Vasculitis sistémicas: nuevos conceptos

"THE TOP FIVE"

Dra. Roser Solans Laqué
Servicio de Medicina Interna
Unidad de Enfermedades sistémicas autoinmunes
Hospital Universitario Vall d'Hebrón. Barcelona.
Universitat Autònoma de Barcelona (U.A.B.)

Vall d'Hebron Hospital

UAB Universitat Autònoma de Barcelona

GEAS

2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides

J. C. Jennette,[1] R. J. Falk,[1] P. A. Bacon,[2] N. Basu,[3] M. C. Cid,[4] F. Ferrario,[5] L. F. Flores-Suarez,[6] W. L. Gross,[7] L. Guillevin,[8] E. C. Hagen,[9] G. S. Hoffman,[10] D. R. Jayne,[11] C. G. M. Kallenberg,[12] P. Lamprecht,[13] C. A. Langford,[10] R. A. Luqmani,[14] A. D. Mahr,[15] E. L. Matteson,[16] P. A. Merkel,[17] S. Ozen,[18] C. D. Pusey,[19] N. Rasmussen,[20] A. J. Rees,[21] D. G. I. Scott,[22] U. Specks,[16] J. H. Stone,[23] K. Takahashi,[24] and R. A. Watts[25]

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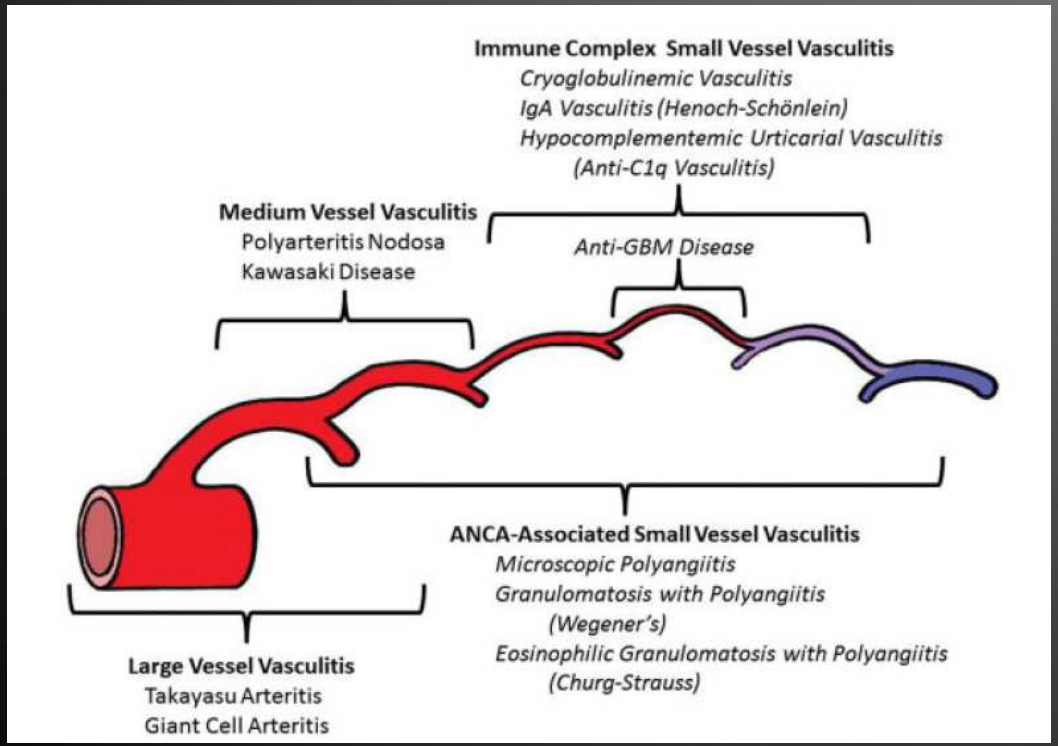


