Novedades en vasculitis

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- Etiopatogenia
- Tratamiento:
  - inducción de remisión
  - mantenimiento de la remisión

E T I C P A T O G E N I A

Review article: The role of CD4+ T cells in ANCA-associated systemic vasculitis

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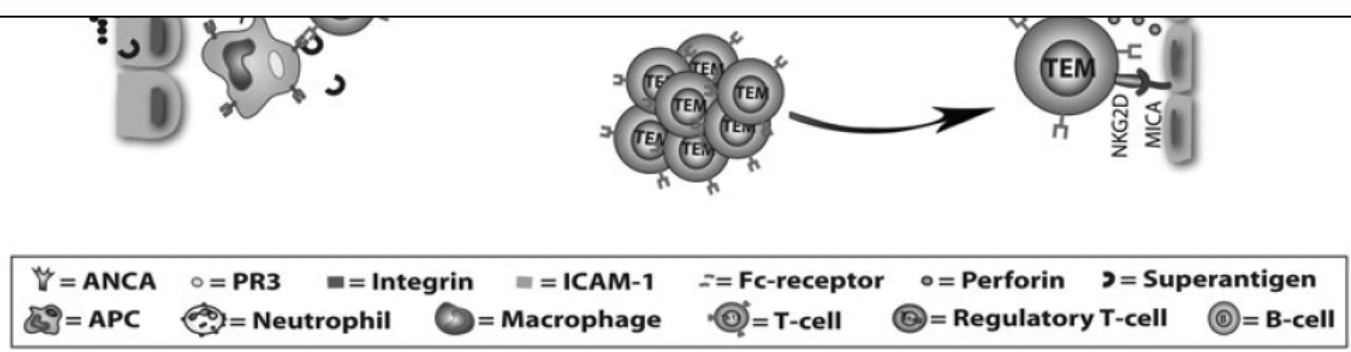
SUMMARY: Antineutrophil cytoplasmic autoantibody (ANCA)-associated systemic vasculitis (AASV) constitutes a group of primary vasculitides associated with antineutrophil cytoplasmic autoantibodies, which are either directed to proteinase-3 or myeloperoxidase. In contrast to other forms of vasculitis, immuohistologic evaluation of affected tissues in patients with AASV, particularly the kidneys, demonstrated an absence or paucity of immunoglobulins, which could suggest involvement of cell-mediated injury in this disorder. Several studies have shed light on T cell-mediated immune responses playing a role in the pathophysiology of AASV. Imbalance of CD4+ T-cell subsets has been demonstrated in the peripheral blood of patients with AASV. The trigger that leads to this imbalance remains to be defined, but clinical evidence shows that nasal carriage of *Staphylococcus aureus* constitutes a risk factor for disease exacerbation. Recent data show that superantigens and peptidoglycans from these Gram-positive bacteria can induce skewing of T-cell responses towards pathogenic interleukin (IL)-17-producing T-helper cells (Th17). Overproduction of IL-17 in response to this infection might aggravate inflammatory responses and contribute to the production of autoantibodies as well as to granuloma formation and tissue injury in patients with AASV. Next to Th17 cells, memory CD4+ T cells with the effector cytotoxic phenotype (CD4+ T_{EM}) have also been demonstrated to constitute a major effector pathway of tissue injury in patients with pauci-immune glomerulonephritis. Therefore, future perspectives for treatment of AASV could be built on neutralization of IL-17 and depletion of CD4+ T_{EM} cells.



Review article: Pathogenic role of complement activation in anti-neutrophil cytoplasmic auto-antibody-associated vasculitis

MIRJAN M VAN TIMMEREN,[1]* MIN CHEN[2]* and PETER HEERINGA[1]

