Intravenous Cyclophosphamide and Plasmapheresis in Dialysis-Dependent ANCA-Associated Vasculitis

Ruth J. Pepper,† Dimitrios Chanouzas,‡ Ruth Tarzi,† Mark A. Little,* Alina Casian,§ Michael Walsh,‖ Charles D. Pusey,† Lorraine Harper,‡ and Alan D. Salama,* European Vasculitis Study (EUVAS) investigators*

Summary

Background and objectives Induction therapy with oral cyclophosphamide (CYP) has been a mainstay of treatment in patients with severe renal failure secondary to ANCA-associated vasculitis (AAV). Recent evidence proposes using pulsed intravenous CYP in less severe disease to minimize adverse events. It is unclear if this can be translated to those with dialysis-dependent renal insufficiency.

Design, setting, participants, & methods All AAV patients presenting between 2005 and 2010 requiring dialysis at presentation were retrospectively analyzed. Patients were treated with plasma exchange, corticosteroids, and intravenous CYP. Rate of dialysis independence at 3 and 12 months and adverse effects were assessed and compared with the outcome of the plasmapheresis, prednisolone, and oral CYP arm of the randomized MEPEX (methylprednisolone versus plasma exchange) trial.

Results Forty-one patients were included. At 3 months, 3 (7.3%) patients had died on dialysis, 12 (29.3%) remained dialysis dependent, and 26 (63.4%) were dialysis independent (creatinine, 2.5 mg/dl; GFR, 26 ml/min per 1.73 m^2). Four patients subsequently reached ESRD at a median time of 83 days. Thirty-seven (90%) patients reached 1 year follow-up, 13 (35%) remained dialysis dependent, and 24 (65%) had independent renal function. Eleven patients (27%) had episodes of leukopenia (white cell count $<4\times10^9$/L) during CYP therapy and 17 (41%) experienced infectious complications. This compares favorably with the dialysis-dependent cohort treated with plasmapheresis in the MEPEX study in which 51% were alive with independent renal function at 1 year.

Conclusions Intravenous CYP used with corticosteroids and plasmapheresis may be an effective alternative to oral CYP in patients with dialysis-dependent AAV.

Clin J Am Soc Nephrol 8: 219–224, 2013. doi: 10.2215/CJN.03680412

*UCL Centre for Nephrology, Royal Free Hospital, London, United Kingdom; †West London Renal and Transplant Centre, Hammersmith Hospital, London, United Kingdom; ‡Renal Immunobiology, School of Infection and Immunity, University of Birmingham, Birmingham, United Kingdom; §Vasculitis Clinic, Addenbrooke's Hospital, Cambridge, United Kingdom; and ‖McMaster University, Hamilton, Ontario, Canada

Correspondence: Dr. Alan D. Salama, UCL Centre for Nephrology, Royal Free Hospital, London NW3 2PF, UK. Email: a.salama@ucl.ac.uk

Introduction

Cyclophosphamide (CYP) has long been part of the treatment regimen in patients presenting with ANCA-associated vasculitis (AAV), providing benefits with respect to both renal and patient survival (1,2). However, its use is associated with significant adverse events and it has a dose-dependent toxicity. Importantly, in patients with AAV, the first-year mortality is more commonly related to adverse events than due to active vasculitis (3). In addition, despite maintenance immunosuppression, relapse rates are high (4), increasing patients' exposure to immunosuppression therapy. Previous treatment regimens, no longer in standard use, consisted of long-term oral cyclophosphamide and the resultant cumulative dose led to substantial urotoxicity, with 16% of patients at 15 years developing bladder cancer (5). Moreover, there was an apparent increased rate of urotoxicity in patients receiving oral rather than intravenous CYP, even when correcting for cumulative dose (6). However, even with reduced duration of CYP exposure, a higher cancer rate than the general population has been found in AAV patients, suggesting that further improvements with regard to malignant risk are desirable (7).