Table 2. Names for vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides

- **Large vessel vasculitis (LVV)**
  - Takayasu arteritis (TAK)
  - Giant cell arteritis (GCA)
- **Medium vessel vasculitis (MVV)**
  - Polyarteritis nodosa (PAN)
  - Kawasaki disease (KD)
- **Small vessel vasculitis (SVV)**
  - Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)
    - Microscopic polyangiitis (MPA)
    - Granulomatosis with polyangiitis (Wegener's) (GPA)
    - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
  - Immune complex SVV
    - Anti–glomerular basement membrane (anti-GBM) disease
    - Cryoglobulinemic vasculitis (CV)
    - IgA vasculitis (Henoch-Schönlein) (IgAV)
    - Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)
- **Variable vessel vasculitis (VVV)**
  - Behçet's disease (BD)
  - Cogan's syndrome (CS)
- **Single-organ vasculitis (SOV)**
  - Cutaneous leukocytoclastic angiitis
  - Cutaneous arteritis
  - Primary central nervous system vasculitis
  - Isolated aortitis
  - Others
- **Vasculitis associated with systemic disease**
  - Lupus vasculitis
  - Rheumatoid vasculitis
  - Sarcoid vasculitis
  - Others
- **Vasculitis associated with probable etiology**
  - Hepatitis C virus–associated cryoglobulinemic vasculitis
  - Hepatitis B virus–associated vasculitis
  - Syphilis-associated aortitis
  - Drug-associated immune complex vasculitis
  - Drug-associated ANCA-associated vasculitis
  - Cancer-associated vasculitis
  - Others

Revisiting the classification of clinical phenotypes of anti-neutrophil cytoplasmic antibody-associated vasculitis: a cluster analysis

Alfred Mahr, Sandrine Katsahian, Hugo Varet, et al.

Ann Rheum Dis 2013;**72**:1003–1010.

- PAM y PAMG se diferencian por hallazgos histológicos y clínicos, pero a veces se superponen (overlap)
- A partir de pacientes de reciente diagnóstico incluidos en estudios multicéntricos, se intenta identificar distintos “clusters” a partir de los datos clínicos y a partir de la especificidad de los ANCA

