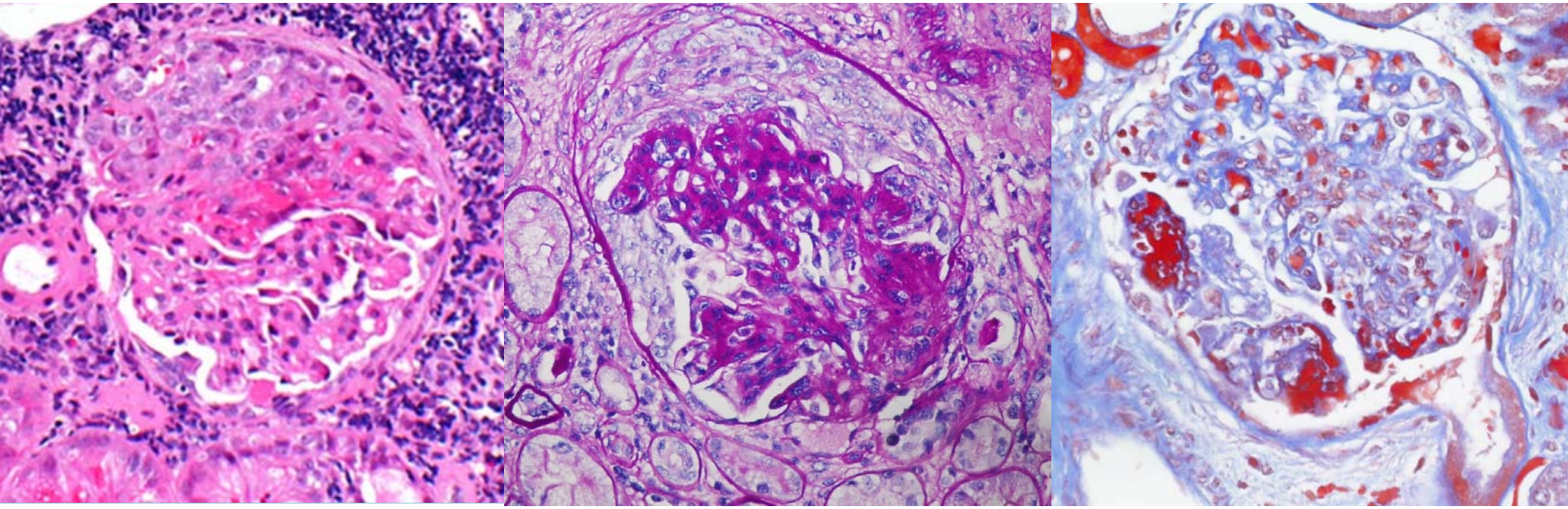
JUNTOS CONSTRUIMOS, JUNTOS AVANZAMOS

Hospital Universitario 12 de Octubre

SaludMadrid

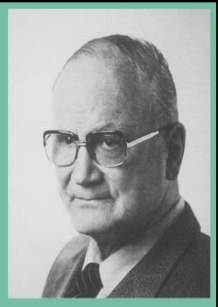


ACTUALIZACIÓN DE TRATAMIENTO EN VASCULITIS ASOCIADA A ANCA

Teresa Cavero

SGAN
sociedad gallega de nefrología

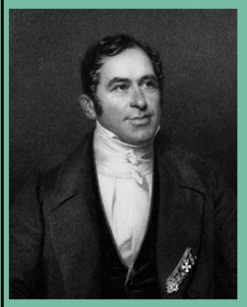
- Redefinieron las vasculitis
- **Se eliminaron los epónimos**
  - NO S. Wegener → GPA
  - NO S. Churg-Strauss → EGPA
  - NO Púpura Schölein-Henoch → Vasculitis IgA
  - NO S. Goodpasture → Enfermedad por Ac antiMBG



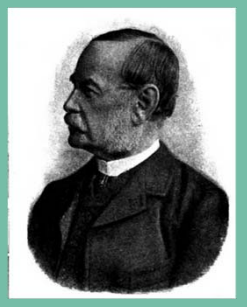
Friedrich WEGENER

Jacob CHURG

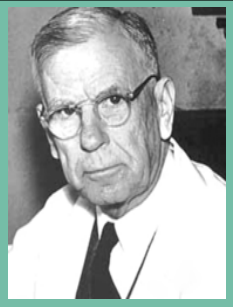
Lotte STRAUSS



Johann Lukas SCHÖLEIN



Eduard Heinrich HENOCH



Ernest W GOODPASTURE

Poliangeítis granulomatosa

Poliangeítis granulomatosa eosinofílica

Vasculitis IgA

Enfermedad por Ac antiMBG

CHAPEL HILL 2012 INTERNATIONAL CONSENSUS

CHAPEL HILL 2012 INTERNATIONAL

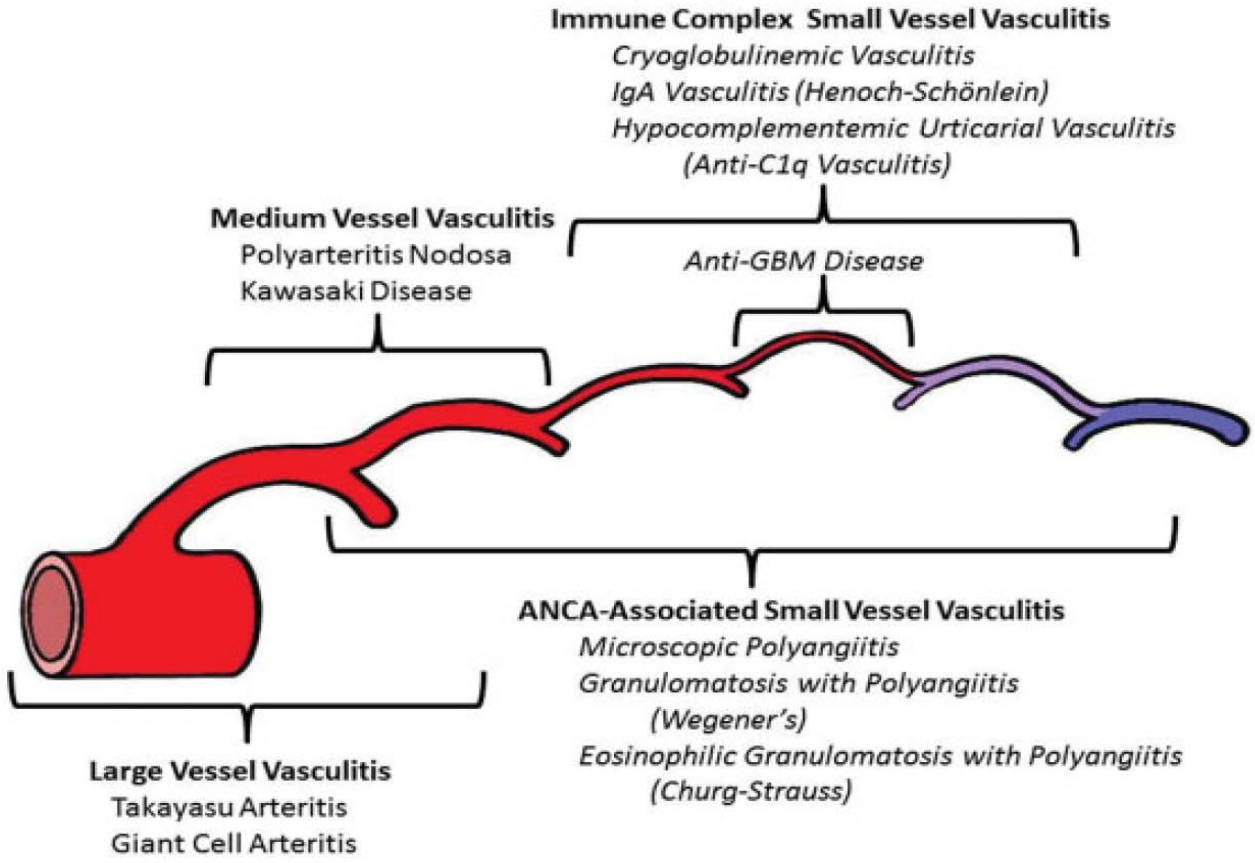
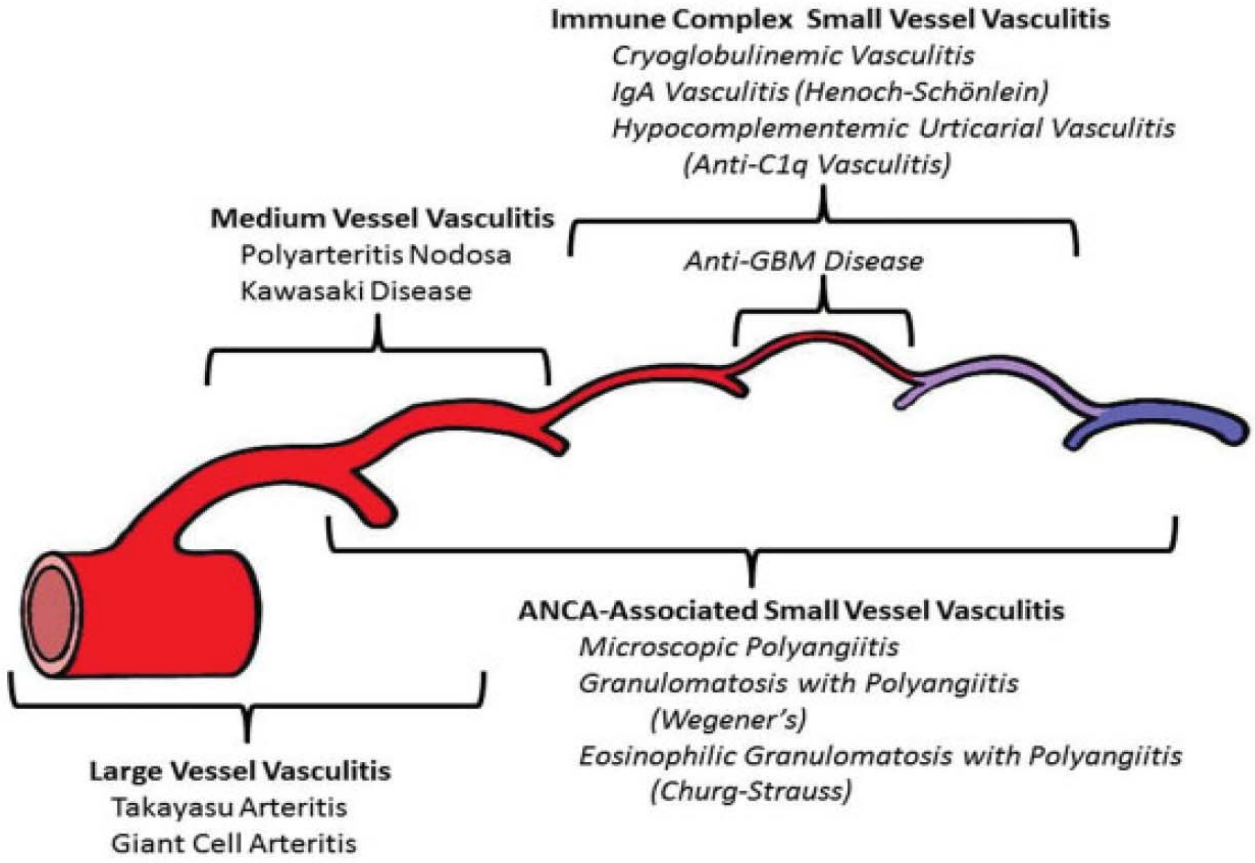


Table 2. Names for vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides

- **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

Jennette et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arth & Rheum. 2013; 65(1): 1-11

CHAPEL HILL 2012 INTERNATIONAL



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  - Cancer-associated vasculitis
  - Others

Jennette et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arth & Rheum. 2013; 65(1): 1-11

ARTICLE

Pulse Versus Daily Oral Cyclo in Antineutrophil Cytoplasmic

A Randomized Trial

Kirsten de Groot, MD; Lorraine Harper, MD, PhD; David R.\ Wolfgang L. Gross, MD; Rashid Luqmani, MD; Charles D. F Vladimir Tesar, MD, PhD; Philippe Vanhille, MD; Kerstin W Vasculitis Study Group)

Background: Current therapies for antineutrophil cytoplasr body (ANCA)–associated vasculitis are limited by toxicity.

Objective: To compare pulse cyclophosphamide with d cyclophosphamide for induction of remission.

Design: Randomized, controlled trial. Random assignmer computer-generated; allocation was concealed by faxing ce treatment assignment to providers at the time of enrollm tients, investigators, and assessors of outcomes were not bl assignment.

Setting: 42 centers in 12 European countries.

Patients: 149 patients who had newly diagnosed ger ANCA-associated vasculitis with renal involvement but no diately life-threatening disease.

Intervention: Pulse cyclophosphamide, 15 mg/kg every weeks (76 patients), or daily oral cyclophosphamide, 2 mg day (73 patients), plus prednisolone.

Measurement: Time to remission (primary outcome); ch renal function, adverse events, and cumulative dose of cy phamide (secondary outcomes).

Wegener granulomatosis, microscopic polya and the renal-limited variant of microscopic giitis are all associated with antineutrophil cytoplasm bodies (ANCAs) and are therefore referred to collect ANCA-associated vasculitis. The justification for gr these diseases together as a single clinical entity g yond ANCA seropositivity; they cause similar his changes in the kidney, are associated with similar genic autoantibodies, and respond similarly to inc immunosuppressive treatment. However, they also c important respects; for example, granuloma formati relapse after treatment are more common in W granulomatosis (1, 2).

See also:

Print
Editors' Notes . . . . . .

Web-Only
Appendixes
Conversion of graphics into slides

CLINICAL RESEARCH www.jasn.org

Randomized Trial of Plasm Methylprednisolone as Ac Renal Vasculitis

David R.W. Jayne,* Gill Gaskin,† Niels Rasn Loic Guillevin,¶ Eduardo Mirapeix,** Carolir Coen A. Stegeman,‡‡ Kerstin W. Westman, Robert A.F. de Lind van Wijngaarden,¶¶ an Vasculitis Study Group†

*Department of Medicine, Addenbrooke's, Hospital, Cambr Imperial College, London, United Kingdom; †Department o ‡Department of Immunology, Free University of Brussels, Br Carlo Borromeo, Milan, Italy; §Hôpital Cochin, Paris, France; Nephrology, University of Birmingham, Birmingham, United Groningen and University of Groningen, Groningen, Nether Hospital of Malmö, Malmö, Sweden; ‡‡Department of Neph ¶¶Department of Pathology, Leiden University Medical Cent

ABSTRACT

Systemic vasculitis associated with autoantibodies frequent cause of rapidly progressive glomerulone risk for ESRD and death despite immunosuppressi of plasma exchange was more effective than intr recovery in those who presented with a serum cre with a new diagnosis of ANCA-associated systemic >500 μmol/L (5.8 mg/dl) were randomly assigned of intravenous methylprednisolone ($n = 67$). Both nisolone. The primary end point was dialysis indepe patient survival at 1 yr and severe adverse event prednisolone compared with 48 (69%) or 70 after (95% confidence interval for the difference 18 to prednisolone, plasma exchange was associated wit confidence interval 6.1 to 41%), from 43 to 19%, at 1 yr were 51 (76%) of 67 and 32 of 67 (48%) in t 70 and 35 of (50%) 70 in the plasma exchange gr renal recovery in ANCA-associated systemic vascul intravenous methylprednisolone. Patient survival ar

J Am Soc Nephrol 18: 2180–2188, 2007. doi: 10.1681/ASN.2007

Wegener's granulomatosis and microscopic polyang itis are primary systemic vasculitic disorders that a closely associated with circulating autoantibodies t neutrophil cytoplasmic antigens (ANCA) with spec ficity for proteinase 3 (PR3) or myeloperoxida (MPO).[1,2] Kidney involvement occurs in 70% of pa tients with histologic features of an intense, neutr phil-predominant inflammatory infiltrate; seg

 ISSN : 1046-6673/1807-2180

ORIGINAL CONTRIBUTION

Mycophenolate Mofe for Remission Maint Cytoplasmic Antibod

A Randomized Controlled T

Thomas F. Hiemstra, MD, MRCP
Michael Walsh, MD, MSc
Alfred Mahr, MD, PhD
Caroline O. Savage, MD, PhD
Kirsten de Groot, MD
Lorraine Harper, MD, PhD
Thomas Hauser, MD
Irmgard Neumann, MD
Vladimir Tesar, MD, PhD
Karl-Martin Wissing, MD, PhD
Christian Pagnoux, MD, PhD
Wilhelm Schmitt, MD
David R. W. Jayne, MD
for the European Vasculitis Study Group (EUVAS)

ANTINEUTROPHIL CYTOPLASmic antibodies (ANCAs) are frequently found in patients with Wegener granulomatosis and microscopic polyangiitis. Together, Wegener granulomatosis and microscopic polyangiitis are considered ANCA-associated vasculitis (AAV) due to their similarity in clinical and histological features, prognosis, and treatment. Standard therapy for patients with AAV consists of induction of remission with cyclophosphamide and glucocorticoids, followed by remission maintenance with azathioprine or methotrexate and a tapering course of glucocorticoids.[1,2] Relapses of

For editorial comment see p 2413.