A meta-analysis comparing continuous oral CYP with pulsed intravenous CYP for induction of remission in AAV demonstrated a significantly lower risk of infections and leukopenia in the pulsed group, although it was less effective in preventing relapses (8). In addition, the risk of mortality increased with increasing severity of leukopenia (3). In those patients with AAV and active GN (creatinine <5.7 mg/dl [500 μmol/L]), a pulsed regime induced remission as well as the daily oral regimen, with a decreased cumulative dose and fewer instances of leukopenia (9). Although long-term data demonstrated that the pulsed CYP regimen was associated with higher relapse rates, there was no difference in mortality or morbidity (10).

Both renal function and age are important predictors of AAV outcome, and CYP dosage requires adjustment for these two factors, with older patients and those with worse renal function more likely to develop leukopenia and infection (11). The MEPEX (methylprednisolone versus plasma exchange) trial recruited patients with severe renal disease and utilized daily oral CYP, as well

as corticosteroids and either plasmapheresis or pulsed methylprednisolone, and mandated a CYP dose adjustment only for age. In both treatment groups, serious adverse events developed in approximately half of the patients. Adjunctive plasmapheresis increased the rate of renal recovery compared with methylprednisolone at both 3 and 12 months of follow-up. Therefore, MEPEX established a protocol for treatment of patients with severe renal disease, which was based on oral CYP (12). Whether pulsed CYP is equivalent for treating patients with severe renal disease has not been addressed, although some physicians have already adopted this approach.

We investigated the effectiveness of pulsed CYP in a cohort of patients presenting with dialysis-dependent renal failure who received adjunctive plasma exchange, assessing renal survival, disease relapse, and adverse events as outcome measures. We compared the results with those of the equivalent plasmapheresis patients in the MEPEX study.

Materials and Methods

This study was a retrospective analysis of patients from two large tertiary renal units in the United Kingdom. All patients who presented with new or relapsing AAV and were dialysis dependent between 2005 and 2010 were considered for inclusion. Patients had a diagnosis of AAV based on clinical features (pulmonary renal syndrome), positive ANCA serology, and characteristic features on biopsy. All patients required hemodialysis during their initial presentation. Patients were excluded if serum creatinine was >5.7 mg/d but they were dialysis independent, or if circulating antiglomerular basement membrane antibody was positive.

All patients were prescribed the same regimen of oral corticosteroids, intravenous CYP, and plasmapheresis. Prednisolone was commenced at a dose of 1 mg/kg (maximum 60 kg) with a weekly decrease in dose for the first 3 weeks, followed by a more gradual decrease aiming for 12.5 mg by 3 months, 10 mg by end of month 5, and 7.5 mg by 12 months. The dose of CYP was 7.5–12.5 mg/kg depending on age (age <60 years, 12.5 mg/kg; 60–70 years, 10 mg/kg; >70 years, 7.5 mg/kg). The first 3 doses of pulsed cyclophosphamide were administered every 2 weeks. This was followed by an additional three to seven doses of cyclophosphamide given every 3 weeks, aiming for a total of 6 to 10 doses over a minimum induction period of 13 weeks. CYP was not given if white cell count (WCC) was $<4\times10^9$/L. Mesna was only administered in the Birmingham Hospital cohort (n=20). Patients received plasmapheresis (aiming for seven exchanges over 2 weeks) against human albumin solution, or fresh frozen plasma if bleeding or a biopsy was performed, aiming for a 60 ml/kg exchange (with a maximum 4 L). Prophylaxis against gastritis, fungal infection, and *Pneumocystis jirovecii* pneumonia was routinely prescribed. After the induction regimen, patients were switched to azathioprine maintenance therapy at a dose of 2 mg/kg (maximum 150 mg) or 1 mg/kg if thiopurine methyltransferase activity was found to be low. Patients who were unable to tolerate azathioprine were converted to mycophenolate mofetil (MMF).

The following parameters were recorded: serum creatinine at 3 months and 12 months (data collected as μmol/L and converted to SI units), leukopenic episodes, documented infections, adverse events, relapses, and dosage of CYP. Estimated GFR (eGFR) was calculated using the abbreviated Modified Diet in Renal Disease (MDRD) study equation. Time on hemodialysis was recorded, as well as time to return to hemodialysis in those patients who initially regained independent renal function but then progressed to end stage renal failure.

