of severe AH)
AES = 4.7/patient-year vs 11.8 in the original study phase

Arthritis Rheumatol. 2014 Jul 21
Long-Term Outcome of Patients with GPA Treated with Rituximab

Single-center retrospective study:
- **105 GPA patients** (55 F) who received ≥1 RTX course
- for **relapses** (85) or persistent disease (15), few for maintenance after a relapse (5)
- **77** received a 1g x 2 scheme
- **Iº Efficacy = 97%** (few refractory, with lung disease)

**Maintenance** (n=47) with AZA (29), MTX (11), MMF (7)

**No maintenance** (n=42)

Median f/up 23 (1-137) months

**Relapses at M18**
- 35% with vs. 61% without (M24: 55% vs 70%)

**Median to 1st relapse**
- 13 (2.5-66) mo

41% were still B cell depleted at relapse!

**adjusted HR of relapse 0.43** [95% CI 0.22-0.84]

SAE 7.6% with vs 6.9% w/o

Rituximab for Remission Maintenance in Relapsing Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Rona M. Smith,¹ Rachel B. Jones,¹ Mary-Jane Guerry,¹ Simona Laurino,¹ Fausta Catapano,¹ Afzal Chaudhry,¹ Kenneth G. C. Smith,² and David R. W. Jayne¹

→ 1g every 6 months
MAINRTSAN

MAINtenance of remission using RITuximab for Systemic ANCA-associated vasculitides

Systemic GPA or MPA or KLD with FFS ≥ 1
Newly diagnosed or after a relapse treated with CS–CYC
>18 and <75 years old at enrolment

Guillevin and Pagnoux et al. for the NEJM, Nov. 6, 2014
6−9 pulses

Induction

MP pulses d1–3

CS

± PE

Maintenance

Rituximab 500 mg
d1,14, 6, 12, 18 mo

Azathioprine 2 mg/kg/d

10 mg/d

5 mo

18 mo

18 mo

18 mo

newly diagnosed relapsing (up to 1/3)

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

ENDPOINT

+10 mo

28
115 patients
(65 M / 50 F; 55 ± 13 yr; 87 GPA, 23 MPA, 5 KLD; 92 new / 23 relapsing)

58 AZA
Relapses
17 (29%)

57 RTX
Relapses
3 (5%)

Induction

- **MP pulses D1−3**
- **0.5 or 1 mg/kg**
- **CS**
- **10 mg/d**
- **3 mo**

± Plasmapheresis

**RTX**

- 375 mg/m² x 4

Maintenance

**Rituximab 1000 mg**

- m4, 8, 12, 16, 20

**Azathioprine 2 mg/kg/d (MTX or MMF)**

- 2 mg/kg/d

3 Stratas:
- **ANCA type**, severe/non-severe,
- **initial PDN dose**

ENDPOINT

- **Relapsers (1M or 3m) ANCA+**

**RITAZAREM**

Drs. D. Jayne & P. Merkel

- N=190 → 160 RDM
- 40 in North America across 12 centers (2 CA)

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

Closure: last patient reaches M36
<table>
<thead>
<tr>
<th>Drug</th>
<th>Unit</th>
<th>Cost per unit*</th>
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</thead>
<tbody>
<tr>
<td>Rituximab (Rituxan ®) 10mg/ml</td>
<td>10 ml vial</td>
<td>$450</td>
</tr>
<tr>
<td>Rituximab (Rituxan ®) 10mg/ml</td>
<td>50 ml vial</td>
<td>$2250</td>
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<tr>
<td>Cyclophosphamide (Procytox ®) 20mg/ml</td>
<td>100 ml vial</td>
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</table>
REIMBURSEMENT CRITERIA

For the induction of remission of severely active Granulomatosis with Polyangiitis (GPA) OR microscopic polyangiitis (MPA) as combination treatment with glucocorticoids, in patients who meet all of the following criteria:

1. The patient must have severe active disease that is life- or organ-threatening. At least one supporting laboratory and/or imaging report must be provided. The organ(s) and how the organ(s) is(are) threatened must be specified.
2. There is a positive serum assays for either proteinase 3-ANCA (anti-neutrophil cytoplasmic antibodies) or myeloperoxidase-ANCA. A copy of the laboratory report must be provided.
3. Cyclophosphamide cannot be used for the patient for at least ONE of the following reasons:
   a) The patient has failed a minimum of six IV pulses of cyclophosphamide; OR
   b) The patient has failed three months of oral cyclophosphamide therapy; OR
   c) The patient has a severe intolerance or an allergy to cyclophosphamide; OR
   d) Cyclophosphamide is contraindicated; OR
   e) The patient has received a cumulative lifetime dose of at least 25 g of cyclophosphamide; OR
   f) The patient wishes to preserve ovarian/testicular function for fertility.

