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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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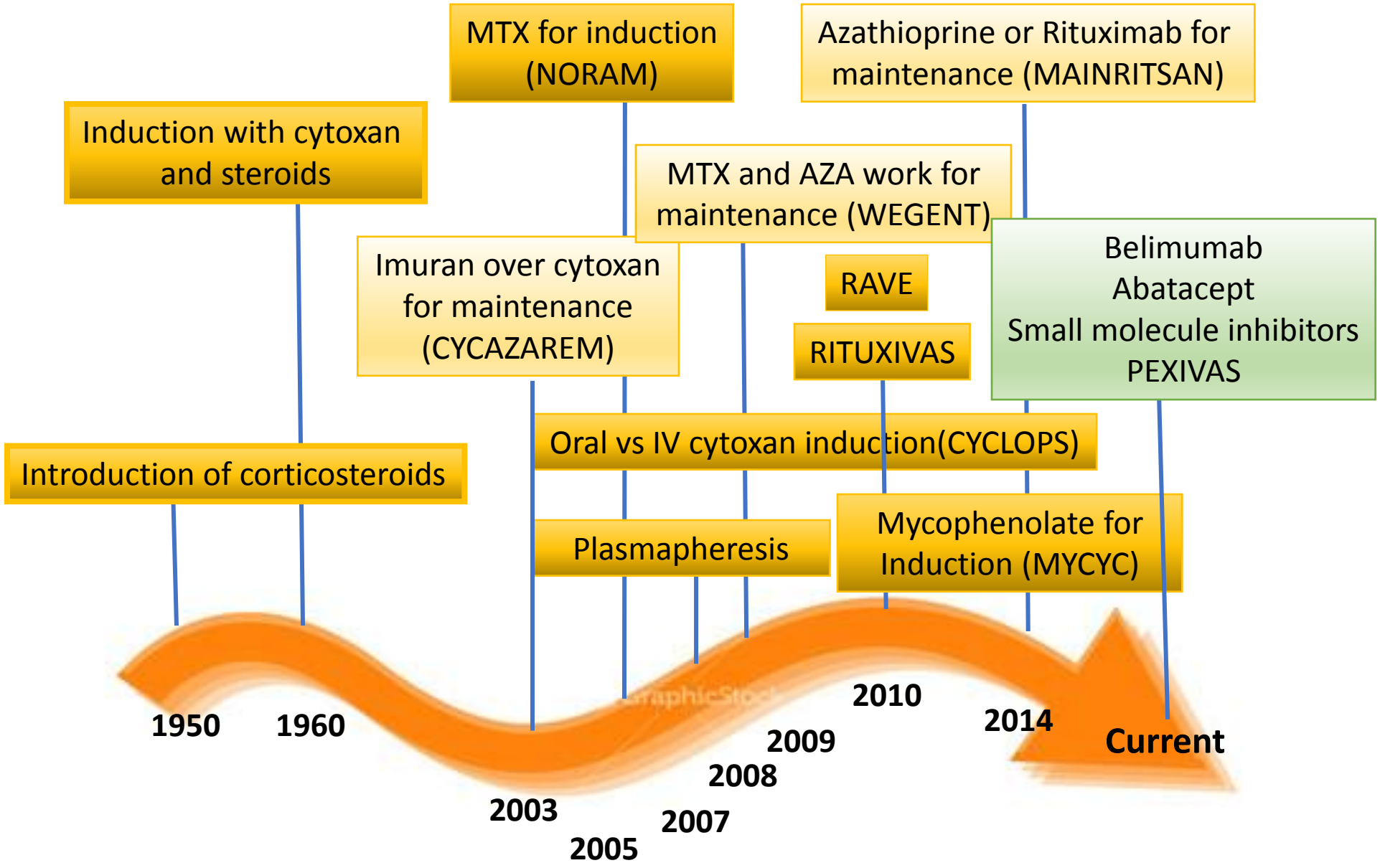
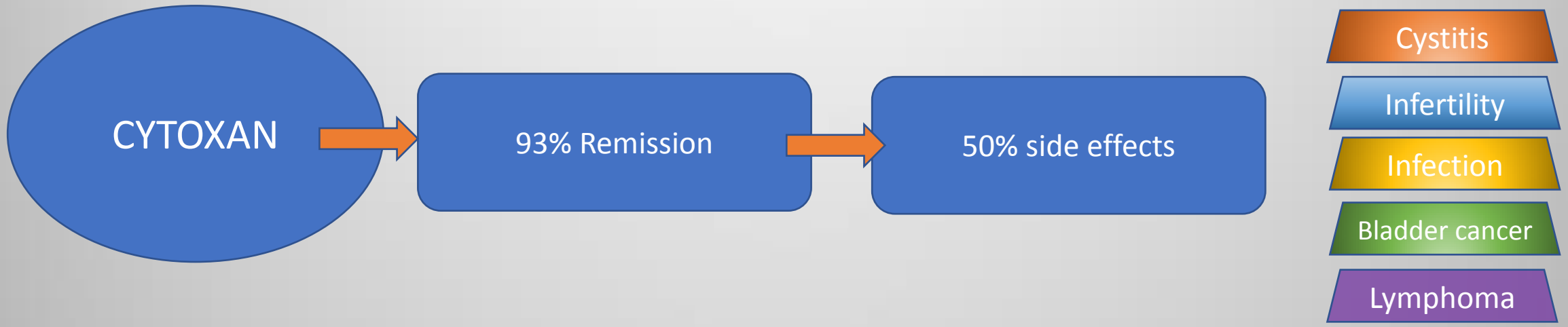
Therapeutic Goals

