

Wegener's Granulomatosis



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- Definition
- History
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- Pathophysiology
- Treatment



Wegener granulomatosis (WG) is a complex, immune-mediated disorder, which along with microscopic polyangitis and Churg-Strauss syndrome, comprises a category of small vessel vasculitis related to antineutrophil cytoplasmic antibodies (ANCA), characterized by a paucity of immune deposits.

History



- 1931: **Klinger** described a 70-year-old physician with constitutional symptoms, joint symptoms, proptosis, widespread upper respiratory tract inflammation, saddle nose deformity, glomerulonephritis, and pulmonary lesions.
- 1936: **Wegener** reported three patients with similar clinical features and published his findings on their distinct clinical and histopathologic findings. Postulated 'septic' vasculitis.
- 1954: **Goodman and Churg**: definitive description of WG characterized by triad of pathological features:
 - 1) systemic necrotizing angiitis
 - 2) necrotizing granulomatous inflammation of the respiratory tract
 - 3) necrotizing glomerulonephritis

Epidemiology of WG



- Incidence in US: appx. 10 per million
- Prevalence in US: appx. 3 per 100.000 persons.
- Much higher prevalence as 80% of 5year survival with treatment.
- Age specific increase: peak age 65-74
- More common in individuals of northern European descent
- Slight male predominance

Clinical Features of Wegener's Granulomatosis

General

Weight loss

Malaise

Fever

Arthralgia

Myalgia

Upper respiratory tract
disease

Mouth ulcers

CNS manifestation

Major

Glomerulonephritis

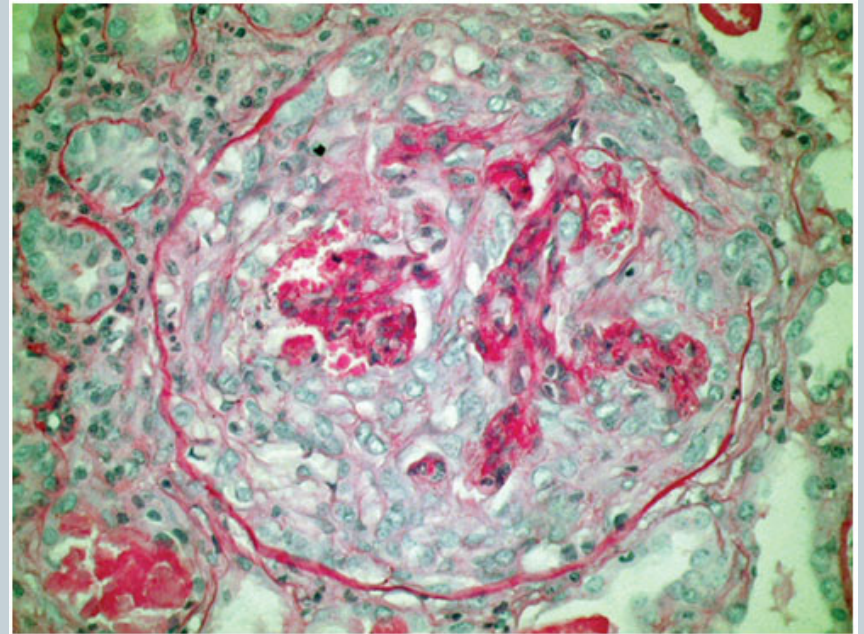
progressing to renal failure:
70-80% with WG

Lung involvement: pulmonary
hemorrhage, granulomas

Renal Pathology

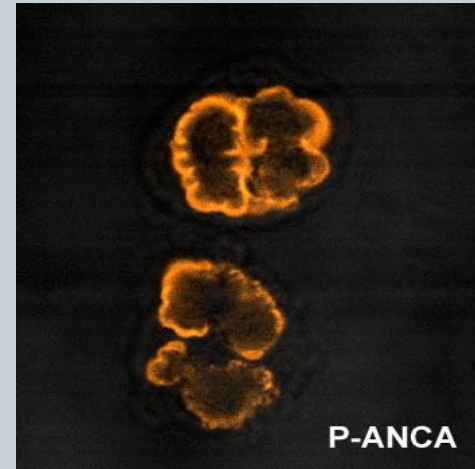
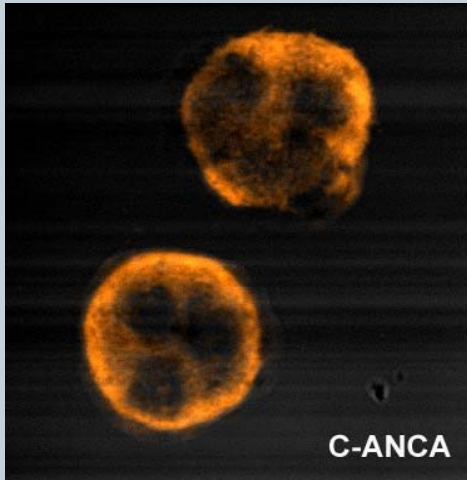


- Early
Fibrinoid necrosis of capillary loops
- Later
Diffuse proliferative, pauci-immune GN with basement membranes ruptures and cells in Bowman's space with **crescent formation**.
- End-Stage
Sclerosed glomeruli



Main pathologic difference between WG and MPA is the absence of granulomatous inflammation in MPA

Anti-Neutrophil Cytoplasmic Antibodies



- ANCAs are directed against antigens (PR3 (C-ANCA), MPO (P-ANCA)) present within the primary granules of neutrophils and monocytes; these antibodies produce tissue damage via interactions with primed neutrophils and endothelial cells.

