# EXPERIENCIA CLINICA EN VASCULITIS SITÉMICAS

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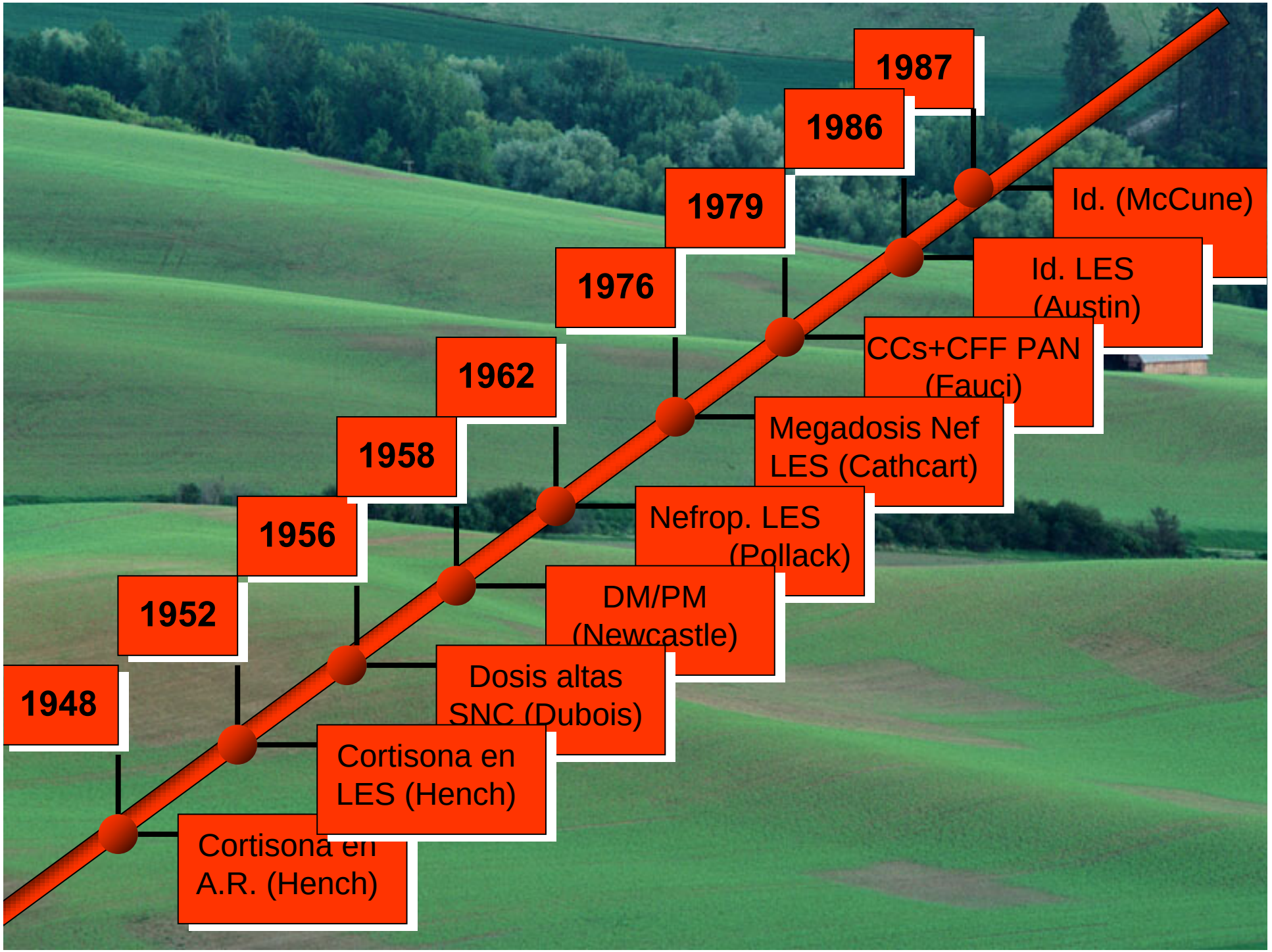

1948
Cortisona en A.R. (Hench)
1952
Cortisona en LES (Hench)
1956
Dosis altas SNC (Dubois)
1958
DM/PM (Newcastle)
1962
Nefrop. LES (Pollack)
1976
Megadosis Nef LES (Cathcart)
1979
CCs+CFF PAN (Fauci)
1986
Id. LES (Austin)
1987
Id. (McCune)

## Efectos adaverosos CICLOFOSFAMIDA (dosis dependiente)

- Mielotoxicidad
- Infecciones
- Amenorrea
- Toxicidad Vesical
- Neoplasias

# EVOLUCIÓN EN EL TRATAMIENTO DE LAS VASCULITIS

**1979.- FAUCI: Ciclofosfamida (CFF).**

**1982.- HOFFMAN: Metotrexate (MTX).**

**1996.- STEGEMAN: Cotrimoxazol.**

**1997.- GUILLEVIN: CFF via i.v. versus vía oral.**

**2000.- JAYNE: Gammaglobulinas i.v.**

**2003.- CYCAZAREM: CFF vs azatioprina (AZA) en mantenimiento.**

**2005.- NORAM: CFF + GCC vs AZA + GCC (inducción/mantenimiento)**

**2008.- PAGNOUX: AZA vs MTX en mantenimiento.**

**2009.- IMPROVE: Micofenolato (MFMF) vs AZA**

**2010.- RAVE y RITUXIVAS: Rituximab (RTX) vs CFF en inducción.**

## EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis

Bernhard Hellmich, Oliver Flossmann, Wolfgang L Gross, et al.

*Ann Rheum Dis* 2007 66: 605-617 originally published online December 14, 2006
doi: 10.1136/ard.2006.062711

## EULAR recommendations for the management of primary small and medium vessel vasculitis

C Mukhtyar,[1] L Guillevin,[2] M C Cid,[3] B Dasgupta,[4] K de Groot,[5] W Gross,[6] T Hauser,[7] B Hellmich,[8] D Jayne,[9] C G M Kallenberg,[10] P A Merkel,[11] H Raspe,[6] C Salvarani,[12] D G I Scott,[13] C Stegeman,[10] R Watts,[14] K Westman,[15] J Witter,[16] H Yazici,[17] R Luqmani,[1] for the European Vasculitis Study Group

*Ann Rheum Dis* 2009;**68**:310–317. doi:10.1136/ard.2008.088096

## TRATAMIENTO DE INDUCCION

*EUVAS Grading of Disease Severity and First-Line Treatment Options for Induction Therapy*

MTX (AZA)

| Disease Classification | Constit Symp | Renal Function | Threatened Organ Function | Treatment Options for Induction |
|---|---|---|---|---|
| Limited | No | Serum creatinine < 120 µmol/L (1.4 mg/dL) | No | Corticosteroids OR methotrexate OR azathioprine |
| Early, generalized | Yes | Serum creatinine < 120 µmol/L (1.4 mg/dL) | No | Cyclophosphamide + corticosteroids or methotrexate + corticosteroids |
| Active, generalized | Yes | Serum creatinine < 500 µmol/L (5.7 mg/dL) | Yes | Cyclophosphamide + corticosteroids |
| Severe | Yes | Serum creatinine > 500 µmol/L (5.7 mg/dL) | Yes | Cyclophosphamide + corticosteroids + plasma exchange |
| Refractory | Yes | Any | Yes | Consider investigational or compassionate use agents (see text) |

CFF

GCC

*Frankel et al. Update in the Diagnosis and Management of Pulmonary Vasculitis. CHEST, 2006*

**INDUCCIÓN MTX**

# Randomized Trial of Cyclophosphamide Versus Methotrexate for Induction of Remission in Early Systemic Antineutrophil Cytoplasmic A

***NORA***

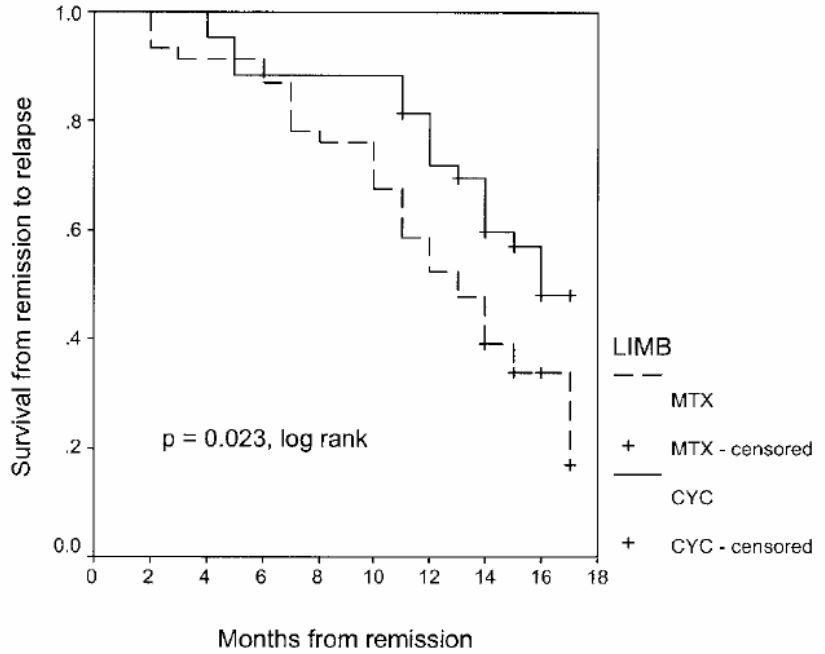



**Figure 4.** Time to first relapse from remission (Kaplan-Meier curve) in the methotrexate (MTX) and cyclophosphamide (CYC) groups. Patients who did not achieve remission within the first 12 months are excluded.

- **Similar nº de remisiones (6 m.)**
- **Retraso de la inducción**
- **Mayor número de recaídas**
- **Menor tiempo hasta la recaída**

***CONCLUION: Solo formas leves***

**INDUCCIÓN MICOFENOLATO**

| ESTUDIOS DE INDUCCION CON MICOFENOLATO | | | | | | |
|---|---|---|---|---|---|---|
| ***Autores*** | ***Diseño*** | ***Nº Pctes*** | ***Dosis (g/día)*** | ***Seguim. (meses)*** | ***Remision (%)*** | ***Recaída (%)*** |
| Joy, 2005 (&) | Retrosp. | 12 | 2 | 6 | 72 | 44 |
| Stassen, 2007(i) | Retrosp. | 32 | 2 | 19 | 78 | 59,3 |
| Kazderova, 2008 | Retrosp. | 34 | 2 | 12 | ? | 15 |
| Hu, 2008* | Prosp.(R) | 29 | 2 | 36 | 78 | ? |
| Silva, 2010* | Prosp. | 17 | 2 | 18 | 70 | 12 |

(&) Recidivas o enfermedad persistente

(¡) Solo en pacientes con contraindicación de ciclofosfamida

* ANCA anti - MPO

***MYCYC clinical trial protocol. European Vasculitis Study Group (EUVAS) Trial***

**INDUCCION**

**EULAR 2009**

6. We recommend a combination of cyclophosphamide (intravenous or oral) and glucocorticoids for remission induction of generalised primary small and medium vessel vasculitis (level of evidence 1A for WG and MPA, grade of recommendation A; level of evidence 1B for PAN and CSS, grade of recommendation A)

## ¿CFF oral o en pulsos i.v. ?

ARTICLE

Annals of Internal Medicine
2009;150:670-680.

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

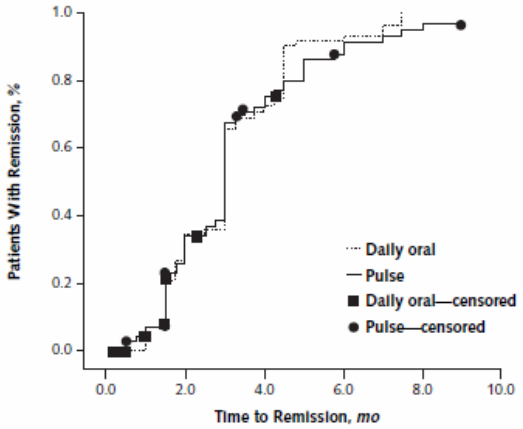
## A Randomized Trial

Kirsten de Groot, MD; Lorraine Harper, MD, PhD; David R.W. Jayne, MD, PhD; Luis Felipe Flores Suarez, MD, PhD; Gina Gregorini, MD; Wolfgang L. Gross, MD; Rashid Luqmani, MD; Charles D. Pusey, MD, PhD; Niels Rasmussen, MD; Renato A. Sinico, MD; Vladimir Tesar, MD, PhD; Philippe Vanhille, MD; Kerstin Westman, MD, PhD; and Caroline O.S. Savage, MD, PhD, for the EUVAS (European Vasculitis Study Group)

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

**INDUCCION**

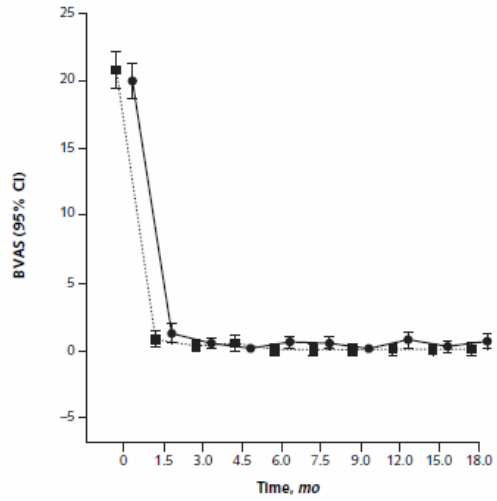
*Figure 2.* Time to remission (Kaplan–Meier curves) for the pulse and daily oral cyclophosphamide groups.




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

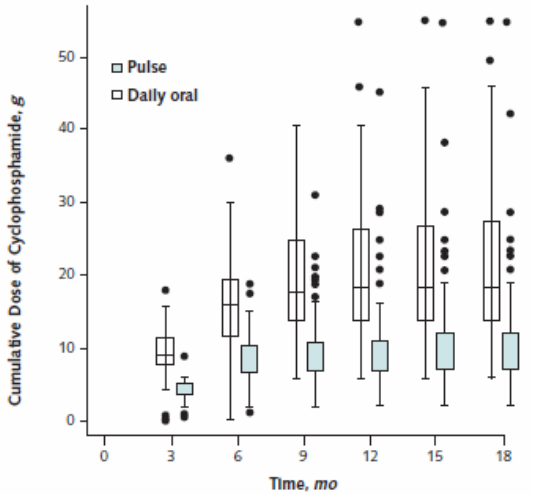
Sample sizes are listed for each group; missing data are from patients who were withdrawn or died.

*Figure 4.* Measures of disease activity for the pulse and daily oral cyclophosphamide groups.




| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Daily oral | 71 | 63 | 63 | 60 | 56 | 55 | 52 | 58 | 54 | 50 |
| Pulse | 73 | 63 | 66 | 58 | 67 | 58 | 61 | 62 | 59 | 54 |

*Figure 5.* Cumulative cyclophosphamide dose per person over time.




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Daily oral | 73 | 73 | 64 | 60 | 58 | 55 | 54 |
| Pulse | 76 | 76 | 72 | 66 | 63 | 62 | 62 |

**EULAR 2009**

## Pulsed CYC dose reductions for renal function and age

| | Creatinine (μmol/litre) | |
|---|---|---|
| **Age, years** | **<300** | **300–500** |
| <60 | 15 mg/kg/pulse | 12.5 mg/kg/pulse |
| 60–70 | 12.5 mg/kg/pulse | 10 mg/kg/pulse |
| >70 | 10 mg/kg/pulse | 7.5 mg/kg/pulse |

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

**INDUCCION**

| Parameter | Baseline | | 3 Months | | 6 Months | |
|---|---|---|---|---|---|---|
| | Pulse Group | Daily Oral Group | Pulse Group | Daily Oral Group | Pulse Group | Daily Oral Group |
| **Total patients, *n*** | 76 | 73 | 72 | 65 | 66 | 60 |
| **Disease status, *n*** | | | | | | |
| Active disease | 76 | 73 | 23 | 22 | 5 | 5 |
| Achieved remission | 0 | 0 | 49 | 43 | 61 | 55 |
| **Censored (in remission), *n*** | | | | | | |
| Died | 0 | 0 | 1 (0) | 4 (0) | 3 (0) | 7 (2) |
| Lost to follow-up | 0 | 0 | 1 (0) | 0 | 2 (1) | 1 (1) |
| Withdrew | 0 | 0 | 2 (0) | 4 (0) | 5 (2) | 5 (1) |
| **Relapse after initial remission, *n*** | 0 | 0 | 1 | 1 | 1 | 3 |
| **Renal outcomes** | | | | | | |
| End-stage renal disease, *n* | 0 | 0 | 1 | 0 | 4 | 0 |
| Median estimated glomerular filtration rate (IQR), *mL/min per 1.73 m²*† | 32 (15–52) | 29 (18–48) | 45 (28–64) | 44 (30–63) | 40 (28–60) | 50 (37–64) |
| **Cumulative cyclophosphamide dose** | | | | | | |
| Median dose for patients still in study (IQR), *g* | 0 | 0 | 4.34 (3.5–11.3) | 9.0 (7.65–11.33) | 8.18 (6.5–10.0) | 15.75 (11.48–19.6) |

IQR = interquartile range.