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


MTX for induction (NORAM)
Azathioprine or Rituximab for maintenance (MAINRITSAN)
Induction with cytoxan and steroids
MTX and AZA work for maintenance (WEGENT)
Imuran over cytoxan for maintenance (CYCAZAREM)
RAVE
Belimumab
Abatacept
Small molecule inhibitors
PEXIVAS
RITUXIVAS
Oral vs IV cytoxan induction(CYCLOPS)
Introduction of corticosteroids
Plasmapheresis
Mycophenolate for Induction (MYCYC)
1950
1960
2003
2005
2007
2008
2009
2010
2014
Current

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

TRIAL	OUTCOME
CYCLOPS (DeGroot, Ann Int Med 2009)	Cytoxan IV versus oral—IV Cytoxan not inferior to oral Cytoxan. But, trend toward relapses in IV group
NORAM (DeGroot, Arth Rheum 2005)	Methotrexate can be used to induce remission in patients with mild disease and no renal involvement, but may relapse sooner
MEPEX (Jayne, JASN 2007)	Plasmapheresis in severe life threatening disease with renal involvement→can improve renal survival and decrease risk of ESRD
MYCYC (Jones, JASN 2012)	Mycophenolate is not inferior to Cytoxan in inducing remission in new MPA/GPA with mild/mod renal disease
RITUXIVAS (Jones, NEJM 2010)	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

