Manejo de Vasculitis ANCA refractarias.

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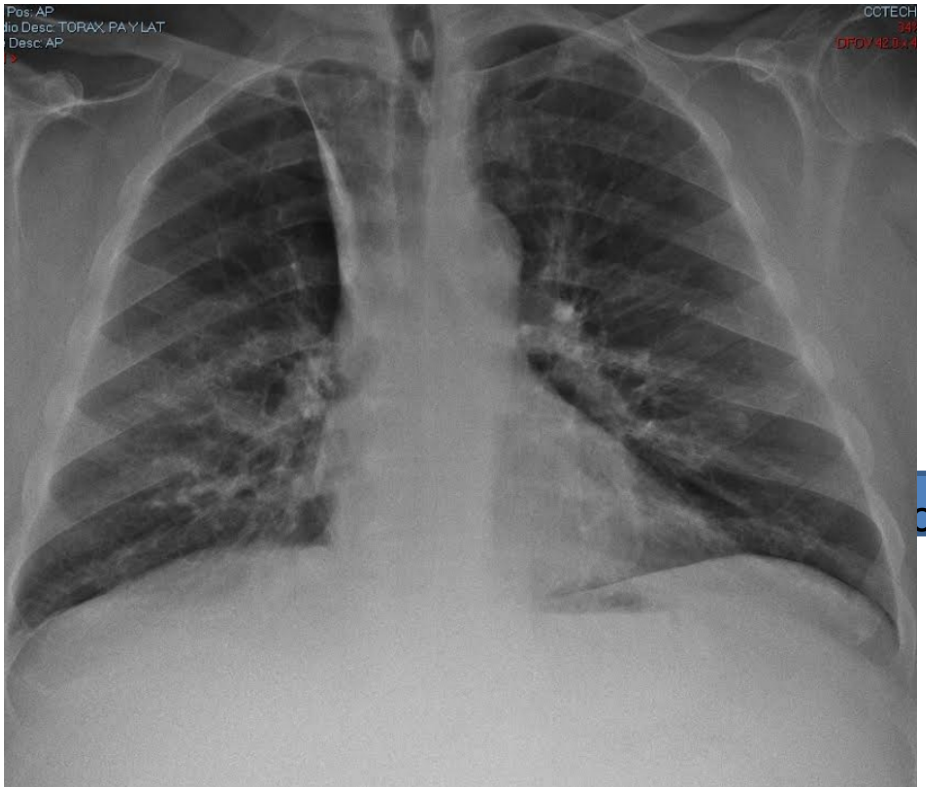
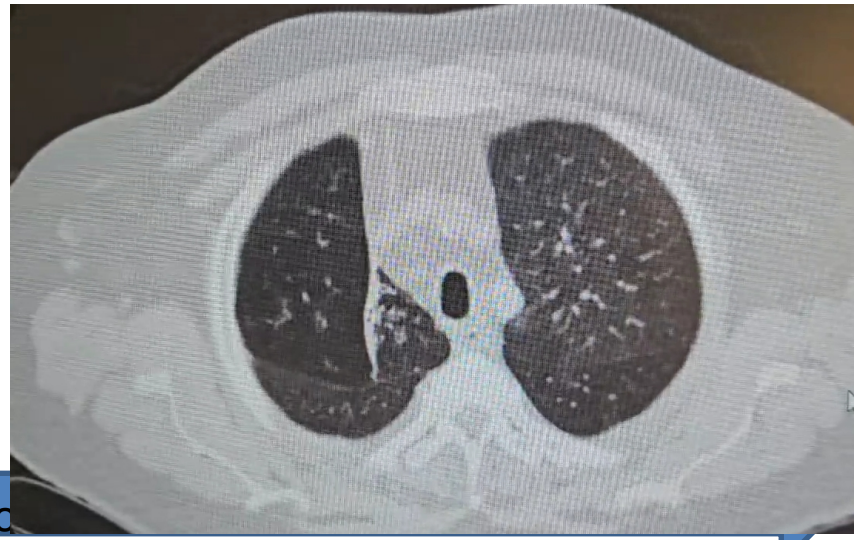
XII CONGRESO DE AADEA

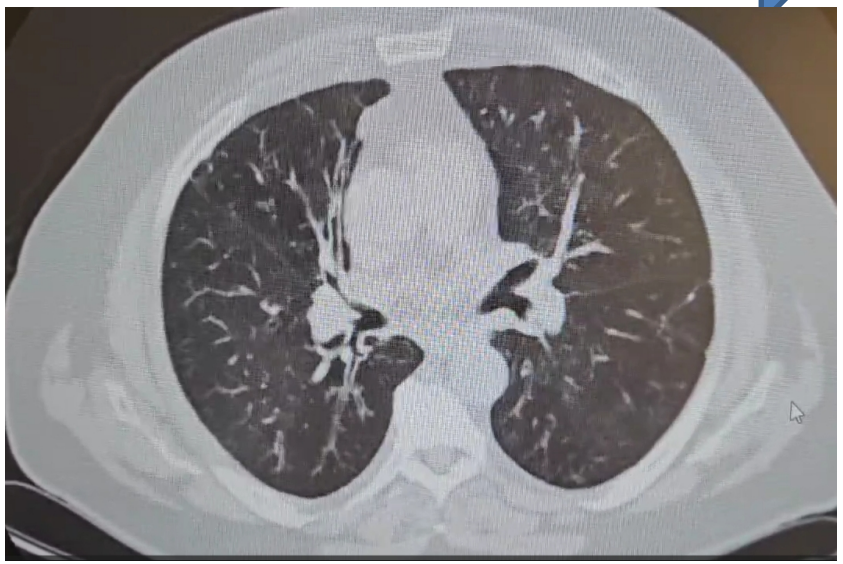
Conflicto de interés

He recibido transferencia en los 12 meses por parte de laboratorios GSK, MSD y ASTRAZENECA

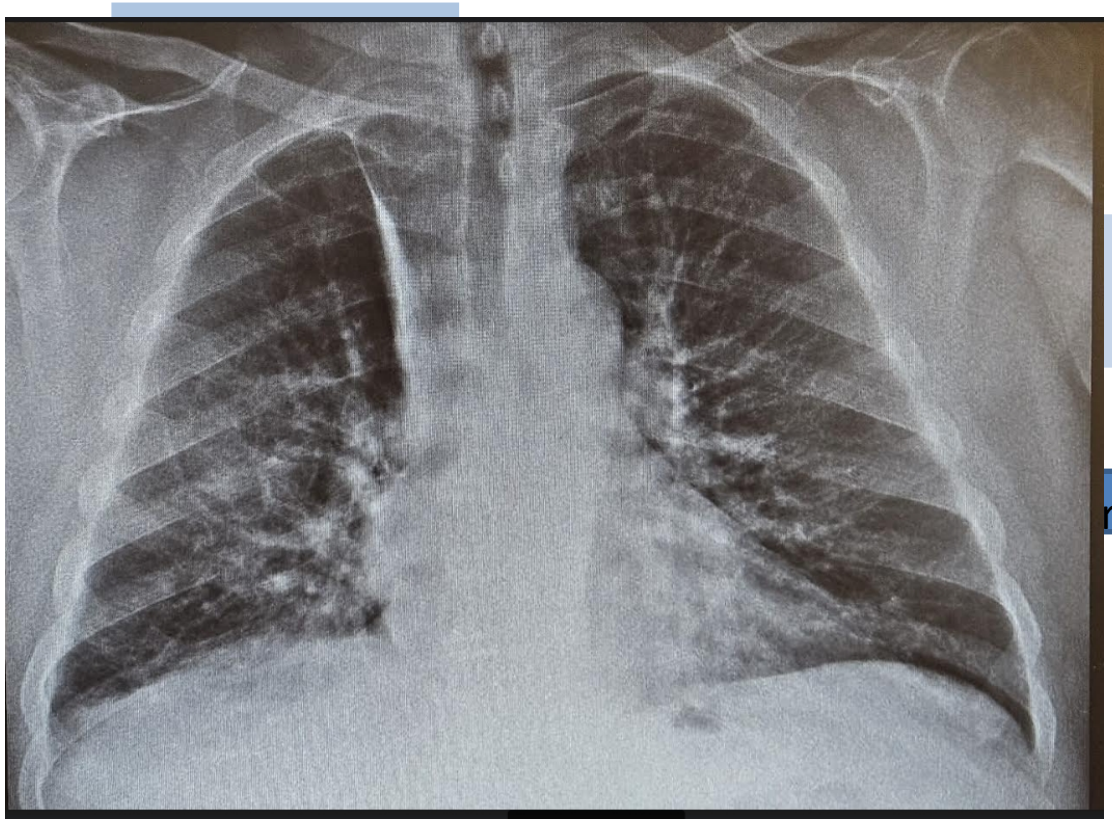
Caso 1 Varón de 64 años pluripatológico con VAA







