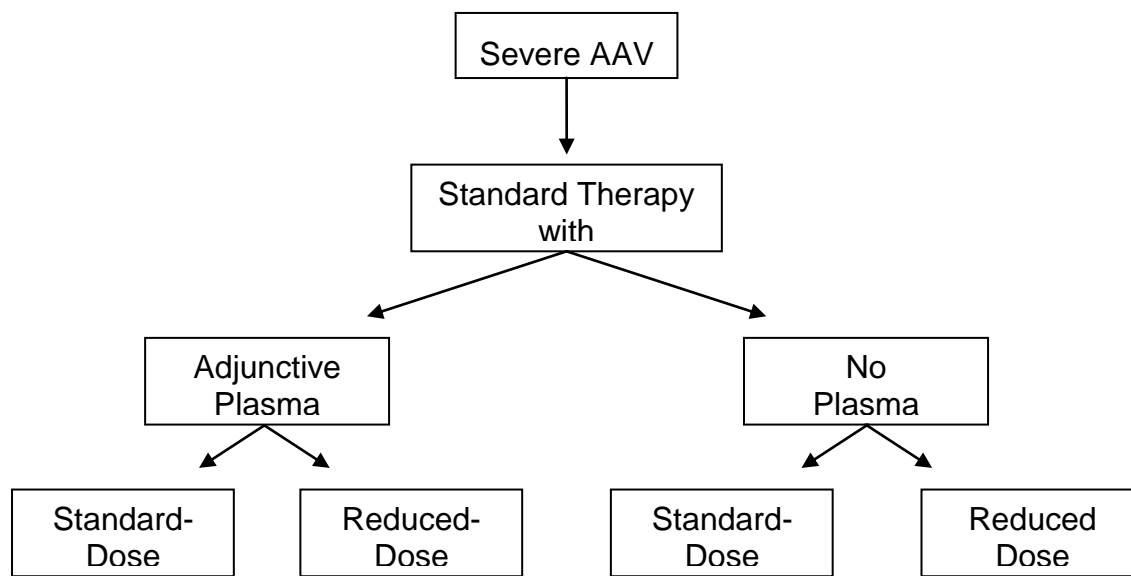


1 Protocol Version 1.1 Synopsis

Title	Plasma exchange and glucocorticoid dosing in the treatment of ANCA-associated vasculitis: a multicentre randomised controlled trial - PEXIVAS
Study Design	Multi-centre, international, phase III, open label, 2x2 factorial, randomised controlled trial of plasma exchange and glucocorticoid dosing for severe ANCA-associated vasculitis (AAV). Randomisation is via the internet, using a computer generated minimisation algorithm.



Inclusion Criteria (all must apply)	<ol style="list-style-type: none">1. New or previous relapsing clinical diagnosis of Wegener’s granulomatosis or microscopic polyangiitis consistent with the Chapel-Hill consensus definitions AND2. Positive test for proteinase 3-ANCA or myeloperoxidase-ANCA AND3. Severe vasculitis defined by at least one of the following:<ol style="list-style-type: none">a. Renal involvement with both:<ol style="list-style-type: none">i. Renal biopsy demonstrating focal necrotizing glomerulonephritis or active urine sediment characterized by glomerular haematuria or red cell casts and proteinuria ANDii. eGFR <50 ml/min/1.73 m²b. Pulmonary hemorrhage due to active vasculitis defined by:<ol style="list-style-type: none">i. A compatible chest x-ray or CT scan (diffuse pulmonary infiltrates) ANDii. The absence of an alternative explanation for all pulmonary infiltrates (e.g. volume overload or pulmonary infection) ANDiii. At least one of the following:<ol style="list-style-type: none">1. Evidence of alveolar hemorrhage on bronchoscopic examination or increasingly bloody returns with bronchoalveolar lavage2. Observed hemoptysis3. Unexplained anemia (<10 g/dL) or documented drop in
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hemoglobin (>1 g/dL)

4. Increased diffusing capacity of carbon dioxide

4. Provision of informed consent by patient or a surrogate decision maker. In some participating countries permission has also been granted to use deferred consent for enrolling a patient until a legal representative becomes available to consent on their behalf. Please check your national regulations for further guidance.

Exclusion
Criteria
(exclude if any
apply)

1. A diagnosis of vasculitis other than Wegener's granulomatosis or microscopic polyangiitis
2. Positive anti-glomerular basement membrane antibody test or renal biopsy demonstrating linear glomerular immunoglobulin deposition
3. Receipt of dialysis for >21 days immediately prior to randomization or prior renal transplant
4. Age <15 years (age <18 years at centres that do not treat pediatric patients)
5. Pregnant at time of study entry
6. Treatment with >1 IV dose of cyclophosphamide and/or >14 days of oral cyclophosphamide and/or >14 days of prednisone/prednisolone (>30 mg/day) and/or >1 dose of rituximab within the 28 days immediately prior to randomization
7. A comorbidity that, in the opinion of the investigator, precludes the use of cyclophosphamide, glucocorticoids, or plasma exchange or absolutely mandates the use of plasma exchange

Treatment
Description

Plasma Exchange:

- Seven plasma exchanges of 60 mL/kg, will be performed within 14 days after randomisation.
- Plasma exchange may be provided by centrifugation or filter separation according to local practice and availability.

Immunosuppressive and glucocorticoid therapy will be determined by the protocol for the first 12 months after trial entry

Glucocorticoids:

- All patients will receive between 1 and 3 g of IV methylprednisolone over 1 to 3 days, then daily oral GC.
- Oral GC may consist of prednisone or prednisolone and administered through a weight-based protocol.
- All participants will receive either 50, 60 or 75 mg/day (based on weight) of oral GC for 7 days
 - Participants in the standard-dose group will continue at 50, 60 or 75 mg/day for 7 additional days and taper to between 12.5 and 20 mg/day at 3 months and 5 mg/day at 6 months.
 - Participants in the low-dose group will continue at 25, 30 or 40 mg/day for 7 days and taper to between 6 and 10 mg/day by 3 months and 5 mg/day by 6 months.
- All patients will receive 5 mg/day from 6 months to 12 months after randomisation.

Immunosuppressive Remission-Induction Therapy:

To consist of either cyclophosphamide or rituximab, as per preference of site investigators/patients.

Sample Size	500 patients over 60 months
Study Duration	84 months
Follow-up Schedule	Screen, baseline, PLEX visit (if randomised to PLEX), then at 2, 4, 8 and 12 weeks, end of induction (between weeks 13 and 26), 26 and 52 weeks, and then every 26 weeks thereafter for at least 2 years (maximum follow-up is 7 years).
Outcome Measures	<ol style="list-style-type: none">1. All-cause mortality or end-stage renal disease (ESRD)2. Sustained remission; all-cause mortality; ESRD; serious adverse events; serious infections, quality of life (using Short Form – 36 (SF-36) and EuroQoL EQ5D Index Score).