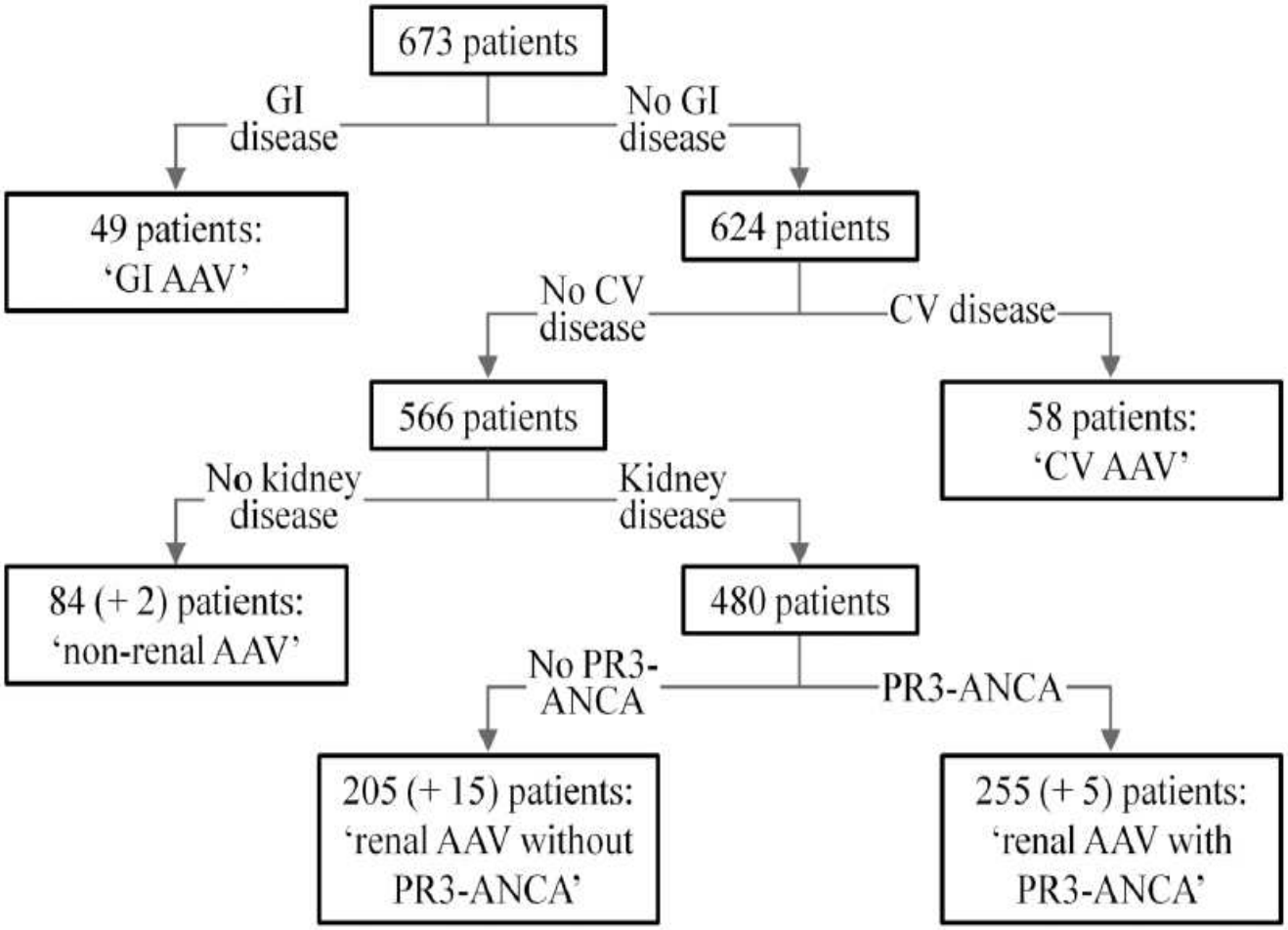

673 patients
GI disease
No GI disease
49 patients: 'GI AAV'
624 patients
No CV disease
CV disease
566 patients
58 patients: 'CV AAV'
No kidney disease
Kidney disease
84 (+ 2) patients: 'non-renal AAV'
480 patients
No PR3-ANCA
PR3-ANCA
205 (+ 15) patients: 'renal AAV without PR3-ANCA'
255 (+ 5) patients: 'renal AAV with PR3-ANCA'

Table 1 Baseline phenotypic characteristics and follow-up data of 673 patients with anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), within subgroups with GPA and MPA and within each cluster generated by cluster model 2 including nine clinical variables plus PR3-ANCA and MPO-ANCA positivity as input variables

		By clinical diagnosis		Clusters				
Variable	All	GPA	MPA	Non-renal AAV	Renal AAV with PR3-ANCA	Renal AAV without PR3-ANCA	CV AAV	GI AAV
No	673 (100)	396 (58.8)	277 (41.2)	84 (12.5)	270 (40.1)	212 (31.5)	58 (8.6)	49 (7.3)
Diagnosis								
GPA	396 (58.8)	396 (100)	0	80 (95.2)	217 (80.4)	38 (17.9)	37 (63.8)	24 (49.0)
MPA	277 (41.2)	0	277 (100)	4 (4.8)	53 (19.6)	174 (82.1)	21 (36.2)	25 (51.0)
Age at diagnosis, mean (SD) (year)	57.9 (14.1)	55.2 (14.3)	61.8 (12.9)	52.3 (14.1)	55.3 (14.7)	61.7 (12.4)	60.1 (14.3)	62.1 (12.1)
Male sex*								
Symptoms								
Kidney*								
Lung*								
ENT*								
Eye*								
Skin*								
Neuropathy*								
CV*								
GI*								
ANCA positivity								
PR3-ANCA*	376 (55.9)	311 (78.5)	65 (23.5)	68 (81.0)	255 (94.4)	5 (2.4)	34 (58.6)	33 (67.3)
MPO-ANCA*	212 (31.5)	42 (10.6)	170 (61.4)	7 (8.3)	0	176 (83.0)	16 (27.6)	13 (26.5)
PR3-ANCA and MPO-ANCA	19 (2.8)	14 (3.5)	5 (1.8)	N/A*	N/A*	N/A*	N/A*	N/A*
Neither	66 (9.8)	29 (7.3)	37 (13.4)	9 (10.7)	15 (5.6)	31 (14.6)	8 (13.8)	3 (6.1)
BVAS, mean (SD)	19.5 (8.5)	20.6 (8.6)	17.9 (8.2)	12.1 (6.0)	20.7 (8.2)	17.6 (7.1)	26.2 (8.2)	25.1 (8.5)
Creatinine, mean (SD) (μl/litre)	295.0 (294.1)	214.2 (234.2)	408.1 (330.4)	88.4 (56.0)	271.4 (269.6)	392.8 (335.6)	298.0 (276.2)	330.3 (293.5)
Trial								
Early systemic AAV	92 (13.7)	86 (21.7)	6 (2.2)	50 (59.5)	30 (11.1)	5 (2.4)	3 (5.2)	4 (8.2)
Generalised AAV	148 (22.0)	91 (23.0)	57 (20.6)	5 (6.0)	81 (30.0)	49 (23.1)	7 (12.1)	6 (12.2)
Generalised renal AAV	147 (21.8)	56 (14.1)	91 (32.9)	4 (4.8)	58 (21.5)	71 (33.5)	6 (10.3)	8 (16.3)
Systemic AAV	172 (25.6)	127 (32.1)	45 (16.3)	25 (29.8)	57 (21.1)	33 (15.6)	31 (53.5)	26 (53.1)
Severe renal AAV	114 (16.9)	36 (9.1)	78 (28.2)	0	44 (16.3)	54 (25.5)	11 (19.0)	5 (10.2)
Events								
Death	137 (20.4)	55 (13.9)	82 (29.6)	5 (6.0)	36 (13.3)	66 (31.1)	15 (25.9)	15 (30.6)
Relapse	238 (35.4)	184 (46.5)	54 (19.5)	46 (54.8)	116 (43.0)	46 (21.7)	22 (37.9)	8 (16.3)
Follow-up, mean (SD) (year)	4.45 (3.03)	4.75 (2.98)	4.02 (3.05)	4.68 (2.65)	5.21 (3.06)	4.09 (3.09)	2.82 (2.41)	3.35 (2.64)