Caso 1 Varón de 64 años pluripatológico con VAA

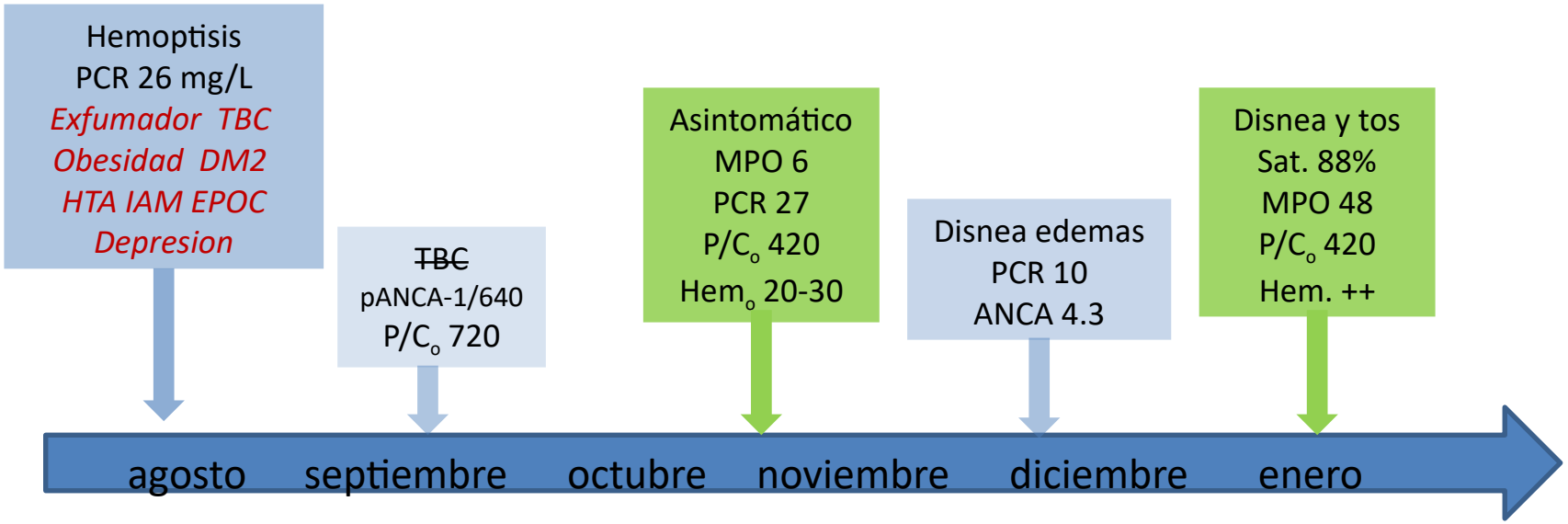


Disnea edemas
PCR 10
MPO 4.3

re diciembre enero

Furosemida
Pred LD

Caso 1 Varón de 64 años pluripatológico con VAA



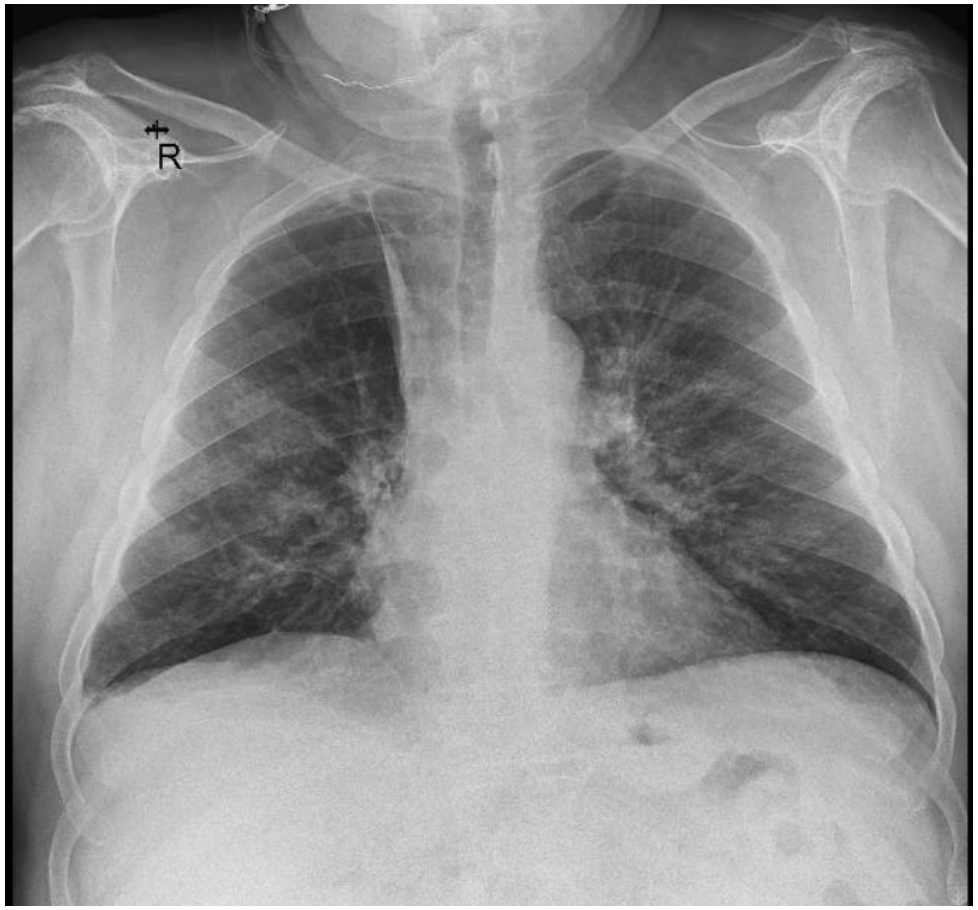
Antibiótico

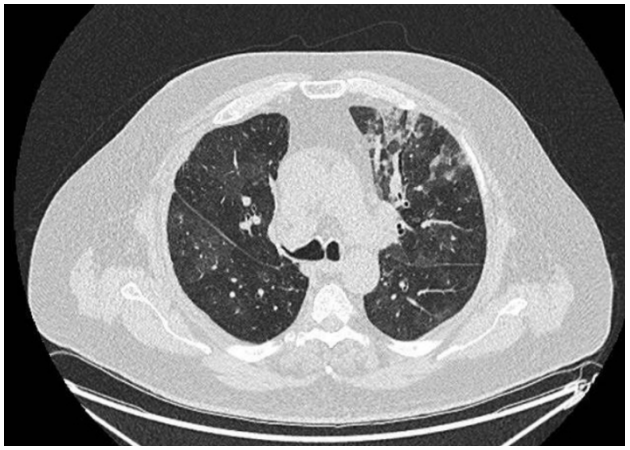
Pred (mg/kg)

