Clinical research in adult vasculitis

Calgary – October 8th, 2015

Disclosures

- Consulting and speaker fees
  - Hoffmann-La Roche
  - BMS
- Advisory boards
  - Hoffmann-La Roche
  - GSK
- Educational subventions (CanVasc)
  - Hoffmann-La Roche
  - Terumo BCT
  - Abbott Immunology
  - BMS
  - Pfizer-Amgen
  - Janssen-Cilag
  - Euroimmun

Learning Outcomes

1. To review some of the existing international research networks and groups

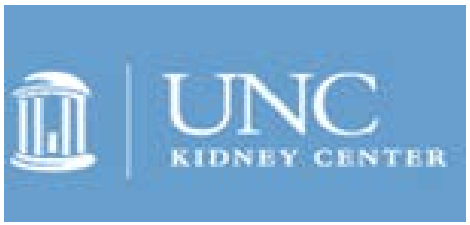
2. To review some of the ongoing studies on adult vasculitis, in which Canada participates

3. To discuss issues pertinent to various specialties (internal medicine, rheumatology, nephrology and respirology) including research collaboration in Canada

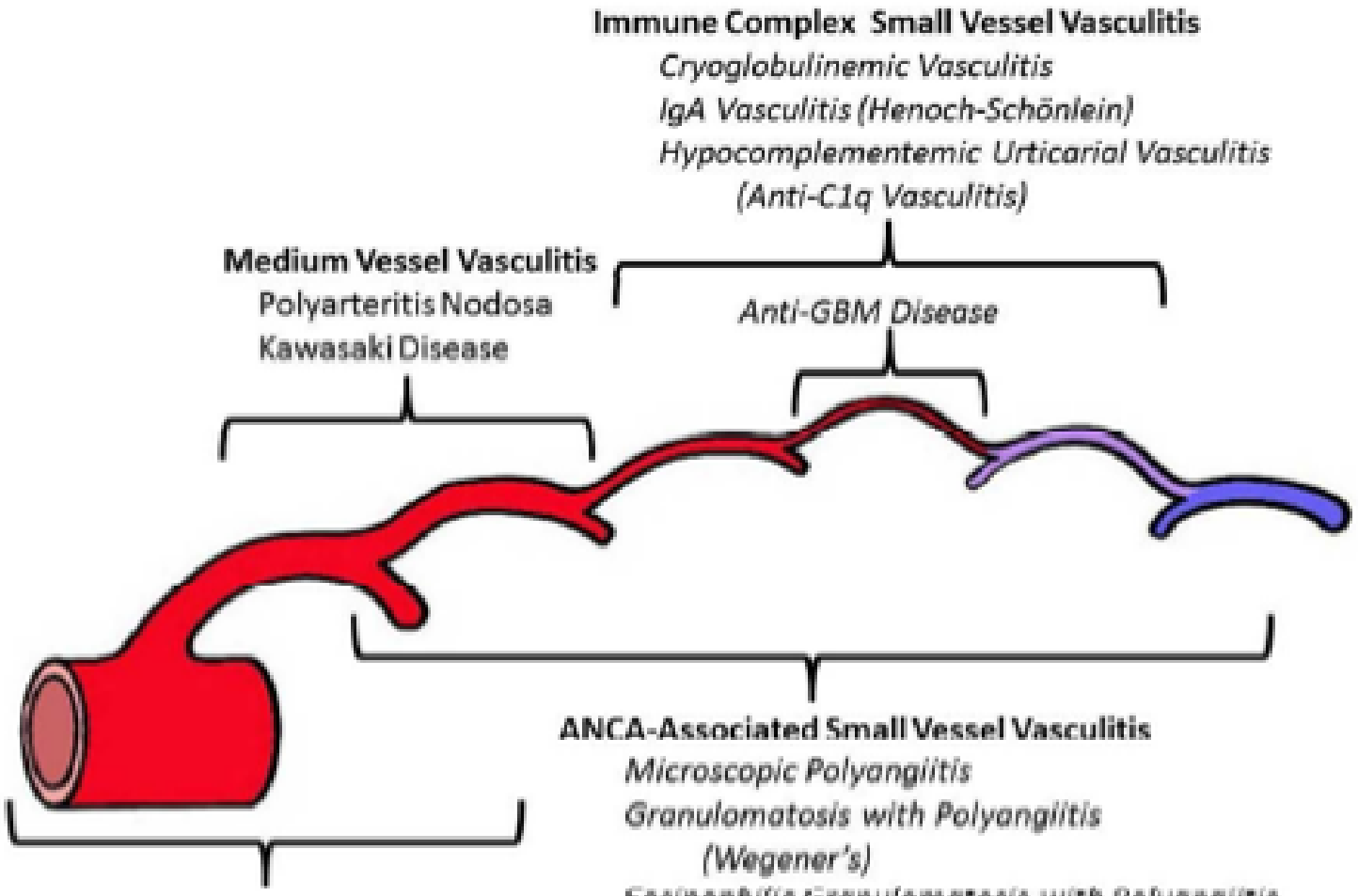
4. To be aware of CanVasc and its activities in adult vasculitis

BRAINWORKS

The International Inflammatory Brain Diseases Study

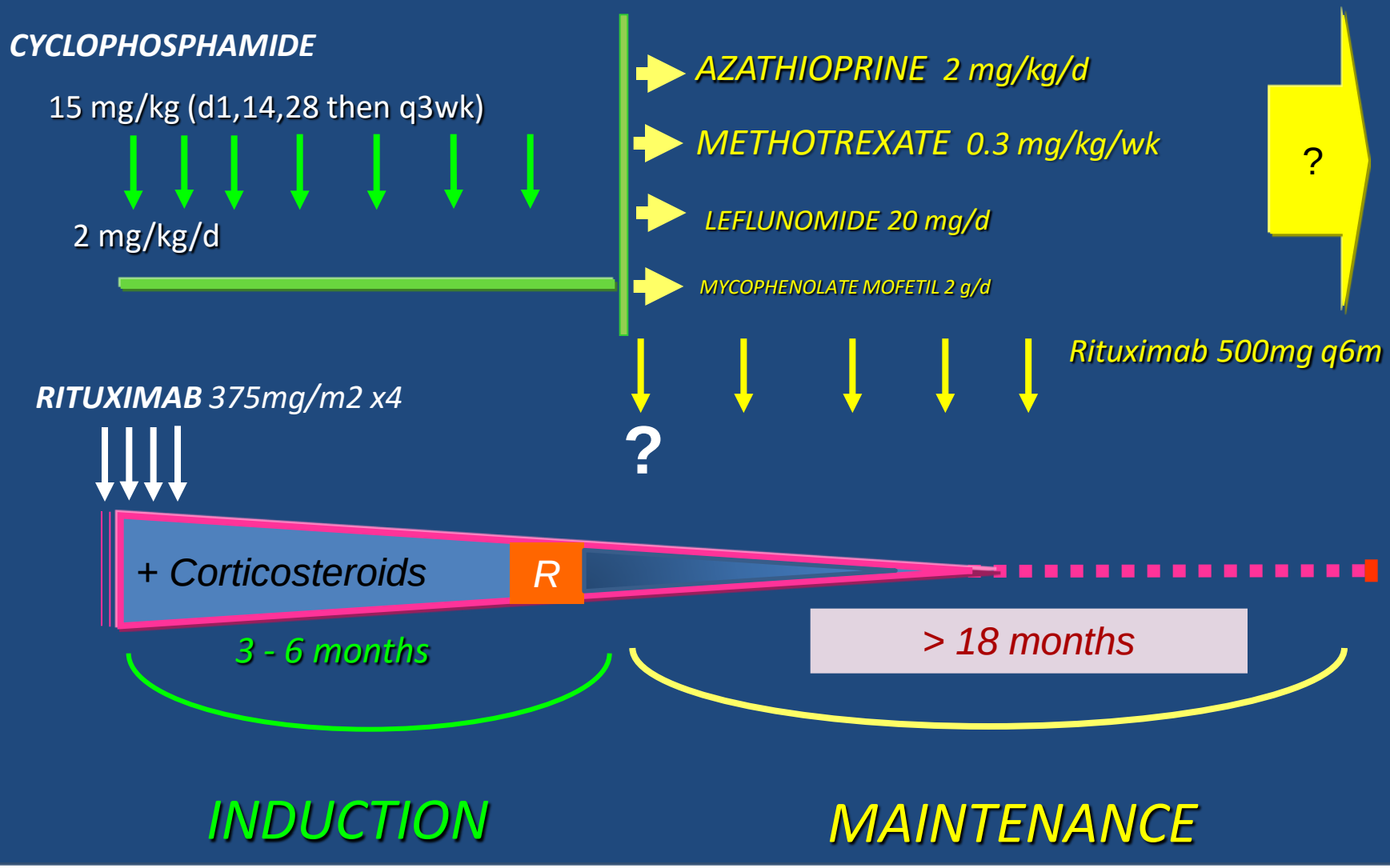


2012 revised Chapel hill nomenclature



Jennette et al. Arthritis Rheum. 2013

Treatment of severe GPA/MPA



DCVAS Study

- ACR/EULAR diagnostic and classification criteria for vasculitis
- Number of centres: 118

This project anticipates to produce the following:

- 1) A new validated set of **<u>classification</u>** criteria for the primary systemic vasculitides.
- 2) A validated set of **<u>diagnostic</u>** criteria for the primary systemic vasculitides.

