Vasculitis Updates

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19 November 2015

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
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  - 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).

The CanVasc website

English - French

Home | About CanVasc | Vasculitides | Ongoing studies | Meetings | Tools for physicians | Links

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, Carette 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 (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 too 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 this first recommendations for the management of ANCA-assocaited 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, DCVAS, 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

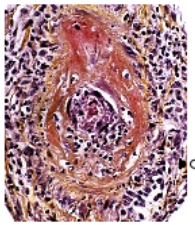
- READ the latest **CanVasc reviews of recent articles:** commented summaries of selected and important articles on vasculitis, for physicians to keep up the pace with scientific publications on vasculitis on the Vasculitis page !
  - **How the classification of vasculitides can help and impact their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

The CanVasc website

English - French

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 fibrinoid necrosis and/or 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 levamisole-tainted cocaine). According to the 1994 Chapel Hill nomneclature, **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 **Polyarteritis 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 it has a predilection for the coronary arteries.

- **Small vessel vasculitides** include several entities. The most "famous" ones are associated with the presence of antineutrophil cytoplasm 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 antiGBM antibodies in the glomeruli) and/or alveolar 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** (obliterans 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

Severe GPA/MPA with lung or kidney	PEXIVAS (<2 weeks) - website
Not too severe GPA/MPA	CLASSIC
GPA/MPA entering remission	BREVAS (<2 wks remission)
GPA on prednisone for maintenance	TAPIR (website)
Relapsing non-severe GPA	ABROGATE
Relapsing severe GPA/MPA	RITAZAREM (at relapse) - website
All	VCRC cohort (any time)
	VCRC contact registry (any time)
	DCVAS (<2 years)
PACNS	INTERSpace
	BrainWorks (for children; adults soon)

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 (tocilizumab 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 enrollement 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, EUVAS and NIH. Several centers in Canada are participating, including centers involved in CanVasc, like Hamilton, where Dr. M. Walsh (associated 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/TWH-Toronto, Montreal, Ottawa) are now also opened and have enrolled patients. At present and after almost 4 years of recruitment, more than 500patients (around 200 in Canada, just after the U.K. for the countries with the greatest numbers of patients recruited) have already been

The CanVasc website

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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

CanVasc homepage | CanVasc Forum - Index

forum.canvasc.ca/index.php

rbbb cause chest pain

msn PubMed utoronto canvasc Google News GIM Rheumatology MSH numbers Pexivas DCVAS DI-r Viewer RDCRN RITAZAREM webCV MDCalc | MDRD GFR E...

Canadian Vasculitis research network

Hello CanVasc Forum Administrator

Show unread posts since last visit.
Show new replies to your posts.
There are 2 members awaiting approval.
28 April 2015, 10:54:41

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CanVasc Forum

Forum and CanVasc Information		Unread Posts
Forum Information Information about the the forum, its content, rules etc	0 Posts 0 Topics	
CanVasc Activities and Information Information on CanVasc annual and core member meetings, teleconferences etc	1 Posts 1 Topics	**Last post** by CanVasc Forum Administrator in 2014 CanVasc annual meet... on 16 June 2014, 15:15:32
CanVasc Dropbox Link to CanVasc dropbox (including top articles, CanVasc documents for core members etc)	1 Posts 1 Topics	**Last post** by CanVasc Forum Administrator in DropBox link on 06 February 2013, 21:07:56
Material for review and guidance for member Miscellaneous material for members to review and/or to help in the administrative tasks	3 Posts 1 Topics	**Last post** by avfifima in Redcap use for database on 22 May 2014, 23:48:01

Vasculitis Information		Unread Posts
General Discussion on Vasculitis	0 Posts 0 Topics	
Difficult Cases Discussion about difficult cases (no patient ID allowed)	9 Posts 5 Topics	**Last post** by CanVasc Forum Administrator in GPA and large vessel TAK... on 28 January 2015, 15:19:52
CanVasc Consensus and Recommendations Discussion about the CanVasc recommendations for the management of vasculitis	3 Posts 2 Topics	**Last post** by CanVasc Forum Administrator in NAQ published in the Ope... on 16 April 2015, 15:11:57

New Posts No New Posts Redirect Board

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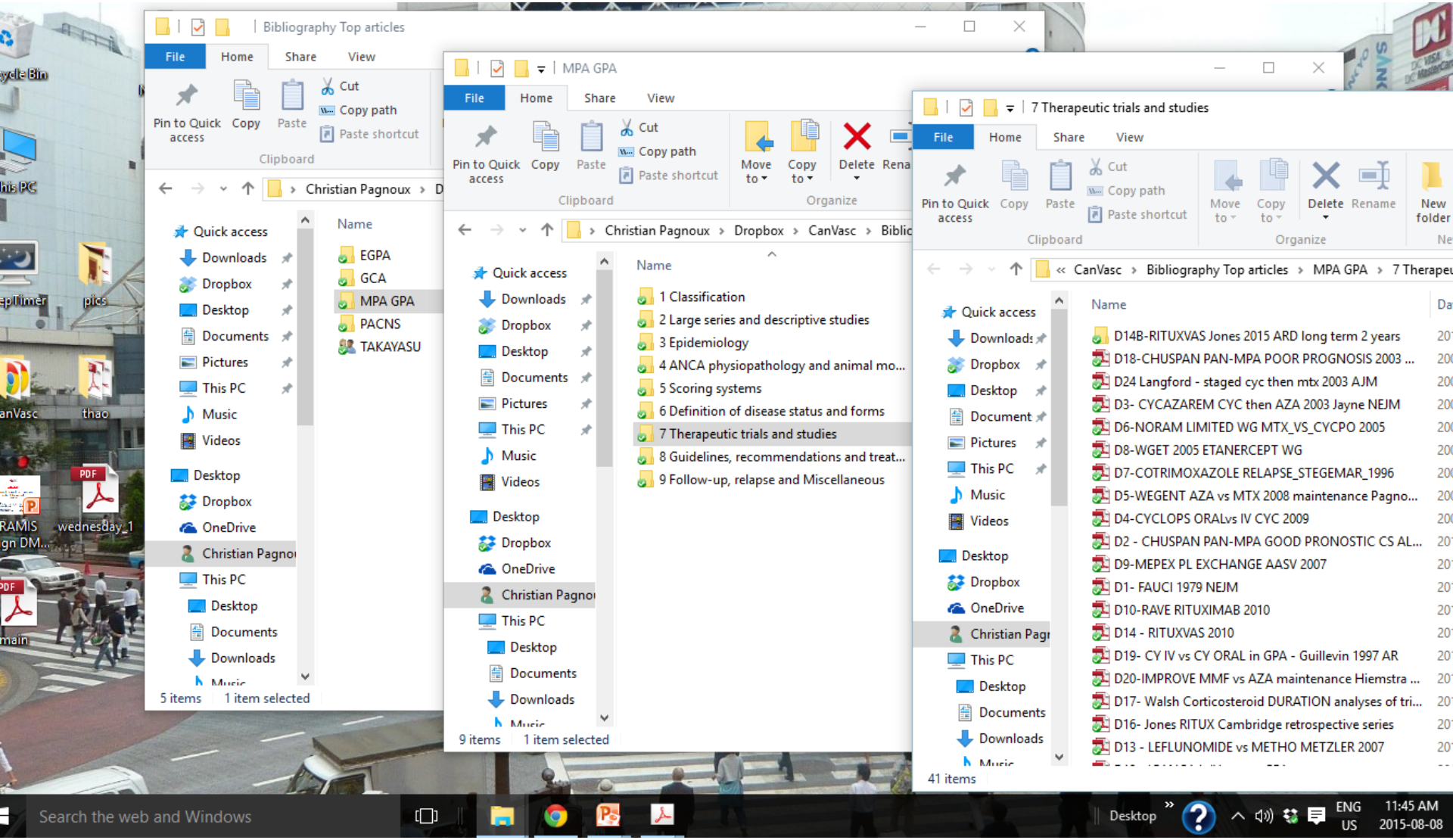
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Christian Pagnoux › Dropbox › CanVasc
Name
1 Classification
2 Large series and descriptive studies
3 Epidemiology
4 ANCA physiopathology and animal mo...
5 Scoring systems
6 Definition of disease status and forms
7 Therapeutic trials and studies
8 Guidelines, recommendations and treat...
9 Follow-up, relapse and Miscellaneous
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7 Therapeutic trials and studies
« CanVasc › Bibliography Top articles › MPA GPA › 7 Therapeu
New folder
D14B-RITUXVAS Jones 2015 ARD long term 2 years
D18-CHUSPAN PAN-MPA POOR PROGNOSIS 2003 ...
D24 Langford - staged cyc then mtx 2003 AJM
D3- CYCAZAREM CYC then AZA 2003 Jayne NEJM
D6-NORAM LIMITED WG MTX_VS_CYCPO 2005
D8-WGET 2005 ETANERCEPT WG
D7-COTRIMOXAZOLE RELAPSE_STEGEMAR_1996
D5-WEGENT AZA vs MTX 2008 maintenance Pagno...
D4-CYCLOPS ORALvs IV CYC 2009
D2 - CHUSPAN PAN-MPA GOOD PRONOSTIC CS AL...
D9-MEPEX PL EXCHANGE AASV 2007
D1- FAUCI 1979 NEJM
D10-RAVE RITUXIMAB 2010
D14 - RITUXVAS 2010
D19- CY IV vs CY ORAL in GPA - Guillevin 1997 AR
D20-IMPROVE MMF vs AZA maintenance Hiemstra ...
D17- Walsh Corticosteroid DURATION analyses of tri...
D16- Jones RITUX Cambridge retrospective series
D13 - LEFLUNOMIDE vs METHO METZLER 2007
41 items
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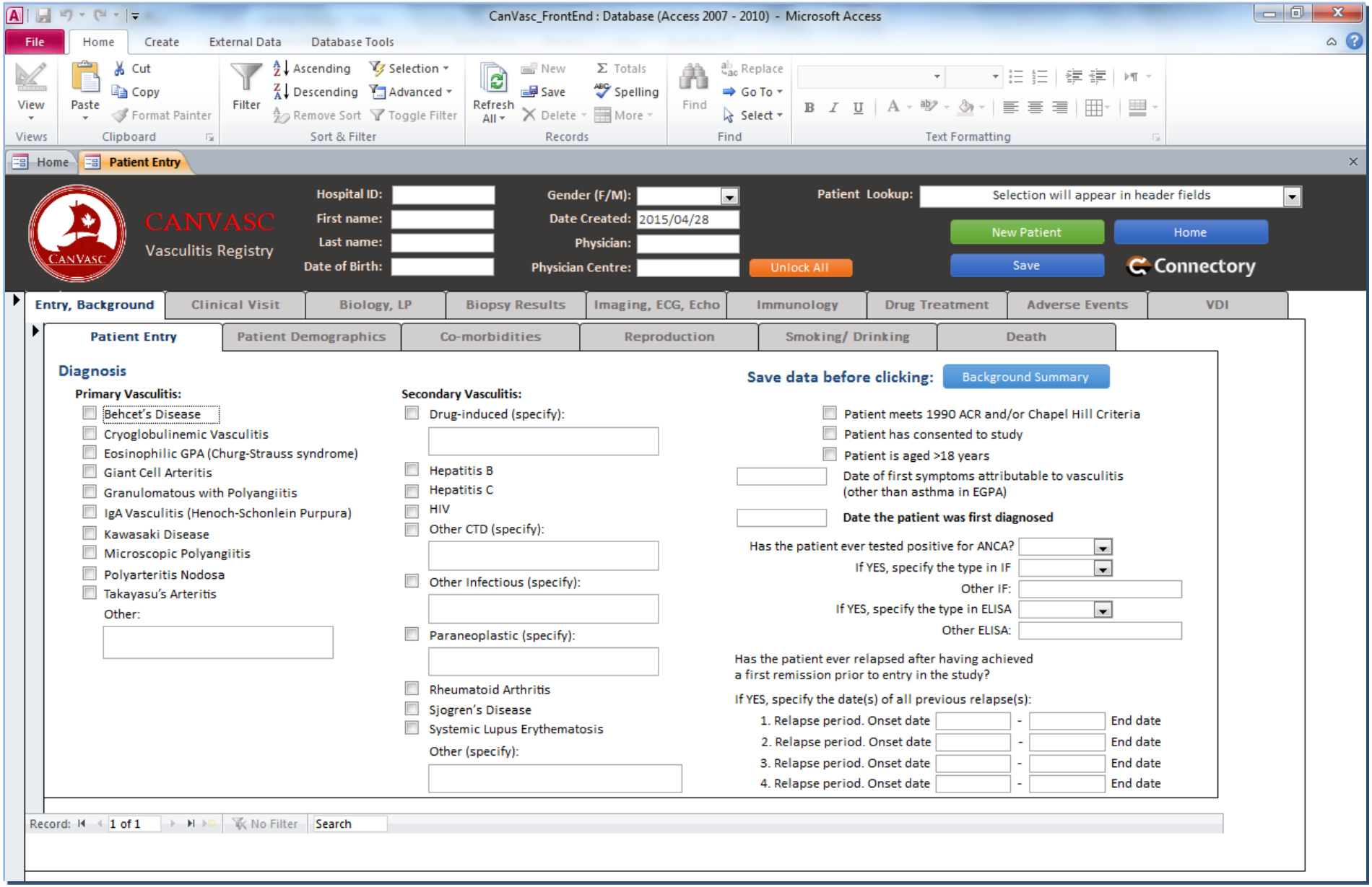
CanVasc_FrontEnd : Database (Access 2007 - 2010) - Microsoft Access
File
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External Data
Database Tools
View
Paste
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Format Painter
Filter
Ascending
Descending
Remove Sort
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Find
Text Formatting
Home
Patient Entry
CANVASC
Vasculitis Registry
Hospital ID:
First name:
Last name:
Date of Birth:
Gender (F/M):
Date Created: 2015/04/28
Physician:
Physician Centre:
Unlock All
Patient Lookup:
Selection will appear in header fields
New Patient
Home
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Connectory
Entry, Background
Clinical Visit
Biology, LP
Biopsy Results
Imaging, ECG, Echo
Immunology
Drug Treatment
Adverse Events
VDI
Patient Entry
Patient Demographics
Co-morbidities
Reproduction
Smoking/ Drinking
Death
Diagnosis
Primary Vasculitis:
Behcet's Disease
Cryoglobulinemic Vasculitis
Eosinophilic GPA (Churg-Strauss syndrome)
Giant Cell Arteritis
Granulomatous with Polyangiitis
IgA Vasculitis (Henoch-Schonlein Purpura)
Kawasaki Disease
Microscopic Polyangiitis
Polyarteritis Nodosa
Takayasu's Arteritis
Other:
Secondary Vasculitis:
Drug-induced (specify):
Hepatitis B
Hepatitis C
HIV
Other CTD (specify):
Other Infectious (specify):
Paraneoplastic (specify):
Rheumatoid Arthritis
Sjogren's Disease
Systemic Lupus Erythematosis
Other (specify):
Save data before clicking:
Background Summary
Patient meets 1990 ACR and/or Chapel Hill Criteria
Patient has consented to study
Patient is aged >18 years
Date of first symptoms attributable to vasculitis (other than asthma in EGPA)
Date the patient was first diagnosed
Has the patient ever tested positive for ANCA?
If YES, specify the type in IF
Other IF:
If YES, specify the type in ELISA
Other ELISA:
Has the patient ever relapsed after having achieved a first remission prior to entry in the study?
If YES, specify the date(s) of all previous relapse(s):
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2. Relapse period. Onset date - End date
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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

Lucy McGeoch, Marinka Twilt, Leilani Famorca, Volodko Bakowsky, Lillian Barra, Susan M. Benseler, David A. Cabral, Simon Carette, Gerald P. Cox, Navjot Dhindsa, Christine S. Dipchand, Aurore Fifi-Mah, Michelle Goulet, Nader Khalidi, Majed M. Khraishi, Patrick Liang, Nataliya Milman, Christian A. Pineau, Heather N. Reich, Nooshin Samadi, Kam Shojania, Regina Taylor-Gjevre, Tanveer E. Towheed, Judith Trudeau, Michael Walsh, Elaine Yacyshyn, and Christian Pagnoux, for the Canadian Vasculitis Research Network

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

McGeoch et al. Canadian Journal of Kidney Health and Disease (2015) 2:43
DOI 10.1186/s40697-015-0078-1

Canadian Society of Nephrology/
Société canadienne de néphrologie
CSN/SCN

CANADIAN JOURNAL OF
KIDNEY HEALTH AND DISEASE
Journal canadien de la santé et de la maladie rénale

REVIEW Open Access

CanVasc recommendations for the management of antineutrophil cytoplasm antibody (ANCA)-associated vasculitides – Executive summary

Lucy McGeoch[1,2], Marinka Twilt[3], Leilani Famorca[4], Volodko Bakowsky[5], Lillian Barra[6], Susan Benseler[3], David A. Cabral[7], Simon Carette[1], Gerald P. Cox[8], Navjot Dhindsa[9], Christine Dipchand[10], Aurore Fifi-Mah[11], Michele Goulet[12], Nader Khalidi[13], Majed M. Khraishi[14], Patrick Liang[15], Nataliya Milman[16], Christian A. Pineau[17], Heather Reich[18], Nooshin Samadi[19], Kam Shojania[20], Regina Taylor-Gjevre[21], Tanveer E. Towheed[22], Judith Trudeau[23], Michael Walsh[24], Elaine Yacyshyn[25], Christian Pagnoux[1*] and for the Canadian Vasculitis research network (CanVasc)

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/m^2 x 4 weekly infusions) to be non-inferior to cyclophosphamide at inducing remission in adults with organ or life-threatening disease[40, 50]. 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[51-53]. 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[21]

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[20]

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[7]

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

KDIGO[13]

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:
Drs. Volodko Bakowsky, Lillian Barra, Susan Benseler, David Cabral, Simon Carette, Navjot Dhindsa, Leilani Famorca, Aurore Fifi-Mah, Michele Goulet, Nader Khalidi, Majed Khraishi, Patrick Liang, Nataliya Milman, Christian Pineau, Nooshin Samadi, Kam Shojania, Regina Taylor-Gjevre, Tanveer Towheed, ***Judith Trudeau,*** *Elaine Yacyshyn*

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Additional reviewers for Draft 2:
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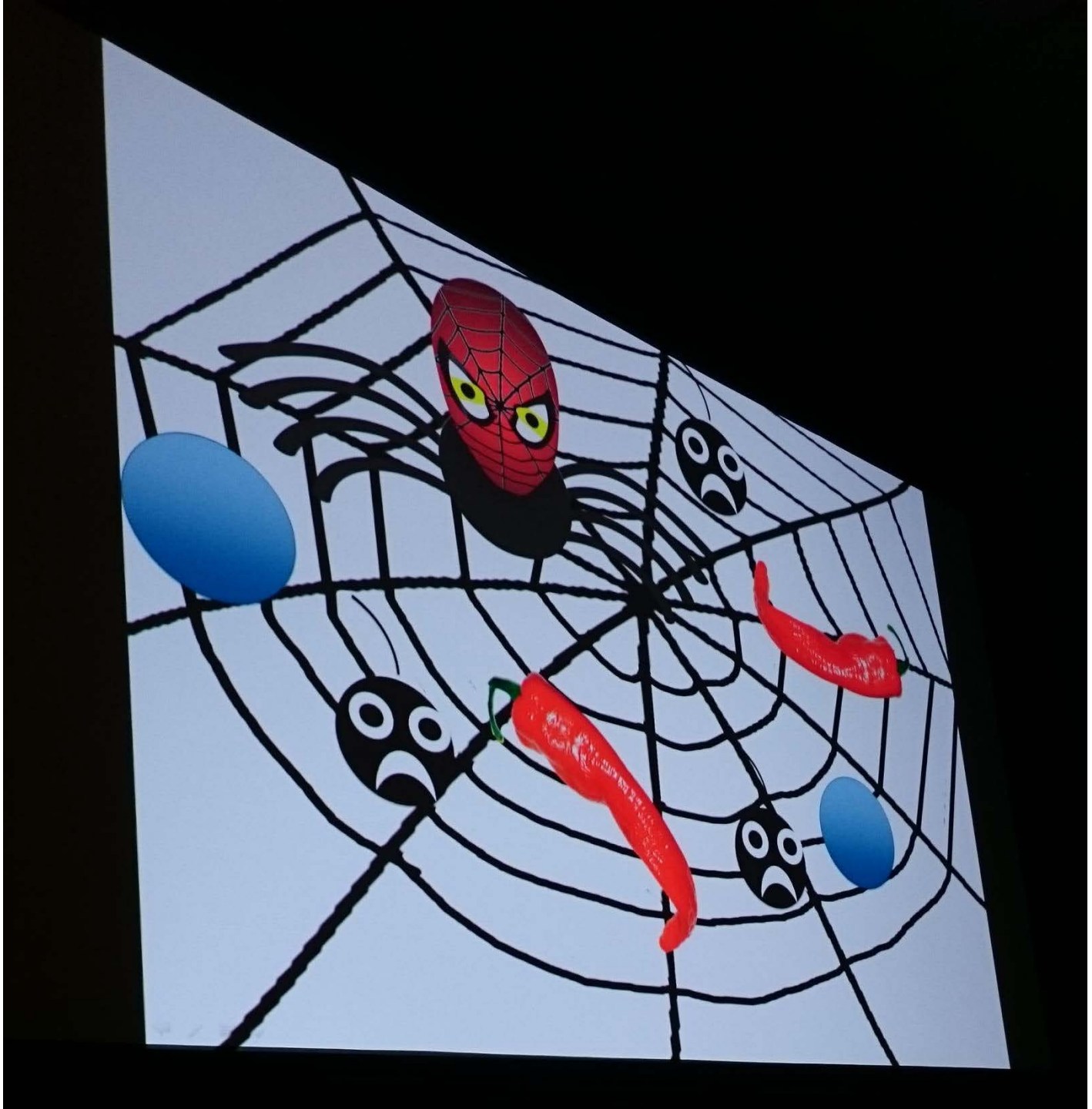
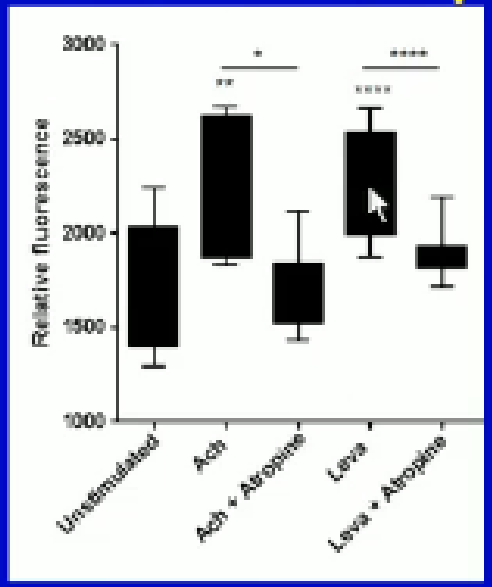
VF Canada: *John Stewart, Katherine Smith, Barbara Tuntoglu (board)*

Sandra Messier, admin. support

Quoi de neuf dans les vascularites (à ANCA)?