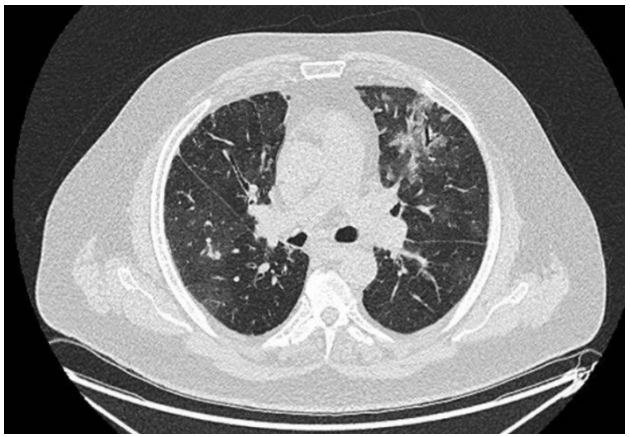
Rit x 2
Pred LD

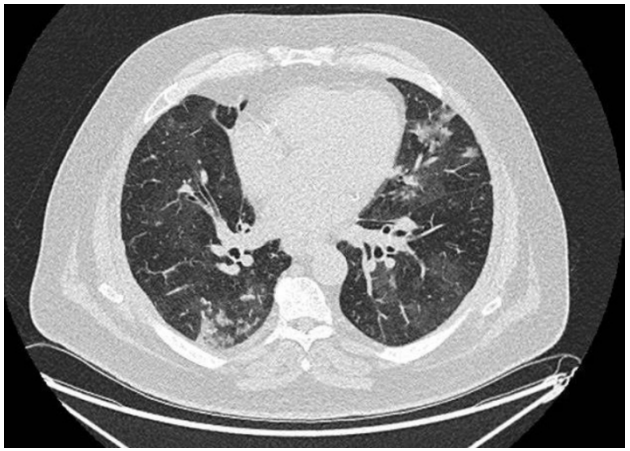
Furosemida
Pred LD

22/01/2024

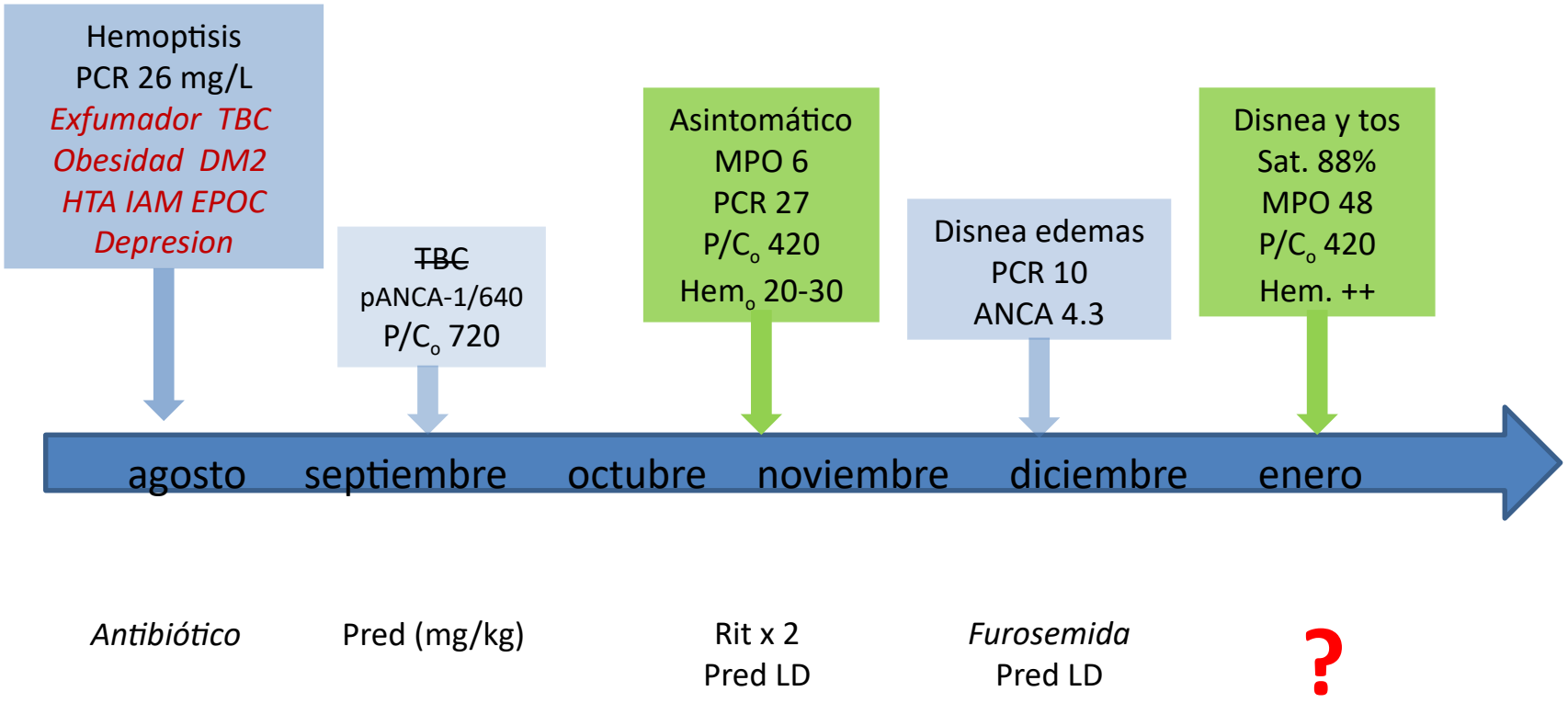




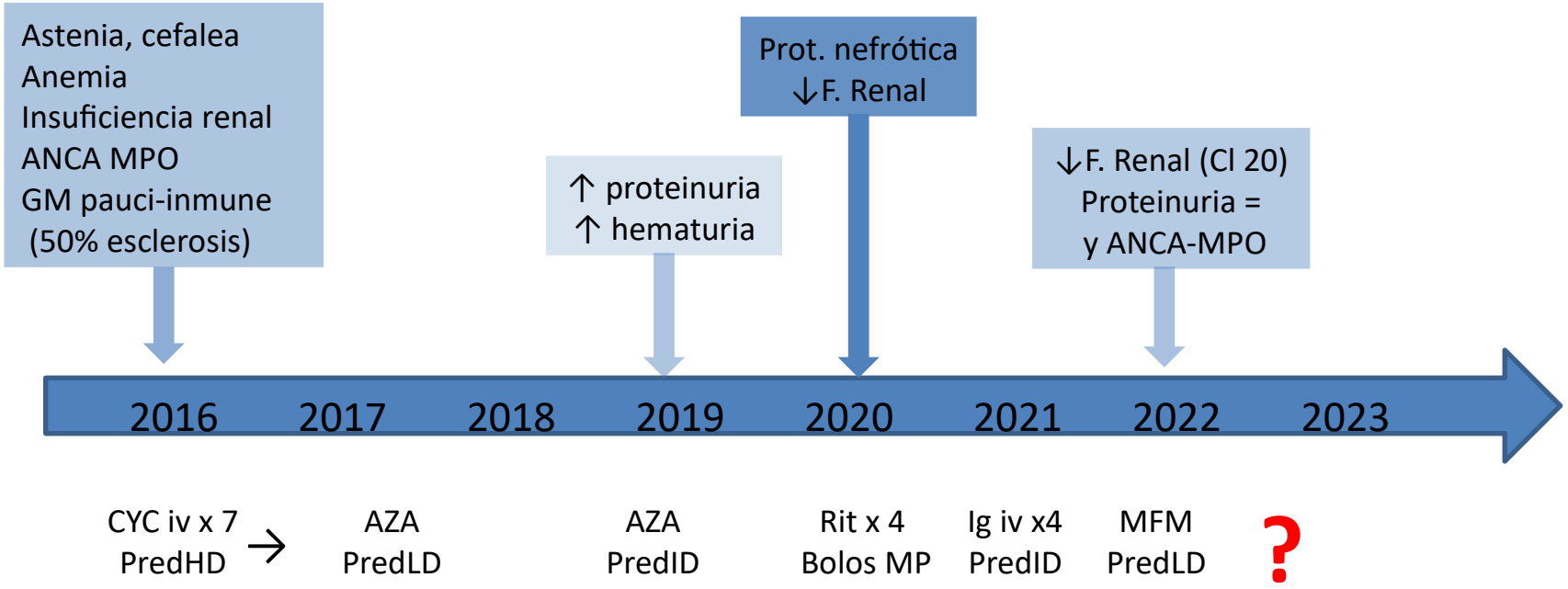




Caso 1 Varón de 64 años pluripatológico con VAA



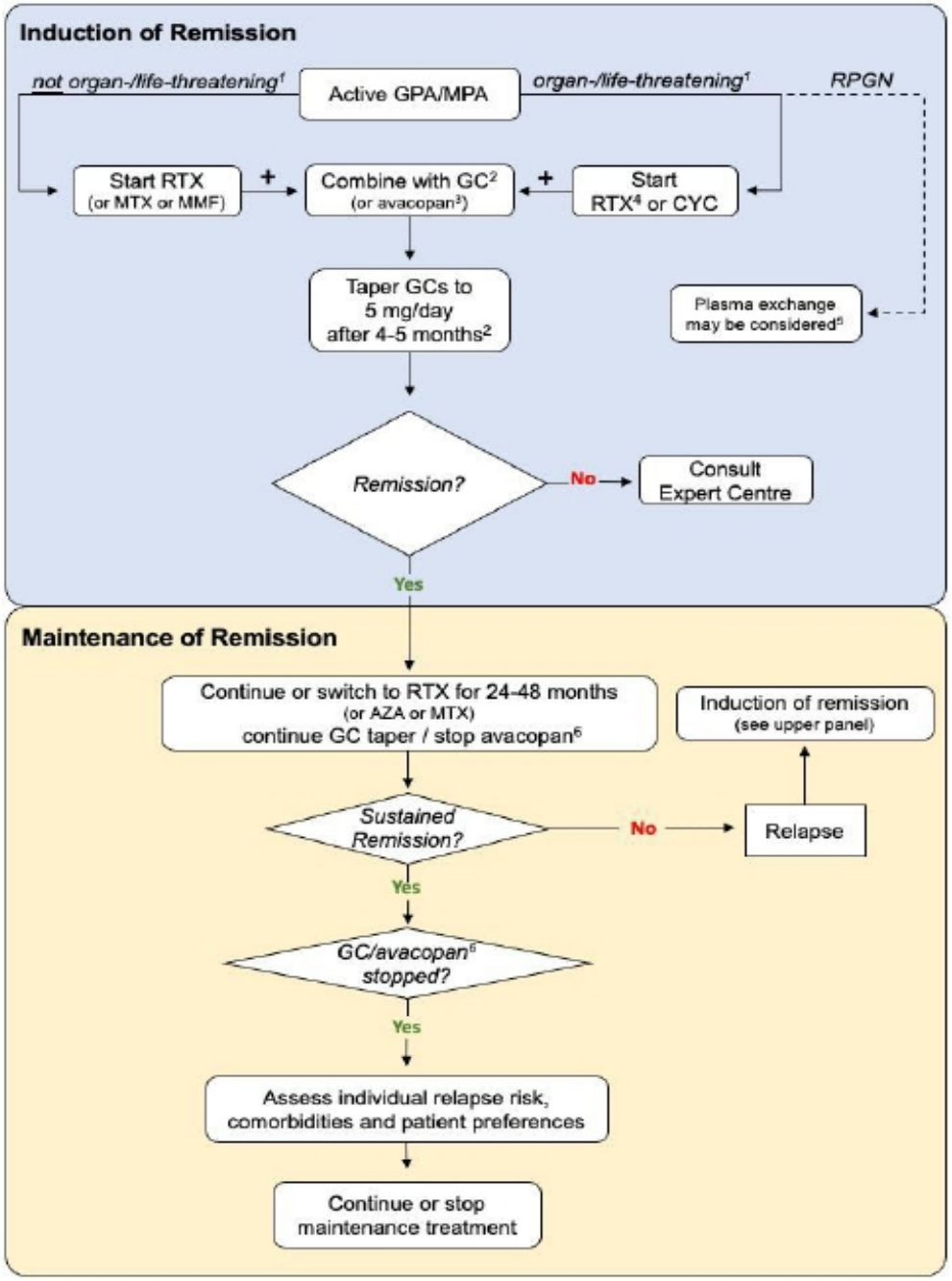
Caso 2 Mujer de 17 años con VAA desde los 10 años



+ bloqueo SRAA + estatinas

The 2022 EULAR algorithm for treatment of GPA and MPA

Hellmich B, et al. Ann Rheum Dis 2023;0:1–18.



