The Treatment of Pauci-Immune Vasculitis

Presented to

Creto-Cypriot Rheumatology Forum

Presented by

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Saturday, October 24 2015

Child Theodora C.

Age now: 10 years

Age 1.5 years old:	Allergic Rhinitis and Sinusitis
	Right 'pneumonia', chest drain
Age 2 years:	Pyrexia, exanthema, ?Varicella
	Pericarditis, pneumonitis, cutaneous vasculitis, gangrene of 3/5 digits of Right hand
	ANCA –negative
	IV Cyclophosphamide and Steroids
	IV Epoprostenol
	Excellent Recovery
Investigations:	Normal Renal Arteriography

Child Theodora C.

Age 3 years old: Well. Weight 15 kg

Azathioprine and Prednisolone

Urinary Infections

Respiratory Infections

Age 4.5 years old: Asymptomatic Right Middle Lobe Pneumonia

Positive p-ANCA

Increased Azathioprine+Oral Prednisone

Minor Neutropenia 1184 (normal TPMT)

Age 6: Varicella Relapse

Positive c-ANCA

Increased Azathioprine

Child Theodora C.

Age 7 years old: **Hypertension, Haematuria, high Creatinine**

Pyrexia, Urinary Infection

Left Renal Biopsy under GA:

Acute Pyelonephritis

1 Granuloma, 30% Crescents

(*GOS: Diffuse Endocapillary GN*)

Negative IF (*except C3*)

