Evidence-based management of ANCA-related vasculitides

Simon Carette, MD, MPhil, FRCPC
Professor of Medicine
University of Toronto

Disclosures

- Advisory Board, Roche

Objectives

1. Present evidence-based strategies for the management of ANCA-related vasculitides using conventional drugs

Cyclophosphamide remains the drug of choice in 2012 for the induction of remission in life or organ-threatening manifestations of ANCA related vasculitides

Cyclophosphamide

Oral or IV pulse?

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)

Annals Intern Med 2009;150:670-80

Inclusion criteria

- NEWLY diagnosed WG, MPA or renal-limited MPA
- Renal involvement due to active vasculitis
  - serum creatinine level >150μmol/L
  - biopsy showing necrotizing GN
  - red cell casts or hematuria (> 30 RBC/HPF) and proteinuria (>1 g/day)
- Confirmatory histology or ANCA positivity

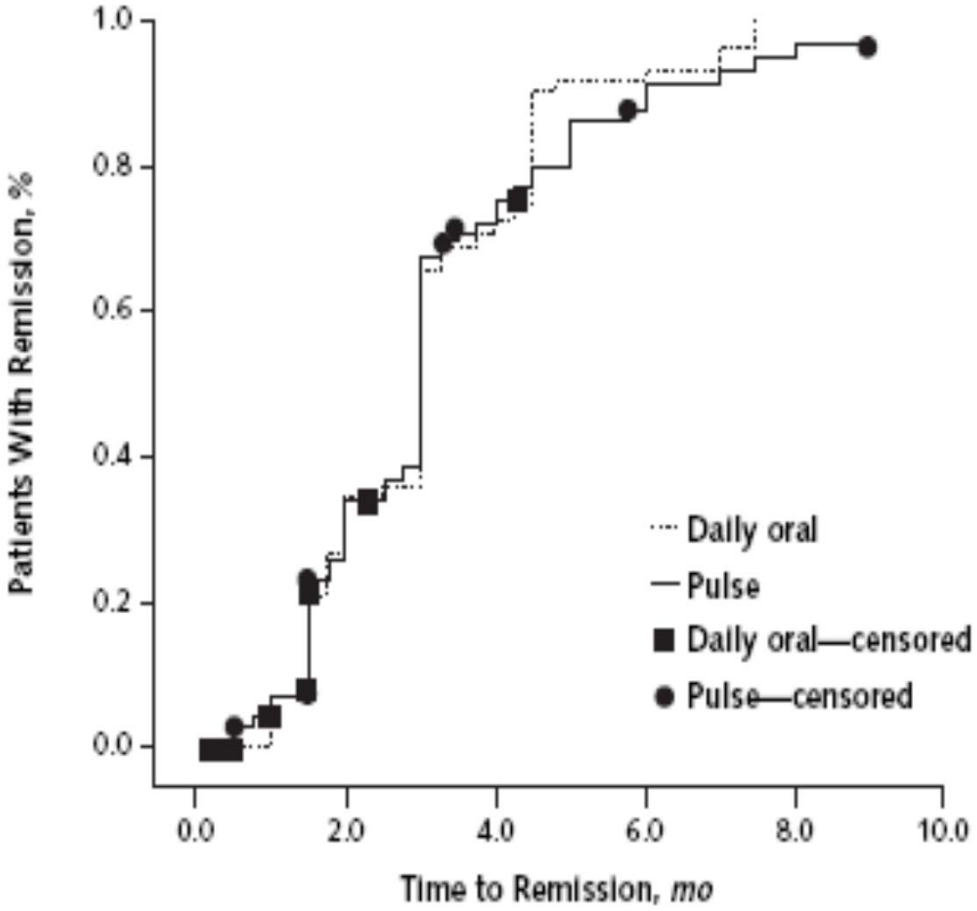
Interventions

- IV CYC 15 mg/kg q 2 weeks x 3 and q 3 weeks until 3 months after remission*

  *** or oral pulses 5 mg/kg x 3 consecutive days**

- Oral cyclophosphamide
  - 2 mg/kg/day until remission
  - **1.5 mg/kg/day for another 3 months**