* Numbers are cumulative over time. Patients who had active disease, achieved remission, died, withdrew, and were lost to follow-up always total the number of patients recruited to the study. Patients with relapse are described separately in the daily oral or pulse group. We censored those patients who did not achieve remission at 9 months because we had no treatment protocol for those who still had active disease after this time point. One patient achieved remission at 12 months and 1 had active disease until 18 months. One hundred thirty-two patients achieved remission; however, for the primary analysis, only 131 achieved remission. The pulse and daily oral groups did not differ in remission, relapse, or mortality rates at the end of study.

† Estimated by using the Modification of Diet in Renal Disease Study equation (16).

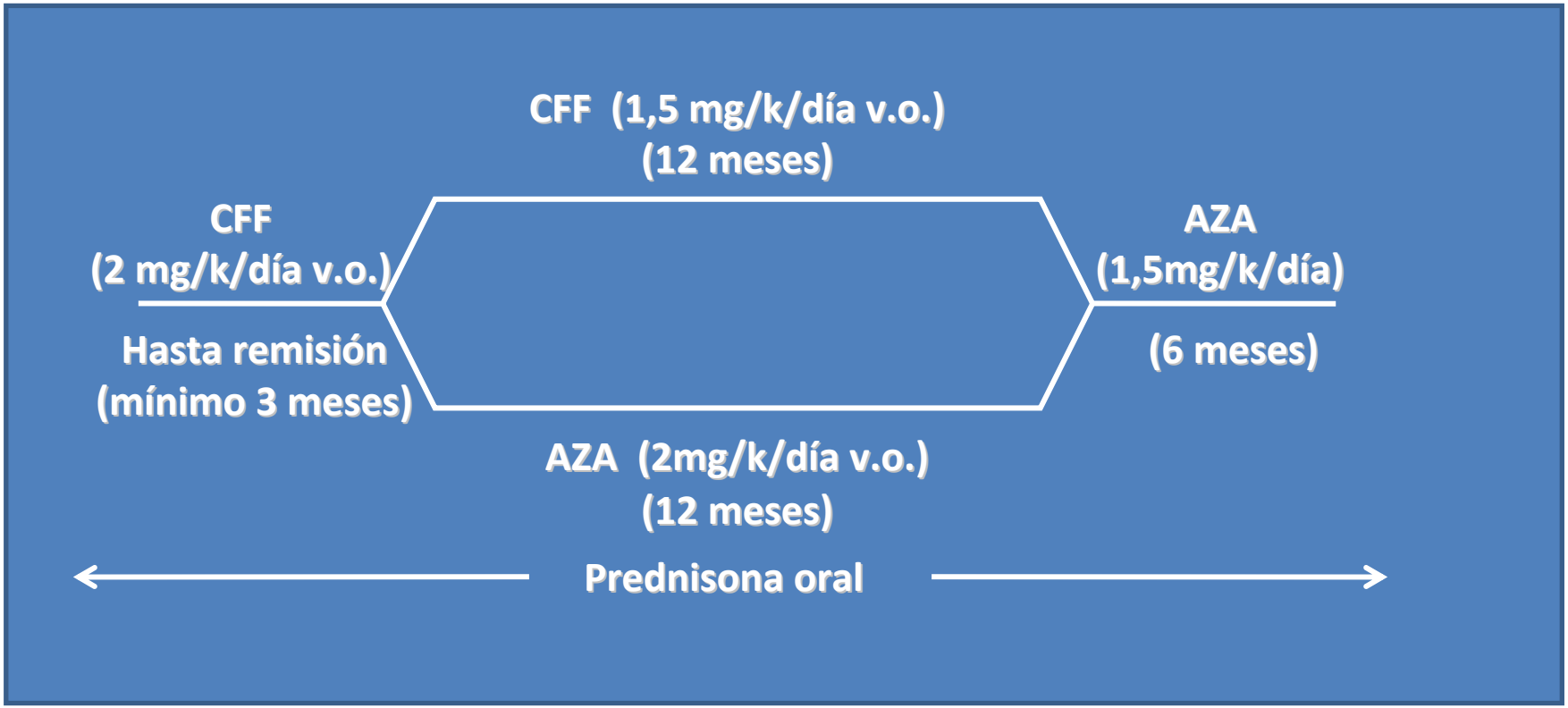
MANTENIMIENTO

## *EULAR 2009*

10. We recommend remission-maintenance therapy with a combination of low-dose glucocorticoid therapy and, either azathioprine, leflunomide or methotrexate (level of evidence 1B for azathioprine, grade of recommendation A; level of evidence 1B for leflunomide, grade of recommendation B; level of evidence 2B for methotrexate, grade of recommendation B)

**MANTENIMIENTO**
**¿AZA o CFF?**

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

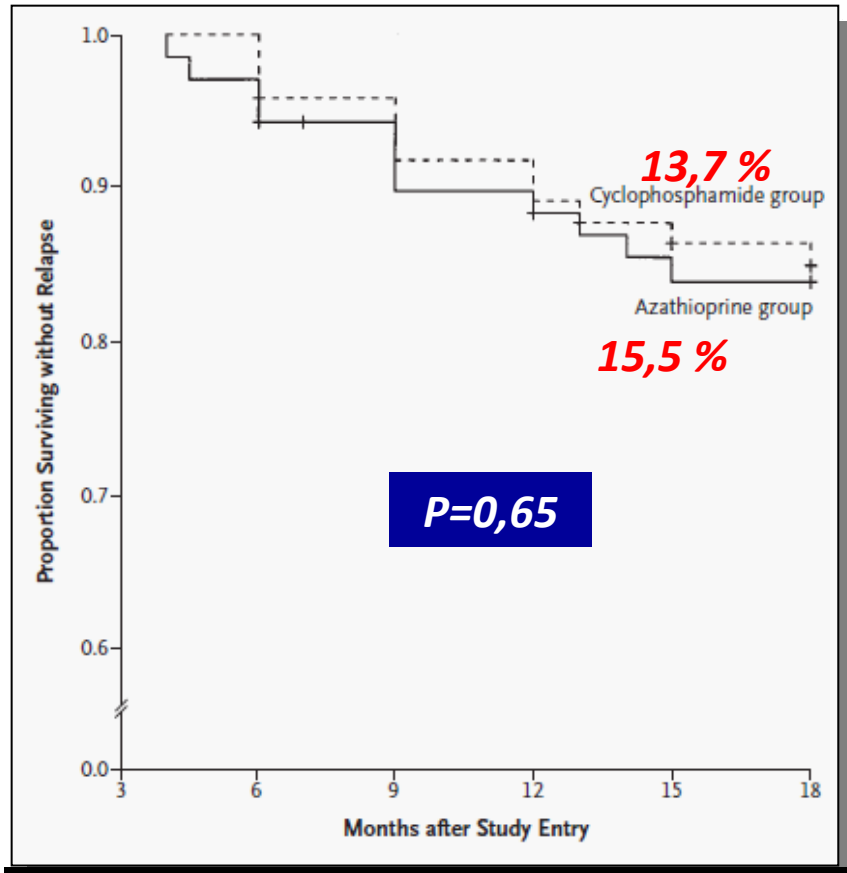


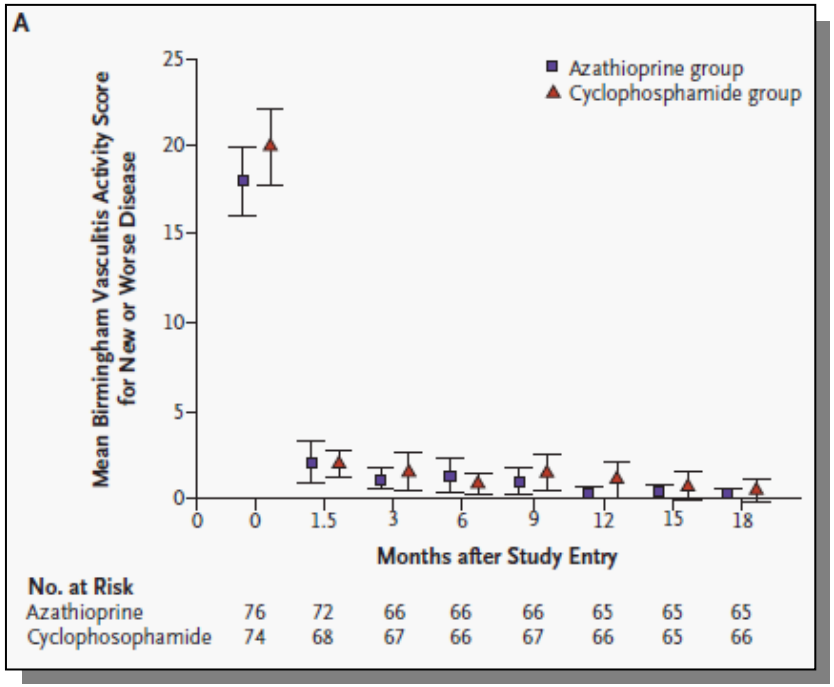

Jayne *et al (*CYCAZAREM*)*N Engl J Med 2003;349:36-44.

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

**MANTENIMIENTO**
**¿AZA o CFF?**

Jayne et al (CYCAZAREM) N Engl J Med 2003;349:36-44.




***Pero….***

- **La CFF se empleó por vía oral.**
- **Se trata de un estudio a sólo 18 meses.**

**Conclusión:** ***En pacientes con vasculitis generalizada la sustitución de CFM por AZA, después de la remisión, no aumenta la tasa de recidiba.***

## MANTENIMIENTO ¿AZA o CFF?

**En otros estudios retrospectivos se comprueba que la tasa de recaídas es mayor en pacientes sometidos a tratamiento de mantenimiento con azatioprina que la observada en los tratados con ciclofosfamida cuando la valoración se realiza a más largo plazo.**

**** especialmente en pacientes ANCA+***


- ***Sanders JSF et al***. Azathioprine as compared to cyclophosphamide maintenance therapy for ANCA-associated vasculitis is associated with increased long-term relapse risk. *Kidney Blood Press Res. 2005;28:195.*

- **Slot MC et al.** Positive classic antineutrophil cytoplasmic antibody (C-ANCA) titer at switch to azathioprine therapy associated with relapse in proteinase 3-related vasculiis. *Arthritis Rheum. 2004;51:269-23.*

- ***Sanders JS et al.*** Maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies.*NEngl JMed. 2003;* 349:2072-3.

# Azathioprine or Methotrexate Maintenance for ANCA-Associated Vasculitis

**MANTENIMIENTO ¿AZA o MTX?**

*Pagnoux C et al.N Engl J Med 2008;359:2790-803.*

- 123 pacientes

# Azathioprine or Methotrexate Maintenance for ANCA-Associated Vasculitis

**MANTENIMIENTO ¿AZA o MTX?**

**Table 2. Adverse Events after the Initiation of Assigned Maintenance Therapy.*** ***(Resumida)***

| Variable | All Patients (N=126) | Azathioprine Group (N=63) | Methotrexate Group (N=63) | P Value |
|---|---|---|---|---|
| | | *no. of patients (%)* | | |
| Venous thrombotic event | 3 (2) | 1 (2) | 2 (3) | 1.00 |
| Death due to study drug | 1 (1) | 0 | 1 (2) | 1.00 |
| Any adverse event | | | | |
| Any | 64 (51) | 29 (46) | 35 (56) | 0.29 |
| Severe | 16 (13) | 5 (8) | 11 (18) | 0.11 |
| Requiring study-drug withdrawal or causing death | 19 (15) | 7 (11) | 12 (19) | 0.21 |

**No se confirma la hipótesis que MTX es más seguro que AZA para el mantenimiento.**

*Pagnoux C et al.N Engl J Med 2008;359:2790-803.*

# Azathioprine or Methotrexate Maintenance for ANCA-Associated Vasculitis

**MANTENIMIENTO ¿AZA o MTX?**

**Table 3. Studies Involving Patients with ANCA-Associated Vasculitides Who Received Corticosteroids and Cyclophosphamide Induction in a Staged-Treatment Strategy.***

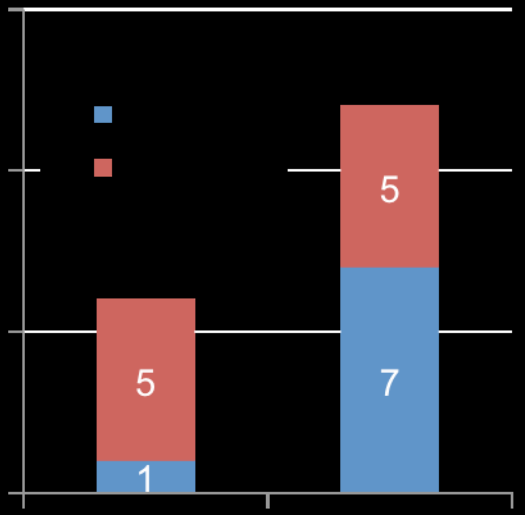
| Study | Patients† | | Maintenance Therapy | Follow-up from Diagnosis‡ | Relapse-free Survival after Diagnosis | Relapse Rate§ | Toxicity |
|---|---|---|---|---|---|---|---|
| | No. | Diagnosis | | | | | |
| WEGENT (ClinicalTrials.gov number, NCT00349674) | 126 | Newly diagnosed systemic Wegener's granulomatosis or microscopic polyangiitis with FFS ≥1 | AZA vs. MTX for 12 mo | 37.3±14.3 mo | At 18 mo: AZA 88.9% vs. MTX 90.5% | At 18 mo: AZA 17.8% vs. MTX 13.7% | Grade 3/4: AZA 7.9% vs. MTX 17.4% |
| | | | | | At 36 mo: AZA 64.1% vs. MTX 69.0% | At 36 mo: AZA 50.1% vs. MTX 46.7% | Requiring drug withdrawal: AZA 11.1% vs. MTX 19.0% |
| CYCAZAREM[6] | 144 | Newly diagnosed Wegener's granulomatosis, microscopic polyangiitis, or renal-limited vasculitis, with mild or moderate renal or other vital-organ involvement | Continued oral CYC vs. AZA | 18 mo for all patients | At 18 mo: AZA 84.5% vs. CYC 86.3% | At 18 mo: AZA 15.5% vs. CYC 13.7% | Grade 1/2: AZA 41% vs. CYC 44%; grade 3/4: AZA 11% vs. CYC 10% |
| WGET[21] (ClinicalTrials.gov number, NCT00005007) | 180 | Newly diagnosed or relapsing Wegener's granulomatosis: limited (52 patients) or severe (118 patients) with BVAS ≥3¶ | MTX or AZA (when serum creatinine level >2 mg/dl [177 μmol/liter]) alone, or combined with ETN¶ | 27 mo | | At 27 mo: MTX or AZA 32.8% vs. MTX or AZA plus ETN 30.6% | Grade 3/4 or death: MTX or AZA 57.1% vs. MTX or AZA plus ETN 56.2% |
| Langford et al.[9] | 42 | Newly diagnosed or relapsing Wegener's granulomatosis | MTX for >2 yr | 3 (range, 1–12) mo induction plus 32 mo (range, 5–71) maintenance | | At 16 mo: 16%; at 32 mo: 52% | Requiring withdrawal of maintenance drug: 5% |
| Sanders et al.[22] | 136 | Newly diagnosed or relapsing Wegener's granulomatosis or microscopic polyangiitis | Continued oral CYC vs. AZA (retrospective; total duration of therapy, 18–24 mo)‖ | Up to 5 yr for some patients | At 18 mo: AZA 89.6% vs. CYC 88.1%<br>At 5 yr: AZA 42.3% vs. CYC 57.4% | | |

Pagnoux C et al.N Engl J Med 2008;359:2790-803.

# Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis

**MANTENIMIENTO ¿MTX o LFM?**

- **Estudio multicéntrico, prospectivo, randomizado de 2 años de duración de 54 pacientes en remisión (tras inducción con CFF):**
  - ✓ **26 con LF (30 mg/día)**
  - ✓ **28 con MTX (7,5->20 mg/día).**
- **End point: tasa de recaídas**




| | RECAÍDAS (N) | | COMPLICACIONES (N) |
|---|---|---|---|
| **TRATAMIENTO** | **MAYORES** | **MENORES** | |
| **LEFLUNOMIDA** (26 pacientes) | Granul./inf.pulm.(1) | Granuloma ENT (3)<br>Episcleritis (2) | HTA (2)**.<br>Neuropatía (1)**<br>Neutropenia (1)** |
| **METOTREXATO** (28 pacientes) | Brotes renales (4).<br>Hemorrag.pulm.(2).<br>Granuloma SNC (1)* | Granuloma ENT (3)<br>Atritis (1).<br>S´.constituci.1) | ---- |
| *(*) Obligó a interrumpir el estudio*<br>*(**) Retirada del estudio* | | | |

*Metzler C.et al. Rheumatology 2007;46;1087–1091*

**MANTENIMIENTO MICOFENOLATO**

| ESTUDIOS DE MANTENIMIENTO CON MICOFENOLATO * | | | | | | |
|---|---|---|---|---|---|---|
| ***Autores*** | ***Diseño*** | ***Nº Pacts*** | ***Dosis (g/día)*** | ***Seguim. (meses)*** | ***Remision (%)*** | ***Recaída (%)*** |
| Novack ,1999 | Prosp. | 11 | 2 | 14 | 90 | 9 (10m) |
| Langford ,2004 | Retrosp. | 14 | 2 | 18 | 40 | 60 (14m) |
| Koukoulaki ,2006 | Retrosp. | 51 | 1 | 36 | 82 | 56 |
| Iatrou, 2009 | Retrosp. | 22 | ? | 42 | 100 | 31,6 |
| **(*) tras remisión en inducción con CFF** | | | | | | |

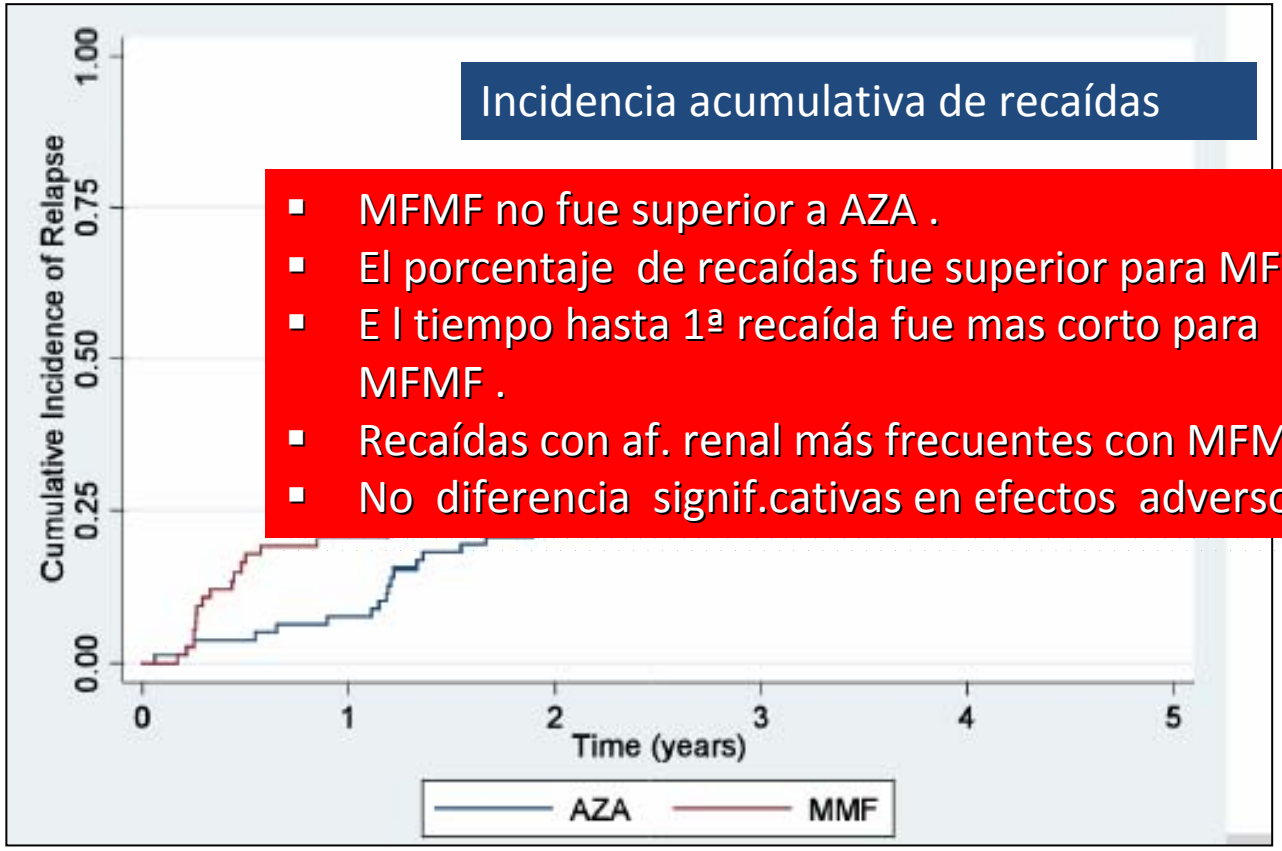
Hiemstra et al , 2009 (IMPROVE)

**Inducción: CYC + CCs durante tres meses.**

**Mantenimiento:**

- **AZA: 2 mg/kg/d (12 meses)→ 1 mg/kg/d (42 meses)**
- **MFMF: 2 g/día.**

# MANTENIMIENTO MICOFENOLATO vs AZATIOPRINA



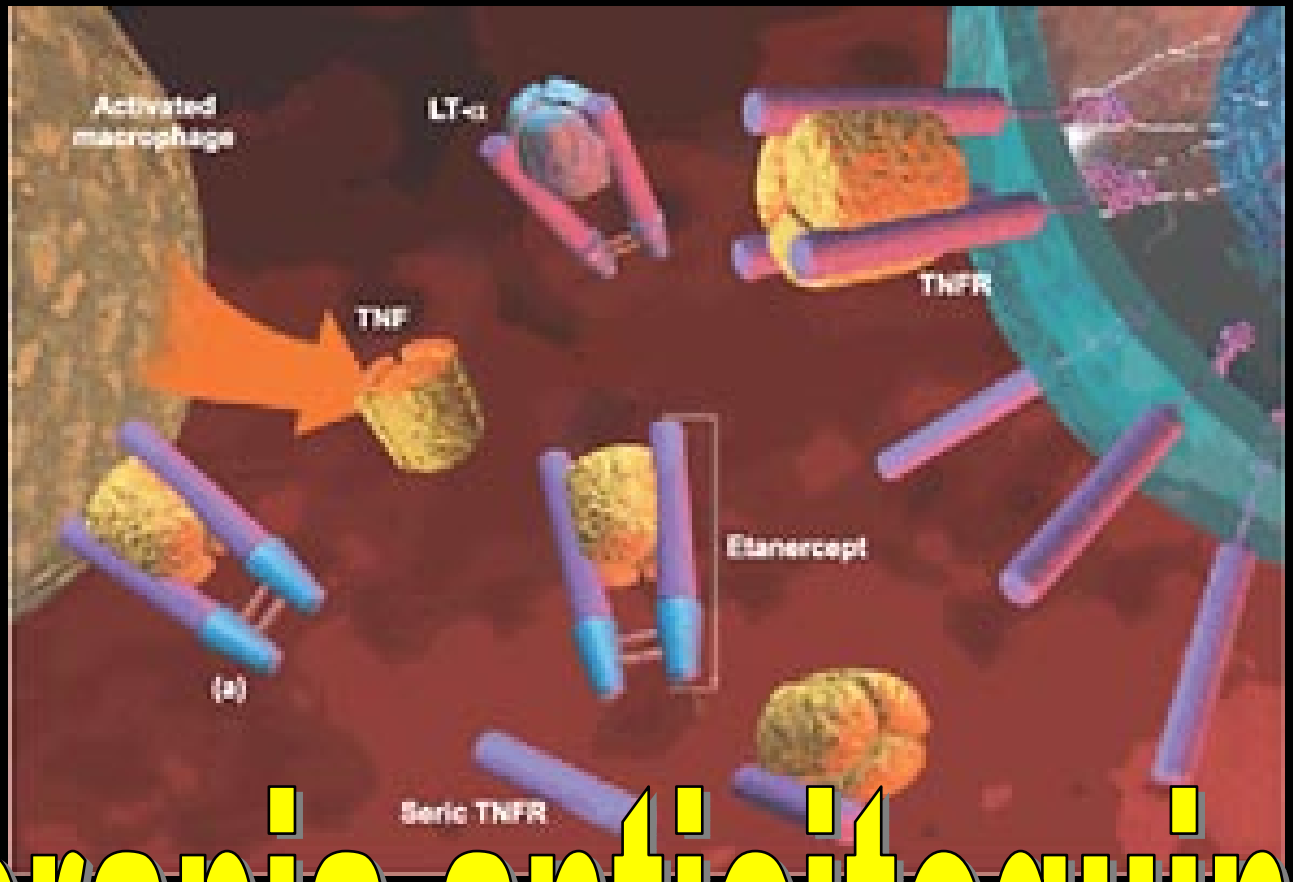

- MFMF no fue superior a AZA .
- El porcentaje de recaídas fue superior para MFMF.
- E l tiempo hasta 1ª recaída fue mas corto para MFMF .
- Recaídas con af. renal más frecuentes con MFMF.
- No diferencia signif.cativas en efectos adversos

*Hiemstra et al (IMPROVE).*
*14 International Vasculitis and ANCA Workshop. Lund, 2009.*

# EULAR 2009: ALTERNATIVAS

**Table 7** Alternative remission induction treatments in relapsing, refractory or persistent disease

| Drug | Dose | Reference |
|---|---|---|
| Intravenous immunoglobulin | 2 g/kg over 5 days | Muso *et al*, Jayne *et al*[77 78] |
| 15-Deoxyspergualin | 0.5 mg/kg/day till white cell count nadir of 3000/μl, then wait until the white cell count returns to ⩾ 4000/μl and repeat the dose for six cycles | Burke *et al*[79] |
| Anti-thymocyte globulin | 2.5 mg/kg/day for 10 days adjusted according to lymphocyte count: no anti-thymocyte globulin if <150/μl, 1.5 mg/kg/day if 150–300/μl, full dose if >300/μl | Schmitt *et al*[35] |
| Infliximab | 3–5 mg/kg/infusion every 1 to 2 months | Booth *et al*[80] |
| Mycophenolate mofetil | 2 g/day | Koukoulaki *et al*, Stassen *et al*[74 81] |
| Rituximab | 375 mg/m$^2$ body surface area weekly for 4 weeks | Keogh *et al*, Keogh *et al*, Stasi *et al*, Brihaye *et al*, Eriksson *et al*[82–86] |




# Terapia anticitoquinas

**INFLIXIMAB**

# Infliximab Improves Endothelial Dysfunction in Systemic Vasculitis

## A Model of Vascular Inflammation

A.D. Booth, MRCP; D.R.W. Jayne, FRCP; R.K. Kharbanda, MRCP; C.M. McEniery, PhD; I.S. Mackenzie, MRCP; J. Brown, FRCP; I.B. Wilkinson, MRCP

***(Circulation. 2004;109:1718-1723.)***

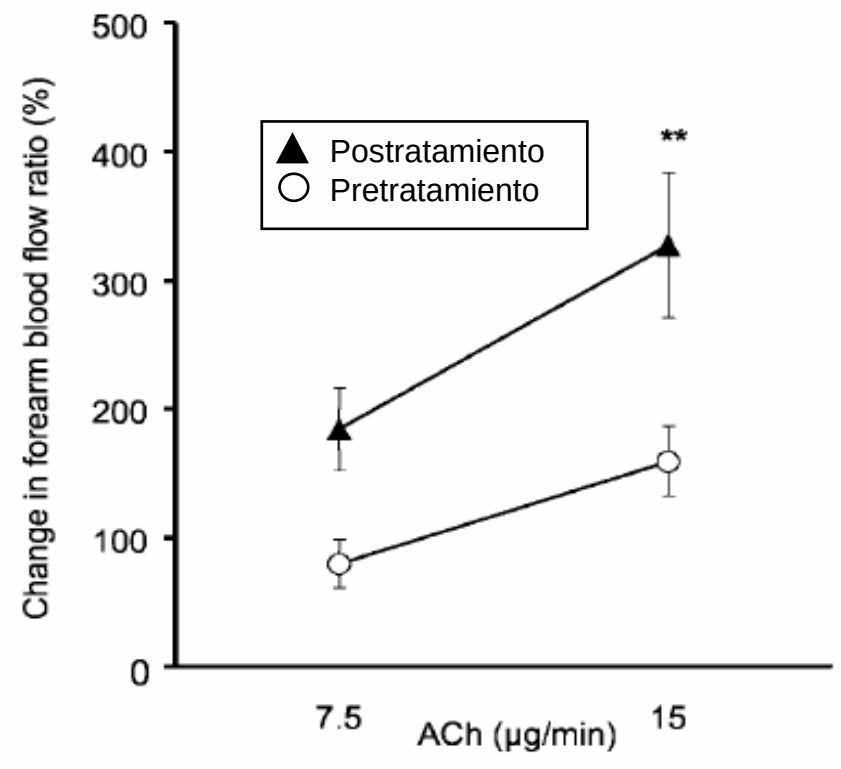



**TABLE 2. Effect of Treatment on Disease Activity and Circulating Biochemical Markers**

| | Before Treatment (n=10) | After Treatment (n=10) | Significance |
|---|---|---|---|
| BVAS | 12±1 | 0±1 | <0.001 |
| CRP, mg/L | 40.4±13.8 | 2.0±0.5 | 0.01 |
| IL-6, pg/mL | 10.8±0.8 | 6.3±0.9 | 0.002 |
| TNF-α, pg/mL | 12.7±4.8 | 15.0±5.2 | 0.8 |
| ANCA level, IU/mL | 51±13 | 23±13 | 0.1 |
| Creatinine, µmol/L | 159±48 | 126±26 | 0.6 |

Values represent mean±SEM.

***(14 pacientes)***

*Infliximab: 5 mg/kg en la semana 0, 2, 6, y 10*

***En las vasculitis ANCA hay disfunción endotelial. El tratamiento con Anti–TNF aislada o en combinación con tratamiento estándar induce remisión, reduce la inflamación, y mejora la respuesta vasomotora dependiente de endotelio.***

**INFLIXIMAB**

## Prospective Study of TNF Blockade with Infliximab in Anti-Neutrophil Cytoplasmic Antibody-Associated Systemic Vasculitis

A. BOOTH, L.HARPER, T.HAMMAD, P.BACON, M.GRIFFITH, J.LEVY, C. SAVAGE, C PUSEY, D. JAYNE

**32 pacientes** *(solo 3 [9%] con af. pulmonar)*

- **Estudio I: 16 pacientes en fase aguda (inicio o recaída). BVAS>9**
- **Estudio II: 16 pac. con enfermedad**

**Tratamiento concomitante:**

- **Predn.+CFF (estudio I)**
- **Tratamiento previo (estudio II)**

**Resultados:**

- **Remisión en 88 %.**
- **Recaídas en 18 %**
- **Efectos adversos graves en 38 %**

| Adverse Event | |
|---|---|
| Time (wk) | Nature |
| 6 | Death (pulmonary hemorrhage) |
| 18 | Death (bronchopneumonia) |
| 10 and 30 | Bronchopneumonia |
| 10 | Urinary tract sepsis |
| 39 | Leg abcess |
| 30 | Endophthalmitis |
| 39 | Skin ulcer/urinary tract infection |
| 37 | Diarrheal illness |
| 6 | B cell lymphoma |
| 6 | Pulmonary embolus |
| 0 | Axillary vein thrombosis |

*J Am Soc Nephrol 15: 717–721, 2004*

**INFLIXIMAB**

# Infliximab in patients with systemic vasculitis that is difficult to treat: poor outcome and significant adverse effects

**Shirish R Sangle, Graham R V Hughes, David P D'Cruz**

*Ann Rheum Dis* 2007;66:564–565. doi: 10.1136/ard.2006.065623

**Table 1** Adverse effects/flares after infliximab infusions

| Diagnosis | Number of infusions | New autoantibodies | Adverse events/flares | Hospital admission | Treatment for flares/ adverse reaction | Deaths |
|---|---|---|---|---|---|---|
| Wegener's granulomatosis | 5 | Nil | Hearing and vision deterioration | No | CPM+M pred | No |
| Wegener's granulomatosis | 5 | ANA, DNA | Hearing loss and lupus-like reaction | No | Prednisolone+CPM | No |
| Wegener's granulomatosis | 3 | Nil | Leucopenia and anaemia | No | Blood transfusion | No |
| Churg strauss disease | 2 | Nil | Brain stem event and lupus-like reaction | Yes | M pred +IVIG | No |
| Behçet's disease | 5 | Nil | Severe lupus-like syndrome and flare | Yes | M pred and IVIG | No |
| Behçet's disease | 5 | ANA, DNA | Scleritis, nodular vasculitis | No | Prednisolone 80 mg/ day | No |
| Henoch Schonlein purpura | 1 | Nil | Severe lupus-like reaction | Yes | M pred+IVIG | No |
| Relapsing polychondritis | 3 | ANA, DNA and lupus anticoagulant | Tired and progressive tracheal stenosis | No | Prednisolone 20 mg/ day | No |
| Adult-onset Still's disease | 5 | ANA, DNA and smooth muscle | Severe flare (serum ferritin >14 000, CRP >300 and ESR 110) | Yes | M pred+IVIG | Yes, after 6 months |

ANA, antinuclear antibodies; CPM, intravenous cyclophosphamide; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IVIG, intravenous immunoglobulins; M pred, intravenous methyl prednisolone.