Rituximab-RAVE

197 participants
All rec'd 1-3g IV methylpred

Months 0-6

Steroids discontinued at 5.5 months

Primary endpoint
Month 6
BVAS =0
PRED =0

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

63

CYC
2mg/kg po daily
N = 98

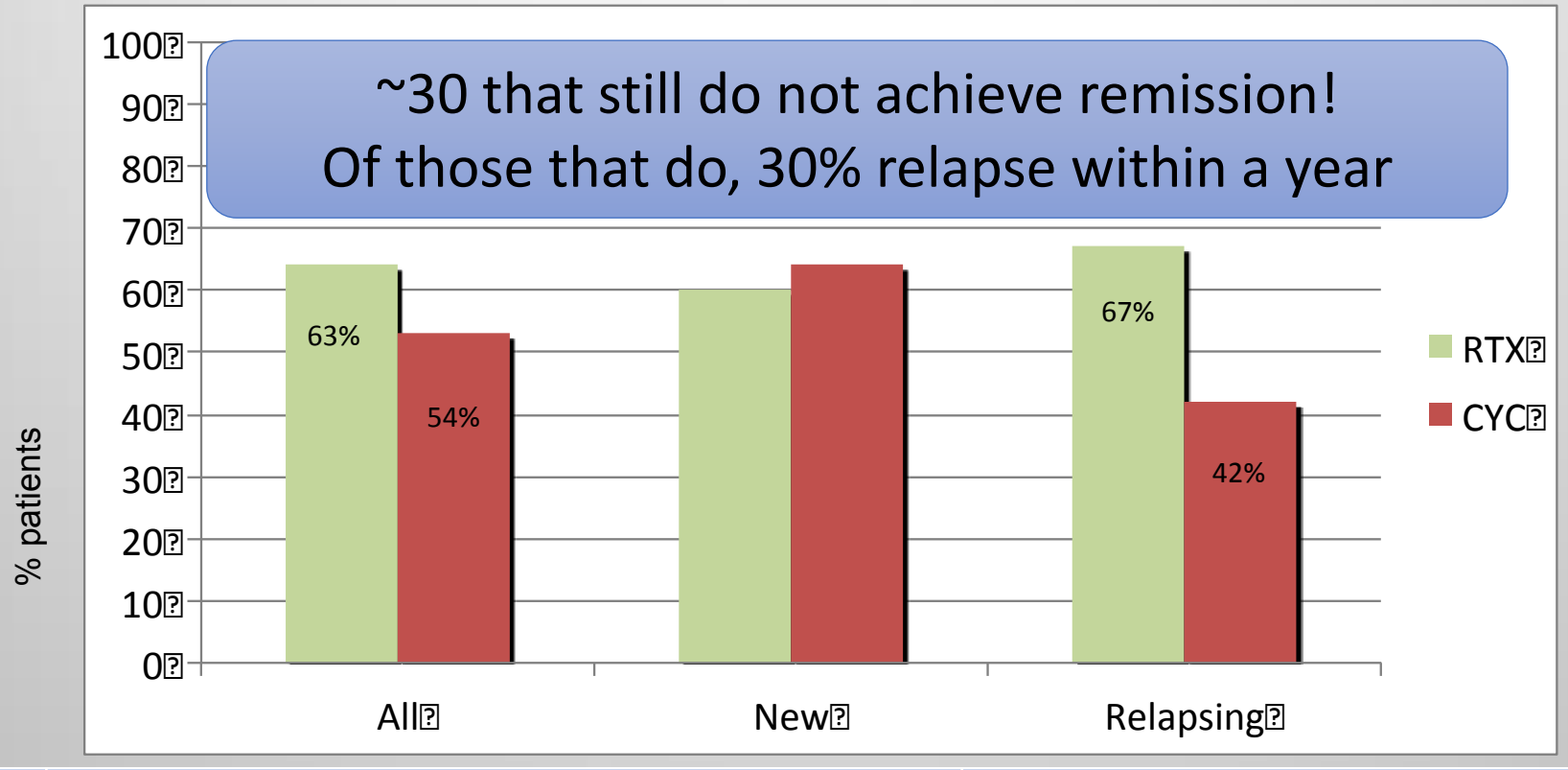
52

Maintenance

PLACEBO

AZATHIOPRINE