Time to remission



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

HR 1.098
95% CI 0.78 to 1.55
P= 0.59

Relapse

- 19 (14.5%) of the 131 patients who achieved remission had a relapse
  - Pulse CYC: 13 (7 major, 6 minor)
  - Oral CYC : 6 (3 major, 3 minor)

    HR: 2.01 (CI, O.77 to 5.30)

Deaths

- 14 (4.7%) of the 149 patients died
  - Pulse CYC: 5*
  - Oral CYC : 9** P=0.79

  * Sepsis (1), bowel perforation (1), MI (1), PE (1), pharyngeal cancer (1)

  **Sepsis (5), progressive disease (2), pulmonary fibrosis (1), GI bleed (1)

Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up

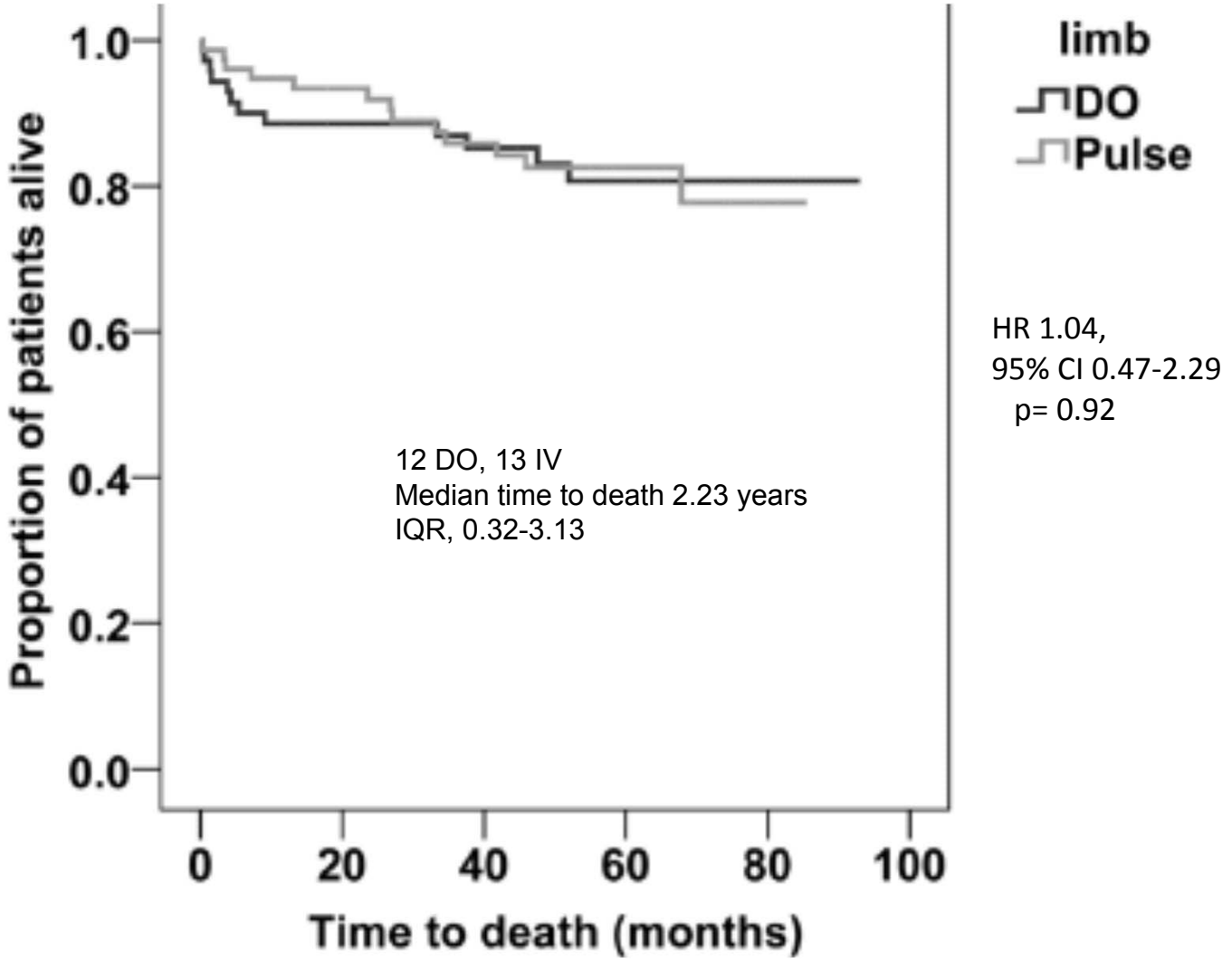
Lorraine Harper,[1] Matthew D Morgan,[1] Michael Walsh,[2] Peter Hoglund,[3] Kerstin Westman,[4] Oliver Flossmann,[5] Vladimir Tesar,[6] Phillipe Vanhille,[7] Kirsten de Groot,[8] Raashid Luqmani,[9] Luis Felipe Flores-Suarez,[10] Richard Watts,[11] Charles Pusey,[12] Annette Bruchfeld,[13] Niels Rasmussen,[14] Daniel Blockmans,[15] Caroline O Savage,[1] David Jayne[1] on behalf of EUVAS investigators