The initial treatment would be a once weekly infusion dosed at 375 mg/m² x 4 weeks.

The physician must confirm that the treatment would not be a maintenance infusion as maintenance infusions will not be funded.

Renewals will be considered provided that, the patient meets the same criteria for initial approval and the request for retreatment is made no less than 6 months after the last does of the patient’s last treatment cycle with Rituxan.
Mainritsan: Preliminary f/up data

Relapse-free survival (%)

Late / delayed relapses

Last RTX infusion

Stop AZA

HR = 0.34 (0.18-0.61)

p = 0.0004

Months

RTX
AZA
Main predictors of relapse

GPA
antiPR3+
ENT
Lung (nodules)
Low creatinine <100
Cardiovascular

Risk of relapse

Persistent ANCA?  
CD19+ B?  
CD5+ B?  
LDG?

MPA
antiMPO+
High creatinine

Pagnoux et al, Arthritis Rheum 2008;58(9):2908-18
Walsh et al, Arthritis Rheum 2012;64(2):542-8
Grayson et al, Arthritis Rheumatol 2015;67(7):1922-32
Bunch et al, Ann Rheum Dis. 2015;74(9):1784-6
**Mainritsan 2**

**Induction**
- MP pulses d1–3
- CS ± PE

**Maintenance**
- Newly diagnosed (2/3)
- Relapsing (1/3)
- >18 y.-o.
- GPA, MPA, KLD
- ANCA+ and/or Bx

- 10 mg/d d1,14, 6, 12, 18 mo
- Rituximab 500 mg d1,14, 6, 12, 18 mo
- Every / 3 months if CD19 or ANCA x2

**Closed 10/2013**
166 enrolled in 1 year!
HBV reactivation

PJP

PML

HBV reactivation
BREVAS

Study 1006-C1100

Induction

Remission

BVAS score = 0 and ≤10mg prednisone equiv. on two visits at least 14 days apart

≥6 wks and ≤26 wks

R

N = 300-400

Belimumab + azathioprine

Placebo + azathioprine

Endpoint = time from randomization to relapse

Induction therapy:
Steroids + Rituximab or
Steroids + Cyclophosphamide
Complement and vasculitis

Figure 5. Complement depletion prevents anti-MPO splenocyte-induced glomerular necrosis and crescents. Rag2−/− mice were treated with CVF or PBS (n = 8 per group), and then, 4 hours later, were injected with 5 × 10⁷ anti-MPO splenocytes. Pathological examinations were performed at day 13 of receiving anti-MPO splenocytes. In noncomplement-depleted Rag2−/− mice, transfer of anti-MPO splenocytes induced glomerular necrosis (long arrow) and crescent formation (short arrow) (A) (H&E), moderate glomerular IgG deposition (B) (fluorescein isothiocyanate anti-IgG), and neutrophil and macrophage infiltration (C, D). Complement-depleted Rag2−/− mice that received anti-MPO splenocytes had no lesions by light microscopy (E) (H&E), low-level IgG deposition (F), and no significant increase in glomerular neutrophils or macrophages (G, H).

