SUPPLEMENTARY MATERIAL

Supplementary Table 1: Summary of Protocolized Immunosuppressive Therapies for Trials (adapted from trial protocols)

Treatment	RAVE trial	WGET
Glucocorticoids	Intravenous glucocorticoids for 1-3 days (at discretion of investigator) followed by oral prednisone 1mg/kg/day. Prednisone tapered off by month 6.	Intravenous methylprednisolone 1g/day for 1-3 days (at discretion of investigator) followed by oral prednisone 0.5-1mg/kd/day. Prednisone tapered off by month 6.
Induction therapy	Randomization to either: - Rituximab (375 mg/m2/week times 4) OR - Cyclophosphamide oral (2mg/kg/day)	Severe disease: - Cyclophosphamide oral (2mg/kg/day) for 3-6 months Limited disease: - Methotrexate starting dose of 0.25mg/kg/week and increase to maximum of 25 mg/week. If side effects, switch to azathioprine. All patients randomized to etanercept or placebo.
Maintenance therapy	No additional therapy for rituximab arm. Transition to azathioprine 2mg/kg/day for cyclophosphamide arm between months 3 to 6. Azathioprine continued until month 18 at which time treatment is according to best medical judgment.	Methotrexate or azathioprine (depending on kidney function and side effects). After 12 months, begin slow taper.

Appendix 1: Additional Information for Methods Section

SUBGROUP ANALYSIS

To determine if worsening hematuria predicted renal relapse, we performed a subgroup analysis only among patients enrolled in the RAVE trial since levels of hematuria (not just "present/absent") were available in this trial. In particular, we were interested in whether worsening hematuria was an early harbinger of disease activity in the kidneys. We examined any increase in hematuria level over multiple time periods: i) since last visit, ii) over the past 3 months, iii) over past 6 months, or iv) over past 12 months. Increase in hematuria was analyzed as a time-varying covariate and multivariate analyses adjusted for any decrease in hematuria level during the same time period, ANCA type (anti-PR3 vs anti-MPO), baseline pulmonary involvement, and baseline serum creatinine.

Although detailed data on quantification of proteinuria was not collected in these trials, we examined the relationship between a worsening level of proteinuria (based on urine dipstick) and renal relapse in a secondary analysis.

MISSING DATA

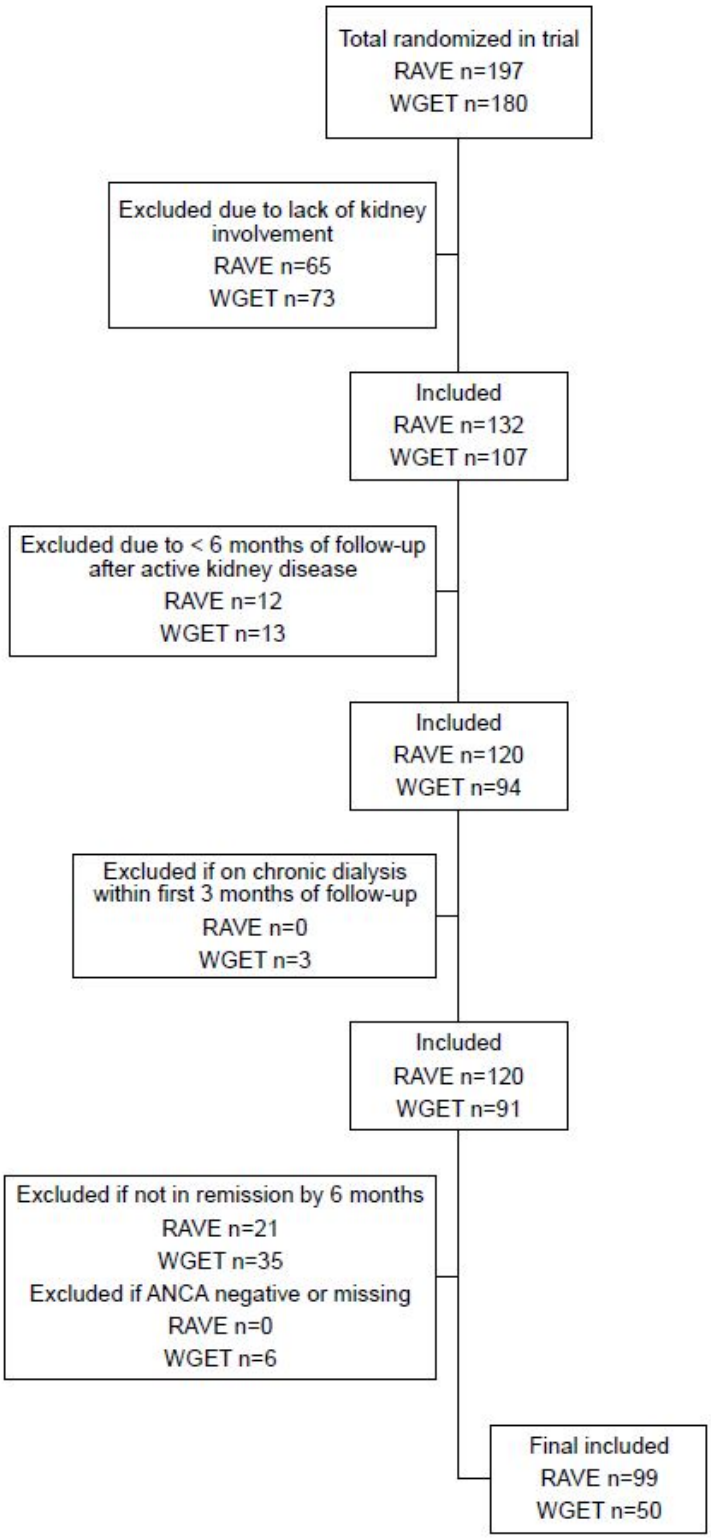
Hematuria was defined first by the presence or absence of microscopic RBCs on urinalysis. If microscopic urinalysis data was missing, blood by dipstick was used to identify hematuria (14 visits). Visits with missing microscopic and dipstick urinalysis data were imputed using last observation carried forward method. Two patients who had missing proteinuria data at more than 50% of visits were not included in the analyses of proteinuria.