Context Curr tibody (ANCA)

Objective T the prevention

Design, Setti national Myc (IMPROVE), t azathioprine fo 11 European c gible patients h angiitis) and w

Intervention kg/d) or myco with cyclopho

Main Outcon was assessed u Vasculitis Dam

Results A to late mofetil (n= 0.66-53.6 mon lapses were mo pared with the adverse events for mycopheno vere adverse ev adverse events adverse events CI, 0.23-1.18); glomerular filtr

Conclusions than azathiopr verse event rat

Trial Registra *JAMA. 2010;304(*

AAV occur in years of diagn icity is comm therapies to m are a priority.

The NEW JOURNAL
ESTABLISHED IN 1812

Rituximab versus Cyclop Ren

Rachel B. Jones, M.R.C.P., M.D., Jan Will Raashid Luqmani, D.M., F.R.C.P., F.R.C.P.(E.), Mat Caroline O. Savage, Ph.D., F.R.C.P., F.Med.Sci., Pieter van Paassen, M.D., Ph.D., Dorot Kerstin Westman, M.D., Ph.D., and David R.W.

BACKGROUND

Cyclophosphamide induction regimens for antin (ANCA)–associated vasculitis are effective in 70 t associated with high rates of death and adverse ev has led to remission rates of 80 to 90% among pati ciated vasculitis and may be safter than cyclophosp

METHODS

We compared rituximab with cyclophosphamide as i ated vasculitis. We randomly assigned, in a 3:1 rat nosed ANCA-associated vasculitis and renal involv coid regimen plus either rituximab at a dose o body-surface area per week for 4 weeks, with two pulses (33 patients, the rituximab group), or intrave 6 months followed by azathioprine (11 patients, t points were sustained remission rates at 12 month

RESULTS

The median age was 68 years, and the glomerular per minute per 1.73 m² of body-surface area. A tota group (76%) and 9 patients in the control group ((P=0.68). Severe adverse events occurred in 14 patie and 4 patients in the control group (36%) (P=0.77). imab group (18%) and 2 of the 11 patients in the co The median increase in the GFR between 0 and 1 in the rituximab group and 15 ml per minute in th

CONCLUSIONS

A rituximab-based regimen was not superior to s phamide for severe ANCA-associated vasculitis. high in both groups, and the rituximab-based regi ductions in early severe adverse events. (Funded by National Health Service Foundation Trust and F. Controlled Trials number, ISRCTN28528813.)

ORIGINAL ART

Rituximab versus Cycl for ANCA-Associat

John H. Stone, M.D., M.P.H., Peter A. Merkel, M Philip Seo, M.D., M.H.S., Carol A. L Gary S. Hoffman, M.D., Cees G.M. K E. William St. Clair, M.D., Anthony Turkiewic Lisa Webber, R.N., Linna Ding, M.D., Ph.D., Lo Kathleen Mieras, C.C.R.P., David Weitzenk Vicki Seyfert-Margolis, Ph.D., Mark Mueller, B. Nancy B. Allen, M.D., Fernando C. Fervenza, M Karina A. Keogh, M.D., Eugene Y. Kissin, M.D Tobias Peikert, M.D., Coen Stegeman, M.D., and Ulrich Specks, M.D., for the RAV

ABSTRACT

BACKGROUND

Cyclophosphamide and glucocorticoids have b induction therapy for severe antineutrophil cytop vasculitis for 40 years. Uncontrolled studies sug may be safer than a cyclophosphamide-based re

METHODS

We conducted a multicenter, randomized, double ity trial of rituximab (375 mg per square meter 4 weeks) as compared with cyclophosphamide (per day) for remission induction. Glucocorticoid point was remission of disease without the use

RESULTS

Nine centers enrolled 197 ANCA-positive patient tosis or microscopic polyangiitis. Baseline disea the proportion of patients with relapsing disease groups. Sixty-three patients in the rituximab gr point, as compared with 52 patients in the con the criterion for noninferiority (P<0.001). The r efficacious than the cyclophosphamide-based relapsing disease; 34 of 51 patients in the rituxi 21 of 50 patients in the control group (42%) reach Rituximab was also as effective as cyclophosph with major renal disease or alveolar hemorrhag ences between the treatment groups with respec

CONCLUSIONS

Rituximab therapy was not inferior to daily cycl tion of remission in severe ANCA-associated va lapsing disease. (Funded by the National Instit eases, Genentech, and Biogen; ClinicalTrials.go

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 NOVEMBER 6, 2014 VOL. 371 NO. 19

Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

L. Guillevin, C. Pagnoux, A. Karras, C. Khouatra, O. Aumaître, P. Cohen, F. Maurier, O. Decaux, J. Ninet, P. Gobert, T. Quéméneur, C. Blanchard-Delaunay, P. Godmer, X. Puéchal, P.-L. Carron, P.-Y. Hatron, N. Limal, M. Hamidou, M. Ducret, E. Daugas, T. Papo, B. Bonnotte, A. Mahr, P. Ravaud, and L. Mouthon, for the French Vasculitis Study Group*

ABSTRACT

BACKGROUND

The combination of cyclophosphamide and glucocorticoids leads to remission in most patients with antineutrophil cytoplasm antibody (ANCA)–associated vasculitides. However, even when patients receive maintenance treatment with azathioprine or methotrexate, the relapse rate remains high. Rituximab may help to maintain remission.

METHODS

Patients with newly diagnosed or relapsing granulomatosis with polyangiitis, microscopic polyangiitis, or renal-limited ANCA-associated vasculitis in complete remission after a cyclophosphamide–glucocorticoid regimen were randomly assigned to receive either 500 mg of rituximab on days 0 and 14 and at months 6, 12, and 18 after study entry or daily azathioprine until month 22. The primary end point at month 28 was the rate of major relapse (the reappearance of disease activity or worsening, with a Birmingham Vasculitis Activity Score >0, and involvement of one or more major organs, disease-related life-threatening events, or both).

RESULTS

The 115 enrolled patients (87 with granulomatosis with polyangiitis, 23 with microscopic polyangiitis, and 5 with renal-limited ANCA-associated vasculitis) received azathioprine (58 patients) or rituximab (57 patients). At month 28, major relapse had occurred in 17 patients in the azathioprine group (29%) and in 3 patients in the rituximab group (5%) (hazard ratio for relapse, 6.61; 95% confidence interval, 1.56 to 27.96; P=0.002). The frequencies of severe adverse events were similar in the two groups. Twenty-five patients in each group (P=0.92) had severe adverse events; there were 44 events in the azathioprine group and 45 in the rituximab group. Eight patients in the azathioprine group and 11 in the rituximab group had severe infections, and cancer developed in 2 patients in the azathioprine group and 1 in the rituximab group. Two patients in the azathioprine group died (1 from sepsis and 1 from pancreatic cancer).

CONCLUSIONS

More patients with ANCA-associated vasculitides had sustained remission at month 28 with rituximab than with azathioprine. (Funded by the French Ministry of Health; MAINRITSAN ClinicalTrials.gov number, NCT00748644; EudraCT number, 2008-002846-51.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Guillevin at Département de Médecine Interne, Hôpital Cochin, 27, rue du faubourg Saint-Jacques, 75679 Paris CEDEX 14, France, or at loic.guillevin@cch.aphp.fr.

Drs. Guillevin and Pagnoux contributed equally to this article.

*A complete list of additional investigators and members of the French Vasculitis Study Group who participated in the study is provided in the Supplementary Appendix, available at NEJM.org.

This article was updated on November 6, 2014, at NEJM.org.

N Engl J Med 2014;371:1771-80.
DOI: 10.1056/NEJMoa1404231

TRATAMIENTO

TRATAMIENTO

TRATAMIENTO DE INDUCCIÓN

- Choque de esteroides (máx 3 g)
- Ciclofosfamida oral
- Ciclofosfamida intravenosa
- Micofenolato
- Rituximab
- Plasmaféresis

TRATAMIENTO DE MANTENIMIENTO

- Prednisona oral
- Azatioprina
- Micofenolato
- Rituximab
- Nuevas terapias

TRATAMIENTO DE INDUCCIÓN

CLINICAL REVIEW

Wegener's Granulomatosis: Prospective Clinical and Therapeutic Experience With 85 Patients for 21 Years

ANTHONY S. FAUCI, M.D.; BARTON F. HAYNES, M.D.; PAUL KATZ, M.D.; and SHELDON M. WOLFF, M.D.; Bethesda, Maryland

with this disease was extremely grave. Untreated, the disease usually ran a rapidly fatal course, particularly after the recognition of functional renal impairment. The mean survival of untreated Wegener's granulomatosis was 5 months with 82% of patients dying within 1 year, and more than 90% of patients dying within 2 years (9).

Although the use of corticosteroids was felt in earlier

Table 4. Results of Therapy in Wegener's Granulomatosis

Patients with induction of complete remission, *n/total (%)*	79/85 (93)
Treatment failures (death due to active disease), *n/total (%)*	6/85 (7)
Mean duration of remission in living patients (range)	48.2 ± 3.6 mos (7 mos-13.2 yrs)
Patients off all therapy, *n*	23
Mean duration of time off all therapy	35.3 ± 6.3 mos

Tratamiento:

- **Ciclofosfamida oral** 2mg/kg durante 1 año. Después descenso hasta suspensión individualizado
- **Prednisona oral** 1mg/kg.

Annals of Internal Medicine. 1983;98:76-85.

CLINICAL REVIEW

Wegener's Granulomatosis: Prospective Clinical and Therapeutic Experience With 85 Patients for 21 Years

Wegener Granulomatosis: An Analysis of 158 Patients

Gary S. Hoffman, MD; Gail S. Kerr, MD; Randi Y. Leavitt, MD, PhD; Claire W. Hallahan, MS; Robert S. Lebovics, MD; William D. Travis, MD; Menachem Rottem, MD; and Anthony S. Fauci, MD

Cyclophosphamide-Induced Cystitis and Bladder Cancer in Patients with Wegener Granulomatosis

Cheryl Talar-Williams, MPH, PA-C; Yasmine M. Hijazi, MD; McClellan M. Walther, MD; W. Marston Linehan, MD; Claire W. Hallahan, MS; Irina Lubensky, MD; Gail S. Kerr, MD; Gary S. Hoffman, MD; Anthony S. Fauci, MD; and Michael C. Sneller, MD

1 March 1996 • *Annals of Internal Medicine* • Volume 124 • Number 5

Table 2. Clinical Characteristics of the 73 Patients Treated with Cyclophosphamide Who Developed Nonglomerular Hematuria

Characteristic	Patients, *n*(%)
Initial episode of hematuria	
Microscopic	41 (56)
Gross	32 (44)
Had initial episode of hematuria while receiving cyclophosphamide	55 (75)
Had initial episode of hematuria after discontinuation of cyclophosphamide	18 (25)
Had recurrent episodes of hematuria	28 (38)
Examined by cystoscopy	60 (82)
Cystitis documented	42/60 (70)
Developed bladder cancer	7 (10)

Efectos secundarios graves

- Cáncer de vejiga: Dosis acumulada > 36g
- Otros neoplasias como leucemia aguda o linfoma: Dosis acumulada > 36g
- Fallo ovárico precoz (aunque depende de la edad de la paciente): Dosis acumulada > 28g

CYCLOPS

ARTICLE | Annals of Internal Medicine

Pulse Versus Daily Oral Cyclophosphamide for Induction of Remission in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

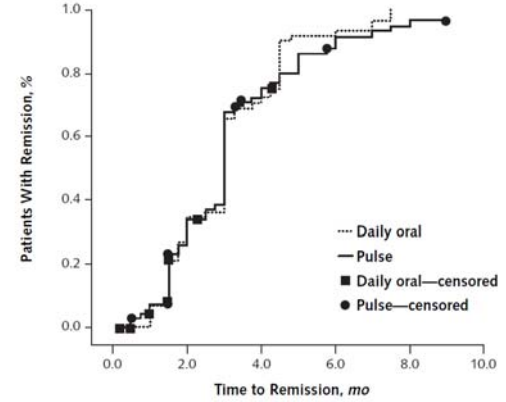
A Randomized Trial

Criterios de inclusión:
- Nuevo diagnóstico de VAA
- Afectación renal leve-moderada (Cr 1.7-5.7 mg/dl)
- No órganos vitales (HAD, SNC, cardiaca)

Grupos de tratamiento:
- **Ciclofosfamida IV**: 3 dosis c/2 semanas + 3 dosis c/3 semanas
- **Ciclofosfamida oral**: 2 mg/kg/día hasta remisión. 1.5 mg/kg/día (3 meses)
- Posteriormente:
  - Azatioprina 2 mg/kg/día hasta mes 18
  +
  - Prednisona 1 mg/kg/día con descenso progresivo

Objetivos:
- **Primario**: tiempo hasta conseguir remisión (BVAS ≤1)
- **Secundarios**:
  - % pacientes en remisión al mes 6 y mes 9
  - % pacientes con recidivas mayores y menores
  - Otros: muertes, cambios en función renal, eventos adversos

Figure 2. Time to remission (Kaplan–Meier curves) for the pulse and daily oral cyclophosphamide groups.



Daily oral	73	43	18	4	0
Pulse	76	46	15	4	2

CYCLOPS

Pulse Versus Daily Oral Cyclophosphamide for Induction of Remission in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

A Randomized Trial

Parameter	Baseline		6 Months		9 Months		18 Months	
	Pulse Group	Daily Oral Group	Pulse Group	Daily Oral Group	Pulse Group	Daily Oral Group	Pulse Group	Daily Oral Group
Total patients, *n*	76	73	66	60	63	58	62	54
Disease status, *n*								
Active disease	76	73	5	5	2	0	1	0
Achieved remission	0	0	61	55	61	58	61	54
Censored (in remission), *n*								
Died	0	0	3 (0)	7 (2)	4 (1)	8 (3)	5 (2)	9 (4)
Lost to follow-up	0	0	2 (1)	1 (1)	2 (1)	1 (1)	2 (1)	1 (1)
Withdrew	0	0	5 (2)	5 (1)	7 (4)	6 (2)	7 (4)	9 (5)
Relapse after initial remission, *n*	0	0	1	3	7	3	13	6
Renal outcomes								
End-stage renal disease, *n*	0	0	4	0	4	0	5	1
Median estimated glomerular filtration rate (IQR), *mL/min per 1.73 m²*†	32 (15–52)	29 (18–48)	40 (28–60)	50 (37–64)	44 (29–62)	52 (38–66)	50 (30–70)	48 (36–69)
Cumulative cyclophosphamide dose								
Median dose for patients still in study (IQR), *g*	0	0	8.18 (6.5–10.0)	15.75 (11.48–19.6)	8.28 (6.55–10.68)	17.5 (13.8–24.75)	8.58 (6.76–11.9)	18.05 (13.5–27)

CYCLOPS

ARTICLE | Annals of Internal Medicine

Pulse Versus Daily Oral Cyclophosphamide for Induction of Remission in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

A Randomized Trial

Table 3. **Adverse Events, by Treatment Group***

Event	Pulse Cyclophosphamide Group (n = 76)	Daily Oral Cyclophosphamide Group (n = 73)
Any adverse event		
Patients, *n* (%)	58 (77)	56 (77)
Episodes, *n*		
Mild or moderate	77	101
Severe or life-threatening	19	31
Mild or moderate	15	19
Severe or life-threatening	7	10
New or worsening diabetes, *n*	8	4
Liver dysfunction, *n*	2	3
Alopecia, *n*	0	2
Hypersensitivity reaction to azathioprine, *n*	10	5
Osteoporosis, *n*	2	0
Cancer, *n*	1	0
Hemorrhagic cystitis, *n*	2	1
Amenorrhea, *n*	1	0
Cataracts, *n*	0	3
Hypertension, *n*	0	2
Cardiovascular events (cerebrovascular accident or myocardial infarction), *n*	3	2
Pulmonary embolism or deep venous thrombosis, *n*	2	4
Other, *n*	15	18

* All numbers refer to number of episodes, except where specifically noted.

CONCLUSIONES: Ciclofosfamida IV es tan eficaz como la ciclofosfamida oral para inducir remisiones, con menor dosis acumulada del fármaco y menor número de efectos adversos graves

EXTENDED REPORT

Induction of remission in active anti-neutrophil cytoplasmic antibody-associated vasculitis with mycophenolate mofetil in patients who cannot be treated with cyclophosphamide

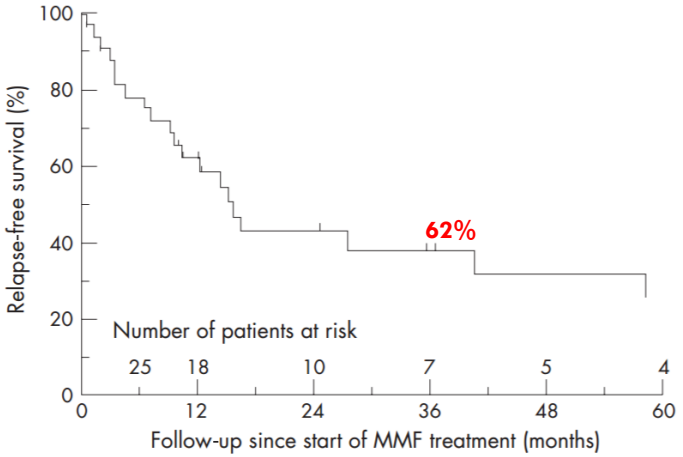
Patricia M Stassen, Jan Willem Cohen Tervaert, Coen A Stegeman

Ann Rheum Dis 2007;**66**:798–802. doi: 10.1136/ard.2006.060301

Table 1 Baseline characteristics at the moment of start of mycophenolate mofetil induction treatment in 32 patients with active anti-neutrophil cytoplasmic antibody-associated vasculitis.