IV MethylPrednisolone Pulses *3

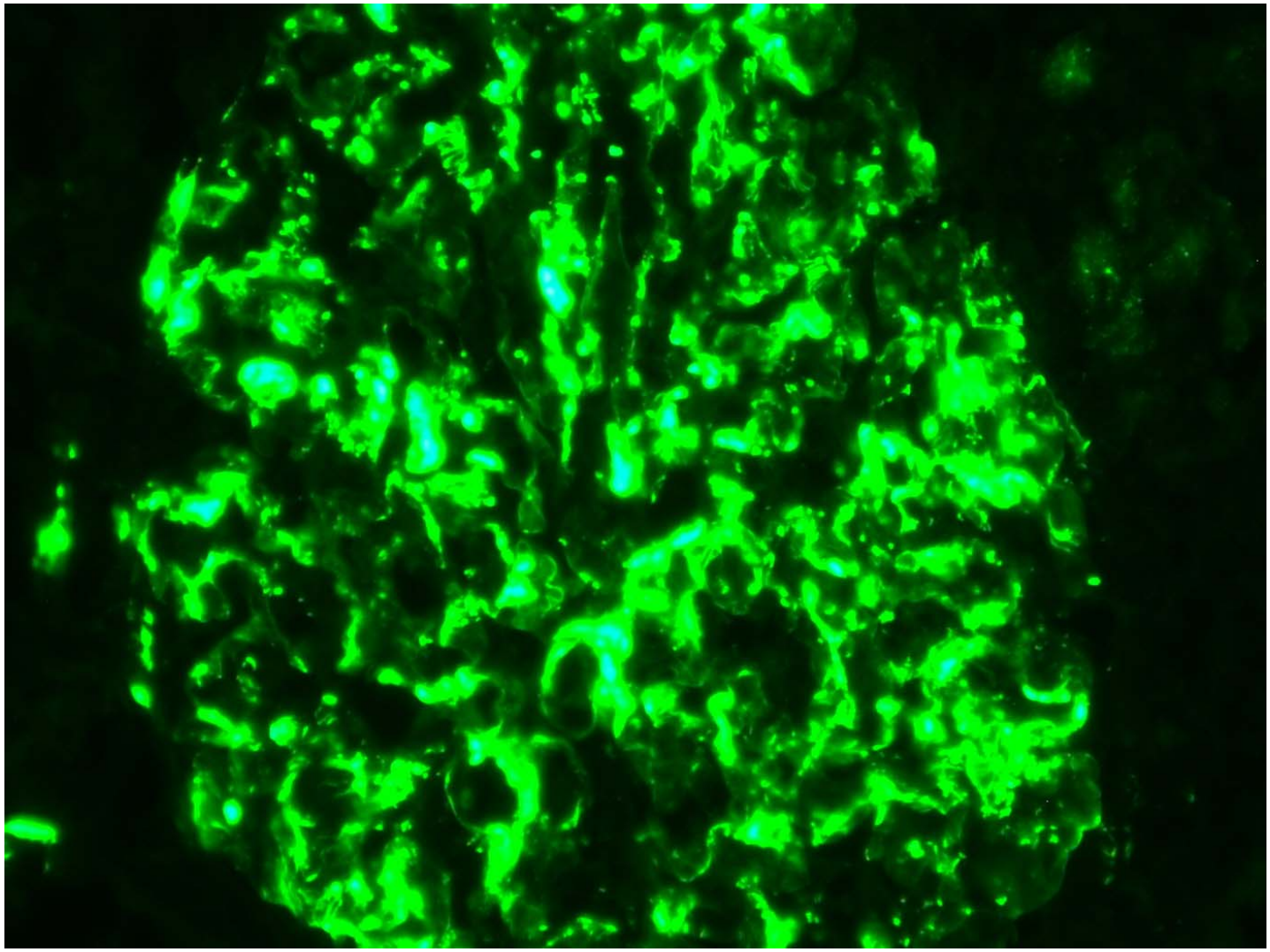
IV Rituximab 375 mg/sqm *4 weeks +

Phase in MMF 600 mg bd

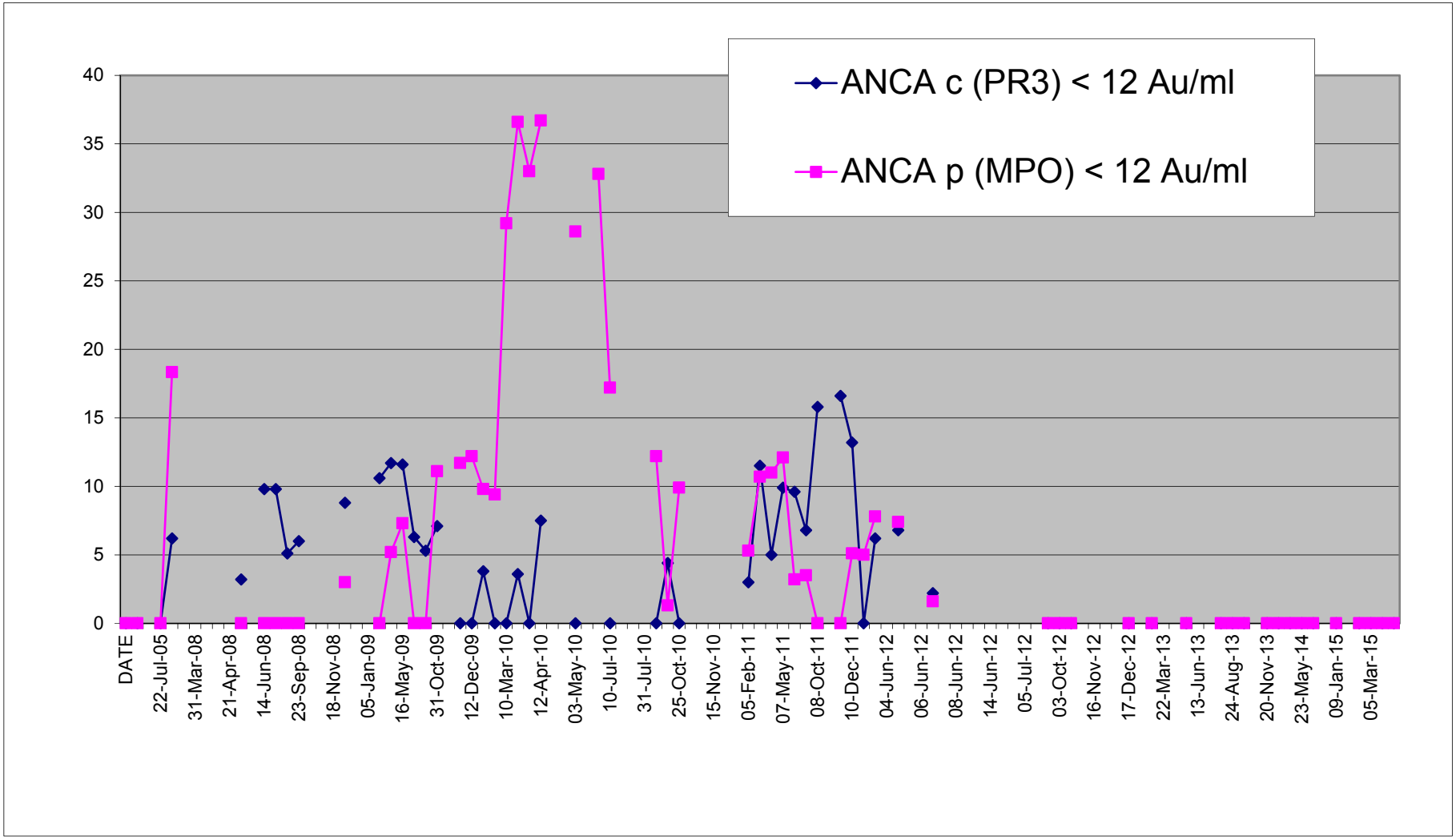
Salmonella Enteritis

Cystitis

C3 Immunofluorescence



ANCA Titres


ANCA c (PR3) < 12 Au/ml
ANCA p (MPO) < 12 Au/ml
40
35
30
25
20
15
10
5
0
DATE
22-Jul-05
31-Mar-08
21-Apr-08
14-Jun-08
23-Sep-08
18-Nov-08
05-Jan-09
16-May-09
31-Oct-09
12-Dec-09
10-Mar-10