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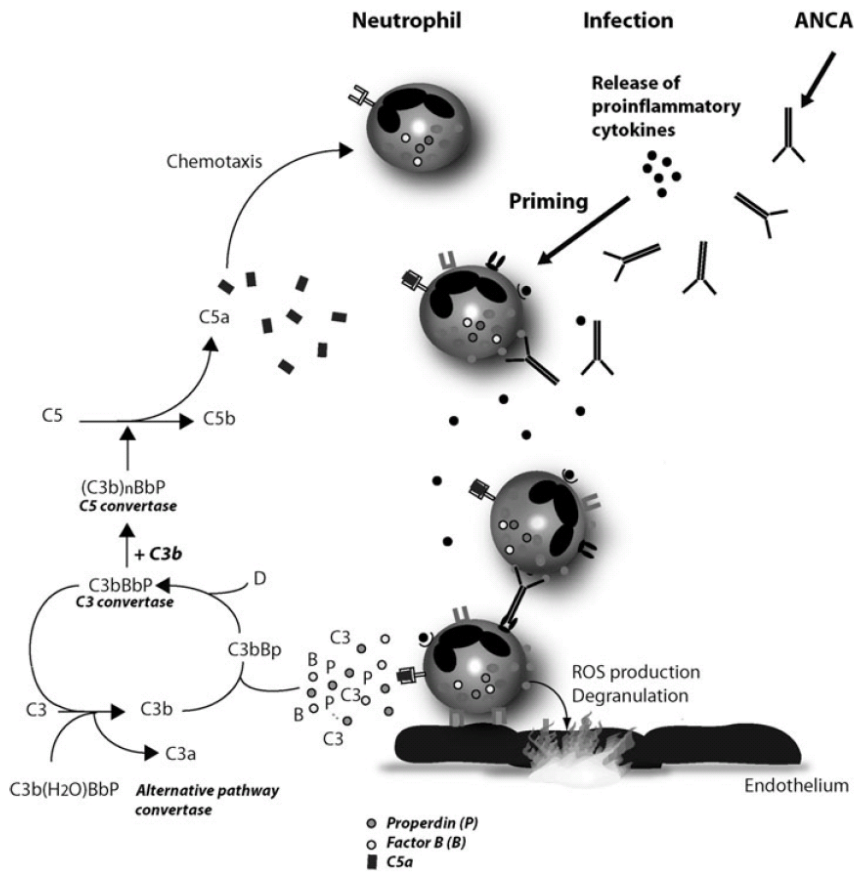
NEPHROLOGY 2009; **14**, 16–25

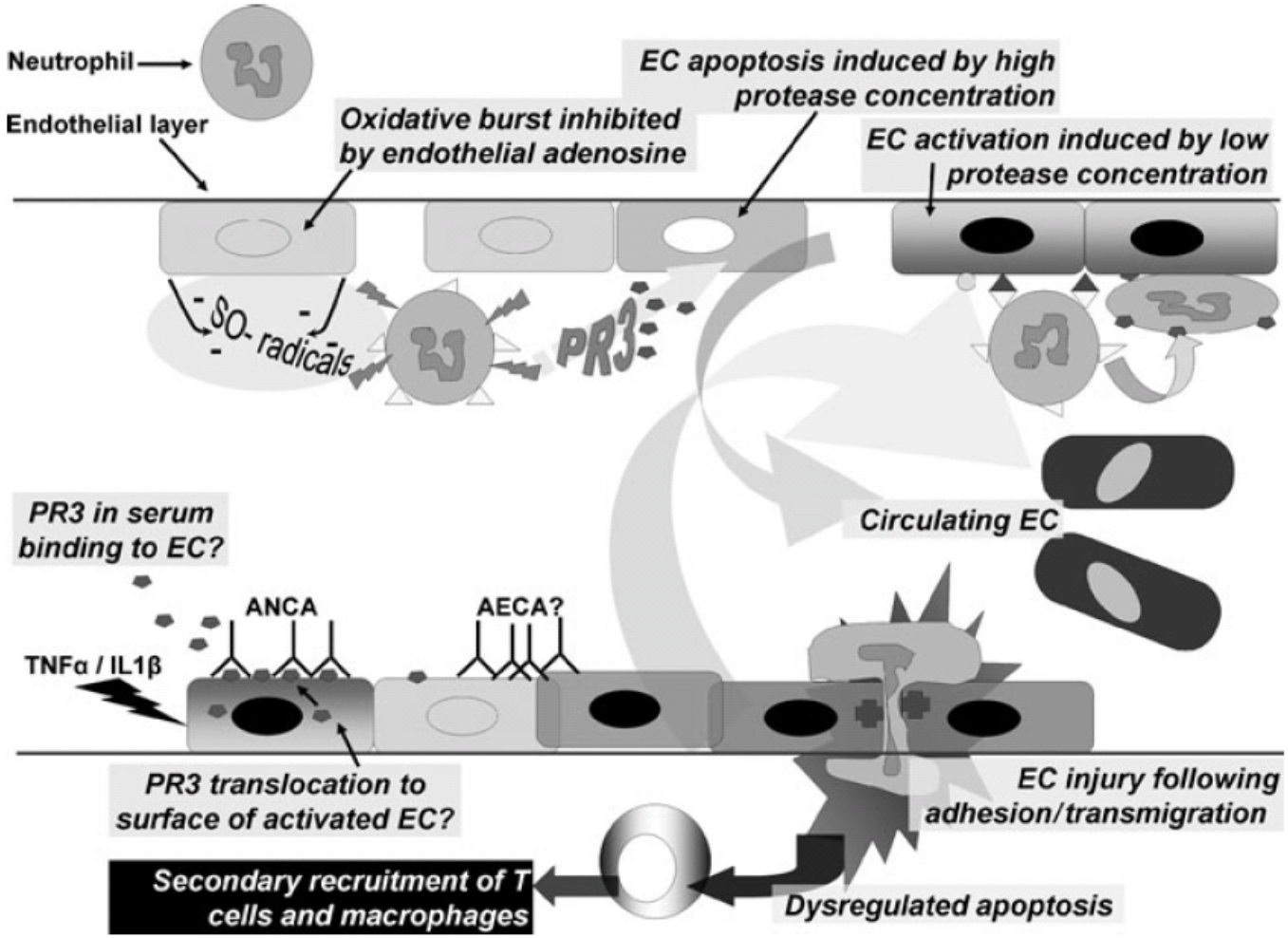


Review article: Leukocyte-endothelial dysregulation in systemic small vessel vasculitis