	Median (range) or n (%)
Age (years)	52 (23–81)
Men/women	16/16
WG/MPA	29/3
ANCA PR3/MPO/negative	27/3/2
Duration of disease (years)	6.0 (0–21.6)
Previous relapses	4 (0–14)
Interval between previous and current relapse (months)	17 (3–134)
BVAS	14 (5–29)
CRP (normal <10 mg/l)	39 (1–361)
Creatinine (normal <125 µmol/l)	106 (73–542)
Organ involved	
Nose	23 (72)
Eye	9 (28)
Airway/lung	14 (44)
Kidney	15 (47)
Nervous system	5 (16)
Musculoskeletal	20 (63)
Skin	7 (22)

ANCA, anti-neutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; CRP, C reactive protein; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; WG Wegener's granulomatosis.



32 pacientes incluidos

Results: Complete remission (CR) was obtained in 25 (78%) patients, partial remission (PR) in 6 (19%), whereas 1 (3%) patient did not respond. 19 patients relapsed, 13 (52%) after CR, 14 (3–58) months after starting the treatment and 6 (100%) after PR, 6 (2–10) months after starting the treatment. The median relapse-free survival was 16 months, comparable with the interval between the previous relapse and the current MMF-treated relapse (17 (3–134) months). Relapse-free survival at 1, 3, and 5 years was 63%, 38% and 27%, respectively. Patients who had been treated successfully with cyclophosphamide before responded better (CR 84%, relapse 50%) than those who had not (CR 50%, relapse 100%). Minor gastrointestinal side effects and infections occurred frequently. MMF was prematurely discontinued due to adverse effects in two patients.

Ann Rheum Dis. 2007;66(6):798-802

Mycophenolate mofetil versus cyclophosphamide for inducing remission of ANCA vasculitis with moderate renal involvement

Weixin Hu[1], Chunbei Liu[2], Honglang Xie[1], Huiping Chen[1], Zhihong Liu[1] and Leishi Li[1]

NDT Nephrology Dialysis Transplantation

35 pacientes incluidos

MATERIAL Y MÉTODOS

Criterios de inclusión:
- Nuevo diagnóstico de VAA
- Afectación renal leve-moderada (Cr 1.7-5.7 mg/dl)
- No órganos vitales (HAD, SNC)

Grupos de tratamiento: 0.5 g IV 6MP x3 +
- **Ciclofosfamida IV**: 3 dosis c/2 semanas + 3 dosis c/3 semanas
- **Micofenolato**: 2 g/día (6 meses)
- Posteriormente:
  - Azatioprina 2 mg/kg/día hasta mes 18
    +
  - Prednisona 1 mg/kg/día con descenso progresivo

CONCLUSIONES

MMF disminuye la actividad de la enfermedad y mejora considerablemente la función renal

RESULTADOS

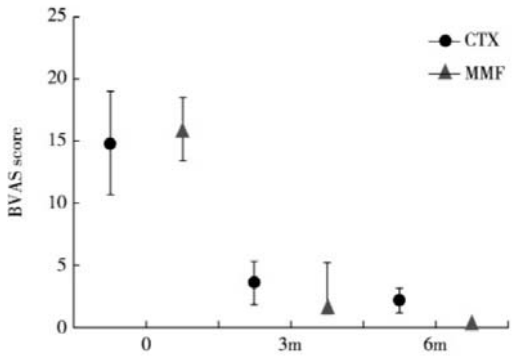


Fig. 2. BVAS score after the treatment showing that BVAS score decreased more significantly in the MMF group.

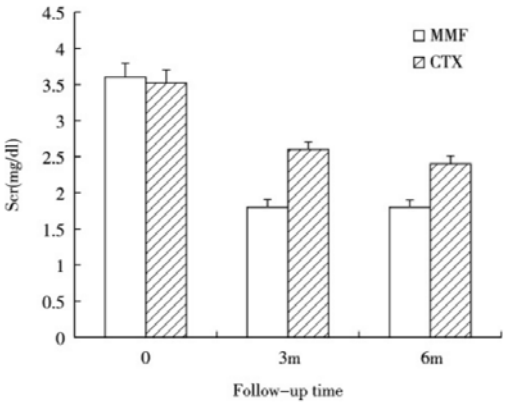


Table 3. Adverse events in the two groups

	MMF group ($n = 18$)	CTX group ($n = 17$)
GI symptoms	2 (11.1%)	4 (23.5%)
Herpes zoster	1 (5.6%)	0
Bacteria pneumonia	1 (5.6%)	1 (5.9%)
Leukopenia	0	1 (5.9)

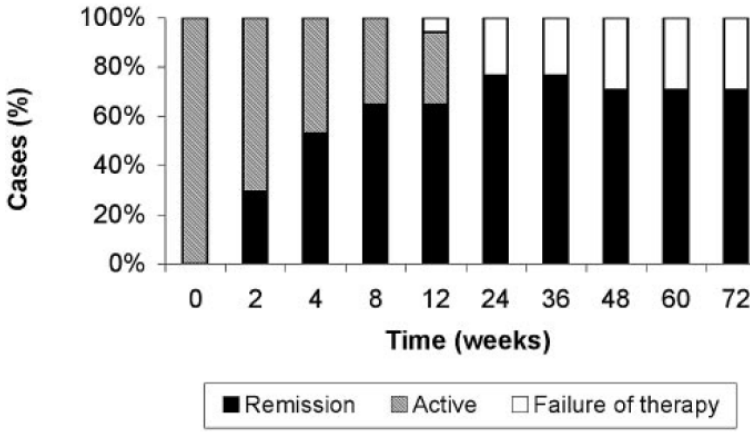
Nephrol Dial Transplant (2008) 23: 1307–1312

Mycophenolate Mofetil for Induction and Maintenance of Remission in Microscopic Polyangiitis with Mild to Moderate Renal Involvement—A Prospective, Open-Label Pilot Trial

17 pacientes incluidos

Criterios de inclusión: - Solo MPA (poliangeítis microscópica)
- Afectación renal leve-moderada (Cr <3 mg/dl)
- ANCA-MPO (NO PR3)

Tratamiento: 1 g IV 6MP x1-3 + Prednisona 1 mg/kg + MMF 2g/día (18 m)



Clinical Outcomes

The primary outcome of remission at 6 months was achieved by 13 patients (76%). Four patients (24%) failed to achieve the primary outcome. Two of these did not respond to treatment, one experienced a major relapse, and one achieved remission but discontinued the study therapy because of gastrointestinal intolerance (Figure 1). Sustained remission until 18 months was maintained in 12 patients (70%). One patient relapsed at month 9. The cumulative BVAS/WG scores for all patients are shown

whom MMF was discontinued because of intolerance remained in remission and ANCA negative. A total of nine patients became ANCA negative; all of these achieved disease remission. Of the eight patients who remained ANCA positive, four achieved complete remission (median MPO-ANCA of 27 EU/ml) and four experienced disease flares (median MPO-ANCA of 53 EU/ml).

Side Effects

MMF was associated with detectable side effects in ten patients (58%). These were mild and included gastrointestinal upset (diarrhea, nausea, or bloating) in six patients, mild leucopenia (total white cell count between 3000 and 4000/mm^3) in three, headache in one, and weakness in one. These side effects

CONCLUSIONES

MMF puede ser una alternativa a ciclofosfamida en pacientes con vasculitis renal leve-moderada

Clin J Am Soc Nephrol 5: 445–453, 2010. doi: 10.2215/CJN.06010809

CLINICAL SCIENCE

Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial

Criterios de inclusión: - Vasculitis AA nuevo diagnóstico
- NO órganos vitales (HAD, corazón, afectación intestinal severa)
- GFR <15 ml/min/1.73m^2 o GNRP (disminución del GFR >20% en últimas 2 semanas)

Grupos de tratamiento: 6MP hasta 3g +/- PLEX +

- **Ciclofosfamida IV**: 3 dosis c/2 semanas + 3-6 dosis c/3 semanas
- **Micofenolato**: 2 g/día (3-6 meses)
- Posteriormente:
  - Azatioprina 2 mg/kg/día hasta mes 18
    +
  - Prednisona 1 mg/kg/día con descenso progresivo (5mg/día a los 6 meses)

Objetivo principal: Remisión a los 6 meses

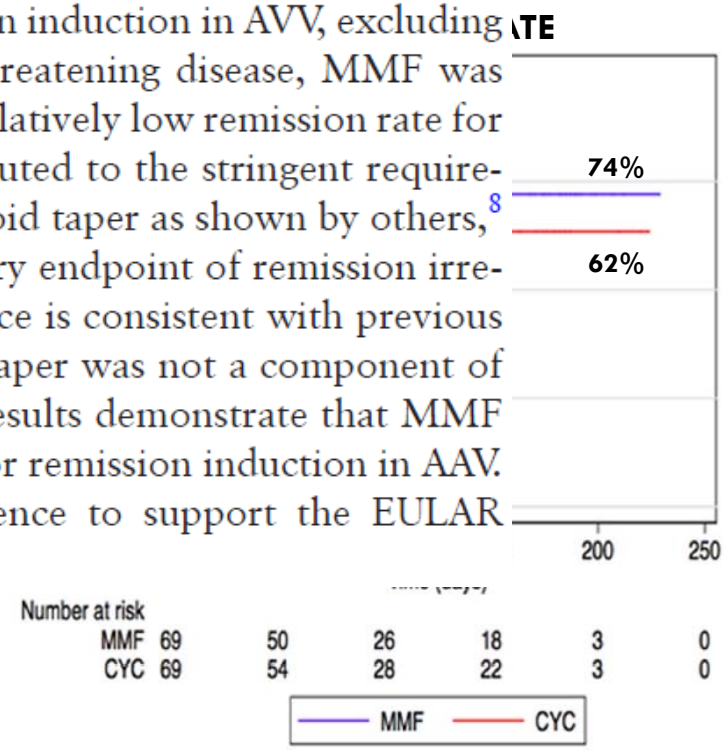
Objetivos secundarios: Progresión de enfermedad, Tiempo hasta remisión, Cambios en GFR, Dosis acumulada de CE, Recaídas, Negativización de ANCA, VDI

Jones RB, *et al*. *Ann Rheum Dis* 2019;**78**:399–405. doi:10.1136/annrheumdis-2018-214245

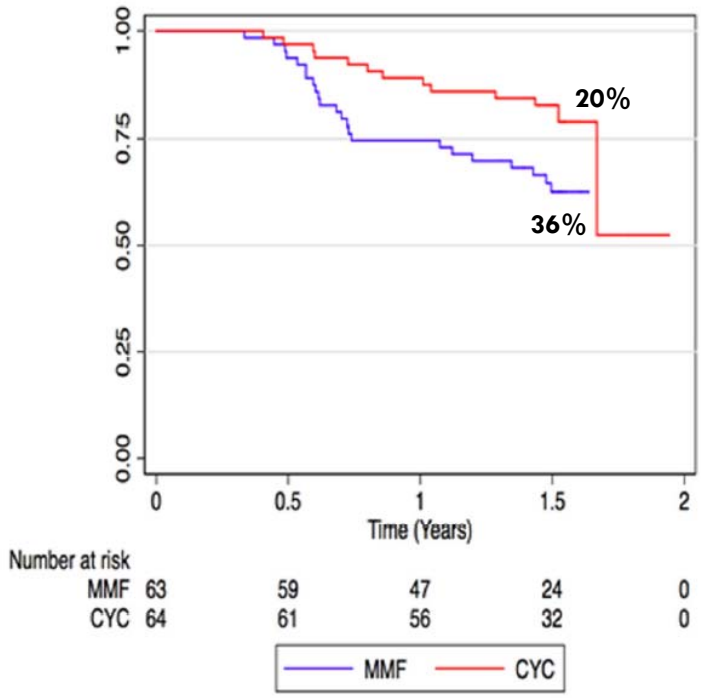
Table 1

Variable		
Age (years		
Paediatric		
Male sex,		
Diagnosis,		
GPA		
MPA		
ANCA, n (		
PR3 or		
MPO o		
Negativ		
ANCA ELI		
PR3-AN		
MPO-A		
Negativ		
eGFR at entry (mL/min/m^2), median (IQR)		
All patients	51 (29–92)	51 (31–79)
Patients with renal disease	47 (27–70)	46 (29–74)
Organs involvement*, n (%)		
Renal	57 (81)	57 (81)
Lung	30 (43)	35 (50)
ENT	41 (59)	38 (54)
BVAS†, median (IQR)	19 (13–25)	18 (14–23)
CRP (mg/L), median (IQR)	22 (7.5–52)	19 (5–83)
ESR (mm/hour), median (IQR)	54 (31–98)	59 (33–90)
Cyclophosphamide prerandomisation		
Patients, n (%)	17 (24)	22 (31)
Total dose (g), median (IQR)	1 (0.55–1.1)	1 (0.6–1.07)
Intravenous methylprednisolone prerandomisation		
Patients, n (%)	41 (59)	35 (50)
Total dose (g), median (IQR)	1.5 (1.5–3)	1.5 (1.5–2)
Plasma exchange prerandomisation		
Patients, n (%)	8 (11)	4 (6)
Total exchanges, median (IQR)	5 (5–7)	7 (6–7)

In this randomised trial of remission induction in AVV, excluding patients on dialysis or with life-threatening disease, MMF was non-inferior to pulsed CYC. The relatively low remission rate for the primary outcome can be attributed to the stringent requirement for adherence to glucocorticoid taper as shown by others,[8] and the higher rate of the secondary endpoint of remission irrespective of glucocorticoid adherence is consistent with previous reports where the glucocorticoid taper was not a component of the remission definition.[6 25] Our results demonstrate that MMF represents an alternative to CYC for remission induction in AAV. This study provides further evidence to support the EULAR guidelines on management of AAV.



RELAPSE RATE



CONCLUSIONS

Jones RB, *et al*. *Ann Rheum Dis* 2019;**78**:399–405. doi:10.1136/annrheumdis-2018-214245

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 15, 2010 VOL. 363 NO. 3

RITUXVAS

Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

CRITERIOS INCLUSIÓN **44 pacientes incluidos**

- Nuevo diagnóstico
- **CrS > 1.7 mg/dl**

CARACTERÍSTICAS BASALES

- GFR (ml/min/m^2): - RTX group: **20** (5-44)
  - CYC group: **12** (9-33)

TRATAMIENTO INDUCCIÓN

- RTX group: 4 dosis 375mg/m^2 + CYC 2 dosis IV
- CYC group: 3 dosis IV c/2 sem + 3 dosis IV c/3 sem

TRATAMIENTO MANTENIMIENTO

- RTX group: prednisona oral
- CYC group: prednisona oral + azatioprina (hasta **mes 12**)

N Engl J Med 2010;363:211-20.

RAVE

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

CRITERIOS INCLUSIÓN **197 pacientes incluidos**

- Nuevo diagnóstico y recidivas
- **CrS < 4 mg/dl**

CARACTERÍSTICAS BASALES

- GFR (ml/min/m^2): - RTX group: **54** (±30)
  - CYC group: **69** (±42)

TRATAMIENTO INDUCCIÓN

- RTX group: 4 dosis 375mg/m^2
- CYC group: 2 mg/kg/día durante 6 meses

TRATAMIENTO MANTENIMIENTO

- Suspensión de prednisona oral al 5° mes si consiguen remisión. Seguimiento **6 meses.**

N Engl J Med 2010;363:221-32.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 15, 2010 VOL. 363 NO. 3

RITUXVAS

Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

RESULTADOS

	Rituximab group (n=33)	Cyclophospamide group (n=11)
Remisión mantenida (12 meses), n(%)	25 (76)	9 (82)
Remisión a 6 meses, n(%)	30 (91)	10 (91)
Recidivas (12 meses), n(%)	4 (15)	1 (10)
Tiempo hasta remisión (días)	90	94
Aumento GFR (12 meses)	19	15
Efectos adversos graves, n(%)	14 (42)	4 (36)
Muertes, n(%)	6 (18)	2 (18)

N Engl J Med 2010;363:211-20.