Conclusions This analysis suggests that AAV encompasses five classes associated with different outcomes. As compared with the traditional GPA–MPA separation, this classification system may better reflect the phenotypic spectrum of AAV.

Classification of Antineutrophil Cytoplasmic Autoantibody Vasculitides

ARTHRITIS & RHEUMATISM
Vol. 64, No. 10, October 2012, pp 3452–3462

The Role of Antineutrophil Cytoplasmic Autoantibody Specificity for Myeloperoxidase or Proteinase 3 in Disease Recognition and Prognosis

Table 2. Frequency of short- and long-term outcomes across classification systems*

Classification system, disease (n)	Treatment resistance (n = 109/483)	Relapse (n = 147/374)	ESRD (n = 161/502)	Death (n = 139/502)
Chapel Hill Consensus Conference				
GPA (117)	20/117 (17)	58/97 (60)	24/117 (21)	20/117 (17)
MPA (264)	56/255 (22)	74/199 (37)	80/264 (30)	79/264 (30)
Kidney-limited disease (121)	33/111 (30)	15/78 (19)	57/121 (47)	40/121 (33)
P	0.0711	<0.0001	<0.0001	0.0091
European Medicines Agency				
GPA (324)	68/317 (22)	110/249 (44)	92/324 (28)	84/324 (26)
MPA (178)	41/166 (25)	37/125 (30)	69/178 (39)	55/178 (31)
P	0.4244	0.0071	0.0214	0.2520
ANCA specificity				
MPO ANCA (283)	7			
PR3 ANCA (219)	3			
P				

* Values are the number/total number
granulomatosis with polyangiitis (Wegene
cytoplasmic antibody; MPO ANCA = A
with proteinase 3 specificity.

Conclusion. **ANCA specificity independently predicts relapse among patients with AAV with renal disease. Classification and diagnostic systems that incorporate ANCA specificity, such as PR3 ANCA–positive MPA and MPO ANCA–positive MPA, provide a more useful tool than the clinical pathologic category alone for predicting relapse.**

Antineutrophil cytoplasmic antibody-associated vasculitides: is it time to split up the group?

Arnaud Millet,[1,2,3,4] Magali Pederzoli-Ribeil,[1,2,3,4] Loïc Guillevin,[5] Véronique Witko-Sarsat,[1,2,3,4] Luc Mouthon[1,2,3,4]

Ann Rheum Dis 2013;**72**:1273–1279.