12-Apr-10
03-May-10
10-Jul-10
31-Jul-10
25-Oct-10
15-Nov-10
05-Feb-11
07-May-11
08-Oct-11
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16-Nov-12
17-Dec-12
22-Mar-13
13-Jun-13
24-Aug-13
20-Nov-13
23-May-14
09-Jan-15
05-Mar-15

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Management of Pauci-Immune Vasculitis

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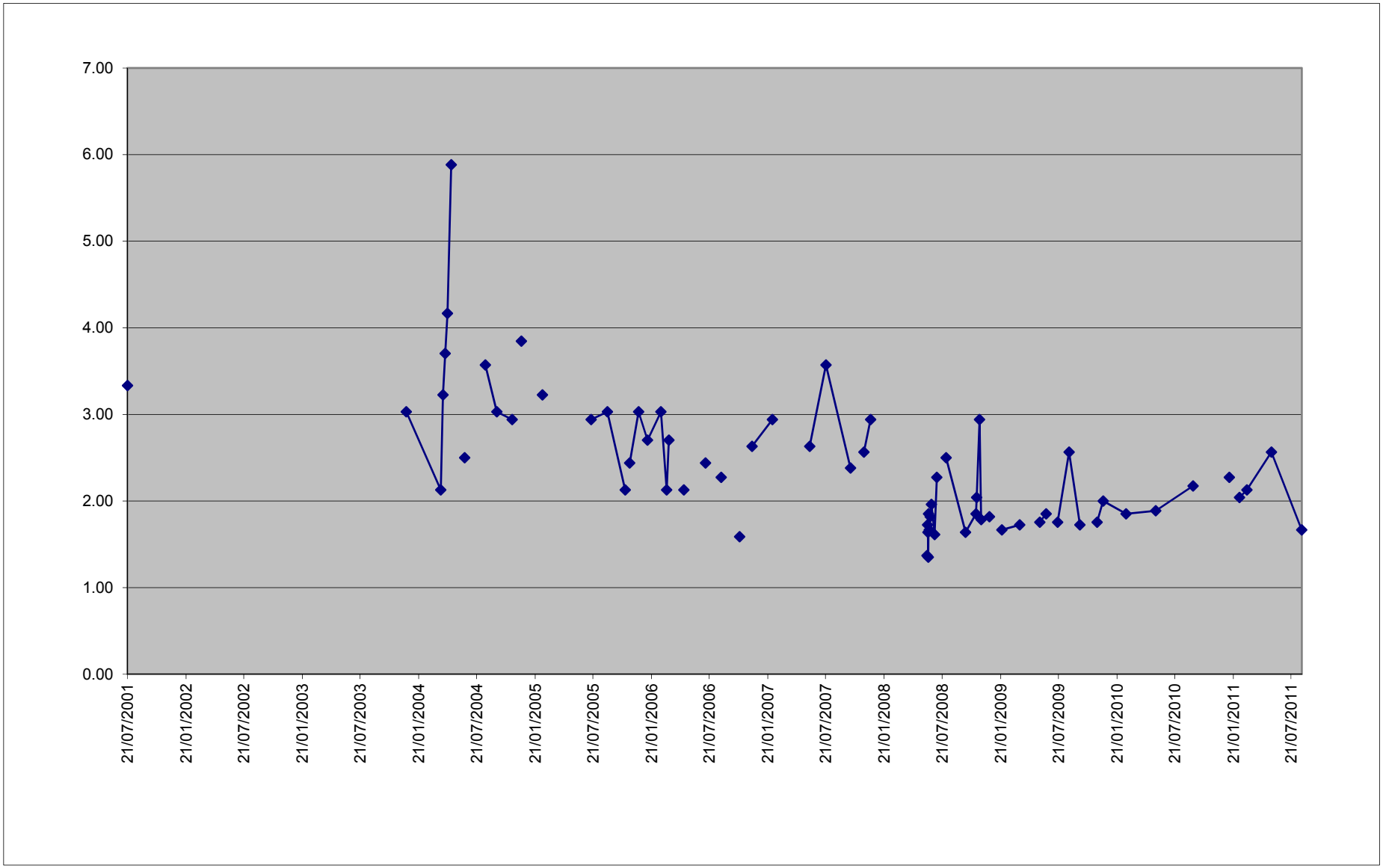
1/Creatinine