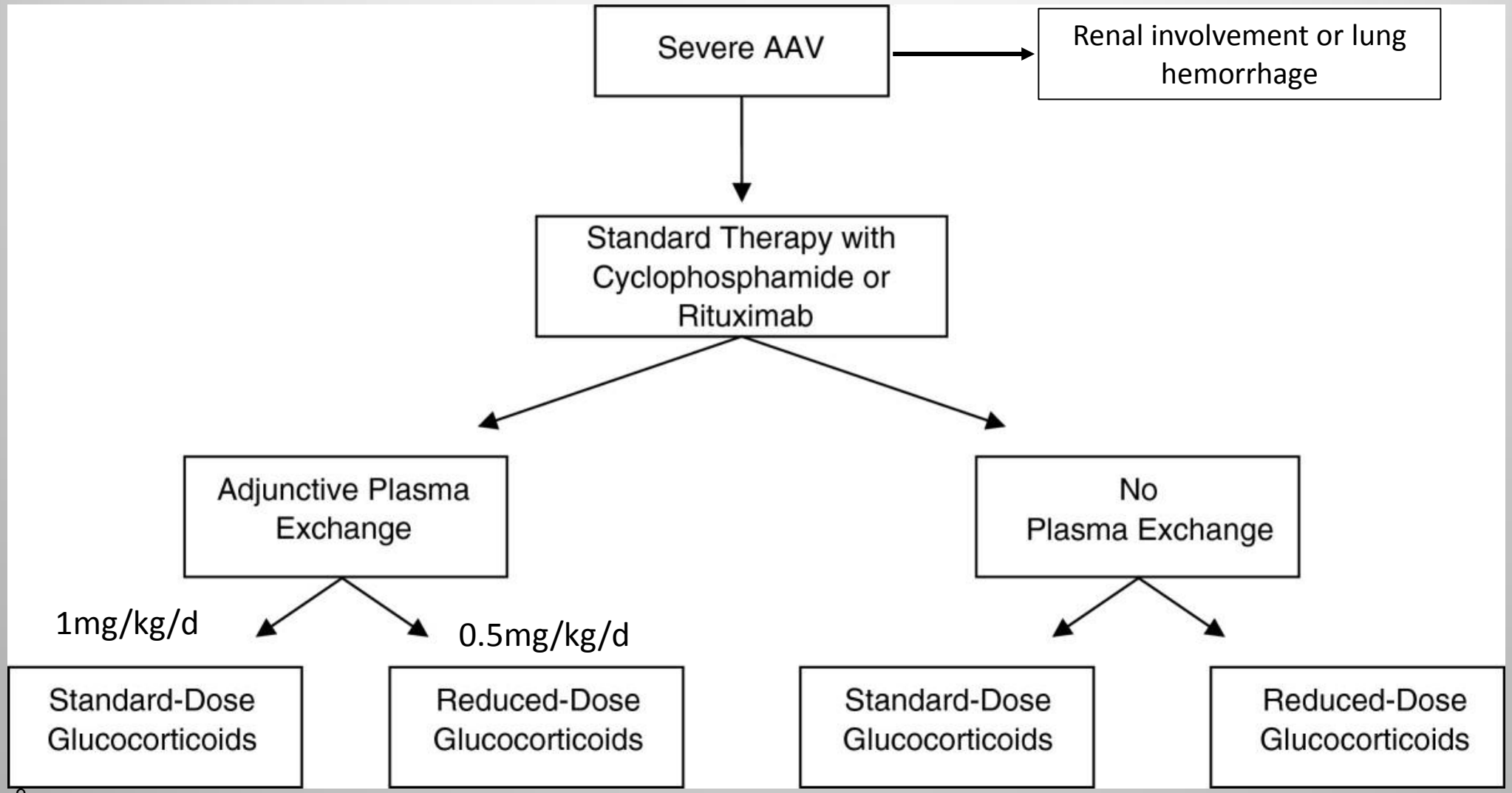
RAVE – remission rates



TRIAL	OUTCOME	CAVEATS
RAVE (Stone, NEJM 2010)	Rituximab is not inferior to oral cyclophosphamide in inducing remission in new or relapsing MPA/GPA RTX is better in patients with relapsing disease	No patients with severe renal disease or requiring intubation permitted in trial