The MEPEX study was a multinational randomized controlled study that recruited patients with serum creatinine >500 μmol/L (5.7 mg/dl) between 1995 and 2004 and utilized oral cyclophosphamide (at 2 mg/kg) and similar regimens for steroids and plasmapheresis. We compared our data with those patients in the MEPEX study who were classified as being dialysis dependent at time of entry into the study and who were randomized to plasmapheresis.

Statistical analysis comparing the survival of MEPEX patients with our cohort and time to relapse was done using the Log-rank test and Kaplan–Meier survival, whereas renal function was analyzed by one-way ANOVA with GraphPad Prism software.

Results

Patients were identified from the vasculitis clinic databases from the Imperial College National Health Service (NHS) Trust Hammersmith Hospital and Birmingham University Hospitals NHS Foundation Trust. All patients with AAV and severe renal disease who presented between 2005 (2006 for the Hammersmith cohort) and 2010 and required renal replacement therapy during their disease presentation were included. Forty-one patients who fulfilled the criteria were identified, 13 (32%) of whom had additional pulmonary hemorrhage and 18 (44%) had extrarenal involvement. The cohort consisted of 14 female and 27 male patients (Table 1). The median age of the patients was 62 years (interquartile range [IQR], 49–71 years).

Sixty-eight percent (28 of 41) of patients underwent a renal biopsy. Three participants were known AAV patients (with previous pauci immune GN) who presented with a

Table 1. Patient characteristics

Characteristic	Intravenous CYP	MEPEX
Number of patients	41	37
Age (yr), median (range)	62 (19–98)	64 (28–80)
ANCA type, *n*		
MPO	20	19
PR3	19	12
ANCA negative	1	6
MPO and PR3	1	
Pulmonary hemorrhage, *n* (%)	13 (32)	7 (19)
Extrarenal involvement, *n* (%)	18 (44)	24 (65)

CYP, cyclophosphamide; MPO, myeloperoxidase; PR3, proteinase 3; MEPEX, methylprednisolone versus plasma exchange (oral cyclophosphamide cohort).

renal flare, in the context of a high ANCA titer and an acute deterioration in renal function, and were therefore not biopsied. An additional patient had a skin biopsy demonstrating a granulomatous vasculitis with a strongly positive proteinase-3 (PR3)–ANCA and dialysis-dependent renal failure. The remaining nine patients were initially unfit for a biopsy and were diagnosed with AAV based on clinical symptoms (pulmonary hemorrhage in six patients), with a positive ANCA test and ARF. Two patients who died shortly after presentation and initiation of treatment also did not undergo a renal biopsy. We analyzed the available adequate renal biopsies from 27 of 28 patients: 16 of whom went onto recover renal function and 11 of whom remained hemodialysis dependent (summarized in Table 2). The cohort who remained dialysis dependent had a greater number of patients with tubular atrophy of >50% compared with the cohort who regained independent renal function (chi-squared test: $P<0.05$), and had a lower proportion of normal glomeruli ($P=0.05$) and more sclerosed glomeruli, but this did not reach statistical significance.

Treatment

All patients received pulsed intravenous CYP based on the European Vasculitis Study Group regimen used in those with less severe renal involvement (9). The median number of CYP pulses was 6 (IQR, 5–10) and the median total cumulative dose of cyclophosphamide was 4.75 g (IQR, 2.96–7.38 g). Twelve patients (29%) received fewer than the planned six doses for the following reasons: three patients died during the course of cyclophosphamide; one very elderly patient received five doses, regained independent renal function, and treatment was terminated in order to avoid immunosuppression-related complications; and two patients remained dialysis dependent and two patients returned to dialysis after three to five doses and had treatment terminated. The remaining four patients, who were all dialysis dependent, had treatment complications with leukopenia or infection and treatment was curtailed. Overall, those patients who remained hemodialysis dependent received significantly less total CYP than those who regained independent renal function (median dialysis dependent 2 g [IQR, 0.58–4 g] versus dialysis independent 6.55 g [IQR, 4.6–9.4 g]; $P<0.001$). The median number of plasmapheresis sessions was 7 (IQR, 7–7.5).