DCVAS Study

- *How will the final revisions differ from the current ACR criteria?*
- The main differences will be:
- Use modern diagnostic tests (e.g. ANCA, use of diagnostic ultrasound for GCA), new tools of disease activity (BVAS) and tools measuring vasculitis damage (VDI) to further refine the criteria.
- Develop a reference standard by using clustering of clinical features, from real and hypothetical cases so that an expert panel may define a boundary around these clinical features to define each disease
- Develop diagnostic criteria which can be used in daily clinical practice. The current ACR criterion was never intended for, and does not function well for this purpose.

DCVAS Study

Latest recruitment is over 5032 patients from 129 sites

DCVAS top recruiting sites end June 2015

	Region	Country	Site	Site Name	Site Investigator	Total Patients
1	EU	SI	JJ	University Medical Centre Ljubljana	Alojzija Hočevar	327
2	EU	GB	NO	Nuffield Orthopaedic Centre Oxford	Joanna Robson	249
3	EU	GB	NU	Nottingham University Hospitals NHS Trust	Peter Lanyon	222
4	NA	CA	ON	St Joseph's Healthcare London, Ontario	Lillian Barra	199
5	EU	DE	TU	Universitätsklinikum Tübingen	Joerg Henes	177
6	OR	RU	MO	First Moscow State Medical University	Sergey Moiseev	155
7	NA	US	BU	Boston University Medical Campus	Peter Grayson	139
8	NA	CA	TO	Mount Sinai Hospital, Toronto	Christian Pagnoux	130
8	EU	DE	JE	Universitätsklinikum Jena	Thomas Neumann	130
8	EU	IT	SS	Santa Maria Nuova Hospital, Reggio Emilia	Carlo Salvarani	130
9	EU	GB	IP	Ipswich Hospital NHS Trust	Richard Watts	118
10	NA	CA	SJ	St Joseph's Healthcare Hamilton, Ontario	Nader Khalidi	117
11	EU	CH	UB	University Hospital Basel	Thomas Daikeler	114
12	EU	GB	SE	Southend University Hospital NHS Trust	Bhaskar Dasgupta	113
13	EU	DE	SH	Klinikum Bad Bramstedt	Julia Holle	111
14	EU	CZ	PR	General University Hospital, Prague	Vladimir Tesar	100
15	OR	CN	PU	Peking Union Medical College Hospital, Beijing	Xinping Tian	95
15	EU	IE	VU	St Vincent's University Hospital, Dublin	Eamonn Molloy	95
15	EU	TR	IS	Istanbul University, Istanbul Medical School	Sevil Kamali	95
16	NA	US	CS	Cedars- Sinai Medical Centre, Los Angeles	Michael Weisman	93
17	EU	GB	GR	NHS Grampian, Aberdeen, Scotland	Neil Basu	90
18	EU	TR	HU	Hacettepe University	Ömer Karadağ	85
19	EU	DE	ES	Kreiskliniken Esslingen	Bernhard Hellmich	78
19	NA	US	KU	University of Kansas Medical Centre	Jason Springer	78
20	EU	DE	BE	Immanuel Krankenhaus Berlin	Wolfgang Schmidt	77

Protocol	Accruing Site	Current Year (Aug 1st - Jul 31st)	Cumulative	Current Year (Aug 1st - Jul 31st)	Cumulative
5502 −	*9 accruing sites*	**5**	**315**	**4**	**313**
	Boston University School of Medicine (VCRC)	0	20	0	20
	Cleveland Clinic Foundation (VCRC)	0	23	0	23
	Johns Hopkins University (VCRC)	0	19	0	19
	Mayo Clinic (VCRC)	2	67	1	66
	Mount Sinai Hospital, Toronto (VCRC)	0	25	0	25
	St. Joseph's Healthcare Hamilton (VCRC)	2	126	2	126
	University of Pennsylvania (VCRC)	0	2	0	1
	University of Pittsburgh (VCRC)	0	19	0	19
	University of Utah (VCRC)	1	14	1	14
5503 +	*10 accruing sites*	**2**	**194**	**2**	**192**
5504 +	*9 accruing sites*	**0**	**101**	**0**	**99**
5505 +	*10 accruing sites*	**12**	**793**	**12**	**785**
5506 +	*9 accruing sites*	**1**	**218**	**1**	**215**
5510 +	*13 accruing sites*	**5**	**590**	**5**	**584**
5515 +	*5 accruing sites*	**0**	**26**	**0**	**26**
5522 +	*3 accruing sites*	**0**	**20**	**0**	**20**
5523 +	*11 accruing sites*	**0**	**98**	**0**	**83**
5526 +	*7 accruing sites*	**7**	**42**	**6**	**40**
5527 +	*5 accruing sites*	**2**	**8**	**2**	**8**

5502	VCRC Longitudinal Protocol for Giant Cell Arteritis
5503	VCRC Longitudinal Protocol for Takayasu's Arteritis
5504	VCRC Longitudinal Protocol for Polyarteritis Nodosa
5505	VCRC Longitudinal Protocol for Granulomatosis with Polyangiitis (...
5506	VCRC Longitudinal Protocol for Eosinophilic granulomatosis with p...
5510	VCRC Genetic Repository One-Time DNA Protocol
5515	VCRC Imaging Protocol for Magnetic Resonance and Positron Emissio...
5522	A Multi-Center, Open-label Pilot Study of Abatacept (CTLA4-lg) in...
5523	Concurrent Pilot Studies in Giant Cell Arteritis and Takayasu's A...
5526	The Assessment of Prednisone in Remission Trial (TAPIR)
5527	Abatacept (CTLA4-Ig) for the Treatment of Relapsing, Non Severe, ...
5531	Reproductive Health in Men and Women with Vasculitis
5533	Illness Perception, Fatigue, and Function in Systemic Vasculitis ...
5534	Educational Needs of Patients with Systemic Vasculitis- an Intern...
5535	VCRC Patient Contact Registry Patient-Reported Data Validation

5503 +	*10 accruing sites*	**2**	**194**	**2**	**192**
5504 +	*9 accruing sites*	**0**	**101**	**0**	**99**
5505 −	*10 accruing sites*	**12**	**793**	**12**	**785**
	Boston University School of Medicine (VCRC)	0	78	0	77
	Cleveland Clinic Foundation (VCRC)	0	130	0	129
	Johns Hopkins University (VCRC)	0	81	0	81
	Mayo Clinic (VCRC)	3	117	3	116
	Mount Sinai Hospital, Toronto (VCRC)	0	155	0	153
	St. Joseph's Healthcare Hamilton (VCRC)	8	125	8	124
	University of Pennsylvania (VCRC)	0	30	0	30
	University of Pittsburgh (VCRC)	0	42	0	40
	University of Utah (VCRC)	0	34	0	34
	VCRC Lab (VCRC)	1	1	1	1
5506 −	*9 accruing sites*	**1**	**218**	**1**	**215**
	Boston University School of Medicine (VCRC)	0	30	0	28
	Cleveland Clinic Foundation (VCRC)	0	24	0	24
	Johns Hopkins University (VCRC)	0	26	0	26
	Mayo Clinic (VCRC)	0	20	0	20
	Mount Sinai Hospital, Toronto (VCRC)	1	53	1	52
	St. Joseph's Healthcare Hamilton (VCRC)	0	28	0	28
	University of Pennsylvania (VCRC)	0	14	0	14
	University of Pittsburgh (VCRC)	0	10	0	10
	University of Utah (VCRC)	0	13	0	13
5510 +	*13 accruing sites*	**5**	**590**	**5**	**584**
5515 +	*5 accruing sites*	**0**	**26**	**0**	**26**
5522 +	*3 accruing sites*	**0**	**20**	**0**	**20**
5523 +	*11 accruing sites*	**0**	**98**	**0**	**83**
5526 +	*7 accruing sites*	**7**	**42**	**6**	**40**
5527 +	*5 accruing sites*	**2**	**8**	**2**	**8**
5531	Contact Registry Protocol (Online accrual)	**0**	**467**	**0**	**467**
5533	Contact Registry Protocol (Online accrual)	**0**	**707**	**0**	**707**

5505	VCRC Longitudinal Protocol for Granulomatosis with Polyangiitis (...
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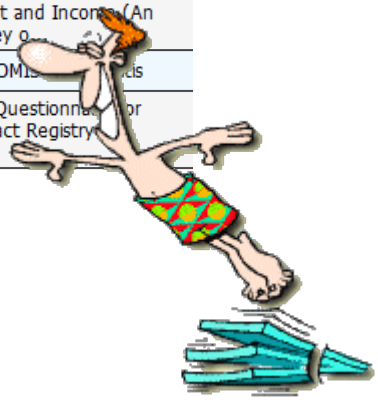
5535	VCRC Patient Contact Registry Patient-Reported Data Validation St...
5536	Impact of Vasculitis on Employment and Incom[illegible] (An online survey o...
5541	PCORI - PROMIS[illegible]tis
5599	Diagnostic Questionnai[illegible]or VCRC Contact Registry Participants



VCRC patient registry

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

> 2,000

V-PPRN Research Studies

The goal of the V-PPRN research program is to conduct high-quality studies that will improve the care and the health of patients with vasculitis by exploring research questions that matter most to patients and advance medical knowledge about vasculitis.