Risk Factors / Initiating Events



- Infection (Anti LAMP2 / mimicry)
- Genetic factors (PTPN22)
- Drugs (thiol, hydrazine containing compounds)
- Alpha-1 antitrypsin deficiency (AAT is primary in vivo inhibitor of PR3)
- Environmental Exposure (silica dust, mercury, lead)

ANCA in WG



- Anti-Proteinase 3 (PR3) in 70 to 80% of patients
- Anti-Myeloperoxidase (MPO) in approximately 10%
- New ANCA subtype: auto-antibodies to lysosomal associated membrane protein-2 (LAMP-2) present in almost all individuals with FNGN

Pathogenicity of ANCA



- **Animal Model:**

MPO knockout mice immunized with mouse MPO > formation of anti-MPO splenocytes and anti-MPO antibodies

RAG-2 deficient mice (lacking T- and B- cells) that received anti-MPO splenocytes developed crescentic GN and systemic necrotizing vasculitis.

Immunization with non-MPO antibody producing splenocytes displayed only a mild immune complex GN.

RAG-2 deficient and wild-type mice were injected with anti-MPO developed a pauci-immune glomerulonephritis.

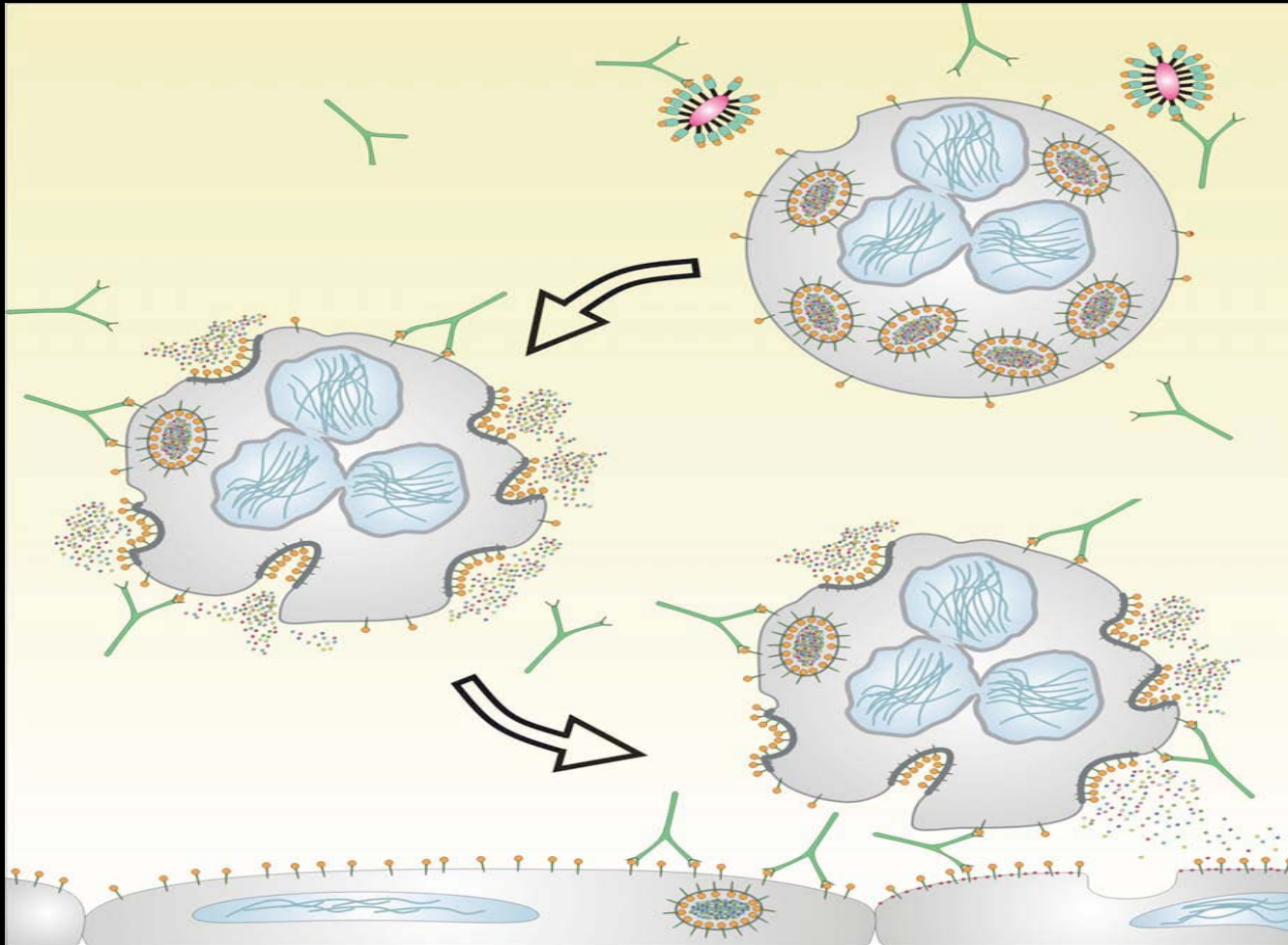
- **Human Model:**