Renal Function and Outcome

All patients commenced dialysis within 72 hours of presentation. Of the 41 patients, 11 (27%) remained dialysis dependent with no renal recovery from the time of their initial presentation. This included three patients who died during their initial admission at 4, 7, and 66 days. Of the remaining eight surviving hemodialysis-dependent patients, six were positive for anti-myeloperoxidase (MPO), one was positive for both anti-MPO and anti-PR3 antibodies, and the remaining patient was ANCA negative. Thirty (73%) patients initially required dialysis but subsequently recovered renal function, with 28 of 30 patients regaining independent renal function by 3 months. During follow-up, four patients (three of four were anti-MPO positive) who initially regained dialysis independence subsequently progressed to ESRD with a median time of 83 days (IQR, 36–195 days).

By 3 months, 3 patients had died on dialysis whereas 12 were alive and remained on dialysis. Twenty-six patients (68%) had independent renal function with a median creatinine of 2.5 mg/dl (IQR, 1.9–3.3 mg/dl) and an eGFR of 26 ml/min per 1.73 m^2 (IQR, 19–40 ml/min per 1.73 m^2).

Thirty-seven patients reached 1 year of follow-up, 13 (35%) remained on dialysis, and 24 (65%) had independent renal function with a median creatinine of 1.9 mg/dl (IQR, 1.6–2.8 mg/dl) and an eGFR of 30 ml/min per 1.73 m^2 (IQR, 22–43 ml/min per 1.73 m^2). Thirty-two patients reached at least 2 years of follow-up, of which 21 (66%) had independent renal function with a median creatinine of 1.8 mg/dl (IQR, 1.5–2.7 mg/dl) and an eGFR of 34 ml/min per 1.73 m^2 (IQR, 26–48 ml/min per 1.73 m^2) and 11 patients had ESRD. No additional patients progressed to ESRD between 1 and 2 years; however, there were four additional deaths.

Table 2. Class of ANCA-associated GN according to Berden classification and renal recovery

Class of GN	Recovered Renal Function (n=16)	No Renal Recovery (n=11)
Crescentic	13 (81)	5 (45)
Focal	1 (6)	2 (18)
Mixed	1 (6)	1 (9)
Sclerotic	1 (6)	3 (27)

Data are shown as n (%).

Relapse

Two of the surviving 37 patients relapsed within the first 12 months. One patient relapsed with a suspected renal relapse (not biopsied). This was treated with a change in immunosuppression from MMF to oral cyclophosphamide for 3 months. The second patient presented with a fever and a new biopsy-proven rash 8 months following the initial presentation, which was treated by changing azathioprine to MMF.

Three patients relapsed after 12 months: one extrarenal relapse at 23 months; one pulmonary hemorrhage at 16 months; and one with ear, nose, and throat symptoms at 19 months.

Adverse Events

Eleven patients (27%) had episodes of leukopenia (WCC $<4\times10^9$/L) during CYP therapy, with eight patients experiencing leukopenia while dialysis dependent. In four of the patients (all dialysis dependent), CYP therapy was terminated because of this complication, with one patient requiring granulocyte-colony stimulating factor rescue therapy. An additional dialysis-dependent patient had an episode of neutropenic sepsis complicating treatment, but continued CYP therapy once the WCC had recovered.

Seventeen patients (41%) had 28 infective complications (Table 3). Four of the patients had concurrent leukopenia. Other adverse events included two episodes of deep vein thrombosis (leading to pulmonary embolism in one) after CYP had been switched to azathioprine, seizures in one patient (related to hypercalcemia), steroid-induced diabetes, depression, and one malignancy, all within the first 12

Table 3. Adverse events: Infectious complications

Site	Number of Episodes	Organisms when Isolated
Pulmonary	9	*Pseudomonas* *Haemophilus* *Aspergillus* *Candida*
Urosepsis	9	*Escherichia coli* VRE *Klebsiella* *Candida*
Blood culture	2	*Klebsiella* CNS
Gastrointestinal	1	*Clostridium difficile*
Other		
Suspected TB	2	
Shingles	2	
Neutropenic sepsis	1	
Fungal cavity	1	
VRE	1	

VRE, vancomycin-resistant *Enterococcus*; TB, tuberculosis; CNS, coagulase negative *Staphylococcus.*

months of therapy. After 12 months, 2 patients were diagnosed with malignancies, leading to death in 1 patient from metastatic disease. One patient had a cerebrovascular event, and another patient was diagnosed with atrial fibrillation and a pulmonary embolus.