Definición de VAA refractaria (EULAR 2022)

- Persistencia o empeoramiento de la actividad de VAA tras un periodo de tratamiento de inducción estándar.

- Debe haberse descartado:
  - Daño
  - Infección
  - Efectos secundarios
  - Comorbilidad

Hellmich B, et al. Ann Rheum Dis 2023;0:1–18.

Definición VAA refractaria

¿cuánto tiempo? - EULAR 2007

1. Falta de mejoría o empeoramiento a las **4 semanas**
2. Reducción en la puntuación de la actividad < 50% a las **6 semanas**.
3. Persistencia de actividad persistente (afectando a un item principal o tres menores del BVAS) principal a **las 8-12* semanas**.

Ann Rheum Dis 2007; 66:605–617
*Ann Rheum Dis 2016;75:1583–1594

WEGENER'S GRANULOMATOSIS: STUDIES IN EIGHTEEN PATIENTS AND A REVIEW OF THE LITERATURE

ANTHONY S. FAUCI AND SHELDON M. WOLFF

INTRODUCTION

. . . Classical or generalized Wegener's granulomatosis (WG) is characterized by necrotizing granulomatous vasculitis of the upper and lower respiratory tract together with glomerulonephritis. Widespread disseminated vasculitis involving both small arteries and veins occurs to a greater or lesser degree as the disease progresses. A localized form of WG limited primarily to the upper and lower respiratory tracts has been described. . .

WG is more common than was previously thought. Up to 1967, approximately 200 cases had been reported. . . The disease . . . is seen at any age from 3 months to as old as 75 years with a peak incidence in the fourth and fifth decades. Untreated, WG runs a rapidly fatal course with a mean survival of 5 months, 82% of patients dying within 1 year and greater than 90% dying within 2 years.

Over the past 12 years we have had the opportunity to follow and study 18 patients with WG at the National Institute of Allergy and Infectious Diseases. The purpose of this paper is to discuss the clinicopathological findings, therapeutic approaches, and follow-up in these patients. . .

MEDICINE 52(6):535–561, 1973.

Pronóstico

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

- Respuesta completa tras tratamiento de inducción 79/85 (93%)
- Fallo terapéutico 6/85 (7%)
- 4 fallecieron de otra causa (no relacionada con actividad)

Ann Intern Med . 1983 Jan;98(1):76-85

Outcome of ANCA-Associated Renal Vasculitis: A 5-Year Retrospective Study

Anthony D. Booth, MD, Mike K. Almond, MD, Aine Burns, MD, Peter Ellis, MA, Gill Gaskin, MD, Guy H. Neild, MD, Martin Plaisance, MD, Charles D. Pusey, MD, and David R.W. Jayne, MD, for the Pan-Thames Renal Research Group

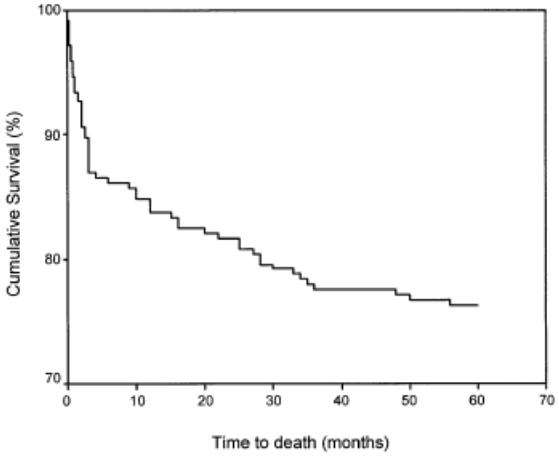


Fig 1. Patient survival.

- Analizan retrospectivamente 246 VAA con afectación renal
- Supervivencia al año 84%, a los 5 años 76%
- Enfermedad renal terminal 28%, con alta mortalidad (47%)
- Remisión a los 6 meses 81% (94% entre los supervivientes)

Am J Kidney Dis . 2003 Apr;41(4):776-84

Long-term patient survival in ANCA-associated vasculitis

Table 1 Summary of trials

Trial	NORAM[8]	CYCAZAREM[9]	MEPEX[10]	CYCLOPS[7]
Disease stage	Early systemic	Mild–moderate renal	Severe renal	Mild–moderate renal
Remission induction	MTX+OCS/poCYC+OCS	poCYC+OCS	ivMP+poCYC+OCS vs PE+poCYC+OCS	ivCYC+OCS vs poCYC+OCS
Remission maintenance	MTX+OCS or poCYC+OCS	poCYC+OCS vs AZA+OCS	AZA+OCS	AZA+OCS

Table 3 Causes of death within and after the first year of follow-up, respectively

	<1 Year	>1 Year	Total (%)

Table 1. Numbers and percentages of refractory cases in the different trials on patients with AAV

Study	Refractory/total	%	
CYCLOPS [16]	7/150	4.7%	3.8%
MEPEX [17]	6/137	4.4%	
NORAM [18]	2/46	4.3%	
RITUXVAS [19]	0/11 (1/33)	0% (3%)	
RAVE [20]	2/98	2.0%	

Ann Rheum Dis 2011;70:488–494

Primera conclusión

- VAA refractaria **poco frecuente**(<10%)
  - Considerar la **variabilidad** en la respuesta al tratamiento
  - Se aconseja valoración en **centros con experiencia**

- Antes de valorar tratamiento debe **descartar**:
  - Infección
  - Daño
  - Ef. colaterales fármacos
  - Comorbilidad

Clínica

Laboratorio

Radiología

Biopsia

Hellmich B, et al. Ann Rheum Dis 2023;0:1–18.

Opciones iniciales de tratamiento en enfermedad refractaria

1. Aumentar dosis GC
   - Solo en caso de síntomas menores
   - Si no hay riesgo adicional de toxicidad
2. Switching: rituximab vs ciclofosfamida
3. Combinación rituximab y ciclofosfamida
   - *J Investig Med High Impact Case Rep. 2024*
4. Asociación de inmunoglobulinas iv (riesgo de infección)

Hellmich B, et al. Ann Rheum Dis 2023;0:1–18.

¿bolos de esteroides?

Intravenous pulse methylprednisolone for induction of remission in severe ANCA associated Vasculitis: a multi-center retrospective cohort study

Chanouzas D, et al. BMC Nephrol. 2019.

Background: Intravenous pulse methylprednisolone (MP) is commonly included in the management of severe ANCA associated vasculitis (AAV) despite limited evidence of benefit. We aimed to evaluate outcomes in patients who had, or had not received MP, along with standard therapy for remission induction in severe AAV.

Methods: We retrospectively studied 114 consecutive patients from five centres in Europe and the United States with a new diagnosis of severe AAV (creatinine > 500 μmol/L or dialysis dependency) and that received standard therapy (plasma exchange, cyclophosphamide and high-dose oral corticosteroids) for remission induction with or without pulse MP between 2000 and 2013. We evaluated survival, renal recovery, relapses, and adverse events over the first 12 months.

Results: Fifty-two patients received pulse MP in addition to standard therapy compared to 62 patients that did not. There was no difference in survival, renal recovery or relapses. Treatment with MP associated with higher risk of infection during the first 3 months (hazard ratio (HR) 2.7, 95%CI [1.4–5.3], $p = 0.004$) and higher incidence of diabetes (HR 6.33 [1.94–20.63], $p = 0.002$), after adjustment for confounding factors.

Conclusions: The results of this study suggest that addition of pulse intravenous MP to standard therapy for remission induction in severe AAV may not confer clinical benefit and may be associated with more episodes of infection and higher incidence of diabetes.