Placental transmission of maternal anti-MPO antibodies caused pulmonary-renal syndrome in the newborn. Syndrome resolved after treatment with glucocorticoids and supportive therapy, and with the eventual disappearance of maternal ANCA.

LAMP-2 in WG / Molecular Mimicry



- prevalence twice that of anti-MPO and anti-PR3 in FNGN
- Human LAMP-2 epitope (P41- 49) has 100% homology with bacterial adhesion molecule FimH (P72-80) of gram negative bacteria (E. Coli, Klebsiella, Proteus)
- Rats immunized with FimH develop pauci-immune FNGN and also develop antibodies to rat and human LAMP-2
- monoclonal antibody to human LAMP-2 induces apoptosis of human microvascular endothelium in vitro.
- 9 of 13 patients (69 percent) were infected with bacteria expressing FimH (most commonly E. Coli) in the 12 wks before the clinical presentation of ANCA-positive FNGN, suggesting the presence of molecular mimicry



Kain R et al, Nat Med. 2008 Oct;14(10):1088-96

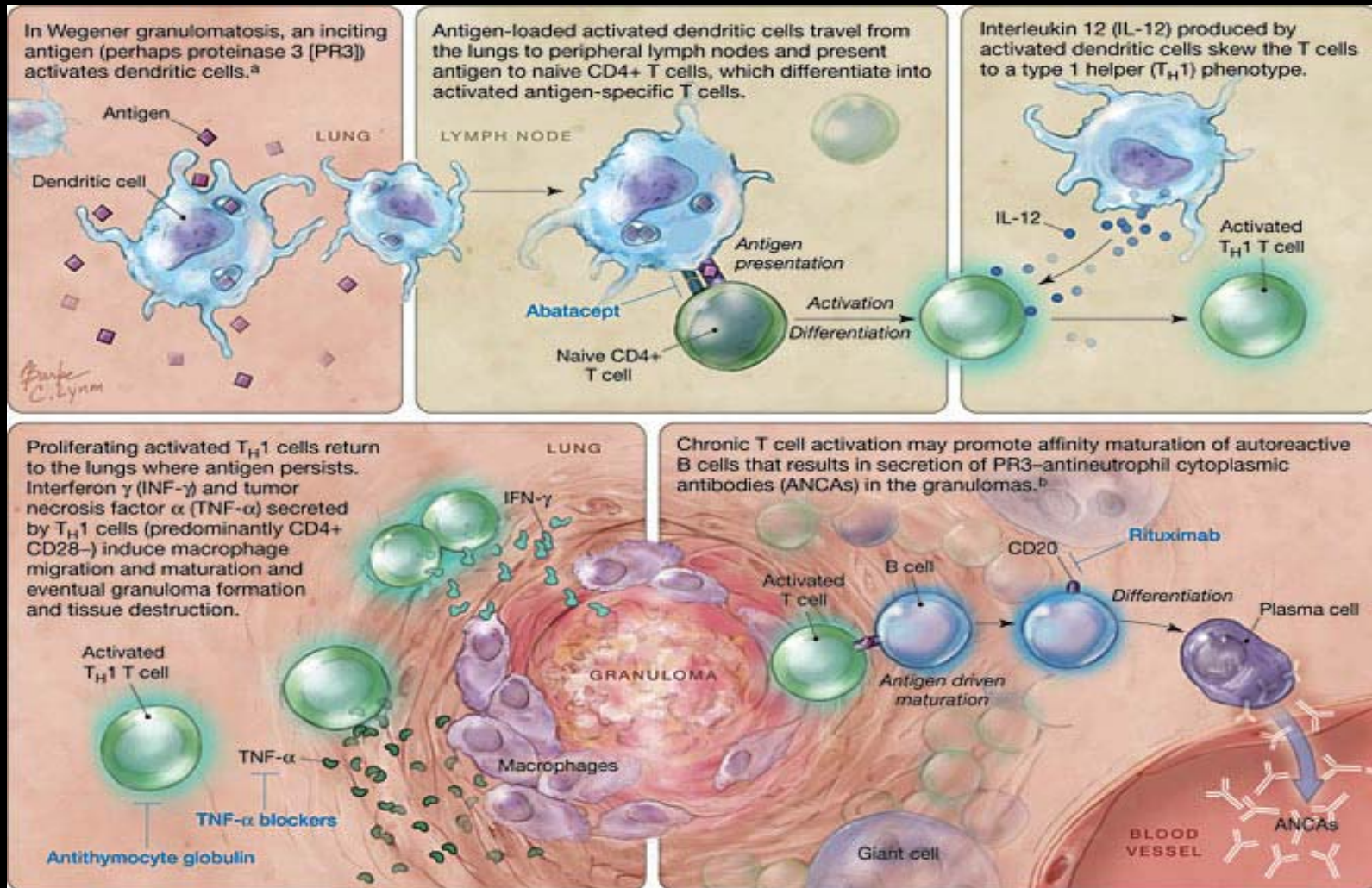
Exposure to FimH during infection induces synthesis of antibodies to an epitope shared by shared by FimH (P72-80) and hLAMP-2 (P41-49)