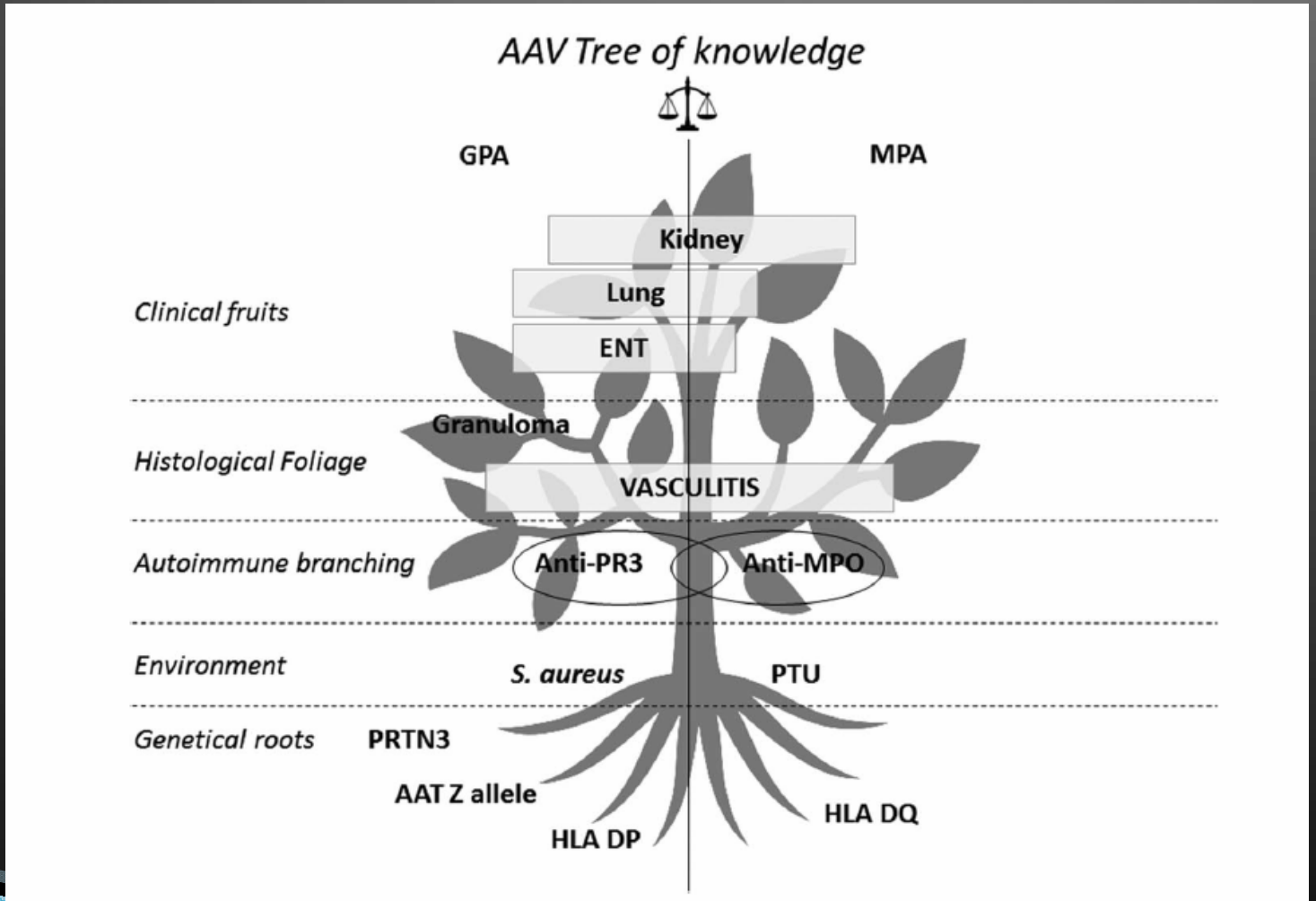


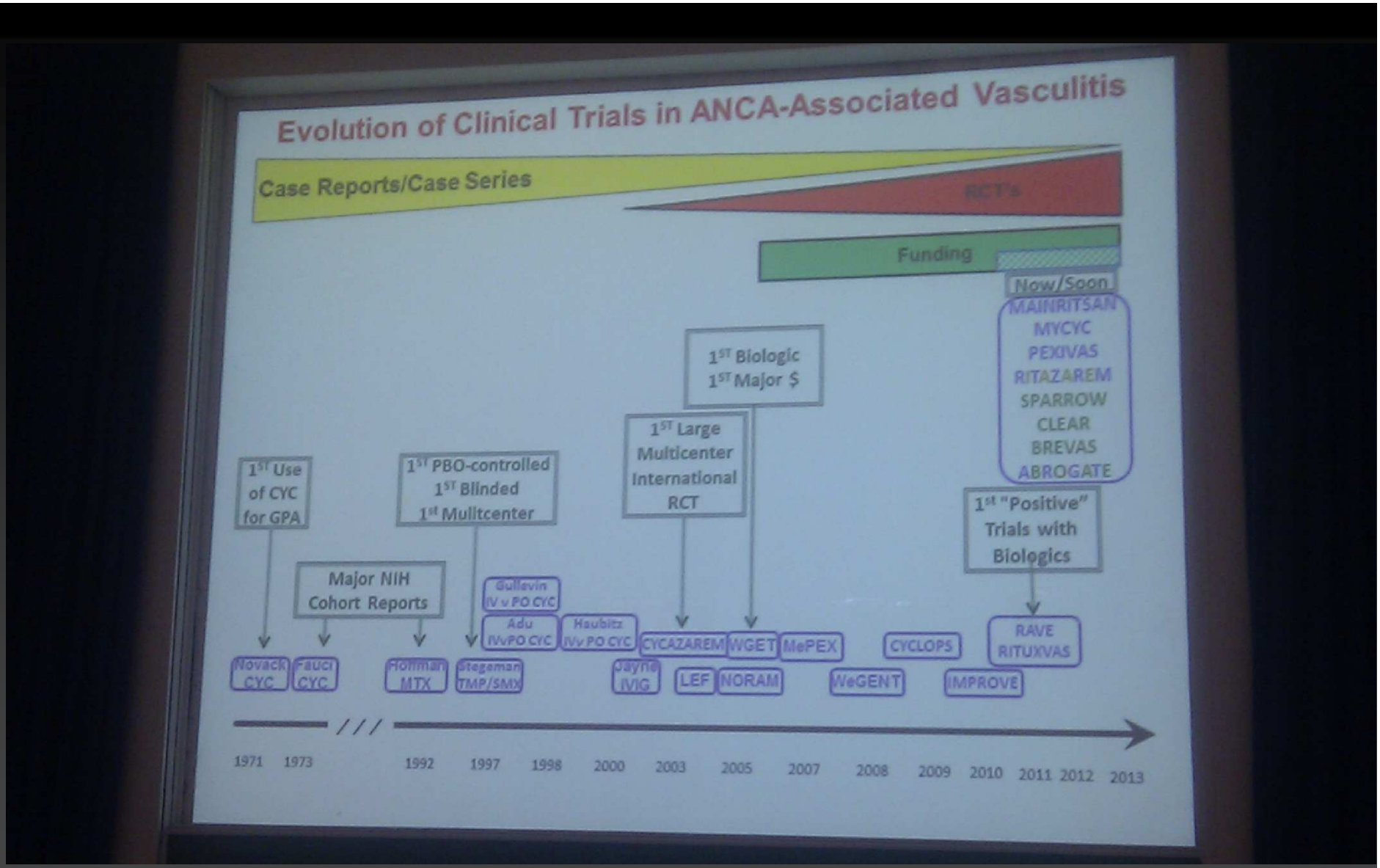
Table 1 Epidemiological, clinical and biological characteristics of patients with granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic GPA (EGPA).[11–20]

	GPA	MPA	EGPA	
Gender	Male>female	Male>female	Male=female	
Peak disease, age (years)	64–74	64–74	40–60	
Geographical distribution	Equator to pole (in Europe)	Pole to equator (in Europe)	NA	
Pattern of appearance	Cyclical	Random	NA	
Environmental factors pharmacological induction	Silica exposure *Staphylococcus aureus*	Silica exposure Propylthiouracil	Silica exposure Leukotriene receptors antagonists	
			ANCA+	ANCA−
Organ involvement (%)				
Skin	30–60	40–70	53–67	51–62
Kidneys	50–80	90–100	31–51	4–16
Lungs	60–80	20–60	34–56	60–76
Ear, nose, throat	80–90	20–30	60–77	53–78
Joints	50–80	30–70	30–40	30–40
Peripheral nervous system	10–50	20–30	71–84	42–65
Eye	30–60	10–30	<10	<10
Bowel	<10	10–30	0–42	14–26
Heart involvement	5–15	10–20	0–12	22–49