RAVE

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

RESULTADOS

	Rituximab group (n=99)	Cyclophosphamide group (n=98)
Remisión mes 6 sin prednisona, n(%)	63 (64)	52 (53)
Remisión mes 6 en recidivas, n(%)	**34/51 (67)**	**21/50 (42)**
Remisión en función de tipo vasculitis, n(%)		
- GPA	46/73 (63)	37/74 (50)
- MPA	16/24 (67)	15/24 (62)
Remisión con afectación renal, n(%)	31/51 (61)	32/51 (63)
Negativización de ANCA:		
- MPO	(40)	(41)
- PR3	**(47)**	**(24)**
Efectos adversos graves, n(%)	30 (30)	36 (36)
Recaídas, n(%)	6 (6)	10 (10)

N Engl J Med 2010;363:221-32.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis

Salvo en las recidivas en las que Rituximab ha demostrado ser más eficaz, CICLOFOSFAMIDA Y RITUXIMAB son comparables en eficacia y seguridad.

Table 1. Efficacy O

Efficacy Measure				
Complete remissio				
6 mo				
12 mo	47 (47)	38 (39)	9 (−5 to 22)	0.22
18 mo	39 (39)	32 (33)	7 (−7 to 20)	0.32
Remission and <10 mg/day of prednisone				
6 mo	70 (71)	60 (61)	10 (−4 to 23)	0.16
12 mo	59 (60)	60 (61)	−2 (−15 to 12)	0.82
18 mo	54 (55)	52 (53)	2 (−12 to 15)	0.84
Complete remission at any time†	76 (77)	70 (71)		0.15
Remission and <10 mg/day of prednisone at any time‡	82 (83)	84 (86)		0.91
Remission at any time‡	89 (90)	89 (91)		0.50
Complete remission in patients with relapsing disease at baseline†				
6 mo	34/51 (67)	21/50 (42)	25 (6 to 44)	0.01
12 mo	25/51 (49)	12/50 (24)	25 (7 to 43)	0.009
18 mo	19/51 (37)	10/50 (20)	17 (0 to 34)	0.06

CONCISE REPORT

Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial

		group (n=11)
PR3-ANCA positive patients	3 of 20 (15%)	1 of 5 (20%)
MPO-ANCA positive patients	4 of 13 (31%)	1 of 6 (17%)
Patients with a major relapse	1 (3%)	2 (18%)
Patients with more than one relapse	4† (12%)	0
Recovery from eGFR<15 mL/min/1.73 m^2	7 of 13§ (54%)	2 of 6*§ (33%)
ESRD	2‡ (6%)	0
Death	6 (18%)	3 (27%)
Composite of death, ESRD and relapse	14 (42%)	4 (36%)

CLINICAL RESEARCH www.jasn.org

MEPEX

Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis

Criterios de inclusión: - Nuevo diagnóstico o recidivas de VAA
- Afectación renal severa (Cr >5.8 mg/dl)

Grupos de tratamiento:
- **Plasmaféresis** 7 sesiones
- **6MP** 3 g IV
- **Tratamiento común:**
  - Prednisona oral
  - Ciclofosfamida oral

Objetivos:
- **Primario:** % pacientes libres de diálisis a 3 meses
- **Secundarios:** - Efectos adversos
  - Supervivencia renal y paciente a 1 año

	PLEX (n=70)	6-MP (n=67)
Pacientes libres de diálisis en mes 3, n (%)	48 **(69)**	33 **(49)**
Supervivencia paciente a 1 año, n (%)	51 (73)	51 (76)
Supervivencia renal a 1 año, n (%)	41/51 **(80)**	29/51 **(57)**
Efectos adversos, n (%)	35 (50)	32 (48)

Plasmaféresis versus choque de esteroides

Disminución de riesgo de ERCT a 3 meses: 22%

Disminución de riesgo de ERCT a 12 meses: 24%

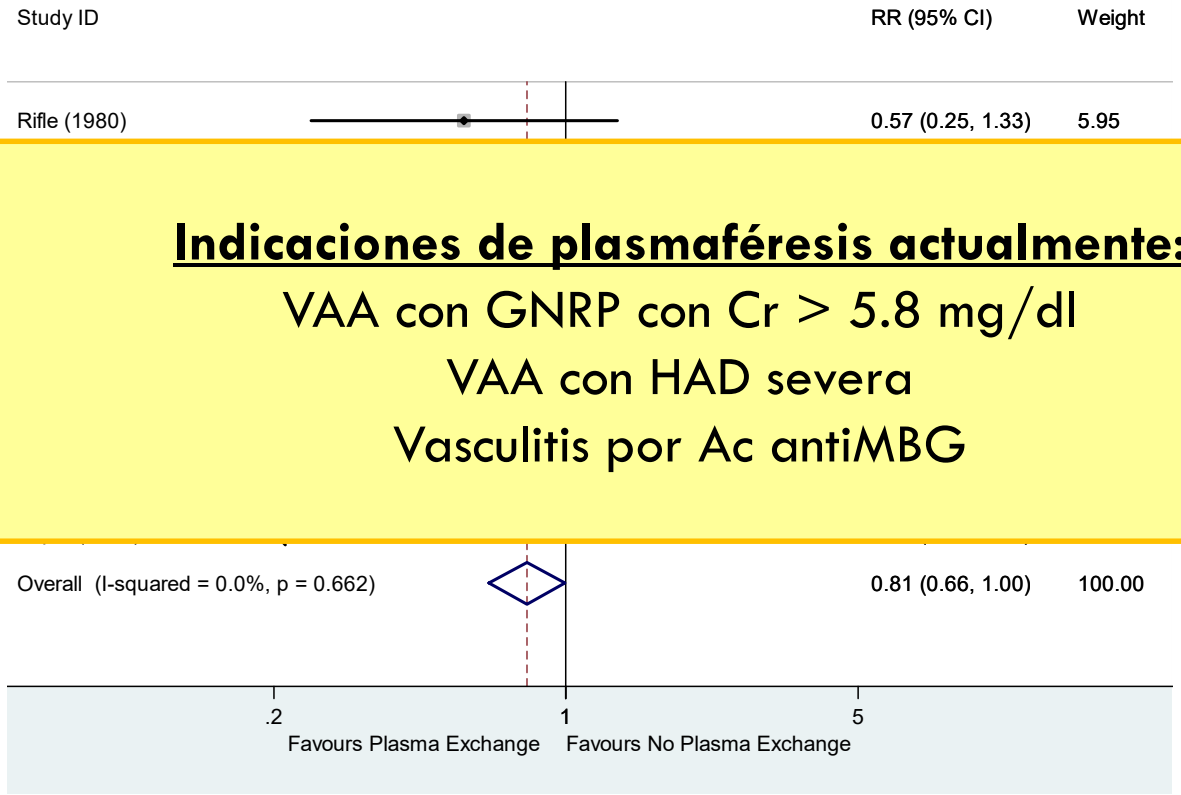
CONCLUSIONES

La plasmaféresis aumenta la probabilidad de recuperación renal en vasculitis asociada a ANCA con afectación renal severa comparado con el uso de choque de esteroides. La supervivencia del paciente y los efectos adversos son similares.

J Am Soc Nephrol 18: 2180–2188, 2007.

AJKD
Original Investigation

Plasma Exchange for Renal Vasculitis and Idiopathic Rapidly Progressive Glomerulonephritis: A Meta-analysis



Indicaciones de plasmaféresis actualmente:

VAA con GNRP con Cr > 5.8 mg/dl

VAA con HAD severa

Vasculitis por Ac antiMBG

Outcome: Composite of end-stage renal disease or death (95% CI, 0.65-0.99; $P = 0.04$)
RR for end-stage renal disease 0.64 (95% CI, 0.47-0.88; $P = 0.006$)
RR for death alone was 1.01 (95% CI, 0.71-1.4; $P = 0.9$)

Am J Kidney Dis. 2011;57(4):566-574

Walsh *et al. Trials* 2013, **14**:73
http://www.trialsjournal.com/content/14/1/73

TRIALS

PEXIVAS

N total= 702 pacientes	PLEX (n= 352)	Control (n= 352)	Reduced dose (n=353)	Standard dose (n=351)
Age, years (SD)	62.8 (14.4)	63.5 (13.7)	63.3 (14.2)	63.3 (13.9)
Female, n(%)	149 (42.3)	158 (44.9)	156 (44.2)	151 (43)
Dominant ANCA, n(%) - PR3 - MPO	 143 (40.6) 209 (59.4)	 143 (40.6) 209 (59.4)	 143 (40.5) 210 (59.5)	 143 (40.7) 208 (59.3)
Lung hemorrhage, n(%) - Any - Severe	 95 (27) 31 (8.8)	 96 (27.3) 30 (8.5)	 96 (27.2) 31 (8.8)	 95 (27) 30 (8.5)
Creatinine - Median (25^{th}-75^{th}) - >500 umol/L, n(%) - On dialysis, n(%)	 327 (206-491) 101 (28.7) 66 (18.8)	 336 (209-495) 104 (29.5) 74 (21)	 320 (190-480) 102 (28.9) 67 (19)	 335 (219-502) 103 (29.3) 73 (20.8)
Immunosupression, n(%) - IV Cyclophosphamide - Oral Cyclophosphamide - Rituximab	 177 (50.3) 120 (34.1) 55 (15.6)	 177 (50.3) 121 (34.3) 54 (15.4)	 179 (50.7) 120 (34) 54 (15.3)	 175 (49.9) 121 (34.5) 55 (15.6)

Data not published

PEXIVAS

Walsh *et al. Trials* 2013, **14**:73
http://www.trialsjournal.com/content/14/1/73

STUDY PROTOCOL Open Access

Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial

Primary end-point: **Fallecimiento de cualquier causa o ERCT**

- 28% de dosis reducida de esteroides versus 26% de dosis estándar
- 28% recibieron PLEX versus 31% no PLEX

Infecciones severas durante el primer año:

- 27% en dosis reducida frente a 33% en dosis estándar → 30% de reducción del riesgo relativo

Conclusions: ***"Plasma exchange does not reduce the risk of end-stage renal disease or death in patients with ANCA-associated vasculitis. Compared to a standard dose, reduced glucocorticoids did not substantially increase the risk of death or end-stage renal disease and resulted in fewer serious infections"***

Data not published

TRATAMIENTO DE MANTENIMIENTO

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Maintenance Therapy for Vasculitis Associated with Antineutrophil Cytoplasmic Autoantibodies

CYCAZAREM

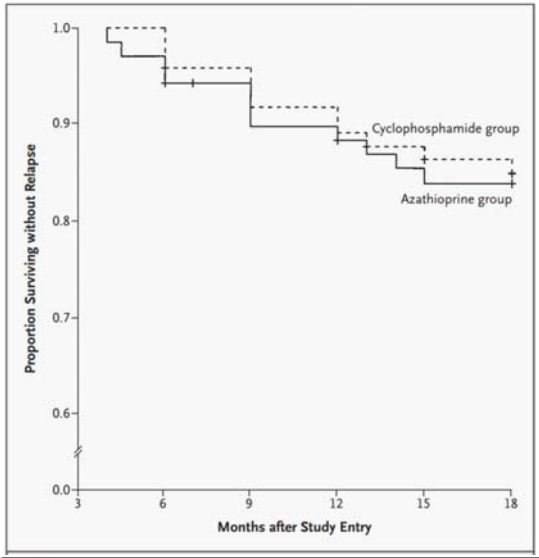
Criterios de inclusión: - Nuevo diagnóstico VAA
- Afectación renal (Cr <5.8 mg/dl)

Grupos de tratamiento:
- **TODOS:** Ciclofosfamida oral hasta entrar en remisión (3-6 m) + Prednisona oral
- **Grupo 1:** Ciclofosfamida oral (1.5 mg/kg/día) durante 12 m
- **Grupo 2:** Azatioprina (2 mg/kg/día) durante 12 m

CONCLUSIONS

In patients with generalized vasculitis, the withdrawal of cyclophosphamide and the substitution of azathioprine after remission did not increase the rate of relapse. Thus, the duration of exposure to cyclophosphamide may be safely reduced.

EFICACIA



SEGURIDAD

Table 2. Adverse Events.

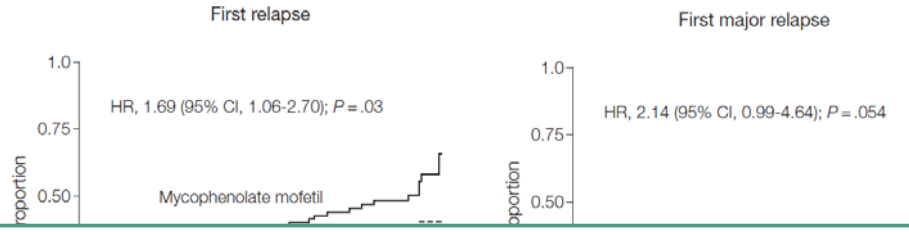
Variable	Induction Phase (0–3 Mo)		Remission Phase (4–18 Mo), Azathioprine Group (N=71)		Remission Phase (4–18 Mo), Cyclophosphamide Group (N=73)		Entire Study Period
	Mild or Moderate	Severe or Life-Threatening	Mild or Moderate	Severe or Life-Threatening	Mild or Moderate	Severe or Life-Threatening	
	number of events (percent)						
Leukopenia	30	7	21	1	32	3	94
Anemia	0	0	2	0	1	0	3
Diabetes	3	2	2	1	2	0	10
Infection	3	4	9	4	10	3	33
Bone fracture	0	0	0	2	0	2	4
Gastrointestinal event	3	0	3	0	2	3	11
Cardiovascular event	0	4	1	2	1	2	10
Cystitis	0	0	1	0	3	0	4
Allergy	3	0	4	1	2	0	10
Amenorrhea	0	0	0	1	0	2	3
Alopecia	3	0	0	0	2	0	5
Psychiatric event	3	0	0	0	0	0	3
Other adverse event	7	1	6	0	14	0	28
Any adverse event	55	18	49	12	69	15	218
≥1 Event	52 (34)	15 (10)	29 (41)	8 (11)	32 (44)	7 (10)	84 (54)

IMPROVE

ORIGINAL CONTRIBUTION

Mycophenolate Mofetil vs Azathioprine for Remission Maintenance in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

A Randomized Controlled Trial



<u>Criterios de inclusión</u>: - Nuevo diagnóstico VAA
- Afectación renal (Cr <5.8 mg/dl)

Conclusions Among patients with AAV, mycophenolate mofetil was less effective than azathioprine for maintaining disease remission. Both treatments had similar adverse event rates.

hasta 42 meses.

- **Grupo 2:** Azatioprina (2 mg/kg/día) durante 12 m. Posterior reducción hasta 42 meses.

<u>Objetivos</u>:

- **Primario:** supervivencia libre de recidiva
- **Secundarios:** GFR, proteinuria y daño crónico (VDI)

Table 2. Summary of Adverse Events

	Azathioprine[a]		Mycophenolate Mofetil[b]			
	No. of Events	No. of Patients	No. of Events	No. of Patients	HR (95% CI)	*P* Value
Severe adverse events	22	13	8	8	0.53 (0.23-1.18)	.12
Severe infection	8	8	3	3	0.52 (0.11-2.36)	.40
Any adverse events	97	28	75	22	0.94 (0.61-1.43)	.77
Any infection	37	17	29	12	0.92 (0.42-2.02)	.84
Cardiovascular	4	3	4	3	1.17 (0.27-5.04)	.83
Neoplasia	5	3	1	1	0.25 (0.02-2.62)	.25
Gastrointestinal tract	10	8	10	8	1.27 (0.52-3.08)	.60
Drug intolerance	6	6	2	2	2.59 (0.55-12.08)	.25
Hepatic dysfunction	3	3	0	0	NA	.16[c]
Leukopenia	11	7	5	4	0.57 (0.21-1.55)	.27
Other	21	8	24	6	1.10 (0.54-2.22)	.79

MAINRITSAN

The NEW ENGLAND JOURNAL of MEDICINE

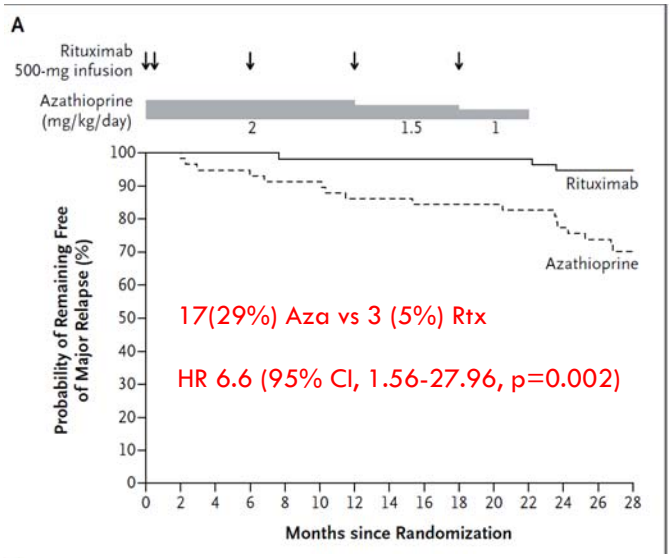
ESTABLISHED IN 1812 NOVEMBER 6, 2014 VOL. 371 NO. 19

Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

Criterios de inclusión: - Nuevo diagnóstico o recidiva VAA
- Remisión tras ciclofosfamida IV-GC

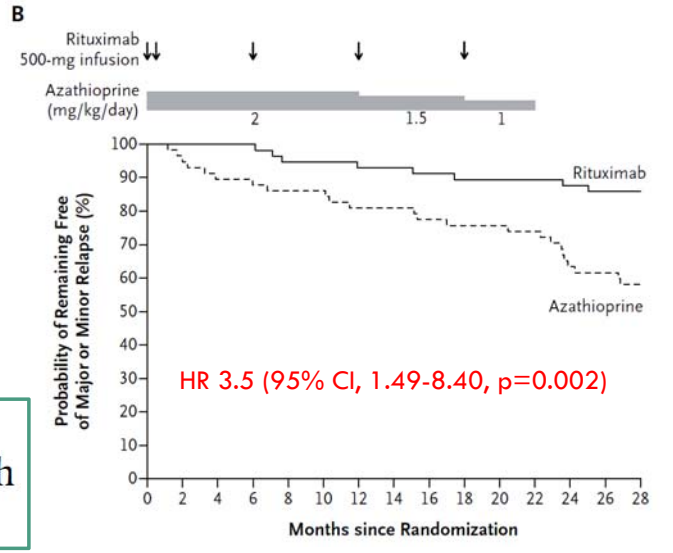
Grupos de tratamiento:
- **Grupo 1:** Rituximab 0.5 g (0, 14 días, después meses 6, 12 y 18)
- **Grupo 2:** Azatioprina hasta mes 22.