The V-PPRN is currently conducting the following studies in partnership with the Vasculitis Clinical Research Consortium. These studies seek to address research questions that are important to both patients and researchers.

VascWork Study

Although much progress has been made towards finding better medical therapies to treat vasculitis, patients with vasculitis often must manage substantial disease and treatment burdens. Patients with systemic vasculitis may have high rates of work disability and significant loss of personal income from employment. This study will ask questions about:

- **Employment status** (Do patients have to take a prolonged sick leave?)
- **Work productivity** (How many patients have to adjust their work because of the physical demands of the job?)
- **Income** (How many patients have a loss of income following the diagnosis of their disease?)

Learn more about this study >

The ANCA Vasculitis Questionnaire (AAV-PRO©)

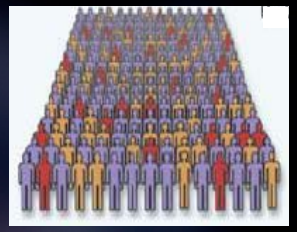
We are developing and validating a questionnaire to assess quality of life in patients with ANCA-associated vasculitis (AAV). Patients with AAV have inflammation in the small blood vessels leading to involvement of a range of organs, for

Closing the net on GPA genes

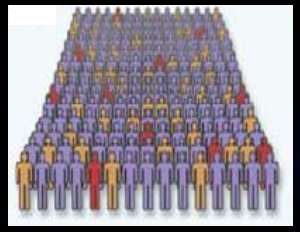
Stage 1

Toronto-based cohort

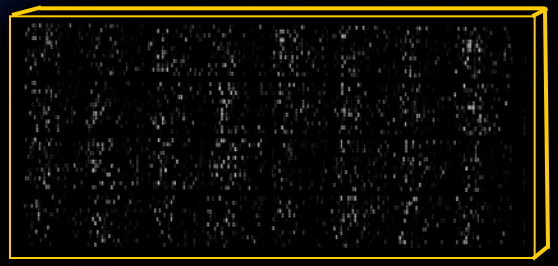
492 Cases



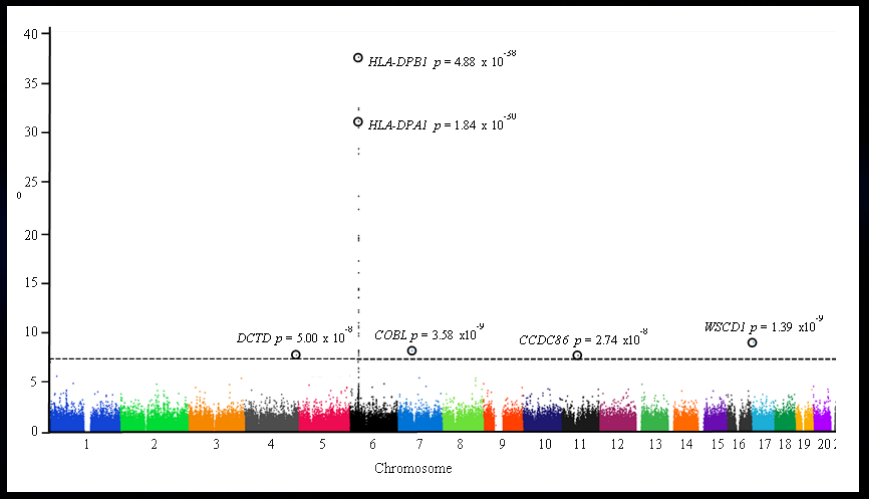
1503 Controls



370,000 markers



5 “hits” at $p < 5x10^{-8}$



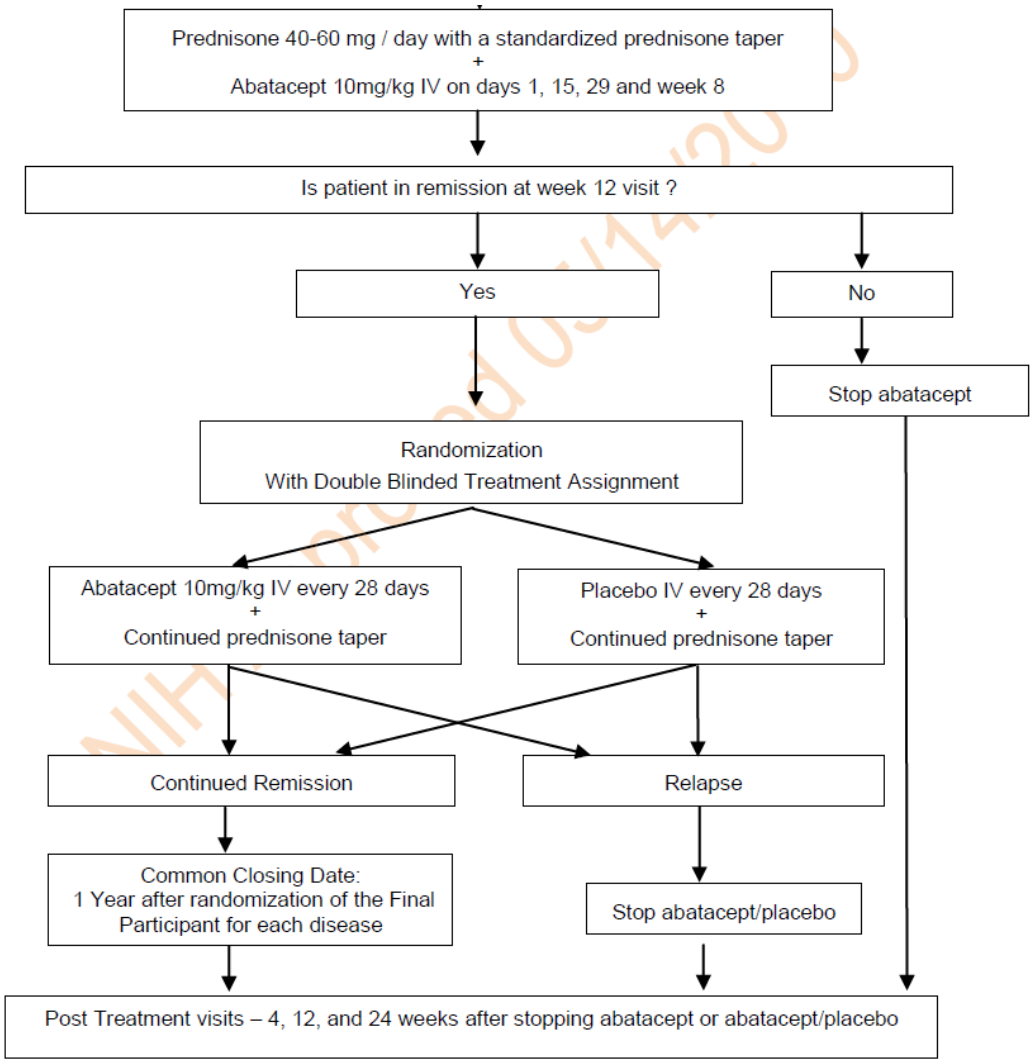
Get enrolled in a study…

Active GCA	GiACTA (<6 wks CS)
GCA	Gevokizumab
Severe GPA/MPA with lung or kidney	PEXIVAS (<2 wks CS)
Active GPA/MPA (not too severe)	CLASSIC
New GPA/MPA entering remission	BREVAS (<6 wks remission)
GPA at 6-12 remission on CS 6-10mg	TAPIR
Relapsing limited GPA	ABROGATE
Relapsing severe GPA/MPA	RITAZAREM (at relapse)
Refractory/relapsing EGPA	**MIRRA**
All	Genetic/cytoflux MSH
	VCRC (any time)
	DCVAS (<2 years)