There were a total of eight deaths, three during the first 3 months (one sepsis and two within a week of presentation), one at 5 months (malignancy), and four between 12 and 24 months (three unknown, one malignancy). Patient survival probability was 93% and 90% at 3 and 12 months, respectively.

Elderly Patients

Our cohort of patients included eight patients aged ≥75 years. Of these eight, three patients either presented dialysis dependent and never regained function, or returned to dialysis within 30 days. One patient aged >75 years died shortly after presentation, and four regained and maintained independent renal function. Within this group, infections were common, with five patients developing infectious complications and another developing severe leukopenia after the first dose of CYP.

Comparison with the MEPEX Study

We obtained detailed follow-up data on the patients in the MEPEX study. We identified patients who were classified as dialysis dependent at time of entry into the study, and who were randomized to the plasmapheresis arm, in addition to receiving oral CYP (n=37) (Table 1). Of the MEPEX patients, 11 of 37 (30%) remained dialysis dependent from time of presentation with no recovery. Three patients progressed to ESRD during long-term follow-up (one patient at 250 days, one between 4 and 5 years, and one patient between 5 and 6 years).

By 3 months, 24 of 37 patients had regained independent renal function, 6 patients remained dialysis dependent, and 7 patients had died. At 1 year, 14 of 37 (38%) had died, with 64% of those patients dying on dialysis.

At 12 months, 23 of 37 MEPEX patients were alive, with 19 patients (51%) alive with independent renal function with a median creatinine of 1.9 mg/dl and an eGFR of 35 ml/min per 1.73 m^2 (IQR, 23–46 ml/min per 1.73 m^2), which was not significantly different to our pulsed intravenous CYP cohort (Figure 1), whereas the remaining four MEPEX patients (11%) were alive on dialysis. One- and 2-year survival using the intravenous pulsed CYP regimen was significantly better (Log-rank test: P=0.05 and P=0.02, respectively) compared with the MEPEX cohort (Figure 2 and Table 4).

Of the MEPEX cohort identified, 15 patients died within the first 24 months, with the commonest cause of death in 7 patients due to infection complications, followed by an unknown cause in 3 patients, and pulmonary hemorrhage, bowel infarction, gastrointestinal hemorrhage, ruptured abdominal aortic aneurysm, and a myocardial infarction in 5 patients. There were four additional deaths after 24 months.

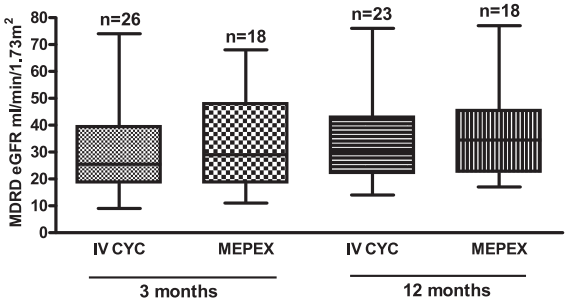

Figure 1. | MDRD eGFR in those who recovered renal function in the intravenous CYP cohort (n=41) and the plasmapheresis cohort from MEPEX (n=37). In the MEPEX cohort there are missing data, 24 patients have independent renal function at 3 months, 19 at 12 months. There was no significant difference in the renal function achieved at 3 or 12 months between the groups. MDRD, Modified Diet in Renal Disease; eGFR, estimated GFR; CYP, cyclophosphamide.