Histopathological findings	Necrotising vasculitis and granulomas	Necrotising vasculitis	Necrotising vasculitis Eosinophilic granulomas	
PR3-ANCA	s-GPA 70–95% l-GPA 40–50%	10–20%	0–3.2%	
MPO-ANCA	0–10%	30–80%	32–92%	
Genetic association GWAS (2012)	AAT deficiency HLA DP PRTN3	HLA DQ	HLA-DRB4	
Major associations from previous studies	AAT Z allele PRTN3§ HLA DPB1*0401 PTPN22‡CTLA4‡	PTPN22‡ CTLA4‡	IL-10 promotor (ANCA-subset)	

§Single nucleotide polymorphisms different from Genome Wide Association Study (GWAS).
‡Not confirmed by the GWAS.
ANCA, antineutrophil cytoplasmic antibody; GPA, granulomatosis with polyangiitis; s-GPA, systemic GPA; l-GPA, localised GPA; EGPA, eosinophilic granulomatosis with polyangiitis; HLA, human leukocyte antigen; MPA, microscopic polyangiitis; NA, non applicable.

- A pesar de que en la mayoría de ensayos clínicos se agrupan pacientes con GPA y MPA, los datos clínicos, epidemiológicos y genéticos sugieren que se trata de entidades distintas y que las estrategias terapéuticas deberían estudiarse por separado.