ANCA production



- Autoantibody response to exposed epitopes of target antigen (PR3, MPO)
- Auto-antigen complementarity
- Role of T Cells (higher CD4+ T cell and monocytic activation, high levels of Th1 cytokines, TNF alpha, IFN-gamma)
- B-Cell activation (target for rituximab)
- Neutrophil activation (Th1 stimulates neutrophils/monocytes)
- Endothelial cell
- Frequent disease flare with infection (“primed neutrophils”)

Model of Pathogenesis of Granulomatous Inflammation in WG Therapeutic Immune Response Targets



Bosch, X. et al. JAMA 2007;298:655-669.

Treatment



Consists of two phases:

- 1. Remission induction**
- 2. Remission maintenance**

EULAR Classification



Category	Definition
Localized	Upper and/or lower respiratory tract disease without any other systemic involvement or constitutional symptoms.
Early systemic	Any, without organ-threatening or life-threatening disease
Generalized	Renal or other organ-threatening disease, serum creatinine ≤ 5.6 mg/dL (500 micromol/L).
Severe	Renal or other vital organ failure, serum creatinine ≥ 5.7 mg/dL (500 micromol/L)
Refractory	Progressive disease unresponsive to glucocorticoids and cyclophosphamide.

Remission Induction



Cyclophosphamide is started at 1.5-2mg/kg/d PO or 0.5 to 1g/m²/month IV until stable remission induced. (3-6 months)

- Alkylates guanine nucleotides
- Blocks cell division
- Lymphopenia, mainly of B cells
- Reduces antibody levels

Daily PO vs. monthly IV show similar rate of remission. Daily PO has lower rate of relapse and higher rate of leukopenia/infection. (CYCLOPS trial)

Glucocorticoid Pulse with methylprednisolone 7-15mg/kg to max. 1000mg/day for 3 days, then 1mg/kg/d prednisone po daily for 2-4 weeks then taper, if significant improvement is seen, decreased by 5mg/wk.

Glucocorticoid monotherapy is NOT generally considered, given low remission rate compared to cyclophosphamide (56 versus 85 percent) and higher relapse rate.

Combination Rx induces remission in 85-90% of patients usually in 2-6months, about 75% experiencing complete remission

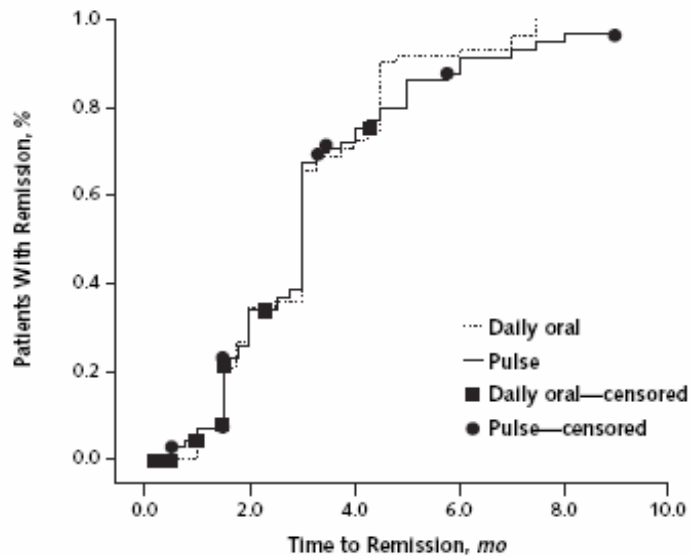
CYCLOPS



- randomized trial of 149 patients with ANCA-associated vasculitis
 - pulse IV cyclophosphamide (15 mg/kg every 2 to 3 weeks) or
 - daily oral cyclophosphamide (2 mg/kg per day until remission then 1.5mg/kg for 3 months).
- No difference in the time to remission or the percentage of patients who achieved remission by 9 months (88 percent in both groups)
- After remission, 19 (14.5 percent) relapsed (10 major and 9 minor). More relapses in the IV pulse cyclophosphamide group (13 versus 6), however not statistically significant and study was not designed or powered to assess an effect on relapse.
- Pulse cyclophosphamide was associated with a significantly lower cumulative cyclophosphamide dose (8.2 versus 15.8 g) and a lower rate of leukopenia (26 versus 45 percent).