Combinación CYC – Rituximab

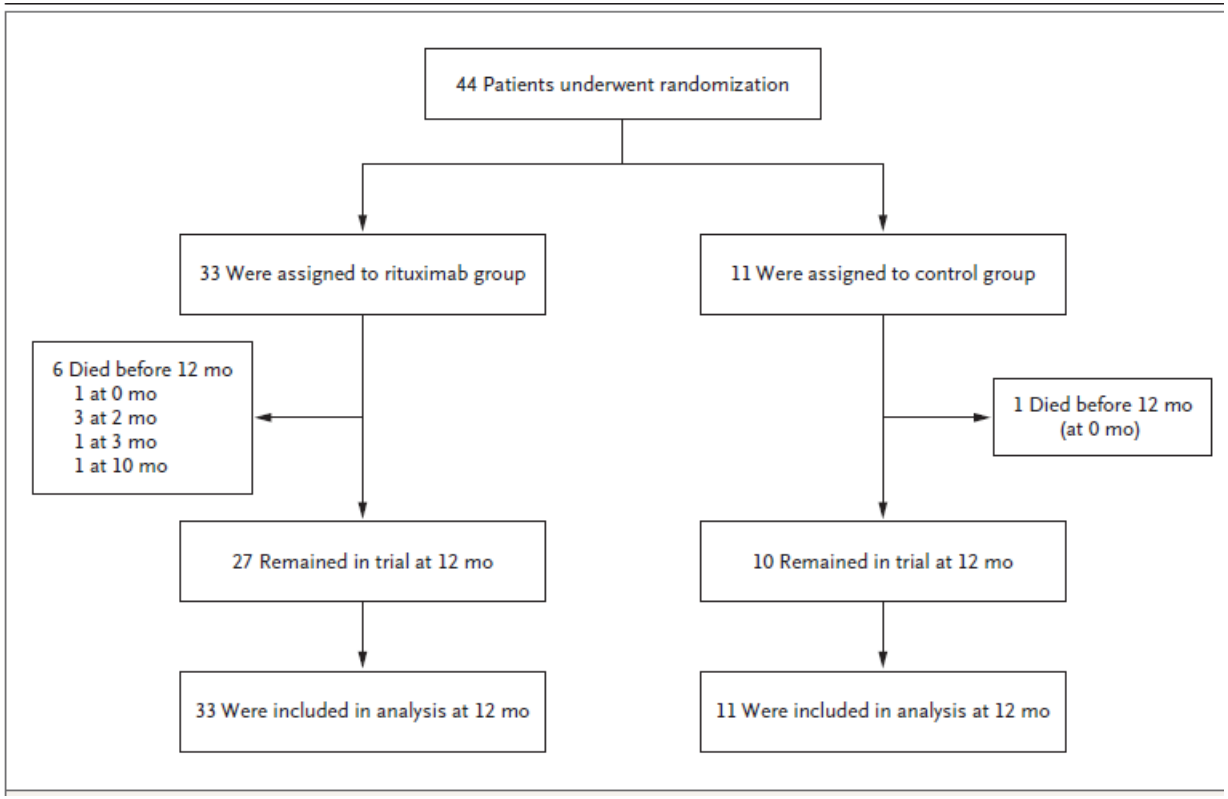
if only minor symptoms persist. The combination of RTX and CYC is used in patients with refractory organ-threatening or life-threatening disease by many centres, but data on this approach in true refractory AAV are lacking. Adding intravenous immuno-

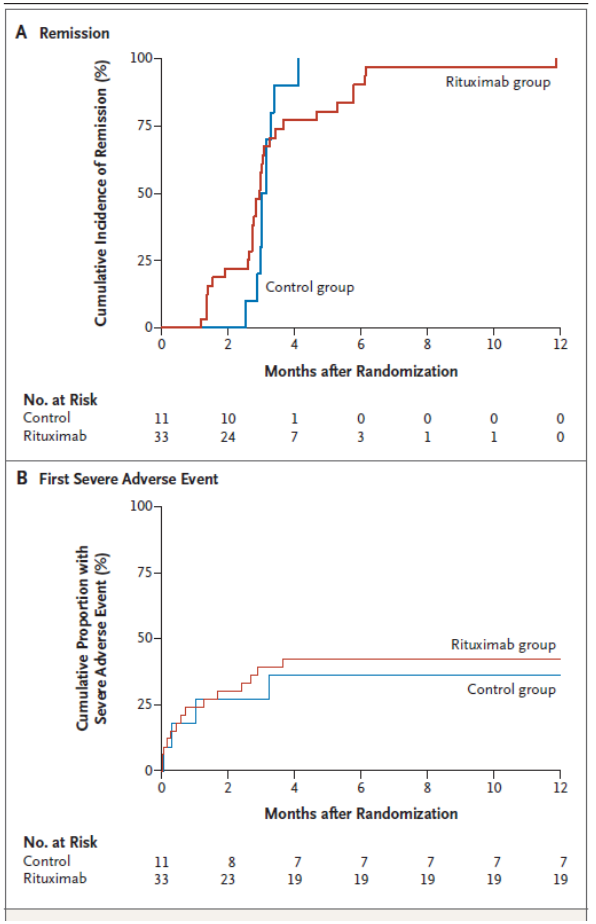
EULAR recommendations for the management of ANCA-associated vasculitis2022

Rituximab preferred	Cyclophosphamide preferred
• Children and adolescents • Pre-menopausal women and men concerned about their fertility • Frail older adults • Glucocorticoid-sparing especially important • Relapsing disease • PR3–ANCA disease	• Rituximab difficult to access • Severe GN (SCr >4 mg/dl [354 µmol/l]), combination of two intravenous pulses of cyclophosphamide with rituximab can be considered

KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases

Estudio RITUXVAS: rituximab vs ciclofosfamida en VAA con afectación renal





En el grupo de rituximab (375 mg/m2 x 4) se administró CYC iv (15 mg/m2 en semana 1 y 3)

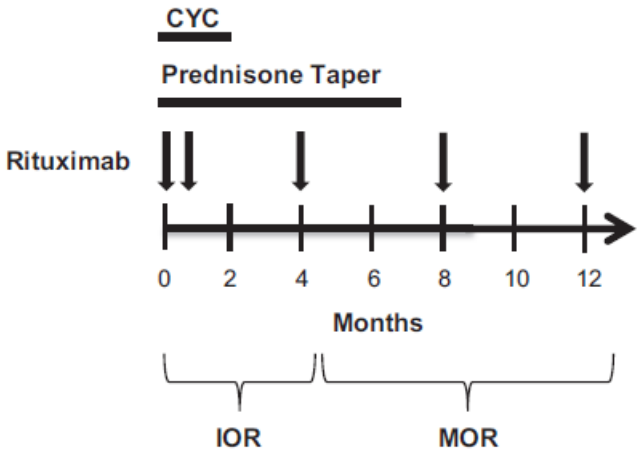
N Engl J Med 2010;363:211-20.

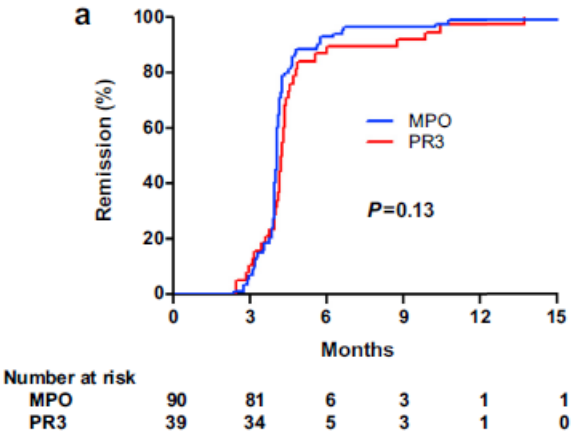
Combination Therapy With Rituximab and Cyclophosphamide for Remission Induction in ANCA Vasculitis

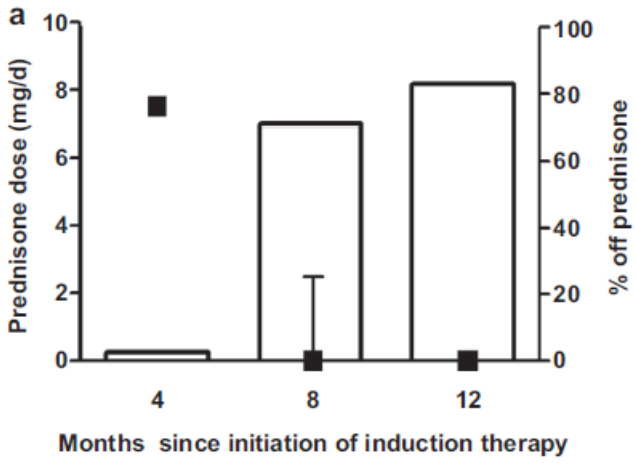
Frank B. Cortazar[1,2], Saif A. Muhsin[1,3], William F. Pendergraft III[4], Zachary S. Wallace[5], Colleen Dunbar[2], Karen Laliberte[2] and John L. Niles[1,2]

Table 1. Baseline characteristics

Baseline characteristics	Overall (n = 129)	MPO (n = 90)	PR3 (n = 39)	P
Age	64.9 (54.2–75.6)	66.2 (58.1–78.0)	57 (49.2–68.6)	0.01
Male	55 (42.6)	38 (42.2)	17 (43.6)	0.86
Recurrent disease	11 (8.5)	7 (7.8)	4 (10.3)	0.73
Initial BVAS-WG	6 (5–8)	6 (5–8)	7 (5–10)	0.03
PLEX	40 (31.0)	28 (31.1)	12 (30.8)	0.99
Organ involvement				
Constitutional	53 (41.0)	34 (37.8)	19 (48.7)	0.33
Pulmonary	63 (48.8)	45 (50.0)	18 (46.2)	0.71
DAH	20 (16)	17 (18.9)	3 (7.7)	0.12
ENT	61 (47)	33 (36.7)	28 (71.8)	<0.001
Renal	87 (67.4)	63 (70.0)	24 (61.5)	0.41
RPGN	75 (58.1)	55 (61.1)	20 (51.3)	0.34







Kidney Int Rep (2018) 3, 394–402

Indicación para uso combinado de rituximab-CYC

1. Considerar en afectación renal grave
2. Respuesta lenta al tratamiento
3. Enfermedad refractaria
4. Riesgo de toxicidad a GC
5. Riesgo de toxicidad a CYC

Chalkia A, Jayne D. ANCA-associated vasculitis - Treatment Standard. Nephrol Dial Transplant. 2023 Nov 8:gfad237.