- Es fundamental conocer mejor el papel que juegan los ANCA (MPO, PR3) en el proceso inflamatorio que subyace en ambas enfermedades para diseñar trtamientos mas específicos


Evolution of Clinical Trials in ANCA-Associated Vasculitis
Case Reports/Case Series
RCT's
Funding
Now/Soon
MAINRITSAN
MYCYC
PEXIVAS
RITAZAREM
SPARROW
CLEAR
BREVAS
ABROGATE
1ST Use of CYC for GPA
1ST PBO-controlled
1ST Blinded
1st Mulitcenter
1ST Large Multicenter International RCT
1ST Biologic
1ST Major $
1st "Positive" Trials with Biologics
Major NIH Cohort Reports
Gullevin IV v PO CYC
Adu IVvPO CYC
Haubitz IVv PO CYC
Novack CYC
Fauci CYC
Hoffman MTX
Stegeman TMP/SMX
Jayne IVIG
CYCAZAREM
WGET
MePEX
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16th
"Institut des Cordeliers"
Paris - France
International
Vasculitis & ANCA Workshop
April 14 - 17 2013

Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis

Ulrich Specks, M.D., Peter A. Merkel, M.D., M.P.H., Philip Seo, M.D., Robert Spiera, M.D., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., and John H. Stone, M.D., M.P.H., for the RAVE-ITN Research Group*

N Engl J Med 2013;369:417-27.
AUGUST 1, 2013

- Estudio RAVE: RTX versus CF + AZA en pacientes con VAA y afección orgánica severa
- RC a los 6 meses en 64% RTX versus 53% CF
- RTX mas eficaz en pacientes con enfermedad recidivante a la entrada en estudio
- No diferencia en cuanto a la duración de la remisión, ni frecuencia y gravedad de recidivas, ni en cuanto a efectos adversos excepto menor frecuencia leucopenia y neumonía en grupo RTX

Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis

Ulrich Specks, M.D., Peter A. Merkel, M.D., M.P.H., Philip Seo, M.D., Robert Spiera, M.D., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D.,

N Engl J Med 2013;369:417-27.
AUGUST 1, 2013

- mayor riesgo de recaída:
  - pacientes PR3 + ($p < 0.001$)
  - pacientes con GPA
  - pacientes con enfermedad recidivante a la entrada en el estudio
- no relación entre gravedad de afección renal y mayor riesgo de recidiva
- CD20 reconstituidos en 88% pacientes tratados con RTX y 55% de tratados con CF + AZA, que presentaron recidiva (no relación con ANCA)

Could we abandon cyclophosphamide in systemic vasculitis and lupus nephritis?

Cees G M Kallenberg

Ann Rheum Dis 2013

- No disponemos de suficiente evidencia que avale el uso de RTX en pacientes con formas graves de VAA ni en pacientes con formas granulomatosas
- no disponemos de suficiente evidencia que avale el uso de Rituximab en el tratamiento de mantenimiento de las VAA (RITAZAREM)
- Desconocemos cuanto tiempo y en que dosis debería administrarse Rituximab en el tratamiento de mantenimiento de las AAV
- Desconocemos si se debe o no administrar conjuntamente CF y RTX en formas graves

Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome

Sophia Kim, MD,[a] Gautham Marigowda, MD,[b] Eyal Oren, MD,[c] Elliot Israel, MD,[b] and Michael E. Wechsler, MD[b]

J Allergy Clin Immunol 2010

Mepolizumab in eosinophilic disorders

J Pablo Abonia[1] and Philip E Putnam[2,†]

Expert Rev Clin Immunol. 2011

Extended follow-up after stopping mepolizumab in relapsing/refractory Churg-Strauss syndrome

K. Herrmann, W.L. Gross, F. Moosig *Clin Exp Rheumatol 2012*

Key issue

Clinical implications: Mepolizumab allows for safe steroid tapering while maintaining clinical stability and appears to be a viable therapeutic option in patients with CSS.

- Mepolizumab may indeed have a positive effect in systemic eosinophilic diseases such as the Churg–Strauss and hypereosinophilic syndromes.
- Limited impact of mepolizumab is noted for both mild/moderate asthma and eosinophilic esophagitis to date, and any future use of mepolizumab will need to be targeted against a subset of patients who achieve significant benefits from its use or from the use of modified dosing regimens.