CYCLOPS

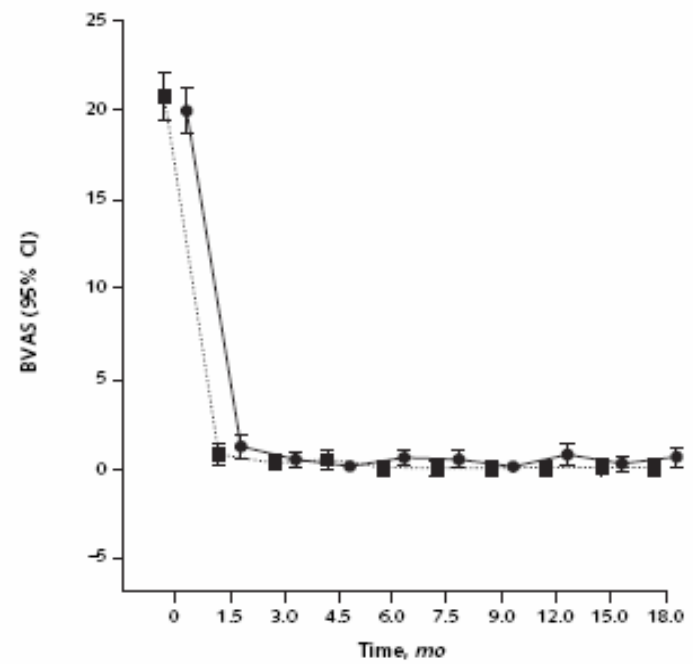
Figure 2. Time to remission (Kaplan–Meier curves) for the pulse and daily oral cyclophosphamide groups.



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.



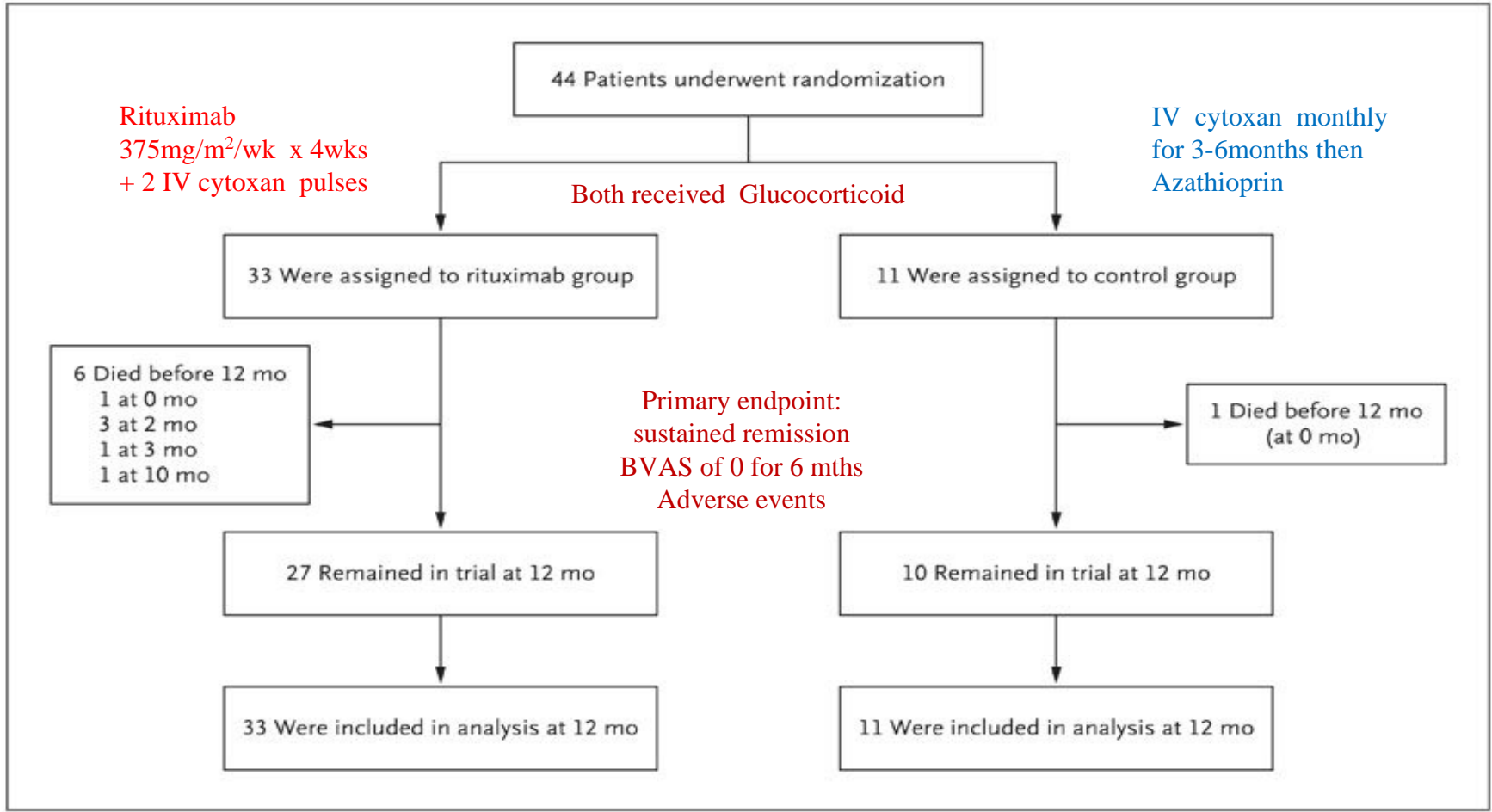
Daily oral	71	63	63	60	56	55	52	58	54	50
Pulse	73	63	66	58	67	58	61	62	59	54