Objetivos:
- **Primario:** % pacientes con recaída grave a mes 28
- **Secundarios:** - % recaídas leves
  - % efectos adversos y gravedad
  - Mortalidad



17(29%) Aza vs 3 (5%) Rtx

HR 6.6 (95% CI, 1.56-27.96, p=0.002)



HR 3.5 (95% CI, 1.49-8.40, p=0.002)

CONCLUSIONS

More patients with ANCA-associated vasculitides had sustained remission at month 28 with rituximab than with azathioprine.

RITAZAREM

STUDY PROTOCOL Open Access

Rituximab versus azathioprine as therapy for maintenance of remission for anti-neutrophil cytoplasm antibody-associated vasculitis (RITAZAREM): study protocol for a randomized controlled trial

Tamaño muestral: 160 pacientes

Criterios de inclusión: - Pacientes con **RECAÍDAS** de VAA
- Remisión tras Rituximab - GC

En MAINRITSAN solo 23/115 pacientes incluidos eran pacientes con RECAÍDA

Grupos de tratamiento:
- **TODOS:** Rituximab 375 mg/m2 x4 + GC
- **Grupo 1:** Rituximab 1 g (cada 4 meses, hasta mes 20)
- **Grupo 2:** Azatioprina 2 mg/kg hasta mes 24.

En MAINRITSAN pacientes recibieron inducción con CICLOFOSFAMIDA

Objetivos:
- **Primario:** Tiempo hasta recidiva
- **Secundarios:** - % pacientes sin recidiva a 24 y 48 meses
  - % efectos adversos
  - Dosis acumulada de GC

En MAINRITSAN Rituximab se administró cada 6 meses, pero recidivas pueden ocurrir antes

ClinicalTrials.gov identifier: NCT01697267.

RITAZAREM

Baseline demographics	Total (n= 170)	Rituximab (n= 85)	Azathioprine (n=85)
Age, years	59 (18-89)	57 (18-89)	61 (27-83)
Disease duration, years	5.3 (0.4-38.5)	5.8 (0.4-38.5)	4.9 (0.4-25.8)
Prior cyclophosphamide therapy - Number of patients (%) - Cumulative dose, grams	 133 (78.2) 10 (0.2-30.1)	 67 (78.8) 7.1 (0.2-30.1)	 66 (77.6) 12 (1-14.6)
Prior rituximab therapy - Number of patients (%) - Cumulative dose, grams	 60 (35.4) 3.9 (1.5-16)	 33 (38.8) 3.2 (2-16)	 27 (31.8) 5.4 (1.5-14)

CONCLUSIONS:

Rituximab was superior to azathioprine for preventing disease relapse in patients with relapsing ANCA associated vasculitis following re-induction of remission with rituximab

Relapses	Rituximab (n= 85)	Azathioprine (n=85)
Total number of patients experiencing a relaps	11 (13)	32 (38)
Major relapse	2/11 (18)	12/32 (38)
Minor relapse	9/11 (82)	20/32 (62)

Adverse events	Rituximab (n= 85)	Azathioprine (n=85)
Number of patients with SAE	19 (22)	31 (36)
Number of patients with serious infections	7 (8)	11 (13)
Number of patients with non serious infections	42 (49)	41 (48)
Hypogammaglobulinaemia (IgG <5g/L)	25 (29)	21 (25)
Death	3 (4)	1 (1)

Data not published

FISIOPATOLOGIA. EL COMPLEMENTO

Alternative Complement Pathway in the Pathogenesis of Disease Mediated by Anti-Neutrophil Cytoplasmic Autoantibodies

Hong Xiao,* Adrian Schreiber,* Peter Heeringa,†
Ronald J. Falk,* and J. Charles Jennette*

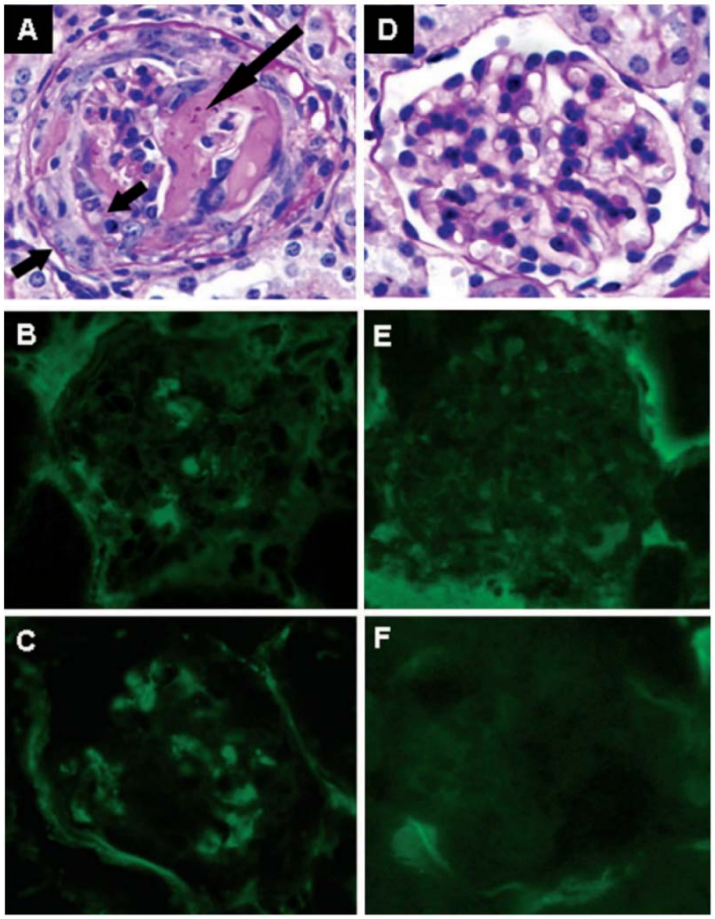
The American Journal of Pathology, Vol. 170, No. 1, January 2007

DOI: 10.2353/ajpath.2007.060573

Clinical and experimental data indicate that anti-neutrophil cytoplasmic autoantibodies (ANCAs) cause glomerulonephritis and vasculitis. Here we report the first evidence that complement is an important mediator of ANCA disease. Transfer of anti-myeloperoxidase (MPO) IgG into wild-type mice or anti-MPO splenocytes into immune-deficient mice caused crescentic glomerulonephritis that could be completely blocked by complement depletion. The role of specific complement activation pathways was investigated using mice with knockout of the common pathway component C5, classic and lectin binding pathway component C4, and alternative pathway component factor B. After injection of anti-MPO IgG, $C4^{-/-}$ mice developed disease comparable with wild-type disease; however, $C5^{-/-}$ and factor $B^{-/-}$ mice developed no disease. To substantiate a role for complement in human ANCA disease, IgG was isolated from patients with myeloperoxidase ANCA (MPO-

SIN DEPLECIÓN DE COMPLEMENTO

CON DEPLECIÓN DE COMPLEMENTO



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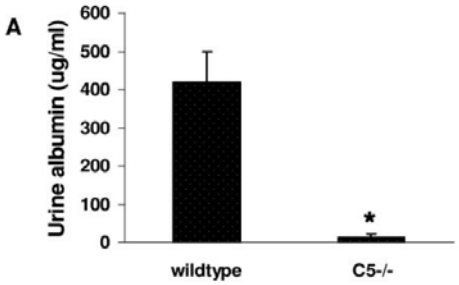

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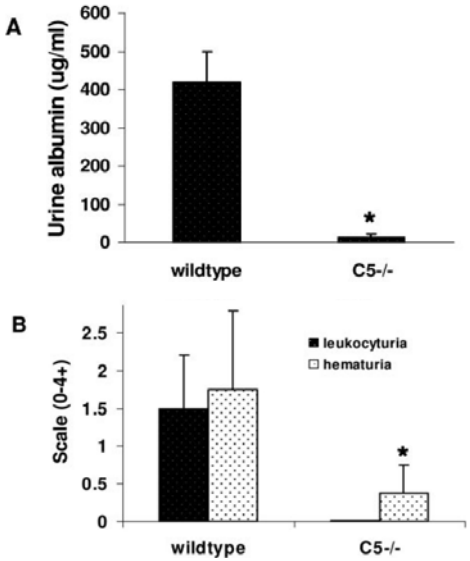

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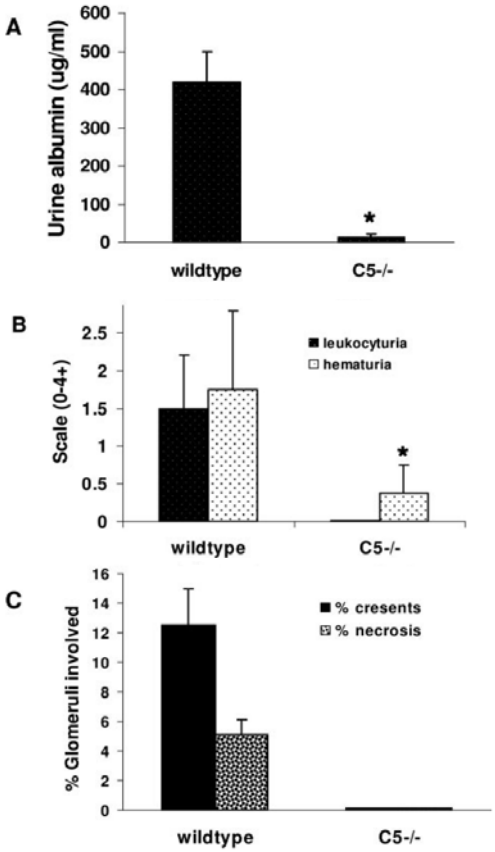

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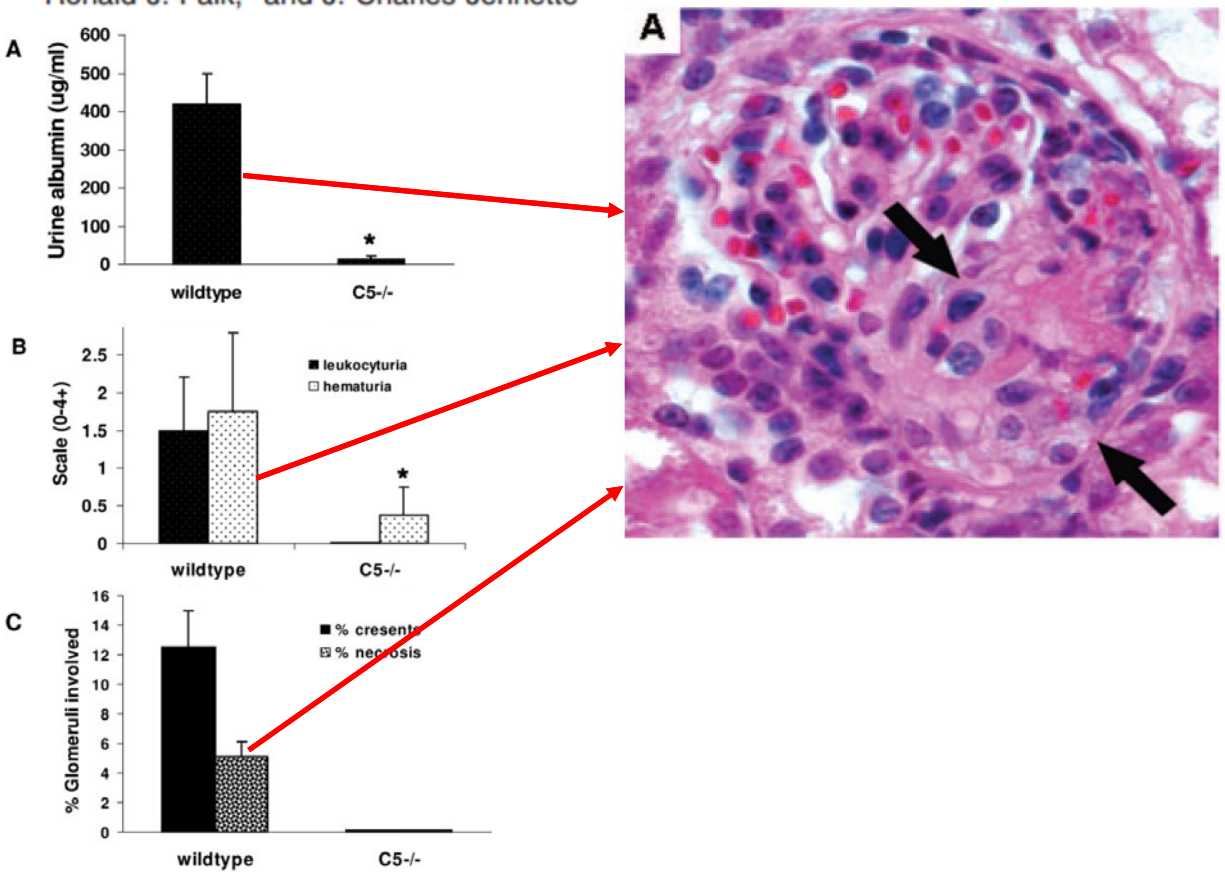

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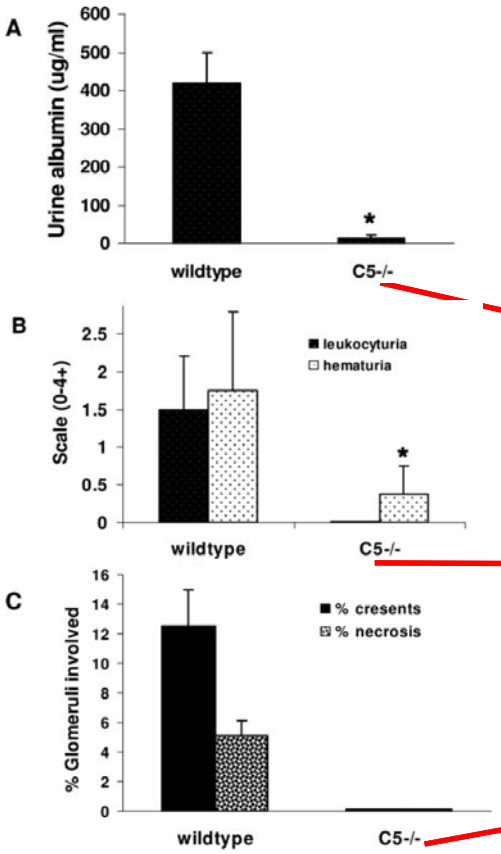