WHERE
are we going?
6DMPTN

PEXIVAS



Walsh, PEXIVAS, Trials 2013

PEXIVAS

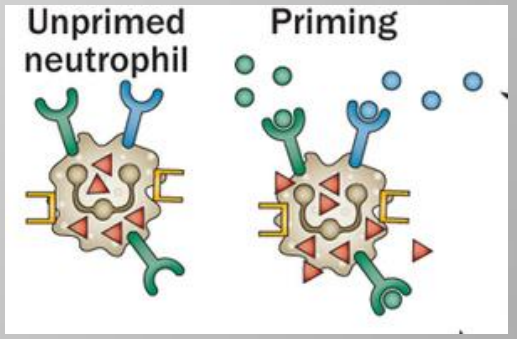
- Patients will be followed for 5-7 years
- The trial will hopefully help answer 2 important questions:

  1) Does plasmapheresis improve outcomes (mortality and ESRD) in severe AAV?

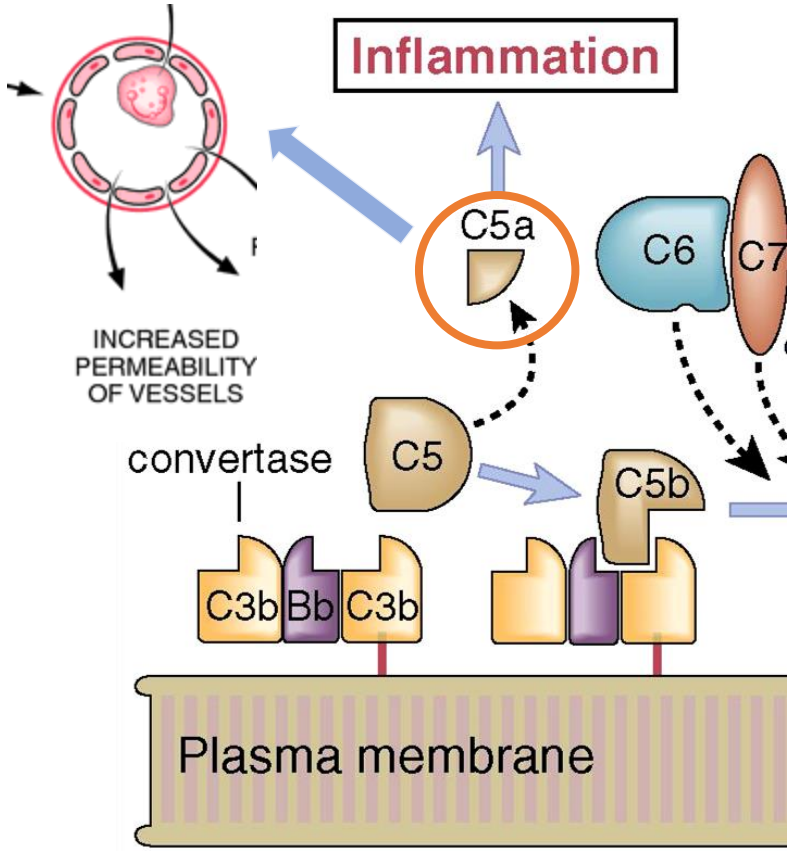
  2) Can we have similar results with use of less steroids in these patients?
- The first patient was randomized into PEXIVAS in June 2010. Goal was recruitment of 500 patients
- The trial recruited 704 patients by September 2016 and is scheduled to end in September 2017