Rituximab vs. Cyclophosphamide



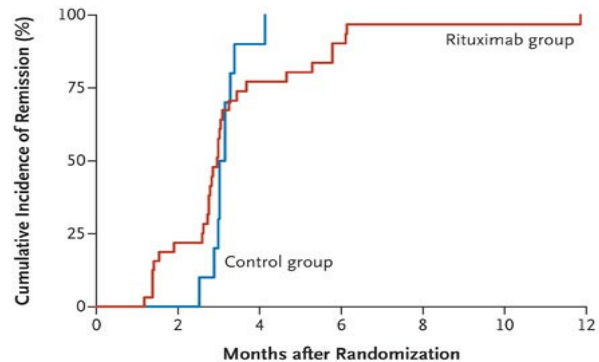
- Cyclophosphamide a/w severe side effects, incl. leukopenia, infections, bladder injury, cancer, ovarian failure.
- B-cell level correlate with disease activity calling for B-cell targeted therapy
- Treatment with rituximab has led to remission rates of 80 to 90% among patients with refractory ANCA-associated vasculitis.
- Uncontrolled studies suggest that rituximab is effective and may be safer

RITUXIVAS



RITUXIVAS

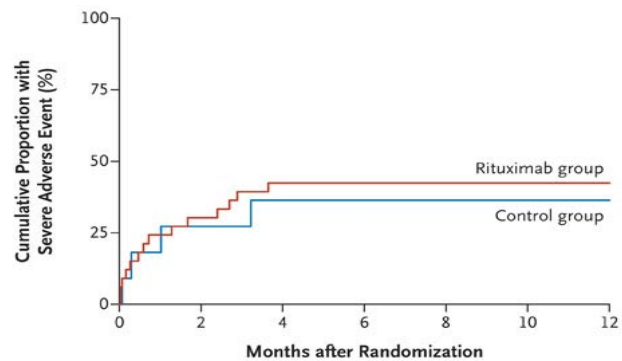
A Remission



No. at Risk

Control	11	10	1	0	0	0	0
Rituximab	33	24	7	3	1	1	0

B First Severe Adverse Event



No. at Risk

Control	11	8	7	7	7	7	7
Rituximab	33	23	19	19	19	19	19

- Sustained-remission rates were not superior in rituximab group. In both groups >90% of survivors had sustained remission
- Rituximab not a/w reductions in early severe adverse events. (42% vs 36%)