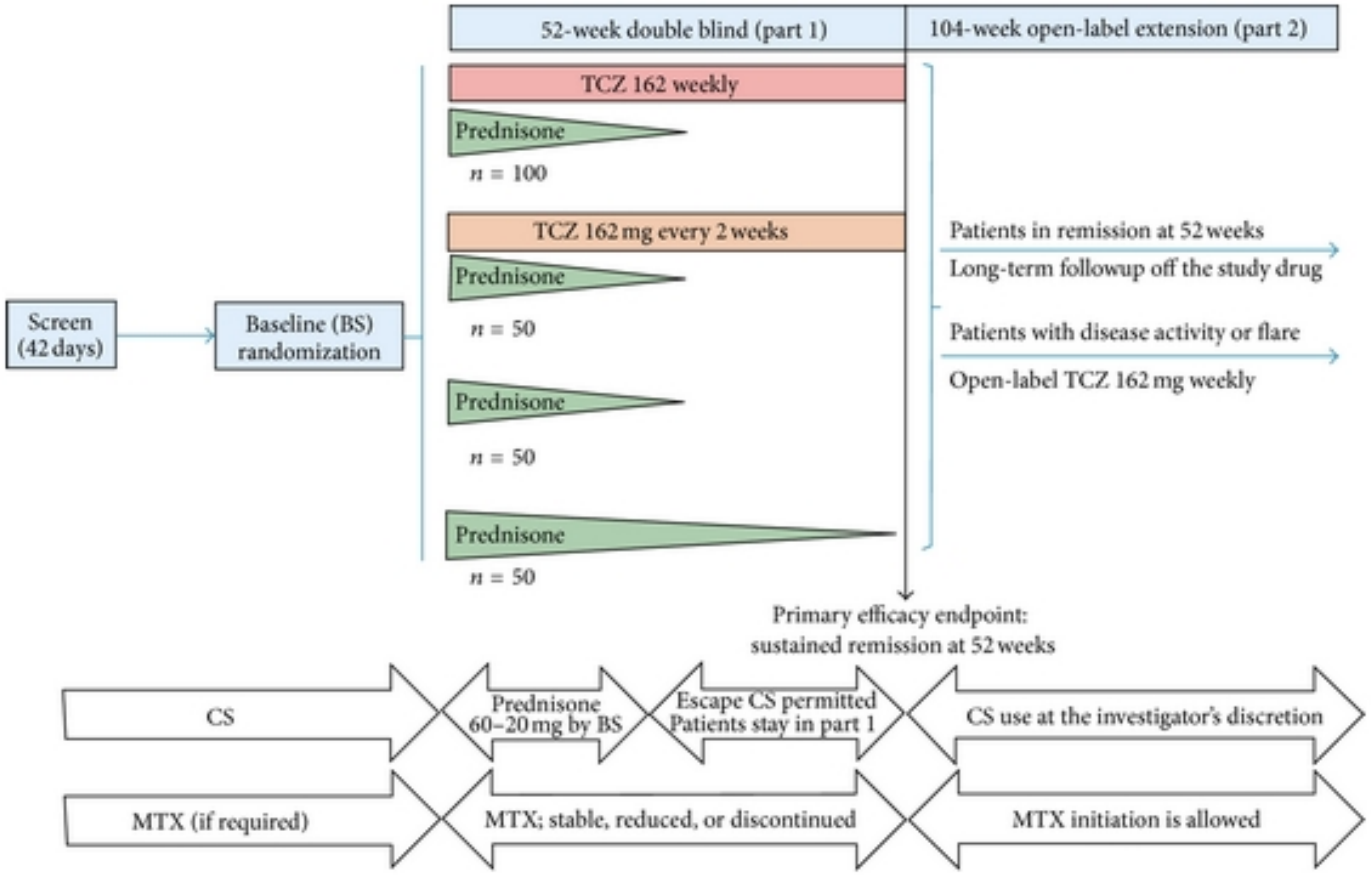
AGATA LVV

- VCRC 5523
- CTLA4-Ig / abatacept

- 15 Hamilton
- 11 Toronto



GiACTA – Giant Cell Arteritis and TCZ



Get enrolled in a study…

Active GCA	GiACTA (<6 wks CS)
GCA	Gevokizumab
Severe GPA/MPA with lung or kidney	PEXIVAS (<2 wks CS)
Active GPA/MPA (not too severe)	CLASSIC
New GPA/MPA entering remission	BREVAS (<6 wks remission)
GPA at 6-12 remission on CS 6-10mg	TAPIR
Relapsing limited GPA	ABROGATE
Relapsing severe GPA/MPA	RITAZAREM (at relapse)
Refractory/relapsing EGPA	**MIRRA**
All	Genetic/cytoflux MSH
	VCRC (any time)
	DCVAS (<2 years)

