





Clinical Trials Update GDCN 2009



Patrick H. Nachman



Plasmapheresis for ANCA-vasculitis

Treatment of ANCA-GN (Chapel Hill-style)

IV pulse methylprednisolone 7 mg/kg x 3 days

Prednisone 1 mg/kg X 4 weeks then tapered

with either

IV cyclophosphamide 0.5-1 g/m²* X 6 months

or

Oral cyclophosphamide 2 mg/kg* X 6 to 12 months

*adjusted based on leukocyte count



Plasmapheresis for ANCA Vasculitis

- ▶ Several small controlled trials suggesting higher rates of renal recovery for patients with dialysis dependent renal failure due to AASV when treated with plasmapheresis in addition to standard therapy compared to standard therapy alone.
- ▶ Inconsistencies in the cytotoxic regimens used, small sample sizes, relatively short follow-up periods.



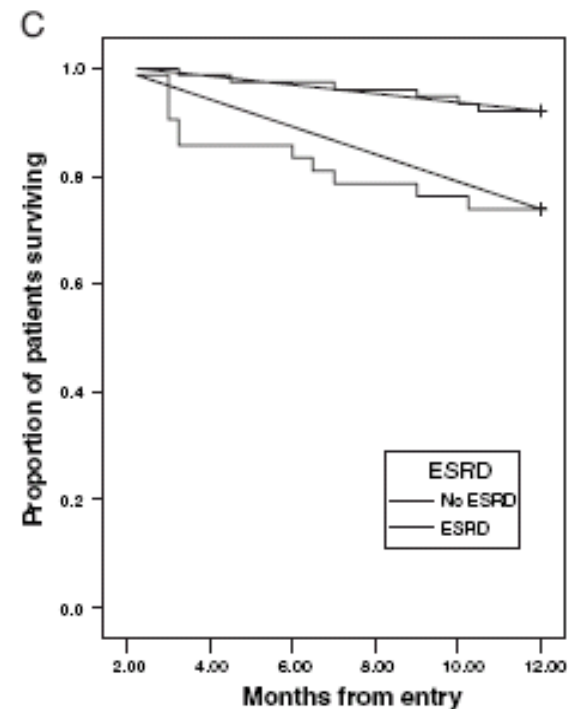
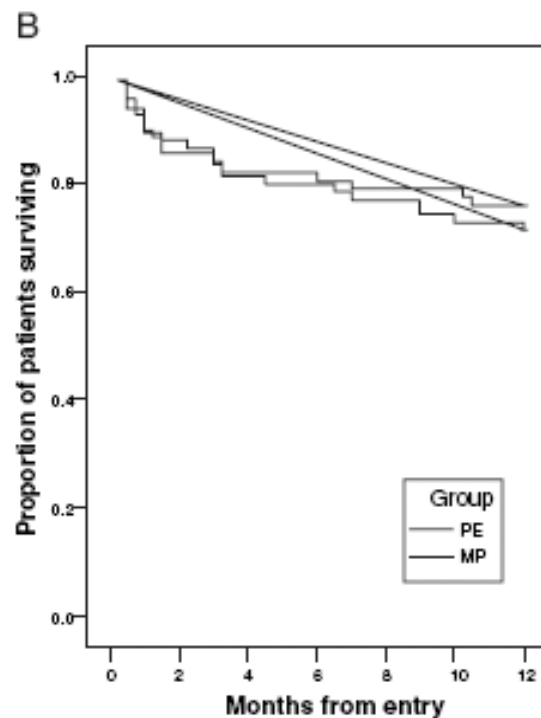
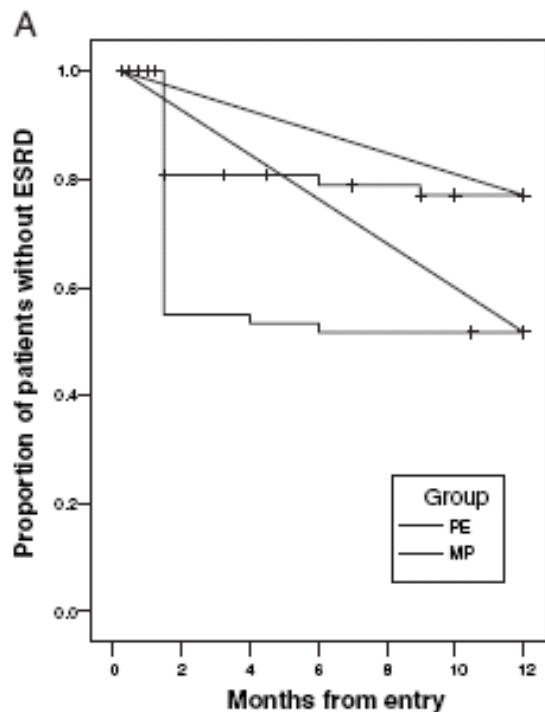
Plasmapheresis for Diffuse Alveolar Hemorrhage