TANYA PANKHURST, CAROLINE OS SAVAGE and MARK A LITTLE

Renal Institute of Birmingham, School of Infection, Immunity and Inflammation, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

NEPHROLOGY 2009; **14**, 3–10



VASCULITIS SYNDROMES

LAMP-2 illuminates pathogenesis of ANCA glomerulonephritis

Xavier Bosch and Eduard Mirapeix

The discovery that antibodies to a bacterial antigen can cross-react with a mammalian protein to cause pauci-immune necrotizing and crescentic glomerulonephritis opens up new possibilities for the diagnosis and treatment of this condition.

DNA sequences complementary to the proteinase 3 gene have been identified in microorganisms including *Staphylococcus aureus*, which supports the role of infectious agents as triggers of proteinase 3 autoimmunity via molecular mimicry.[5]

El antígeno envuelto no es PR3 sino LAMP-2

LAMP-2 = proteína de membrana, glicosilada tipo I, localizada en la membrana de los gránulos de los neutrófilos que contienen PR3/MPO, y en la membrana endotelial

LAMP-2 interviene en la presentación del antígeno y en la adhesión de los monocitos al endotelio

TRATAMIENTO

EULAR Recommendations for the management of primary small and medium vessel vasculitis

Chetan Mukhtyar, Loic Guillevin, Maria C Cid, Bhaskar Dasgupta, Kirsten de Groot, Wolfgang Gross, Thomas Hauser, Bernhard Hellmich, David Jayne, Cees GM Kallenberg, Peter A Merkel, Heiner Raspe, Carlo Salvarani, David GI Scott, Coen Stegeman, Richard Watts, Kerstin Westman, James Witter, Hasan Yazici and Raashid Luqmani

Ann Rheum Dis published online 15 Apr 2008;

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]

CF oral (2mg(kg/día) : disminuir 25% dosis > 60 años y 50% dosis > 70 años

CF pulsos (15 mg/kg/día): 12.5 mg/kg/día en > 60 años y 10 mg/kg/día en > 70 años

Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial.

Ann Intern Med. 2009 May 19;150(10):670-80.

BACKGROUND: Current therapies for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis are limited by toxicity.
OBJECTIVE: To compare pulse cyclophosphamide with daily oral cyclophosphamide for induction of remission. DESIGN: Randomized, controlled trial. Random assignments were computer-generated; allocation was concealed by faxing centralized treatment assignment to providers at the time of enrollment. Patients, investigators, and assessors of outcomes were not blinded to assignment. SETTING: 42 centers in 12 European countries. **PATIENTS:** 149 patients who had newly diagnosed generalized ANCA-associated vasculitis with renal involvement but not immediately life-threatening disease. **INTERVENTION**: **Pulse cyclophosphamide, 15 mg/kg every 2 to 3 weeks (76 patients), or daily oral cyclophosphamide, 2 mg/kg per day (73 patients), plus prednisolone.** MEASUREMENT: Time to remission (primary outcome); change in renal function, adverse events, and cumulative dose of cyclophosphamide (secondary outcomes).
RESULTS: Groups did not differ in time to remission (hazard ratio, 1.098 [95% CI, 0.78 to 1.55]; P = 0.59) or proportion of patients who achieved remission at 9 months (88.1% vs. 87.7%). Thirteen patients in the pulse group and 6 in the daily oral group achieved remission by 9 months and subsequently had relapse. Absolute cumulative cyclophosphamide dose in the daily oral group was greater than that in the pulse group (15.9 g [interquartile range, 11 to 22.5 g] vs. 8.2 g [interquartile range, 5.95 to 10.55 g]; P < 0.001). The pulse group had a lower rate of leukopenia (hazard ratio, 0.41 [CI, 0.23 to 0.71]). LIMITATIONS: The study was not powered to detect a difference in relapse rates between the 2 groups. Duration of follow-up was limited.
CONCLUSION: The pulse cyclophosphamide regimen induced remission of ANCA-associated vasculitis as well as the daily oral regimen at a reduced cumulative cyclophosphamide dose and caused fewer cases of leukopenia.