**INTERRUPCION PRECOZ DEL ESTUDIO**

# Infliximab efficacy and safety against refractory systemic necrotising vasculitides: long-term follow-up of 15 patients

**INFLIXIMAB**

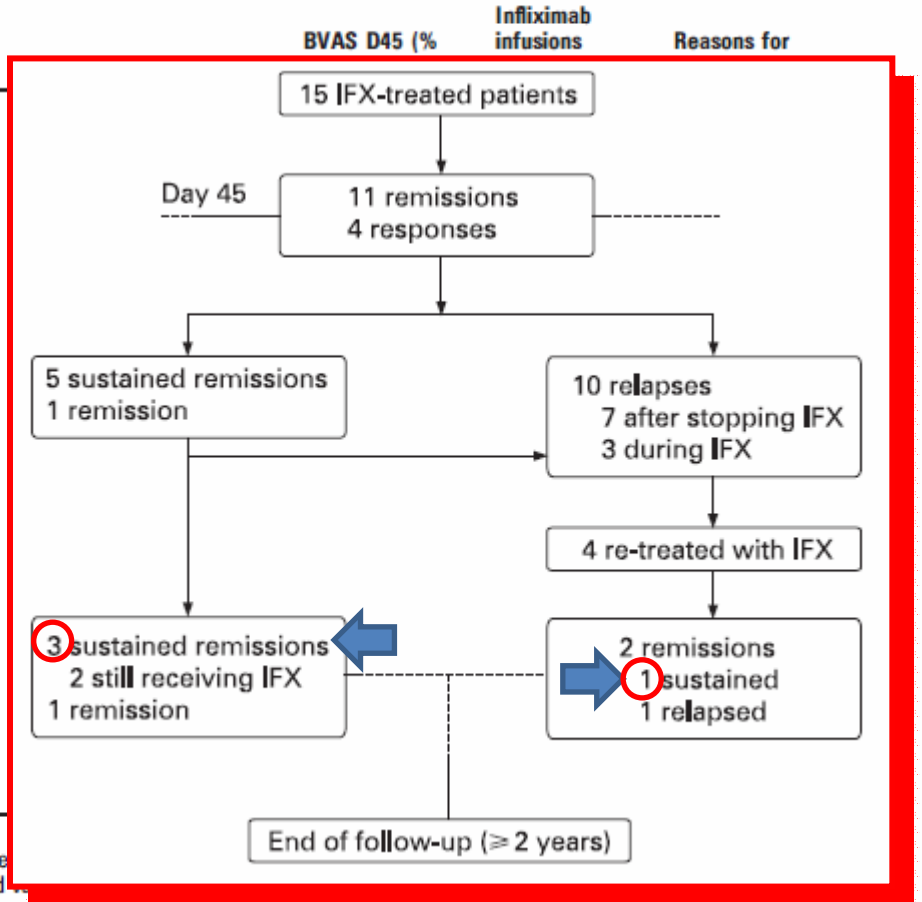
*Ann Rheum Dis* 2008;67:1343–1346. doi:10.1136/ard.2007.083584

L Josselin,[1] A Mahr,[1] P Cohen,[1] C Pagnoux,[1] G Guaydier-Souquières,[2] G Hayem,[3] C Job-Deslandre,[4] F Liferman,[5] J Pourrat,[6] L Guillevin[1]

**Table 1** Characteristics of the 15 patients with refractory systemic necrotising vasculitides (SNV)

| Patient | Sex/age (years) | Diagnosis | SNV duration (years) | Active disease site |
|---|---|---|---|---|
| 1 | F/38 | RAAV | 0.25 | PNS, skin |
| 2 | M/21 | MPA | 20 | Skin |
| 3 | M/43 | WG | 3 | ROP and scleritis, CNS, ENT |
| 4 | F/51 | WG | 4 | Uveitis, CNS (hypophysial involvement), ENT |
| 5 | F/42 | WG | 16 | Lung, CNS |
| 6 | F/63 | MC | 13 | Kidney, skin |
| 7 | M/61 | WG | 12 | GI tract, lung |
| 8 | M/71 | RAAV | 0.91 | PNS, skin |
| 9 | M/63 | WG | 9 | Lung |
| 10 | M/43 | WG | 5 | Skin, lung, ENT |
| 11 | F/19 | WG | 2 | Lung, ENT |
| 12 | M/38 | WG | 4 | ENT, CNS (pachymeningitis) |
| 13 | M/64 | WG | 0.58 | CNS (stroke) |
| 14 | F/66 | RAAV | 0.58 | Skin |
| 15 | M/31 | WG | 5 | ROP, lung, ENT |

*All patients were taking corticosteroids.
AZA, azathioprine; BVAS, Birmingham Vasculitis Activity Score; CNS, central ne
immunosuppressant; IV, intravenously; MC, mixed cryoglobulinaemia-associated
peripheral nervous system; po, by mouth; RAAV, rheumatoid arthritis-associated vasculitis; ROP, retro-orbital pseudotumour; WG, Wegener's granulomatosis.

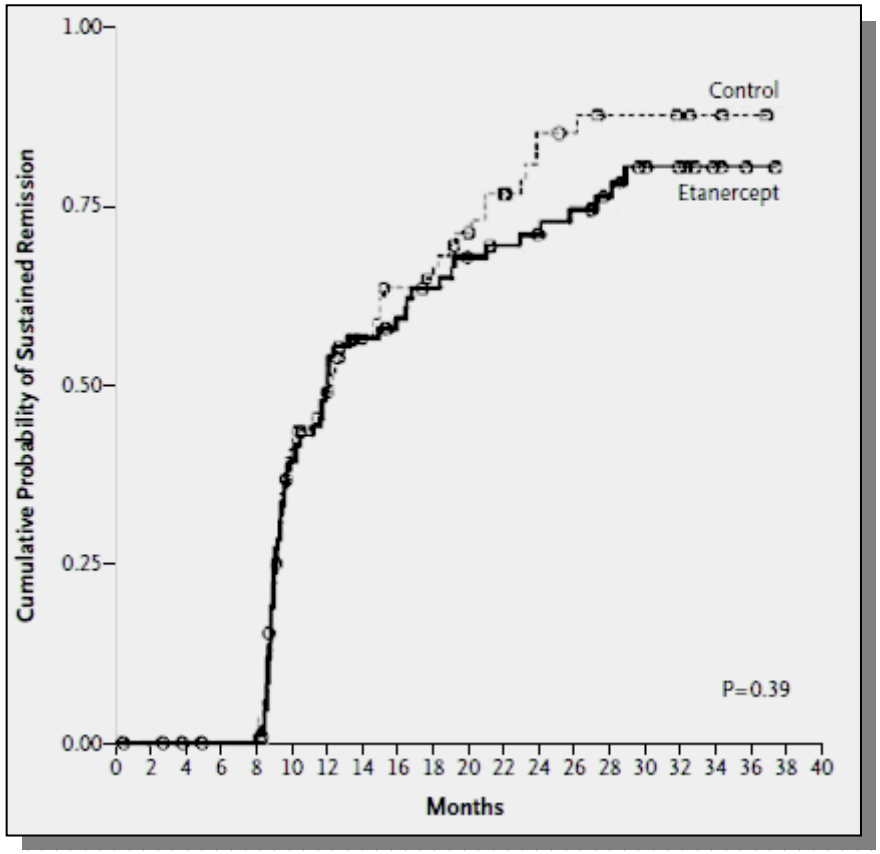


**ETANERCEPT (WGET)**

# Etanercept plus Standard Therapy for Wegener's Granulomatosis

The Wegener's Granulomatosis Etanercept Trial (WGET) Research Group

N Engl J Med 2005;352:351-61.




- Estudio prospectivo, controlado y randomizado.
- 180 pacientes con GW en tratamiento. estándar *(60% con af. Pulmonar)*
  - ✓ *en 89 se añade ETN*
  - ✓ *en 91 se añade placebo*
- No se observaron diferencias
  - ✓ *en % de remisión*
  - ✓ *en % de recaídas*
  - ✓ *en efectos adversos*
- Incremento de neoplasias en grupo ETN *(6 pcts)*

**Prospective study of TNFα blockade with adalimumab in ANCA-associated systemic vasculitis with renal involvement.**

*Laurino S, Chaudhry A, Booth A, Conte G, Jayne D. Nephrol Dial Transplant. 2010 Oct;25(10):3307-14.*

**ADALMIMUMAB/ INDUCCIÓN**

- ***Estudio en fase II, abierto, prospectivo.***

✓**14 pacientes** con brotes de actividad (inicIal o recaída) vasculitis ANCA+

✓ **Adalimumab** 40 mg s.c./2 semanasa X 3 meses + **CFM** i.v.. + **PRD**

- **Objetivos primarios:**

  1.- Inducción de la remislón en las primeras 14 semanas.

  2.- Tiempo hasta la inducción.

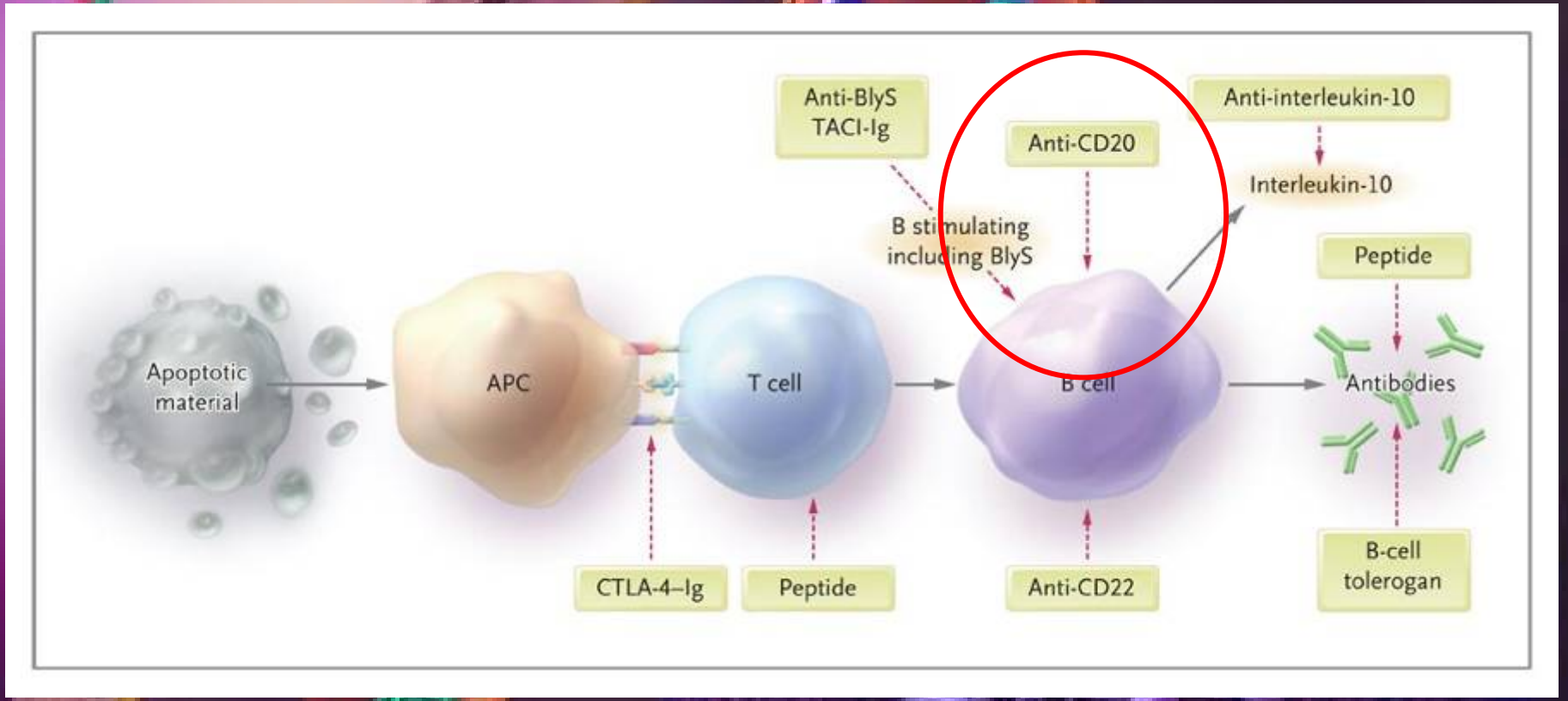
  3.- Seguridad.

- **Concluisones:** ningún beneficio.

# TRATAMIENTO CON ANTI-TNF EN GW.
# Experiencia del HUVR

| Sexo | Edad | Manifestaciones | Motivo tratamiento | TTo previo | Anti-TNF | Respuesta | TTo posterior |
|---|---|---|---|---|---|---|---|
| M | 31 | Fiebre/otitis/nódulo pulmonar | Estenosis subglótica | Gc Cfm/Rtx | Eta | RC | Mtx/Mfn/Cfm |
| H | 41 | Pioderma gangrenoso + otitis + sinsusitis+ polineuropatía + artritis + nódulos pulmonares + deformidad nasal + c-ANCA+ | Pioderma | Gc/Cfm/ Cp/ Rxm | Eta<br>Inf+Mtx | RP<br>RP | Perdido |
| M | 44 | fiebre + artralgias + otitis + obstrucción nasal + nódulos pulmonares bilaterales. | Nódulos pulmonares/fiebre | Gc + Cf + Mfm + Rtx | Ad | NR | Gc +Mfn + Gusperimus |
| M | 74 | Fiebre + pansinusitis + otitis media +estenosis + dacriocistitis+ laríngea + nódulos pulmonares + microhematuria + C-ANCA+ | Pansinusitis grave | Gc + Cf | Eta | RP | RTX |

Gc: glucocorticoides. Cf: ciclofosfamida. Mfm: Micofenolato de mofetilo. Eta: Etanercept. Mtx: metotrexato. Cp: Ciclosporina. Az: azatioprina. Cch: Colchicina. Ptx: Pentoxifilina. Td: Talidomida. Msz: Mesalazina. Ad: Adalimumab. If: Interferón. Ig: Inmunoglobulinas. MfNa: Micofenolato sódico. Lf: Leflunomida. If: Infliximab. Adm




# Terapia antilinfocito-B

# A Multicenter Survey of Rituximab Therapy for Refractory Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

***Bones RB. Arthritis Rheum. 2009 Jul;60:2156-68*.**

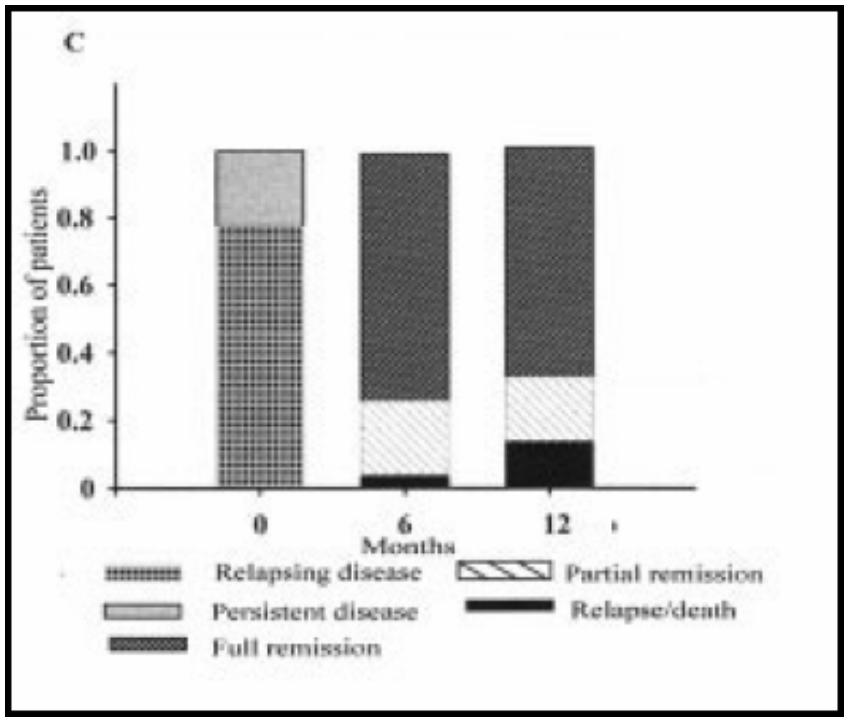
**RITUXIMAB**

- ✓ 65 *pacientes* *VASCULTIS ANCA+, REFRACTARIA,*
- ✓
- ✓
  - ❑
  - ❑
    - •
    - •
    - •