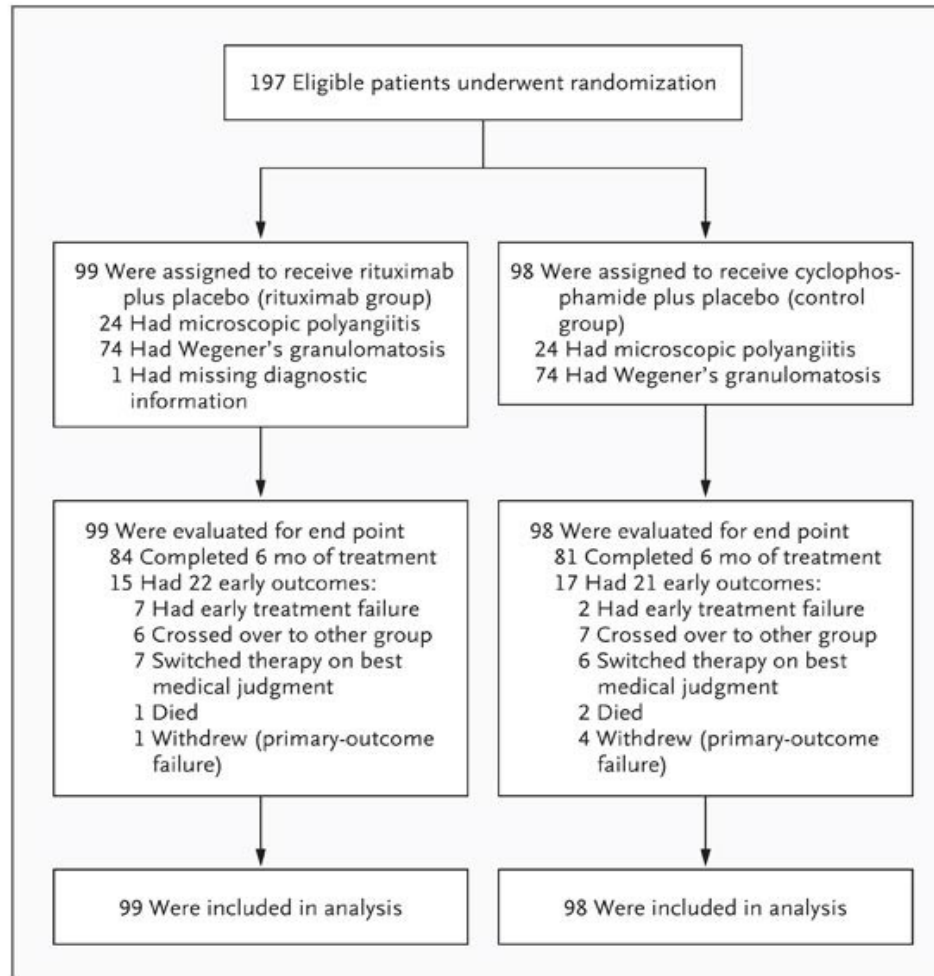
RAVE



Rituximab 375mg/m²/wk
x 4wks
+ daily placebo-cytoxan

Pt w/ remission between
3-6m, switched from
placebo-cytoxan to
placebo-AZA

Inclusion criteria:
+ ANCA, severe disease,
BVAS >3



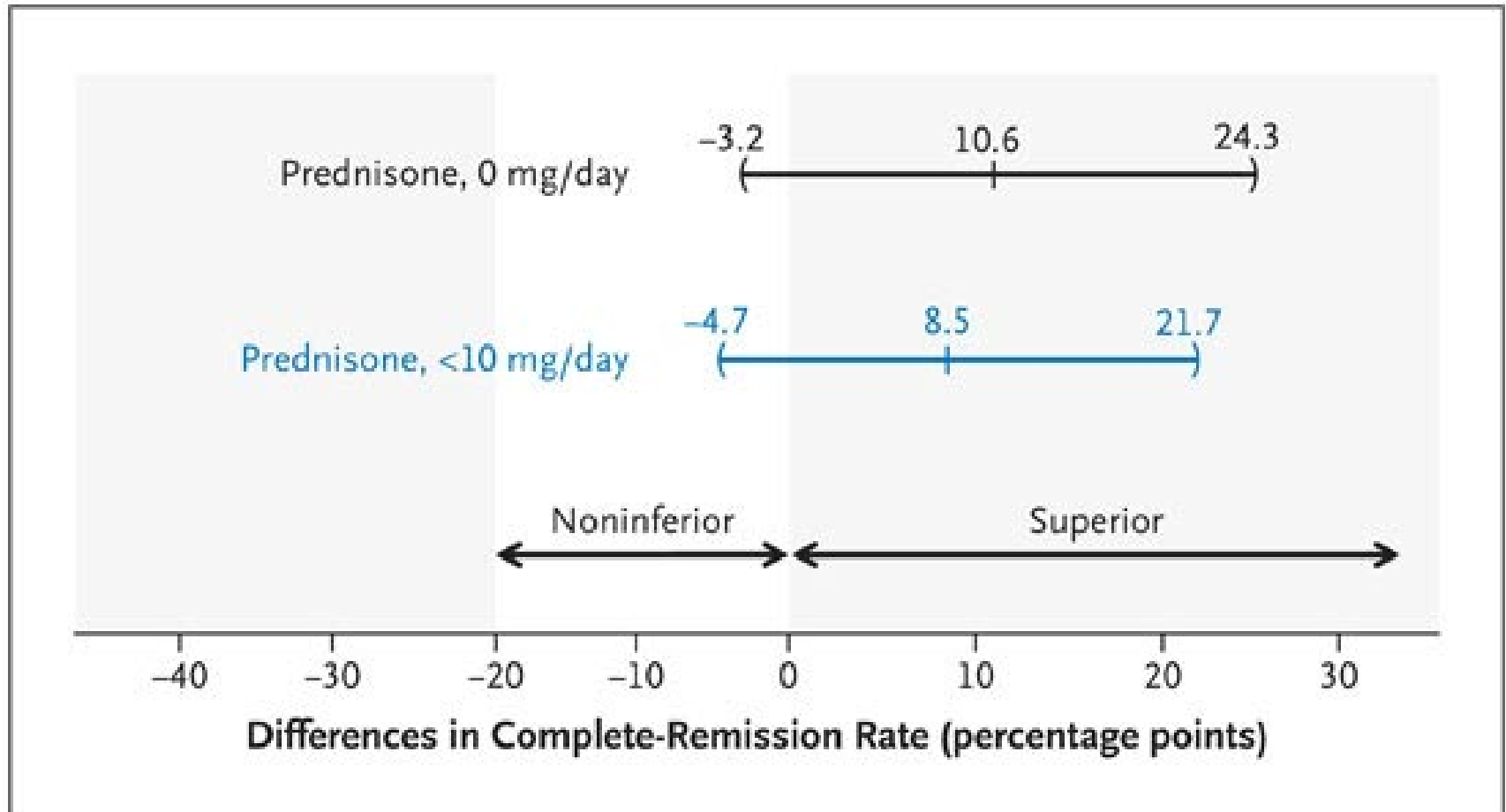
Daily po cytoxan 2mg/kg
+ placebo-rituximab
infusion