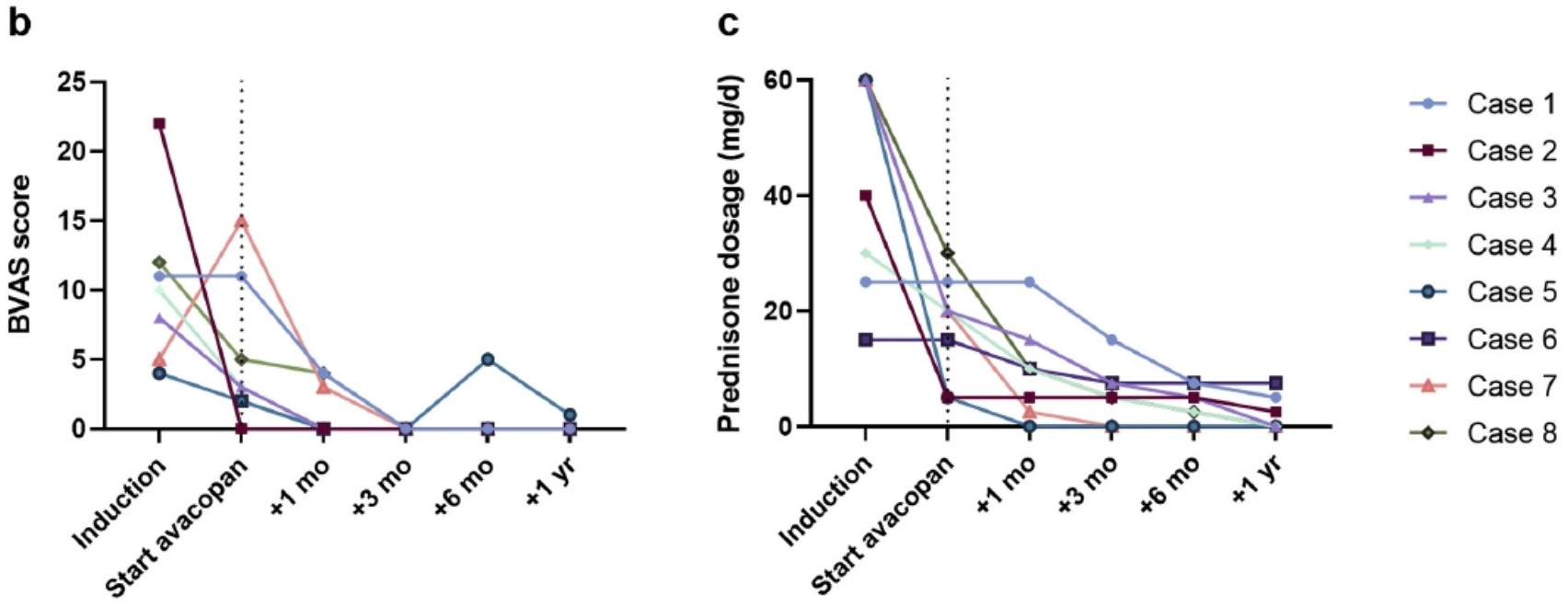
Diferentes opciones evaluadas en VAA refractaria

Fármaco	Estudio	Tipo estudio	Grupo control	Resultados
Inmunoglobulinas	Jane et al 2000 N=34	Ensayo doble ciego, aleatorizado y controlado	Placebo	Respuesta 83% vs 35 Sin diferencia a 3 meses
Micofenolato	MYCYC 2020 (N= 140)	Aleatorizado VAA naive	CYC iv	El MMF no inferior CYC para inducción, mayor tasa recaída
Leflunomida	Mustapha et al 2021 N=65	Observacional (VAA refractaria o intolerancia tratamiento)	MTX oral	Respuesta en el 70%
15-deoxispergualina	Birck et al 2003 N=20	Prospectivo no controlado refractarios (GPA)	–	Respuesta en el 70%
Globulina antitimocito	Schmitt et al 2004 N=15	Prospectivo no controlado 7 GPA refractario	–	Remisión en 4, parcial en 9 Evitar infección, precaución sobrecarga hídrica
AntiTNF	Infliximab 2004 Etarnercept 2005 Adalimumab 2010	Prospectivo no controlado	Adyuvante frente a placebo	Exceso de neoplasia (etanercept) Aumento infección (infliximab) Reducción GC (adalimumab)
Tocilizumab	Sakai et al 2017 N=7	Prospectivo no controlado (monoterapia)	–	Baja tasa de respuesta
Anti CD 20	Ofatumumab McAdoo et al 2016 Obinutuzumab Amudala et al 2022	Casos aislados (anafilaxia a Rituximab)	–	Eficacia en remisión y mantenimiento
Daratumumab Anti CD 134	Ostendorf et al 2023 N= 2	Casos aislados (refractario Rituximab y CYC)	–	Eficacia
Alentuzumab Anti CD 52	ALEVIATE 2022 N= 12	Prospectivo aleatorizada abierto (pacientes refractarios)	30 vs 60 mg	70% eficacia (sólo 30% sostenida)

Avacopan en VAA refractaria

REFRACTARIO ***CORTICODEP.*** ***EVITAR GC***

Table 1. Patient, AAV, and treatment characteristics



Prednisone at start (mg/d)	25	5	20	20	5	15	20	30
BVAS at start	11	0	3	3	2	2	15	5
Concomitant maintenance treatment	Prednisone (5 mg/d)	Prednisone (2.5 mg/d)	+2 mo RTX (1000 mg) +8 mo RTX (500 mg)		+14 mo: RTX (1000 mg)	Prednisone (7.5 mg/d) +1 yr: RTX (1000 mg)	+1 yr: RTX (500 mg)	
Extra induction therapies					+8 mo RTX (2000 mg)			

ANCA, antineutrophil cytoplasmic antibody; AZA, azathioprine; BVAS, Birmingham vasculitis activity score; CYC, cyclophosphamide; ENT, ear, nose, throat; F, female; PR3, proteinase 3; M, male; MMF, mycophenolate mofetil; MP, methylprednisolone; MPO, myeloperoxidase; MTX, methotrexate; N/A, not applicable; PE, plasma exchange; RTX, rituximab.

Kidney Int Rep. 2021 Dec 8;7(3):624-628

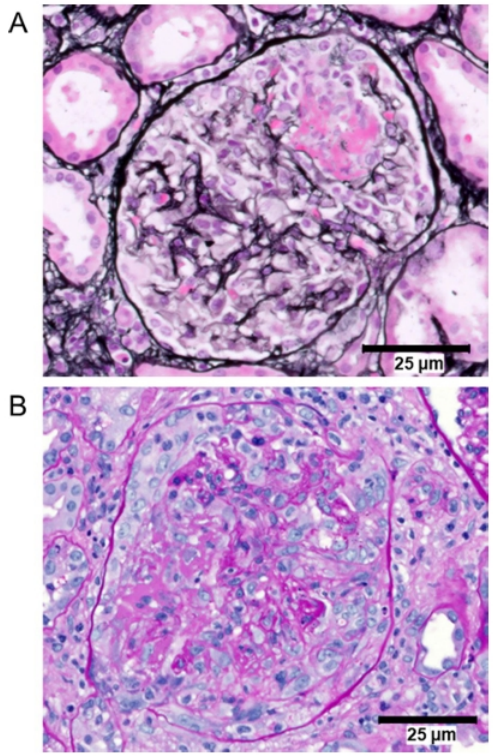
Journal of Nephrology (2023) 36:2365–2370
https://doi.org/10.1007/s40620-023-01614-y

CASE REPORT

Renal improvement and remission in a patient with refractory ANCA-associated vasculitis treated with avacopan

Luis Alvarez[1] · Neeraja Kambham[2] · Robert Su[3]

- Tras inducción con bolos MP y rituximab, presenta un nuevo deterioro de función renal
- Buena respuesta a la asociación de avacopan



g. 1 Renal biopsy. **A** Glomerulus with fibrinoid necrosis charac-

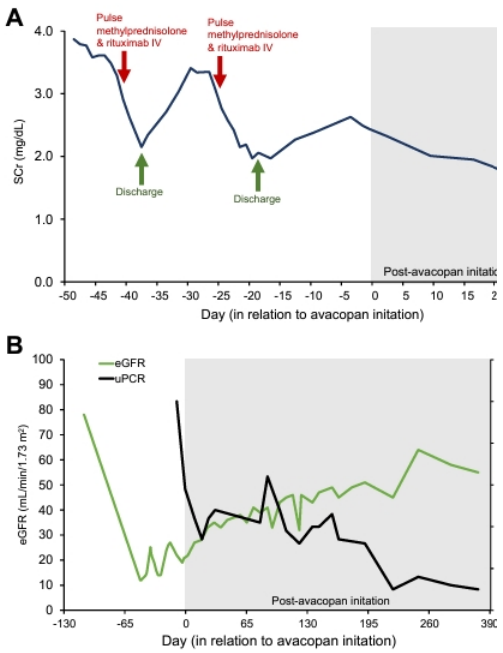
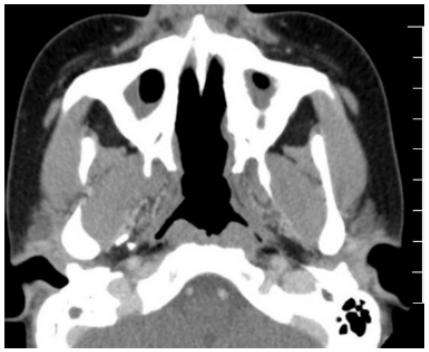
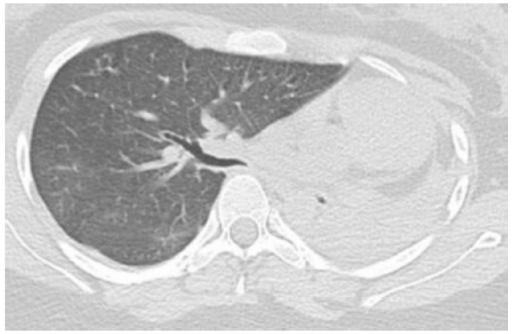