Levamisole stimulates NETs through muscarinic receptors

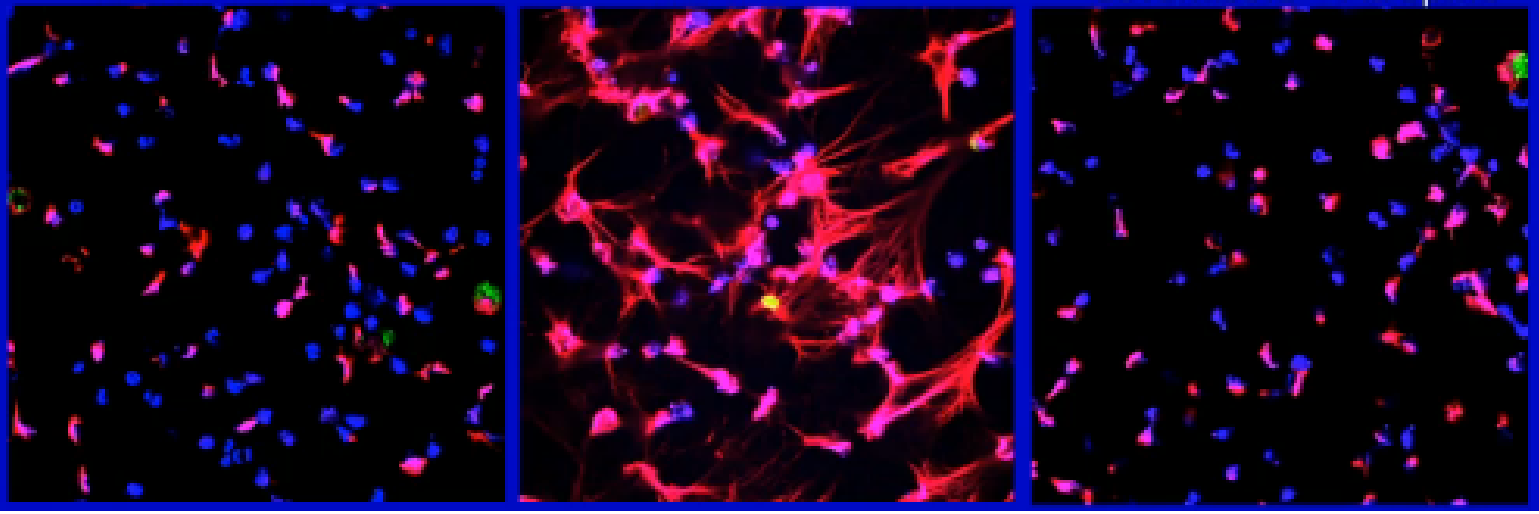


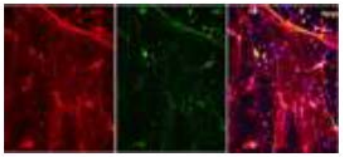
Unstimulated

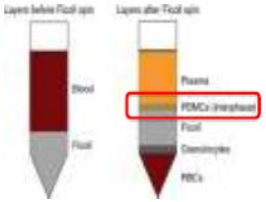
Levamisole

Levamisole + Atropine

Vas007d NEU







- LDGs are pro-inflammatory, vaculopathic and readily undergo NETosis
- Associated with disease activity in SLE and AAV

Denny et al, *J Immun 2010*
Villanueva et al, *J Immun 2011*
Grayson et al, *A&R 2015*

ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 7, July 2015, pp 1922–1932
DOI 10.1002/art.39153

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**

The Rituximab in ANCA-Associated Vasculitis (RAVE) trial

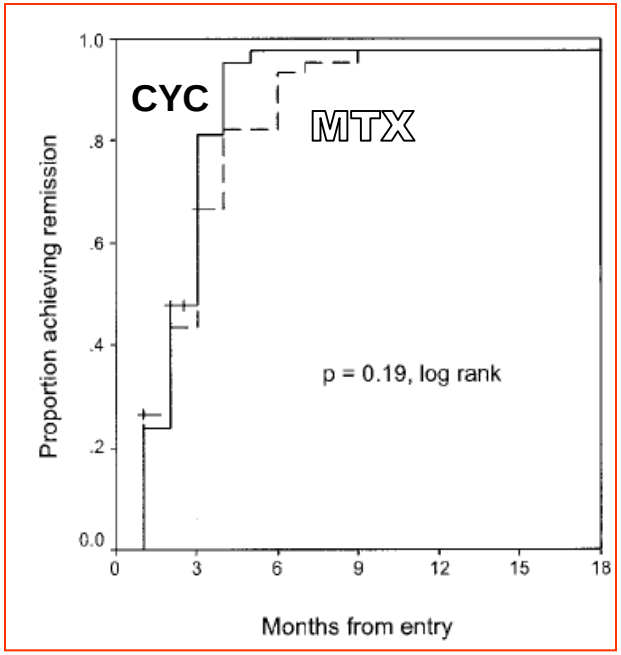
NORAM

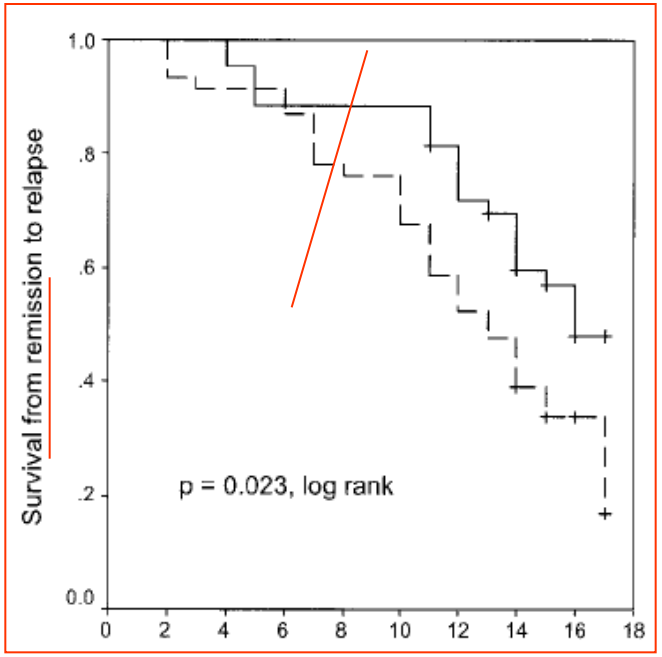
- MTX vs oral CYC for induction for 12 months
- Non-inferiority trial (d=15%) for remission at 6 mo
- 100 p. with “early systemic” WG for 12 mo.

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





de Groot et al. *Arthritis Rheum* 2005;52:2461–9
Faurschou et al. Arthritis Rheum. 2012 Oct;64(10):3472-7

Abatacept

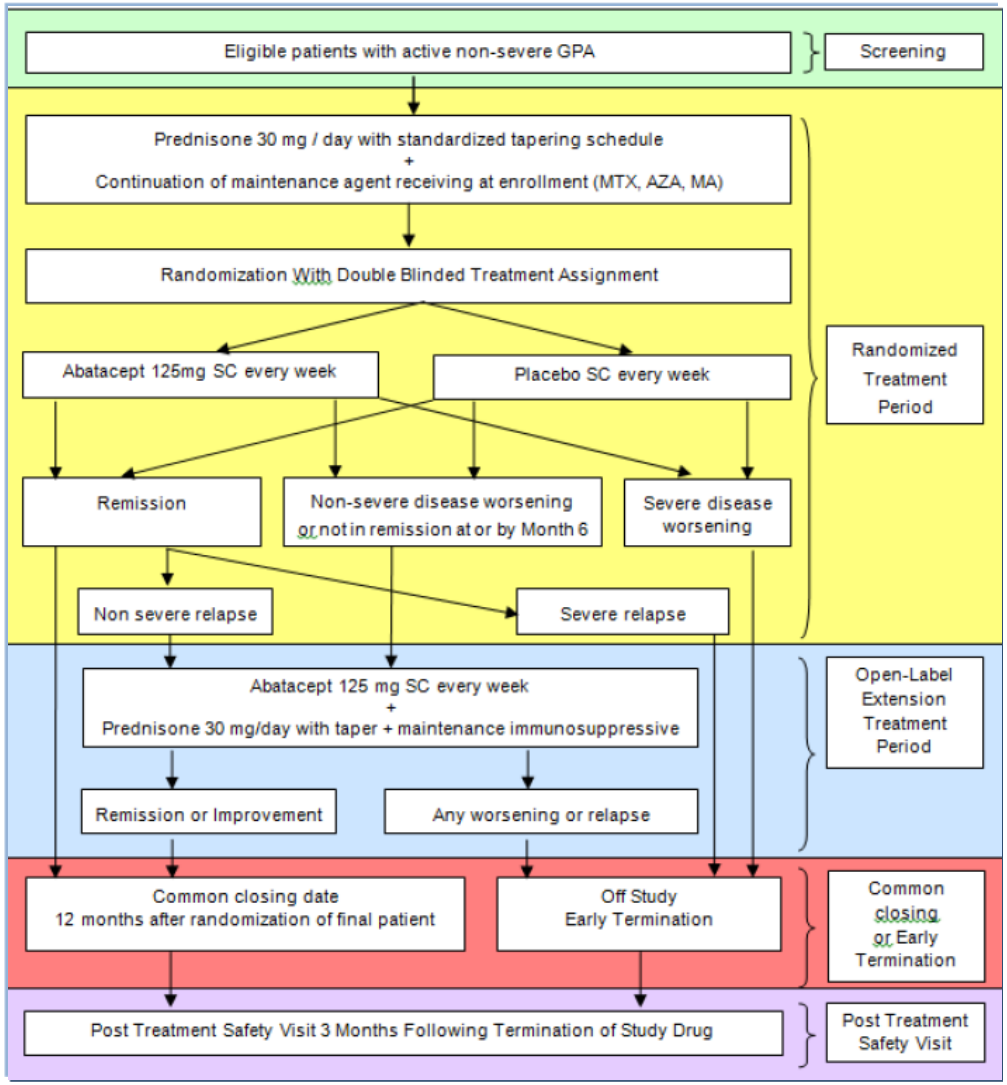
Table 2 Summary of efficacy endpoints

Parameter	n (%)	
Disease improvement	18 (90)	
Remission (BVAS/WG=0)	16 (80)	
Relapse	3 (19)	
Reached common closing	14 (70)	
Parameter	**Median**	**Range**
Time from entry to remission (months)	1.9	1–19
Time from remission to relapse (months)	6.7	5–9
Time on study before common closing/early termination	12.3	2–35
Remission duration before common closing (months)	14.4	4–20
VDI at common closing/early termination	3.0	0–7

BVAS/WG, Birmingham Vasculitis Activity Score for Wegener's Granulomatosis; VDI, Vasculitis Damage Index.