→ Alternative pathway

CCX168 Group Showed Higher Incidence of “Renal Remission”* Based on Improvement in eGFR AND Hematuria vs. CYC + High Dose Steroid Treatment

* Partial renal response defined as no worsening from baseline in urinary RBCs and improvement in renal function based on eGFR; Renal remission is defined as a reduction from baseline in urinary RBCs and improvement in renal function based on eGFR;
Quoi de neuf dans les vascularites des gros vaisseaux?
A Large-Scale Genetic Analysis Reveals
a Strong Contribution of the HLA Class II Region
to Giant Cell Arteritis Susceptibility

F. David Carmona,1,4,5 Sarah L. Mackie,6,7 José-Ezequiel Martin,4,5 John C. Taylor,8,9 Augusto Vaglio,4,10
Stephen Fye,11 Lara Bozoni-Castillo,12 Santos Castañeda,12 Martha C. Cid,1,11 José Hernández-Rodríguez,13
Sergio Pérez-Cabrera,14 Roberto Solans,14 Marcos Ramírez-Santos,8,14 Manuel Ramírez-Brashiano,14
Loules Ortiz-Fernández,15 Immaculada C. Morado,16 Javier Navarro,17 José A. Miranda-Piñeyro,18 Spanish
GCA Group, Lorenzo Bertetta,19 Claudio Lunardi,16 Marco A. Grimin,20 Davide Gianfreda,21
Daniele Santulli,21 Giuseppe A. Ramirez,19 Alessandra Soriano,19 Francesco Muratore,22 Giulia Paolino,22
Olga Addimando,19 Cinzia Wijmenga,23 Toonien Witte,23 Jan H. Schirmer,23 Frank Moonen,23
Verena Schömaier,19 Andrea Branke,23 György Molnár,23 Andreas P. Diamantopoulos,23
Simon Carette,21 David Cuttinhorn,21 Lindsey J. Forbes,21 Gary S. Hoffman,21 Nader A. Khalidi,21
Curt L. Koening,23 Carol A. Anglard,23 Carol A. McAlner,23 Larry Morland,23 Paul A. Monach,23
Christian Ragno,19 Philip Seo,20 Robert Spiera,23 Antoine G. Strel,23 Kenneth J. Warrington,23
Steven R. Vittinghoff,23 Michael Green,23
Bhaskar Dastu,23 Jane Worton,21 Bobby P.C. Koelman,21 Paul I.W. de Bakker,21
Jennifer H. Barrett,23 Carlo Salvanari,23 Peter A. Merek,23 Miguel A. González-Gay,23,5,3
Ann W. Morgan,23,3,5 and Javier Martin,4,5

Instituto de Patología y Biomecánica “Alfonso NYE,” CINCS, P7, Granada, Granada 18016, Spain, Sha’s L.A., Institute of Rheumatic and Musculoskeletal Disease and NHS Leeds Musculoskeletal Biomedical Research Unit, University of Leeds, Leeds, UK, School of Medicine and Biotechnology, University of Athens, Athens, Greece, 2018 Manchester Musculoskeletal Biomedical Research Unit, Manchester Academy of Health Science, Manchester, UK, Arthritis Research UK Epidemiology Unit, Lahey Clinic, Burlington, VT, USA, Department of Medicine, University of Connecticut, Farmington, CT, USA, Rheumatology, University Hospital of Madrid “12 de Octubre,” Madrid, Spain, 2018 National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA, Department of Internal Medicine, University Hospital of Valencia, Valencia, Spain, 2018 National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA, Department of Medicine, University of Oporto, Oporto, Portugal, 2018 Collaboration for the Visualization of Genotypes, Bern, Switzerland, 2018 Collaboration for the Visualization of Genotypes, Bern, Switzerland, 2018 Collaboration for the Visualization of Genotypes, Bern, Switzerland, 2018 Collaboration for the Visualization of Genotypes, Bern, Switzerland

Revisited HLA and non-HLA genetics of Takayasu arteritis—where are we?

Chikako Terasu1,2,3,4

Takayasu arteritis (TAK) is an immune-mediated vasculitis affecting large arteries first reported in 1908 from Japan. Case reports from Japan and other countries indicated genetic contribution to TAK onset beyond ethnicity. Genetic studies of TA have been performed mainly addressing the human leukocyte antigen (HLA) locus. HLA genetic studies of TA have been previously reported and are reviewed in this manuscript. HLA-B*52:01 is associated with TA onset. Association of HLA-B*52:01 with TA has been confirmed in the Japanese population. Further independent associations are suggested in the HLA locus. Involvement of the 171st and 67th amino acid positions with TA onset has been indicated. The 67th amino acid may explain the difference in susceptibility effects to TA and Behçet’s disease between HLA-B*52:01 and *51:01. HLA-

B*52:01 is associated with not only TA susceptibility but also with clinical phenotypes. Recent genome-wide association studies of Takayasu arteritis showed evidence of susceptible genetic markers. The IL-12B region seems to have a central role in TAK onset and progression. Whether TA and giant cell arteritis (GCA), the other vasculitides affecting large arteries, are the same disease is an interesting question to address in spite of different clinical manifestations between the two diseases. GCA is associated with HLA-DR4, which is not associated with TA. GCA is not associated with HLA-Dw8. These two diseases seem not to share non-HLA susceptibility loci based on the recent genetic studies.

