Plasma exchange and glucocorticoids to delay death or end-stage renal disease in anti-neutrophil cytoplasm antibody-associated vasculitis: PEXIVAS non-inferiority factorial RCT

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Scientific summary

PEXIVAS non-inferiority factorial RCT

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Scientific summary

Background

Anti-neutrophil cytoplasm antibody-associated vasculitis (AAV) is an inflammatory multisystem autoimmune disease that frequently involves the lungs and kidneys, resulting in end-stage renal disease and premature death. Treatment with high-dose glucocorticoids and immunosuppressive drugs controls the disease, but patients presenting with impaired renal or respiratory function continue to be at risk of these outcomes, and the morbidity and mortality rates of the treatments rival those of the disease. Patients with a glomerular filtration rate (GFR) of < 50 ml/minute/1.73 m^2 have a 40% chance of end-stage renal disease or death by 5 years, based on previous clinical trial data [Walsh M, Merkel PA, Peh CA, Szpirt W, Guillevin L, Pusey CD, *et al.* Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial. *Trials* 2013;**14**:73]. Those with lung haemorrhage and hypoxia have a 10–50% risk of early death from respiratory failure. Overall, AAV gives a threefold increase in standardised mortality ratio. Anti-neutrophil cytoplasm autoantibodies (ANCA) contribute to disease pathogenesis, and their physical removal by plasma exchange (PLEX) has been a treatment option for 40 years, in the absence of a robust evidence base. The speed of action of PLEX has been particularly appealing because drug therapy takes weeks to months to be effective, and because PLEX is of benefit in related forms of antibody-mediated kidney injury, including anti-glomerular basement membrane disease and antibody-mediated kidney transplant rejection. Although steroids have been used in vasculitis therapy since the late 1940s, there is little good-quality evidence to guide optimal steroid dosing, although steroids are known to contribute to the early infective mortality from vasculitis treatment and to the accumulation of chronic damage and incapacity, which are common in vasculitis patients. Standard steroid regimens have evolved from personal experiences and consensus statements, but they have not been subjected to detailed study.

Objectives

The PEXIVAS (Plasma Exchange In VAScultis) trial aimed to determine whether or not PLEX would delay the onset of end-stage renal disease or death in AAV patients presenting with adverse prognostic features, and assessed the safety risks of PLEX in this population. It also assessed whether or not a reduced-dose oral steroid regimen was as effective for the prevention of end-stage renal disease and death as a standard-dose regimen, and if it was safer than the standard-dose regimen. The secondary objectives reviewed the impact of these two interventions on end-stage renal disease and death separately, and the impact on sustained vasculitis remission, serious infections and quality of life.

Methods

This was an international, multicentre, open-label, randomised controlled trial of patients with new or relapsing AAV of the major subgroups, granulomatosis with polyangiitis or microscopic polyangiitis. Eligibility also required a GFR of < 50 ml/minute/1.73 m^2 attributable to renal vasculitis, lung haemorrhage, or both, and current positivity for ANCA: either proteinase 3 ANCA or myeloperoxidase ANCA.

Patients were randomised in a 2 × 2 factorial design to either PLEX or no PLEX, and then to either reduced- or standard-dose oral steroid regimens. A minimisation algorithm was designed to balance randomisation according to age, ANCA subtype, severity of renal failure, presence and severity of lung haemorrhage and planned type of induction immunosuppression therapy.

All patients received initial intravenous steroids and an immunosuppressive (either cyclophosphamide or rituximab). The PLEX dose was seven exchanges within the first 14 days, following local procedures. Oral steroid regimens commenced in all patients at 1 mg/kg/day of prednisolone and reduced to 5 mg/kg/day over different lengths of time, so that the patients allocated to the reduced-dose regimen received an ≈ 50% reduction in oral steroid exposure over the first 6 months compared with those allocated to the standard-dose regimen. Prednisolone was continued in all patients at 5 mg per day from 6 to 12 months, and then patients were treated in accordance with local practice. All patients were followed to a common close-out: 10 months after the recruitment of the final patient.