Langford et al. Ann Rheum Dis. 2014 Jul;73(7):1376-9

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**

Treatment of severe GPA/MPA

CYCLOPHOSPHAMIDE

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

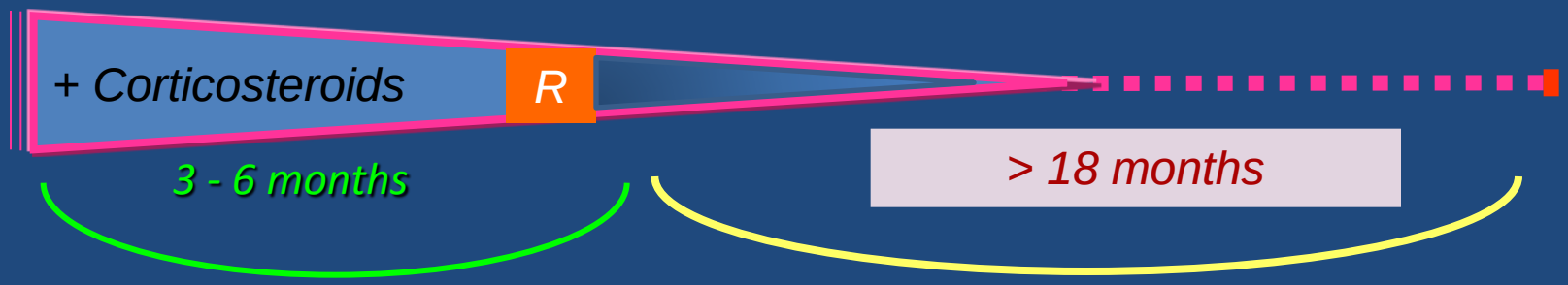
2 mg/kg/d

AZATHIOPRINE 2 mg/kg/d

METHOTREXATE 0.3 mg/kg/wk

LEFLUNOMIDE 20 mg/d

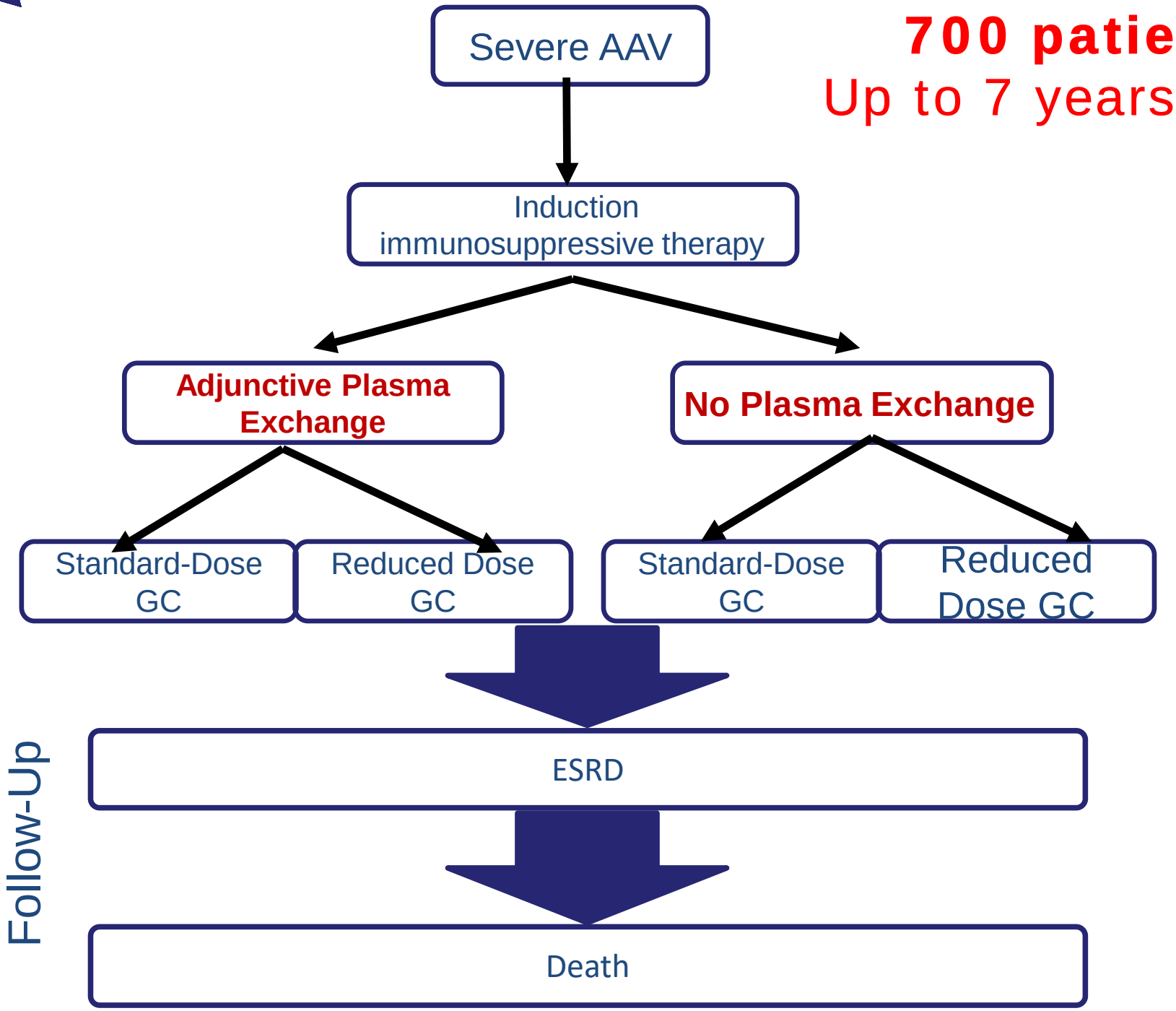
MYCOPHENOLATE MOFETIL 2 g/d



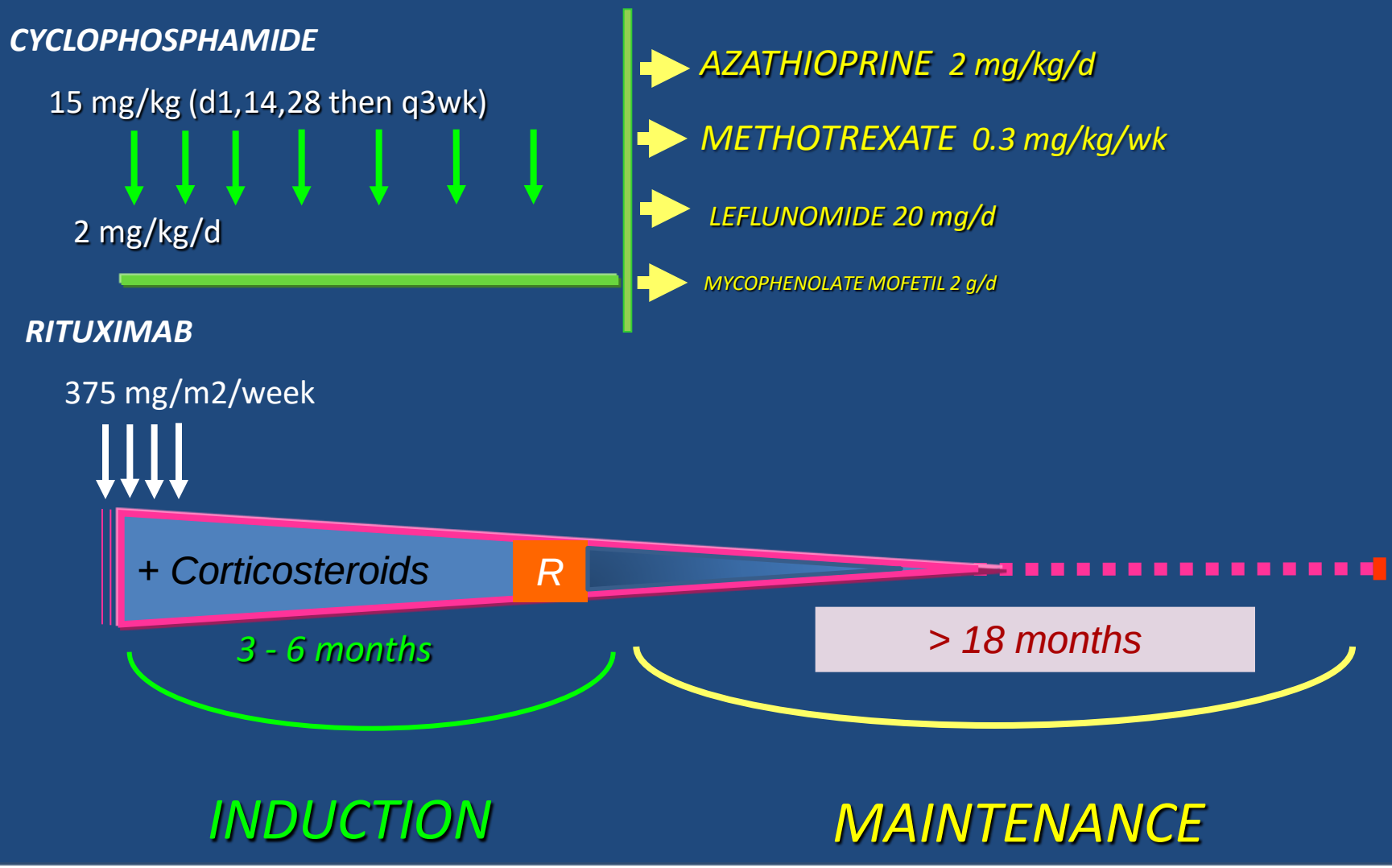
INDUCTION

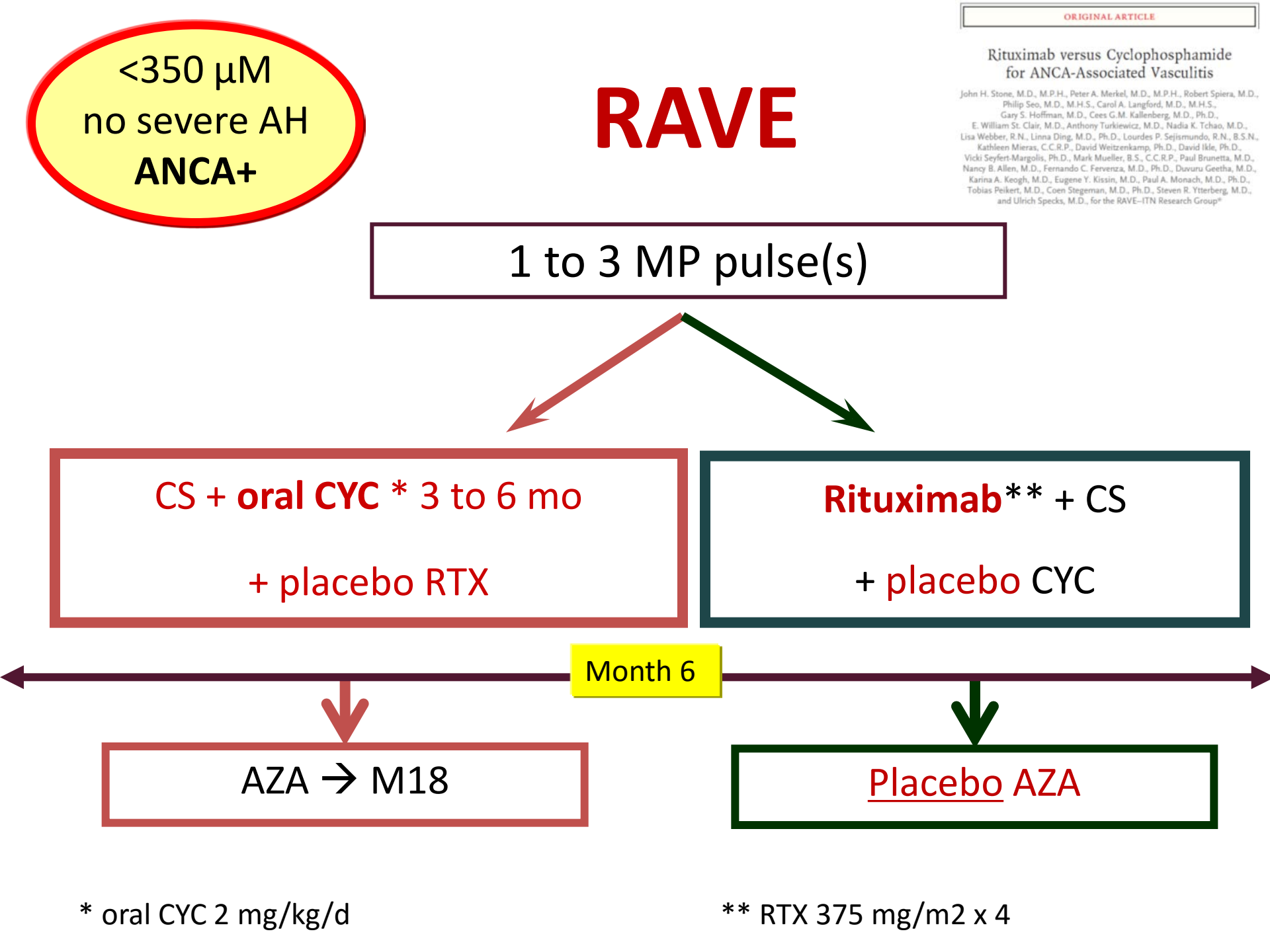
MAINTENANCE

700 patients
Up to 7 years f/u

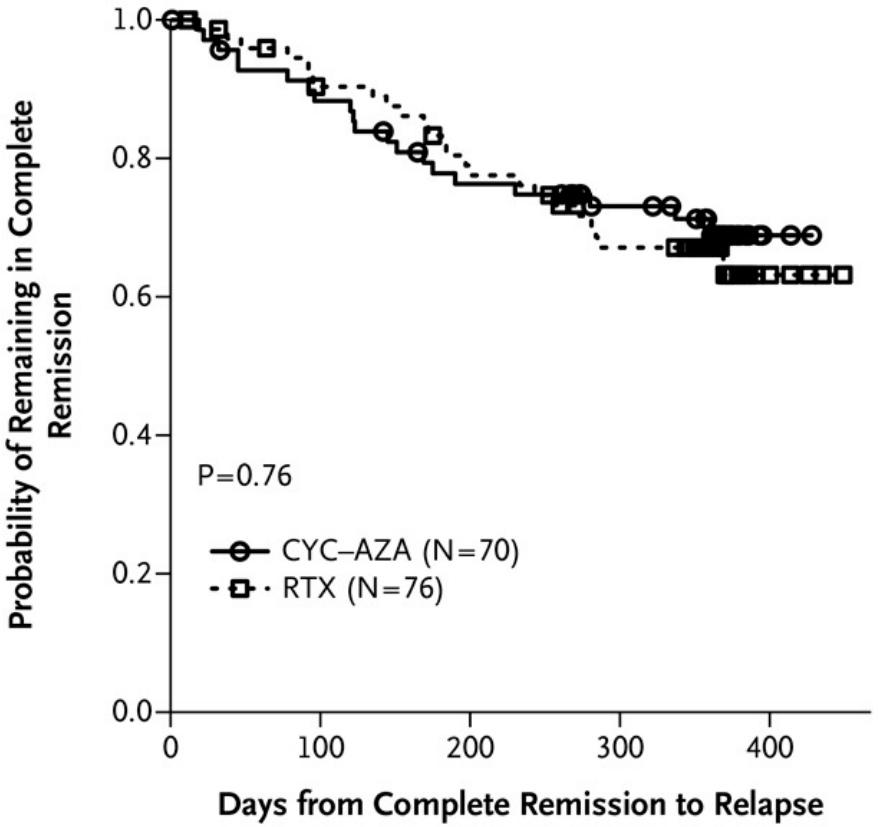


Treatment of severe GPA/MPA




<350 µM
no severe AH
ANCA+
RAVE
ORIGINAL ARTICLE
Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis
1 to 3 MP pulse(s)
CS + oral CYC * 3 to 6 mo
+ placebo RTX
Rituximab** + CS
+ placebo CYC
Month 6
AZA → M18
Placebo AZA
* oral CYC 2 mg/kg/d
** RTX 375 mg/m2 x 4

A Time to First Relapse after Complete Remission, According to Treatment

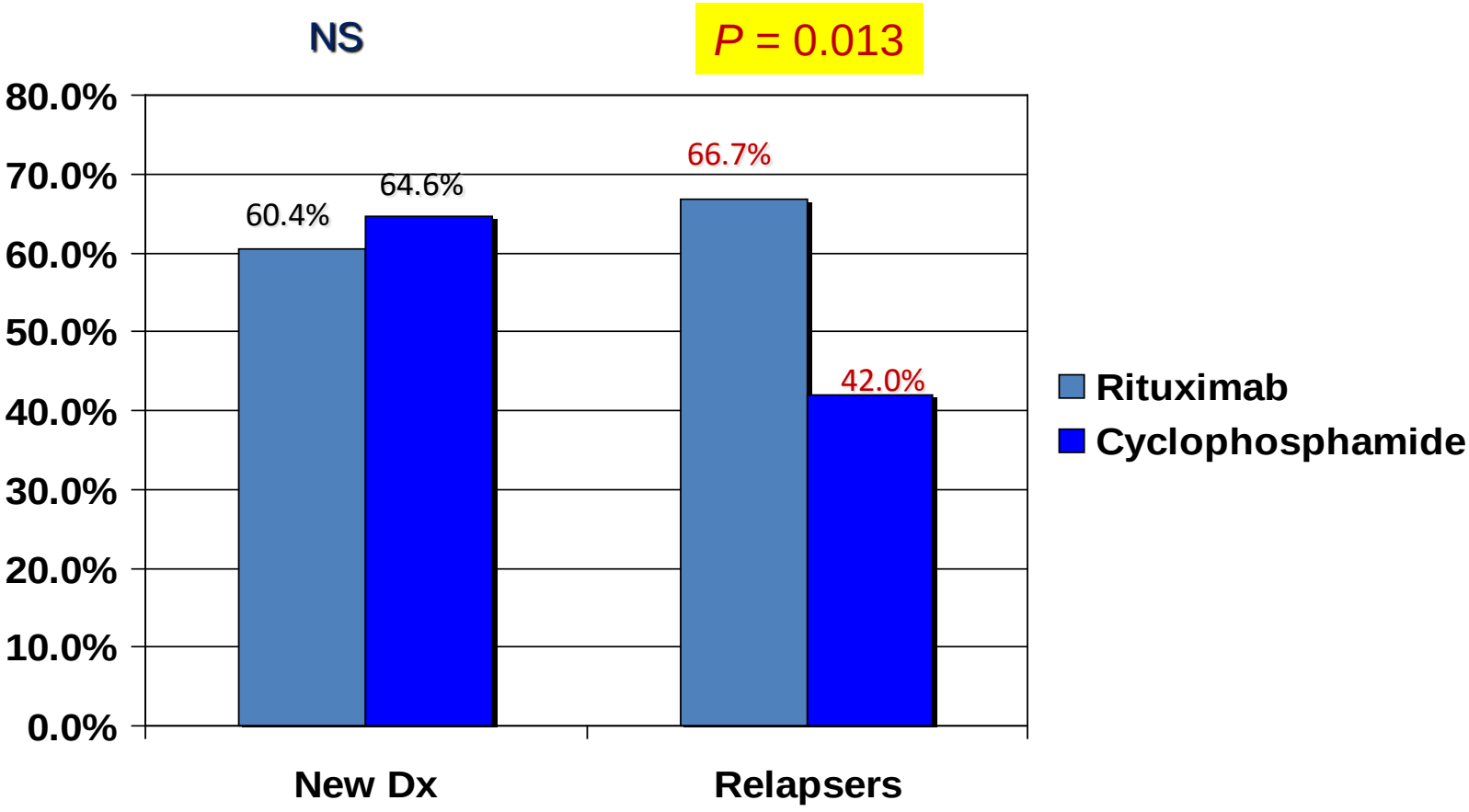


No. at Risk					
CYC–AZA	70	61	51	43	3
RTX	76	65	55	45	5

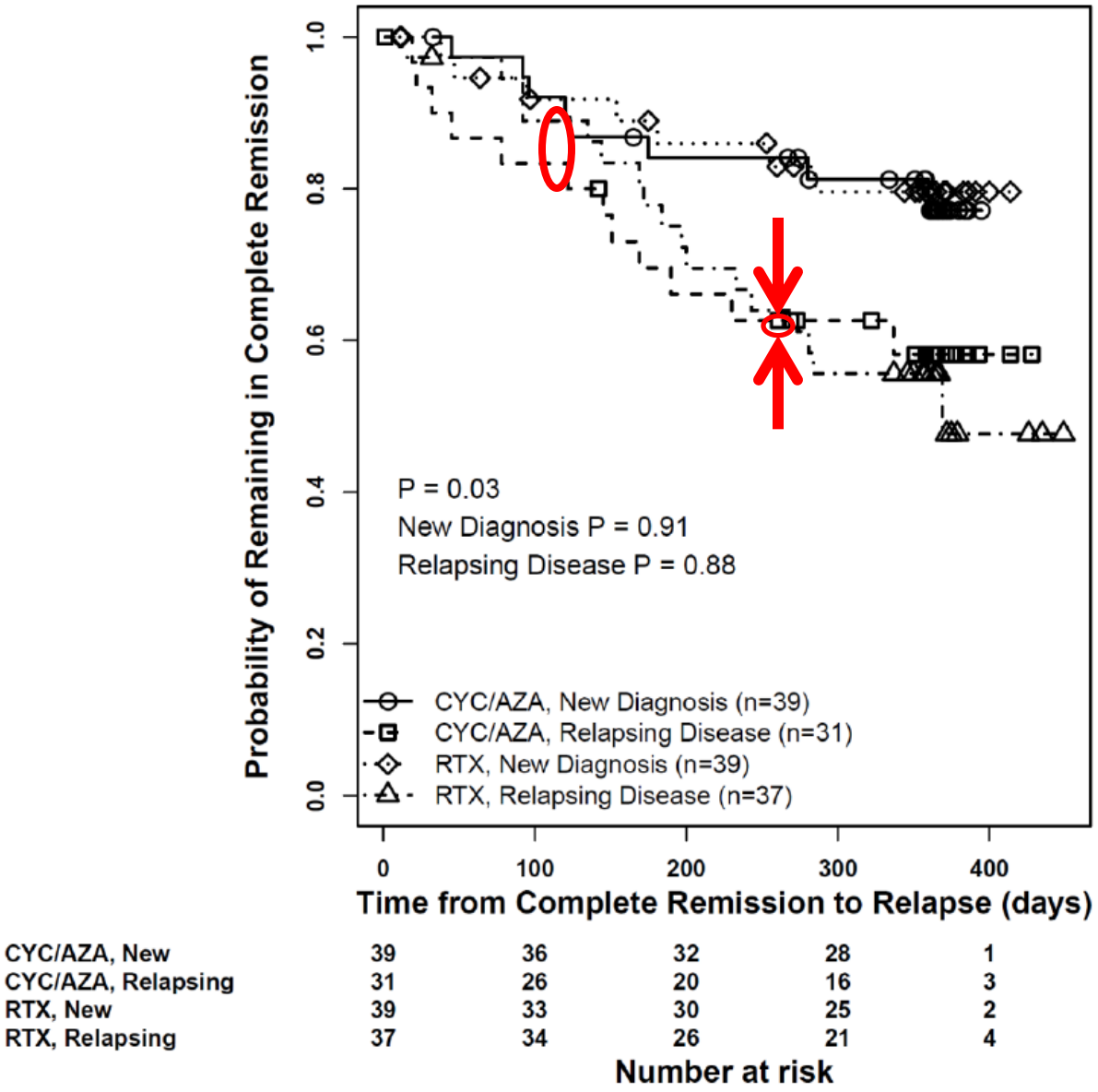
Specks U et al. N Engl J Med 2013;369:417-427

Better response in relapsers

(vs newly-diagnosed)



Stone JH et al, *N Engl J Med* 2010;363(3):221-32



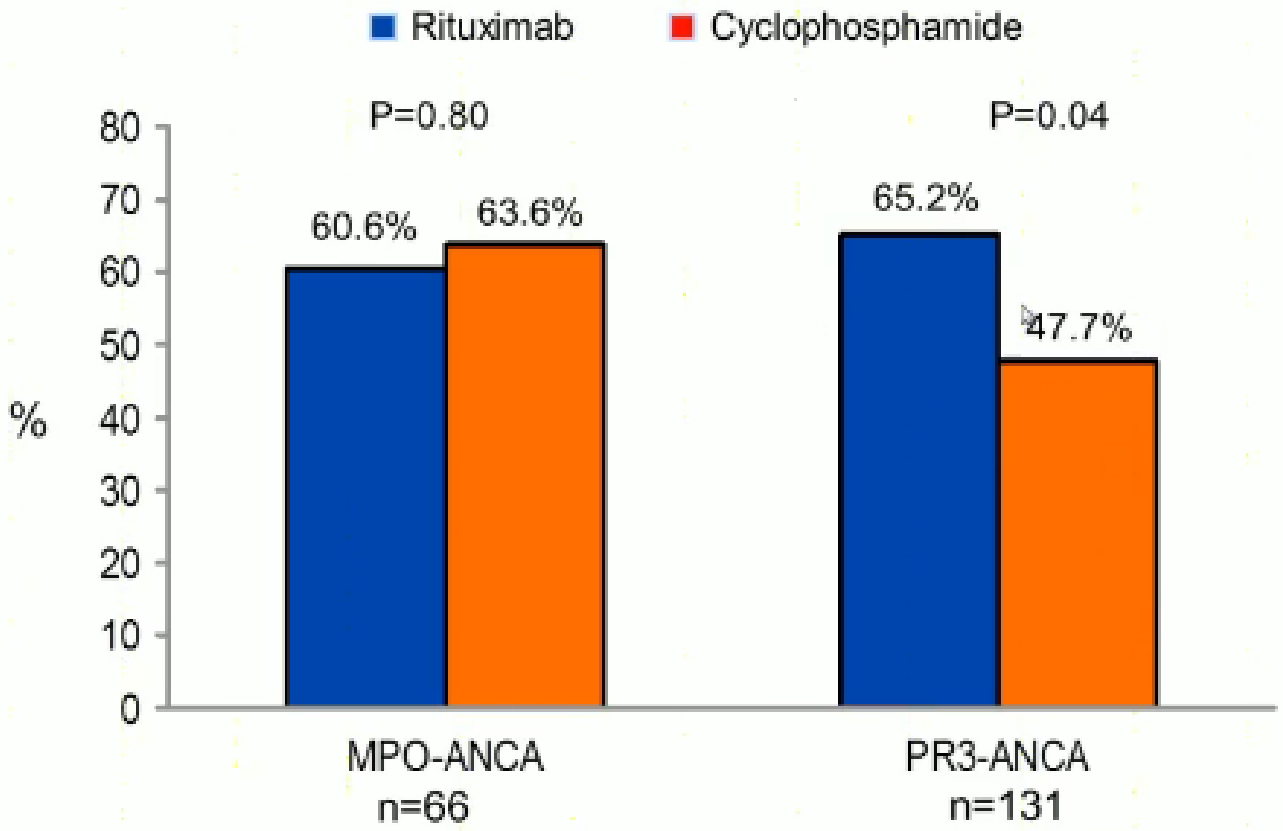
CYC/AZA, New	39	36	32	28	1
CYC/AZA, Relapsing	31	26	20	16	3
RTX, New	39	33	30	25	2
RTX, Relapsing	37	34	26	21	4

Number at risk

Specks U et al. N Engl J Med 2013;369:417-427

ANCA-type and Treatment Response

Achievement of Complete Remission by 6 Months in RAVE

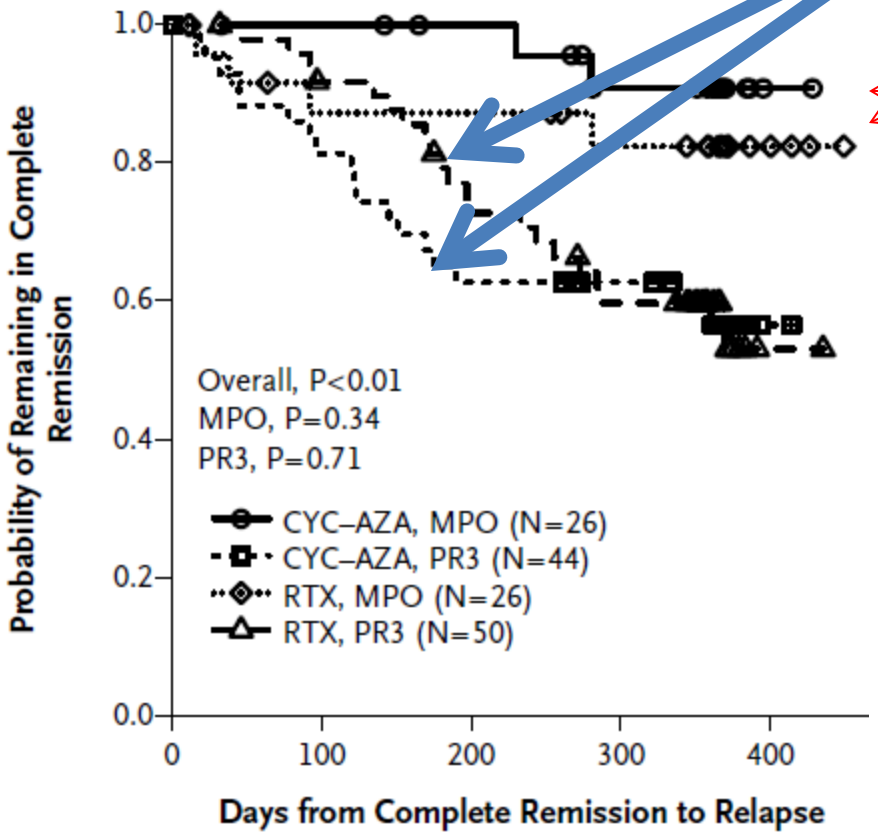


Unizony S et al. Ann Rheum Dis. 2015 in press

PR3+

MPO

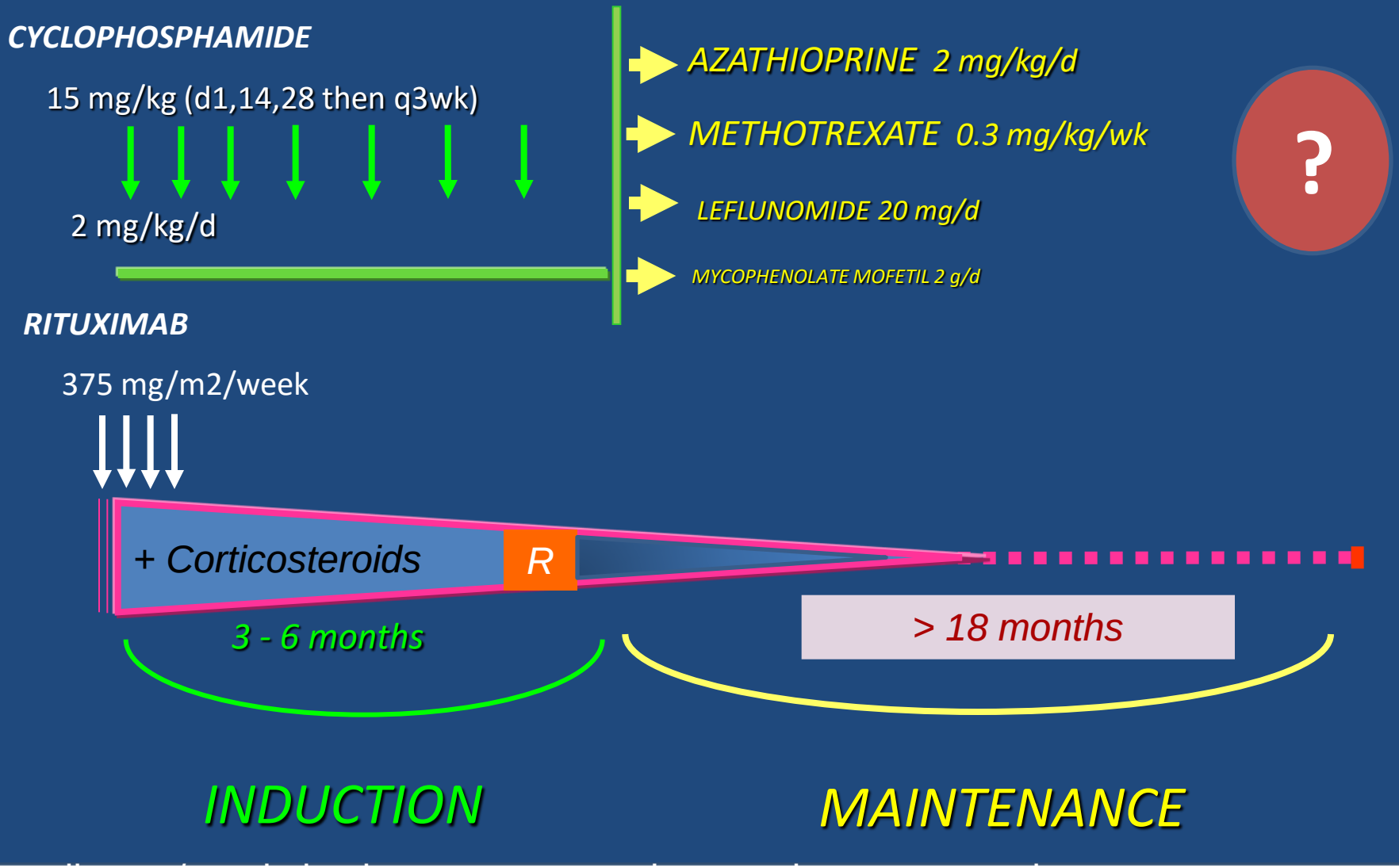
C Time to First Relapse after Complete Remission, According to Treatment and Baseline Type of ANCA