Child Theodora C.

Age 8 years old: ***MMF 1200 mg bd in error***

Cystitis

Rotating Antibiotics, Prophylactic Antibiotics

Acute Pyelonephritis

Age 9 years old: Rising CRP. Normal CD19+ cells

IV Rituximab 500 mg

absence of CD19 & CD20 & CD25

Age 10 years old: Well. **Stop Steroids**

Child Theodora C.

WELL Weight 40 kg

PRESENT DRUGS

1. **Mycophenolate Mofetil suspension 600 mg morning and night**
2. **Enalapril 5 mg night**
3. **Cholecalciferol 800 iu daily**
4. **Co-Trimoxazole 240 mg night**

CURRENT TESTS

Hb 12.8, ESR 12, CRP 5-23 mg/l, ANCA negative

Creatinine 0.4-0.6 mg/dl, urinalysis clear microalbuminuria 10 mg/g

Ann Intern Med. 1978 Nov;89(5 Pt 1):660-76.

The spectrum of vasculitis: clinical, pathologic, immunologic and therapeutic considerations.

Fauci AS, Haynes B, Katz P.

Abstract

Vasculitis is a clinicopathologic process characterized by inflammation and necrosis of blood vessels. Certain disorders have vasculitis as the predominant and most obvious manifestation, whereas others have various degrees of vasculitis in association with other primary disorders. Within the entire spectrum of vasculitis virtually any size or type of blood vessel in any organ system can be involved. Most of the vasculitides can be associated directly or indirectly with immunopathogenic mechanisms. In this regard, immune complex mediation is being increasingly recognized as the underlying mechanism in several of the vasculitides. With clinical, pathologic, and immunologic criteria, certain vasculitic disorders can be clearly recognized and categorized as distinct entities, whereas in others there is an overlap of different diseases within a broader category. In recent years, several of the more serious vasculitides, such as Wegener's granulomatosis and the systemic necrotizing vasculitides of the polyarteritis nodosa group, which formerly had extremely poor prognoses, have been shown to be extraordinarily responsive to chronic low-dose cytotoxic therapy, particularly cyclophosphamide

Trials of Induction Treatment

1. **ORAL Cyclophosphamide** -NIH, 1992
2. **CYCAZAREM** -EUVAS, 2003
3. **RAVE** -NIH, 2010
4. **RITUXVAS** -EUVAS, 2010
5. **IMPROVE** -2010
6. **CGDN** -*last* 2015

Guidelines

1. **KDIGO** -ISN, 2011

Oral Cyclophosphamide NIH.

