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The Vasculitis Foundation supports and empowers our community through education, awareness, and research.
Induction therapies in MPA

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Therapeutic Goals

- Control inflammation and prevent end-organ damage – induce remission
- Minimize cytoxan exposure
- Prevent relapses
Introduction of corticosteroids

1950

Induction with cytoxan and steroids

1960

MTX for induction (NORAM)

2003

Imuran over cytoxan for maintenance (CYCAZAREM)

2005

MTX and AZA work for maintenance (WEGENT)

2007

Plasmapheresis

2008

Oral vs IV cytoxan induction (CYCLOPS)

2009

Mycophenolate for Induction (MYCYC)

2010

Azathioprine or Rituximab for maintenance (MAINRITSAN)

2014

Azathioprine or Rituximab for maintenance (MAINRITSAN)

Current

Belimumab
Abatacept
Small molecule inhibitors
PEXIVAS

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ANCA Vasculitis Therapy

• Standard induction therapy leads to remission in 80-90% of patients

• Discovery of new agents for inducing remission in MPA has driven improvement in morbidity and mortality from the disease

• BUT, At least 50% of patients who respond to initial therapy experience relapses within 5 years

Fauci, Ann Int Med, 1983
Hoffman, Ann Int Med, 1992
Jayne, NEJM, 2003
Booth, Am J Kid Dis, 2003
## Highlights from Prior Induction Trials

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>OUTCOME</th>
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<tbody>
<tr>
<td>CYCLOPS (DeGroot, Ann Int Med 2009)</td>
<td>Cytoxan IV versus oral—IV Cytoxan not inferior to oral Cytoxan. But, trend toward relapses in IV group</td>
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<tr>
<td>NORAM (DeGroot, Arth Rheum 2005)</td>
<td>Methotrexate can be used to induce remission in patients with mild disease and no renal involvement, but may relapse sooner</td>
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<tr>
<td>MEPEX (Jayne, JASN 2007)</td>
<td>Plasmapheresis in severe life threatening disease with renal involvement → can improve renal survival and decrease risk of ESRD</td>
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<tr>
<td>MYCYC (Jones, JASN 2012)</td>
<td>Mycophenolate is not inferior to Cytoxan in inducing remission in new MPA/GPA with mild/mod renal disease</td>
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<tr>
<td>RITUXIVAS (Jones, NEJM 2010)</td>
<td>Rituximab was not inferior to CYC in severe ANCA associated vasculitis (newly diagnosed, severe renal disease, older) High rate of infections, mortality and adverse events in both groups</td>
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Rituximab-RAVE

- **Primary endpoint**: Month 6
  - BVAS = 0
  - PRED = 0

- **Months 0-6**
  - Steroids discontinued at 5.5 months

- **RITUXIMAB**
  - 375mg/m2 q week x 4
  - N = 99

- **CYC**
  - 2mg/kg po daily
  - N = 98

- **197 participants**
  - All rec’d 1-3g IV methylpred

- **Maintenance**
  - PLACEBO
  - AZATHIOPRINE

- **63**
- **52**
RAVE – remission rates

~30 that still do not achieve remission!
Of those that do, 30% relapse within a year

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<tr>
<th>TRIAL</th>
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<th>CAVEATS</th>
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<tr>
<td>RAVE (Stone, NEJM 2010)</td>
<td>Rituximab is not inferior to oral cyclophosphamide in inducing remission in new or relapsing MPA/GPA RTX is better in patients with relapsing disease</td>
<td>No patients with severe renal disease or requiring intubation permitted in trial</td>
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WHERE
are we going?
PEXIVAS

Severe AAV → Renal involvement or lung hemorrhage

Standard Therapy with Cyclophosphamide or Rituximab

- Adjunctive Plasma Exchange
  - 1mg/kg/d
  - 0.5mg/kg/d
- No Plasma Exchange
  - Standard-Dose Glucocorticoids
  - Reduced-Dose Glucocorticoids
  - Standard-Dose Glucocorticoids
  - Reduced-Dose Glucocorticoids

Down to 5mg by week 15  Down to 5mg by week 23
PEXIVAS

• Patients will be followed for 5-7 years
• The trial will hopefully help answer 2 important questions:
  1) Does plasmapheresis improve outcomes (mortality and ESRD) in severe AAV?
  2) Can we have similar results with use of less steroids in these patients?
• The first patient was randomized into PEXIVAS in June 2010. Goal was recruitment of 500 patients
• The trial recruited 704 patients by September 2016 and is scheduled to end in September 2017
Complement: A new target

• Greater understanding of the disease process has led to awareness of the role that complement plays in AAV
• The complement system is part of our innate immune system and consists of a number of small proteins found in the blood
• They assist in clearing microbes and damaged cells from our body and stimulate activation of our immune system
• A new drug has been developed that targets the C5a receptor that is found on activated neutrophils (specific cells that are critical in the ANCA vasculitides)—hence the name anti-neutrophilic cytoplasmic antibody
CCX 168, now named avacopan, is an oral C5aR blocker

By blocking the C5aR, avacopan is thought to reduce vasculitis by reducing neutrophil activation, accumulation, and adhesion, as well as vascular permeability.
CLEAR/CLASSIC Trials (Phase II)

• The CLEAR trial → study to see if avacopan treatment would allow for the elimination or reduction of high-dose corticosteroids, without compromising efficacy or safety

• CLASSIC trial → study to look for additional safety concerns in patients with AAV
CLEAR: 67 patients

SOC RTX or CYC +

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<th>Primary Outcome: BVAS response at week 12</th>
<th>Prednisone 60mg</th>
<th>Prednisone 20mg + Avacopan 30mg BID</th>
<th>Avacopan 30mg BID</th>
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<tr>
<td></td>
<td>75%</td>
<td>86%</td>
<td>81%</td>
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All treatment groups receiving Avacopan were comparable in clinical improvement to those who were in the standard of care group

Jayne, NDT, 2016
Even Better...

- Patients given the study drug had a more rapid onset of improvement
  - beneficial changes in proteinuria
  - rapid reductions from baseline in BVAS (disease activity measure)
  - reductions in a marker of kidney inflammation
  - Better patient reported quality of life
- Avacopan appeared safe and well tolerated in the trial
- Improvements in kidney function seen in all three groups
- These results indicate that Avacopan (CCX168), a target-specific complement inhibitor, can replace chronic steroids in the treatment of AAV with at least equal efficacy

PHASE 3 trial ADVOCATE currently recruiting
Take Home Points on MPA Induction Therapies

- We have made significant progress in identifying patients and inducing remission in patients with MPA.
- Approval of Rituximab.
- New insights into complement pathways.
- Working towards steroid replacement.
- Looking at the role of plasmapheresis and low dose steroid regimens.

Some patients still do not respond to our induction regimens, so there remains work to be done.

Once we induce remission, how do we prevent flares or grumbling disease???

How long should we continue maintenance treatment?

What are the options?

Should we continue low dose steroids indefinitely?

Does every flare require re-induction?