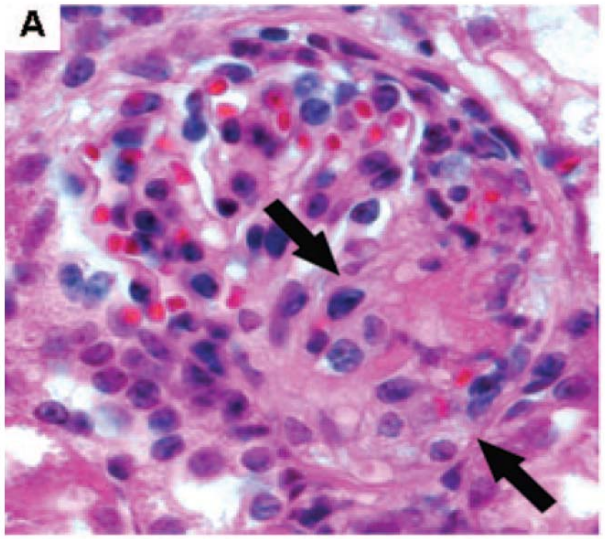

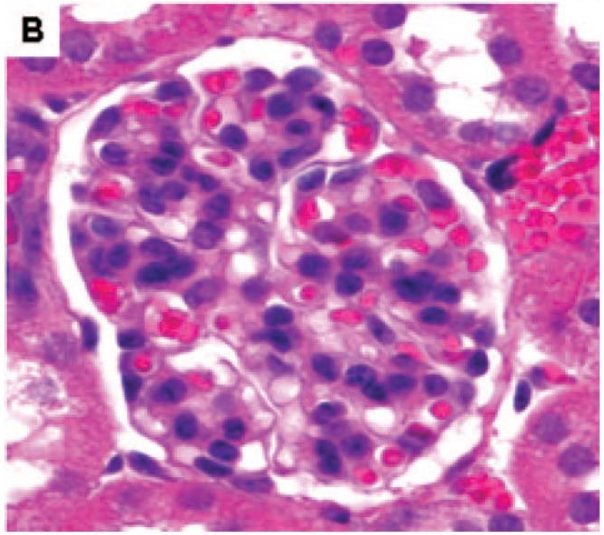

BASIC RESEARCH www.jasn.org

C5a Receptor Mediates Neutrophil Activation and ANCA-Induced Glomerulonephritis

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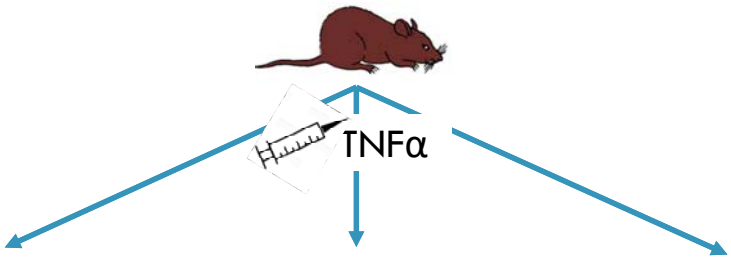

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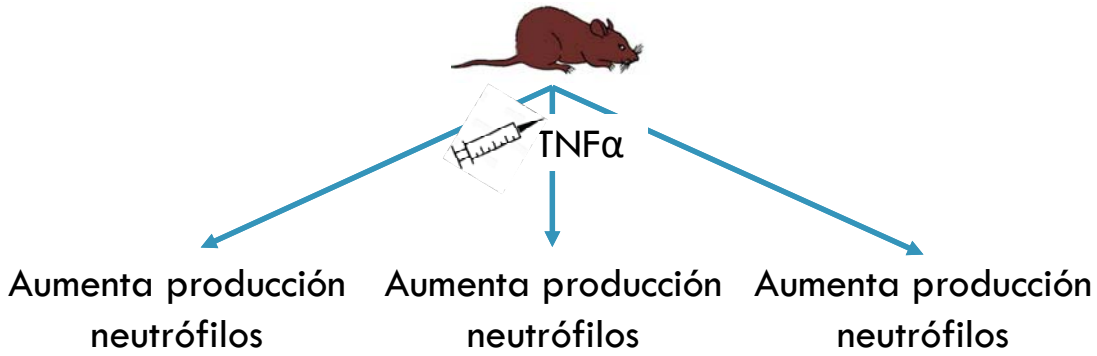

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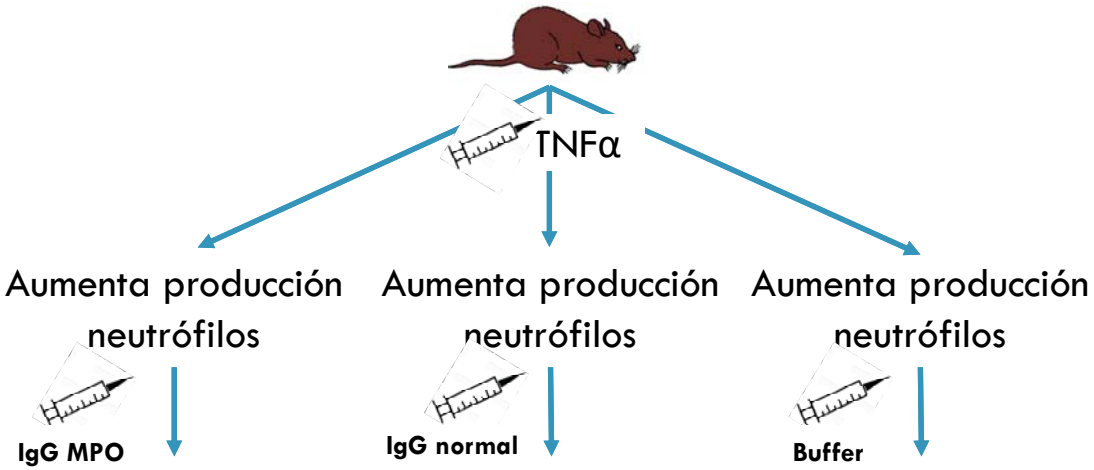

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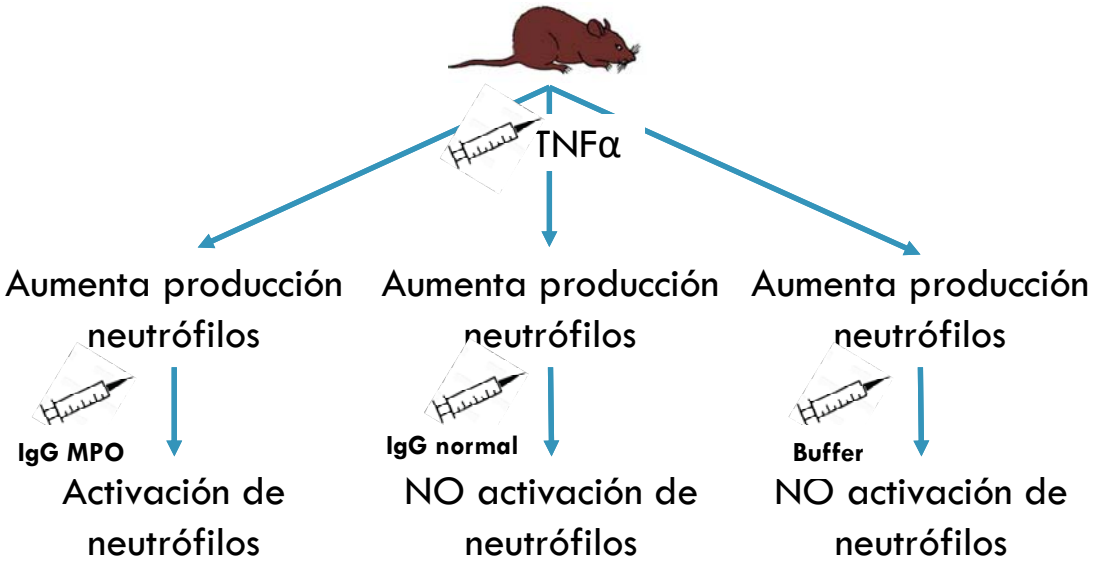

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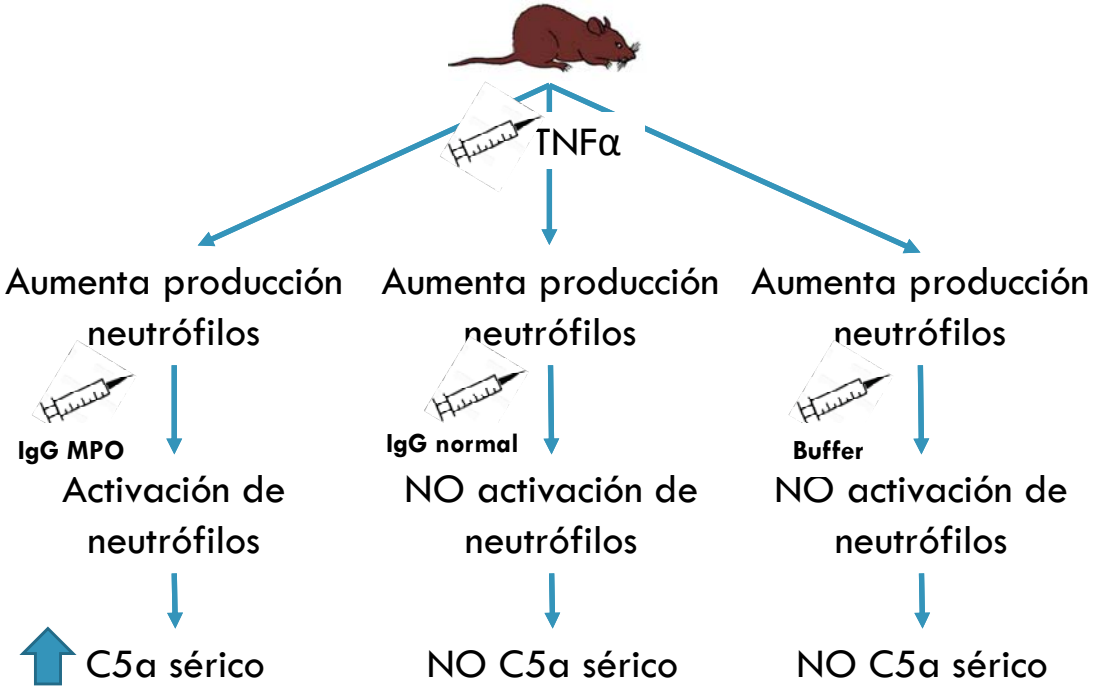

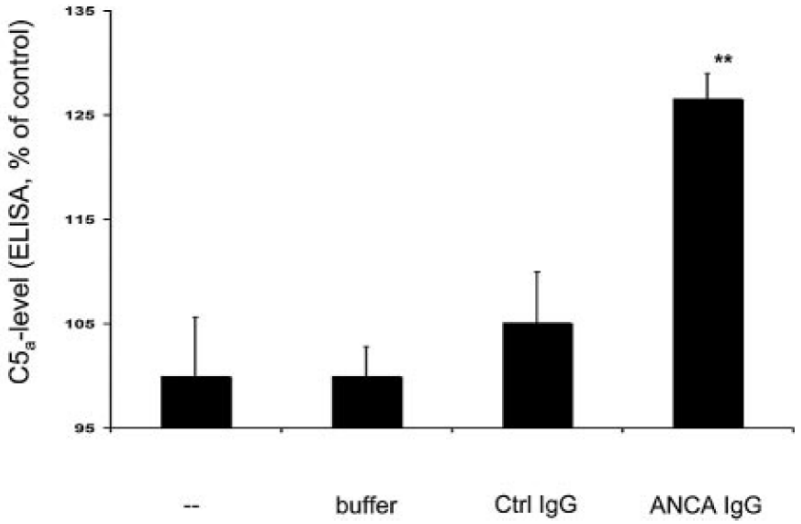

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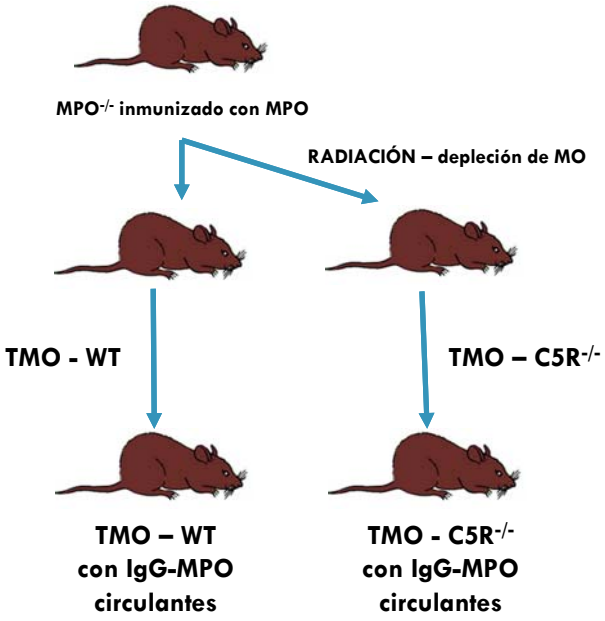

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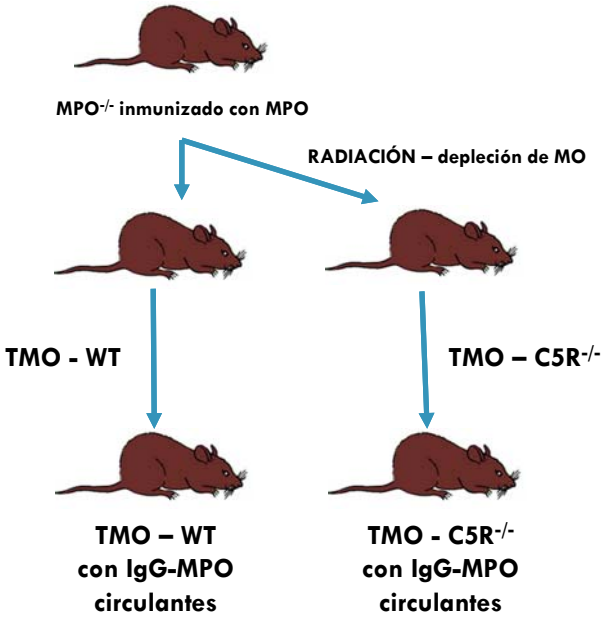
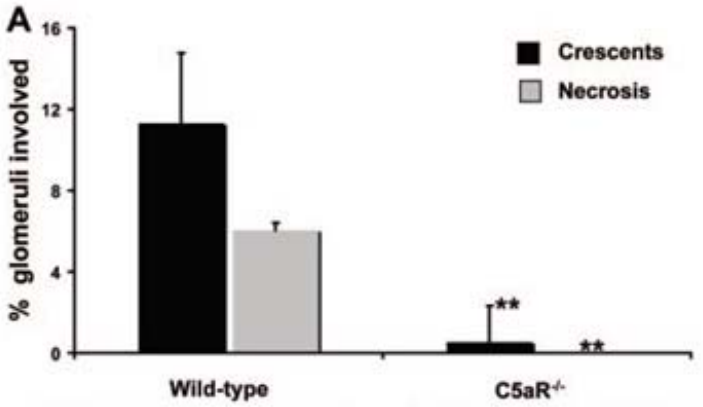
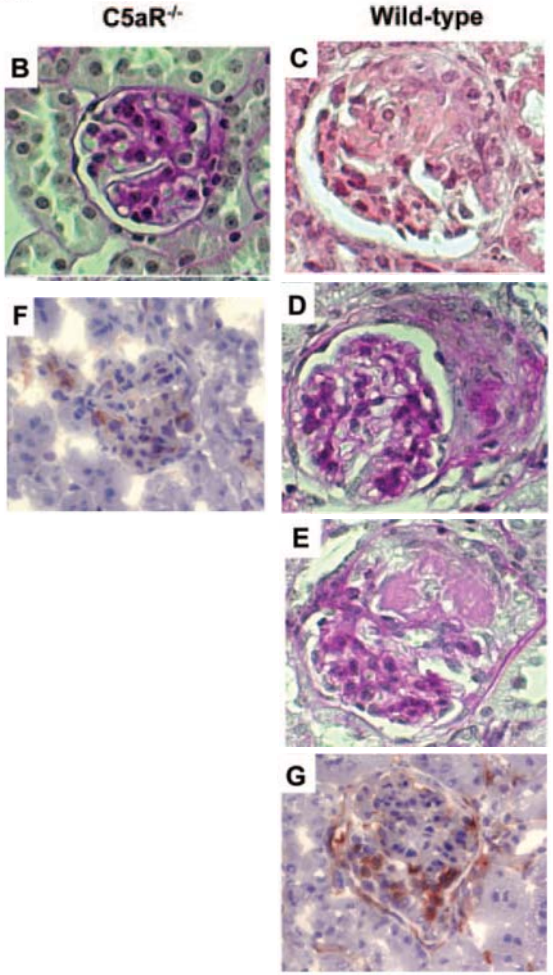


