Vasculitis STUDIES in Canada and CanVasc projects
Ongoing CanVasc activities and studies

- Why CanVasc?
- What is it?
- What are its objectives?
- Identify some ongoing and future projects
CanVasc creation

- Drs. Pagnoux, Carette, Khalidi
- CanVasc = created on November 1st, 2010
Objectives

- organize a dedicated health and research network **across Canada** for patients with vasculitis with identification of referral (multidisciplinary) centers.
The network
CanVasc core member meetings

- 1\textsuperscript{st} core member meeting 12 Feb. 2011 (CRA)
- 2\textsuperscript{nd} core member meeting, 9 June 2011
- 3\textsuperscript{rd} core member meeting, 29 March 2012 (CRA)

- 4\textsuperscript{th} core member meeting, 14 or 15 February 2013 (CRA, Ottawa)
Objectives

- organize a dedicated health and research network across Canada
- Develop educational and awareness programs for health care providers
Recent Evidence in Vasculitis Science and Treatment

Management of AAV in the clinical setting
Discover CanVasc and its affiliated centers across Canada

CanVasc is the Canadian network for research on vasculitides. It was created November 2010 by Drs. Pagnoux, Caradoc and Khalidi. The first task 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. 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 providers and, eventually, optimize the therapeutic management of patients with these rare diseases.

[Click here](http://example.com) for more information on CanVasc.

The 2012 annual CanVasc meeting will be held on November 22nd, 2012 in Montréal

[Pre-program](http://example.com) [Registration form](http://example.com) [meeting webpage](http://example.com)

Update your knowledge on vasculitis with CanVasc online material

Creator and webmaster: Dr. Christian Pagnoux
2nd annual CanVasc meeting

Montréal, QC
November 22nd, 2012

Registration and information on http://www.canvasc.ca
Objectives

- organize a dedicated health and research network across Canada
- Develop educational and awareness programs for health care providers
- **Initiate, conduct, and promote studies on vasculitis** across Canada using an existing, efficient and rapidly mobilisable network
Studies

- **Creation of a Canadian database** for all Canadian centers (ongoing process) for adult vasculitis patients (Drs. Barra, Pagnoux – Twilt, Benseler, Cabral)

- Extension of pediatric **CNS vasculitis database** to Canadian adults (Dr. Twilt, Milman, Benseler, Pagnoux → Dr. Lanthier)
« Support » for core members’ initiatives

- Dr. Yacyshyn, Edmonton: PD Survey, Takayasu systematic review
- Dr. Liang, Sherbrooke: Management of AASV / influence of guidelines
- Dr. Pagnoux, Nair, Khalidi, Carette: Cytokine profile in EGPA
Other potential collaborations / studies « affiliated » with CanVasc

- Dr. Ma Donglai (Toronto) and Marvin Fritzler (Calgary)
- Dr. Siminovitch: Genetic study on GPA/MPA
- Dr. Siminovitch: Cytoflux study on GPA/MPA
Two Biomarker Discovery Strategies

A) Genotype Profiling
Use genome-wide association and whole exome sequencing to identify clinically-relevant genetic profiles.

B) Immunophenotyping
Use multiparameter flow cytometry to classify and monitor disease.
Canada-initiated study of GPA genetics

- Genotype 459 cases/1503 controls (Canadian)
- GWAS 700,000 markers
- Replicate 578 cases/1228 controls (WGGER, VCRC)

<table>
<thead>
<tr>
<th>GENE</th>
<th>Proposed Function</th>
<th>P-value</th>
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<tbody>
<tr>
<td>HLA-DPB1</td>
<td>Immunoregulation</td>
<td>1.9x10^{-50}</td>
</tr>
<tr>
<td>HLA-DPA1</td>
<td>Immunoregulation</td>
<td>2.1x10^{-39}</td>
</tr>
<tr>
<td>SEMA6A</td>
<td>Immunoregulation</td>
<td>2.0x10^{-8}</td>
</tr>
</tbody>
</table>

Data from K. Siminovitch et al.
McMaster’s GCA / MRI study

- Dr. Khalidi
- Dr. Clements-Baker
- Dr. Rebello
- Dr. Ioannidis

Other potential collaborations / studies from « affiliated » CanVasc

- Dr. Licht: complement
- Dr. Swartz, Mikulis, Mandell: CNS vessel imaging
- Dr. Milman: International Classification of Function in vasculitis