EULAR Recommendations for the management of primary small and medium vessel vasculitis

Chetan Mukhtyar, Loic Guillevin, Maria C Cid, Bhaskar Dasgupta, Kirsten de Groot, Wolfgang Gross, Thomas Hauser, Bernhard Hellmich, David Jayne, Cees GM Kallenberg, Peter A Merkel, Heiner Raspe, Carlo Salvarani, David GI Scott, Coen Stegeman, Richard Watts, Kerstin Westman, James Witter, Hasan Yazici and Raashid Luqmani

Ann Rheum Dis published online 15 Apr 2008;

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]

Inducción remisión:

CS:

- 3 pulsos MTPDN 1gr/día
- PDN:1 mg/kg peso/día x 3 sem y disminución progresiva a 12,5 mg/dia a los 6 meses

CF: 3 pulsos (0.6 gr/m^2) cada 15 días + pulsos (0.7 gr/m^2) cada 3 semanas hasta remisión (3-6 meses) + 3 pulsos trisemanales de consolidación (media pulsos: 10.1 ± 2.3)

Mantenimiento:

- AZA 2mg/kg/día
- MTX 25 mg/semana
- PDN disminución progresiva de 12,5 mg/día hasta alcanzar 5 mg/día a los 18 meses y stop a los 24 meses (duración media CS 26.9 ± 7.1 meses)

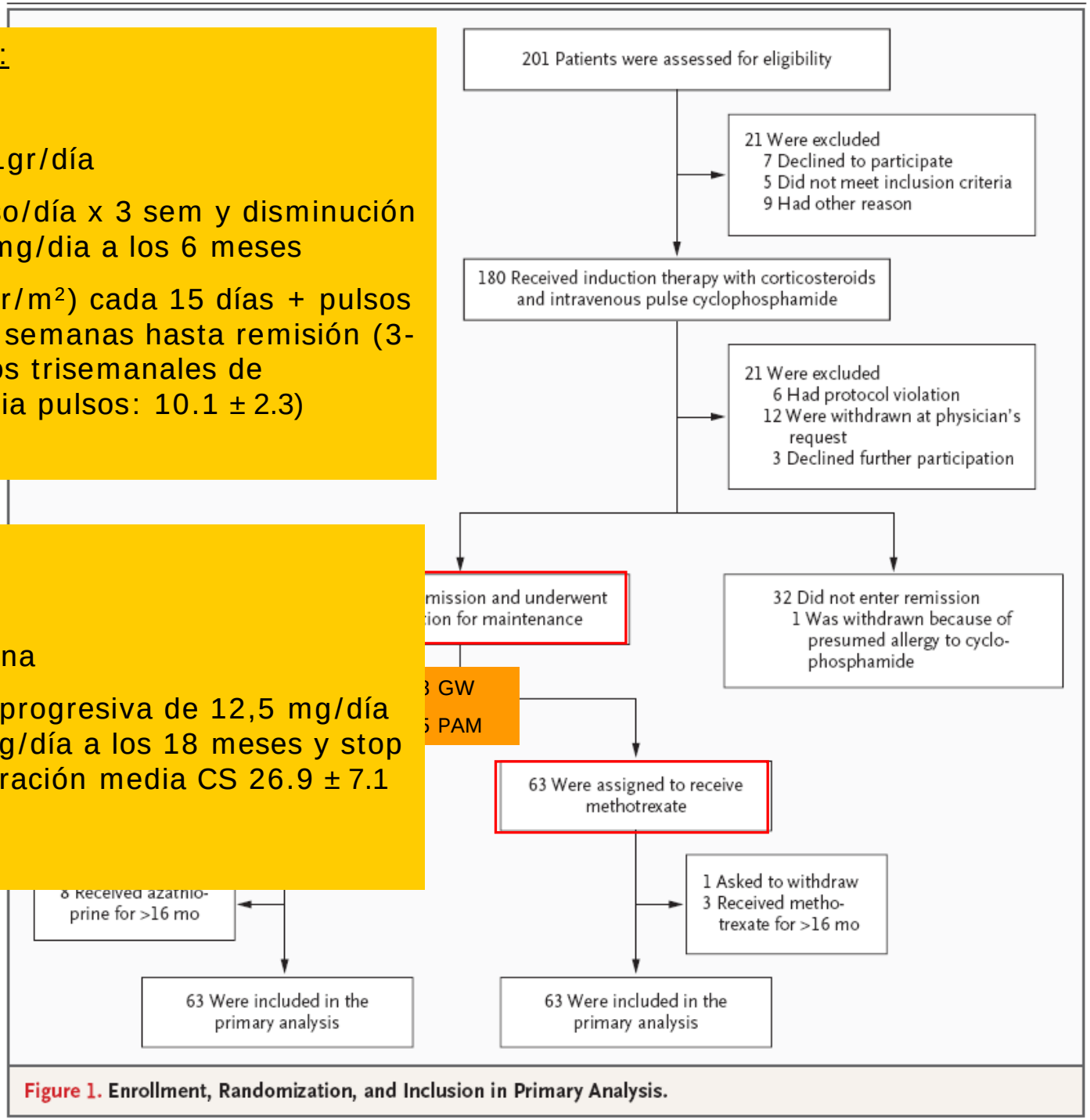
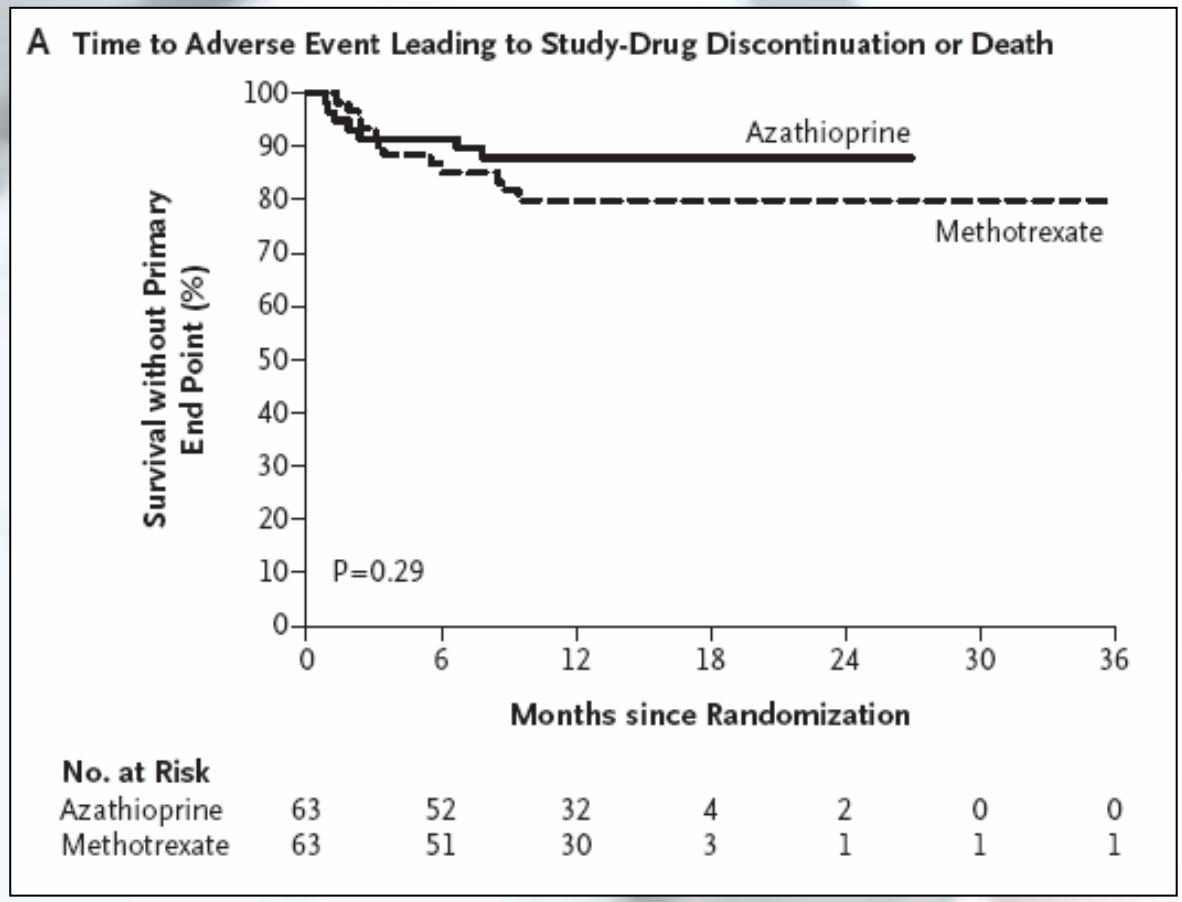