# A Multicenter Survey of Rituximab Therapy for Refractory Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

***Arthritis Rheum. 2009 Jul;60:2156-68*.**

**RITUXIMAB**

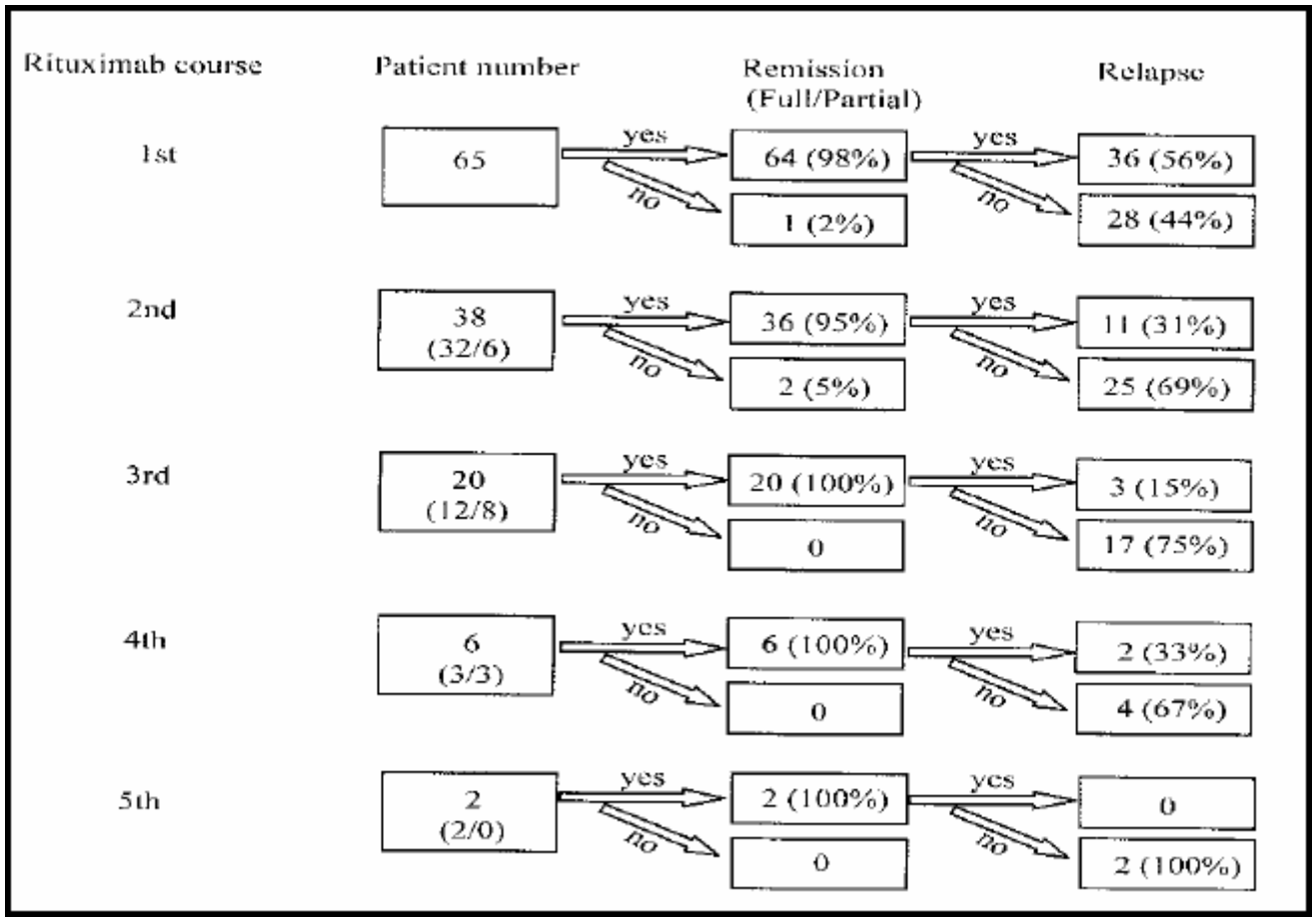



- **Remisón completa en 75%**
- **Remsión parcial en 23%**
- **No respuesta 2%**

# A Multicenter Survey of Rituximab Therapy for Refractory Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

***Bones RB. Arthritis Rheum. 2009 Jul;60:2156-68*.**

**RITUXIMAB**



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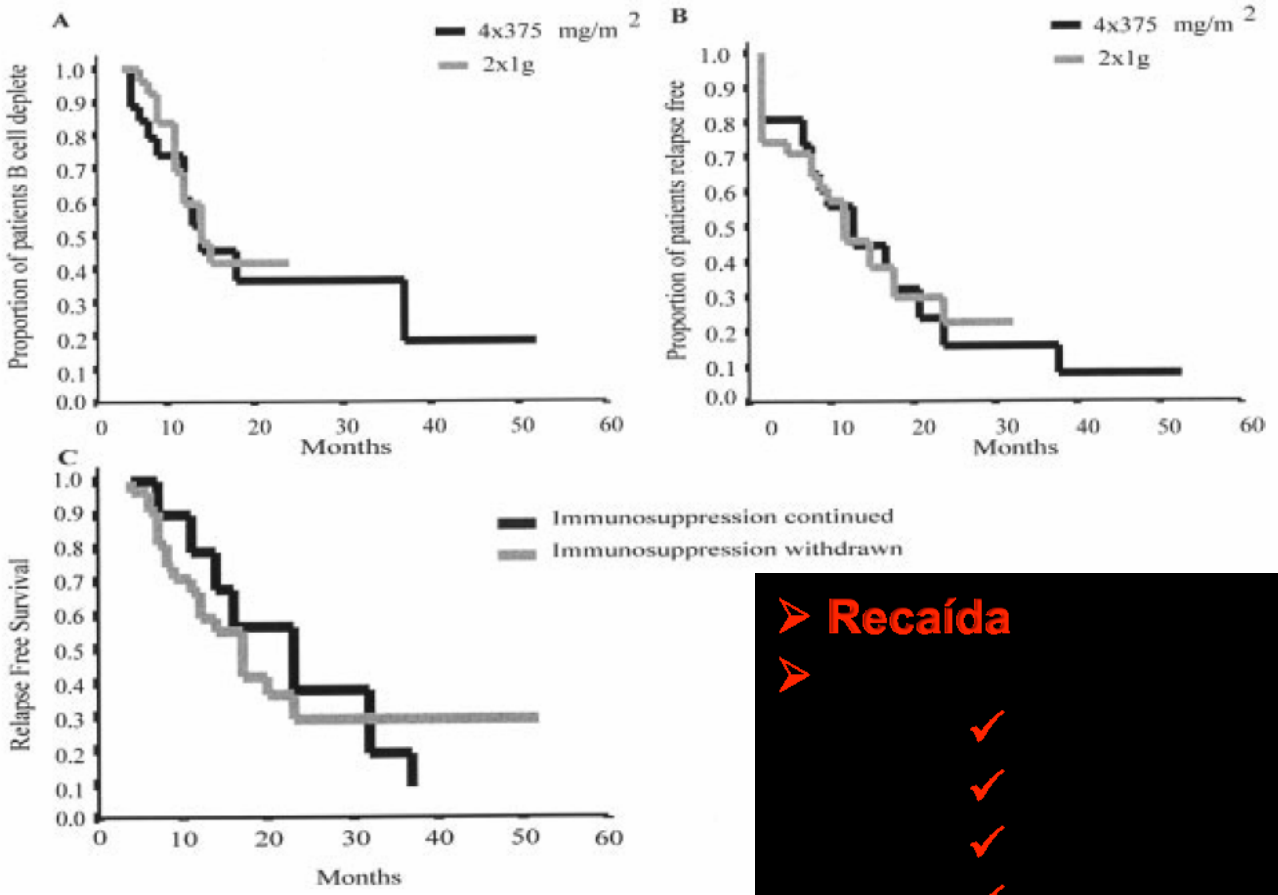



- Recaída
-
  - ✓
  - ✓
  - ✓
  - ✓

# Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

*Jones RB et al. N Engl J Med 2010; 363:211-20.*

**RITUXIMAB (RITUXIVAS)**

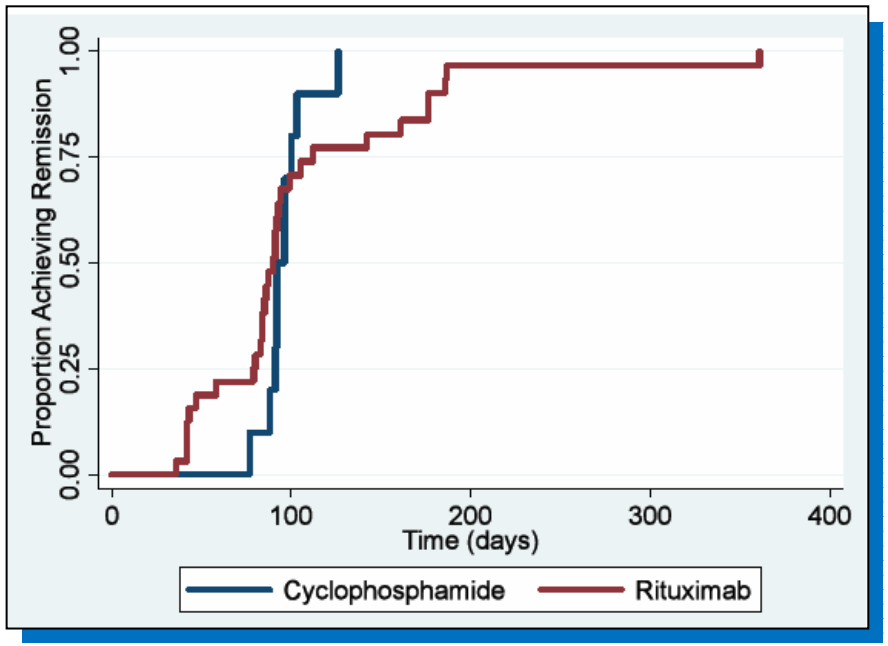
- Pacientes: diagnóstico reciente
- 
  - 33 pacientes
  - i.v
    - ✓ mantenimiento con AZA (3 mg/kg/d).
      11 pacientes

# Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

***Jones RB et al. N Engl J Med 2010; 363:211-20.***

**RITUXIMAB (RITUXIVAS)**

## Tiempo hasta la remisión* (a 1 año)




| | RTX | CFF |
|---|---|---|
| Remisión mantenida | 25/33 (76 %) | 9/11 (82 %) |
| Remisión no mantenida | 2 (incomp.) | 1 (incomp.) |

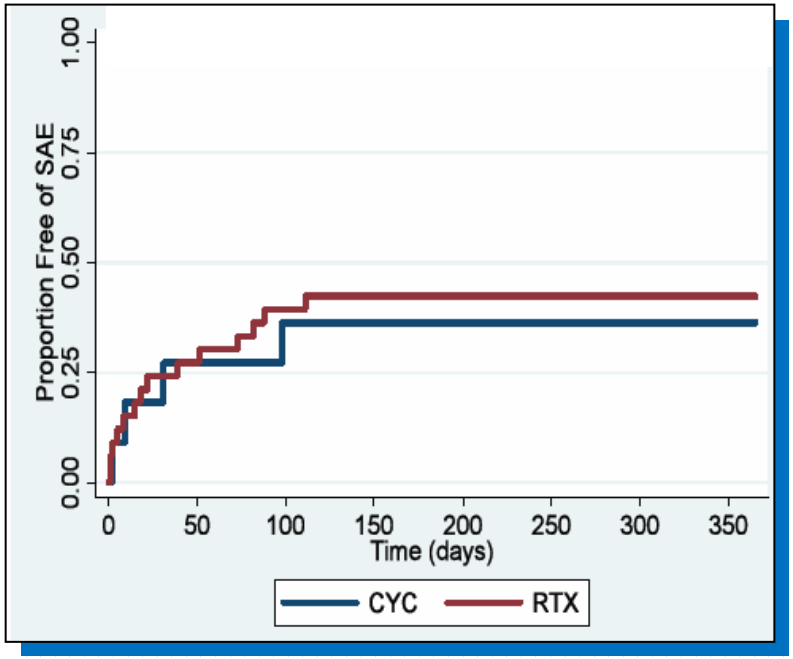
(*) Remisión : BVAS=0 (6 meses)

# Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

***Jones RB et al. N Engl J Med 2010; 363:211-20.***

**RITUXIMAB (RITUXIVAS)**

**% de pacientes libres de EAG* (a 1 año)**



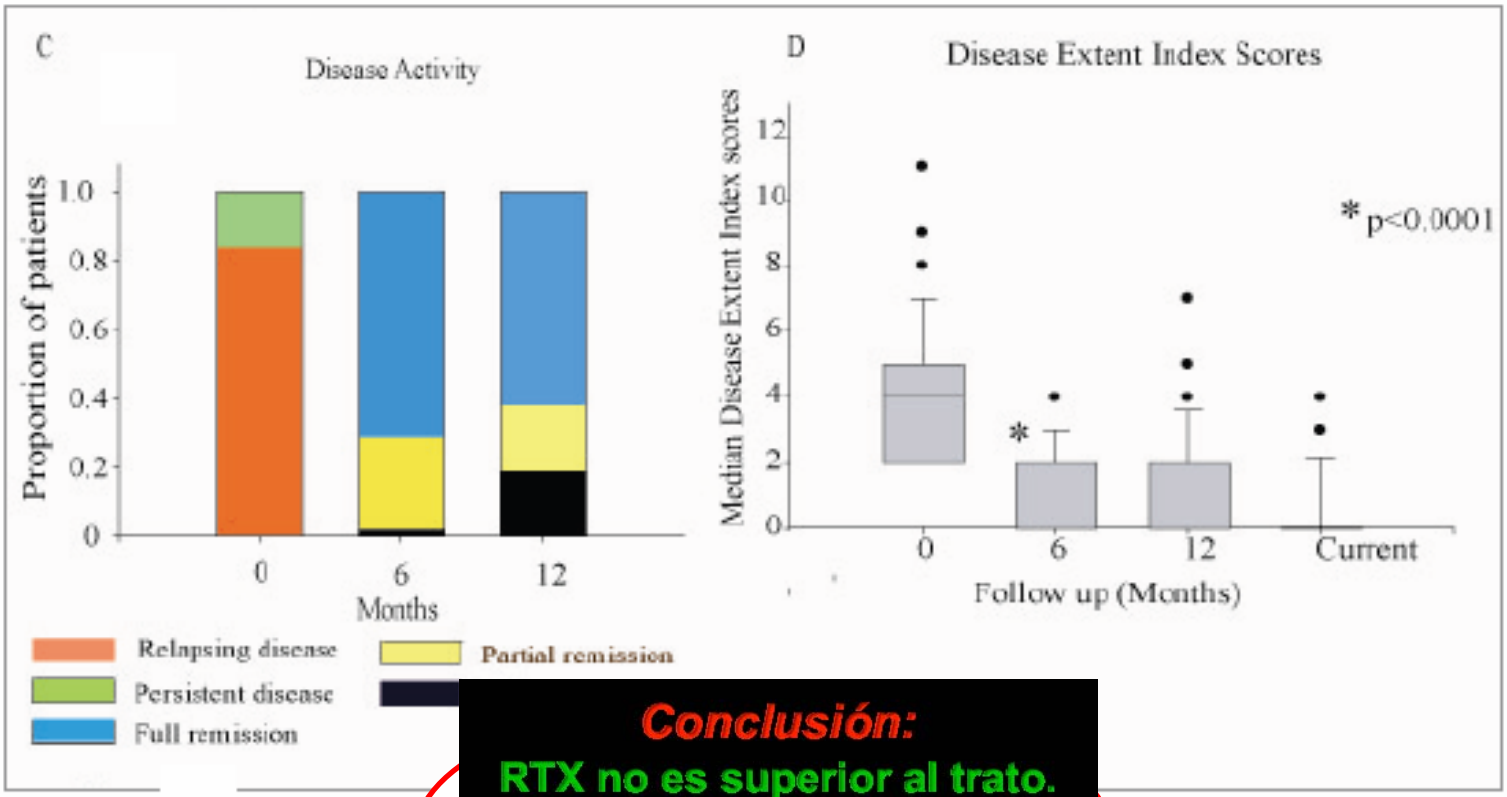

| | RTX | CFF |
|---|---|---|
| EAGs | 31 (42%)<br>1,0/pc.año | 12(36%)<br>1,1 /pac.año |
| Infección | 21 (39%)<br>0,66 pac.año | 7 (21%)<br>0,60/pac.año |
| Muerte | 6 (18%) | 2 (18%) |

(*) EAG: efecto adverso grave.

# Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

***Jones RB et al. N Engl J Med 2010; 363:211-20.***

**RITUXIMAB (RITUXIVAS)**




**Conclusión:**

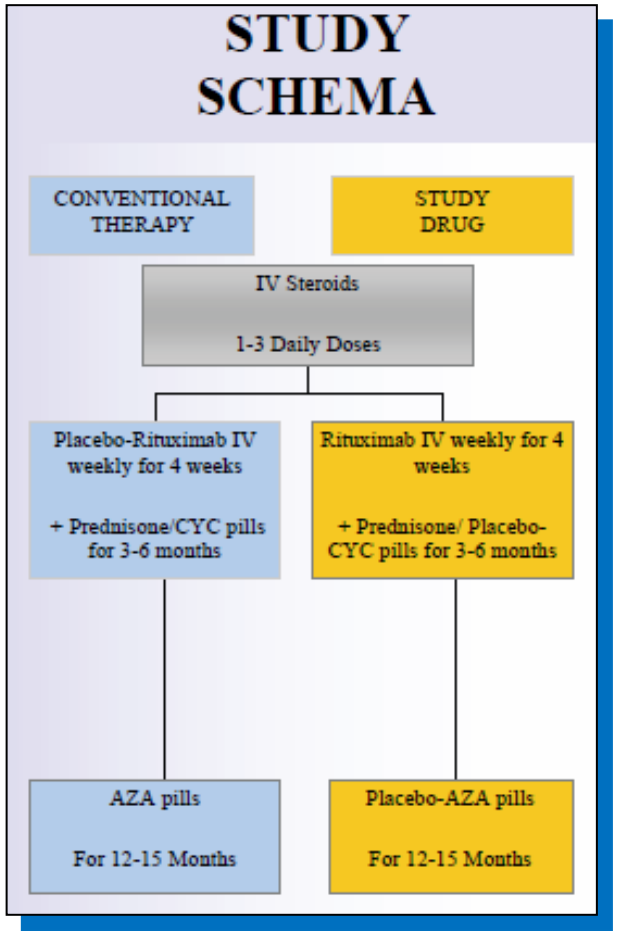
**RTX no es superior al trato. de inducción standard con CFM**

**No hay diferencia significativa en efectos**

# Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

*Stone et al. N Engl J Med 2010;363:221-32.*

**RITUXIMAB/INDUCCIÓN (RAVE)**



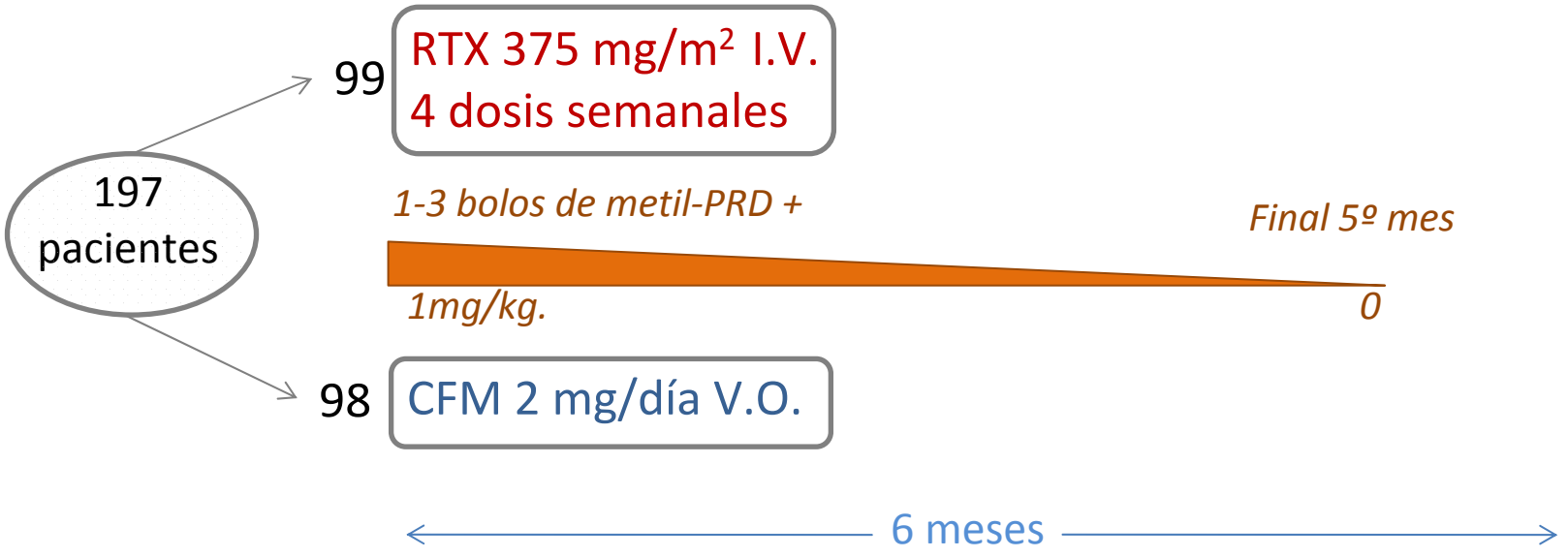

- **Estudio multicéntrico, randomizado, controlado con placebo.**

- **Valora si RTX es no inferior a CFF oral para inducir remisión.**

# Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

***Stone et al. N Engl J Med 2010;363:221-32.***

**RITUXIMAB/INDUCCIÓN (RAVE)**



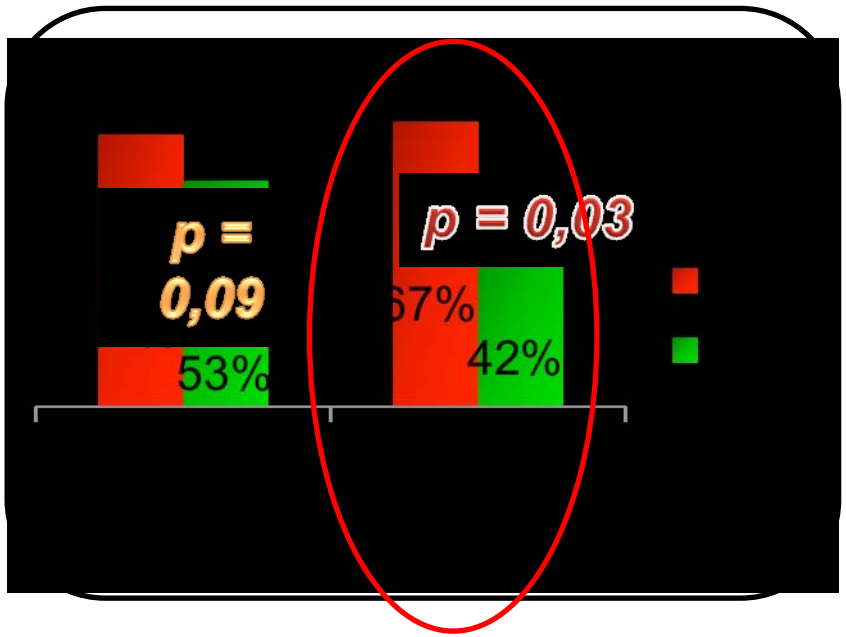

- ***PAM 24% / GW 75%.***
- **Nuevo diagnóstico 49% /recaídas 51%**

***Objetivo primario: remisión a los 6 meses sin necesidad de PRD***

# Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

*Stone et al. N Engl J Med 2010;363:221-32.*

**RITUXIMAB/INDUCCIÓN (RAVE)**




**RESULTADOS MUY SEMEJANTES:**

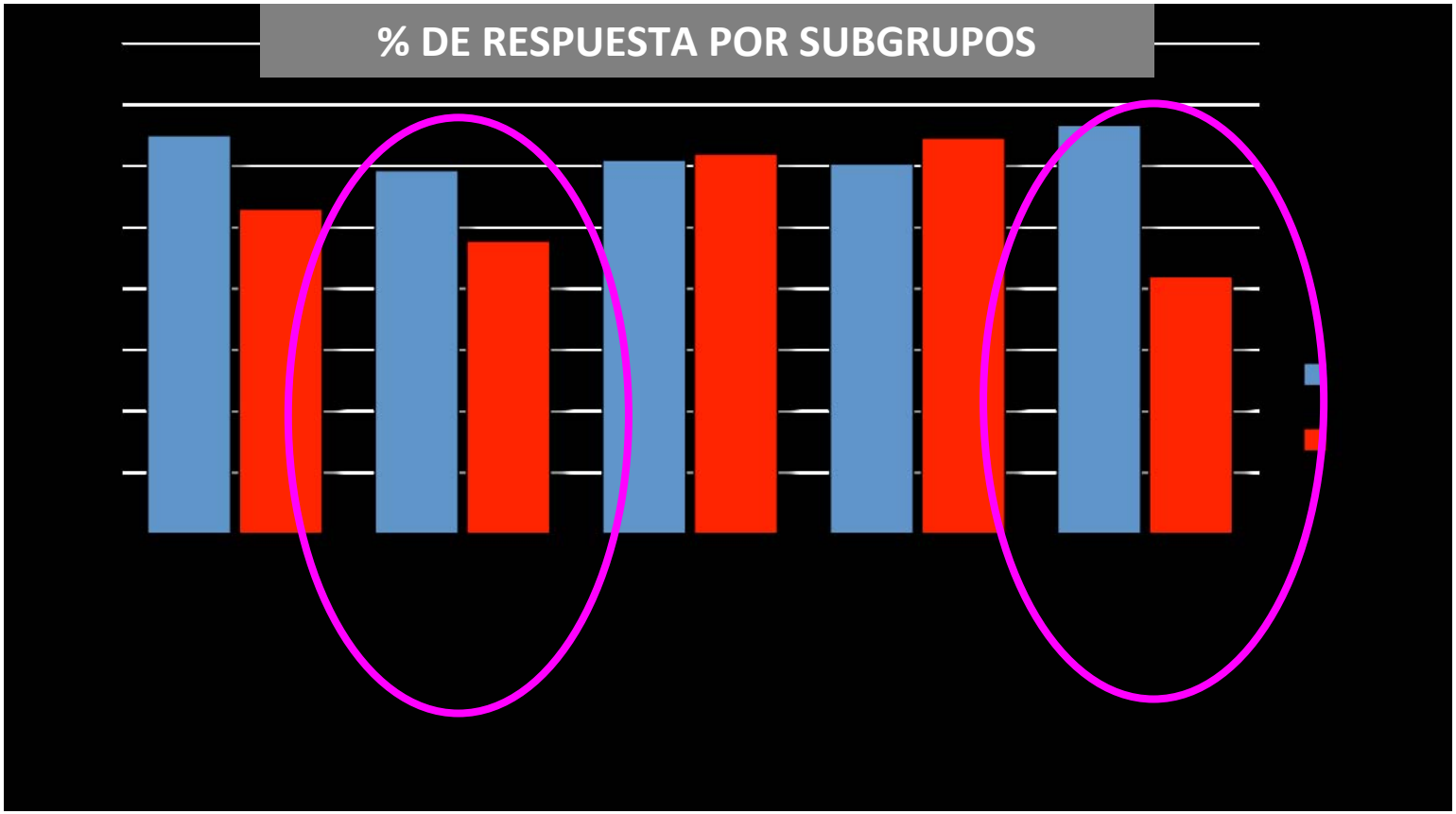
- En porcentaje de remisión (ventaja NS para RTX: 65% vs 55%)
- En recaídas
- En efectos adversos
- En relación con subgrupos
  - ✓ *Afectación renal (99 pac)*
  - ✓ *Hemorragia alveolar (50 pac)*

***Significativamente mas eficaz en recaídas.***

# Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

***Stone et al. N Engl J Med 2010;363:221-32.***

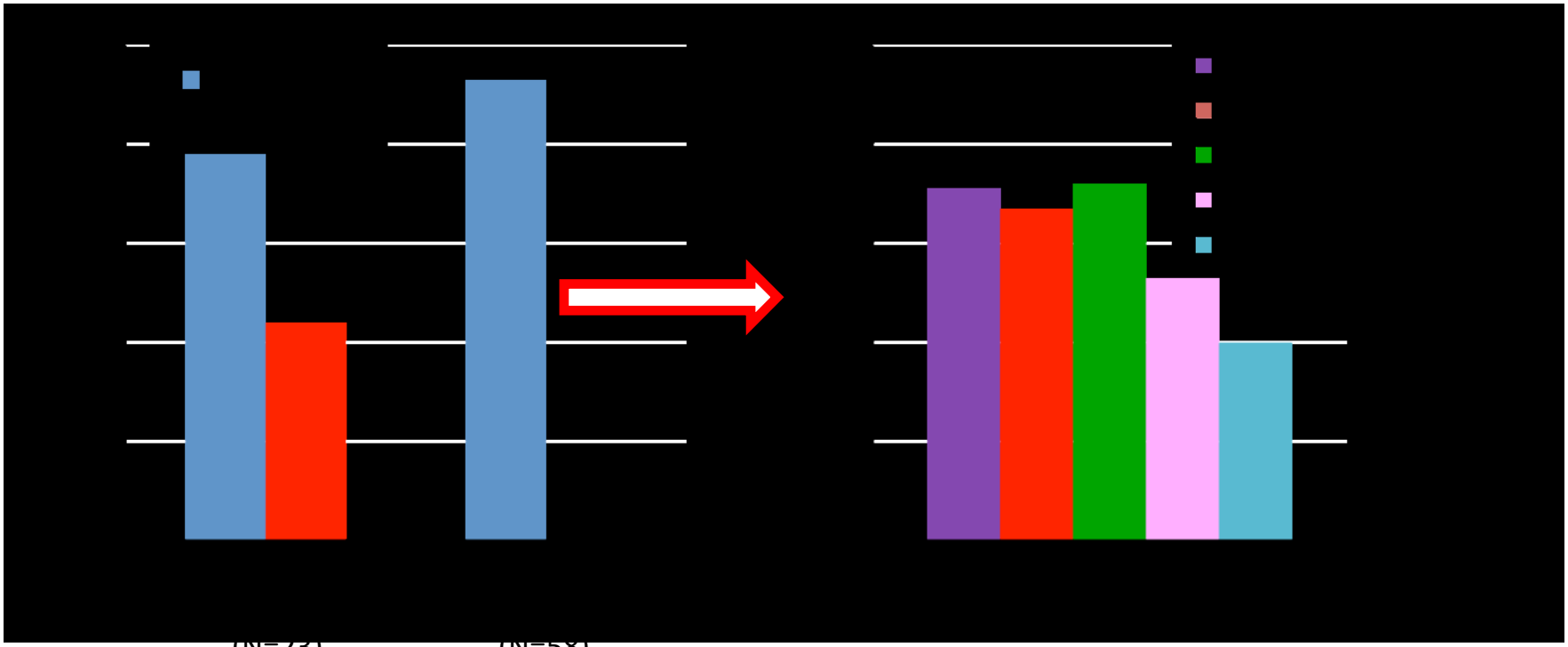
**RITUXIMAB/INDUCCIÓN (RAVE)**



EULAR, European League Against Rheumatism

Rome, 16th to 19th June 2010

**Porcentaje de respuestas a RITUXIMAB en 2 series de pacientes con GW.**



(N=23) (N=58)

Originales

Localizador web
Artículo 120.014

**Reumatol Clin, 2006; 2:23-30**

# Experiencia con rituximab en el tratamiento de pacientes con lupus eritematoso sistémico

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[a]Unidad de Colagenosis e Hipertensión Pulmonar. Hospital Virgen del Rocío. Sevilla. España.
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Notas clínicas 32655 / ex

## *NOTAS CLÍNICAS*

**Med Clín, 2007; 128:458-62**

# Utilidad del rituximab en el tratamiento de pacientes con enfermedades sistémicas autoinmunitarias resistentes

Francisco José García Hernández, Celia Ocaña Medina, Rocío González León, Rocío Garrido Rasco, Regi... María Jesús Castillo Palma y Julio Sánch...

Title: EVALUACIÓN DE LA EFICACIA DEL TRATAMIENTO CON RITUXIMAB ASOCIADO A CICLOFOSFAMIDA EN PACIENTES CON MIOPATÍA INFLAMATORIA IDIOPÁTICA RESISTENTE.
Order of Authors: Francisco Jose Garcia-Hernandez, M.D.; Eduardo Chinchilla-Palomares, Ph.D.; Maria J Castillo-Palma, M.D.; Cristina Gonzalez-Pulido, Ph.D.; Celia Ocaña-Medina, M.D.; Julio Sanchez-Roman, Prof., M.D.

**Med Clin (en prensa)**

Caso clínico

**Reumatol Clin, 2009; 5**

# Eficacia de ritu... con ciclofosfamida en una paciente con lupus eritematoso si... asculitis peritoneal resistente a tratamiento inmunosupres...convencional

Rocío Garrido Rasco, Francisco José García Hernández*, Rocío González León, María Jesús Castillo Palma, Celia Ocaña Medina y Julio Sánchez Román

*Unidad de Colagenosis e Hipertensión Pulmonar, Servicio de Medicina Interna, Hospitales Universitarios Virgen del Rocío, Sevilla, España.*

# RITUXIMAB EN ENFERMEDADES AUTOINMUNES

## Pacientes HUVR

- *Lupus eritematoso sistémico:* *62 pacientes.* *94 ciclos.*
- *Miopatía inflamatoria:* *20 “* *33 “*
- *Vasculitis sistémicas:* *16 “* *19 “*

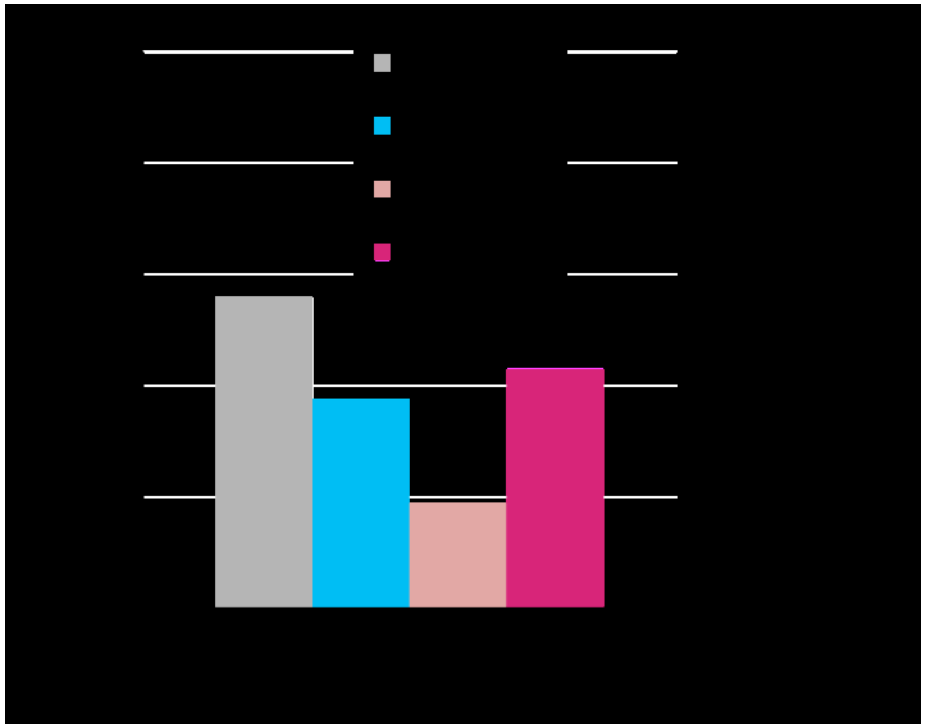
  - *Gr. de Wegener.* *(7/8)*
  - *Churg-Strauss* *(1/1)*
  - *Enf. de Takayasu.* *(2/4 + 2 dosis sueltas)*
  - *Crioglobulinemia.* *(3/3)*
  - *Enf. de Behçet.* *(1/2)*
  - *Urtic. vasculítica .* *(1/1)*