...others

Talk low, talk slow and don’t say too much
Objectives

- organize a dedicated health and research network across Canada
- Develop educational and awareness programs for health care providers
- Establish and regularly update Canadian recommendations for the diagnostic and therapeutic management of patients with vasculitis
Management of SNV patients

- Canadian consensus for the management of ANCA vasculitides
  - Ongoing process
  - under the aegis of CRA therapeutic committee
  - Led by Drs. Pagnoux and Liang (CanVasc)
  - By Fellows: Dr. Famorca (adult) and Twilt (pediatrics)
VASCULITIS NEEDS ASSESSMENT QUESTIONNAIRE
Results

136 physicians

English - 121

French - 15
Indicate which of the following 5 topics, would you like to see included in the upcoming Canadian ANCA-associated vasculitis recommendations?

- 1. Remission Induction Treatment
- 2. Treatment of refractory cases
- 3. Treatment of relapsing patients
- 4. Indication of the use of Biologics
- 5. Remission maintenance treatment
Canadian consensus for the management of ANCA vasculitides

- Needs assessment questionnaire
- Review of literature on the ~25 identified points to cover
- Writing of draft with grading of evidence (GRADE)
  → Dr. Lucy McGeoch
- Reviewing by CanVasc core members (Spring 2013)
- Revised draft → subgroups (CSN, CRA, CSN committees)
- Revised draft V2 → Final version (Fall 2013)
Objectives

- organize a dedicated health and research network across Canada
- Develop educational and awareness programs for health care providers
- Canadian Recommendations for the diagnostic and therapeutic management
- Initiate, conduct, and promote studies on vasculitis across Canada using an existing, efficient and rapidly mobilisable network
- **Stand as the Canadian advisory group in vasculitis**
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 autoantibodies) 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 dose of the patient’s last treatment cycle with Rituxan.
Ongoing NON-CanVasc studies in Canada

VCRC studies: Hamilton + Toronto

International studies: several co-investigator sites
  - Institutional/research group studies: PEXIVAS, DCVAS
  - Pharmaceutical companies: (to start soon)
VCRC longitudinal studies

- GCA, TA, PAN, MPA/GPA, EGPA

- Visits every
  - 3 months for 2 years then yearly
  - Every year
<table>
<thead>
<tr>
<th>Protocol Management Tools</th>
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<tbody>
<tr>
<td>5502</td>
<td>VCRC Longitudinal Protocol for Giant Cell Arteritis</td>
</tr>
<tr>
<td>5503</td>
<td>VCRC Longitudinal Protocol for Takayasu’s Arteritis</td>
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<tr>
<td>5504</td>
<td>VCRC Longitudinal Protocol for Polyarteritis Nodosa</td>
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<td>5505</td>
<td>VCRC Longitudinal Protocol for Granulomatosis with Polyangiitis (GPA) and Wegener’s Granulomatosis (WG)</td>
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<td>5506</td>
<td>VCRC Longitudinal Protocol for Churg-Strauss Syndrome</td>
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<td>5510</td>
<td>VCRC Genetic Repository One-Time DNA Protocol</td>
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<tr>
<td>5515</td>
<td>VCRC Imaging Protocol for Magnetic Resonance and Positron Emission Tomography (PET) Imaging</td>
</tr>
<tr>
<td>5522</td>
<td>A Multi-Center, Open-label Pilot Study of Abatacept (CTLA4-Ig) in Patients with Active Parenchymal Involvement in Vasculitis</td>
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<tr>
<td>5523</td>
<td>Concurrent Pilot Studies in Giant Cell Arteritis and Takayasu’s Arteritis</td>
</tr>
<tr>
<td>5531</td>
<td>Reproductive Health in Men and Women with Vasculitis</td>
</tr>
</tbody>
</table>
Mild relapsing: confined to ≥1 sites, with Rx being the reinstitution or increase in CS to <30mg OD and/or an increase or addition of a 2nd immunosuppressant but not CYC (no AH, no renal)

CTLA4-Ig, abatacept 10 mg/kg IV D1, 14, 28 then monthly

On top of ongoing Rx with CS (15), AZA (3), MTX (7), MMF (4)