Figure 1. Enrollment, Randomization, and Inclusion in Primary Analysis.



29 AZA/ 35 MTX: al menos un evento adverso (46% vs 56%, p=0.29)

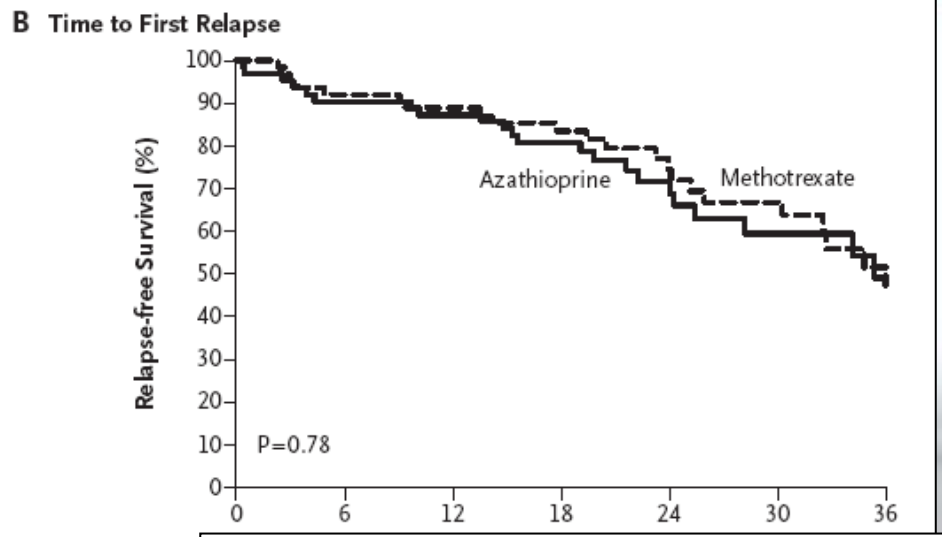
Supresión del fármaco 7 AZA (1%) vs 12 MTX (19%)