No. at Risk					
CYC–AZA, MPO	26	26	24	19	2
CYC–AZA, PR3	44	36	28	25	2
RTX, MPO	26	21	21	18	4
RTX, PR3	50	45	35	28	2

Specks U et al. N Engl J Med 2013;369:417-427

Treatment of severe GPA/MPA

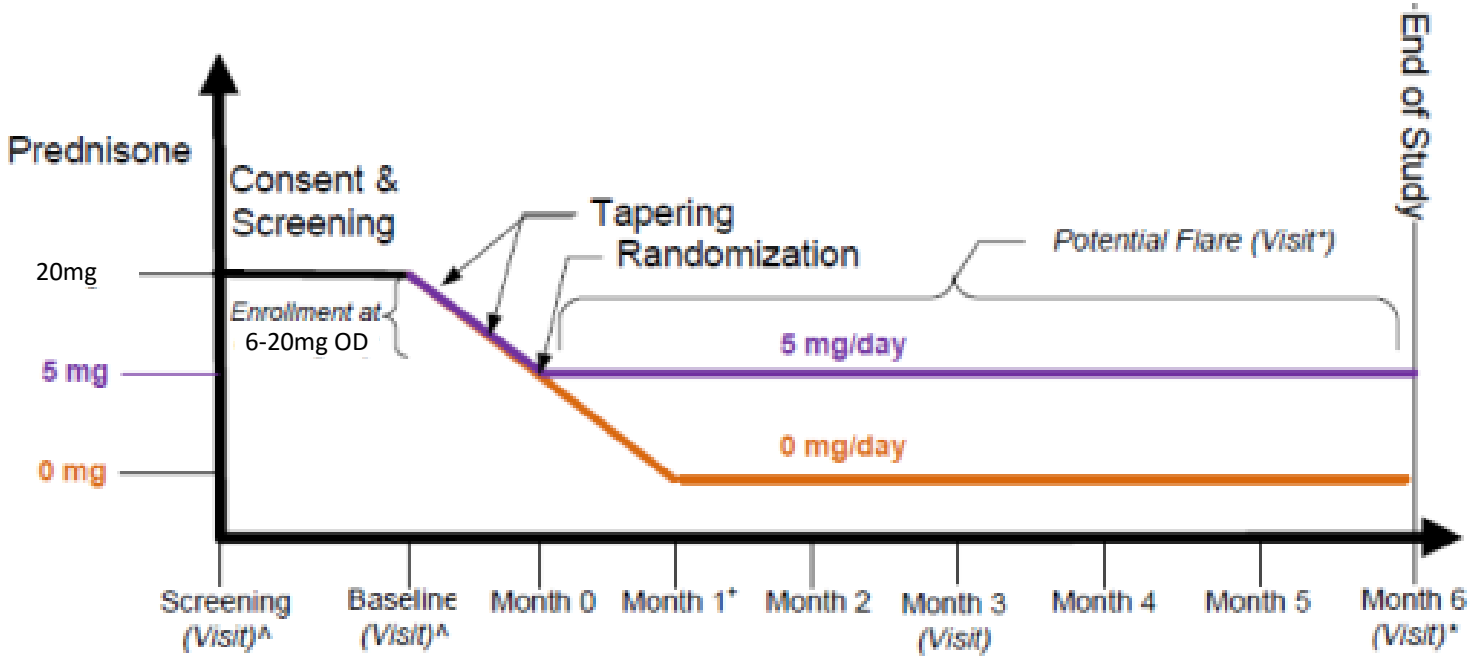


VASCULITIS CLINICAL RESEARCH CONSORTIUM

TAPIR

The Assessment of Prednisone In Remission Trial (TAPIR)

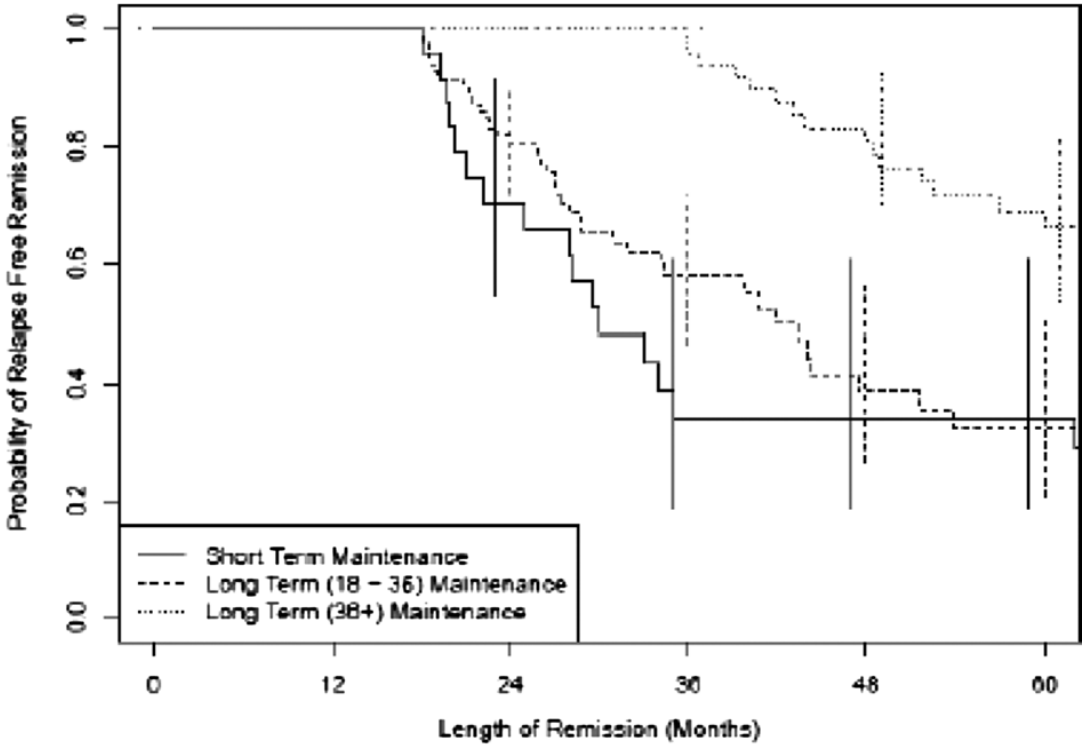
- Key eligibility criteria include:
  - Diagnosis of granulomatosis with polyangiitis (GPA)
  - Required ≥ 20 mg/day of prednisone at some point in the last 12 months
  - GPA currently in remission
  - Currently taking between 6 mg and 20 mg of prednisone per day
  - Age 18 or older
- Randomized to reduce 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.



Short Term Maintenance						
N At Risk	24	24	17	8	8	8
N Events	0	0	7	16	16	16
Long Term (18 – 36) Maintenance						
N At Risk	82	82	56	26	14	11
N Events	0	0	16	28	35	37
Long Term (36+) Maintenance						
N At Risk	50	50	50	50	36	26
N Events	0	0	0	0	0	16

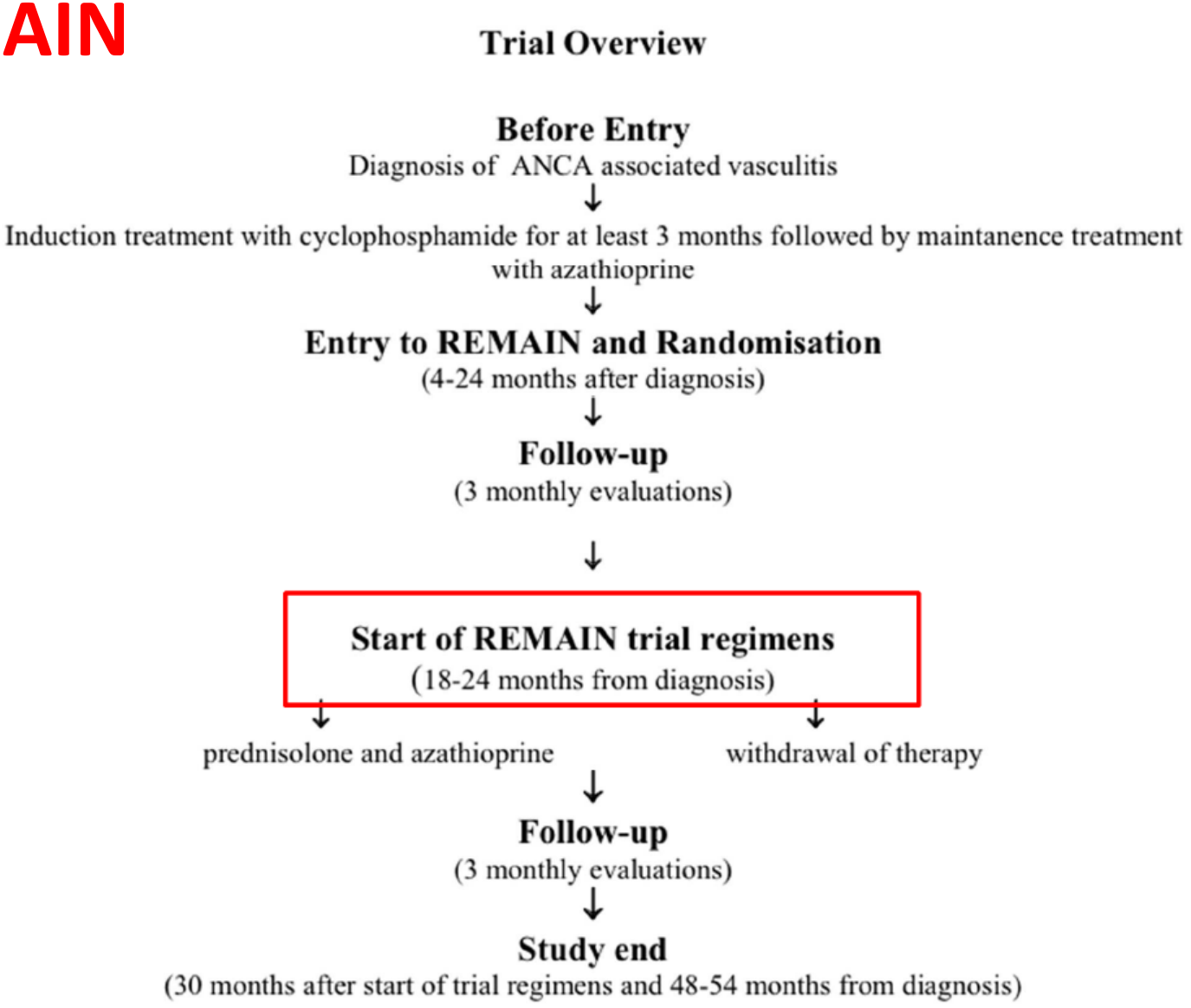
157 patients with a median follow-up of 3.1 years

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

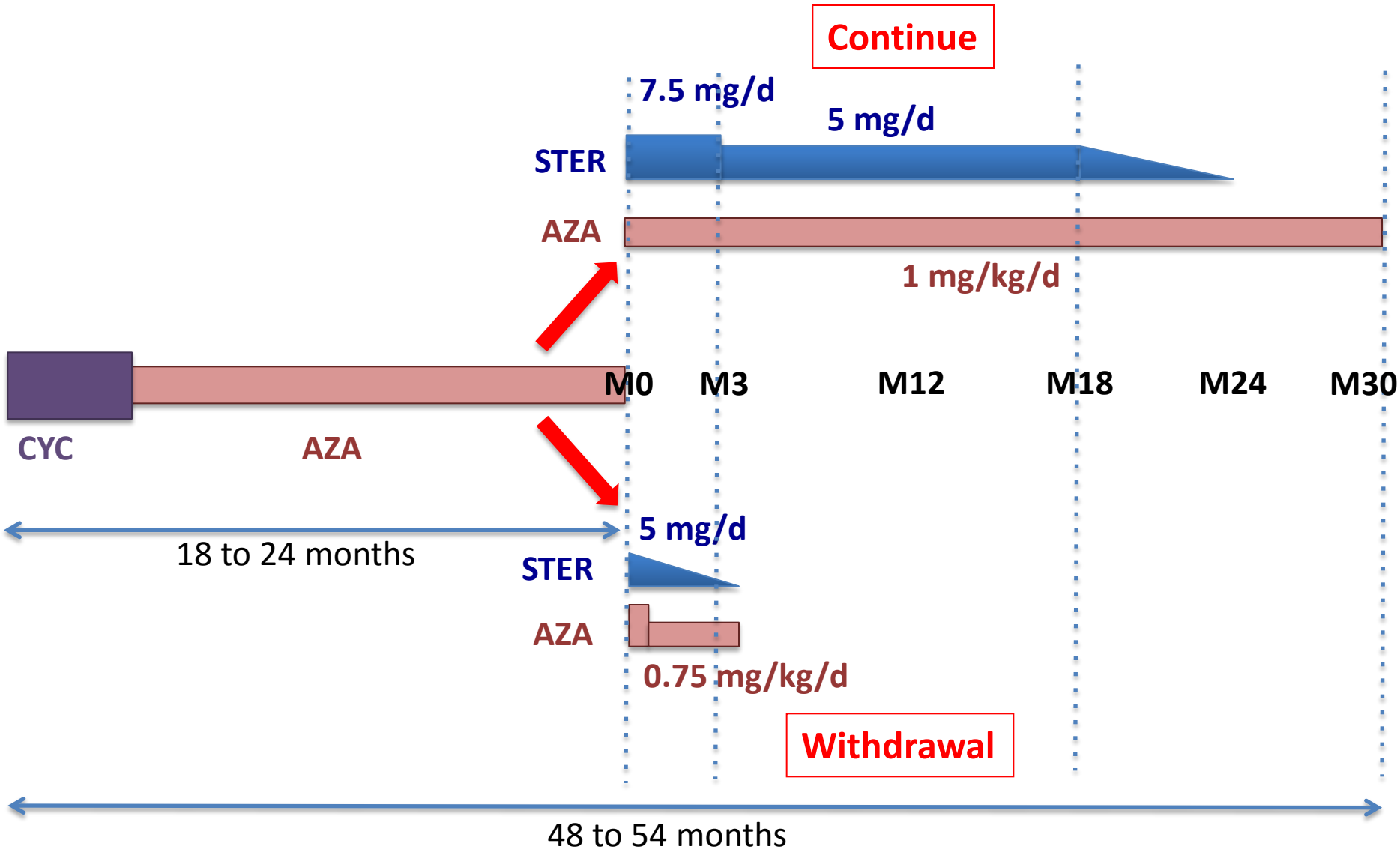
IS for >36 months,
a 66% reduction
(HR, 0.34; 95% CI, 0.15–0.76; p = 0.008)

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

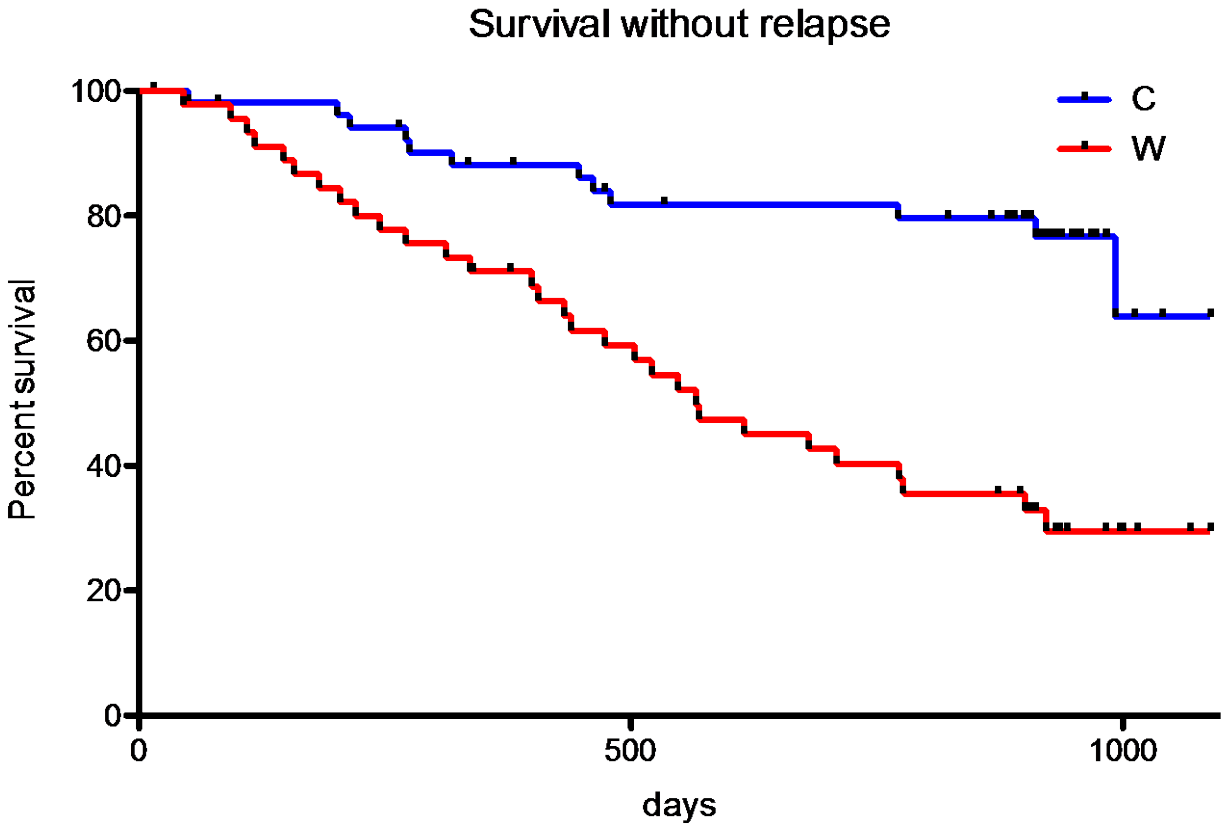
REMAIN


Trial Overview
Before Entry
Diagnosis of ANCA associated vasculitis
Induction treatment with cyclophosphamide for at least 3 months followed by maintanence 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