- ▶ 20 patients between 1995-2001 with massive pulmonary hemorrhage
- ▶ Treatment with Medrol, IV Cytoxan, and plasmapheresis
- ▶ 20/20 patients had resolution of lung symptoms with 4-9 exchanges

Treatment of patients with severe renal disease: MEPEX Trial

- ▶ Plasma exchange (PE) versus pulse methylprednisolone (MeP) as adjunctive therapy with initial creatinine > 5.8mg/dl
- ▶ 137 patients with new dx of ANCA vasculitis given either:
 - ▶ 7 PE treatments of 60 ml/kg each within 14 days, vs iv MeP 1000 mg iv daily x 3
 - ▶ All patients received:
 - ▶ oral cyclophosphamide: 2.5 mg/kg/day x 3 months then 1.5 mg/kg/day x 3 months; then azathioprine 2 mg/kg/day.
 - ▶ prednisolone started at 1 mg/kg/day down to 0.25 mg/kg/d by week 10 then tapered to 10 mg/day from month 5 to 12.
- ▶ The primary end point was dialysis independence at 3 mo.
- ▶ Secondary end points included renal and patient survival at 1 yr and severe adverse event rates.

MEPEX: Outcomes



Major cause of death: infection (n=19); pulmonary hemorrhage (n=6); CVD (n=4)

Glucocorticoids and plasma
exchange in ANCA vasculitis: a
randomized control trial

PEXIVAS

Principal Questions

- 1) Does the addition of PLEX to cyclophosphamide (CYC) and glucocorticoids (GC) therapy improve the composite endpoint of ESRD or all-cause mortality in severe AASV?
- 2) Is a low cumulative dose GC protocol as good or better at preventing the composite endpoint of ESRD or all-cause mortality compared to a standard, high dose protocol in patients with severe AASV?



Study Design

Randomized Controlled Trial in a two-by-two factorial design.

- 1- Randomization (1:1) to standard vs. low GC dose
- 2- Randomization (1:1) to adjunctive PLEX vs. no PLEX.
Minimum target of 7 exchanges of at least 1 plasma volume over 2 weeks.

All patients will receive “standard” immunosuppressive induction therapy.

The primary outcome: combined endpoint of all-cause mortality or ESRD.



Glucocorticoid Therapy

All patients receive_Methylprednisolone 0.5 g iv qd x 3

High-dose/control group:

- ▶ oral prednisolone 1 mg/kg/day with a tapering schedule to a goal of ~ 15 mg/day at 3 months.

Low-dose/intervention group:

- ▶ oral prednisolone 0.5 mg/kg/day with a tapering schedule to a goal of ~ 7.5 mg/day at 3 months.

GC therapy will continue to at least 18 months in both groups.



“Standard” Immunosuppressive Therapy

Induction therapy:

- ▶ Cyclophosphamide (CYC) x 3-6 months either oral or IV CYC. The CYC regimens will be identical for all treatment groups.



Maintenance Therapy:

- ▶ After at least 12 weeks of CYC if in complete remission (Birmingham Vasculitis Activity Score = 0).
- ▶ All patients will be converted to maintenance therapy after a maximum of 26 weeks of CYC.
- ▶ Azathioprine:
 - ▶ 2.5 mg/kg/day between 12 and 26 weeks of study
 - ▶ 2 mg/kg/day thereafter for the remainder of the study. (Patients intolerant of azathioprine can be maintained on either a lower dose or on an alternative agent e.g. methotrexate or mycophenolate mofetil).



Inclusion Criteria

- ▶ **Active WG, MPA or renal limited vasculitis and**
- ▶ **Severe vasculitic manifestation:**
 - ▶ **Renal involvement:**
 - ▶ eGFR \leq 50 ml/min **and** hematuria and proteinuria or a renal biopsy with focal necrotizing glomerulonephritis
 - ▶ **Pulmonary hemorrhage due to active vasculitis:**
 - ▶ A compatible CXR **and**
 - ▶ At least one of the following: increasingly bloody returns on BAL, hemoptysis, a documented drop in hemoglobin, an increased DLCO **and,**
 - ▶ The absence of an alternative explanation for the lung infiltrates



Exclusion Criteria

- ▶ Anti-GBM antibodies in serum or on biopsy
- ▶ Known CKD (baseline Cr ≥ 300 $\mu\text{mol/L}$) or on dialysis for > 14 days before randomization
- ▶ Treatment with immunosuppressive medication for > 14 days or > 3 g of methylprednisolone before randomization
- ▶ For patients entered with a relapse of AASV, treatment with an immunosuppressive within the last 6 months or receiving > 10 mg/day of prednisolone within the last 6 months



PEXIVAS

- ▶ Study is funded by the FDA in the US
- ▶ Cost of plasmapheresis will be covered by the study.
- ▶ Other medications are NOT paid by study
- ▶ Anticipated to start in late 2009