HR evento adverso 1.65 para MTX comparado con AZA

23 AZA vs 21 MTX: 1 recidiva

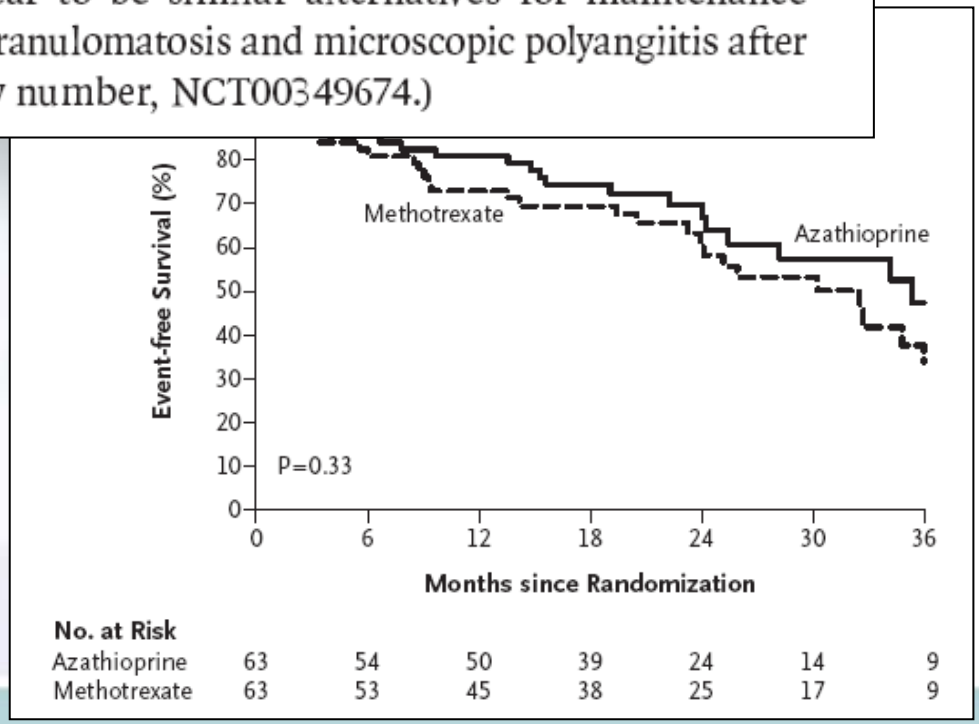
Tiempo medio hasta recidiva: 20.6 ±13.9 meses

43% recidivas tras la supresión del tratamiento



CONCLUSIONS

These results do not support the primary hypothesis that methotrexate is safer than azathioprine. The two agents appear to be similar alternatives for maintenance therapy in patients with Wegener's granulomatosis and microscopic polyangiitis after initial remission. (ClinicalTrials.gov number, NCT00349674.)



14th International Vasculitis and ANCA Workshop
6 June - 9 June, 2009, Lund

Roche EUROIMMUN EURO-DIAGNOSTICA

Randomized trial of mycophenolate mofetil vs azathioprine for maintenance therapy in ANCA-associated vasculitis (IMPROVE)

T Hiemstra, M Walsh, K De Groot, T Hauser, A Mahr, C Pagnoux, L Harper, C Savage, V Tesar, I Neumman, K M Wissing, W Schmitt, D Jayne

IMPROVE: MMF vs AZA

- Objective: to compare MMF with a standard AZA-based regimen for remission maintenance after induction with cyclophosphamide (CYC) and glucocorticoids (CS).
  - Primary endpoint: disease free period.
  - Secondary endpoints: relapse rate, adverse events, BVAS

- Methods:
  - Prospective randomized trial open label
  - 37 centers in 11 European countries between 2002 and 2004
  - newly diagnosed ANCA positive vasculitis and age 18-75
  - Induction therapy: CYC 3 months + CS 1mg/kg/day tappered to 25 mg at 3 months.
  - Maintenance therapy:
    - AZA 2 mg/kg/day x 12 months and then 1 mg/day to 42 months
    - MMF 2 g/day. GC stopped at 24 months