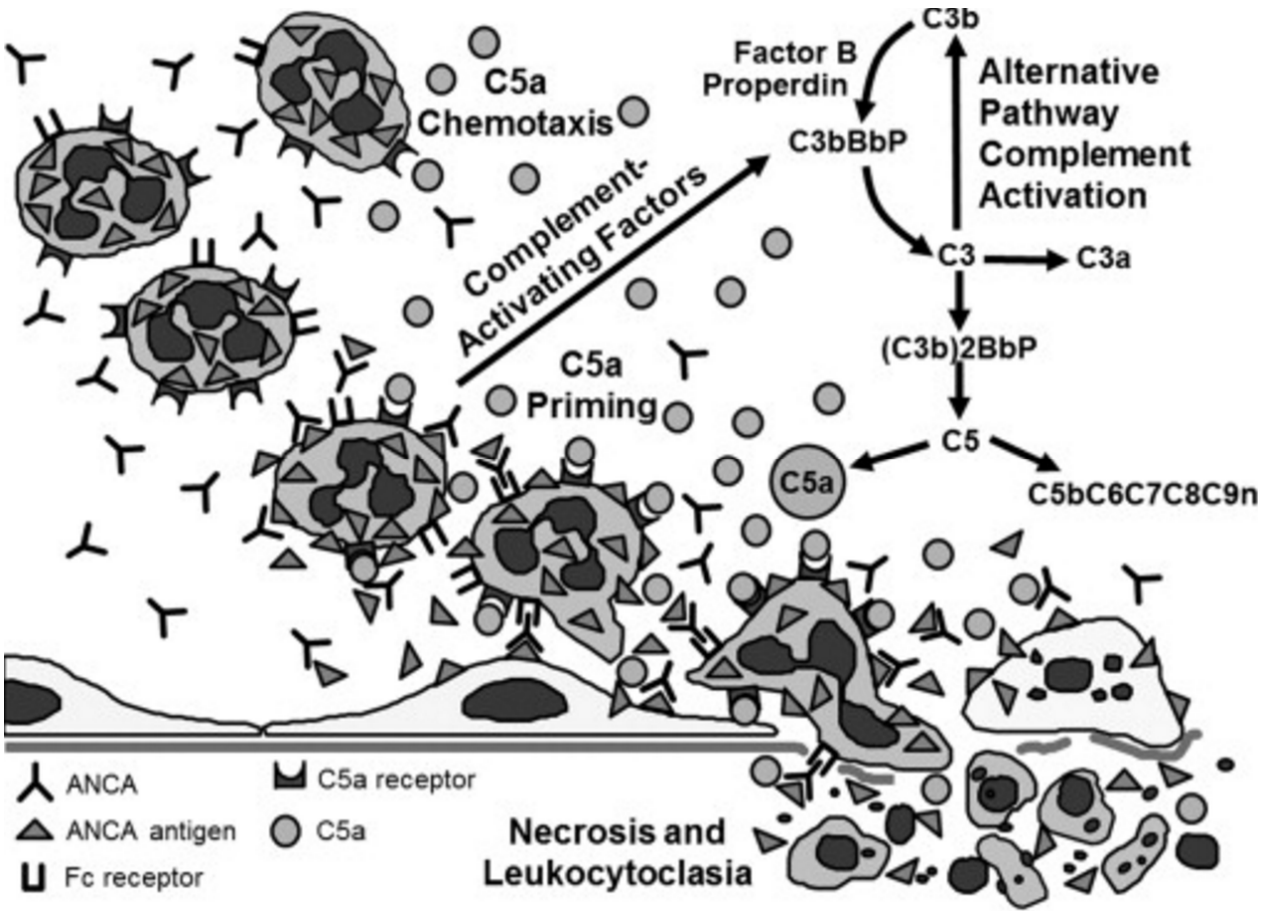




J Am Soc Nephrol 20: 289–298, 2009. doi: 10.1681/ASN.2008050497

Complement in ANCA-Associated Vasculitis

J. Charles Jennette, MD, Hong Xiao, MD, and Peiqi Hu, MD



ANCA
(antibodies against neutrophil citoplasmic antigen)

↓

Activan neutrófilos

↓

Activación de vía alternativa del complemento

↓

Aumenta producción de **C5a**

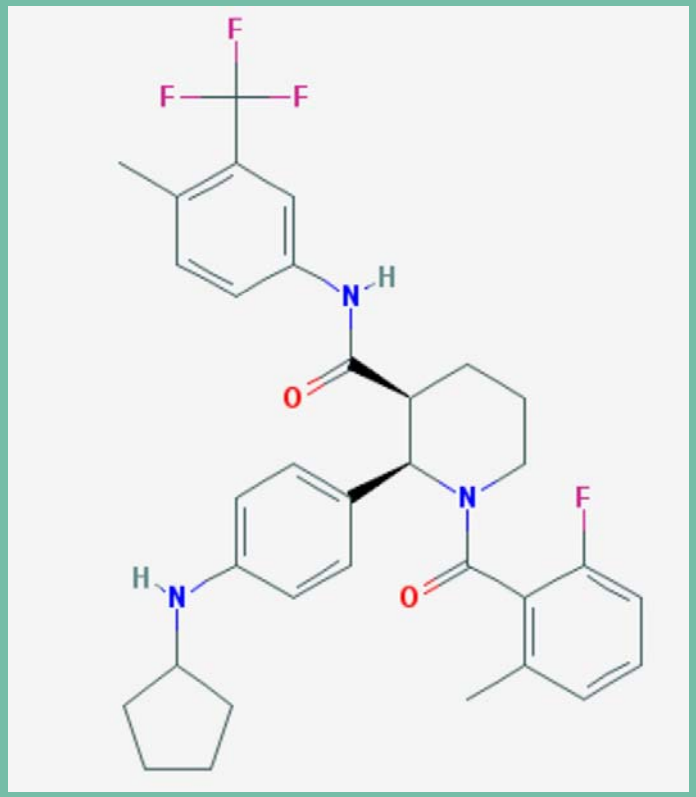
↓

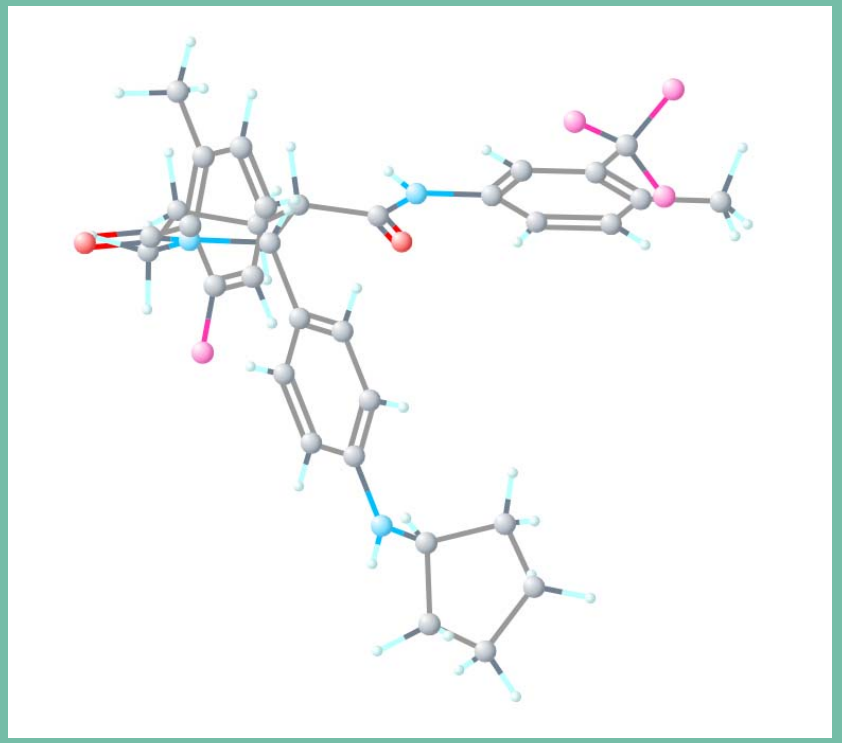
Atracción neutrófilos, monocitos, céls T, eosinófilos

↓

Leucocitoclasia y necrosis

Seminars in Nephrology, Vol 33, No 6, November 2013, pp 557–564





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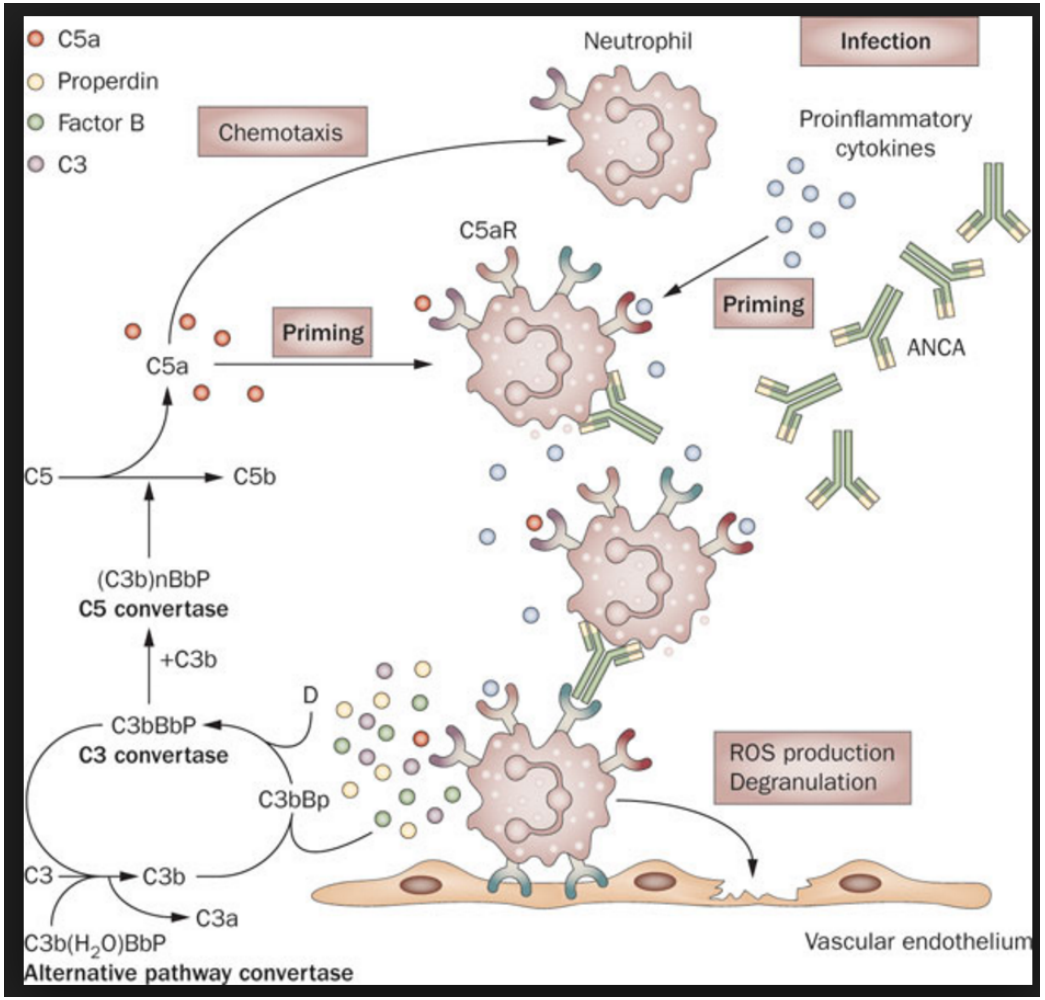
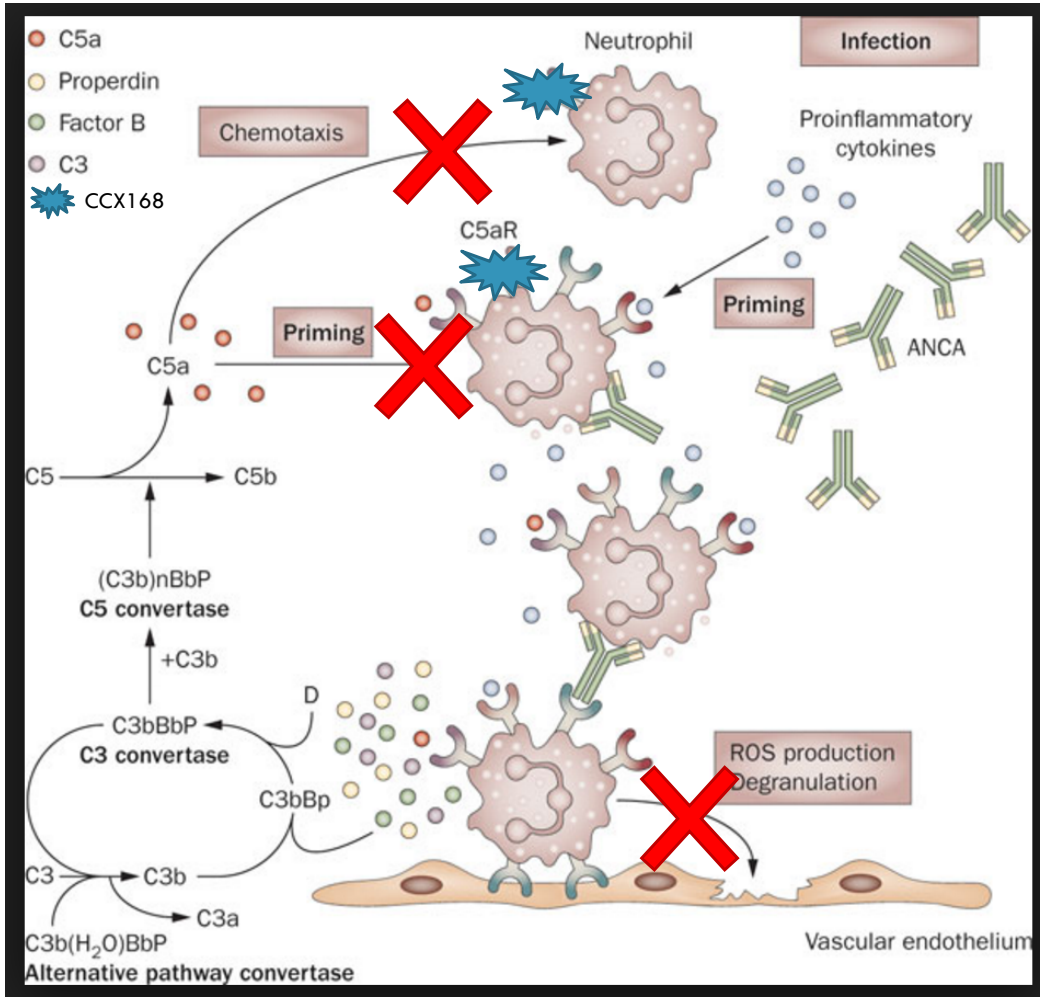

C5a
Properdin
Factor B
C3
Neutrophil
Infection
Chemotaxis
Proinflammatory cytokines
C5aR
Priming
Priming
ANCA
C5a
C5
C5b
(C3b)nBbP
C5 convertase
+C3b
D
C3bBbP
C3 convertase
C3bBp
ROS production
Degranulation
C3
C3b
C3a
C3b(H2O)BbP
Alternative pathway convertase
Vascular endothelium


C5a
Properdin
Factor B
C3
CCX168
Neutrophil
Infection
Chemotaxis
Proinflammatory cytokines
C5aR
Priming
Priming
ANCA
C5a
C5
C5b
(C3b)nBbP
C5 convertase
+C3b
D
C3bBbP
C3 convertase
C3bBp
ROS production
Degranulation
C3
C3b
C3a
C3b(H2O)BbP
Alternative pathway convertase
Vascular endothelium

1 **Completed** Open-Label Study to Evaluate Safety and Efficacy of CCX168 in Subjects With Immunoglobulin A Nephropathy on Stable RAAS Blockade

Condition: Immunoglobulin A Nephropathy

Intervention: Drug: CCX168

---

2 **Terminated** Complement Inhibition in aHUS Dialysis Patients

Condition: Atypical Hemolytic Uremic Syndrome

Intervention: Drug: CCX168

---

3 **Completed** A Study to Evaluate the Safety and Efficacy of CCX168 in Subjects With ANCA-Associated Vasculitis

Condition: Vasculitis

CLASSIC study

Interventions: Drug: Placebo; Drug: CCX168

---

4 **Recruiting** A Phase 3 Clinical Trial of CCX168 (Avacopan) in Patients With ANCA-Associated Vasculitis

Condition: ANCA-Associated Vasculitis

ADVOCATE study

Interventions: Drug: CCX168; Drug: Prednisone; Drug: Cyclophosphamide; Biological: Rituximab; Drug: Azathioprine

---

5 **Completed** Clinical Trial to Evaluate Safety and Efficacy of CCX168 in ANCA-Associated Vasculitis

Condition: ANCA-associated Vasculitis

CLEAR study

Interventions: Drug: CCX168 low dose plus standard of care; Drug: CCX168 high dose plus standard of care; Other: Placebo BID plus standard of care

---

www.clinicaltrials.gov

CLEAR

Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis

Criterios de inclusión: - Nuevo diagnóstico o recaidas de VAA

Grupos de tratamiento: 12 semanas seguimiento
- **TODOS:** Rituximab o Ciclofosfamida en inducción
- **Grupo 1:** Prednisona 60 mg/día
- **Grup**
- **Grup**

Objetivo
- Efica
- Seguridad: % efectos adversos

CONCLUSION: C5a receptor inhibition with avacopan was effective in replacing high-dose glucocorticoids in treating vasculitis.