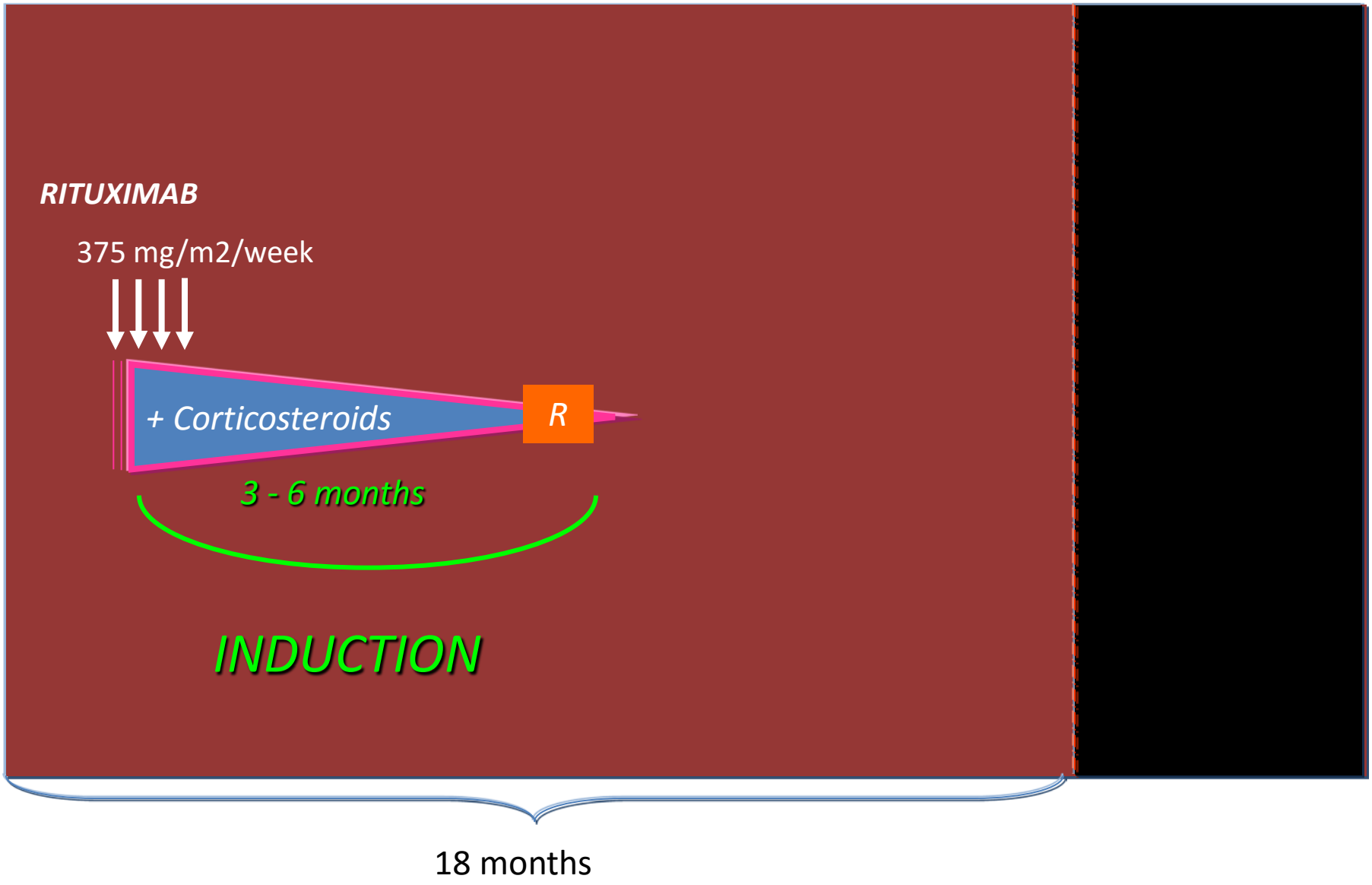
Treatment of severe GPA/MPA

CYCLOPHOSPHAMIDE

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

2 mg/kg/d

INDUCTION


RITUXIMAB
375 mg/m2/week
+ Corticosteroids
R
3 - 6 months
INDUCTION
18 months

PEXIVAS

a RCT of plasma exchange and glucocorticoid dosing in ANCA associated vasculitis

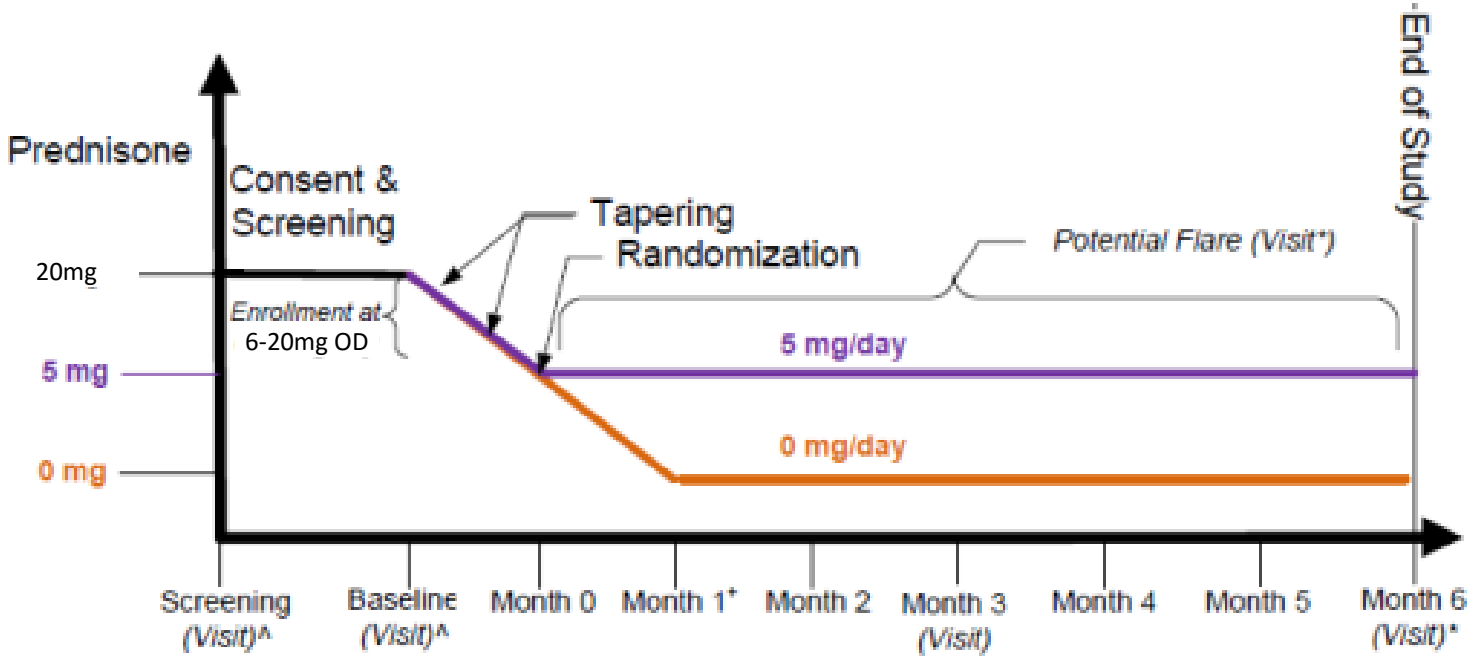
On behalf of the PEXIVAS Trial Group

VASCULITIS CLINICAL RESEARCH CONSORTIUM

TAPIR

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



^The Screening and Baseline visits may be combined into 1 visit
*Visit will take place either at the first incidence of a flare or at Month 6
+At month 1, Coordinator will call subject to confirm prednisone dose

60 patients

Primary hypothesis is a difference of ≥30% in the relapse rate.

TAPIR

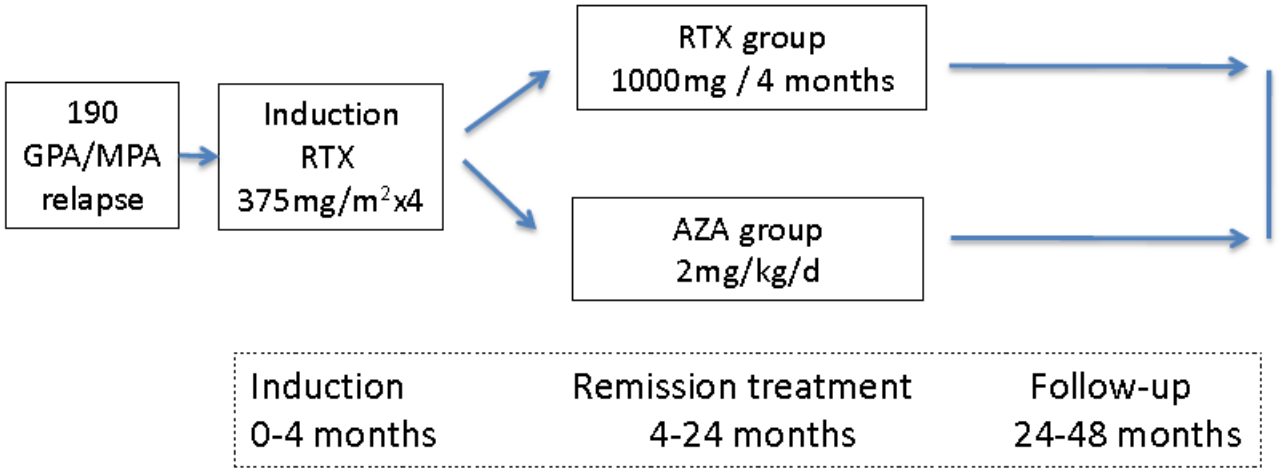
Protocol	Accruing Site	Current Year (Aug 1st - Jul 31st)	Cumulative	Current Year (Aug 1st - Jul 31st)	Cumulative
5526 −	*7 accruing sites*	**7**	**42**	**6**	**40**
	Cleveland Clinic Foundation (VCRC)	1	4	1	4
	Mayo Clinic (VCRC)	0	8	0	8
	Mount Sinai Hospital, Toronto (VCRC)	3	14	3	14
	St. Joseph's Healthcare Hamilton (VCRC)	2	5	2	5
	University of Pennsylvania (VCRC)	0	6	0	5
	University of Pittsburgh (VCRC)	0	1	0	1
	University of Utah (VCRC)	1	4	0	3

VASCULITIS CLINICAL RESEARCH CONSORTIUM

+ **Patient-centric approach**…

RITAZAREM

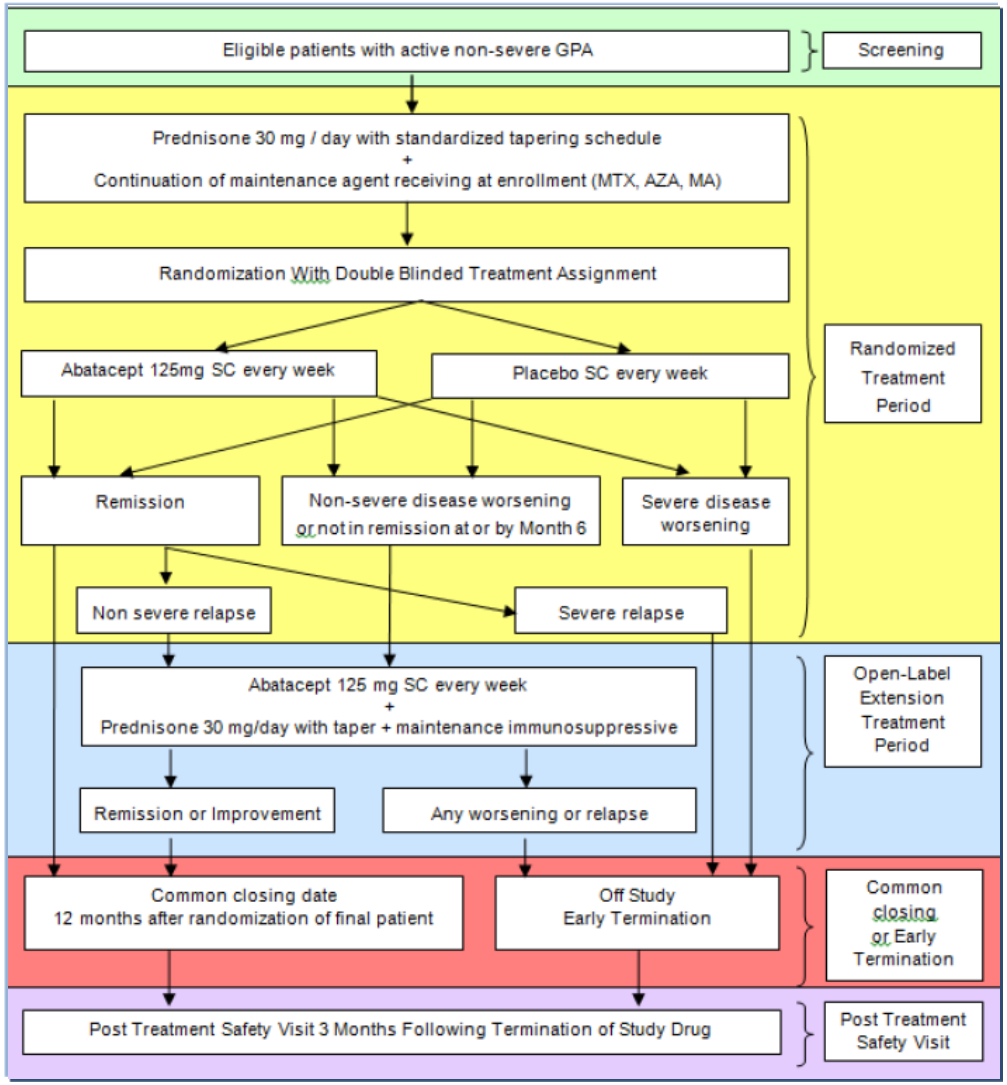
rituximab (RTX) or azathioprine (AZA) for remission after RTX induction



EUVAS VASCULITIS CLINICAL RESEARCH CONSORTIUM Arthritis Research UK Providing answers today and tomorrow NIAMS National Institute of Arthritis and Musculoskeletal and Skin Diseases

"These won't cure your allergy, but they'll send it a message."