IMPROVE

- Results:
  - 175 patients recruited: 21 excluded during induction (6 by no remission)
  - 154 randomized: 78 AZA and 76 MMF (99 WG, 55 PAM)
  - median age: 58 (18-75)
  - PR3 +: 64.5%, MPO 33%, dual 2.6%
  - No differences in demographic and laboratory data at baseline.
  - No differences in organ involvement

IMPROVE

- Results:
  - cumulative incidence of relapse:46%
    - 30/79 (38%) in AZA

Conclusions:

- MMF was not superior to AZA for maintenance therapy in ANCA associated vasculitis
- time to first relapse was shorter in MMF group
- incidence of relapse was higher in MMF group

  - systems involved at relapse: more renal in MMF
  - no differences in first major relapse
  - adverse events: 19 in AZA and 13 in MMF (p= 0.49).No differences in infection or cardiovascular events

Randomized trial of rituximab vs cyclophosphamide for ANCA-associated renal vasculitis: RITUXIVAS

R Jones, JW Cohen Tevaert, T Hauser, R Luqmani, CHA Peh, C Savage, M Segelmark, V Tesar, PV Paasen, M Walsh, D Walsh, K Werstman, D Jayne

- Objetive: to compare RTX vs standard induction therapy with CYC + CS for new ANCA associated vasculitis. Primary endpoint: sustained remission at 12 months. Secondary endpoint: adverse events

- Results: 44 patients randomized (50% WG, 60% PR3 +):
  - 33 RTX 4 x 375 mg/m2 + 2 x 15 mg/kg iv CYC + CS
  - 11 iv CYC 6-10 x 15 mg/kg + CS

- Primary endpoint:
  - Sustained remission: 25/33 (76%) RTX vs 9/11 (82%) CYC (p=0.68)
  - Severe adverse events: 42% RTX (31 events, 14 patients) vs 35% CYC (12 events, 4 patients), p= 0.60
  - 8 patients died: 6/33 (18%) RTX vs 2/11 (18%) CYC

- Secondary endpoints:
  - remission (BVAS= 0 for 2 evaluations) in 27/33 (82%) RTX vs 10/11 (91%) CYC
  - no significant difference in time to remission
  - 89% in RTX and 81% in CYC became ANCA negative by 6 months
- Conclusions:
  - there is no evidence that a RTX-based regimen is less effective than iv CYC for remission induction in ANCA associated vasculitis.
  - severe adverse events were similar in both groups
  - RTX spares the use of CYC

Deoxyspergualin in relapsing and refractory Wegener's granulomatosis

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]

Ann Rheum Dis 2009;**68**:1125–1130

Proteína derivada del *Bacillus laterospolus*
Inhibe proliferación linfocitos T y de los monocitos

Objectives: Conventional th
lomatosis with cyclophospha
limited by incomplete remiss
The efficacy and safety of a
suppressive drug, deoxyspe
patients with relapsing or re

Methods: A prospective, international, multicentre, single-limb, open-label study. Entry required active Wegener's granulomatosis with a Birmingham vasculitis activity score (BVAS) ⩾4 and previous therapy with cyclophosphamide or methotrexate. Immunosuppressive drugs were withdrawn at entry and prednisolone doses adjusted according to clinical status. Deoxyspergualin, 0.5 mg/kg per day, was self-administered by subcutaneous injection in six cycles of 21 days with a 7-day washout between cycles. Cycles were stopped early for white blood count less than 4000 cells/mm^3. The primary endpoint was complete remission (BVAS 0 for at least 2 months) or partial remission (BVAS <50% of entry score). After the sixth cycle azathioprine was commenced and follow-up continued for 6 months.

Results: 42/44 patients (95%) achieved at least partial remission and 20/44 (45%) achieved complete remission. BVAS fell from 12 (4–25), median (range) at baseline to 2 (0–14) at the end of the study ($p<0.001$). Prednisolone doses were reduced from 20 to 8 mg/day ($p<0.001$). Relapses occurred in 18 (43%) patients after a median of 170 (44–316) days after achieving remission. Severe or life-threatening (⩾ grade 3) treatment-related adverse events occurred in 24 (53%) patients mostly due to leucopaenias.