Rituximab for IgA Nephropathy

Rituximab for IgA Nephropathy

- ▶ Aim: compare Rituximab to standard therapy (tight blood pressure control and fish oil) in lowering proteinuria in patients with IgAN.
- ▶ Design:
 - ▶ Open-label multicenter Randomized (1:1) Controlled Trial
 - ▶ 50 patients
 - ▶ Primary Outcome: *Percentage of patients in each group achieving complete (<300 mg proteinuria, $\leq 10\%$ \downarrow eGFR) or partial (> 50% \downarrow proteinuria and $\leq 25\%$ \downarrow eGFR) response at 12 months.*



Treatment

- ▶ All patients will receive Standard therapy:
 - ▶ Dual RAAS blockade to achieve a BP goal of 125/75 (MAP 90 mm Hg)
 - ▶ Omega-3 Fatty Acid Fish Oil Supplements, 3.6 gm EPA/day.
- ▶ Rituximab group:
 - ▶ will receive a total of 4 doses (375 mg/m²) on days #1; 15; 168 and 182.
- ▶ Patients will be followed for 12 months.



Inclusion Criteria

- ▶ Renal biopsy with a diagnosis of IgAN within 12 months, with <10% cellular crescents.
- ▶ 18 to 70 years old
- ▶ eGFR < 90 mls/min and > 30 mls/min.
- ▶ Proteinuria:
 - ▶ ≥ 1000 mg /24 hours while on stable ACEi, ARB, or a renin inhibitor x 2 months.
 - ▶ ≥ 500 mg /24 hours if on dual RAAS blockade.
- ▶ Blood Pressure <130/80 mmHg.
- ▶ Females must agree to 2 years of contraception.



Rituximab for IgA Nephropathy

- ▶ Investigator initiated study
- ▶ Industry sponsor: Genentech will provide rituximab
- ▶ Other medications are NOT provided by study
- ▶ Study Principal Investigator:
Fernando Fervenza, MD PhD
Mayo Clinic
- ▶ VERY long gestation but anticipated to start in 2009





Autosomal Dominant Polycystic Kidney Disease



A Phase 3, Multi-center, Double-blind, Placebo-controlled, Parallel-arm Trial to
Determine Long-term Safety and Efficacy of Oral Tolvaptan Tablet Regimens in Adult Subjects with Autosomal Dominant Polycystic Kidney Disease

TEMPO 3:4

Sponsor: Otsuka



TEMPO 3:4

- ▶ Multi-center, double-blind, placebo-controlled, parallel-arm trial. (2:1 randomization)
- ▶ Subjects:
 - ▶ 1445 subjects (18 - 50 years) with ADPKD stratified by glomerular filtration rate (GFR), renal size and presence of hypertension.
 - ▶ recruited from > 100 sites
 - ▶ Estimated GFR ≥ 60 mL/min/1.73m² (by Cockcroft-Gault)
 - ▶ Rapid estimated rate of renal volume increase based on total renal size ≥ 750 cc by MRI at randomization.



TEMPO 3:4

- Duration of participation: ~ 3.5 years
- After screening and baseline visit, subjects will need to come
 - weekly x 3 weeks for dose titration
 - Every 4 months for 3 years (total of 15 visits)
- Baseline + yearly MRI WITHOUT gadolinium to determine kidney volume
- Primary endpoint: change in kidney volume
- Secondary endpoints: change in eGFR, pain, albuminuria, HTN



TEMPO 3:4

Risks

- ▶ Most commonly reported adverse events (>10%)
 - ▶ thirst, dry mouth, and non-specific headache.
 - ▶ urinary frequency; thirst; dry mouth; nocturia, pneumonia; dizziness; and diarrhea.
- ▶ Some reports of temporary worsening of kidney function (Acute Renal Failure) (most in studies of severe CHF)
- ▶ Abnormal Transaminases, which resolved with interruption of study medication
- ▶ Reproductive risks? Unknown



TEMPO Status

(as of 12/31/08)

- ▶ Enrollment closed as on December 31; 2008
- ▶ Total screened: 2118
- ▶ Randomized: 1445

Country	# Sites	# Patients Randomized
USA	30	379
Japan	30	177
Germany	5	158
France	9	115
Poland	3	93



TEMPO at UNC

- ▶ 29 patients consented; Randomized: 16
- ▶ Withdrawals:
 - ▶ Due to fertility concern (1)
 - ▶ Due to intolerability of side effects : increased urination (1), headaches (1)
 - ▶ Due to unwillingness to take the study drug regularly (1)
- ▶ 7 patients have completed 1 year.
- ▶ 92% Caucasian
- ▶ 50% women



Polycystic Kidney Disease Registry

- ▶ Ongoing registry
- ▶ In preparation for future studies / clinical trials





Anne Froment
Anne_froment@med.unc.edu



phone:(919) 923 1382