ABROGATE



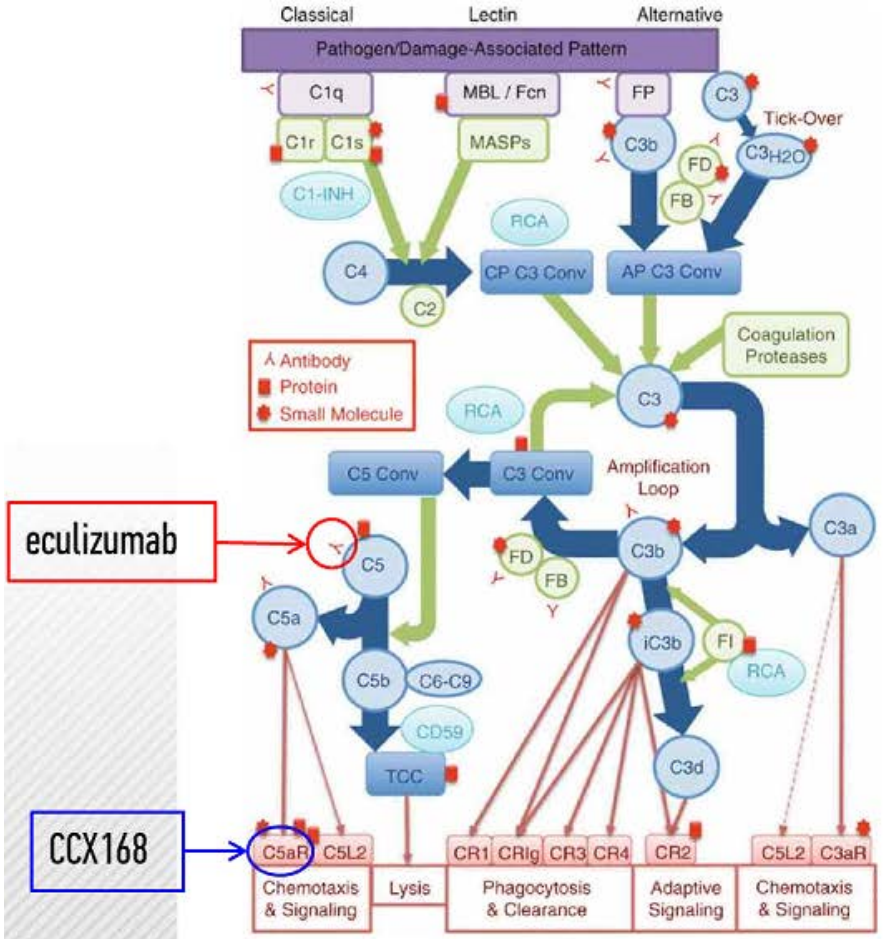
Relapsing non-severe GPA within <28 days (modified ACR criteria):

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**

Complement Cascade and C5aR



- Complement cascade comprised by over 30 proteins
- Can be activated by three distinct pathways
- All pathways merge to form C3a, C5a, C3b and C5b-9
- Eculizumab (Soliris®) is an anti-C5 antibody
  - IV, expensive, risk of *Neisseria* infection (C5b-9 formation is blocked)
- CCX168 is a C5aR inhibitor
  - Oral, no risk of *Neisseria* infection

ChemoCentryx

CCX168 Phase 2 Clinical Trial

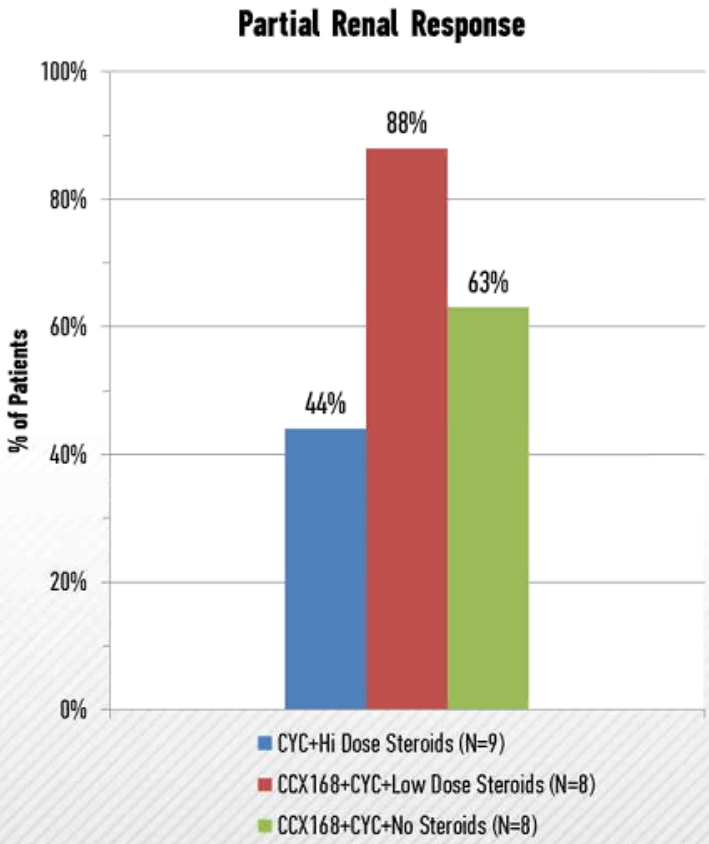
A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Renal Vasculitis on Background Cyclophosphamide Treatment

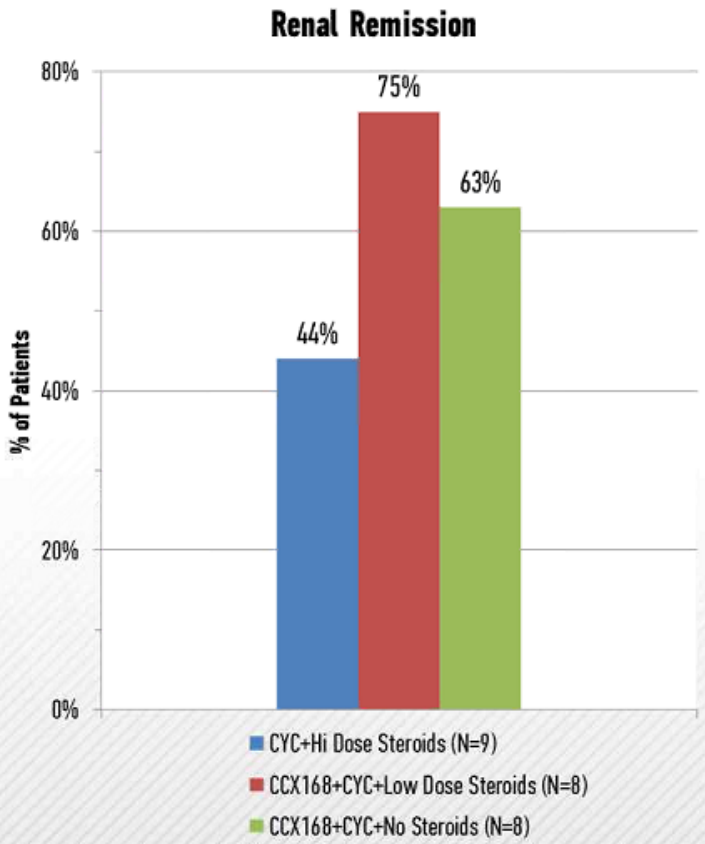
Three groups:

1. Control: Cyclophosphamide + High Dose Steroids
   - Good response but high risk (cancer, infections, infertility)
2. CCX168 + Cyclophosphamide + Low Dose Steroids
   - Tested in Step 1 of the current trial
3. CCX168 + Cyclophosphamide + NO Steroids
   - Tested in Step 2 of the current trial

ChemoCentryx

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;

ChemoCentryx

Next step = A RCT in europe and USA-canada

Naïve or relapsing ANCA+ GPA/MPA/RLD, not too severe (1 “major” item, or ≥3 other items, or ≥2 renal items on the BVAS v.3; eGFR ≥ 20 mL per minute; no severe AH, Sat O2 >88%)