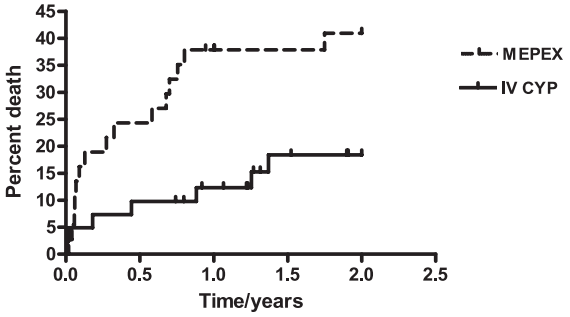

Figure 2. | Two year survival curves for patients from the intravenous CYP cohort (n=41) and the dialysis-dependent MEPEX cohort (n=37) demonstrating a significantly lower rate of survival in the MEPEX cohort (Log-rank test: P=0.02). CYP, cyclophosphamide.

Table 4. Comparison of outcome between the intravenous CYP cohort and the MEPEX cohort

Characteristic	Intravenous CYP	MEPEX
Number of patients	41	37
Alive at 3 mo	38/41 (93%)	30/37 (81%)
On dialysis	12	6
Dialysis free	26	24
Alive at 12 mo	37/41 (90%)	23/37 (62%)
On dialysis	13	4
Dialysis free	24	19
Death in first 12 mo	4/41(10%)	14/37 (38%)
Death in first 12 mo presumed due to sepsis	1 (25%)	7 (50%)

CYP, cyclophosphamide; MEPEX, methylprednisolone versus plasma exchange (oral cyclophosphamide cohort).

Discussion

This retrospective analysis demonstrates a high rate of renal recovery in patients with AAV and renal involvement requiring dialysis who were treated with pulsed CYP and adjunctive plasmapheresis. For our comparison, we used data on those patients in the plasmapheresis arm of the MEPEX study who required dialysis at presentation, which was an analogous cohort to ours. Renal recovery was achieved in the MEPEX study in 24 of 37 (65%) of patients at 3 months, whereas it was achieved in 68% of our cohort. At 1 year, the MEPEX plasmapheresis cohort had 51% of patients alive with independent renal function, whereas this occurred in 65% of patients in our cohort. The 1-year median serum creatinine was 1.9 mg/dl in the two groups.

One limitation of this study is that not all patients had a renal biopsy. However, of the renal biopsies available for analysis, more patients who remained dialysis dependent had a significant degree of tubular atrophy than those patients who regained dialysis independence, whereas no difference in glomerulosclerosis was found, unlike previous analysis of MEPEX samples (13). Return to hemodialysis occurred in four patients in our cohort by 265 days, with no further patients progressing to ESRD after this period of time, whereas in the MEPEX cohort, only three patients returned to dialysis at 250, 1686, and 2008 days.

Both morbidity and mortality in AAV are highest in patients remaining dialysis dependent, with age >60 years and renal impairment being significant prognostic factors (14). Our cohort had 90% patient survival at 1 year, which is similar to previous studies (9) and higher than survival in the MEPEX study. One possible explanation for this may be the retrospective data acquisition. Despite careful attempts not to miss any patients, it is possible that some, especially those who may have died during the very early stages of presentation, may have been missed, lowering the overall death rate. Alternatively, it may be a real improvement in survival, because deaths in the first year have been attributed to therapy-related adverse effects (3) and our adverse event rates were lower than previously reported. Previous studies have demonstrated that patients presenting with more severe renal involvement are more likely to be MPO-ANCA positive (12), although our cohort was almost equally split between MPO-ANCA and PR3-ANCA. In addition, patients positive for MPO-ANCA are more likely to present with irreversible renal lesions unresponsive to immunosuppressive therapy (15), and a greater proportion of our patients progressing to ESRD were MPO-ANCA positive. The two patients who relapsed in the first year were PR3-ANCA positive, consistent with previous studies that demonstrated that PR3-ANCA positivity is a risk factor for relapse in AAV (15,16). However, more patients with longer follow-up would be required to investigate whether this regimen results in an increased risk of long-term disease relapse.