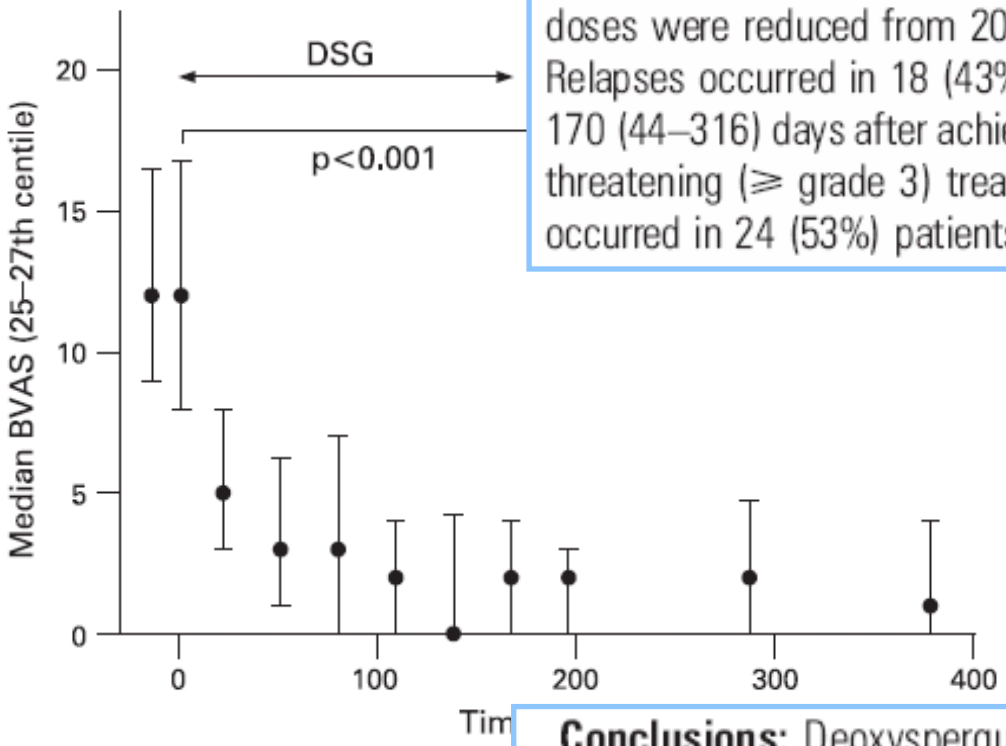


Figure 3 Disease activity as meas
activity score (BVAS). DSG, deoxys

Conclusions: Deoxyspergualin achieved a high rate of disease remission and permitted prednisolone reduction in refractory or relapsing Wegener's granulomatosis. Adverse events were common but rarely led to treatment discontinuation.

Risk factors for major infections in Wegener granulomatosis: analysis of 113 patients

C Charlier, C Henegar, O Launay, C Pagnoux, A Berezné, B Bienvenu, P Cohen, L Mouthon, L Guillevin

Ann Rheum Dis 2009;**68**:658–663

However, major infections appeared closely associated to immunosuppression. Only 7.6% of all infectious episodes arose after immunosuppressants had been stopped, while 71.7% occurred during induction therapy or relapses and 39.6% within the first year of WG treatment. CYC and high-doses of CS (>20 mg/day), which are the pillars of WG induction treatment, may indeed be responsible for this early development of major infections, as no significant association has been detected between maintenance drugs and infectious complications. Other infections were delayed from the moment of WG induction therapy, reflecting the cumulative effect of the treatment-induced immunosuppression.

Churg-Strauss Syndrome in Patients Treated With Omalizumab.
Chest 2009
Wechsler ME, Wong DA, Miller MK, Lawrence-Miyasaki L.

From the Brigham & Women's Hospital and Harvard Medical School (Dr. Wechsler), Boston, MA; and Genentech, Inc (Dr. Wong, Ms. Miller, and Ms. Lawrence-Miyasaki), South San Francisco, CA.

Background: Churg-Strauss Syndrome (CSS) is a rare systemic vasculitis associated with asthma, eosinophilia, sinusitis, and pulmonary infiltrates. CSS has been reported in association with asthma therapies.
Methods: The objective is to describe the characteristics of CSS in patients treated with the anti-IgE antibody omalizumab (Xolair). A retrospective review of available data to identify cases of CSS was performed using the Novartis Argus global drug safety database for omalizumab in asthma patients.
Results: We identified 34 potential cases of CSS. Of these, 13 of the 34 fulfilled at least 4 of the 6 criteria identified in the American College of Rheumatology Classification Criteria. Eight of these 13 definite or probable cases (62%) had CSS symptoms prior to omalizumab or described symptom onset just after corticosteroid weaning. Six of the 13 (46%) patients were confirmed as treated with corticosteroids for what was perceived to be severe asthma; when corticosteroids were tapered in conjunction with omalizumab treatment, CSS symptoms appeared just after the tapering. There were 4 other cases of possible CSS, and the remaining 17 cases were judged to not have CSS.
Conclusions: CSS may develop in patients taking asthma medications who have an underlying eosinophilic disorder that is unmasked by the withdrawal of corticosteroids, or in patients who delay therapy in favor of other medications. **Omalizumab treatment may unmask CSS due to the weaning of corticosteroids in some asthma patients, or may delay corticosteroid treatment allowing for CSS to manifest.** Trial registration ClinicalTrials.gov Identifier: NCT00252135.