Harper L et al Ann Rheum Dis 2012;71:955-960

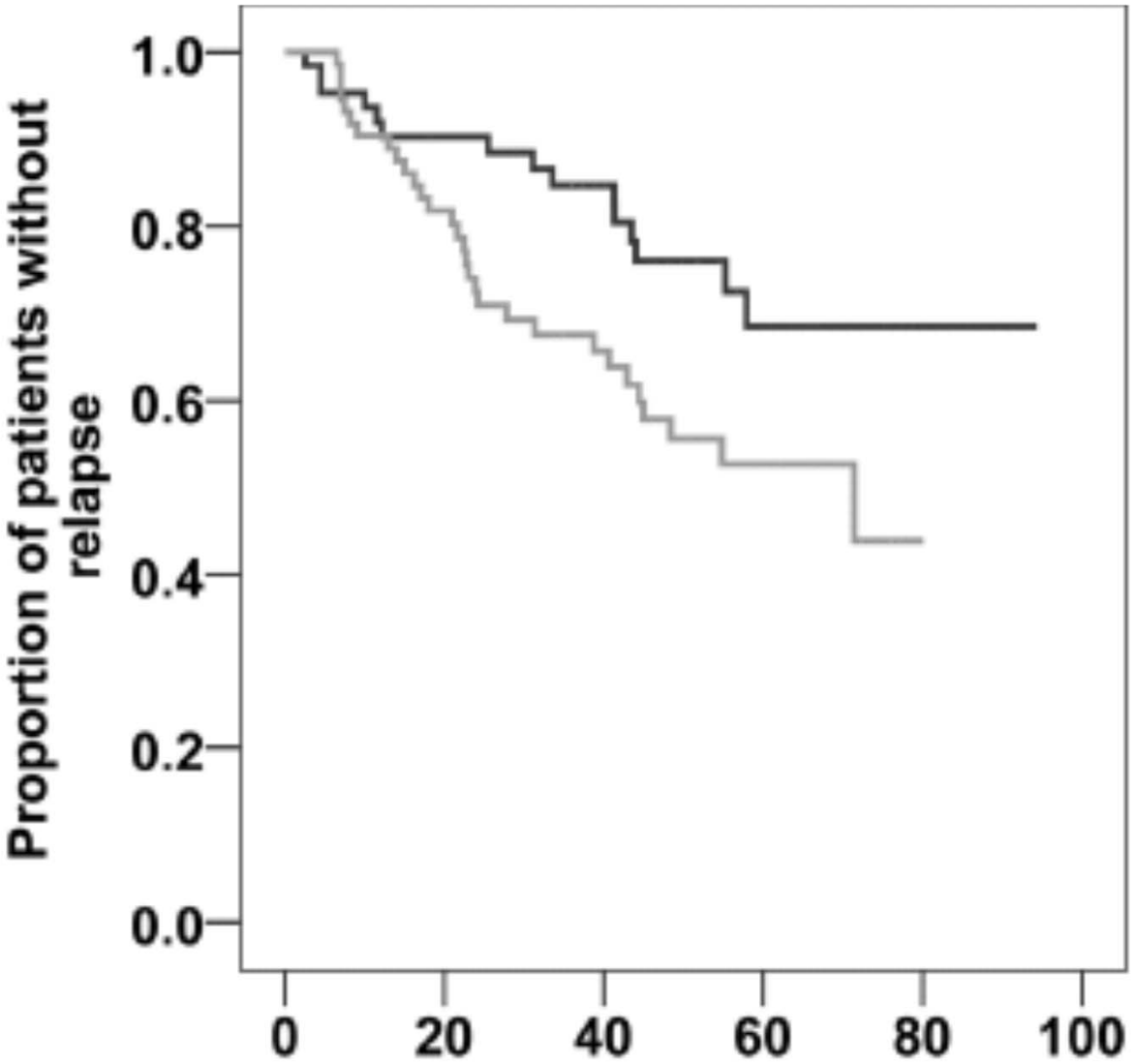
Patient population

- 134/149 patients
- Median follow-up: 4.3 years (2.95-5.44)