Recommendations of the Italian Society of Rheumatology for the treatment of the primary large-vessel vasculitis with biological agents

N. Pipitone[1], I. Olivieri[2], C. Salvarani[1]

Clin Exp Rheumatol 2012; 30 (Suppl. 70): S139-S161.

- No se recomienda el uso de anti-TNF (Infliximab, Etanercept) en monoterapia ni como tratamiento adyuvante, en el tratamiento inicial de la ACG.
- Sólo se recomienda el uso de anti-TNF en pacientes con ACG y ≥ 2 brotes a pesar de tratamiento adecuado con GC y ≥ 1fármaco inmunosupresor (MTX o AZA) (nivel de evidencia 4 C)
- No se recomienda la administración de Tocilizumab (anti-IL6) como monoterapia ni como tratamiento adyuvante en la ACG. Sólo se aconseja en pacientes con ACG y afección de grandes vasos refractaria a GC y ≥ 1 fármaco inmunosupresor (nivel de evidencia 4C)
- No existe evidencia que avale el uso de Rituximab (2 casos)
- Si no existe mejoría a los 4 meses de la administración de terapia biológica, se aconseja discontinuarla

Recommendations of the Italian Society of Rheumatology for the treatment of the primary large-vessel vasculitis with biological agents

N. Pipitone[1], I. Olivieri[2], C. Salvarani[1]

Clin Exp Rheumatol 2012; 30 (Suppl. 70): S139-S161.

- No existe evidencia que avale el uso de anti-TNF en monoterapia en el tratamiento de TAK. Tampoco existe evidencia que avale el uso de Tocilizumab en monoterapia.
- No existe evidencia que avale el uso de anti-TNF ni de Tocilizumab como fármacos de primera línea en el tratamiento del TAK de reciente diagnóstico.
- Los fármacos anti-TNF y el Tocilizumab pueden administrarse en pacientes afectos de TAK de ≥ 6 meses de evolución, con actividad persistente o que hayan presentado ≥ 2 brotes, a pesar de tratamiento con GC y ≥ 1 fármaco inmunosupresor (MTX, AZA, MMF) (nivel de evidencia 4 C)
- Si no existe mejoría a los 4 meses de la administración de terapia biológica, se aconseja discontinuarla

Behçet

Nicolas Noel, Bertrand W
Du Le Thi Huong Bou
Patı

ARTHRITIS & RHEUMATISM
Vol. 65, No. 9, September 2013, ı

Table 1. Characteristics of the 46 patients with BD*

Total pregnancies	76
Age at BD diagnosis, median (IQR) years	23.4 (20.8–27.5)
BD duration, median (IQR) years	3 (0.2–5.7)
Age at pregnancy, median (IQR) years	28.4 (22.8–30.9)
Geographic origin	
Middle East/North Africa	11 (23.9)
Subsaharan Africa	3 (6.5)
Europe	32 (69.6)
No. of pregnancies before BD diagnosis, median (IQR)	1 (1–2)
Patients with BD before pregnancy	37 (80.4)
Patients with BD during pregnancy	6 (13.0)
Patients with BD postpartum	3 (6.5)
BD signs	
Aphthous ulcers	46 (100)
Genital ulcerations	32 (69.9)
Skin involvement	5 (10.9)
Ocular involvement	31 (67.4)
Joint involvement	24 (52.2)
Parenchymal CNS lesions	7 (15.2)
Venous thrombosis	15 (32.6)
Arterial involvement	4 (8.7)
HLA–B51 positivity	14 (45.2)
Followup duration, median (IQR) months	97 (65.5–154)

* HLA–B51 status was available for 31 patients. Except where indicated otherwise, values are the number (%). BD = Behçet's disease; IQR = interquartile range; CNS = central nervous system.

Table 2. Influence of pregnancy on the course of BD*

	Pregnancies without BD flares (n = 49)	Pregnancies with BD flares (n = 27)†
Pregnancies	49 (64.5)	27 (35.5)
Age at pregnancy, mean (IQR) years	28.65 (23.43–32.25)	28.85 (23.05–31.90)
BD duration, median (IQR) years	5.5 (3.1–9.0)	2.0 (0.0–4.7)‡
Treatment received during pregnancy		
Colchicine	31 (63.3)	12 (44.4)
Corticosteroids	11 (22.4)	6 (22.2)
Azathioprine	2 (4.1)	2 (7.4)
Cyc		
Tha		

* Exc
interc
† Dur
‡ P =

Conclusion. **The disease course in BD seems to improve during pregnancy, mostly in patients who are treated with colchicine. Pregnancy in patients with BD appears not to be associated with an increased rate of pregnancy-related complications.**