Up to approximately 45 subjects will be stratified 1:1:1

Group A: CCX168 10 mg BID for 12 weeks + IV CYC-AZA/ritux + CS

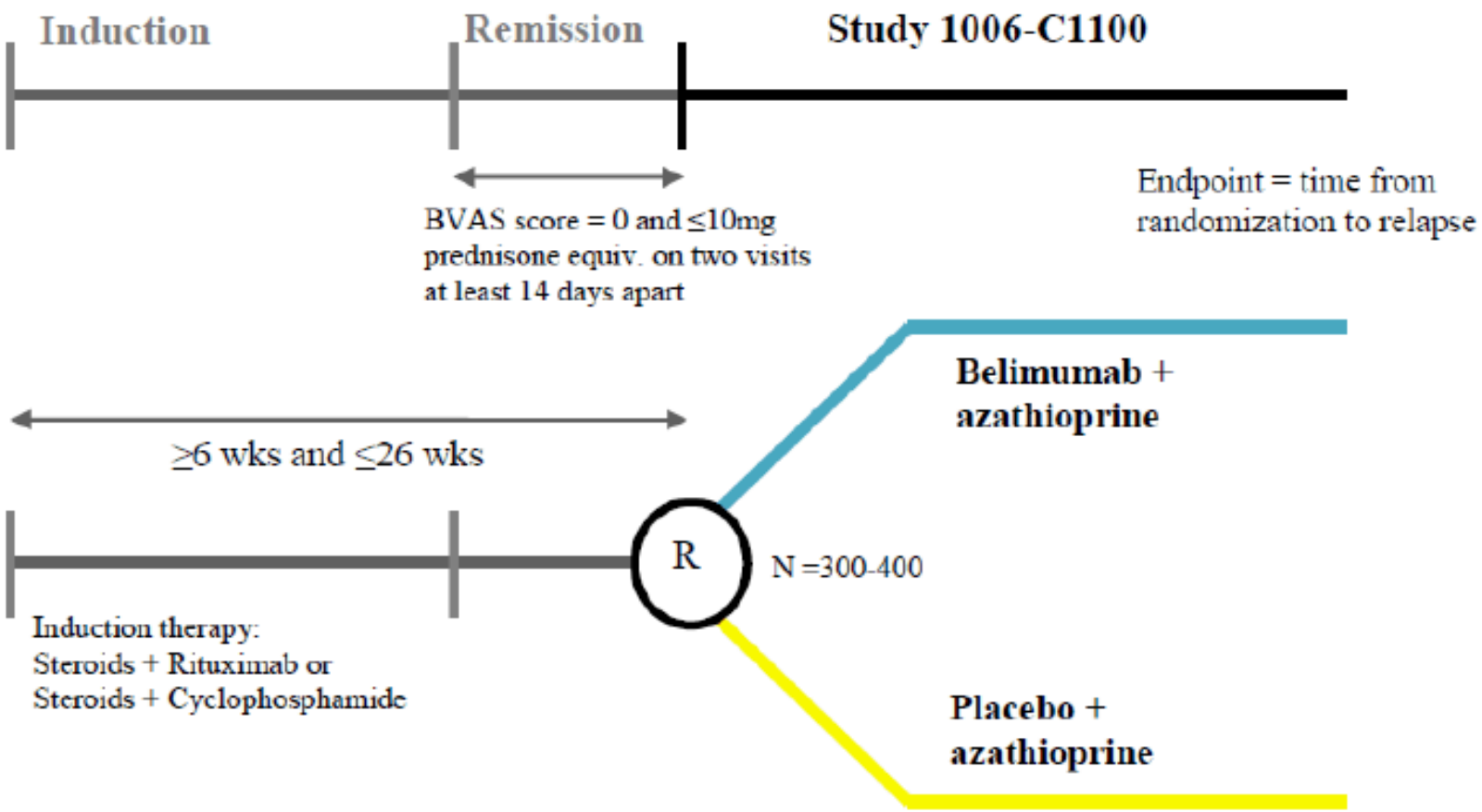
Group B: CCX168 30 mg BID for 12 weeks + IV CYC-AZA/ritux + CS

Group C: Placebo BID for 12 weeks + IV CYC/ritux + CS

End point at week 12 (with follow-up until week 24)

ChemoCentryx

BREVAS



Human Genome Sciences *and* GSK

Targeted Rx / asthma / EGPA

- Anti-IL4:
  - nebulized IL-4R altrakincept?
  - pascolizumab?
  - pitakinra (anti-IL-4Rα, IL-4/IL-13)?
  - dupilumab (anti-IL-4Rα, IL-4/IL-13)?
- Anti-IL 25

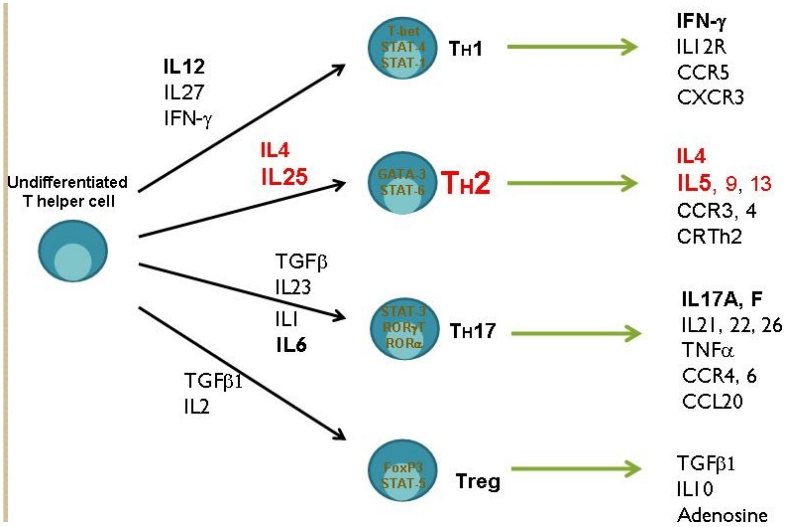
- Anti-IL 13:
  - lebrikizumab (IgG4)?
  - tralokinumab (IgG4)

- Anti-IL9

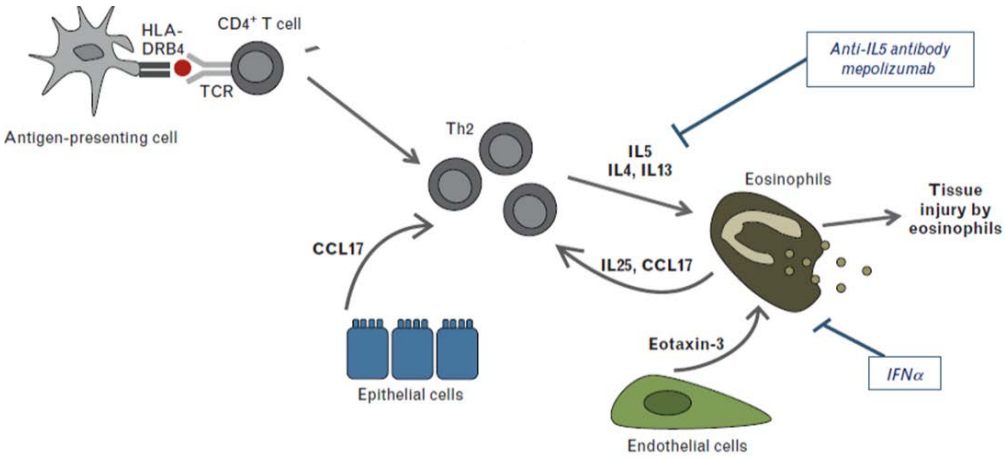
- Neutrophils, IL8/CXCR2??

- IL12/23: ustekinumab?
- Anti-IL17: ixekizumab?

- IL2 low dose (to increase Treg)?
- Anti-IL2Rα (CD25 activated T): daclizumab (IgG1)?



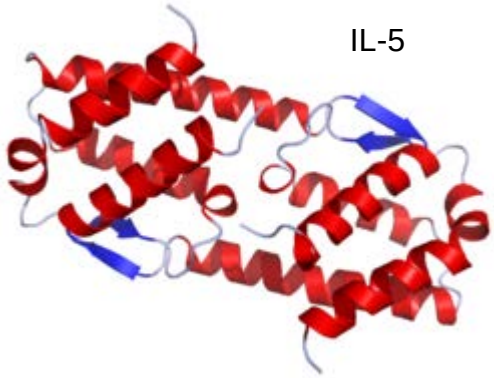
Treatment



- Anti-IL 5:
  - mepolizumab (IgG1k)
  - reslizumab (IgG4k)

- Anti-IL 5 receptor:
  - benralizumab (IgG1k anti-IL5Rα)
  - (TP1) ASM8 (antisense oligonucleotide βc)

Mepolizumab



- Humanized IgG1 kappa mAb
- Specific to human IL-5
- Blocks binding to IL-5 receptor alpha-chain on eosinophil surface

ORIGINAL ARTICLE

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

Hector G. Ortega, M.D., Sc.D., Mark C. Liu, M.D., Ian D. Pavord, D.M., Guy G. Brusselle, M.D., J. Mark FitzGerald, M.D., Alfredo Chetta, M.D., Marc Humbert, M.D., Ph.D., Lynn E. Katz, Pharm.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., and Pascal Chanez M.D., Ph.D., for the MENSA Investigators*

ABSTRACT

BACKGROUND

Some patients with severe asthma have frequent exacerbations associated with persistent eosinophilic inflammation despite continuous treatment with high-dose inhaled glucocorticoids with or without oral glucocorticoids.