Results : primary end-point



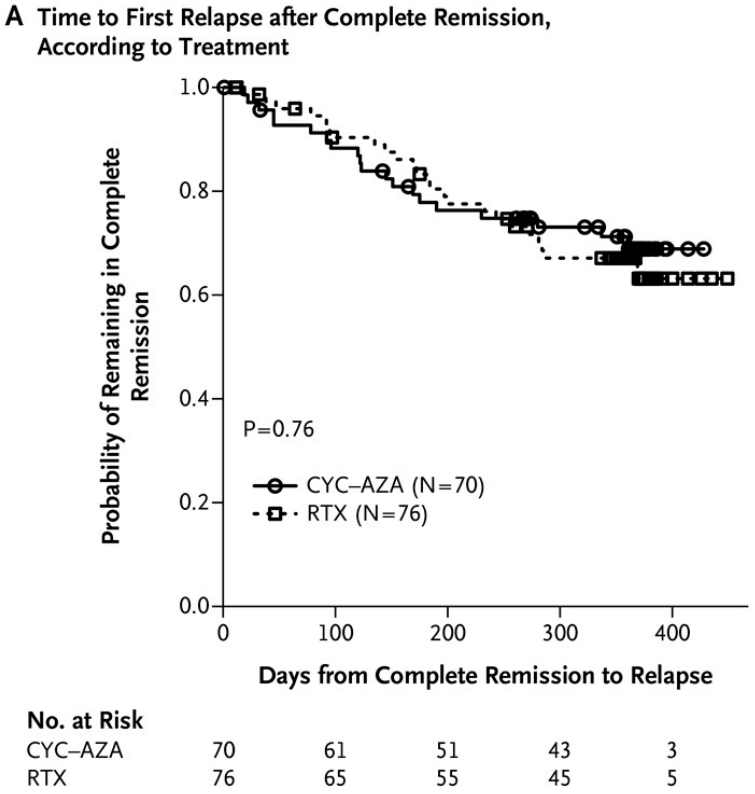
P<0.0001

Subjects at risk					
C (n=53)	50	43	38	37	5
W (n=45)	39	30	21	16	5

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

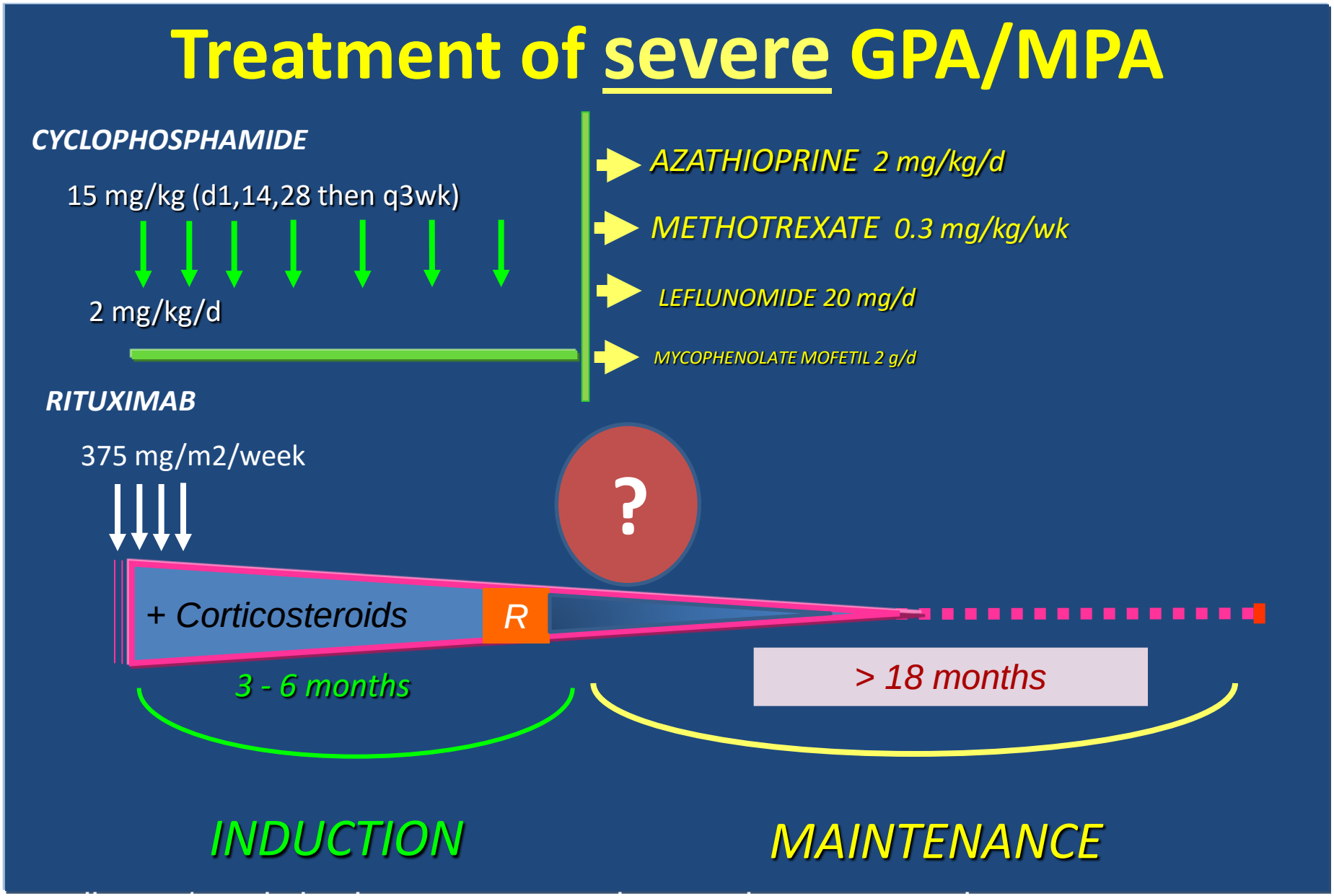
(P=0.16)



The NEW ENGLAND JOURNAL of MEDICINE

Specks U et al. N Engl J Med 2013;369:417-427

Treatment of severe GPA/MPA



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

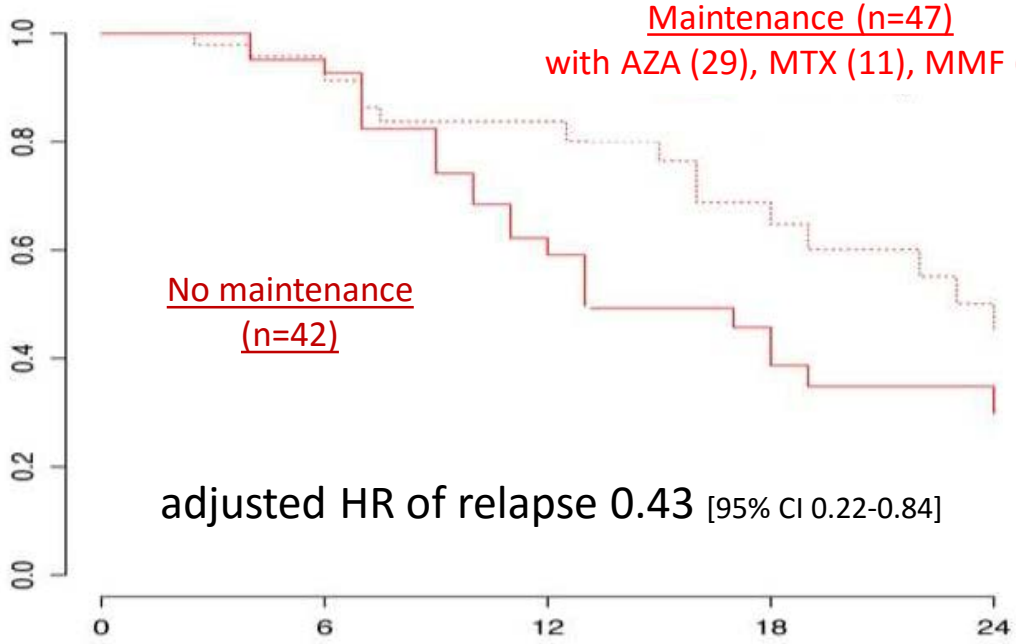
Arthritis Rheumatol. 2014 Jul 21

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)**



SAE 7.6% with vs 6.9% w/o

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!

Azar L et al. Arthritis Rheumatol. 2014 Oct;66(10):2862-70

ARTHRITIS & RHEUMATISM7
Vol. 64, No. 11, November 2012, pp 3760–3769
DOI 10.1002/art.34583

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. Jayne[1]

→ **1g every 6 months**

MAINRITSAN

MAINtenance of remission using RITuximab for Systemic ANCA- associated vasculitides

Systemic GPA or MPA or KLD with FFS ≥ 1

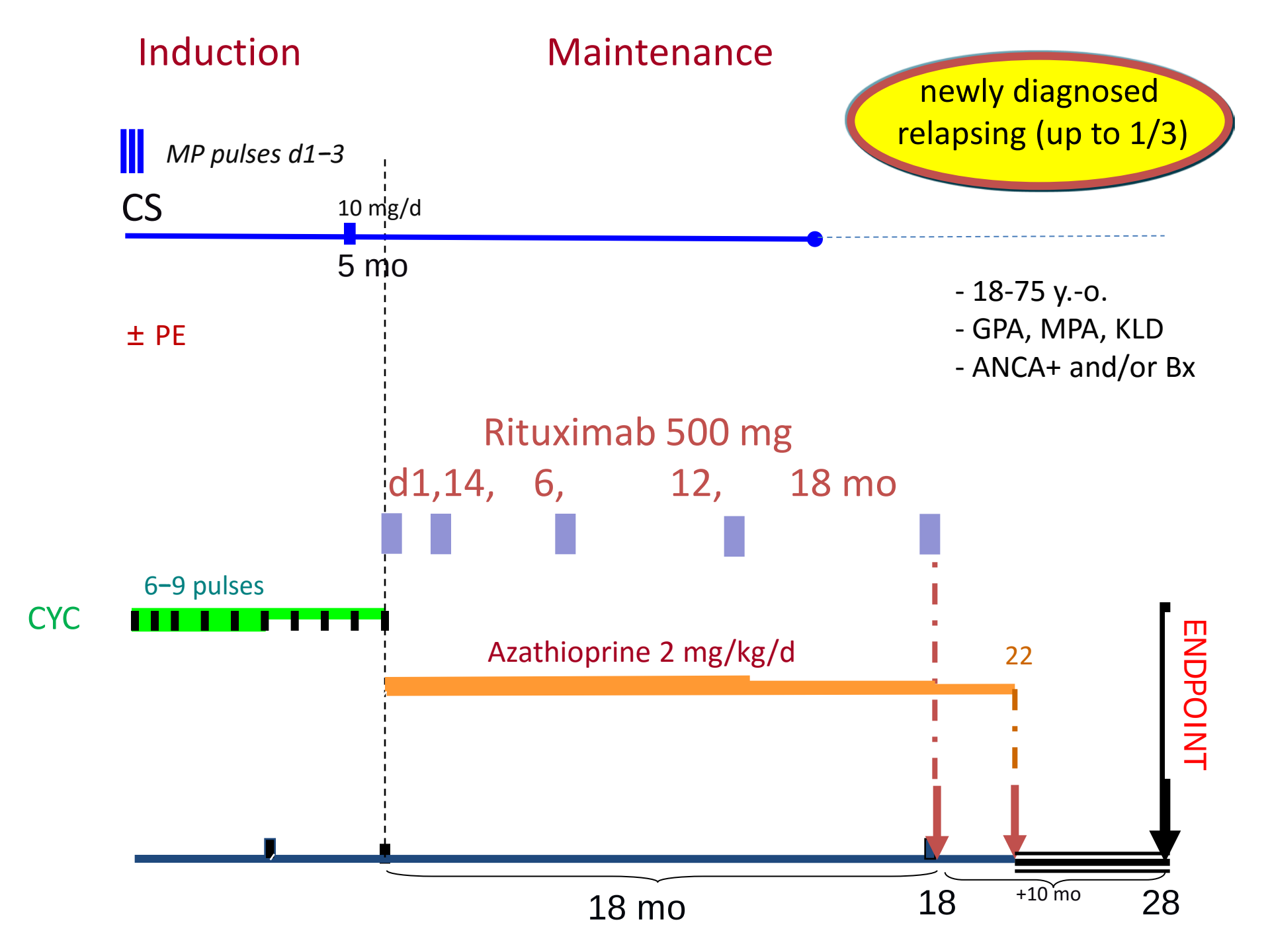
Newly diagnosed or after a relapse treated with CS–CYC

>18 and <75 years old at enrolment

Guillevin and Pagnoux et al. for the

NEJM, Nov. 6, 2014

French Vasculitis Study Group

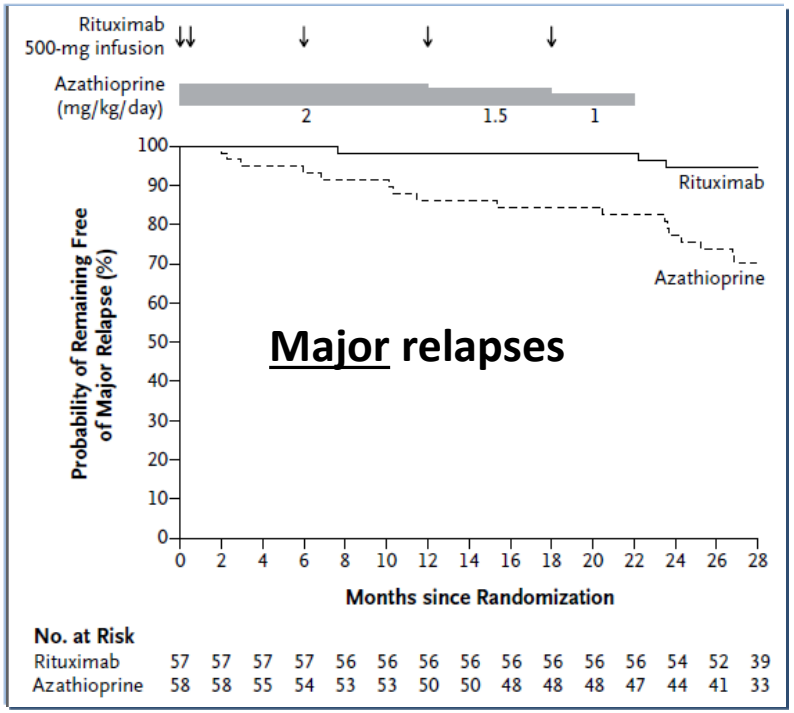

Induction
Maintenance
newly diagnosed
relapsing (up to 1/3)
MP pulses d1−3
CS
10 mg/d
5 mo
± PE
- 18-75 y.-o.
- GPA, MPA, KLD
- ANCA+ and/or Bx
Rituximab 500 mg
d1,14, 6, 12, 18 mo
6−9 pulses
CYC
Azathioprine 2 mg/kg/d
22
ENDPOINT
18 mo
18
+10 mo
28

115 patients

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

58 AZA

Relapses
17 (29%)



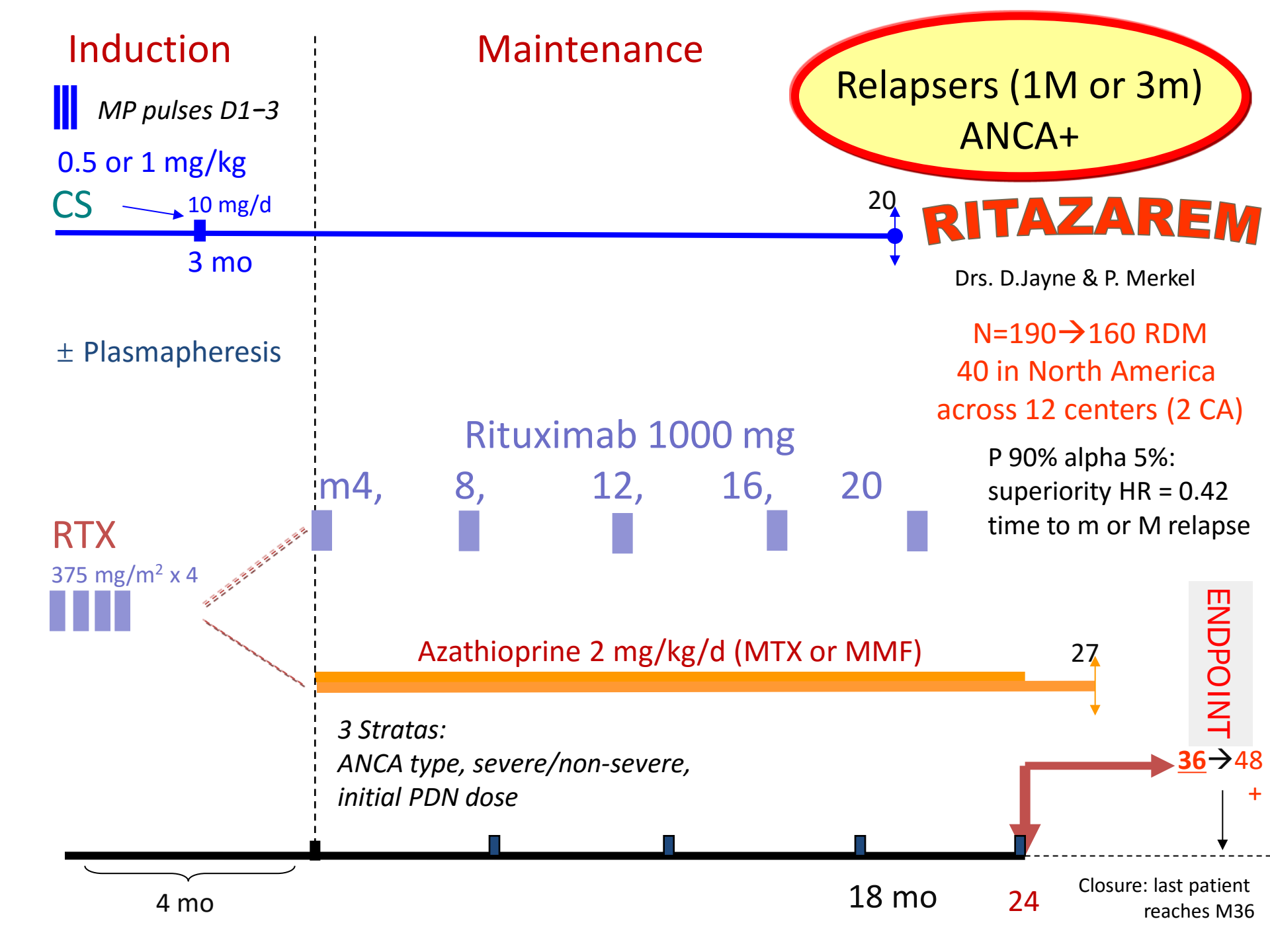
Major relapses

57 RTX

Relapses
3 (5%)

The NEW ENGLAND JOURNAL of MEDICINE

Guillevin, Pagnoux et al. N Engl J Med:1771-80


Induction
Maintenance
Relapsers (1M or 3m)
ANCA+
MP pulses D1−3
0.5 or 1 mg/kg
CS
10 mg/d
20
3 mo
RITAZAREM
Drs. D.Jayne & P. Merkel
± Plasmapheresis
N=190→160 RDM
40 in North America
across 12 centers (2 CA)
Rituximab 1000 mg
m4, 8, 12, 16, 20
P 90% alpha 5%:
superiority HR = 0.42
time to m or M relapse
RTX
375 mg/m² x 4
Azathioprine 2 mg/kg/d (MTX or MMF)
27
ENDPOINT
3 Stratas:
ANCA type, severe/non-severe,
initial PDN dose
36→48
+
4 mo
18 mo
24
Closure: last patient
reaches M36

Drug	Unit	Cost per unit*
Rituximab (Rituxan ®) 10mg/ml	10 ml vial	$450
Rituximab (Rituxan ®) 10mg/ml	50 ml vial	$2250
Cyclophosphamide (Procytox ®) 20mg/ml	100 ml vial	$0.65

FDA April 2011

HC December 2011

Ontario April 2012

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.

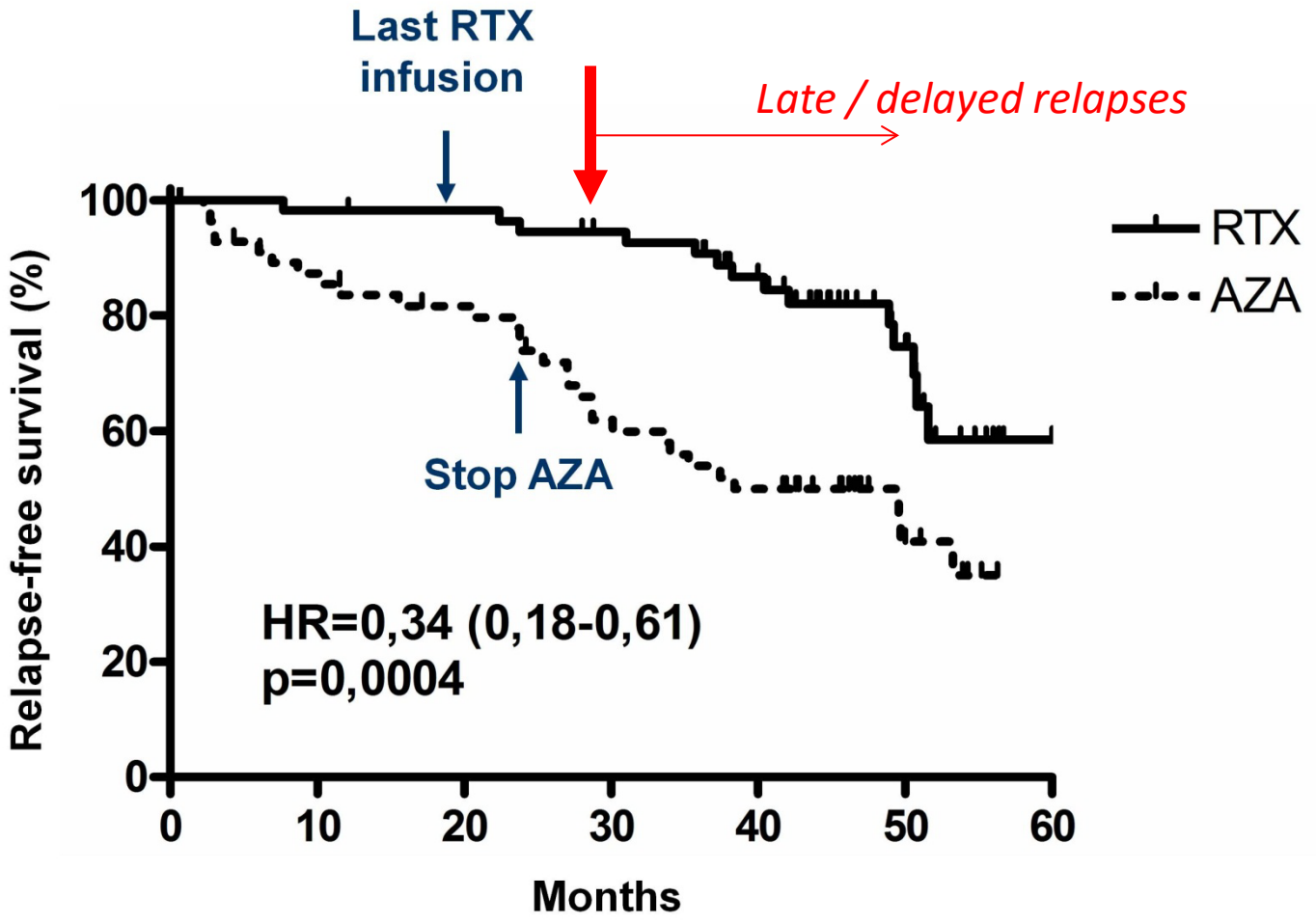
The initial treatment would be a once weekly infusion dosed at 375 mg/m^2 x 4 weeks.

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.