Hoffman GS1, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, Rottem M, Fauci AS. ***Wegener granulomatosis: an analysis of 158 patients.*** *Ann Intern Med. 1992 Mar 15;116(6):488-98*

TRIAL INDUCTION	DESIGN	SUCCESSFUL REMISSION	FOLLOW-UP 8 YEARS	DEATHS AND SEVERE CRF
PATIENTS GPA only	158			
REGIMEN A 133	Oral Daily Cyclophosphamide + Prednisone For 2 years	Improvement 90%	Complete Remission 75% Sustained 5 years >50% Lower Relapse	Survival 80% Death due to disease or treatment 11% ESRD, 42% CKD3-4 Deafness 35%, Saddle Deformity 28%, Tracheal Stenosis 13%
REGIMEN B 8	Oral Daily Cyclophosphamide for 2 years			Possibly More Infections
REGIMEN C 6	Oral Cytotoxic + Steroids			
REGIMEN D 10	Steroids alone			

CYCAZAREM *David Jayne, F.R.C.P., Niels Rasmussen, M.D., Konrad Andrassy, M.D for EUVAS*
N Engl J Med 2003; 349:36-44

TRIAL INDUCTION	DESIGN	SUCCESSFUL REMISSION	FOLLOW-UP	ADVERSE EVENTS
PATIENTS	155		Less Relapse with MPA	10% in induction
REGIMEN A 133	Oral Daily Cyclophosphamide 2 mg/kg/day+ Prednisone Induction, Cyclophosphamide Maintenance	93% 77% ≤ 3 months 16% between 3-6 months	Relapse 13.7% at 18 months	10%
REGIMEN B	Azathioprine Maintenance		Relapse 15.5%	11%

Management of Pauci-Immune Vasculitis

Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomised trial.
De Groot K, Harper L, Jayne DR et al, for EUVAS. Ann Intern Med 2009; 150(10):670

TRIAL INDUCTION	DESIGN	SUCCESSFUL REMISSION	FOLLOW-UP 4.3 YEARS	DEATHS AND SEVERE CRF
PATIENTS	149 ALL Methyl-Pred 1 g iv, 3 pulses Oral Pred. 1 mg/kg/day		134 Patients Retrospectively	
REGIMEN A 161	IV Cyclophosphamide 15 mg/kg Pulses every 2-3 weeks	88% at 9 months, most 2-6 months	More Relapses 54%, *Stat. insign.* At least one Relapse 40% Lower leucopenia 26%	Deaths same 9.7% ESRD same 13%
REGIMEN B 112	Oral Daily Cyclophosphamide 2 mg/kg/day	88% at 9 months, most 2-6 months	Lower Relapse 21% *Stat. insign.* At least one Relapse 21% Higher leucopenia 45%	Death same 8.9% ESRD same 11%

RITUXVAS *Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis.*
Rachel B. Jones, Jan Willem Cohen Tervaert, Thomas Hauser et al
for the European Vasculitis Study Group. N Engl J Med 2010; 363:211-220

TRIAL	DESIGN New Diagnoses	MAINTENANCE	SUCCESSFUL REMISSION	FOLLOW-UP 12 MONTHS	ADVERSE EVENTS
PATIENTS 44	ALL Methyl-Pred 1 g iv, 3 pulses	Oral Pred. 1 mg/kg/day			
REGIMEN A 33	Rituximab 375 mg/sqm * 4 weeks Cyclophosphamide 15 mg/kg *2 iv pulses			Sustained Remission 76%	Death 18% Events 42%
REGIMEN B 11	Cyclophosphamide iv 15 mg/kg *3 fortnightly doses, then every 3 weeks for 3-6 months,	Oral Azathioprine	Induction 53% Relapse 42%	Sustained Remission 82%	Death 18% Events 36%

IMPROVE *Mycophenolate Mofetil Vs Azathioprine for remission maintenance in ANCA-Associated Vasculitis: a randomized controlled trial*
Hiemstra TF, Walsh M, Mahr A, et al
JAMA 2010; 304:2381

TRIAL INDUCTION	DESIGN	TERMINATION 42 MONTHS	ADVERSE EVENTS
PATIENTS 156	Induction with Cyclophosphamide and steroids		
REGIMEN A	Azathioprine 2 mg/kg/day reducing	Relapse 38%	16%
REGIMEN B 11	MMF 2 g/day reducing	Relapse 55%	8%