- *Otras: Anemia hemolítica VHC (1/2), EMTC (2/4), Lupus cutáneo (1), PTI (1), SAF (1), SS (1)*

***Total:*** ***106 pacientes/158 ciclos***

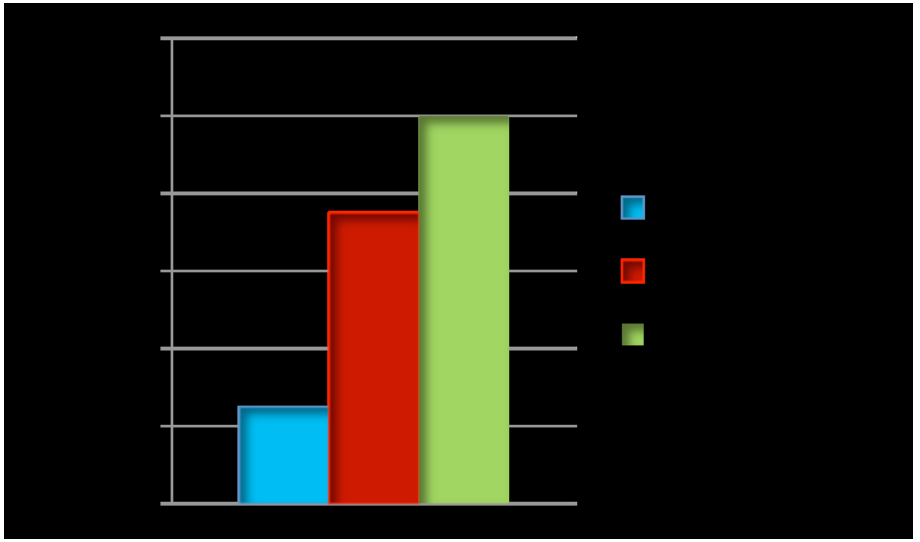
# TRATAMIENTO CON RITUXIMB EN VASCULITIS
## Experiencia del HUVR

| VASCULITIS | Nº |
|---|---|
| Enf de Takayasu | 2 |
| Wegener | 7 |
| Urticaria vasculítica | 1 |
| Crioglobulinemia mixta | 3 |
| Behçet | 1 |
| Churg-Strauss | 1 |
| Poliart. Microscópica | 1 |
| Total | 16 |



# TRATAMIENTO CON RITUXIMB EN GW.
## Experiencia del HUVR

- Pacientes: 7 (Nº de ciclos: 8)
- Tratamiento:
  - ✓ Inicial: 1
  - ✓ Recaídas/Enf persistente: 6
- Respuesta
  - ✓ Remisión completa: 1
  - ✓ Remisión parcial: 3
  - ✓ No Respuesta: 4
- Efectos adversos: 2
  - ✓ Neutropenia
  - ✓ TEP
- Esquema tratamiento
  - RTX 375 mg/Kg/semana x 4
  - CFM 10 mg/Kg/15 días x 2



# TRATAMIENTO CON RITUXIMB EN GW.
## Experiencia del HUVR

| Sexo | Edad | Motivo Tratamiento | TTo previo | TTo Concomi. | Respuesta | TTo posterior |
|---|---|---|---|---|---|---|
| M | 28 | obstruccion subglotica grave | Gc + Cf | Gc | NR | Eta |
| H | 48 | afectacion pulmonar/ sistema nervioso central | Gc | Gc | NR | Falleció |
| M | 73 | sinusitis etmoidal y maxilar bilateral grave y resistente | Gc + Cf + Eta | Gc | NR | Gc indefinidos |
| H | 40 | lesiones cutaneas extensas (pioderma gangrenoso) | Gc + Cf + Cp | Gc | NR | Eta |
| H | 52 | afectacion pulmonar grave (requirió UCI) | Gc + Cf | Gc | RC | No |
| M | 43 | fiebre + astenia + artralgias + otitis + obstrucción nasal + nódulos pulmonares bilaterales. | Gc + Cf + Mfm | Gc | RP | Gc/ Ad/ Mtx/ Cotrimoxazol/ Gusperimus |
| M | 45 | Sinusitis maxilar + iritis + nódulos e infiltrados pulmonares +vasculitis cutánea + afeccion renal | Gc + Msz + Az + Mtx + Lf + Ad + Ifx | Gc | RP | Gc/ MfNa/ Cotrimoxazol/ Cf iv |

Gc: glucocorticoides. Cf: ciclofosfamida. Mfm: Micofenolato de mofetilo. Eta: Etanercept. Mtx: metotrexato. Cp: Ciclosporina. Az: azatioprina. Cch: Colchicina. Ptx: Pentoxifilina. Td: Talidomida. Msz: Mesalazina. Ad: Adalimumab. If: Interferón. Ig: Inmunoglobulinas. MfNa: Micofenolato sódico. Lf: Leflunomida. If: Infliximab. RC: remsión completa. RP: respuesta parcial. NR: no respuesta.

# TRATAMIENTO CON RITUXIMB EN OTRAS VASCULITIS
## Experiencia del HUVR

- 
- 
  - ✓
- 
  - ✓ (1 Churg Strauss/3 criglobulinemia)
  - ✓
  - ✓
- 
  - ✓
  - ✓
- 
  - 
  - 

# TRATAMIENTO CON RITUXIMB EN OTRAS VASCULITIS
## Experiencia del HUVR

| Sexo | Edad | Diagnostico | Motivo del tratamiento | TTo previo | Respuesta | TTo posterior |
|---|---|---|---|---|---|---|
| M | 25 | Arteritis Takayasu | fiebre+afeccion vascular extensa grave (mesentérica + iliaca + renales + troncos supraaorticos) | Gc + Cf + Mfm | RP | Perdida |
| H | 13 | Arteritis Takayasu | Afección vascular extensa grave + retraso del crecimiento por corticoides | Gc + Cf + Az + Mfm + Eta | RP | Gc |
| M | 46 | Urticaria vasculitica hipocomplementem. | urticaria diseminada + artralgias + asma | Gc + Mtx | NR | Gc |
| M | 68 | Crioglobulinemia VHC | purpura vasculitica + artralgias + fiebre + neuropatia periferica | Gc + Interferon + Ribavirina | RC | No |
| M | 47 | Crioglobulinemia antiHBs+) | Púrpura cutánea ulcerada | Gc + Cf + If + Mtx + Ig | RC | No |
| M | 61 | Crioglobulinemia VHC | Púrpura cutánea ulcerada | Gc + PegIf + ribavirina | RC | No |
| M | 15 | Churg-Strauss | fiebre + artritis + vasculitis cutánea + vasculitis intestinal | Gc + Cf + MfNa | RC | No |
| M | 44 | Behçet | Enterobehçet + fiebre + aftosis + eritema nodoso | Gc + Cch + Mtx + Ptx + Td + Msz + Ad | NR | Gc<br>Gc + Td + If |
| M | 53 | PAM | Síndrome neumorrenal | Gc + Cf | NR | Falleció |

**RECAMBIO PLASMÁTICO**

***Jayne DR,et al. Randomized trial of plasma exchange or high dose methyl prednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007; 18:2180-8. (MEPEX)***

- **Respuesta de la afectación renal en pacientes con GW .**
  - ✓ *Grupo A: MTP (3 bolos de 1 gr) + tratº con CFF*
  - ✓ *Grupo B: 7 sesiones de RP + tratº con CFF.*
- **Mejor respuesta (supervivencia sin diálisis) en gupo B.**
- **Tasa de fallecimientos semejante.**
- **Resultados se mantienen al año de seguimiento.**

Sólo analiza la afectación renal

***Klemmer PJ et al.Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small-vessel vasculitis. Am J Kidney Dis. 2003;42:1149-53.***

- **Estudio retrospectivo de 20 ptes con vasculiis-ANCA y hemorragia alveolar.**
- **Tratº con RP + MTP (iv) y/o CFF**
- **Buena evolución:**
  - ✓ *(100 %) para 20 pctes con afectación pulmonar.*
  - ✓ *(50 %) para 14 pctes con afectación renal.*

**RECAMBIO PLASMÁTICO**

***Jayne DR,et al. Randomized trial of plasma exchange or high dose methyl prednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007; 18:2180-8. (MEPEX)***

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Sólo analiza la afectación renal

***Klemmer PJ et al.Plasmaphe***
***patients with small-vessel vo***

- **Estudio retrospectivo**
- **Tratº con RP + MTP (iv**
- **Buena evolución:**
  - ✓ *(100 %) para 20*
  - ✓ *(50 %) para 14 p*

PEXIVAS

Randomised trial of plasma exchange and glucocorticoids in ANCA associated vasculitis

EUVAS

VASCULITIS CLINICAL RESEARCH CONSORTIUM

Version 1; August 2009

**Deoxispergualina (GUSPERIMUS)**

J Am Soc Nephrol 14: 440–447, 2003

# 15-Deoxyspergualin in Patients with Refractory ANCA-Associated Systemic Vasculitis: A Six-Month Open-Label Trial to Evaluate Safety and Efficacy

RAINER BIRCK,* K
MARION HAUBITZ
JOACHIM R. KALI
OSAMU HOTTA,#
LORENZ ‡ MIRA CHOI,§

Nephrol Dial Transplant (2005) 1 of 10
doi:10.1093/ndt/gfh763

Nephrology Dialysis Transplantation

*Original Article*

## Prolonged treatment of refractory Wegener's granulomatosis with 15-deoxyspergualin: an open study in seven patients

Wilhelm H. Sch
Göbel[3], Mira Choi[3],

Rheumatology 2010;49:556–562
doi:10.1093/rheumatology/kep411
Advance Access publication 23 December 2009

RHEUMATOLOGY

Original article

## Long-term treatment of relapsing Wegener's granulomatosis with 1 spergualin

Oliver Floßmann[1] and David R. V

## Deoxyspergualin in relapsing and refractory Wegener's granulomatosis

Ann Rheum Dis 2009;68:1125–1130. doi:10.1136/ard.2008.092429

O Flossmann,[1] B Baslund,[2] A Bruchfeld,[3] J W Cohen Tervaert,[4] C Hall,[7] P Heinzel,[5] B Hellmich,[6] R A Luqmani,[7] K Nemoto,[5] V Tesar,[8] D R W Jayne[1]

J Am Soc Nephrol 14: 440–447, 2003

in Patients with Refractory ANCA-

**Deoxispergualina (GUSPERIMUS)**

| Autor | Nº | Seguimiento (meses) | Respuesta (%) | Recidiva % | Recidiva tardía (%) |
|---|---|---|---|---|---|
| Birk, 2003 | 20 | 6 | 70 | - | - |
| Scmmitt, 2005 | 7 | 26 | 100 | 28 | - |
| Flossman, 2010 | | | | | 87,5 |
| Flossman, 2010 | | | | | - |

Mira Choi[3],

RHEUMATOLOGY

Original article

**Long-term treatment granulomatosis with**

Oliver Floßmann[1] and David R.

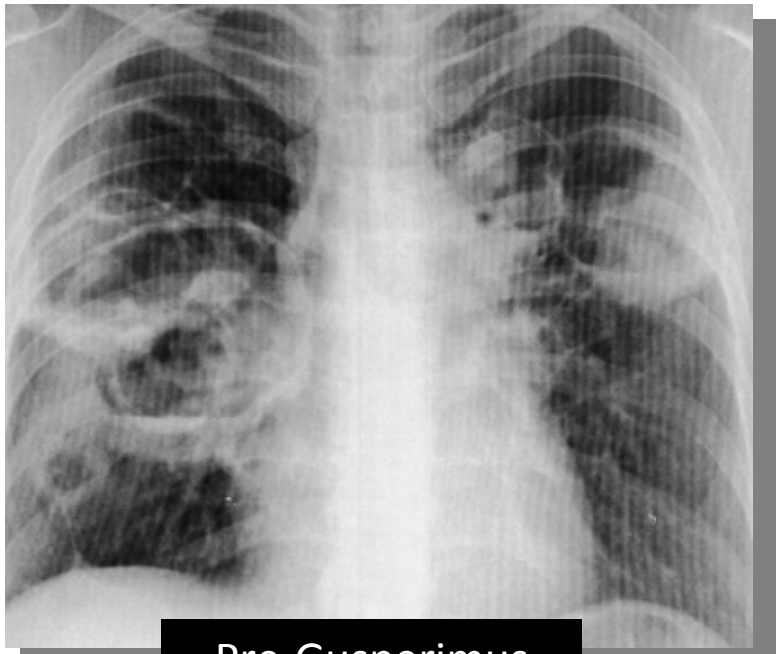
efractory

rvaert,[4] C Hall,[7] P Heinzel,[5] W Jayne[1]

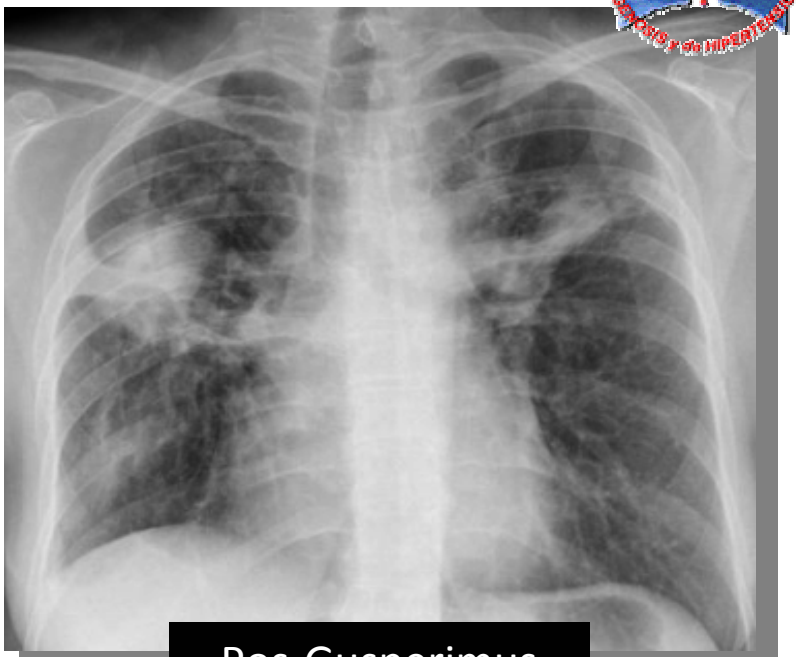
**Table 2** Adverse events

| Event | No of patients (%) | No of patients with severe events (%) |
|---|---|---|
| Anaemia | 8 (17.8) | 5 (11.1) |
| Leucopaenia | 17 (37.8) | 17 (37.8) |
| Thrombocytopaenia | 2 (4.4) | 1 (2.2) |
| All infections | 35 (77.8) | 5 (11.1) |
| Lower respiratory tract | 12 (26.7) | 3 (6.7) |
| Upper respiratory tract | 9 (20) | 0 |
| Urinary tract | 6 (13.3) | 0 |
| Candida | 7 (15.6) | 0 |
| Injection site pain/pruritus | 26 (57.8) | 0 |
| Injection site haemorrhage | 8 (17.8) | 0 |
| Pain oral cavity/throat | 19 (42.2) | 0 |
| Dysgeusia | 8 (17.8) | 0 |
| Stomatitis/mouth ulcers | 9 (20) | 0 |
| Abdominal pain | 5 (11.1) | 0 |
| Anorexia | 8 (17.8) | 2 (4.4) |
| Diarrhoea | 18 (40.0) | 1 (2.2) |
| Nausea | 16 (35.6) | 0 |
| Vomiting | 10 (22.2) | 0 |
| Fatigue | 8 (17.8) | 1 (2.2) |
| Acne | 11 (24.4) | 0 |
| Alopecia | 11 (24.4) | 0 |
| Liver function tests | 1 (2.2) | 0 |