Canadian Drug Expert Committee (CDEC) August 2012

Mainritsan: Preliminary f/up data



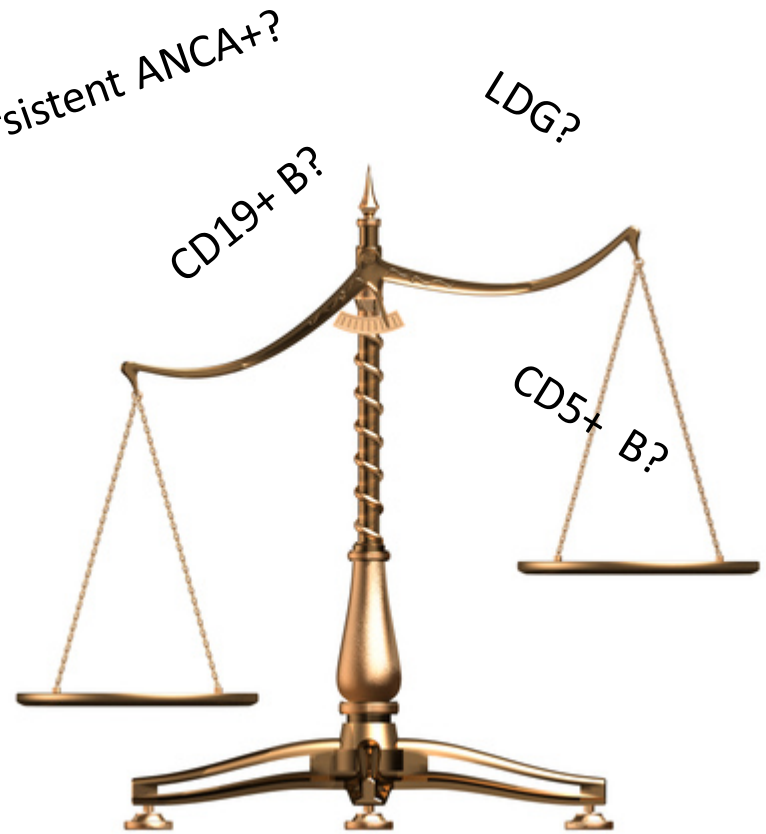
Main predictors of relapse

GPA
antiPR3+

ENT
Lung (nodules)

Low creatinine <100

Cardiovascular

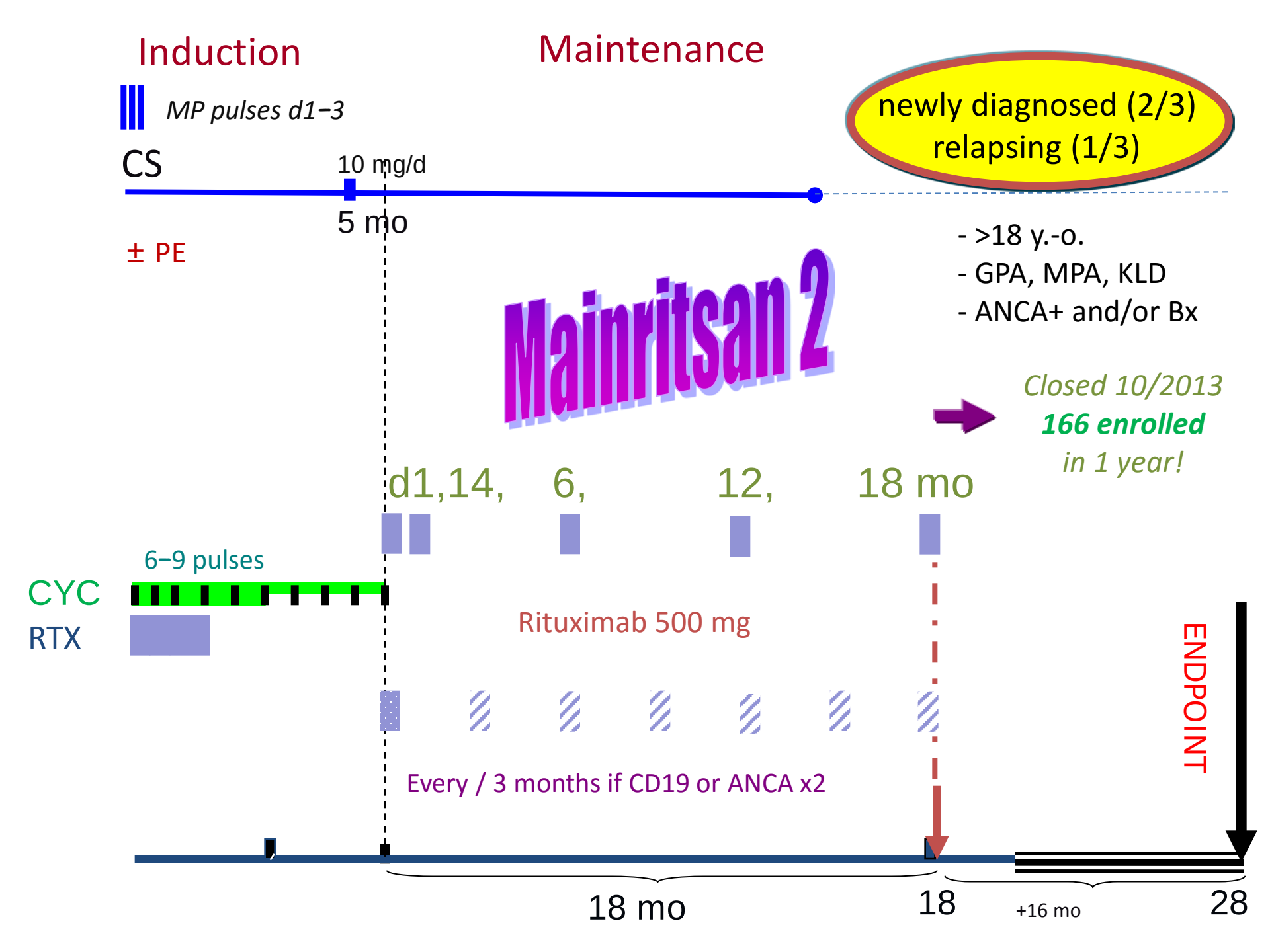


Risk of relapse

MPA
antiMPO+

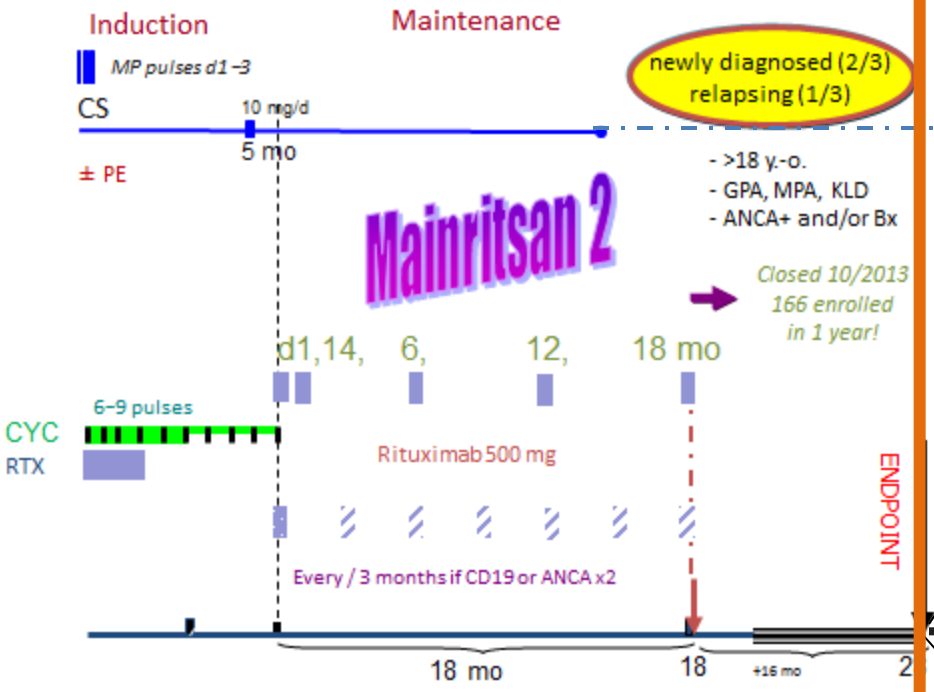
High creatinine

Pagnoux et al, Arthritis Rheum 2008;58(9):2908-18
Pierrot-Deseilligny et al, Rheumatology (Oxford). 2010;49(11):2181-90
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


Induction
Maintenance
MP pulses d1−3
CS
10 mg/d
5 mo
± PE
newly diagnosed (2/3)
relapsing (1/3)
- >18 y.-o.
- GPA, MPA, KLD
- ANCA+ and/or Bx
Mainritsan 2
Closed 10/2013
166 enrolled
in 1 year!
d1,14, 6, 12, 18 mo
6−9 pulses
CYC
RTX
Rituximab 500 mg
Every / 3 months if CD19 or ANCA x2
ENDPOINT
18 mo
18
+16 mo
28

MAINRITSAN 3

mars 2015



<5 mg OD

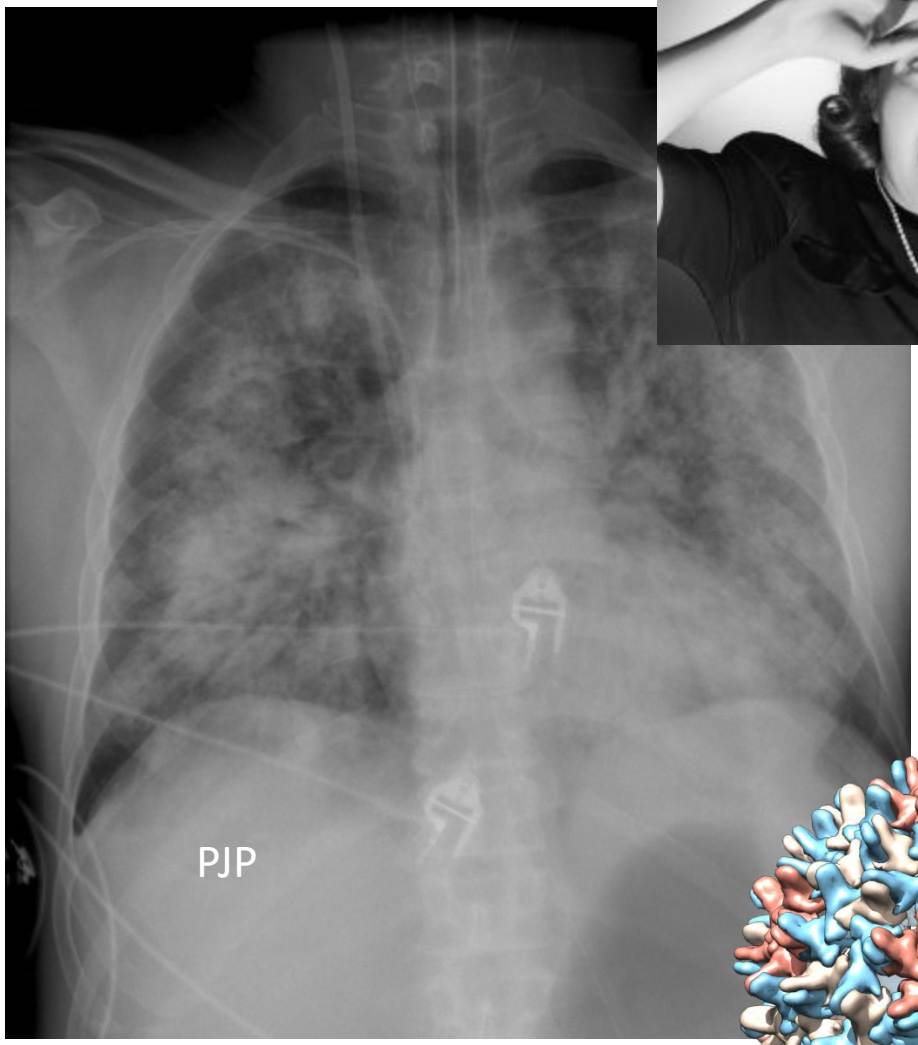
Rituximab 500mg

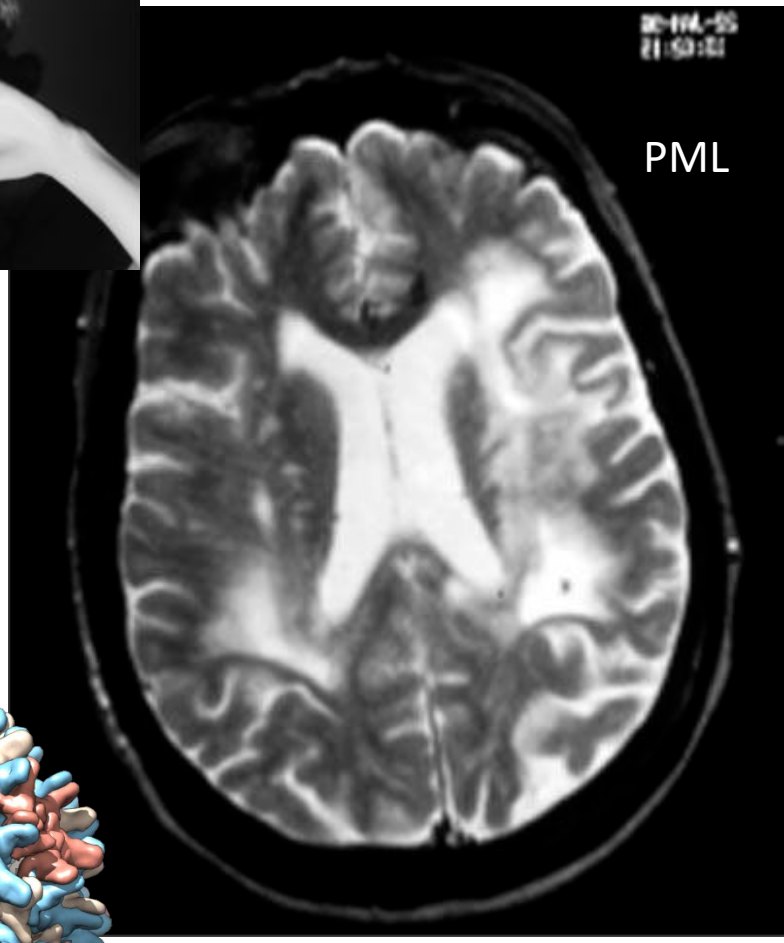
d1 m6 m12 m18

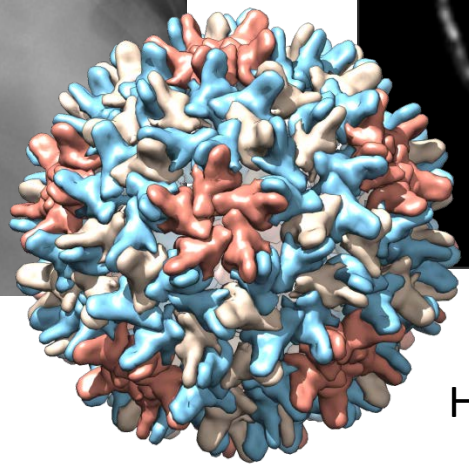
M28 (+28)

placebo

N = 118

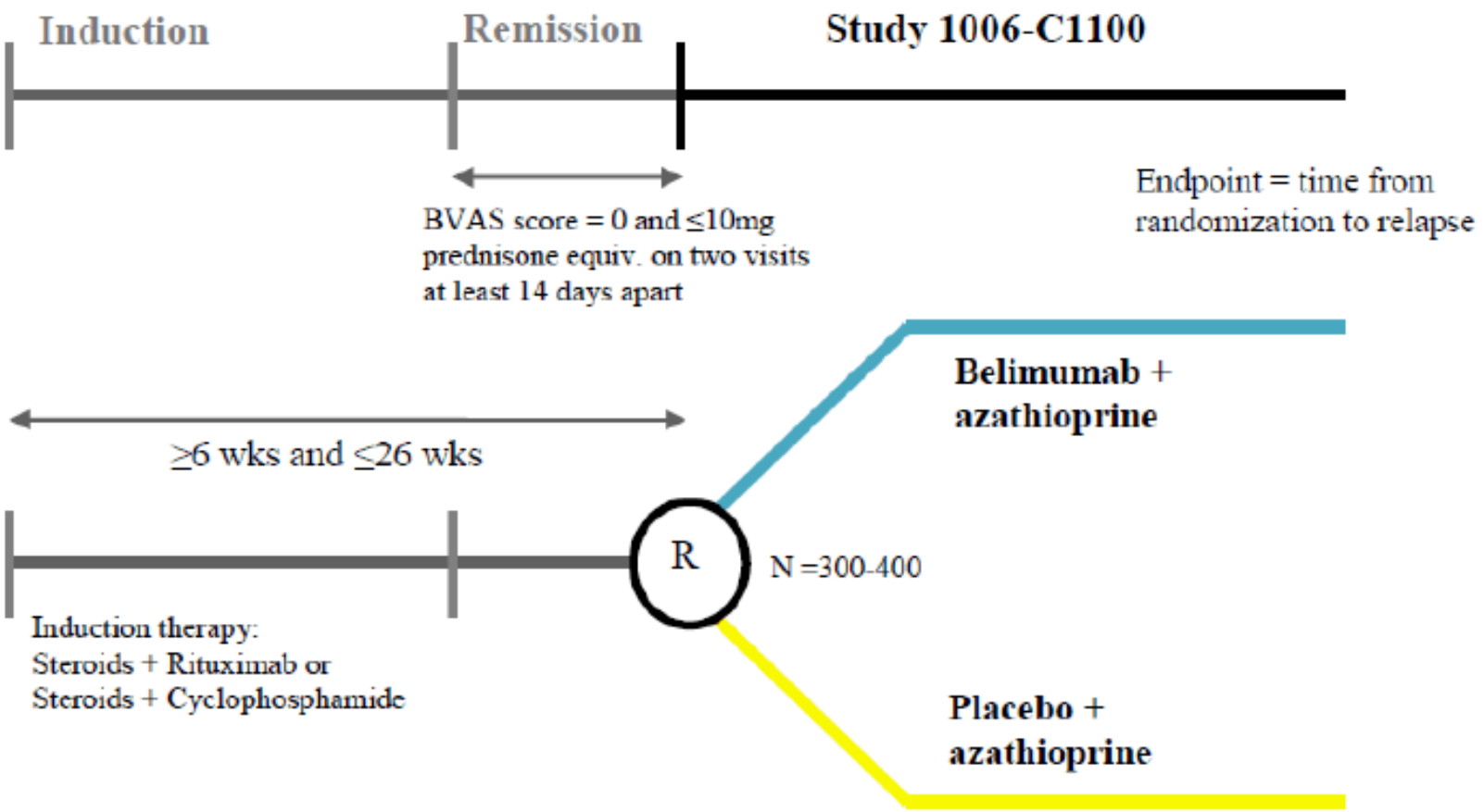






HBV reactivation

BREVAS


Induction
Remission
Study 1006-C1100
BVAS score = 0 and ≤10mg prednisone equiv. on two visits at least 14 days apart
Endpoint = time from randomization to relapse
≥6 wks and ≤26 wks
Belimumab + azathioprine
R
N =300-400
Induction therapy:
Steroids + Rituximab or
Steroids + Cyclophosphamide
Placebo + azathioprine

Complement and vasculitis

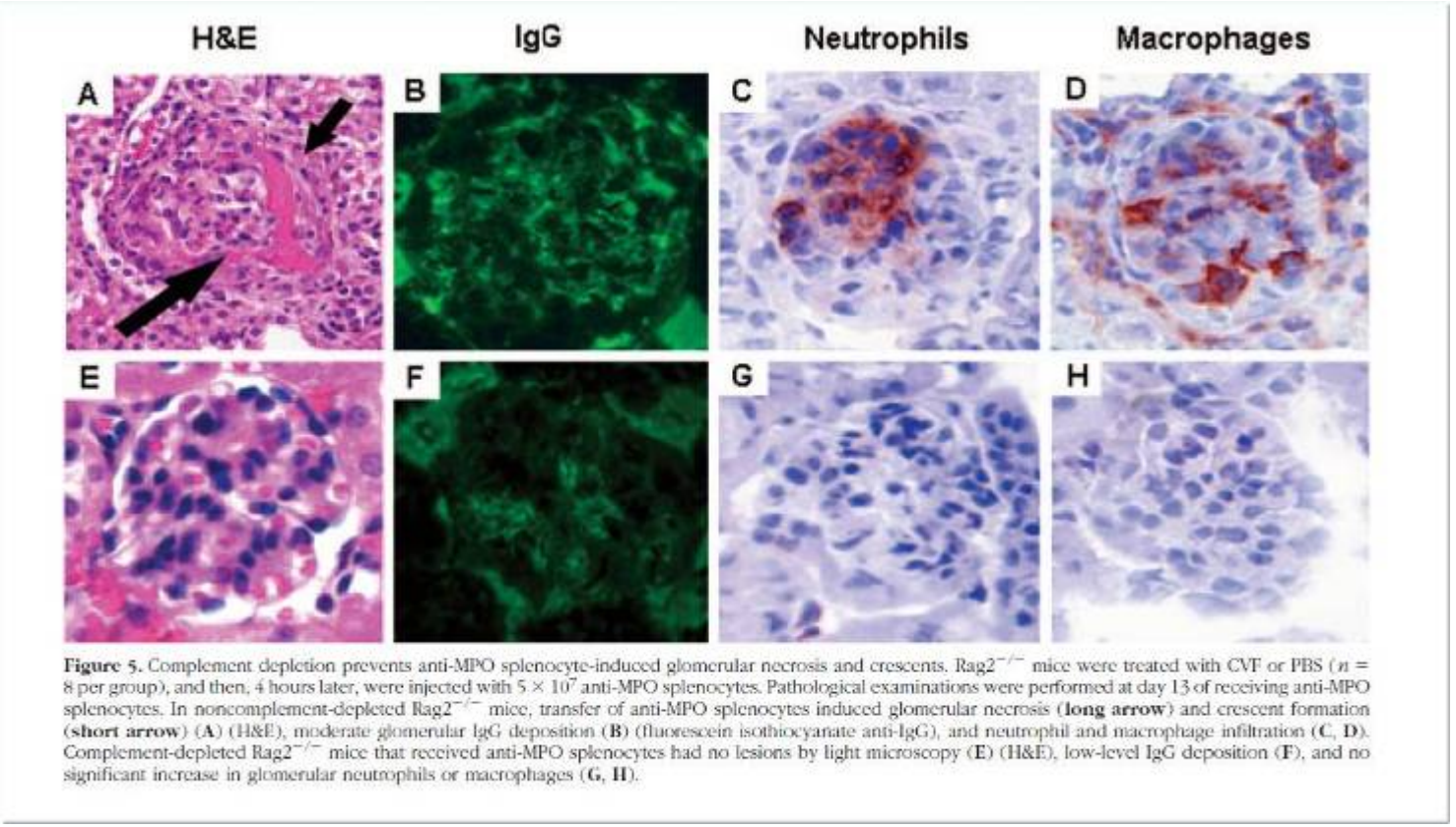
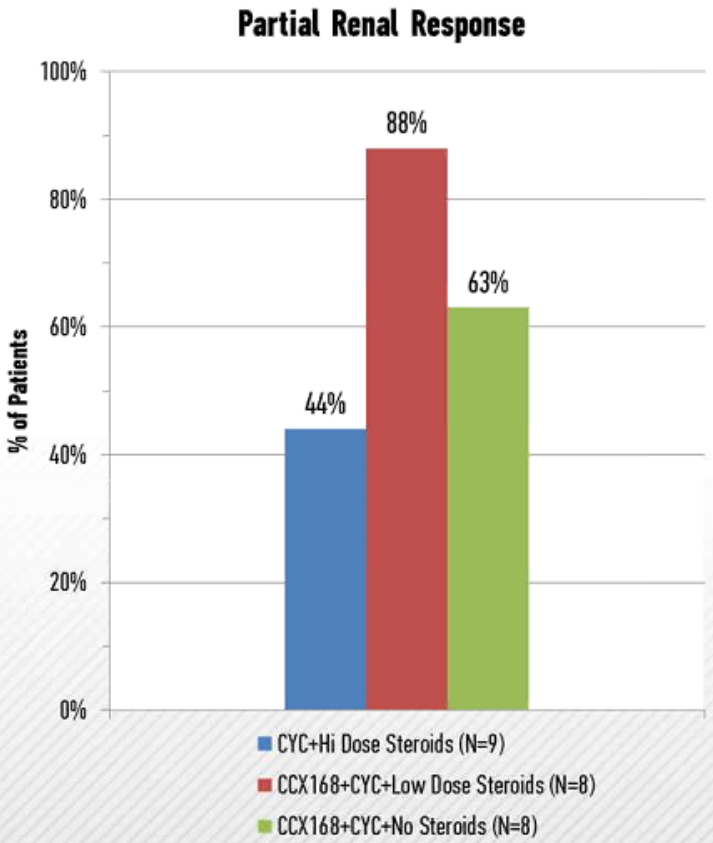