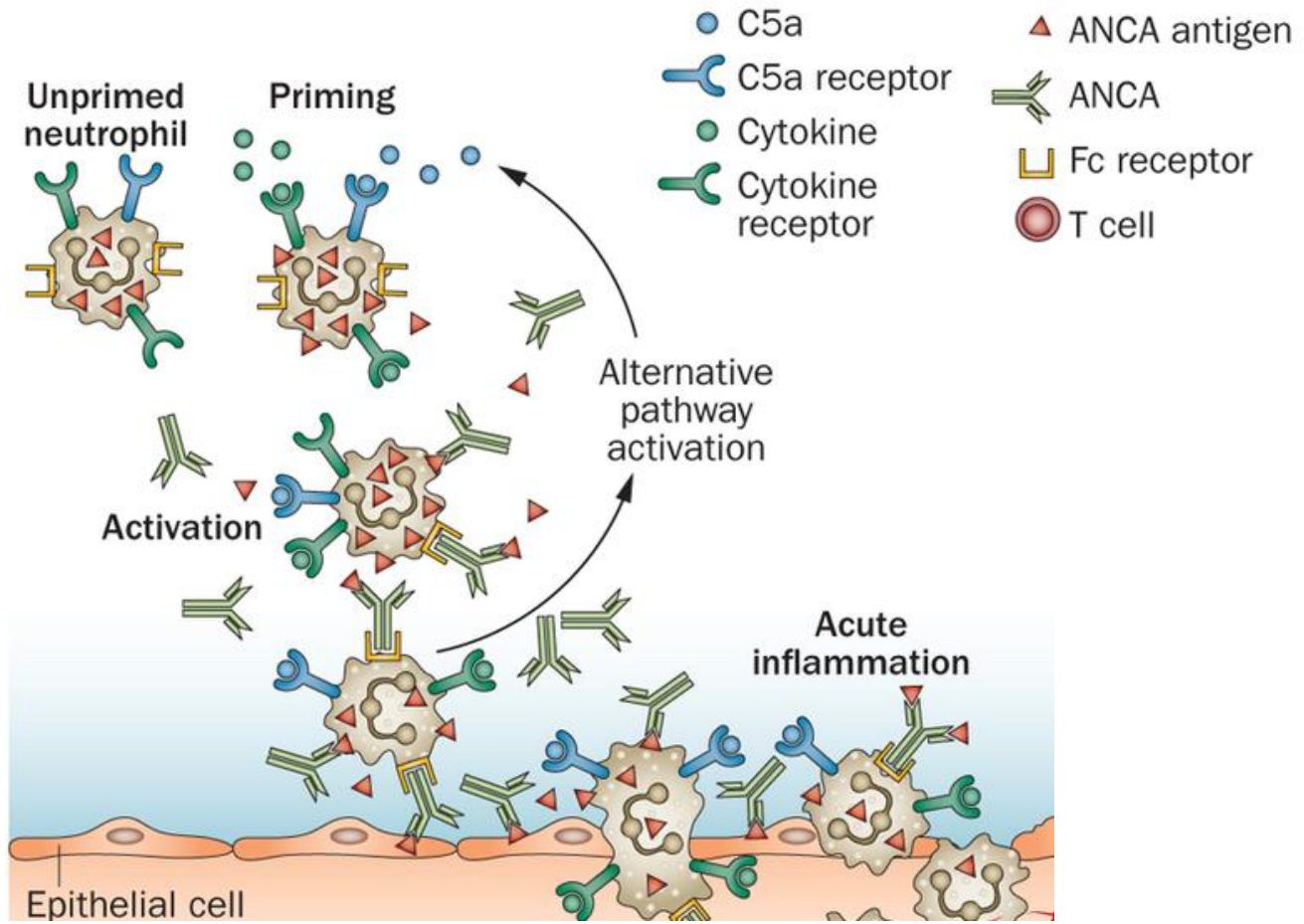
Complement: A new target

- 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 +

Primary Outcome: BVAS response at week 12	Prednisone 60mg	Prednisone 20mg + Avacopan 30mg BID	Avacopan 30mg BID
	75%	86%	81%

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 give … improvement
  - beneficial …
  - rapid redu … re)
  - reductions …
  - Better pati …
- Avacopan ap …
- Improvements in kidney function seen in al 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 Therapies

- We have mad
  inducing remi
  - Approval of Ritixumab
  - New insights into comp
  - Working towards steroi

steroid regimens

d to our induction regimens, so

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

How long should we continue aintenance treatment?

What are the options?

Should we continue low dose steroids indefinitely?

Does every flare require re-induction?

Discussion/Questions??

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