Risk of death by treatment allocation

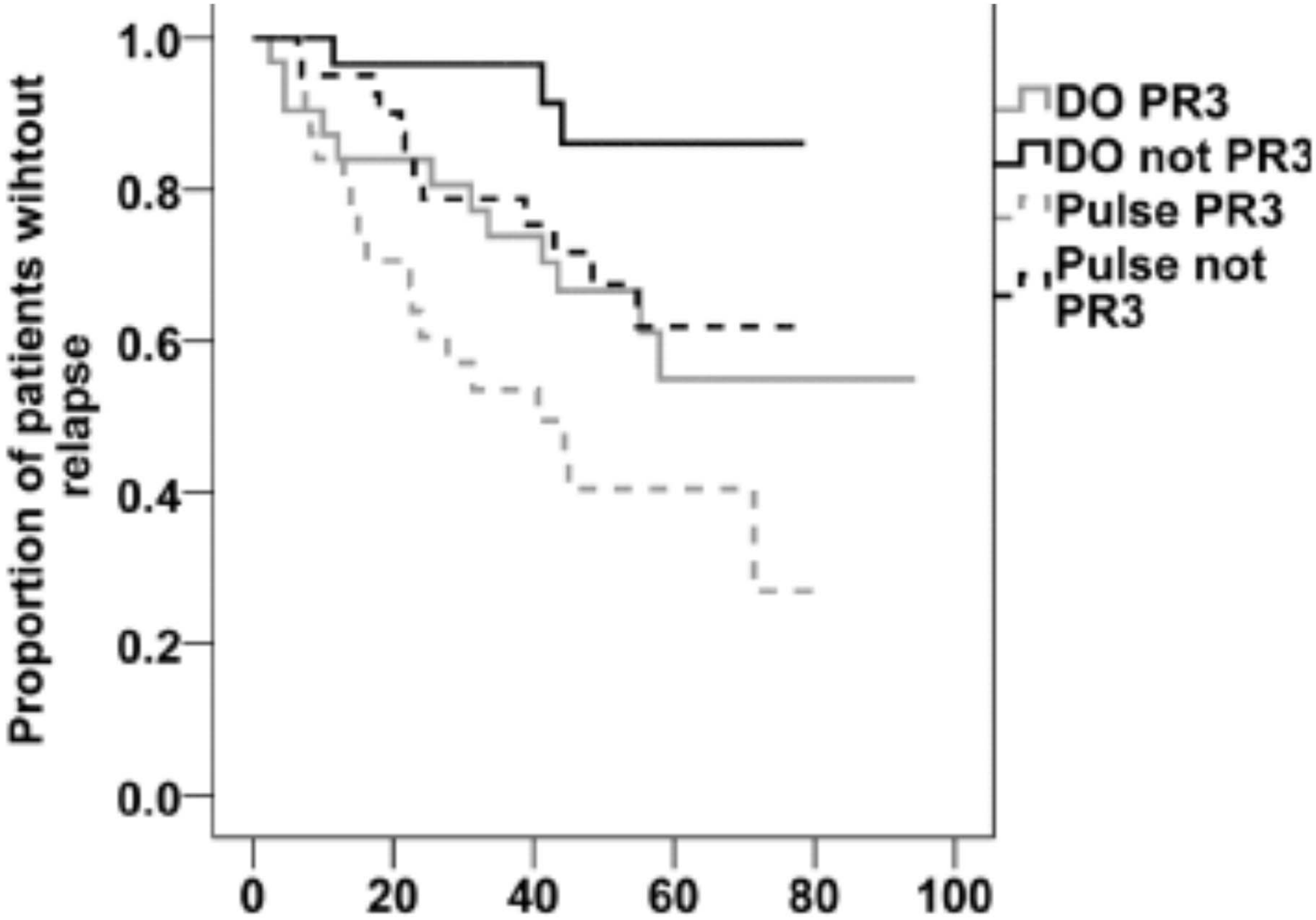


Risk of relapse by treatment allocation



HR 0.50
95% CI, 0.26 to 0.93
P= 0.029

Risk of relapse depending on limb and ANCA status



Factors associated with relapse in the multivariate analysis

		95.0% CI		
	HR	Lower	Upper	p Value
DO vs pulse	0.46	0.25	0.86	0.015
PR3-ANCA positive vs negative	2.47	1.32	4.59	0.004

ANCA, antineutrophil cytoplasm autoantibodies; PR3-ANCA, antiproteinase 3 antibodies; DO, daily oral.