Previous studies of oral CYP in AAV have highlighted hemorrhagic cystitis as a severe adverse effect of the drug. In this cohort, none of the patients developed hemorrhagic cystitis as an adverse effect, although all were initially dialysis dependent. However, during the CYP treatment period, >60% of patients recovered independent renal function and could therefore have been at risk of developing CYP-related bladder toxicities. Elderly patients (aged >65 years) tend to present with more severe renal involvement, develop more infections as a consequence of immunosuppression, and have an increased mortality (11). In addition, older patients have a high rate of ESRD (17). However, a recent study demonstrated the benefit of treating very elderly patients with immunosuppression, despite the increased treatment-related complications (18). Our data suggest that intravenous CYP can be used in this elderly population of patients, with appropriate dose reduction, although infections remain a common problem. Questions regarding whether elderly patients require a dose reduction of corticosteroids remain unanswered because even when the use of CYP is limited and agents such as rituximab are used, adverse events remain common, with high doses of steroids likely to be contributing to this effect (19,20).

One concern regarding the use of intravenous CYP is the relapse rate and the future exposure to further immunosuppression. This study comprises too few patients to address this issue. Short- and long-term follow-up of patients from the CYCLOPS study (randomized trial of daily oral versus pulsed cyclophosphamide) reported more relapses in the pulsed CYP group (9) with no differences in renal relapses, and importantly no difference in long-term renal outcome or mortality (10).

In conclusion, this analysis demonstrates that intravenous CYP together with corticosteroids and plasmapheresis can be effective in this group of patients with AAV and severe renal involvement, allowing patients to regain renal function without exposing them to the adverse effects associated with cumulative doses of oral CYP.

Acknowledgments

We are grateful to the following clinical colleagues who helped care for the patients in the vasculitis clinics: Drs. T. Cairns, M. Griffith, M. Morgan, and Sister Jane Owen.

Disclosures

None.