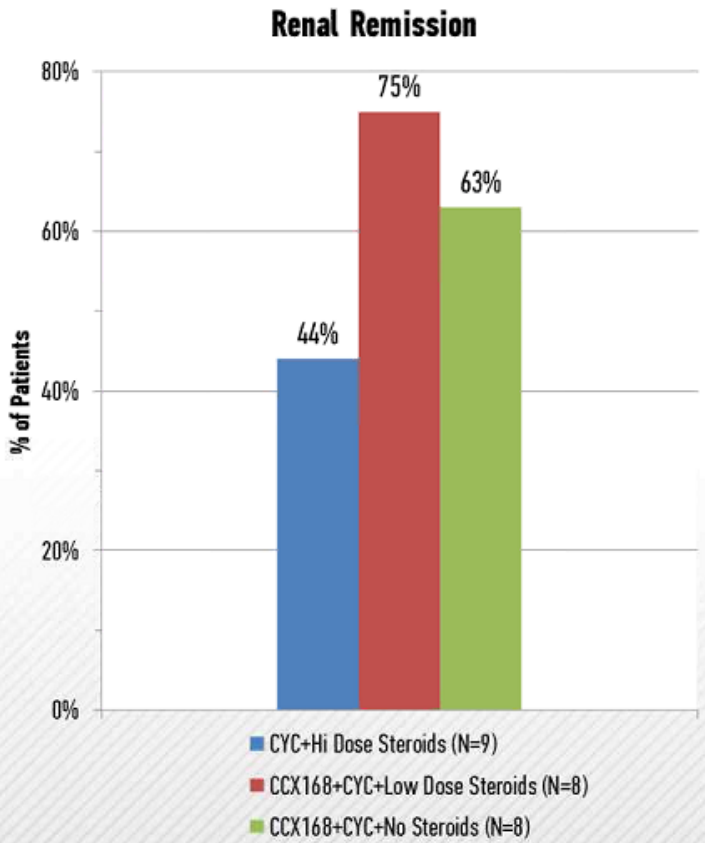
Figure 5. Complement depletion prevents anti-MPO splenocyte-induced glomerular necrosis and crescents. $Rag2^{-/-}$ mice were treated with CVF or PBS (n = 8 per group), and then, 4 hours later, were injected with 5×10^7 anti-MPO splenocytes. Pathological examinations were performed at day 13 of receiving 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

Xiao et al. Am J Pathol. 2007 Jan;170(1):52-64
Schreiber et al., J Am Soc Nephrol. 2009

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

Quoi de neuf dans les vascularites des gros vaisseaux?

Journal of Human Genetics (2015), 1–6

www.nature.com/jhg

REVIEW

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

Chikashi Terao[1,2,3,4,5]

Takayasu arteritis (TAK) is an immune-mediated vasculitis affecting large arteries first reported in 1908 from Japan. Case reports of familial onset of TAK from Japan and other countries indicated genetic contribution to TAK onset beyond ethnicity. Genetic studies of TAK have been performed mainly addressing the human leukocyte antigen (HLA) locus. HLA genetic studies of TAK that have previously been reported are reviewed in this manuscript. HLA-B*52:01 is associated with TAK beyond population. Many of the associations other than HLA-B*52:01 can be explained by a haplotype with HLA-B*52:01. HLA-B*67:01 is a novel susceptibility HLA-B allele to TAK confirmed in the Japanese population. Further independent associations are suggested in the HLA locus. Involvement of the 171st and 67th amino acid residues with TAK onset has been indicated. The 67th amino acid may explain the difference in susceptibility effects to TAK and Behçet's disease between HLA-B*52:01 and *51:01. HLA-B*52:01 is associated not only with TAK susceptibility but also with clinical phenotypes. Recent genome-wide association studies of TAK revealed multiple non-HLA susceptibility genes. In particular, the IL12B region seems to have a central role in TAK onset and its progression. Whether TAK and giant cell arteritis (GCA), the other vasculitis 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 TAK. GCA is not associated with HLA-Bw52. 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.2015.87

A Large-Scale Genetic Analysis Reveals a Strong Contribution of the HLA Class II Region to Giant Cell Arteritis Susceptibility

F. David Carmona,[1,54,*] Sarah L. Mackie,[2,54] Jose-Ezequiel Martin,[1,54] John C. Taylor,[3] Augusto Vaglio,[4] Stephen Eyre,[5] Lara Bossini-Castillo,[1] Santos Castañeda,[6] Maria C. Cid,[7] José Hernández-Rodríguez,[7] Sergio Prieto-González,[7] Roser Solans,[8] Marc Ramentol-Sintas,[8] M. Francisca González-Escribano,[9] Lourdes Ortiz-Fernández,[9] Inmaculada C. Morado,[10] Javier Narváez,[11] José A. Miranda-Filloy,[12] Spanish GCA Group, Lorenzo Beretta,[13] Claudio Lunardi,[14] Marco A. Cimmino,[15] Davide Gianfreda,[16] Daniele Santilli,[17] Giuseppe A. Ramirez,[18] Alessandra Soriano,[19] Francesco Muratore,[20] Giulia Pazzola,[20] Olga Addimanda,[20] Cisca Wijmenga,[21] Torsten Witte,[22] Jan H. Schirmer,[23] Frank Moosig,[23] Verena Schönau,[24] Andre Franke,[25] Øyvind Palm,[26] Øyvind Molberg,[26] Andreas P. Diamantopoulos,[27] Simon Carette,[28] David Cuthbertson,[29] Lindsy J. Forbess,[30] Gary S. Hoffman,[31] Nader A. Khalidi,[32] Curry L. Koening,[33] Carol A. Langford,[31] Carol A. McAlear,[34] Larry Moreland,[35] Paul A. Monach,[36] Christian Pagnoux,[28] Philip Seo,[37] Robert Spiera,[38] Antoine G. Sreih,[34] Kenneth J. Warrington,[39] Steven R. Ytterberg,[39] Peter K. Gregersen,[40] Colin T. Pease,[41] Andrew Gough,[42] Michael Green,[43] Lesley Hordon,[44] Stephen Jarrett,[45] Richard Watts,[46] Sarah Levy,[47] Yusuf Patel,[48] Sanjeet Kamath,[49] Bhaskar Dasgupta,[50] Jane Worthington,[5] Bobby P.C. Koeleman,[51] Paul I.W. de Bakker,[51,52] Jennifer H. Barrett,[3] Carlo Salvarani,[20] Peter A. Merkel,[34] Miguel A. González-Gay,[53,55] Ann W. Morgan,[3,55] and Javier Martín[1,55]

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14-3-3 in Thoracic Aortic Aneurysms

Identification of a Novel Autoantigen in Large Vessel Vasculitis

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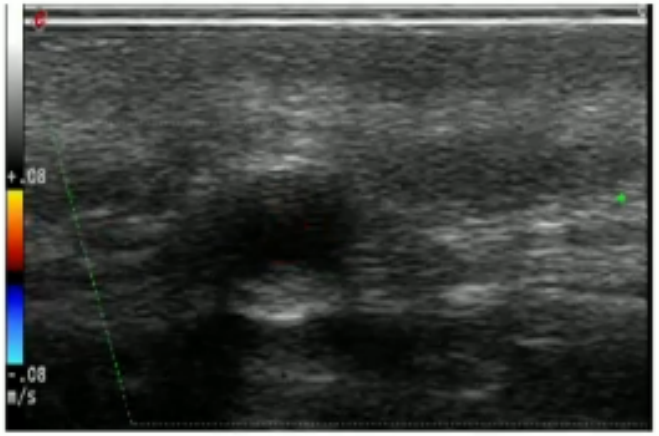
Objective. **Large vessel vasculitides (LVV) are a group of autoimmune diseases characterized by injury to and anatomic modifications of large vessels, including the aorta and its branch vessels. Disease etiology is unknown. This study was undertaken to identify antigen targets within affected vessel 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.**

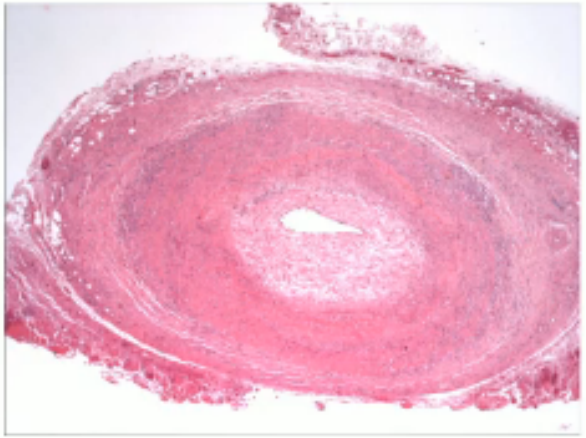
Methods. **Thoracic aortic aneurysm specimens and autologous blood were acquired from consenting patients who underwent aorta reconstruction procedures. Aorta proteins were extracted from both patients with LVV and age-, race-, and sex-matched disease controls with noninflammatory aneurysms. A total 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 (ϵ and ζ) 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





R Luqmani, E Lee, S Singh, M Gillett, W A Schmidt, M Bradburn, B Dasgupta, A P Diamantopoulos, W Forrester-Barker, W Hamilton, S Masters, B McDonald, E McNally, C T Pease, J Piper, J Salmon, A Wailoo, K Wolfe, A Hutchings and the TABUL Study Group

NHS National Institute for Health Research

UNIVERSITY OF OXFORD

TABUL – n=399 patients with suspected GCA

Luqmani et al. ACR 2015

Strategy	Sensitivity	Specificity	% having ultrasound	% having biopsy
Biopsy only (all patients)	39%	100%	0%	100%
Ultrasound only (all patients)	54%	81%	100%	0%
Biopsy & ultrasound (both in all patients)	65%	81%	100%	100%
Ultrasound followed by biopsy if US negative	65%	81%	100%	57%
Ultrasound followed by biopsy if high risk	94%	77%	100%	2%
Ultrasound followed by biopsy if medium or high risk	95%	77%	100%	13%

Luqmani et al. ACR 2015

Multifocal VZV vasculopathy with temporal artery infection mimics giant cell arteritis

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Nelly Khmeleva, BS
Alexander Choe, BA
April Rempel
Philip J. Boyer, MD, PhD
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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 suspect 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

GLOSSARY

AION = anterior ischemic optic
formalin-fixed, paraffin-embedde
saline; **TA** = temporal artery; **VZ**

Giant cell arteritis (GCA)
tenderness, jaw or tongue

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

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Nelly Khmeleva, BS
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Randall J. Cohrs, PhD

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 artery (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 virions. 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 61/82 (74%) GCA-positive TAs compared with 1/13 (8%) normal TAs ($p < 0.0001$, relative risk 9.67, 95% confidence interval 1.46, 63.69). 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 virions 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 18 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

Original Investigation

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

Maria A. Nagel, MD; Teresa White, BS; Nelly Khmeleva, BS; April Rempel, BS; Philip J. Boyer, MD, PhD; Jeffrey L. Bennett, MD, PhD; Andrea Haller, MD; Kelly Lear-Kaul, MD; Balasurbramaniyam Kandasmy, MD; Malena Amato, MD; Edward Wood, MD; Vikram Durairaj, MD; Franz Fogt, MD; Madhura A. Tamhankar, MD; Hans E. Grossniklaus, MD; Robert J. Poppiti, MD; Brian Bockelman, MD; Kathy Keyvani, MD; Lea Pollak, MD; Sonia Mendlovic, MD; Mary Fowkes, MD, PhD; Charles G. Eberhart, MD, PhD; Mathias Buttmann, MD; Klaus V. Toyka, MD; Tobias Meyer-ter-Vehn, MD; Vigdis Petursdottir, MD; Don Gilden, MD

Supplemental content at jamaneurology.com

IMPORTANCE 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, paraffin-embedded GCA-negative, GCA-positive, 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.

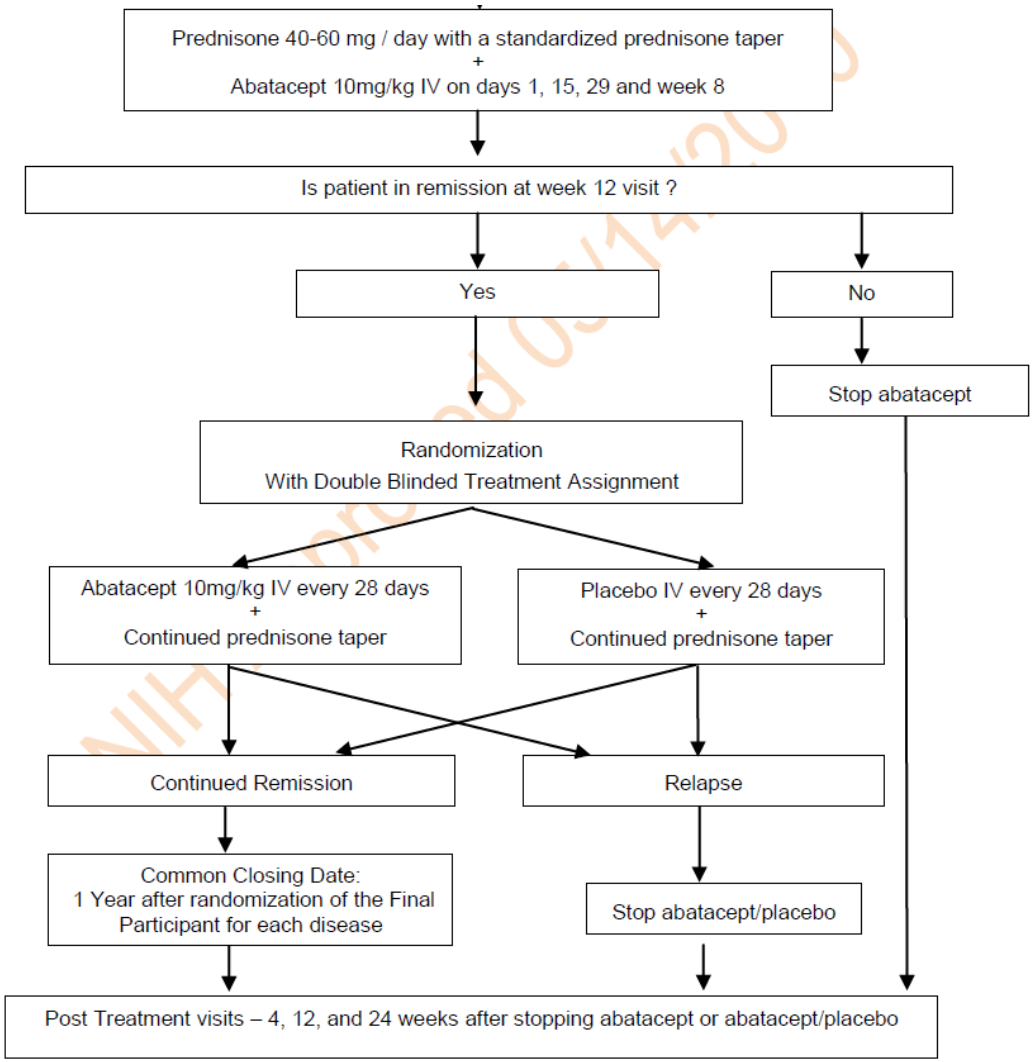
MAIN OUTCOMES AND MEASURES Presence and distribution of VZV antigen in TAs and histopathological changes in sections adjacent to those containing VZV were confirmed by 2 independent readers.

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] = 2.86; 95% CI, 1.75-5.31; $P < .001$). Extension of our earlier study revealed VZV antigen in 68 of 93 GCA-positive TAs (73%), compared with 11 of 49 normal TAs (22%) (RR = 3.26; 95% CI, 2.03-5.98; $P < .001$). Compared with normal TAs, VZV antigen was more likely to be present in the adventitia of