SENSITIVITY ANALYSES

Sensitivity analyses adjusted for induction therapy and mean daily dose of maintenance therapies for each visit (including prednisone, azathioprine, and methotrexate). We chose to use mean daily dose as a proxy for the level of immunosuppression because: i) only cumulative dose of each immunosuppressive was available at each visit, ii) medications were frequently interrupted or discontinued between visits, and iii) medications (particularly prednisone) may have been tapered between visits. Cumulative duration with hematuria or proteinuria and mean daily dose of maintenance therapies were analyzed as time-varying covariates. Due to the possibility of menstrual blood contaminating results of the urinalysis, we performed a sensitivity analysis excluding premenopausal women who were identified by self-report.

Based on a prior study which found that an increase in PR3-ANCA levels was associated with relapse in the RAVE trial, we examined whether adjusting for an increase in PR3-ANCA changed the relationship between persistent hematuria and renal relapse[10]. Data on ANCA levels were available only from a subgroup of patients enrolled in the RAVE trial with PR3-ANCA (n=60). A standardized direct enzyme-linked immunosorbent assay was used (supplied by Euroimmun) and an increase in PR3-ANCA was defined as a doubling of the result or an increase to at least 40 units if the assay had previously become negative, within the preceding 6 months[10].

Figure 1: Flow Diagram for Patient Inclusion and Exclusion in Study



Appendix 2: Description of 18 Renal Relapses

Renal relapse in the 18 patients was identified by new or worsening: RBC cast only (10 patients), RBC cast and rise in serum creatinine (4 patients), hematuria and rise in serum creatinine (3 patients), or rise in serum creatinine only (1 patient). Half the patients who developed a renal relapse (9 patients) also had extra-renal manifestations of disease at the time of relapse. The single patient whose renal relapse consisted of only a rise in serum creatinine also had new or worsening scleritis and bloody nasal discharge.

Ten of the 18 patients who had a renal relapse had available data on PR3-ANCA levels during follow-up. Among these 10 patients, 8 had an increase in ANCA levels prior to the relapse. Prior to renal relapse, 6 patients had negative ANCA which became positive, 2 patients had ANCA which remained positive, and 2 patients had ANCA that became negative and remained negative at the time of relapse.

Supplementary Table 2: Association Between Persistent Proteinuria and Outcomes

Outcome	Adjusted sHR (95% CI)	P-value
Renal relapse	1.44 (0.47, 4.42)	0.53
Any relapse	0.78 (0.42, 1.45)	0.43
ESRD	3.61 (0.40, 32.3)	0.25
Slope of change in eGFR	--	0.75

Results were similar after adjusting for induction therapy and maintenance immunosuppressive therapies. ANCA type did not modify the effect of persistent proteinuria on renal relapse (p for interaction = 0.51).