References

1. Fauci AS, Haynes BF, Katz P, Wolff SM: Wegener's granulomatosis: Prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 98: 76–85, 1983
2. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, Rottem M, Fauci AS: Wegener granulomatosis: An analysis of 158 patients. *Ann Intern Med* 116: 488–498, 1992
3. Little MA, Nightingale P, Verburgh CA, Hauser T, De Groot K, Savage C, Jayne D, Harper L; European Vasculitis Study (EUVAS) Group: Early mortality in systemic vasculitis: Relative contribution of adverse events and active vasculitis. *Ann Rheum Dis* 69: 1036–1043, 2010
4. Westman KW, Bygren PG, Olsson H, Ranstam J, Wieslander J: Relapse rate, renal survival, and cancer morbidity in patients with Wegener's granulomatosis or microscopic polyangiitis with renal involvement. *J Am Soc Nephrol* 9: 842–852, 1998
5. Talar-Williams C, Hijazi YM, Walther MM, Linehan WM, Hallahan CW, Lubensky I, Kerr GS, Hoffman GS, Fauci AS, Sneller MC: Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann Intern Med* 124: 477–484, 1996
6. Le Guenno G, Mahr A, Pagnoux C, Dhote R, Guillevin L; French Vasculitis Study Group: Incidence and predictors of urotoxic adverse events in cyclophosphamide-treated patients with systemic necrotizing vasculitides. *Arthritis Rheum* 63: 1435–1445, 2011
7. Heijl C, Harper L, Flossmann O, Stücker I, Scott DG, Watts RA, Höglund P, Westman K, Mahr A; European Vasculitis Study Group (EUVAS): Incidence of malignancy in patients treated for antineutrophil cytoplasm antibody-associated vasculitis: Follow-up data from European Vasculitis Study Group clinical trials. *Ann Rheum Dis* 70: 1415–1421, 2011
8. de Groot K, Adu D, Savage CO; EUVAS (European Vasculitis Study Group): The value of pulse cyclophosphamide in ANCA-associated vasculitis: Meta-analysis and critical review. *Nephrol Dial Transplant* 16: 2018–2027, 2001
9. de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, Luqmani R, Pusey CD, Rasmussen N, Sinico RA, Tesar V, Vanhille P, Westman K, Savage CO; EUVAS (European Vasculitis Study Group): Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: A randomized trial. *Ann Intern Med* 150: 670–680, 2009
10. Harper L, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O, Tesar V, Vanhille P, de Groot K, Luqmani R, Flores-Suarez LF, Watts R, Pusey C, Bruchfeld A, Rasmussen N, Blockmans D, Savage CO, Jayne D; EUVAS investigators: Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: Long-term follow-up. *Ann Rheum Dis* 71: 955–960, 2012
11. Harper L, Savage CO: ANCA-associated renal vasculitis at the end of the twentieth century—a disease of older patients. *Rheumatology (Oxford)* 44: 495–501, 2005
12. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, Mirapeix E, Savage CO, Sinico RA, Stegeman CA, Westman KW, van der Woude FJ, de Lind van Wijngaarden RA, Pusey CD; European Vasculitis Study Group: Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 18: 2180–2188, 2007
13. de Lind van Wijngaarden RA, Hauer HA, Wolterbeek R, Jayne DR, Gaskin G, Rasmussen N, Noël LH, Ferrario F, Waldherr R, Bruijn JA, Bajema IM, Hagen EC, Pusey CD; EUVAS: Chances of renal recovery for dialysis-dependent ANCA-associated glomerulonephritis. *J Am Soc Nephrol* 18: 2189–2197, 2007
14. Booth AD, Almond MK, Burns A, Ellis P, Gaskin G, Neild GH, Plaisance M, Pusey CD, Jayne DR; Pan-Thames Renal Research Group: Outcome of ANCA-associated renal vasculitis: A 5-year retrospective study. *Am J Kidney Dis* 41: 776–784, 2003
15. Hogan SL, Falk RJ, Chin H, Cai J, Jennette CE, Jennette JC, Nachman PH: Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. *Ann Intern Med* 143: 621–631, 2005
16. Pagnoux C, Hogan SL, Chin H, Jennette JC, Falk RJ, Guillevin L, Nachman PH: Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis: Comparison of two independent cohorts. *Arthritis Rheum* 58: 2908–2918, 2008
17. Panagiotakis SH, Perysinakis GS, Kritikos H, Vassilopoulos D, Vrentzos G, Linardakis M, Bertsias G, Glaser K, Daphnis E, Boumpas DT: The epidemiology of primary systemic vasculitides involving small vessels in Crete (southern Greece): A comparison of older versus younger adult patients. *Clin Exp Rheumatol* 27: 409–415, 2009
18. Bomback AS, Appel GB, Radhakrishnan J, Shirazian S, Herlitz LC, Stokes B, D'Agati VD, Markowitz GS: ANCA-associated glomerulonephritis in the very elderly. *Kidney Int* 79: 757–764, 2011
19. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, Savage CO, Segelmark M, Tesar V, van Paassen P, Walsh D, Walsh M, Westman K, Jayne DR; European Vasculitis Study Group: Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 363: 211–220, 2010
20. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Turkiewicz A, Tchao NK, Webber L, Ding L, Sejismundo LP, Mieras K, Weitzenkamp D, Ikle D, Seyfert-Margolis V, Mueller M, Brunetta P, Allen NB, Fervenza FC, Geetha D, Keogh KA, Kissin EY, Monach PA, Peikert T, Stegeman C, Ytterberg SR, Specks U; RAVE-ITN Research Group: Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 363: 221–232, 2010

Received: April 13, 2012 **Accepted:** October 17, 2012

R.J.P. and D.C. contributed equally to the study and are first co-authors.

Published online ahead of print. Publication date available at www.cjasn.org.

Correction

Pepper RJ, Chanouzas D, Tarzi R, Little MA, Caisian A, Walsh M, Pusey CD, Harper L, Salama AD; European Vasculitis Study (EUVAS) investigators: Intravenous cyclophosphamide and plasmapheresis in dialysis-dependent ANCA-associated vasculitis [published online ahead of print November 15, 2012]. *Clin J Am Soc Nephrol* doi:10.2215/CJN.03680412.

Due to author error, Dr. Alina Casian's name was misspelled in the above-referenced article. The correct spelling of Dr. Casian's name is Dr. Alina Casian.