Journal of Human Genetics advance online publication, 16 July 2015; doi:10.1038/jhg.2015.587
14-3-3 in Thoracic Aortic Aneurysms

Identification of a Novel Autoantigen in Large Vessel Vasculitis


Objective. Large vessel vasculitides (LVV) are a group of autoimmune diseases characterized by injury to and anatomic modifications of large vessels, including the aorta and its branch vessels. Disease etiology is unknown. This study was undertaken to identify antigen targets within affected vessel walls in aortic root, ascending aorta, and aortic arch surgical specimens from patients with LVV, including giant cell arteritis, Takayasu arteritis, and isolated focal aortitis.

Methods. Thoracic aortic aneurysm specimens and autologous blood were acquired from consenting patients who underwent aorta reconstruction procedures. Aorta proteins were extracted from both patients with LVV and age-, race-, and sex-matched disease controls with noninflammatory aneurysms. A total of 108 serum samples from patients with LVV, matched controls, and controls with antinuclear antibodies, different forms of vasculitis, or sepsis were tested.

Results. Evaluation of 108 serum samples and 22 aortic tissue specimens showed that 78% of patients with LVV produced antibodies to 14-3-3 proteins in the aortic wall (93.7% specificity), whereas controls were less likely to do so (6.7% produced antibodies). LVV patient sera contained autoantibody sufficient to immunoprecipitate 14-3-3 protein(s) from aortic lysates. Three of 7 isoforms of 14-3-3 were found to be upregulated in aorta specimens from patients with LVV, and 2 isoforms (s and ξ) were found to be antigenic in LVV.

Conclusion. This is the first study to use sterile, snap-frozen thoracic aorta biopsy specimens to identify autoantigens in LVV. Our findings indicate that 78% of patients with LVV have antibody reactivity to 14-3-3 protein(s). The precise role of these antibodies and 14-3-3 proteins in LVV pathogenesis deserves further study.
The Role of Ultrasound vs Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis: A Diagnostic Accuracy and Cost-Effectiveness Study


Luqmani et al. ACR 2015
<table>
<thead>
<tr>
<th>Strategy</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>% having ultrasound</th>
<th>% having biopsy</th>
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<td>39%</td>
<td>100%</td>
<td>0%</td>
<td>100%</td>
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<tr>
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<td>54%</td>
<td>81%</td>
<td>100%</td>
<td>0%</td>
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<tr>
<td>Biopsy &amp; ultrasound (both in all patients)</td>
<td>65%</td>
<td>81%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Ultrasound followed by biopsy if US negative</td>
<td>65%</td>
<td>81%</td>
<td>100%</td>
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<tr>
<td>Ultrasound followed by biopsy if high risk</td>
<td>94%</td>
<td>77%</td>
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<tr>
<td>Ultrasound followed by biopsy if medium or high risk</td>
<td>95%</td>
<td>77%</td>
<td>100%</td>
<td>13%</td>
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</table>
Multifocal VZV vasculopathy with temporal artery infection mimics giant cell arteritis

ABSTRACT

Objective: To address the incidence of varicella-zoster virus (VZV) infection in patients with biopsy-negative giant cell arteritis (GCA), we examined archived biopsy-negative temporal arteries from subjects with clinically suspected GCA for the presence of VZV antigen.

Methods: Formalin-fixed, paraffin-embedded temporal arteries that were pathologically negative for GCA and normal temporal arteries were analyzed immunohistochemically for VZV and herpes simplex virus-1 (HSV-1) antigen.