METHODS

In this randomized, double-blind, double-dummy study, we assigned 576 patients with recurrent asthma exacerbations and evidence of eosinophilic inflammation despite high doses of inhaled glucocorticoids to one of three study groups. Patients were assigned to receive mepolizumab, a humanized monoclonal antibody against interleukin-5, which was administered as either a 75-mg intravenous dose or a 100-mg subcutaneous dose, or placebo every 4 weeks for 32 weeks. The primary outcome was the rate of exacerbations. Other outcomes included the forced expiratory volume in 1 second (FEV_1) and scores on the St. George's Respiratory Questionnaire (SGRQ) and the 5-item Asthma Control Questionnaire (ACQ-5). Safety was also assessed.

ORIGINAL ARTICLE

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M., for the SIRIUS Investigators*

ABSTRACT

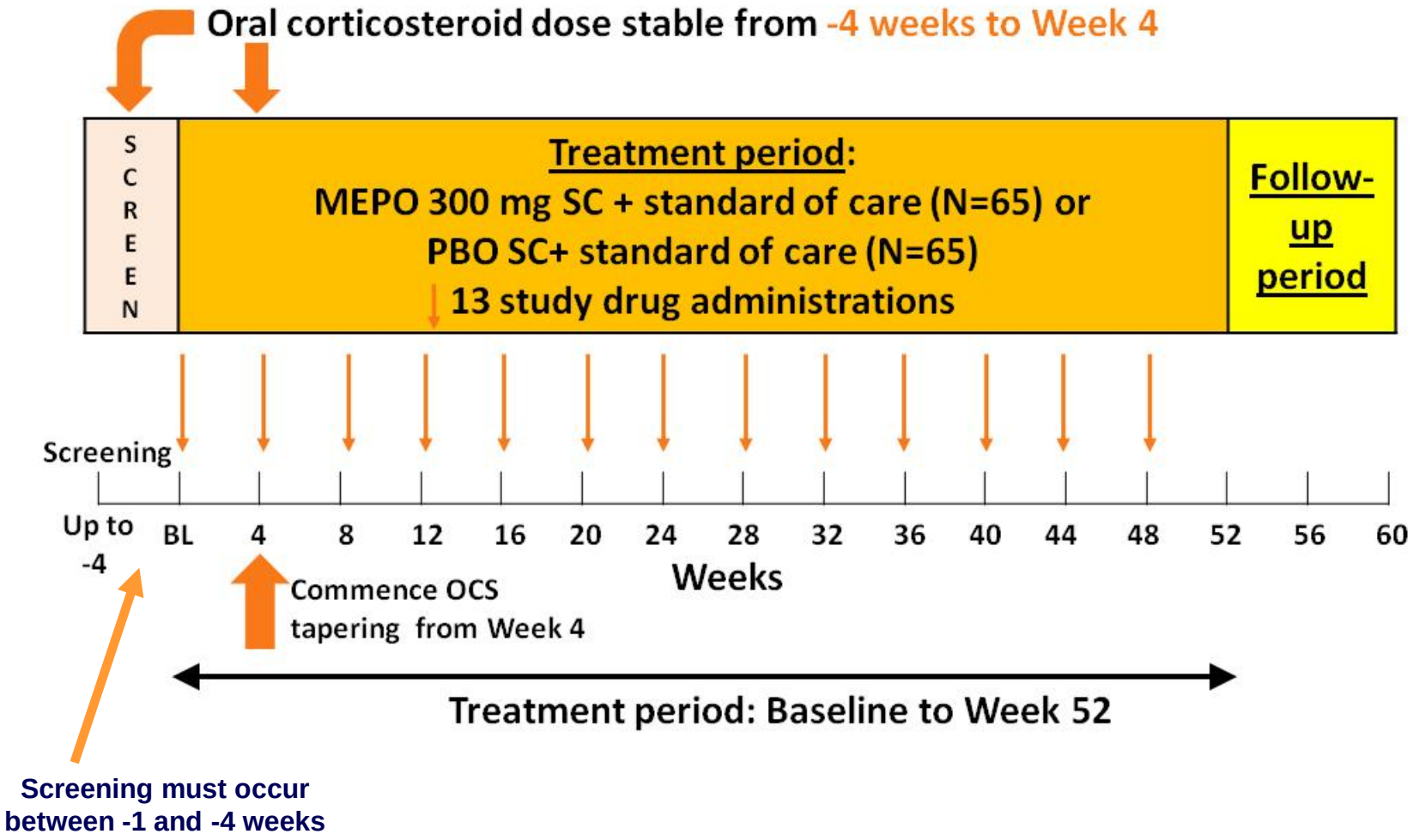
BACKGROUND

Many patients with severe asthma require regular treatment with oral glucocorticoids despite the use of high-dose inhaled therapy. However, the regular use of systemic glucocorticoids can result in serious and often irreversible adverse effects. Mepolizumab, a humanized monoclonal antibody that binds to and inactivates interleukin-5, has been shown to reduce asthma exacerbations in patients with severe eosinophilic asthma.

METHODS

In a randomized, double-blind trial involving 135 patients with severe eosinophilic asthma, we compared the glucocorticoid-sparing effect of mepolizumab (at a dose of 100 mg) with that of placebo administered subcutaneously every 4 weeks for 20 weeks. The primary outcome was the degree of reduction in the glucocorticoid dose (90 to 100% reduction, 75 to less than 90% reduction, 50 to less than 75% reduction, more

Study design



Country	Active sites	Screened (N)	Randomised (N)	Screen fail (N)
Belgium	1	2	2	0
Canada	2	3	3	0
France	5	16	11	4
Germany	5	20	17	2
Italy	4	13	12	1
Japan	2	1	0	0
Spain	1	1	0	0
UK	3	14	12	2
US	1	3	3	0
TOTAL	*24 (~80%)*	*73*	*61 (47%)*	*9*
Target	*31*		*130*	

July 2014

The CanVasc core members centers

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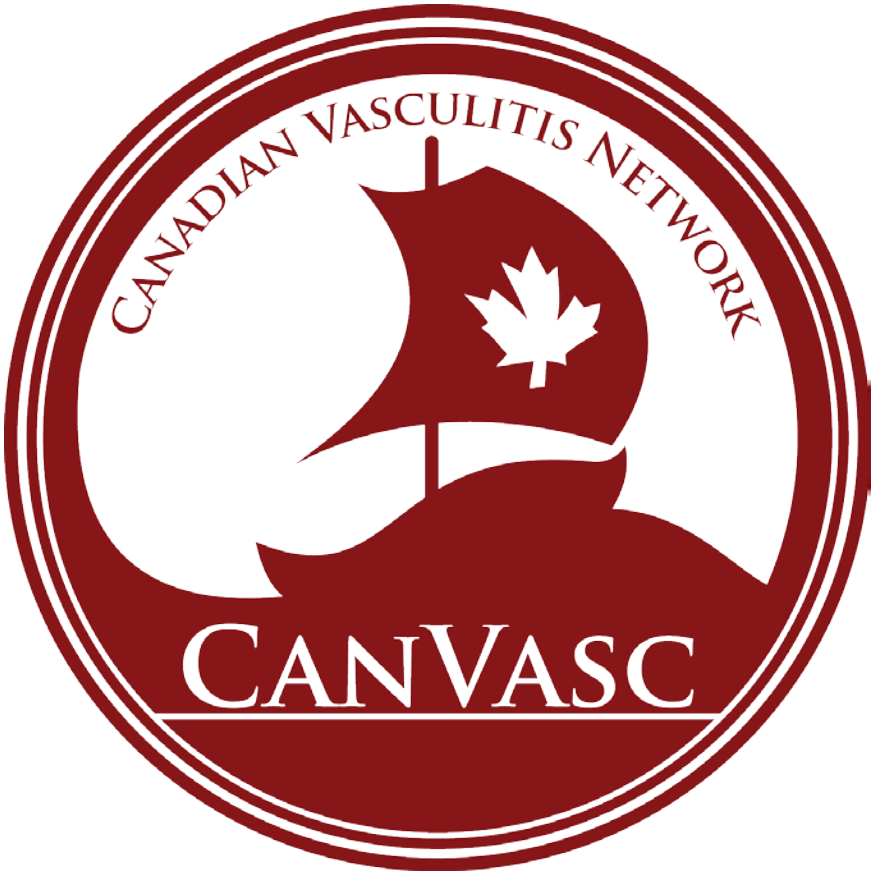
Recommendations for the management of patients with ANCA-associated vasculitis



Thank you!!!

http:/www.canvasc.ca