Adverse events

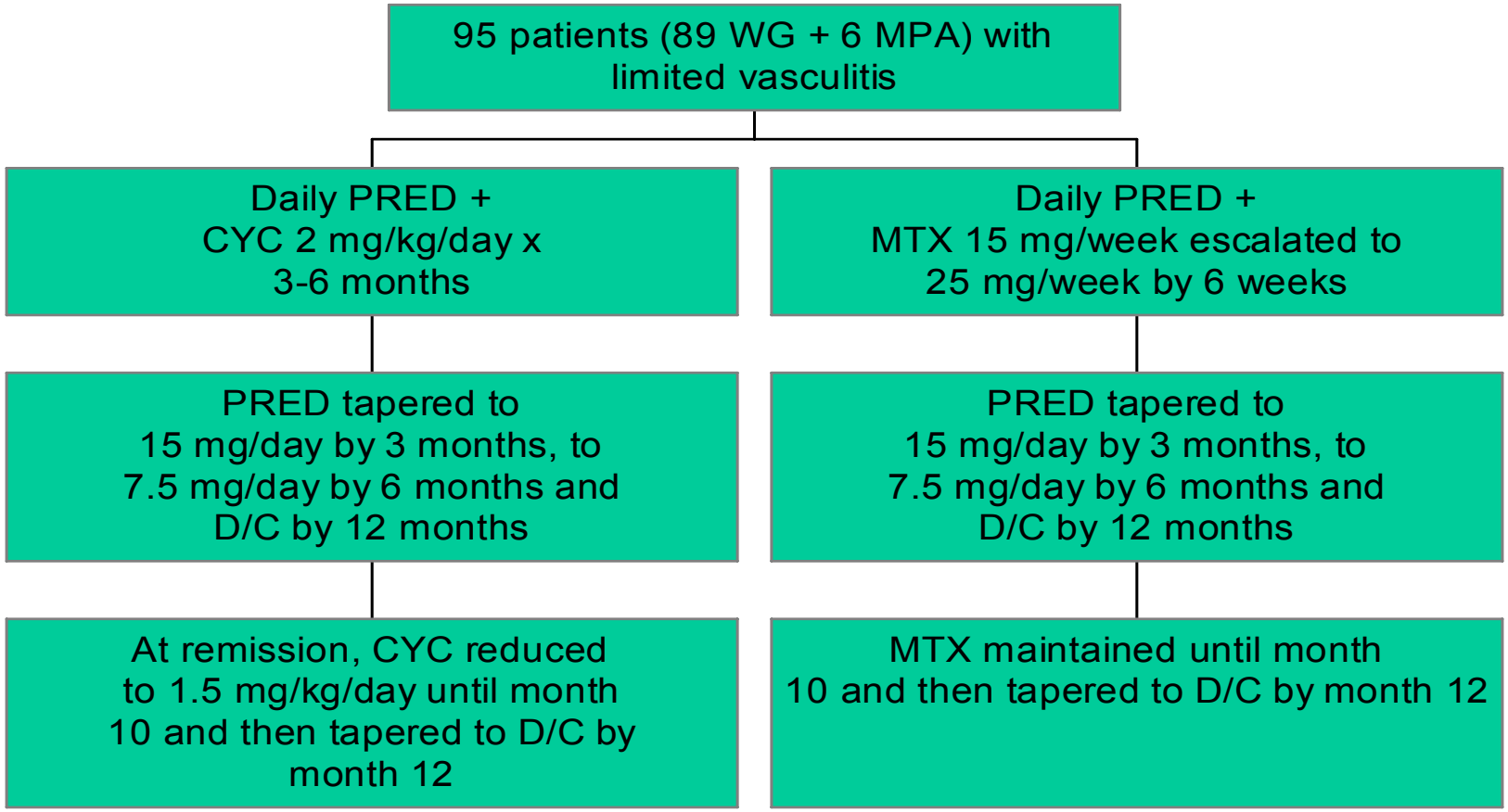
	DO (n=60)	Pulse (n=67)
Malignancy	6	8
Severe infection requiring admission to hospital	15	19
Cardiovascular disease	3	6
Cerebrovascular disease	0	2
Venous thrombotic event	6	6
New onset diabetes mellitus	5	8
Fracture	3	6

DO, daily oral.

Principles of management

- The use of cyclophosphamide should be restricted to 3-6 months Jayne D. et al NEJM 2003;349:36
- Metotrexate or azathioprine can be used interchangeably to maintain remission Pagnoux C. et al NEJM 2008;359:2790
- Methotrexate can be used to induce remission in patients with non life and/or organ threatening manifestations de Groot K. et al Arthritis Rheum 2005;52:2461

Trial design of NORAM



Arthritis Rheum 2005;52:2461-69

NORAM RESULTS

- Remission rate at 6 months:
  - CYC: 94%
  - MTX: 90% P= 0.78
- Relapse rate at 18 months:
  - CYC: 47%
  - MTX: 70% P=0.02
- Cumulative steroid dose:
  - CYC: 6.2 gm (5.4-7.9)
  - MTX: 8.8 gm (6.3-11.1) p= 0.001

Long-term outcome of a clinical trial comparing methotrexate to cyclophosphamide for remission induction of early systemic ANCA-associated vasculitis

Faurschou M et al Arthritis Rheum 2012 May 21, ahead of print

Methods

- Outcome questionnaires sent to investigators
- MTX (n=49), CYC (n=46)
- Median duration of follow-up 6 years (0.1-10.8)

Results

- No difference in mortality and SAE
- MTX treated patients were exposed to steroids, CYC and other immunosuppressive agents for longer periods than CYC treated patients ($p=0.004$; $p=0.037$; $p=0.031$)
- Cumulative relapse-free survival lower in the MTX group ($p=0.056$)

Authors' conclusions

First-line treatment with MTX was associated with less effective disease control than CYC-based Induction-therapy

Principles of management

- Mycophenolate mofetil is inferior to azathioprine to maintain remission Hiemstra TF. et al JAMA 2010;304:2381

Can we devise more effective strategies to prevent relapses?