It was anticipated that 500 patients would be recruited over 5 years to detect a hazard ratio (HR) of 0.64 with PLEX for the primary, composite end point of end-stage renal disease or death, with a power of 80% and two-sided alpha of 0.05. With 164 events, this reflected an absolute risk reduction of 12%, from 44% in the control group to 32% in the PLEX group. This sample size would permit a non-inferiority hypothesis for the reduced-dose steroid regimen, whereby the increase in end-stage renal disease or death would not be > 11% with a power of > 80%. Estimating a severe infection rate of 25%, this sample size also had 80% power to detect a 10% absolute risk reduction (relative risk reduction of 40%) with the reduced-dose steroid regimen. During the trial, the event rate was lower than predicted and the sample size was increased to 700 subjects.

The primary end point was a composite of time to all-cause mortality and end-stage renal disease. Secondary end points were end-stage renal disease and death, separately; sustained remission; serious adverse events (SAEs); serious infections; and quality of life. Prespecified exploratory analyses were the primary composite end point at 1 year for both randomisation groups, and the effect of PLEX on death at 1 year for those with lung haemorrhage.

Results

A total of 704 patients were recruited from 95 sites in 10 European Union countries, Australia, Canada, Japan, New Zealand, Mexico and the USA between June 2010 and September 2016, with a median follow-up of 2.9 years. Randomisations were well balanced in terms of baseline variables, and compliance with the randomised allocated regimen varied from 92% to 96% between the four randomisation groups. Data return was good for the first year (99%), with some drop-off to < 90% after 4 years' follow-up. A total of 100 patients in the PLEX group compared with 109 in the no-PLEX group reached an end point [HR 0.86, 95% confidence interval (CI) 0.65 to 1.13] and 107 in the reduced-dose steroid group compared with 102 in the standard-dose steroid groups (HR 1.00, 95% CI 0.76 to 1.31) in the time-to-event analyses. No significant interactions were seen between interventions. No differences were seen between groups in the proportion of patients achieving a sustained remission, end-stage renal disease or all-cause mortality for either PLEX versus no PLEX, or reduced-dose versus standard-dose steroid regimens. Infection was the most common cause of death.

A total of 1191 SAEs were reported, with infection being the most common SAE reported ($n = 423$). There were no differences in SAE rates between the randomisation groups. There were no statistically significant differences in serious infection rates between the PLEX and no PLEX groups. Fewer serious infections were seen in the reduced-dose steroid group than in the standard-dose oral steroid groups; however, this finding was not statistically significant (incidence rate ratio 0.76, 95% CI 0.57 to 1.01; $p = 0.058$). Although overall quality of life improved over time, there were no clinically meaningful differences between any of the randomisation groups.

Preplanned subgroup analyses for the primary end point were performed for all of the subgroups defined at entry for minimisation, and no differences were seen. Prespecified exploratory analyses of time to death and/or end-stage renal disease at 1 year showed no significant difference between PLEX and no PLEX (HR 0.77, 95% CI 0.56 to 1.06) or between reduced-dose and standard-dose steroid groups (HR 0.80, 95% CI 0.58 to 1.09).

Conclusions

This multicentre rare-disease trial successfully recruited > 700 patients from an international network. The time to death and/or end-stage renal disease was longer than expected from data obtained between 1995 and 2005, implying improved outcomes, despite no major changes in therapeutic agents during this period.

Plasma exchange did not delay the onset of end-stage renal disease or death. There was also no difference between PLEX and no PLEX in sustained remission, SAEs, serious infections or quality of life. The results of this trial do not provide convincing evidence that routine use of PLEX for patients presenting with AAV and renal involvement with a GFR of < 50 ml/minute/1.73 m^2 reduces the time to death or end-stage kidney disease.

The reduced-dose steroid regimen was safer, with fewer serious infections, and was no less effective in delaying death and/or end-stage renal disease than the standard-dose steroid regimen. This is the first trial, to our knowledge, to compare steroid dosing in a randomised controlled trial for AAV patients presenting with a GFR of < 50 ml/minute/1.73 m^2 or lung haemorrhage, and provides key evidence to be considered in future recommendation statements. The availability of a validated steroid regimen will harmonise steroid exposure and directly benefit physicians and their patients. The size and duration of PEXIVAS and the global reach of the investigator network will facilitate the impact of the trial's conclusions on health-care policy and the management of AAV patients in the future.

Trial registration

This trial is registered as ISRCTN07757494, EudraCT 2009-013220-24 and Clinicaltrials.gov NCT00987389.

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