Deoxisperguali
(GUSPERIMU



Pre-Gusperimus

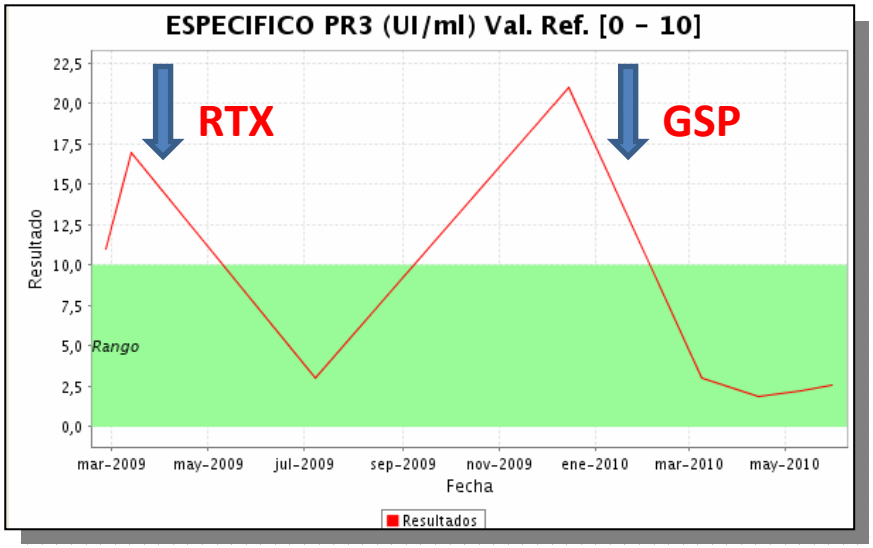


Pos-Gusperimus

**GW diagnosticada en 2006.**

**Resiste (ineficacia) a:**

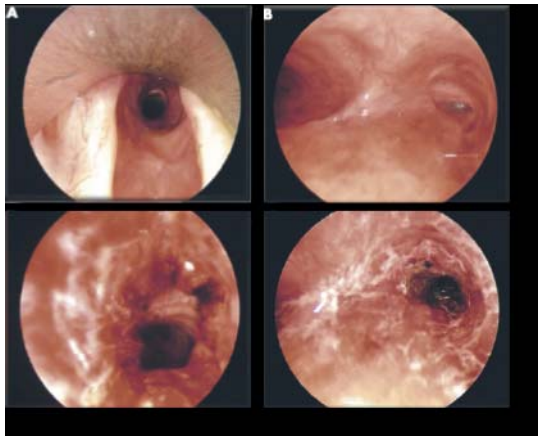
- ***MTP i.v.***
- ***CFF i.v.***
- ***MFMF***
- ***MTX***
- ***Adalimumab***
- ***Rituximab***

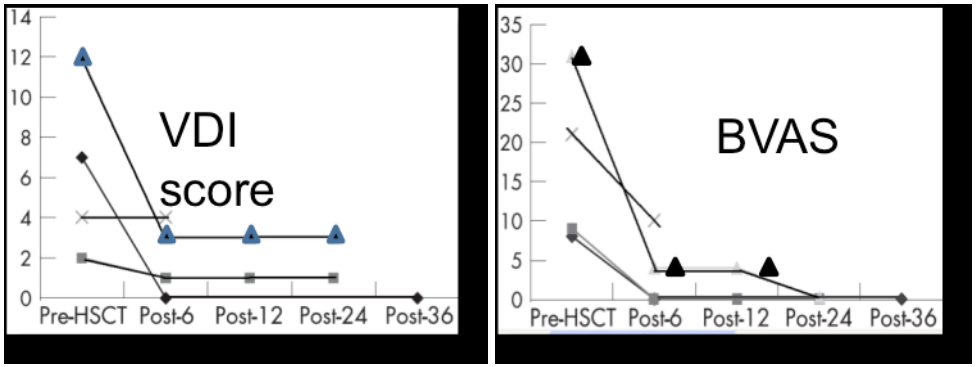


*Y…*

*¿algo más?*

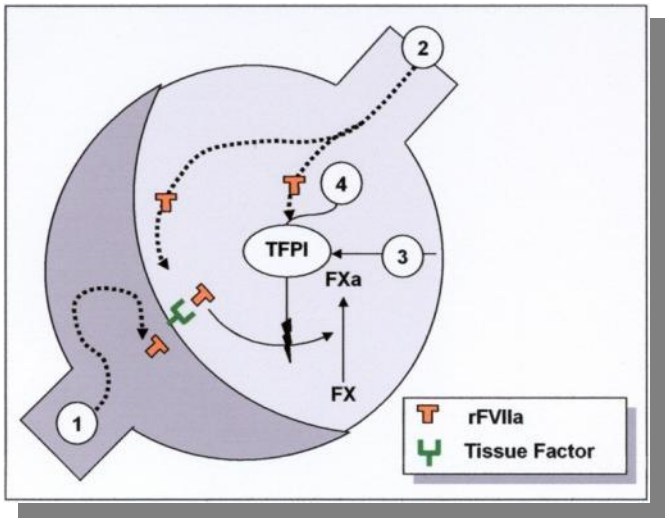
*Nouraei SAR et al. Results of endoscopic surgery and intralesional steroid therapy for airway compromise due to tracheobronchial Wegener's granulomatosis. Thorax 2008;63:49–52.*

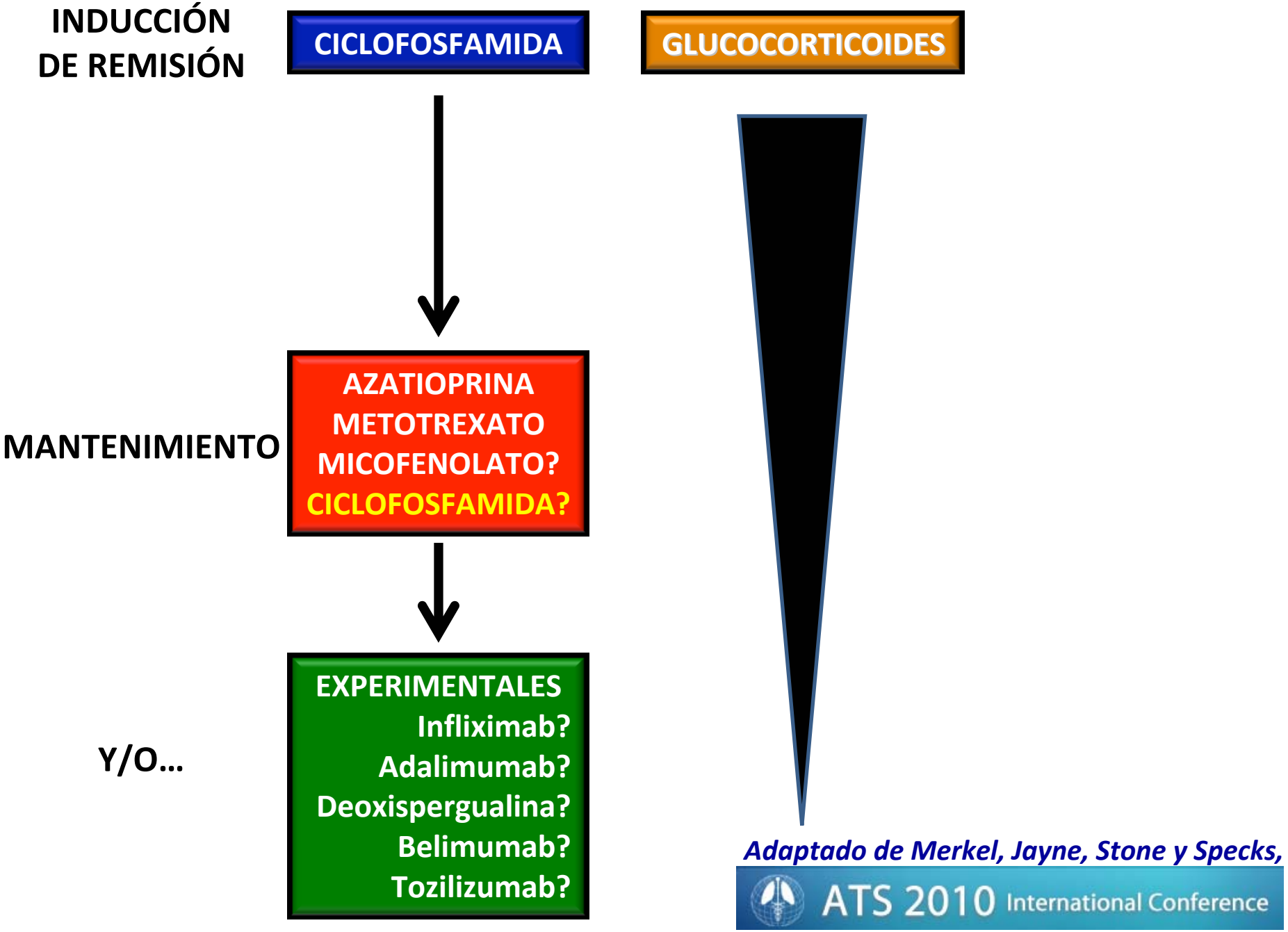


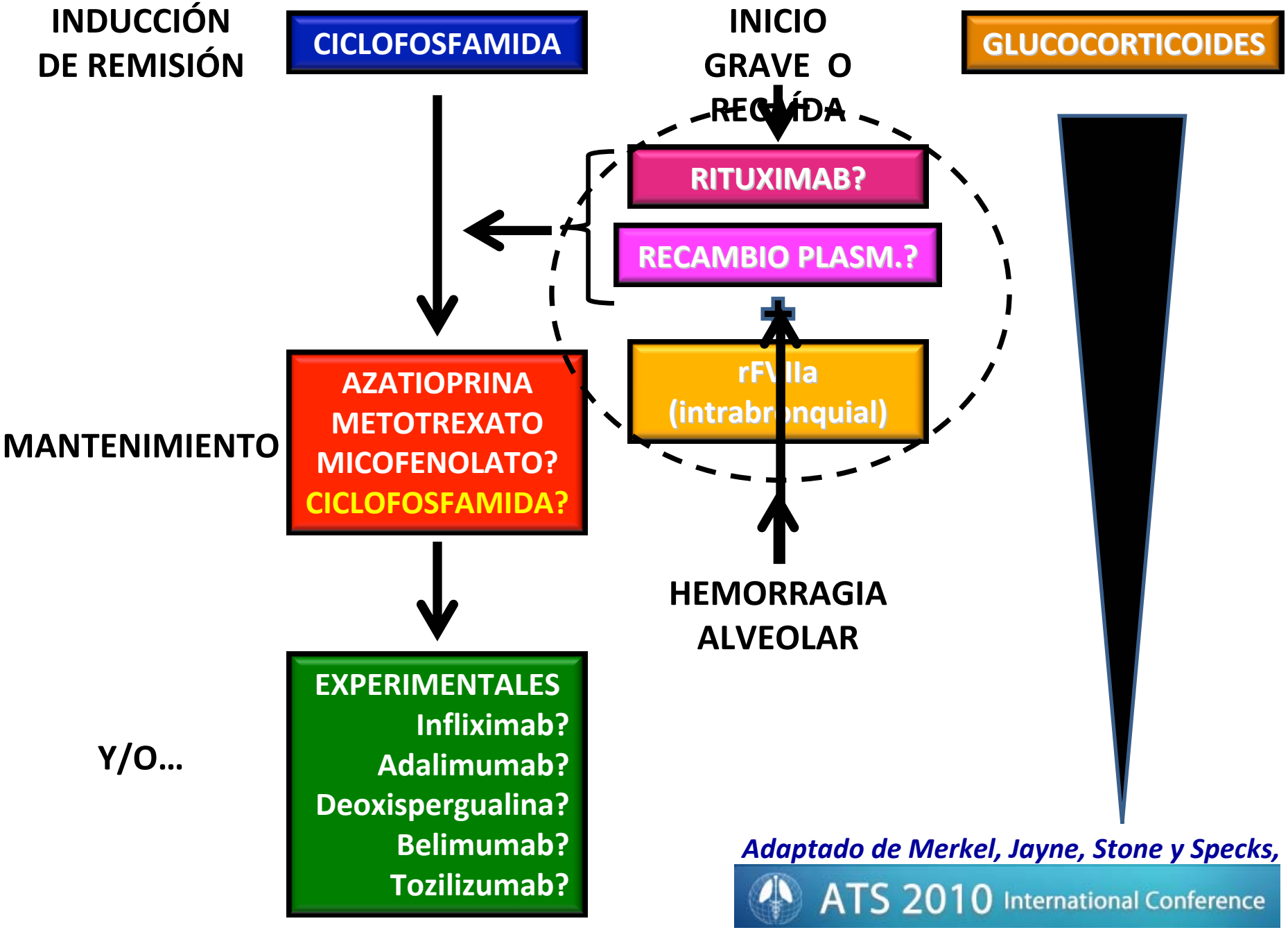



*Statkute L et al. Autologous non-myeloablative haematopoietic stem cell transplantation for refractory systemic vasculitis. Ann Rheum Dis 2008;67:991–7.*

*Heslet L el al. Successful pulmonary administration of activated recombinant factor VII in diffuse alveolar hemorrhage. Critical Care 2006, Vol 10 Nº 6*




INDUCCIÓN
DE REMISIÓN
CICLOFOSFAMIDA
GLUCOCORTICOIDES
MANTENIMIENTO
AZATIOPRINA
METOTREXATO
MICOFENOLATO?
CICLOFOSFAMIDA?
Y/O…
EXPERIMENTALES
Infliximab?
Adalimumab?
Deoxispergualina?
Belimumab?
Tozilizumab?
Adaptado de Merkel, Jayne, Stone y Specks,
ATS 2010 International Conference

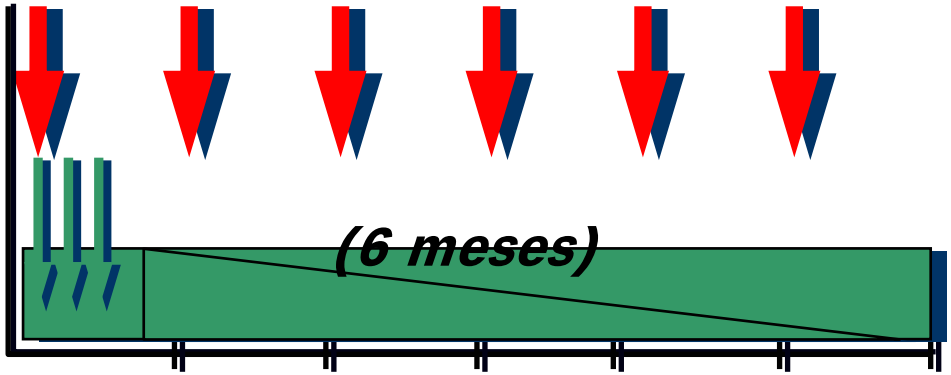



*Adaptado de Merkel, Jayne, Stone y Specks,*

ATS 2010 International Conference

## *Esquema general de tratamiento inmunosupresor en enfermedades sistémicas.*

*1.- Fase de Inducción.*

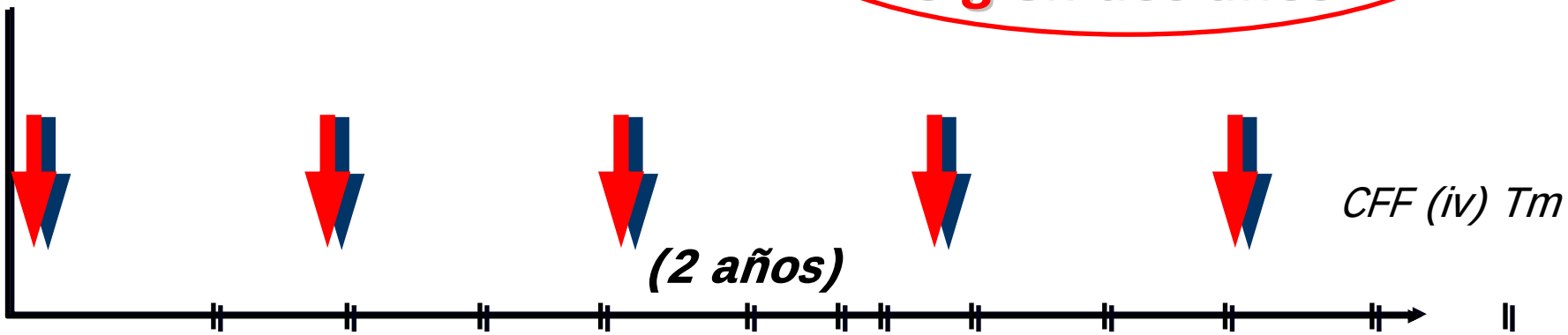



*CFF (iv): 750 mg.*

*Deflazacort (vo): 60 mg/día.*

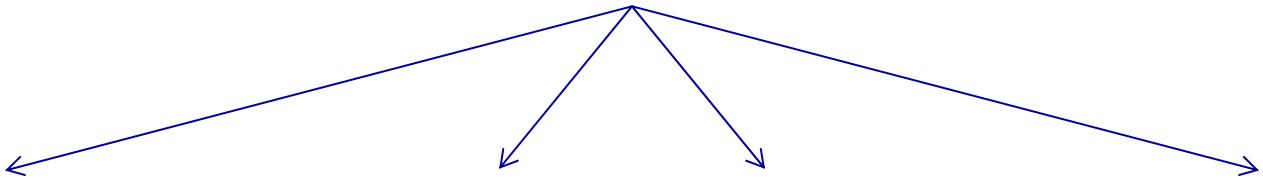
**Dosis acumulada CFM 9 g en dos años**

*1.- Fase de Mantenimiento.*




*CFF (iv) Tm*

# CICLOFOSFAMIDA



## Infecciones

**Antibióticos.**
**Profilaxis**
- *TBC*
- *Staphyllococcus*
- *Pneumocystis*
- *Herpesvirus*
- *VacunaPneumocócica*

## Mielotoxicidad

**Fac. estimulante GM**
**Eritropoyetina**

## Amenorrea

**Leuprorelina**
**Anticonceptivos.**

## Cistitis

**MESNA**

**REDUCCION DE DOSIS**


Muchas gracias
Julio Sánchez Román
Francisco José García Hernández
Celia Ocaña Medina
Rocío González León
María Jesús Castillo Palma.