→ 20 patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value at Study Entry</th>
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<tbody>
<tr>
<td>Age (range)</td>
<td>45 years (17-73)</td>
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<tr>
<td>Female/Male</td>
<td>9/11</td>
</tr>
<tr>
<td>PR3-cANCA</td>
<td>80%</td>
</tr>
<tr>
<td>MPO-pANCA</td>
<td>10%</td>
</tr>
<tr>
<td>GPA duration mean (range)</td>
<td>100 months (5-326)</td>
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<tr>
<td>BVAS/WG mean (range)</td>
<td>3.1 (1-6)</td>
</tr>
<tr>
<td>VDI mean (range)</td>
<td>2.5 (0-7)</td>
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<table>
<thead>
<tr>
<th>Organ Involvement</th>
<th>Before Study Entry (Ever)</th>
<th>Active Disease at Study Entry</th>
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<tbody>
<tr>
<td>Constitutional</td>
<td>85%</td>
<td>30%</td>
</tr>
<tr>
<td>ENT</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>75%</td>
<td>50%</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>Mucous membranes</td>
<td>25%</td>
<td>5%</td>
</tr>
<tr>
<td>Lung</td>
<td>70%</td>
<td>30%</td>
</tr>
<tr>
<td>Kidney</td>
<td>40%</td>
<td>-</td>
</tr>
<tr>
<td>Eye</td>
<td>30%</td>
<td>-</td>
</tr>
<tr>
<td>Nerve</td>
<td>20%</td>
<td>-</td>
</tr>
</tbody>
</table>

Langford C et al – Cleveland Clinic Foundation / VCRC
- 18 (90%) had disease improvement
- 16 (80%) achieved remission with BVAS/WG=0 (median duration of remission before study closure was 12 months [4-21])
- 11/15 on PDN were able to stop PDN
- 3 relapses (19% of those who achieved remission), at a median of 8.3 months
- 6 (30%) dropped out because active disease, not severe (3 relapsers + 3 failures)
- 9 SAEs in 7 patients, including 7 infections, none severe

Langford C et al – Cleveland Clinic Foundation / VCRC

Phase III STUDY IN MILD GPA RELAPSE ????
AGATA LVV

- VCRC 5523
- CTLA4-Ig
- 2 Hamilton
- 1 Toronto
- 33+33 Needed
- Total 71 initial phase but only ~50 rdm

Flowchart:

1. Prednisone 40-60 mg/day with a standardized prednisone taper + Abatacept 10mg/kg IV on days 1, 15, 29 and week 8
2. 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
       - Placebo IV every 28 days + Continued prednisone taper
     - Continued Remission
     - Relapse
   - No
     - Stop abatacept
3. Common Closing Date: 1 Year after randomization of the Final Participant for each disease
4. Post Treatment visits – 4, 12, and 24 weeks after stopping abatacept or abatacept/placebo
VCRC patient registry

http://rarediseasesnetwork.epi.usf.edu/vcrc/index.htm

> 3,000
International studies with Canada!

- PEXIVAS
- DCVAS
International studies with Canada!

- PEXIVAS
- DCVAS

DCVAS Study
- Home
- About this Study
- DCVAS Sites
- Contact Us

Investigators
- Recruitment Update
- How to enrol your site
- Recruitment Guide
- Documentation (*)
- Database (*)
- CRF Feedback form
- Report recruitment

Participants
- What is Vasculitis?
- What is DCVAS?

ACR/EULAR endorsed study to develop classification and diagnostic criteria for primary systemic vasculitis

DCVAS has recruited 1662 patients from 78 sites worldwide

Sites joining DCVAS in Sept/Oct 2012:
- Aalst University, Egypt
- Basildon and Thurrock University Hospitals, UK
- Buckinghamshire Healthcare Stoke Mandeville, UK
- Cairo University, Egypt
- Charanpathi Shahuj Mahaj Medical Center, Lucknow, India
- Christian Medical College & Hospital, Vellore, India
- Heathfieldwood & Weepham Park Hospitals, UK
Identifying participants

Patients over 18 years with

- A new diagnosis of vasculitis
- An established diagnosis
  
  Date of diagnosis must not be more than two years before the date of enrolment
  Patients can have had symptoms for longer