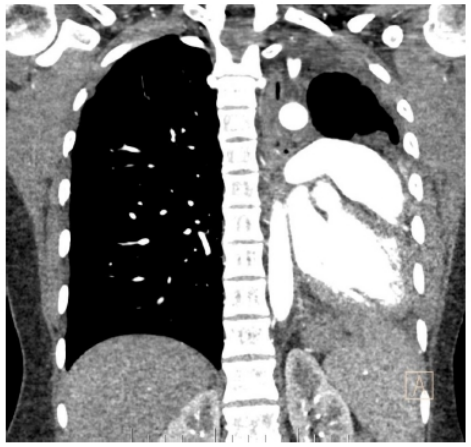
Fig. 2 Renal function changes over time. **A** Serum creatinine l during two hospitalizations and shortly after avacopan initiatio rapid renal improvement as measured by eGFR and uPCR levels avacopan. *eGFR* estimated glomerular filtration rate, *IV* intraver *SCr* serum creatinine, *uPCR* urinary protein:creatine ratio

Avacopan en VAA refractaria

Caso ♀ 9 años







Afect. ORL
Est. bronquial
Nód. pulmonares

Alt sed./FR N
ANCA – PR3

GPA

Rebrote Grave

Múltiples recurrencias
Múltiples complicaciones (osteonecrosis, NPC, CMV

INICIO AVACOPAN

2007 2008 2010 2013 2014 2017 2020

PredHD → LD → dosis variables ≥15 mg → 5 mg

CYC iv x 7 | MFM | Leflunomida

Rituximab semestral → 4 meses → cada 6 meses

metotrexato

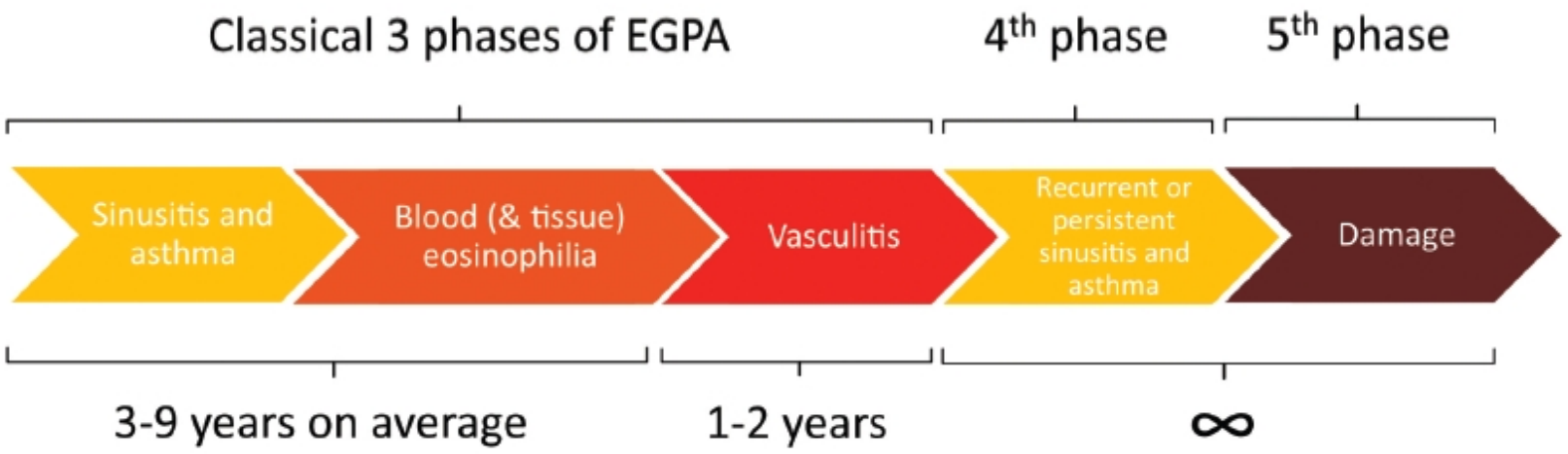
Ig iv

Avacopan

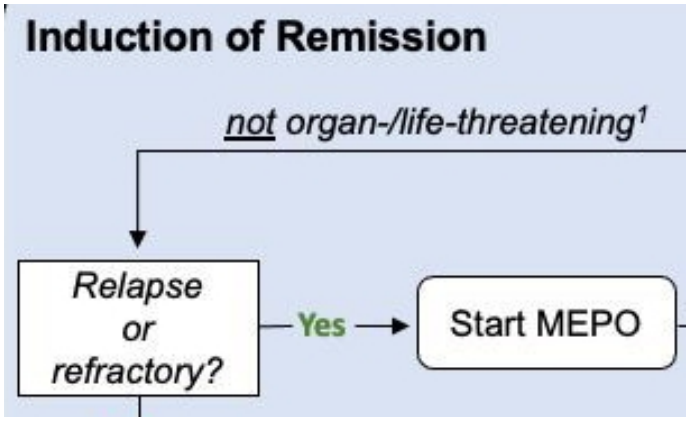
Eculizumab

Ennis D, et al. BMJ Case Rep 2020;13:e236236

Evolución GEPA



Pagnoux C, Berti A. Opinion on Pharmacotherapy, 24:11, 1269-1281



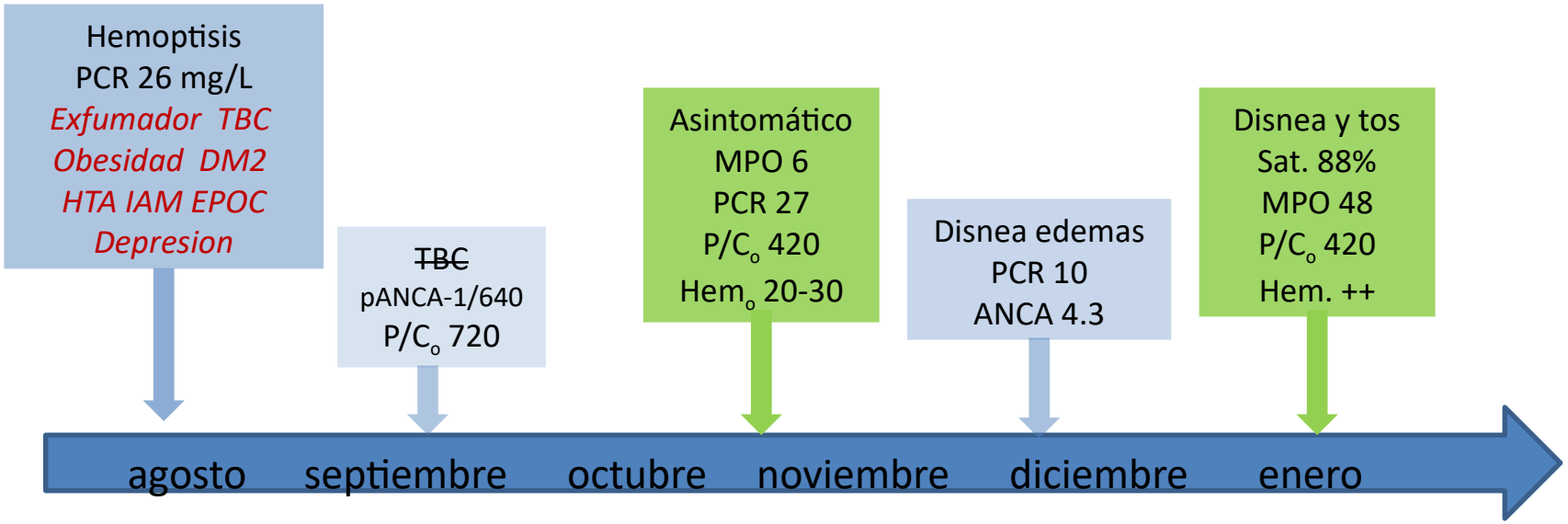
Hellmich B, et al. Ann Rheum Dis 2023;**0:1–18.**

Incertidumbres

1. Definir periodo para respuesta al tratamiento
2. ¿Recambio plasmático?
3. ¿Bolos de metil-prednisolona?
4. ¿Ciclofosfamida oral si no hay respuesta a iv?
5. Tratamiento en función del fenotipo

   (formas destructivas área ORL)
6. Tratamientos secuenciales
7. Tratamiento CART-T en VAA refractaria

Caso 1 Varón de 64 años pluripatológico con VAA



Antibiótico

Pred (mg/kg)