RAVE (NIH)

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis & ┬ Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis

A. *John H. Stone, M.D., M.P.H., Peter A. Merkel, M.D., M.P.H., Robert Spiera, M.D et al.*

B. *Ulrich Specks, M.D., Peter A. Merkel, M.D., M.P.H., Philip Seo, M.Dfor the RAVE−ITN Research Group*

N Engl J Med 2010; 363:221-232 & N Engl J Med 2013; 369:417-427

TRIAL	DESIGN	MAINTENANCE	SUCCESSFUL REMISSION	FOLLOW-UP 18 MONTHS	DEATHS AND SEVERE CRF
PATIENTS 197	ALL Methyl-Prednisolone 1 g iv, 3 pulses	Oral Pred. 1 mg/kg/day, none at 5 months			
INDUCTION/ RELAPSE	100 Vs 97			124	
REGIMEN A	Rituximab 375 mg/sqm *4 weeks	None	Induction 64% Relapse 67%	Sustained Remission 39%	1 Died 21 Changed Inpatients
REGIMEN B	Oral Cyclophosphamide 2 mg/kg/day	Azathioprine at 3-6 months	Induction 53% Relapse 42%	Sustained Remission 33%	2 Died 19 Changed Leucopenia

GDCN *JulieAnne G. McGregor, Susan L. Hogan, Elizabeth S. Kotzen et al*

Rituximab as an immunosuppressant in antineutrophil cytoplasmic antibody-associated vasculitis

Nephrol. Dial. Transplant. (2015) 30 (suppl 1): i123-i131

TRIAL INDUCTION ONLY	DESIGN	SUCCESSFUL REMISSION	FOLLOW-UP 12 MONTHS	DEATHS AND SEVERE CRF
PATIENTS 350	ALL Methyl-Pred 1 g iv, 3 pulses Oral Pred. 1 mg/kg/day			
REGIMEN A 161	Monthly IV Cyclophosphamide 15 mg/kg pulses		Sustained Remission 76%	
REGIMEN B 112	Oral Daily Cyclophosphamide		Lower Relapse	Possibly More Infections

KDIGO Clinical Practice Guideline for Glomerulonephritis. *Kidney inter., Suppl.* 2012; 2: 139–274.

Agent	Route	Initial dose
Cyclophosphamide[a]	i.v.	0.75 g/m^2 q 3–4 weeks. Decrease initial dose to 0.5 g/m^2 if age >60 years or GFR <20 ml/min per 1.73 m^2. Adjust subsequent doses to achieve a 2-week nadir leukocyte count >3000/mm^3.
Cyclophosphamide[b]	p.o.	1.5–2 mg/kg/d, reduce if age >60 years or GFR <20 ml/min per 1.73 m^2. Adjust the daily dose to keep leucocyte count >3000/mm^3.
Corticosteroids	i.v.	Pulse methylprednisolone: 500 mg i.v. daily × 3 days.
Corticosteroids	p.o.	Prednisone 1 mg/kg/d for 4 weeks, not exceeding 60 mg daily. Taper down over 3–4 months.
Rituximab[c]	i.v.	375 mg/m^2 weekly × 4.
Plasmapheresis[d]		60 ml/kg volume replacement. *Vasculitis*: Seven treatments over 14 days If diffuse pulmonary hemorrhage, daily until the bleeding stops, then every other day, total 7–10 treatments. *Vasculitis in association with anti-GBM antibodies*: Daily for 14 days or until anti-GBM antibodies are undetectable.

ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; GFR, glomerular filtration rate; GN, glomerulonephritis; i.v., intravenous; p.o., orally.

[a] Given with pulse and oral steroids. An alternative i.v. cyclophosphamide dosing schema is 15 mg/kg given every 2 weeks for three pulses, followed by 15 mg/kg given every 3 weeks for 3 months beyond remission, with reductions for age and estimated GFR.[705]

[b] Given with pulse and oral steroids.

[c] Given with pulse and oral steroids.

[d] Not given with pulse methylprednisolone. Replacement fluid is 5% albumin. Add 150–300 ml fresh frozen plasma at the end of each pheresis session if patients have pulmonary hemorrhage, or have had recent surgery, including kidney biopsy.

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