AGATA LVV

- VCRC 5523
- CTLA4-Ig / abatacept

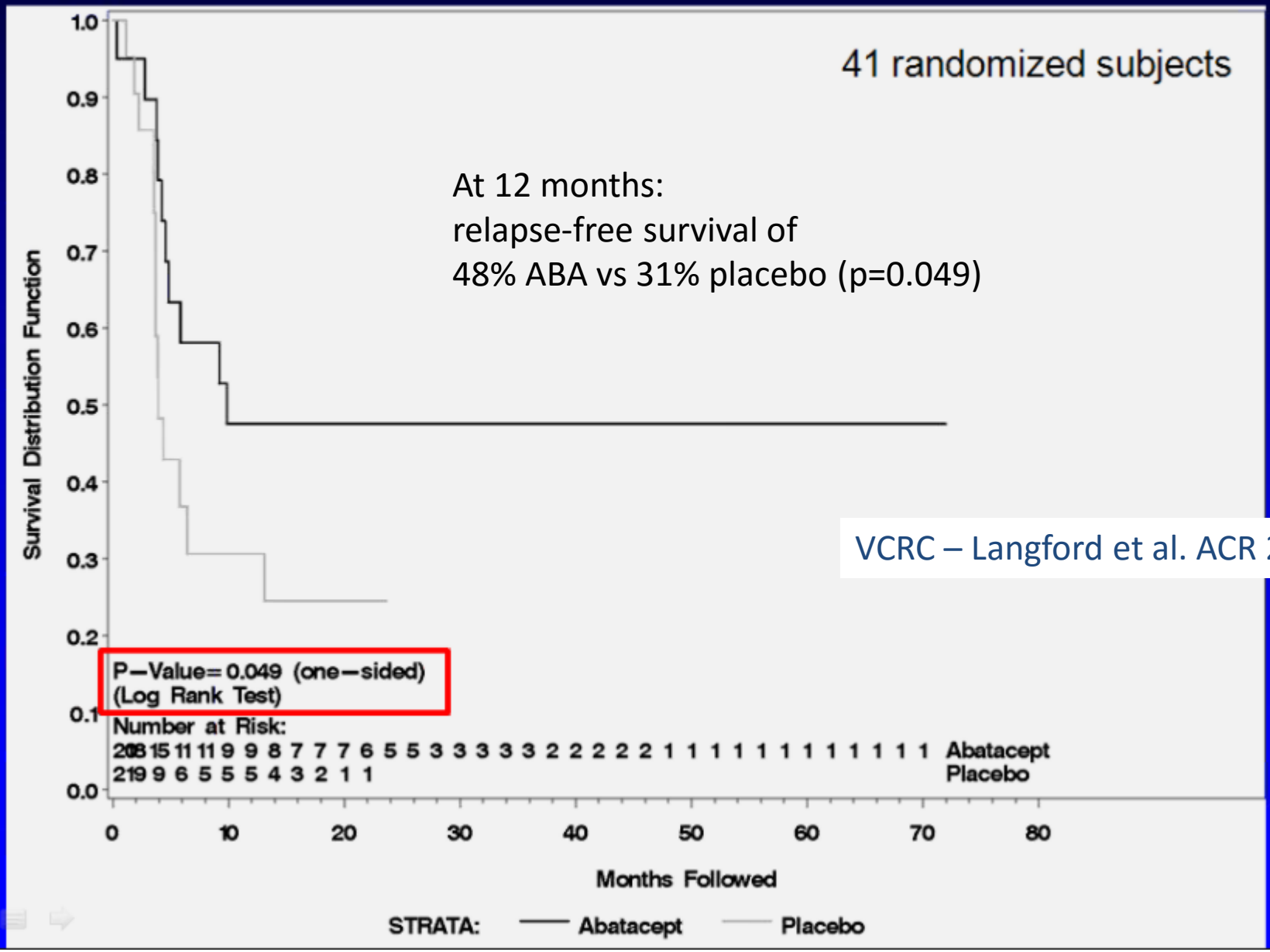
- 15 Hamilton
- 11 Toronto



VCRC – Langford et al. ACR 2015

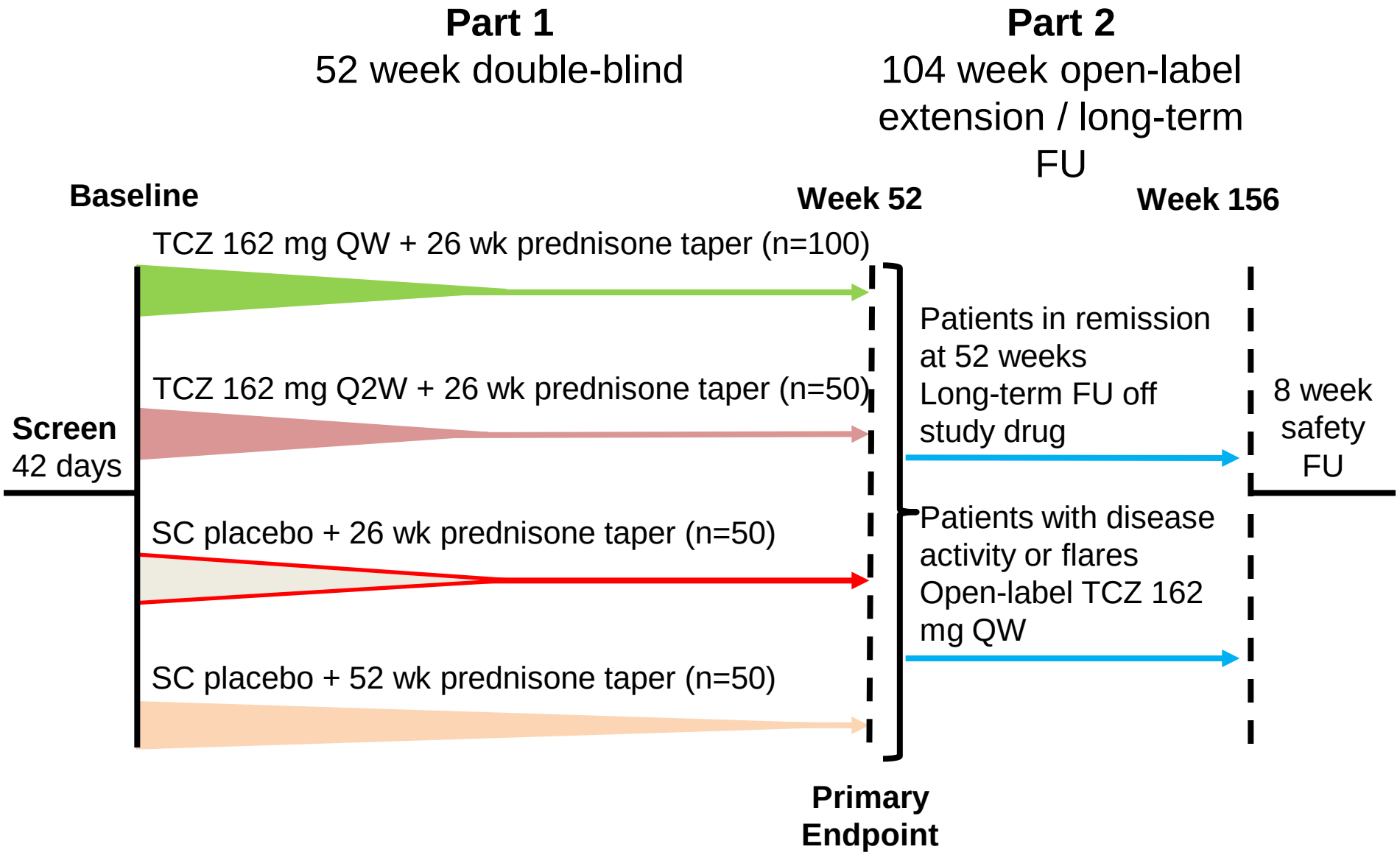
Abatacept in Giant Cell Arteritis

Primary Endpoint - Intent-to-Treat - Kaplan-Meier Plot



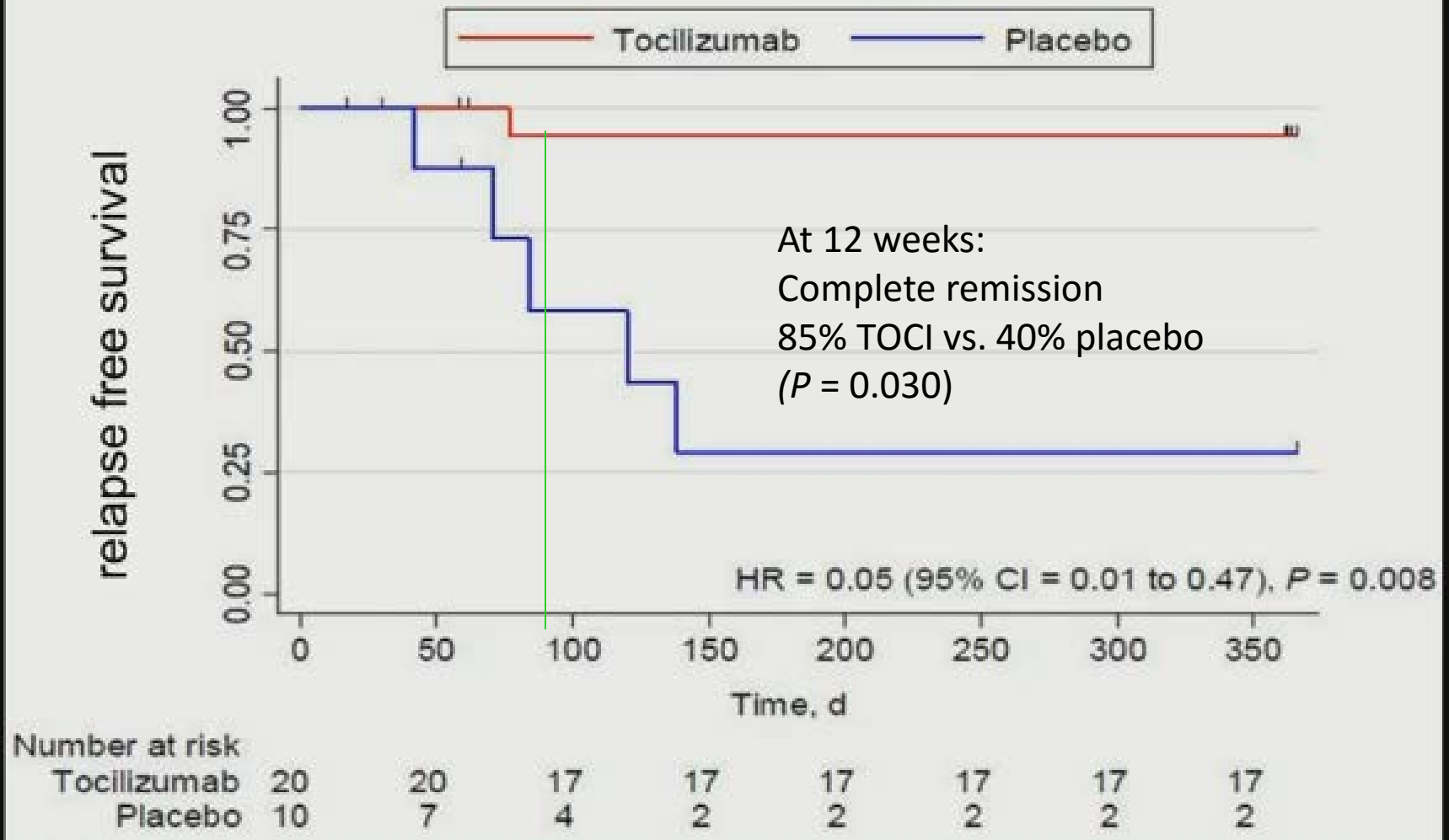
VCRC – Langford et al. ACR 2015

GiACTA Study



Time to first Relapse

TCZ (8 mg/kg IV)

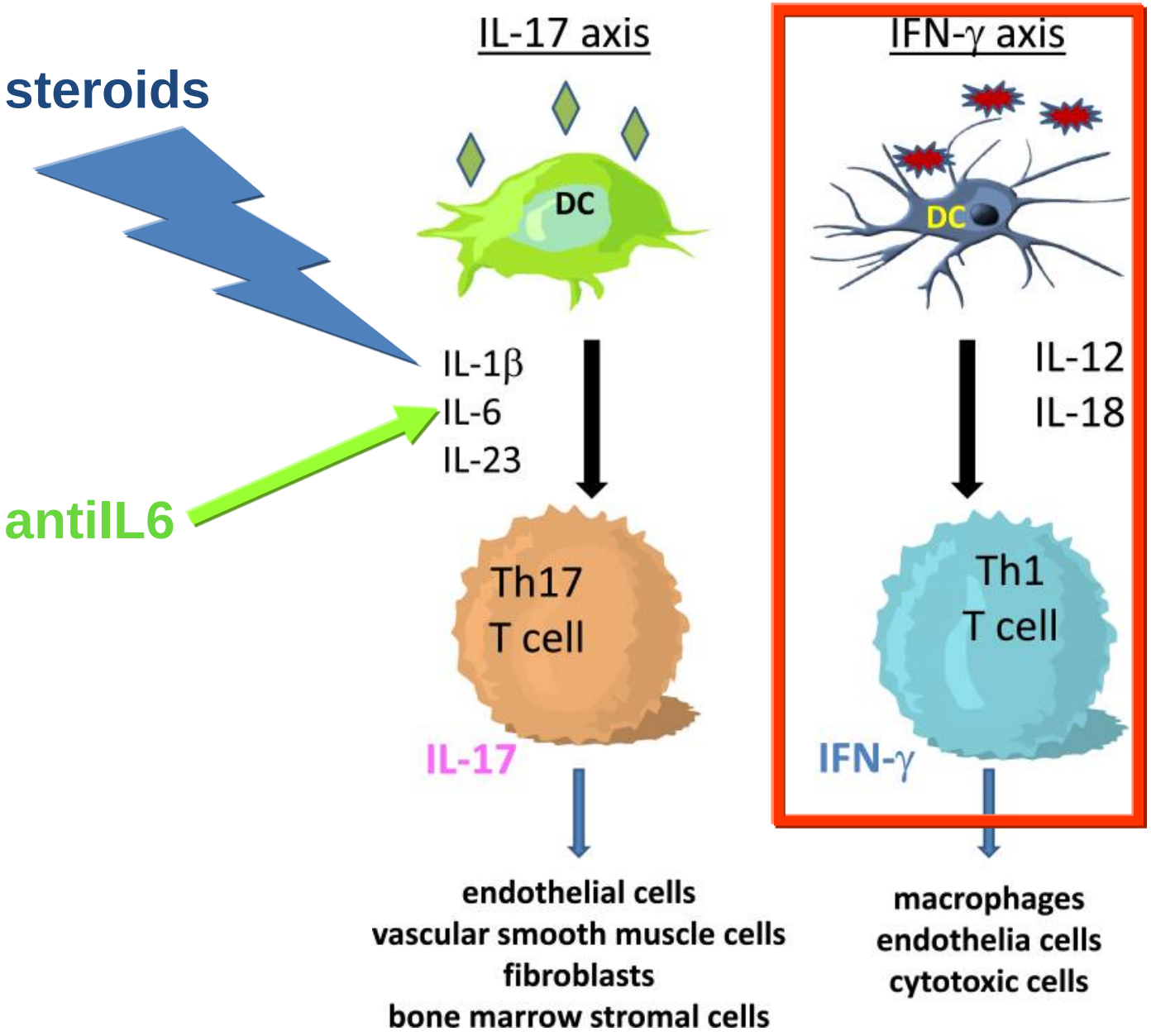


Adler et al. ACR 2015

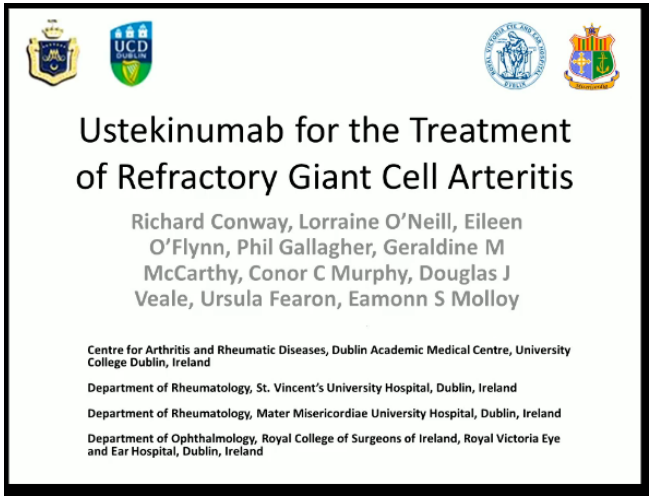
Safety *Serious Adverse Events (SAE)*

	TCZ (n=20)	Placebo (n=10)
SAE	7/20	10/10
characteristics		
cardiovascular	1	3
gastrointestinal	3	1
osteoporotic fracture	0	2
back pain	0	2
glucocorticoid related	1	2
infection	1	0
other	1	0

Adler et al. ACR 2015



Weyand CM et al. Curr Opin Rheumatol. 2011; 23(1): 43–49



Ustekinumab for the Treatment of Refractory Giant Cell Arteritis

Richard Conway, Lorraine O'Neill, Eileen O'Flynn, Phil Gallagher, Geraldine M McCarthy, Conor C Murphy, Douglas J Veale, Ursula Fearon, Eamonn S Molloy

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Department of Ophthalmology, Royal College of Surgeons of Ireland, Royal Victoria Eye and Ear Hospital, Dublin, Ireland

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)

Conway et al. ACR 2015

EXTENDED REPORT

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 Guillevin,[8] P A Merkel,[9] D R W Jayne[1]

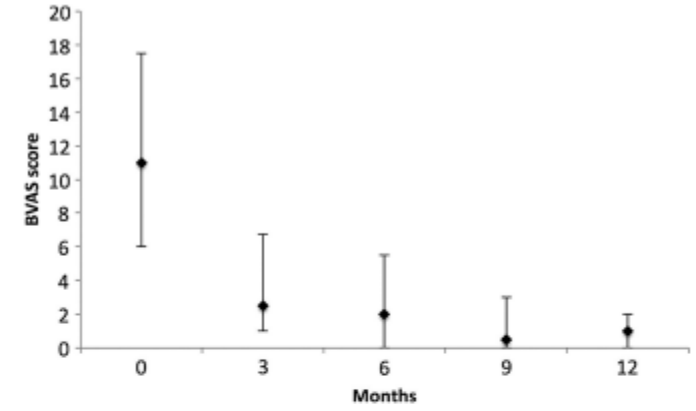
N = 41, with RTX 2003-2013 (15 refractory, 21 relapsing, 5 new)
ANCA= 44%
4 centers USA and EU (Boston, Cochin, Bad Bramstedt, Cambridge)

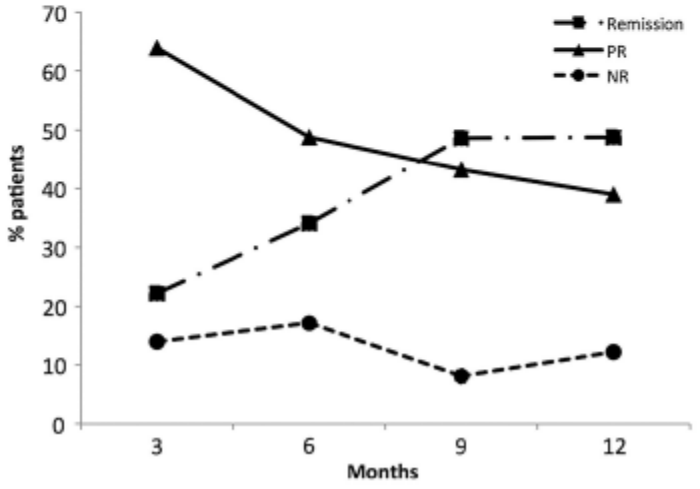
19 one course only, others retreated at M6 or M12
30 with 4x375, 10 with 2x1 (1 with 800x2) – same results

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)

Ann Rheum Dis 2014 (Dec. 2)



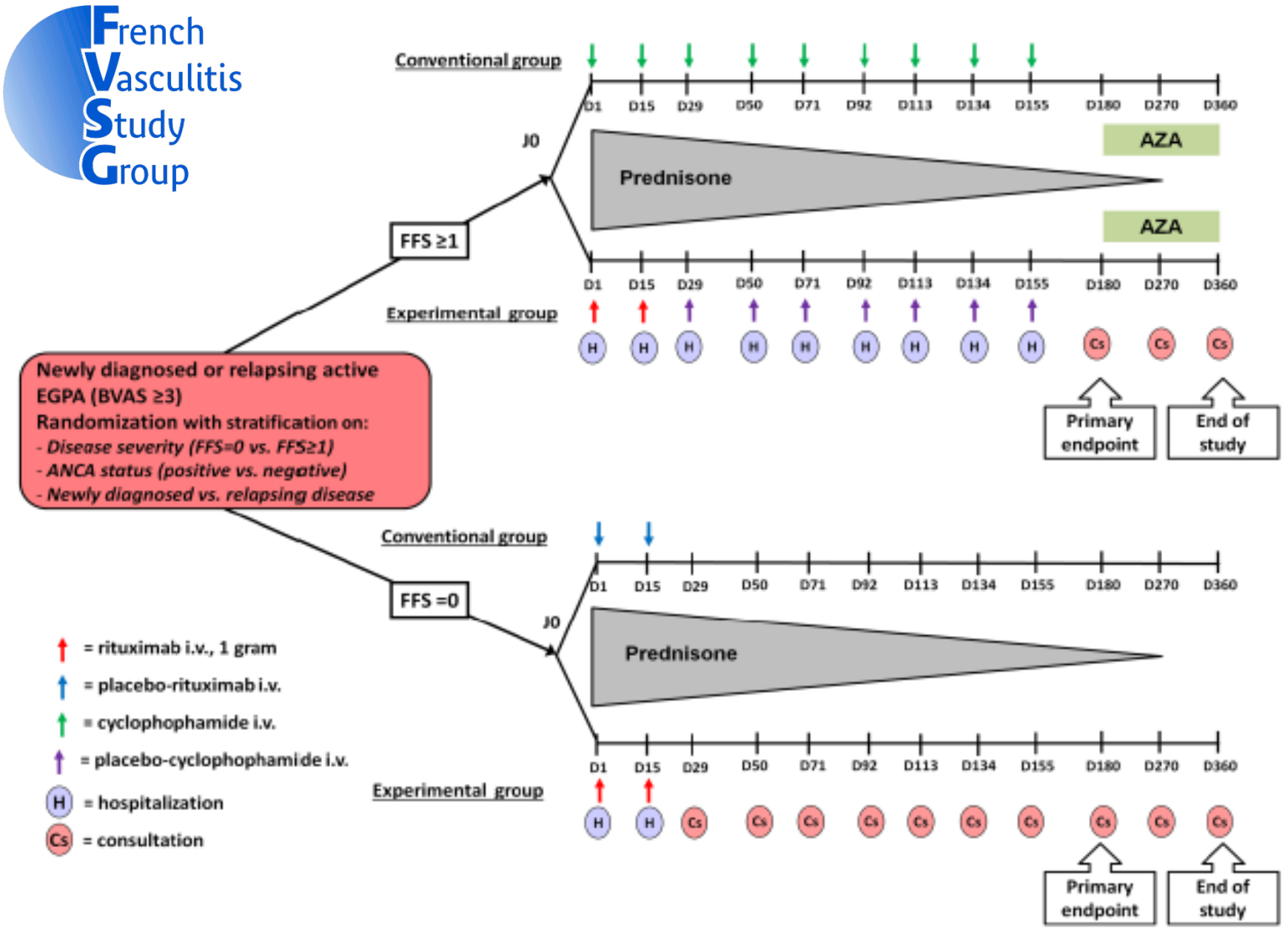


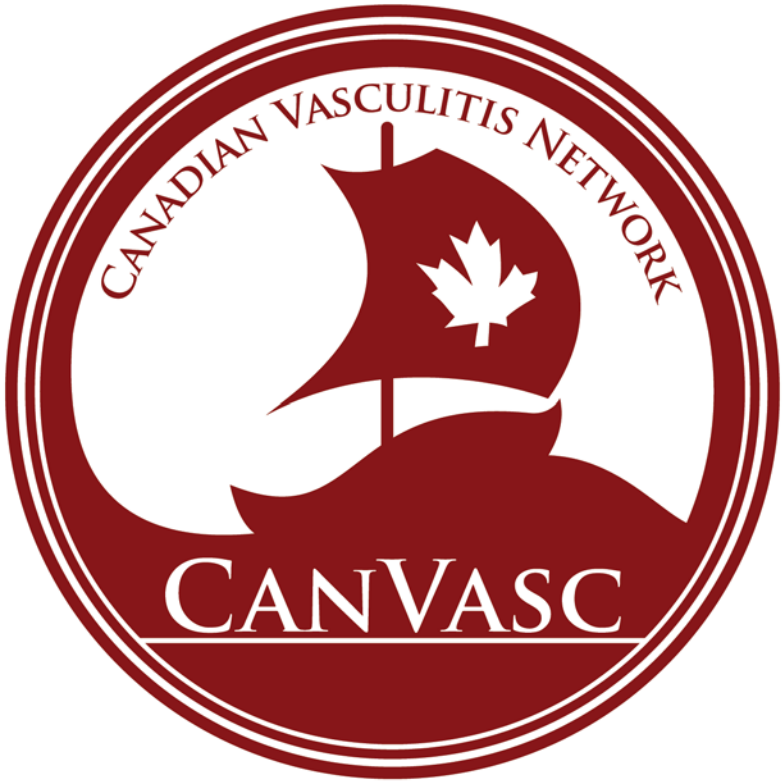
41 patients
18 patients ANCA+
23 patients ANCA-

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

Réponse ANCA+ > ANCA-

Mohammad, Ann Rheum Dis, 2015


French Vasculitis Study Group
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
FFS =0
J0
Conventional group
Experimental group
Prednisone
AZA
AZA
D1 D15 D29 D50 D71 D92 D113 D134 D155 D180 D270 D360
H
Cs
Primary endpoint
End of study
= rituximab i.v., 1 gram
= placebo-rituximab i.v.
= cyclophophamide i.v.
= placebo-cyclophophamide i.v.
= hospitalization
= consultation



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