Results: Five (21%) of 24 temporal arteries from patients who were clinically suspected but biopsy-negative for GCA revealed VZV but not HSV-1 by immunohistochemical analysis. Thirteen normal temporal arteries did not contain VZV or HSV-1 antigen. All 5 subjects whose temporal arteries contained VZV antigen presented with clinical and laboratory features of GCA and early visual disturbances.

Conclusion: Multifocal VZV vasculopathy can present with the full spectrum of clinical features and laboratory abnormalities characteristically seen in GCA. Neurology 2013;80:2017-2021

Prevalence and distribution of VZV in temporal arteries of patients with giant cell arteritis

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Rudall J. Colins, MD

ABSTRACT

Objective: Varicella-zoster virus (VZV) infection may trigger the inflammatory cascade that characterizes giant cell arteritis (GCA).

Methods: Formalin-fixed, paraffin-embedded GCA-positive temporal arteries (TA) biopsies (50 sections/TA) including adjacent skeletal muscle and normal TAs obtained postmortem from subjects >50 years of age were examined by immunohistochemistry for presence and distribution of VZV antigen and by ultrastructural examination for viros. Adjacent regions were examined by hematoxylin & eosin staining. VZV antigen-positive slides were analyzed by PCR for VZV DNA.

Results: VZV antigen was found in 6/18 (74%) GCA-positive TAs compared with 1/13 (8%) normal TAs with p < 0.0001, relative risk 9.67, 95% confidence interval 1.43, 63.68. Most GCA-positive TAs contained viral antigen in skip areas. VZV antigen was present mostly in adventitia, followed by media and intima. VZV antigen was found in 12/32 (38%) skeletal muscles adjacent to VZV antigen-positive TAs. Despite formalin fixation, VZV DNA was detected in 18/45 (40%) GCA-positive VZV antigen-positive TAs, in 6/10 (60%) VZV antigen-positive skeletal muscles, and in one VZV antigen-positive normal TA. Varicella-zoster viruses were found in a GCA-positive TA. In sections adjacent to those containing VZV, GCA pathology was seen in 89% of GCA-positive TAs but in none of the 19 adjacent sections from normal TAs.

Conclusions: Most GCA-positive TAs contained VZV in skip areas that correlated with adjacent GCA pathology, supporting the hypothesis that VZV triggers GCA immunopathology. Antiviral treatment may confer additional benefit to patients with GCA treated with corticosteroids, although the optimal antiviral regimen remains to be determined. Neurology 2015;84:1948-1955

Analysis of Varicella-Zoster Virus in Temporal Arteries Biopsy Positive and Negative for Giant Cell Arteritis

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Rafat Paterostatou, MD
Don Gilden, MD

IMPACT: Giant cell arteritis (GCA) is the most common systemic vasculitis in elderly individuals. Diagnosis is confirmed by temporal artery (TA) biopsy, although biopsy results are often negative. Despite the use of corticosteroids, disease may progress. Identification of causal agents will improve outcomes. Biopsy positive GCA is associated with TA infection by varicella-zoster virus (VZV).

OBJECTIVE: To analyze VZV infection in TAs of patients with clinically suspected GCA whose TAs were histopathologically negative and in normal TAs removed post mortem from age-matched individuals.

DESIGN, SETTING, AND PARTICIPANTS: A cross-sectional study for VZV antigen was performed from January 2013 to March 2015 using archived, deidentified, formalin-fixed, paraaffin-embedded GCA-negative TA, and GCA and normal TAs (50 sections/TA) collected during the past 30 years. Regions adjacent to those containing VZV were examined by hematoxylin & eosin staining. Immunohistochemistry identified inflammatory cells and cell types around nerve-bundles containing VZV. A combination of 17 tertiary referral centers and private practices worldwide contributed archived TAs from individuals older than 50 years.

OUTCOME MEASURES: Presence and distribution of VZV antigen in TAs and histopathological changes in sections adjacent to those containing VZV were confirmed by 2 independent readers.

RESULTS: Varicella-zoster virus antigen was found in 45 of 70 GCA-negative TAs (64%), compared with 11 of 49 normal TAs (22%) (relative risk (RR) = 2.26; 95% CI, 1.75-3.31; P < 0.001). Extension of our earlier study revealed VZV antigen in 8 of 93 GCA-positive TAs (8%). Compared with normal TAs, VZV antigen was more likely to be present in the adventitia of
AGATA LVV

- VCRC 5523
- CTLA4-Ig / abatacept
- 15 Hamilton
- 11 Toronto

Prendisone 40-60 mg / day with a standardized prednisone taper
Abatacept 10mg/kg IV on days 1, 15, 29 and week 8

Is patient in remission at week 12 visit?