- A potential diagnosis of vasculitis
| CA     | St Joseph's Healthcare London, Ontario | 40 |
| CA     | University of Ottawa                  | 10 |
| CA     | St Joseph's Healthcare Hamilton, Ontario | 23 |
| CA     | Mount Sinai Hospital, Toronto         |  7 |
| CA     | University of Manitoba, Winnipeg      |  9 |

+ Calgary?
# Recruitment and Site Update

Top 20 Recruiting Sites

<table>
<thead>
<tr>
<th>Region</th>
<th>Country Code</th>
<th>Site Code</th>
<th>Site Name</th>
<th>Total patients</th>
</tr>
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<tbody>
<tr>
<td>UK</td>
<td>GB</td>
<td>NO</td>
<td>Nuffield Orthopaedic Centre Oxford</td>
<td>136</td>
</tr>
<tr>
<td>NA</td>
<td>US</td>
<td>BU</td>
<td>Boston University Medical Campus</td>
<td>114</td>
</tr>
<tr>
<td>EU</td>
<td>SI</td>
<td>JJ</td>
<td>University Medical Centre Ljubljana</td>
<td>83</td>
</tr>
<tr>
<td>EU</td>
<td>IT</td>
<td>SS</td>
<td>Santa Maria Nuova Hospital, Reggio Emilia</td>
<td>80</td>
</tr>
<tr>
<td>EU</td>
<td>DE</td>
<td>SH</td>
<td>Klinikum Bad Bramstedt</td>
<td>68</td>
</tr>
<tr>
<td>UK</td>
<td>GB</td>
<td>NU</td>
<td>Nottingham University Hospitals NHS Trust</td>
<td>66</td>
</tr>
<tr>
<td>EU</td>
<td>DE</td>
<td>JE</td>
<td>Universitätsklinikum Jena</td>
<td>63</td>
</tr>
<tr>
<td>EU</td>
<td>CZ</td>
<td>PR</td>
<td>General University Hospital, Prague</td>
<td>59</td>
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<tr>
<td>UK</td>
<td>GB</td>
<td>IP</td>
<td>Ipswich Hospital NHS Trust</td>
<td>53</td>
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<tr>
<td>EU</td>
<td>DE</td>
<td>ES</td>
<td>Kreiskliniken Esslingen</td>
<td>50</td>
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<tr>
<td>EU</td>
<td>DK</td>
<td>UC</td>
<td>University Hospital, Copenhagen (Rigshospitalet)</td>
<td>47</td>
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<tr>
<td>EU</td>
<td>TR</td>
<td>IS</td>
<td>Istanbul University, Istanbul Medical School</td>
<td>45</td>
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<tr>
<td>NA</td>
<td>CA</td>
<td>ON</td>
<td>St Joseph's Healthcare London, Ontario</td>
<td>40</td>
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<tr>
<td>UK</td>
<td>GB</td>
<td>NN</td>
<td>Norfolk and Norwich University Hospitals NHS Foundation Trust</td>
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<tr>
<td>EU</td>
<td>CH</td>
<td>UB</td>
<td>University Hospital Basel</td>
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<td>SE</td>
<td>Southend University Hospital NHS Trust</td>
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<td>EU</td>
<td>IT</td>
<td>PA</td>
<td>University of Parma</td>
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<td>EU</td>
<td>DE</td>
<td>TU</td>
<td>Universitätsklinikum Tübingen</td>
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</tbody>
</table>

Sites recruiting highest number of patients per month (recruiting 6 months or more)
Target 1500 comparators for diagnostic criteria

### Diagnosis Code
- **CSS**: Churg-Strauss syndrome
- **GCA**: Giant cell arteritis
- **GPA**: Granulomatosis with polyangiitis (Wegener's)
- **MPA**: Microscopic polyangiitis
- **PAN**: Polyarteritis nodosa
- **TAK**: Takayasu arteritis
- **Other***: Behcet's disease
  - Cryoglobulinaemic vasculitis
  - Henoch-Schönlein purpura
  - Isolated aortitis
  - Other primary vasculitis
  - Other small vessel vasculitis
  - Primary cerebral vasculitis
  - Single organ vasculitis
- **COM**: Comparator group