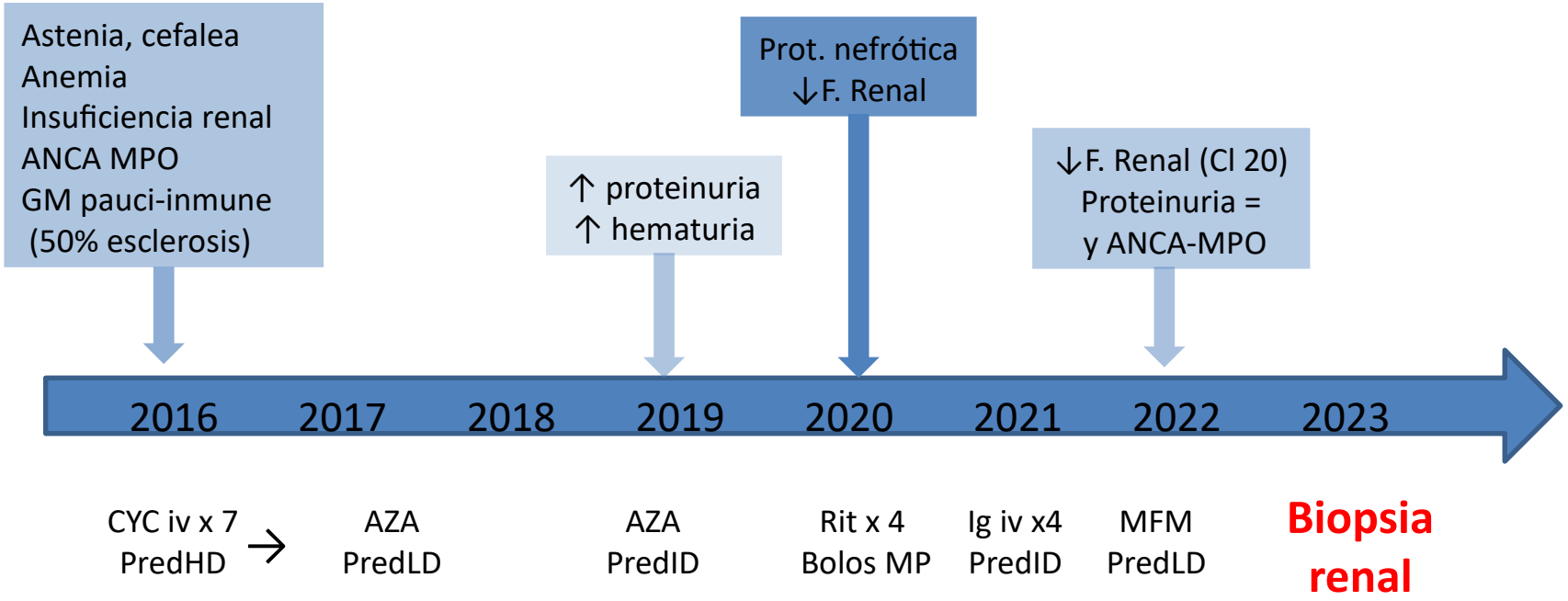
Rit x 2
Pred LD

Furosemida
Pred LD

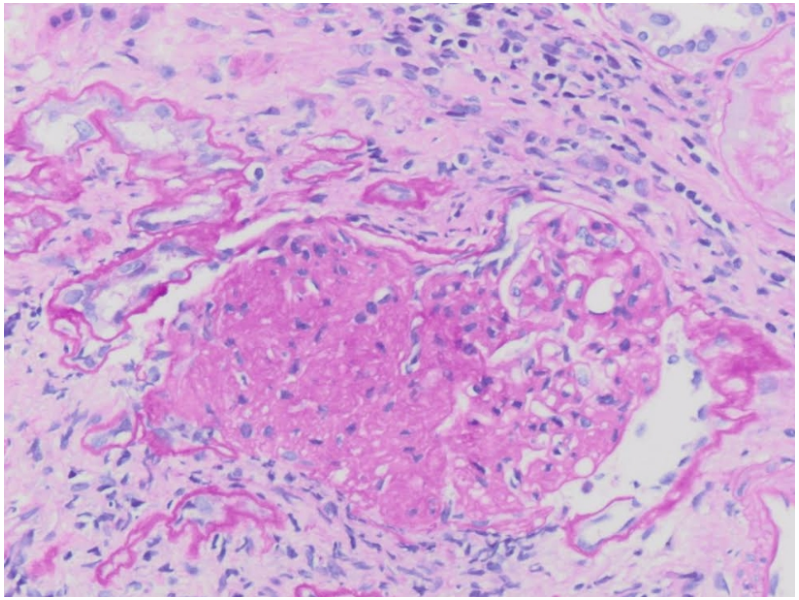
CYC 500 x 3
PredID→LD
Rit / 6 m

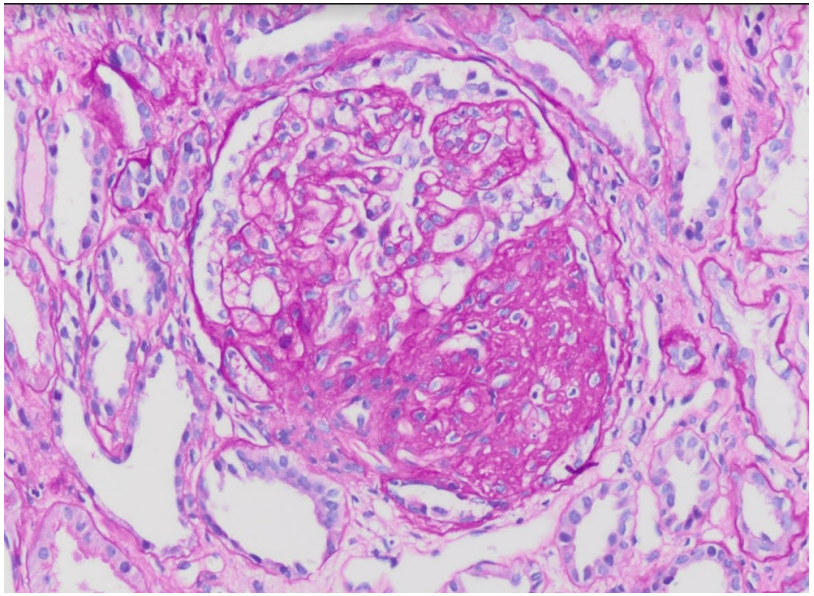
→Avacopan

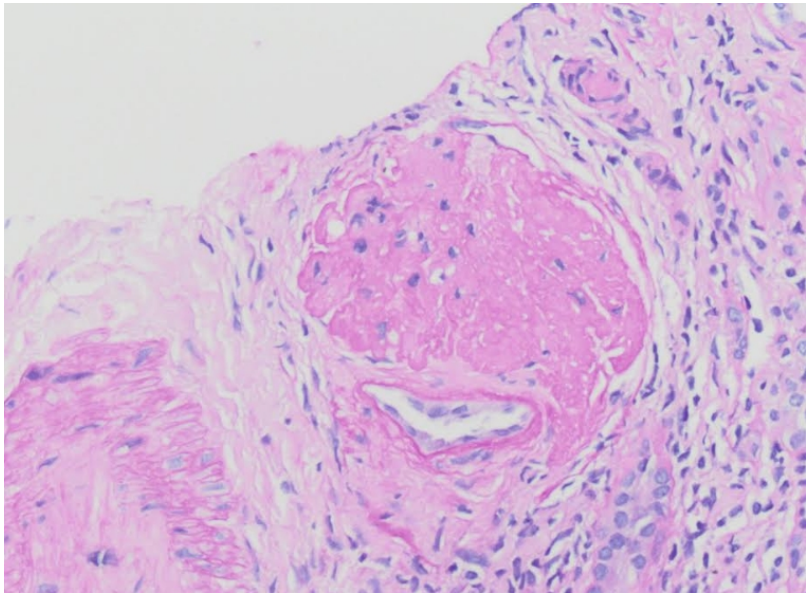
Caso 2 Mujer de 17 años con VAA desde los 10 años

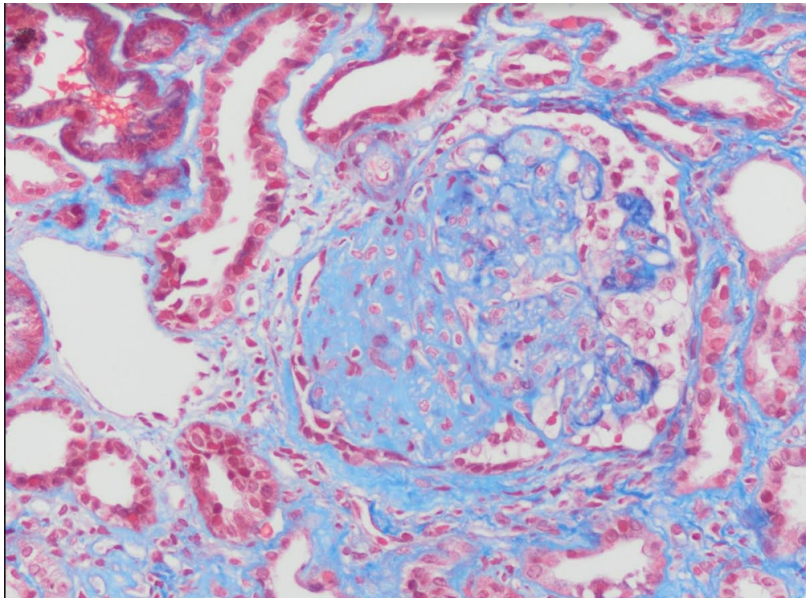


+ bloqueo SRAA + estatinas









Conclusiones

- VAA refractaria es ***poco frecuente***
- En caso de sospecha de VAA refractaria se debe ***descartar*** síntoma en relación con ***infección, daño, efecto colateral o comorbilidad***
- Opciones terapéuticas:
  1. *Switch Rituximab /CYC*
  2. *Combinación Rituximab + CYC*
  3. *+/- Incremento dosis GCs (bolos?)*
  4. *+/- avacopan*
  5. *+/- Inmunoglobulinas (riesgo infección)*
  6. *Mepolizumab en GEPA corticodependiente*