Table 1. Demographics and baseline characteristics[a]

Category	Placebo plus 60 mg Prednisone Control (*n*=23)	Avacopan plus 20 mg Prednisone (*n*=22)	Avacopan without Prednisone (*n*=22)
Organ involvement, no. (%)			
Renal involvement	23 (100)	21 (95)	21 (95)
Rise in serum creatinine	2 (9)	0	0
High serum creatinine	15 (65)	11 (50)	6 (27)[c]
Hematuria	22 (96)	20 (91)	21 (95)
Proteinuria	18 (78)	20 (91)	16 (73)
Hypertension	3 (13)	5 (23)	2 (9)
			54.7±19.6
			283 (25–3051)
			Avacopan without Prednisone (*n*=21)
BVAS and vasculitis damage index end points			
Primary end point: treatment response[b] at week 12, no. (%)	14 (70.0)	19 (86.4)	17 (81.0)
BVAS			
Baseline			
Actual	13.6±1.4	14.3±1.3	13.6±1.4
% Change	–	–	–
Week 4			
Actual	6.6±1.2	4.9±0.7	5.3±1.3
% Change	−40±12	−64±5	−61±9
Week 12			
Actual	5.0±1.6	2.6±0.7	3.6±1.1
% Change	−56±14	−79±5	−73±7
Renal end points			
No. patients	20	18	18
Renal response[d] at week 12, no. (%)	8 (40)	10 (56)	6 (33)

Table 3. Safety results for 12-week treatment period

Variable	Placebo plus 60 mg Prednisone Control (*n*=23)	Avacopan plus 20 mg Prednisone (*n*=22)	Avacopan without Prednisone (*n*=22)
Patients with any adverse event, no. (%)	21 (91)	19 (86)	21 (96)
Patients with any grade 3 or greater adverse	2 (9)	2 (9)	2 (9)
Patients with any serious adverse event,[a] no. (%)	4 (17)	3 (14)	8 (36)
Vasculitis	1 (4)	1 (5)	3 (14)
Infection	1 (4)	1 (5)	1 (5)
Back pain and vertebral fracture	1 (4)	0	0
C-reactive protein increase	0	0	1 (5)
Dehydration	1 (4)	0	0
Hematuria	0	1 (5)	0
Hepatic and pancreatic enzymes increased	0	0	1 (5)
Musculoskeletal chest pain	0	1 (5)	0
Rash	0	0	1 (5)
Renal impairment	0	0	1 (5)

Jayne DRW et al. JASN 2017;28(9):2756-2767

1	Completed	Open-Label Study to Evaluate Safety and Efficacy of CCX168 in Subjects With Immunoglobulin A Nephropathy on Stable RAAS Blockade	**Condition:** Immunoglobulin A Nephropathy **Intervention:** Drug: CCX168
2	Terminated	Complement Inhibition in aHUS Dialysis Patients	**Condition:** Atypical Hemolytic Uremic Syndrome **Intervention:** Drug: CCX168
3	Completed	A Study to Evaluate the Safety and Efficacy of CCX168 in Subjects With ANCA-Associated Vasculitis **CLASSIC study**	**Condition:** Vasculitis **Interventions:** Drug: Placebo; Drug: CCX168
4	Recruiting	A Phase 3 Clinical Trial of CCX168 (Avacopan) in Patients With ANCA-Associated Vasculitis **ADVOCATE study**	**Condition:** ANCA-Associated Vasculitis **Interventions:** Drug: CCX168; Drug: Prednisone; Drug: Cyclophosphamide; Biological: Rituximab; Drug: Azathioprine
5	Completed	Clinical Trial to Evaluate Safety and Efficacy of CCX168 in ANCA-Associated Vasculitis **CLEAR study**	**Condition:** ANCA-associated Vasculitis **Interventions:** Drug: CCX168 low dose plus standard of care; Drug: CCX168 high dose plus standard of care; Other: Placebo BID plus standard of care

www.clinicaltrials.gov

TITLE PAGE

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of CCX168 (Avacopan) in Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Treated Concomitantly with Rituximab or Cyclophosphamide/Azathioprine

Criterios de inclusión:

- Vasculitis asociada a ANCA (MPA/GPA) de nuevo diagnóstico o recidiva
- GFR ≥ 15ml/min/m2

Objetivos:

- Primario:
  - Remisión mantenida a la semana 52 (sin necesidad de corticoides en las 4 semanas previas a la semana 26)

- Secundarios:
  - Valoración de la toxicidad de GC (GTI: glucocorticoid toxicity index)
  - Remisión precoz a la semana 4
  - Efectos adversos
  - Evaluación de la calidad de vida
  - Evaluación de los parámetros renales en pacientes con afectación renal: GFR, proteinuria
  - Cambios en la evaluación de daño crónico a través del VDI (vasculitis damage index)

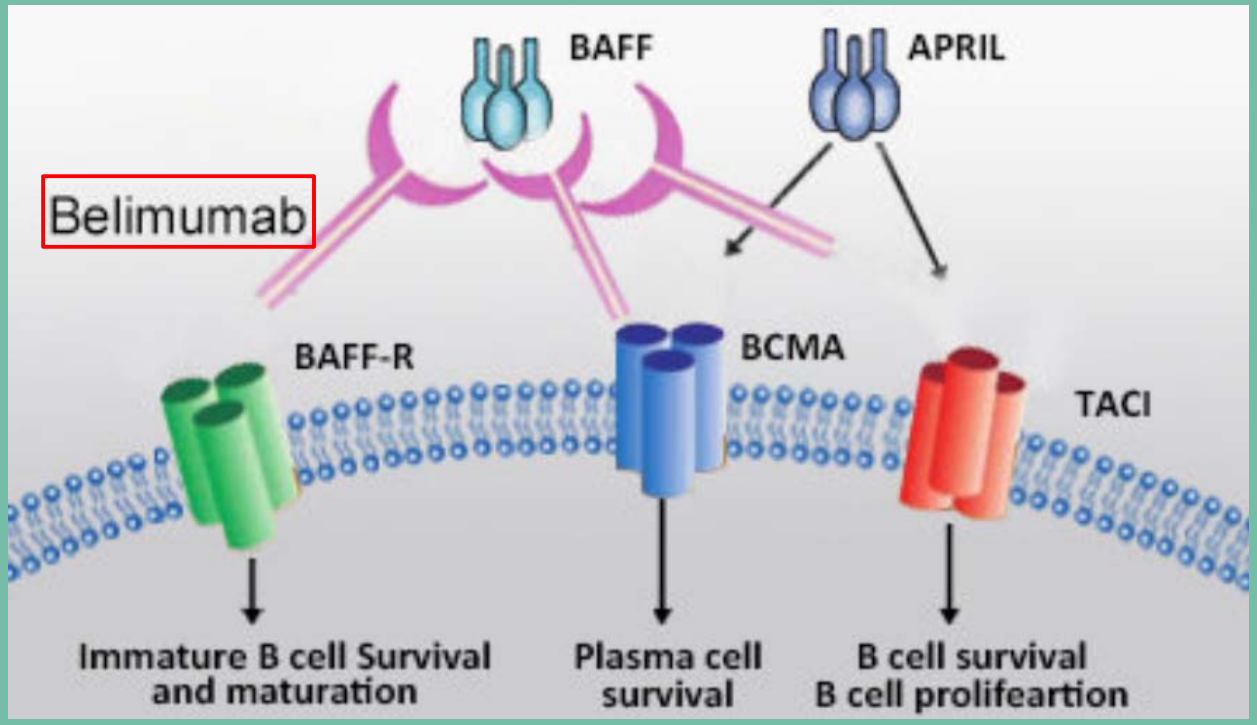
TITLE PAGE

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of CCX168 (Avacopan) in Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Treated Concomitantly with Rituximab or Cyclophosphamide/Azathioprine

Tratamiento:

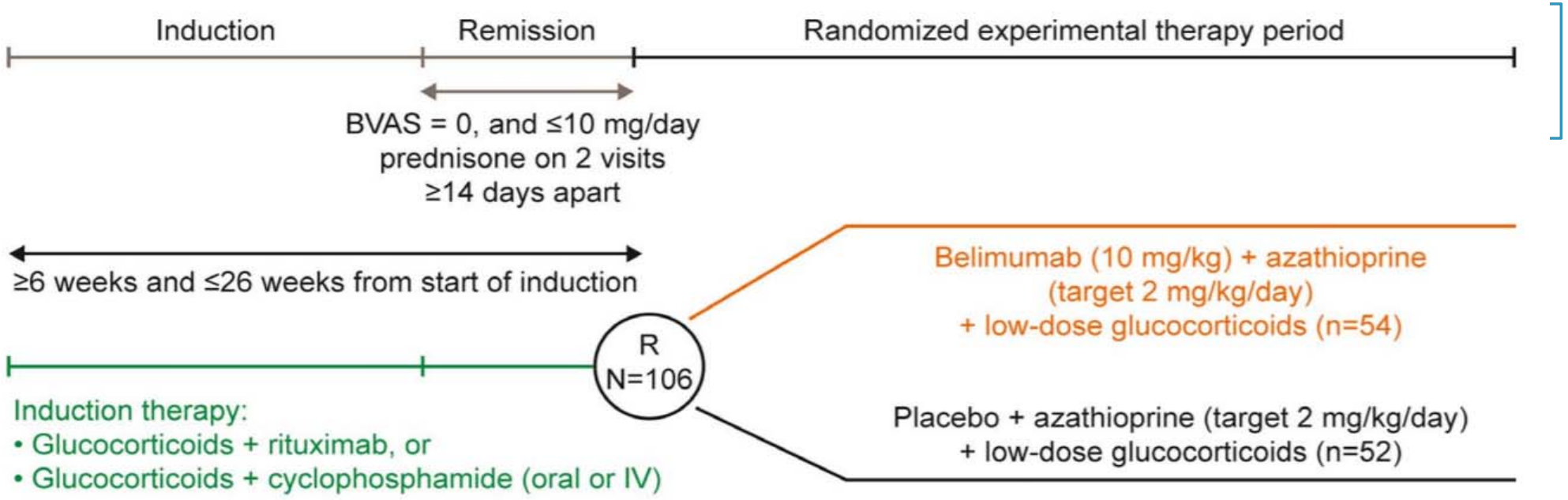
- Inducción: Ciclofosfamida IV/VO + Azatioprina vs Rituximab 375 mg/m2 x4

- Mantemiento:
  - Grupo CCX168: 30 mg c/12 horas Avacopan (durante 52 semanas) + Placebo/Prenisona
  - Grupo Prednisona: Prednisona en pauta descendente (inicialmente 60 mg/día) hasta semana 26 + Placebo/CCX168



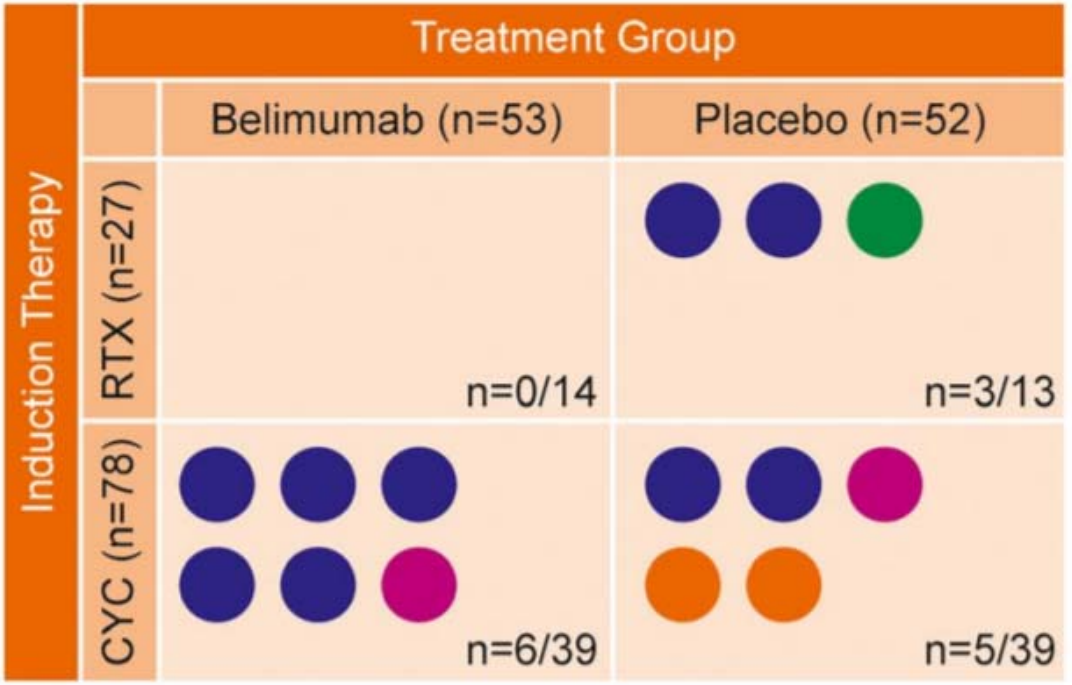
OTROS ENSAYOS EN MARCHA

BREVAS. Belimumab and azathioprine for maintenance of remission in AAV



Características basales

Sex, no. (%) female	
Race, no. (%)	
White	
American Indian or Alaskan Native	
African American/African Heritage	
Asian	
Age, mean ± SD years	
Age group, no. (%)	
<65 years	
≥65 years	
Disease classification, no. (%)	
GPA	
MPA	
BVAS total, median (min–max)†	
ANCA type, no. (%)‡	
PR3-ANCAs	
MPO-ANCAs	
ANCA positivity by immunoassay	
Induction regimen, no. (%)	
IV cyclophosphamide	
Oral cyclophosphamide	
Rituximab	



or

Table 2. Su

Total popu

PSE

Vasculitis

Cyclophosphamide induction regimen

n in the double-blind phase*

ab 10 mg/kg	
HR (95% CI)	*P*
1.07 (0.44–2.59)	0.884
0.88 (0.29–2.65)	0.821

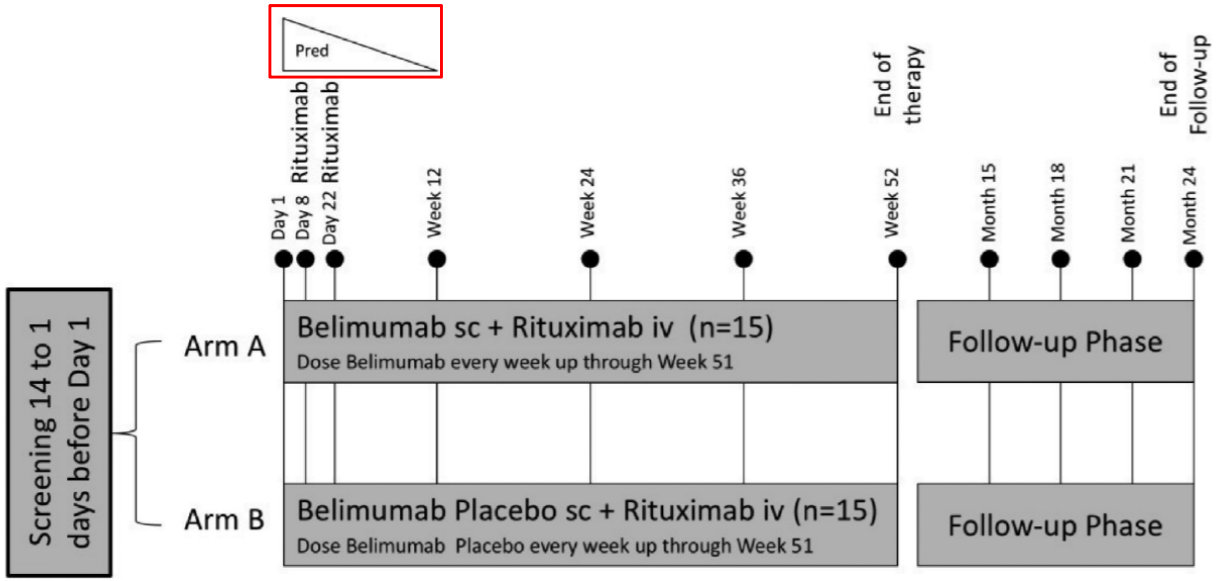
Podría ser interesante el uso de Belimumab como mantenimiento en pacientes que han recibido inducción con Rituximab. Después de inducción con ciclofosfamida, solo aporta eventos adversos

Vasculitis relapse	3/13 (23.1)	0	–	–

COMBIVAS. Rituximab and Belimumab combination therapy in PR3-AAV

Criterios de inclusión:

- Vasculitis asociada a **PR3** de nuevo diagnóstico o recidiva y presentación grave
- GFR ≥ 15ml/min/m2



· Objetivo primario: Tiempo hasta negativización de PR3

· Secundarios:

- Cambios de biomarcadores (células plasmáticas, plasmablastos o células B memoria)
- Tiempo hasta remisión clínica
- Tiempo hasta recidiva
- Efectos adversos graves

MENSAJES IMPORTANTES

- Tratamiento de inducción:
  - Ciclofosfamida o Rituximab, no diferencias *(RAVE, RITUXVAS)*
  - En recaídas: Rituximab primera opción *(RAVE)*
  - Plasmaféresis si Cr >5.8 mg/dl. En resto de afectación renal: solo aporta efectos adversos *(MEPEX, PEXIVAS)*
  - Si no se puede usar Ciclofosfamida o Rituximab: valorar MMF *(MYCYC)*

- Tratamiento de mantenimiento:
  - Rituximab el más eficaz. Pero tras tratamiento de inducción con Rituximab, ¿cuándo iniciar? *(MAINRITSAN, RITAZAREM)*
  - Azatioprina mejor que MMF *(IMPROVE)*
  - Descenso rápido de esteroides → 5 mg/día a partide 3° mes (inicio a 0.5 mg/kg/día en lugar de 1 mg/kg/día) *(PEXIVAS)*

- Muy prometedor el nuevo bloqueante de C5aR para evitar/reducir dosis de esteroides