### No. of patients recruited
- CSS: 109
- GCA: 356
- GPA: 351
- MPA: 146
- PAN: 34
- TAK: 75
- Other*: 307
- COM: 284
- Total: 260
DCVAS SCREENING

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<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Date of birth:</td>
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</table>

Inclusion criteria

1. Is the patient over the age of 18 years?  
   - Yes □  
   - No □

2. Does the patient have a diagnosis of vasculitis?  
   - OR □

   Is vasculitis a potential diagnosis for their current illness?  
   - Yes □  
   - No □

3. Has the patient given informed consent?  
   - OR □

   The patient does not have capacity to provide informed consent but a ‘consultee’ (‘surrogate’) has declared that the patient would want to participate in the study?
   - Yes □  
   - No □

If "No" is ticked for any of the inclusion criteria, then patient is NOT eligible for the study.

I confirm that the patient:

Meets **ALL** the inclusion criteria for the study:  
   - Yes □

   Or □

Does not meet the inclusion criteria for the study
   - Yes □

Signature of investigator: __________________________  
Print name: __________________________
Clinical Features - 3 Skin

Present at any time since the onset of the current illness = Tick the relevant box if symptoms or signs were present during the current illness. The current illness includes the whole period from when you think the vasculitis or mimic disease started until the date of diagnosis. This includes items that may have occurred and disappeared in the course of this illness.

SYMPTOMS

☑ Pruritus

☐ Painful skin lesion of any type

☐ Other Symptom (please specify)
DCVAS

- Each center willing to participate to contact R. Luqmani
dcv@ndorms.ox.ac.uk

- Each center will need local REB approval

- US $15 per patients with full set of data
  (US $10 if paper sheet)
International PHARMA-sponsored or -supported studies with Canada

- RITUXIMAB for maintenance
  (Investigator-driven; pharma-supported)

- TOCILIZUMAB for LVV

- MEPOLIZUMAB for EGPA

- Belimimab for AASV?
**Induction**

- **MP pulses D1–3**
- **CS 10 mg/d**
- ± Plasmapheresis

**RTX (375 mg x4)**

- 0.5 or 1 mg/kg

**Maintenance**

- **Azathioprine 2 mg/kg/d (MTX. MMF)**
- **Rituximab 1000 mg**
  - m4, 8, 12, 16, 20

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

- 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

**3 Stratas:**

- ANCA type, severe/non-severe, initial PDN dose

**ENDPOINT**

- 36 → 48

Closure: last patient reaches M36
A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF TOCILIZUMAB IN SUBJECTS WITH GIANT CELL ARTERITIS
Number of Patients about 250

- 100 sites: US (20) / **Canada (6 to 7:** Hamilton, Newmarket, Kitchener, Toronto, Trois-Rivieres, St Catherine)
- 1 to 5 patients per sites maxi.

- New or refractory (relapsing or non-relapsing) GCA active within 6 wk
  - Age ≥ 50 years
  - ESR > 30 mm/hr and CRP ≥ 1 mg/dL **OR** ESR > 50 mm/hr **AND** ≥1 of the following:
    - Unequivocal *cranial symptoms* of GCA (new-onset localized headache, scalp or temporal artery tenderness, ischemia-related vision loss, otherwise unexplained mouth or jaw claudication)
    - Symptoms of PMR **AND** ≥1 of the following:
      - Temporal artery biopsy revealing features of GCA
      - Evidence of LVV by angiography or cross-sectional imaging study such as MRA, CTA, or PET-CTA
Design of Protocol

New: 40-60mg OD
Refractory: 20-60mg OD

1ºEP = proportion of CS-free at M6 in sustained remission at 52 wk
MEPOLIZUMAB IN CSS

Undifferentiated T helper cell

- IL12
- IL27
- IFN-γ

- IL4
- IL25

- TGFβ
- IL23
- IL1
- IL6

- TGFβ1
- IL2

Th1
- STAT-4
- STAT-1

IFN-γ
- IL12R
- CCR5
- CXCR3

Th2
- GATA-3
- STAT-6

IL4
- IL5
- IL9
- IL13
- CCR3
- CCR4

Th17
- STAT-3
- RORγT
- RORα

IL17A, F
- IL21
- IL22
- IL26
- TNFα
- CCR4
- CCL20

Treg
- FoxP3
- STAT-5

IL10
- Adenosine