MAINRITSAN

- Relapse rate remains high after achieving remission with CS + CYC
  - 18-month: 15%
  - 28-month: 28%

MAINRITSAN

- 114 newly diagnosed (91) or relapsing (23) patients with GPA or MPA who achieved remission with CS+CYC
- Randomized to:
  - 500 mg RTX infusion on D1, D15, 5.5 months and every 6 months x 2 (total of 5 infusions over 18 m)
  - AZA 2 mg/kg x 22 m
- Primary outcome: rate of relapse at 28 m

Guillevin et al. Arthritis Rheum 2012; S706

MAINRITSAN

- Manifestations at diagnosis or relapse:
  - ENT 88 (77.2%)
  - Lung 69 (60.5%)
  - Kidney 82 (71.9%)

MAINRITSAN

- Major Relapse:
  - RTX: 2 (3.6%)
  - AZA: 16 (27.1%)
- Serious adverse events:
  - RTX: 15
  - AZA: 18

Conclusions

- 500 mg of RTX every 6 months was superior to AZA in maintaining remission

How long should we keep patients on maintenance therapy?

Short vs long-term Maintenance?

- Retrospective chart review
- All patients with GPA seen at the Cleveland Clinic between 1992 and 2010

Springer J et al. Arthritis Rheum 2012: S706

Inclusion criteria

1. 1990 ACR criteria for GPA
2. Induction with either oral CYC or MTX
3. Remission achieved
4. Maintenance started immediately after discontinuation of induction therapy
5. Maintenance with either AZA or MTX
6. Duration of remission >18 months
7. Documentation of remission and relapse

Results

- 157 patients out of 797 screened
- CYC (78%), MTX (22%)
- HR for relapse long-term vs short term:

29% reduction 0.71 (95%CI 0.43, 1.18)

- Treatment > 36 months:

66% reduction 0.34 (95%CI 0.15, 0.76)

P= 0.008

Results

- No difference in severity of relapse between groups as measured by BVAS/WG
- **Relapse in long-term group occurred in 88.9% after stopping therapy**
- **Of patients on therapy at relapse, 52% were on <15 mg/wk MTX and 75% on ≤ 50 mg/d AZA**

Conclusions

- Patient on long-term maintenance therapy have fewer relapses and a similar adverse events profile than patients treated < 18 m
- Discontinuation and low doses of maintenance therapy are associated with a high relapse rate

Should we treat patients ≥ 65 years as aggressively as younger patients?

CORTAGE TRIAL

- Multicenter RCT
- Patients ≥ 65 years old
- Newly diagnosed SNV (PAN, GPA, MPA, EGPA)

Pagnoux C et al. Arthritis Rheum 2012; S708

CORTAGE TRIAL

- Conventional therapy:
  - 28 months CS alone or combined with IV CYC 500 mg/m^2 q 2-3 weeks until remission ➔ AZA or MTX
- Experimental regimen:
  - 9 months CS with IV CYC 500 mg fixed-dose q 2-3 weeks (maximum 6) ➔AZA or MTX
- Primary outcome: Time to first SAE
- Secondary outcomes: first remission, death, relapse rates

Results

- 108 patients (July 2005-Feb 2008)
- Mean age : 75.2 ±6.3 yr
- No difference in baseline manifestations
- Mean follow-up: 28 ± 11mo

Results

- Primary endpoint (HR first SAE EXP/Conv):

0.61 (95% CI 0.38-0.97)

- Secondary endpoints:

  No difference in:

  – Rate of remission: (90% vs 85%)
  – Death: (15% vs 25%)
  – Relapses: (47% vs 46%)

Conclusion

- Limiting exposure to CS and fixed low-dose CYC pulses was associated with a lower rate of SAE and similar 3-yr remission and relapses rates

New standard of care for the elderly?