Pt w/ remission between
3-6m, switched to AZA

Primary: BVAS of 0 and
successful prednisone
taper at 6 months

Secondary: BVAS 0 w/
<10mg prednisone at
6months, rates of adverse
events .

RAVE





- In RAVE trial rate of adverse events was equivalent in the 2 study groups.
- Also showed elevated number of malignant conditions within short period.
- Rituximab was superior to po cytoxan for the induction of remission in relapsing disease.
- Confounding effect of glucocorticoid therapy >> long term data needed to answer question of duration of remission, incidence of remission in rituximab+glucocorticoid group.

Plasmapheresis / MEPEX trial

- 137 patients with new Dx of WG/MPA, Cr >5.7mg/dL. 69% required HD
- 3 months survival (69% vs 49%)
- Reduced progression to ESRD at 1 year (19% vs 42%)
- No difference in mortality at one year (27% vs 24%)

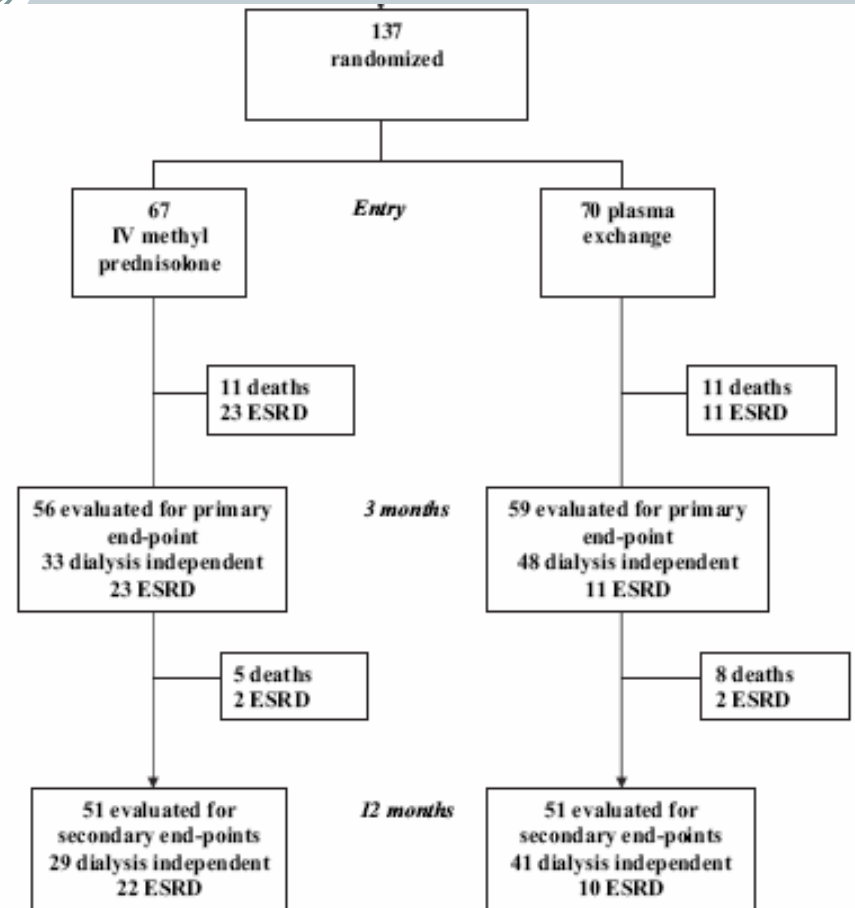


Figure 1. Enrollment, patient survival, and renal outcome during the trial.

Plasmapheresis for Pulmonary Hemorrhage



- No randomized trial performed in ANCA vasculitis, only retrospective review of 20 patients with diffuse alveolar hemorrhage (DAH) and ANCA-associated small vessel vasculitis
- All patients underwent daily full plasma volume plasma exchange until DAH improved, which was then changed to alternative day apheresis therapy until the DAH resolved.
- All received IV methylprednisolone (7 mg/kg per day) for 3 days, and all but 2 received intravenous cyclophosphamide (0.5 g/m² of body surface area).
- DAH resolved in all 20 patients, with the mean number of apheresis treatments being 6.15 (range of 4 to 9). There were no complications due to apheresis. 1 patient died because of a pulmonary embolism. Among the 7 patients who did not require dialysis, the serum creatinine fell significantly by the time of discharge (4.5 to 2.4 mg/dL (398 to 212 micromol/L)).