Yes

Randomization
With Double Blinded Treatment Assignment

Abatacept 10mg/kg IV every 28 days
+ Continued prednisone taper

Continued Remission

Common Closing Date:
1 Year after randomization of the Final Participant for each disease

Post Treatment visits – 4, 12, and 24 weeks after stopping abatacept or abatacept/placebo

No

Stop abatacept

Relapse

Stop abatacept/placebo

VCRC – Langford et al. ACR 2015
At 12 months:
relapse-free survival of
48% ABA vs 31% placebo (p=0.049)

VCRC – Langford et al. ACR 2015
GiACTA Study

Part 1
52 week double-blind

Part 2
104 week open-label extension / long-term FU

Baseline

TCZ 162 mg QW + 26 wk prednisone taper (n=100)
TCZ 162 mg Q2W + 26 wk prednisone taper (n=50)
SC placebo + 26 wk prednisone taper (n=50)
SC placebo + 52 wk prednisone taper (n=50)

Screen 42 days

Week 52

Patients in remission at 52 weeks
Long-term FU off study drug

Week 156

Patients with disease activity or flares
Open-label TCZ 162 mg QW

Primary Endpoint
TCZ (8 mg/kg IV)

At 12 weeks:
Complete remission
85% TOCI vs. 40% placebo
($P = 0.030$)

Adler et al. ACR 2015
# Safety Serious Adverse Events (SAE)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TCZ (n=20)</th>
<th>Placebo (n=10)</th>
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<tbody>
<tr>
<td>SAE</td>
<td>7/20</td>
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<tr>
<td>cardiovascular</td>
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<td>infection</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>other</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Adler et al. ACR 2015
IL-12/23 monoclonal

Open label study, monocentric
N = 14 with refractory GCA (≥2 relapses)

USTK 90mg SQ  D0, M1 then q3months

Median f-up 10.5 months
→ No relapse
→ 4 stopped GC
→ Improvement of wall thickening 7/7

→ 3 stopped / AE
   (hair loss, LRTIs, paresthesia)
Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg–Strauss)

A J Mohammad,1,2 A Hot,3 F Arndt,4 F Moosig,4 M-J Guerry,5 N Amudala,6 R Smith,1 P Sivasothy,7 L Guillemin,8 P A Merkel,9 D R W Jayne1

**N = 41**, with RTX 2003-2013 (15 refractory, 21 relapsing, 5 new)
ANCA= 44%
4 centers USA and EU (Boston, Cochin, Bad Bramstedt, Cambridge)

19 one course only, others retreated at M6 or M12
30 with 4x375, 10 with 2x1 (1 with 800x2) – same results

**Improvement 83% at M6, 88% at M12**
PR+CR 80% at M12 for ANCA+, 38% at M12 for ANCA-

PDN 15 mg OD → 8 mg OD at M12 (only 2 off PDN at M12…)
Eosino: no change (0.26 → 0.2 at M12)
44% with IS → 28% with IS at M12
51% had AEs, including 6 SAE-infections
17% allergic reaction (1 ICU with asthma)
41 patients
18 patients ANCA+
23 patients ANCA-

Réponse à M12 :
Rémission 49%
Réponse partielle 39%
Non réponse 12%

Réponse ANCA+ > ANCA-

Mohammad, Ann Rheum Dis, 2015
Newly diagnosed or relapsing active EGPA (BVAS ≥3)
Randomization with stratification on:
- Disease severity (FFS=0 vs. FFS≥1)
- ANCA status (positive vs. negative)
- Newly diagnosed vs. relapsing disease

FFS ≥1

Conventional group

Experimental group

FFS = 0

Prednisone

AZA

Primary endpoint
End of study

H = hospitalization
Cs = consultation

↑ = rituximab i.v., 1 gram
↑ = placebo-rituximab i.v.
↑ = cyclophosphamide i.v.
↑ = placebo-cyclophosphamide i.v.